Review Article on Lymphedema

Application of imaging in lymphedema surgical therapies

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Abstract: Lymphedema is a chronic, progressive disease caused by primary or secondary reasons. It is currently uncurable and conservative compression therapy is generally applied. Lymphovenous anastomosis and vascularized lymph node transfer (VLNT) are two main surgical treatment that are used in addition to conservative therapy. Lymphovenous anastomosis involves the anastomosing remaining functional lymphatic vessels to vein. When the lymphatic vessels are greatly damaged and in no case can they be used for anastomosis, VLNT provide the affected area with lymph nodes from elsewhere to restore the drainage function. During all these procedures, a clear image to identify related lymphatic structures and venous vessels can be greatly useful for preoperative planning, intraoperative navigation, and postoperative evaluation. Lymphoscintigraphy used to be the gold standard in evaluating lymphedema and mapping lymphatic systems. But due to the downside of radiation, invasive operation and complication, other modalities are gaining attention. In this article, we reviewed the application of Indocyanine green (ICG) lymphography, ultrasound, magnetic resonance lymphography (MRL), and single-photon emission computed tomography-computed tomography (SPECT-CT) in the field of surgical therapy in lymphedema.

Keywords: Indocyanine green (ICG); lymphedema; magnetic resonance imaging; single-photon emission computed tomography-computed tomography (SPECT-CT); ultrasound

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Introduction

Lymphedema is a chronic, progressive disease caused either by congenital lymphatic malformation or secondary destruction to the lymphatic channels. Oncologic treatment is the main cause of secondary lymphedema and it often results in extremity pain, swelling, infections, restrictions in range of motion, and aesthetic disturbances, leading to a decrease in patients' quality of life (1).

Currently, there is no curative treatment for lymphedema. Combination use of manual lymph drainage, compression, exercise, and skin care called complete decongestive therapy (CDT) are recommended. However, for those who do not respond to these therapies, surgical interventions are indicated. Lymphovenous anastomosis (LVA) improves lymphedema by linking lymphatic collecting vessels (LCVs) with vein. Vascularized lymph node transfer (VLNT) involves transferring lymph nodes into the affected limb to restore the drainage function (2,3). In either case, a delicate imaging of the lymphatic system can avoid large incision and intraoperative time-consuming lymphatic vessel dissection. Lymphoscintigraphy used to be the gold standard in evaluating lymphedema and mapping lymphatic systems, but due to the downside of radiation, invasive operation and complication, other modalities are gaining attention and improving the preoperative planning of lymphatic surgeries (4).

We searched the database PubMed and Embase with phrases "lymphovenous anastomosis" "lymphovenous bypass" "LVA", "lymph node transfer" and "LNT".

Then we reviewed articles within the last 20 years with the topic of "imaging" and "mapping" and nailed the four most commonly reported imaging methods. After that, we scrutinized articles related to the four methods using words "magnetic resonance lymphangiography" "MRL" "indocyanine green" "lymphangiography" "ICG" "ultrasound" "SPECT" and "single photon emission computed tomography computed tomography". For each method, anything we considered as clinical important or innovating is included in this paper.

Indocyanine green (ICG) lymphography

Since the first use of ICG lymphography by Unno *et al.* (5,6) for preoperative planning of lyphatico-venous anastomosis, the simplicity, sensitivity, and accuracy has made it a widely used modality in lymphatic imaging (7). Identification of LCVs is essential for a successful LVA. Generally, ICG-enhanced LCVs were considered as functional and ideal for LVA (8-11). This method operates in the near-infrared region (NIR). ICG is injected preoperatively or intraoperatively, and lymphatic systems can be presented with a good spatial resolution of images (12). However, ICG injection location, depth can affect the outcome. The idea of lymphosome may explain why only lymphatic vessels originating from the injection areas can be imaged (13), superficial lymphatic vessels divide the skin into certain lymphatic territories, in which each vessel drains its own part and does not cross in human. The actual number of "functional" LCVs should take those non-ICG enhanced, but flow-positive ones into consideration (14). Preoperatively ICG-negative lymphatics can also be large and high-flow (15,16). Multi-lymphosome injection may also aid in detecting a greater number of LCVs (17).

For postoperative accessing, ICG lymphography can be used to evaluate the effects of LVA (18,19). Patterns were identified in the patent anastomosis areas. However, for areas that are thick more than 2 cm like the lower extremity, the limitation of penetration depth made it hard to observe certain dermal backflow when evaluating lymphatic patency rate (20,21). This disadvantage might not be significant in LVA planning for the lymphatic system that was used usually within the depth <2 cm. Researches on ICG performance in NIR-II (1,000–1,700 nm) showed that compared with NIR-I window (700–900 nm), it enables superior image quality and increase of image depth (22,23). Indicating a potential clinical broaden use of ICG under future NIR-II hardware.

Recent booming computer techniques also provided new aspects in the utility of ICG. Giacalone *et al.* reported a case with lymphatic malformation treated with preoperative virtual reality planning (24). Brebant *et al.* presented an augmented reality intraoperative ICG lymphography navigated LVA (25). These techniques provided surgeons with more intuitive information for preoperative and intraoperative mapping.

In patients with severe lymphedema, lymph node transfer (LNT) was reported to have better relief of symptoms for it reconstructed the damaged or missing lymphatic tissue. ICG was reported to be used in the recipient site for vessel evaluations, vessel patency and perfusion of the transplant (2,26,27). It should be noticed that LNT may result in donor site lymphedema and this could be detected and evaluated by ICG lymphography (28). To reduce the rate of this complication, ICG or Technetium were injected for reverse lymphatic mapping, regarding to reduce the risk of harvesting a draining lymph node (29).

Ultrasound

Compared with ICG lymphography, ultrasound can detect lymphatic flow in deeper layers which ICG cannot reach, even in regions with stardust or diffuse pattern which would conceal lymphatic vessels in ICG lymphography. Ultrasound device is relatively more commonly used than ICG. These make ultrasound a valuable substitute for ICG lymphography and it has been used in examining lymphedema for years. Three typical ultrasound findings in extremities lymphedema includes increased skin thickness, increased subcutaneous tissue thickness and increased subcutaneous echogenicity (30). Healthy lymphatic vessels showed homogeneous, hypoechoic and specular images under ultrasound, as the develop of lymphatic vessel sclerosis, they would present various shape (31). Hayashi *et al.* compared ICG lymphography with ultrasound in lower legs LVA and found that ultrasound had a higher detecting rate in identifying lateral side lymphatic vessels, and provide a better distinguish from the surrounding tissues (32). Nevertheless small caliber lymphatic vessels may be hard to distinguish from blood vessels, the use of color doppler mode and tracing origin can help understand the situation (33). In evaluating LNT donor sites, the application in the groin flap showed satisfactory outcome, but the lack of differentiating functional lymph nodes requires the use of other modalities (34).

Same as all other ultrasound implication scenarios, image quality greatly depends on the operators' skill and experience. Besides, the accessing process could be time-consuming. Especially in case with massive fluid retention, suggesting a need of decongestive therapy under this circumstance (35). Another difficulty in the use of ultrasound is the caliber of small lymphatic vessel. It is relatively easy to detect dilated lymphatic vessels that are greater than 0.5 mm, but difficult to identify a normal collecting lymphatic vessel that is approximately 0.2 mm, thus the combining use of ICG lymphography (36) and magnetic resonance lymphography (MRL) would to be more accurate (36,37).

MRL

MRL has proven to be a feasible way to visualize the lymphatic system in patients with lymphedema (38,39), with better spatial and temporal resolution, as well as ability to depict whole extremity lymphatic system. The contrast enhancement within lymphatic vessels and lymph nodes were brought by the subcutaneous injection of paramagnetic macromolecules (>6–10 nm), which entered the lymphatic system and were retained in the lymphatic channels (39).

One main downside about MRL is that it is hard to distinguish lymphatic vessels from blood vessels when there is concomitant venous presence, several techniques were presented to solve this stigma. The caliber, the morphology and the beaded appearance of the vessels can be used in differentiation. Immunohistochemical staining proved it to be effective (40). Adding an MR venogram after the depiction of the lymphatic system could facilitate the differentiation of superficial veins and lymphatic vessels (41). Another solution was to perform a 3D steady-state free precession (SSFP) balanced electrocardiography-(ECG-) triggered sequence (FIESTA, GE) with spectral fat saturation before 3D gradient-echo T1-weighted MRL, to obtain at the same time the depiction of the severity and distribution of lymphedema and a visualization of a pre-contrast venogram. This method needs well cooperation by the patient for movements would compromise the process (42).

Non-contrast MRL is a noninvasive imaging modality and has been reported in lymphedema evaluation after LNT (43). However, image degradation caused by various biologic motions hampers the use, future hardware and software improvement need to address this (44).

Compared with ICG lymphography and ultrasound, MRL provide the presence, number, course, and location of enhancing lymphatic channels more than 2 cm deep. With the help of multiplanar reconstruction (MPR) and maximum intensity projections (MIP), 3D images can provide a better understanding of interested region for the surgeon (45) and provide additional information about the surrounding tissue which is helpful to decision making (46,47). Postoperative evaluation using MRL can be performed routinely and with no risk (48). Finding a lymphatic channel with suitable caliber is crucial to the success of surgery, however, the reported size of the vessel can be a lot greater than actual, which emphasizes the need of using both ICG and MRL in preoperative lymphatic mapping (49). Contraindications are the same with all other MR techniques, severe claustrophobia, pace makers, and ferromagnetic intracerebral clips. Complications are rare but not unseen.

Single-photon emission computed tomography-computed tomography (SPECT-CT)

SPECT-CT is a hybrid imaging examination that could provide morphologic information on computed tomography and functional information on positron emission tomography at the same time (50). While lymocintigraphy demonstrate function of dynamic flow and leave out detailed spatial and anatomical information, SPECT/CT improved by reducing image-degrading effects of partial volume (51). This technique has been used in the preoperative sentinel lymph node imaging in various diseases (52-55). The elaborate depiction of both functional and morphological information was reported to be useful in both LVA and LVNT (56,57). The disadvantages of SPECT-CT include expensive cost and the share of same extra radiation with the plane Tc99 lymphoscintigraphy (57). Preoperative SPECT/CT contains all the necessary information for the surgery. Intraoperative navigation can be realized with the combination of other modalities. Fusion ultrasound provides information from other techniques during the interpretation of ultrasound, when it is linked to preoperative SPECT/CT mapping, real-time image and related anatomical information would provide a reliable navigation through the virtual navigate system (37).

In this paper, we reviewed the most commonly used modalities during the perioperative period of lymphatic surgery (*Table 1*). However, there are limitations. First, the studies we included are mainly retrospectively studies, therefore, there was a high risk of selection and publication bias. More prospectively double-blind studies are needed. Second, lymphatic surgery is a relatively new technique, at current stage, different imaging modalities have their own

Table 1 Advantages and disadvantages of different imaging modalities

Modalities	Advantages		Disadvantages	
ICG lymphography (6,7)	(I)	No radiation exposure	(I)	Penetration depth <1.5–2 cm
	(II)	Provide information on location and function of lymphatic vessels	(II)	Contrast medium could cause allergy
	(III)	Suitable for intraoperative guidance		
	(IV)	Relatively short operating time		
Ultrasound (32,33,35)	(I)	Noninvasive, no radiation exposure	(I)	Inability to distinguish functional with nonfunctional lymph nodes
	(II)	Moderate penetration depth	(II)	Operator dependent
	(III)	Suitable for intraoperative guidance		
MR lymphography (38-40,42)	(I)	No radiation exposure	(I)	Time-consuming and patient need to stay stable through the process
	(II)	Provide information on deep lymphatic vessels	(II)	Hard to distinguish lymphatic vessels with the venous vessels
	(III)	Provide a whole picture of involved extremity	(III)	Contrast medium could cause allergy
	(IV)	3D reconstruction		
SPECT/CT (53-56)	(I)	Comprehensive morphological and functional information	(I)	Time-consuming
	(II)	Depiction of the whole body	(II)	Radiation exposure
			(III)	Expensive cost

limits. It is impossible to identify one modality that can fit in all scenarios, therefor, the combining use of proper methods would be more reasonable.

Conclusions

Application of imaging modalities in lymphatic surgery can be a complex process, involving preoperative staging of lymphedema, mapping, identifying the proper functional lymph vessels, intraoperative navigation, and postoperative evaluation of vessel patency. Choosing the proper means under specific circumstance is crucial to perform a successful operation and result in a satisfactory outcome. The combination use of different modalities provides a compliment to each other and yield a better result. Besides, techniques like fusion imaging, virtual reality, augmented reality and portable devices can add more possibilities in the use of mapping and intraoperative guidance.

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Footnote

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