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REVIEW ARTICLE

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Use of magnetic resonance imaging lymphangiography for preoperative planning in lymphedema surgery: A systematic review

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Abstract

Background: In recent years, magnetic resonance imaging lymphangiography (MRL) has emerged as a way to predict if patients are candidates for lymphedema surgery, particularly lymphovenous anastomosis (LVA). Our goal was to conduct a systematic review of the literature on the use of MRL for preoperative planning in lymphedema surgery. We hypothesized that MRL could add valuable information to the standard preoperative evaluation of lymphedema patients.

Methods: On February 17, 2020, we conducted a systematic review of the PubMed/MEDLINE, Cochrane Clinical Answers, and Embase databases, without time frame or language limitations, to identify articles on the use of MRL for preoperative planning of lymphedema surgery. We excluded studies that investigated other applications of magnetic resonance imaging, such as lymphedema diagnosis and treatment evaluation. The primary outcome was the examination capacity to identify lymphatic anatomy and the secondary outcome was the presence of adverse effects.

Results: Of 372 potential articles identified with the search, nine studies fulfilled the eligibility criteria. A total of 334 lymphedema patients were enrolled in these studies. Two studies compared MRL findings with those of other standard examinations (indocyanine green lymphography [ICG-L] or lymphoscintigraphy). No adverse effects due to MRL were reported. A study shown that MRL had higher sensitivity to detect lymphatic vessel abnormalities compared with lymphoscintigraphy and a statistically higher chance of successful LVA was observed when the results of MRL agreed with those of ICG-L ($p < .001$).

Conclusions: MRL could be useful for preoperative planning in lymphedema surgery. The scientific evidence has been limited, so further studies with greater numbers of patients and cost analysis are necessary to justify the addition of MRL to current preoperative protocols.

1 | INTRODUCTION

Lymphedema is a chronic condition that occurs secondarily to cancer treatment, such as lymph node dissection and radiotherapy (Cormier et al., 2010; DiSipio et al., 2013; Gallagher et al., 2018; Newman et al., 2012; Weiss et al., 2015). It is estimated that lymphedema will develop in as many as 65% of patients undergoing breast cancer treatment (DiSipio et al., 2013; McLaughlin et al., 2008; Ozcinar

et al., 2012). In recent years, advances in imaging and microsurgery have allowed surgeons to pursue surgical treatment for lymphedema (Masia et al., 2014). Lymphovenous anastomosis (LVA) and vascularized lymph node transplant (VLNT) are often used to manage lymphedema, and the aim of both procedures is to restore lymphatic drainage of the affected limbs (Forte et al., 2019).

Multiple advances in radiographic imaging have been implemented to enhance the field of plastic and reconstructive surgery (Chang, Chu, & Chang, 2018; Rozen et al., 2008). Preoperative imaging for complex reconstructive surgeries is already considered a standard of care among plastic surgeons. Although computed tomographic angiography is the most common imaging modality used for preoperative planning, various other imaging modalities have been reported (Chang, Chu, & Chang, 2018). For example, virtual planning with three-dimensional models can be integrated into complex surgical care, such as in composite tissue head and neck reconstruction (Ramly et al., 2019). Surgical flaps can now be planned with high precision to optimize aesthetic and functional outcomes (Ramly et al., 2019). Similarly, high-quality imaging is important for lymphatic microsurgery because outcomes depend on the accurate identification of functional lymphatic vessels for anastomosis (Pons et al., 2019).

Lymphedema treatment has advanced considerably due to the development of physiologic surgeries such as LVA and VLNT that seek to restore lymphatic function (Forte et al., 2019). One of the most challenging and burdensome parts of these procedures is locating functional lymphatic vessels and lymph nodes (Pons et al., 2019). To improve procedural efficiency and outcomes, surgeons may use indocyanine green lymphography (ICG-L) to preoperatively identify functional lymphatic vessels and decide the locations for the LVA incisions (Unno et al., 2007). However, this technique has limitations, such as its inability to visualize deep lymphatic circulation (Pons et al., 2019). Magnetic resonance imaging lymphangiography (MRL) is done with an intracutaneous injection of a gadolinium-based contrast agent and it is reportedly a safe, noninvasive, and high-resolution examination for lymphatic vessel delineation in lymphedema patients (Lohrmann et al., 2006). Therefore, we conducted a systematic review of the literature on the use of MRL for preoperative planning in lymphedema surgery. We hypothesized that MRL could complement information acquired with other standard preoperative examinations.

2 | MATERIALS AND METHODS

2.1 | Search strategy

This study followed the guidelines outlined in the Preferred reporting items for systematic reviews and meta-analyses (PRISMA). On February 17, 2020, two authors (D. B. and M. T. H.) conducted independent searches of the PubMed/MEDLINE, Cochrane Clinical Answers, and Embase databases, without time frame limitations. The search was performed with the following keywords: "magnetic resonance imaging" OR "MRI" AND "Lymphedema." Initially the title and abstract were screened, and then the full text was reviewed. Duplicate articles were excluded, and disagreements regarding article identification and final selection for inclusion were resolved by another author (A. J. F.). The reference lists of the studies that fulfilled the study eligibility criteria (see the *Selection criteria* section below) were also examined, and we looked for articles not identified with our initial search.

2.2 | Selection criteria

We included studies that met eligibility criteria and reported data about the use of MRL in lymphedema surgery. We excluded studies that investigated other applications of magnetic resonance imaging (MRI), such as lymphedema diagnosis and treatment evaluation. Abstracts, presentations, reviews, meta-analyses, and non-English articles were also excluded.

2.3 | Data extraction and processing

We extracted data regarding the year of publication, country, study design, level of evidence, number of patients, type of MRI, type of contrast agent, comparative examinations, MRI measurements, and adverse effects. The primary outcome was the examination capacity to identify lymphatic anatomy and the secondary outcome was the presence of adverse effects. Two authors (D. B. and M. T. H.) extracted data from the text, tables, and figures, and another author (A. J. F.) confirmed the accuracy of data entry.

3 | RESULTS

3.1 | Study characteristics

Of 372 potential articles identified with the search, nine fulfilled the eligibility criteria (Figure 1 and Table 1). In total, the nine studies evaluated 334 lymphedema patients. Use of MRL for preoperative planning of lymphedema surgery was addressed in studies that used 1.5 or 3.0-T MRI equipment. Lymphedema grading was evaluated with heavily T2-weighted sequences, and lymphatic channel assessment was performed with three-dimensional T1-weighted gradient-echo sequences with spectral fat saturation.

The reports included for analysis demonstrate that MRL could be useful for preoperative planning before lymphedema surgery. Dayan et al. (2014) published a case series of 117 patients undergoing vascularized groin lymph node transfer (VGLNT) who were examined with preoperatively MRL. The examination was able to identify the lymphatic circulation of the superficial transverse inguinal lymph nodes (Dayan et al., 2014). Asuncion et al (Asuncion et al., 2018) conducted a retrospective study on 15 patients with upper or lower limb lymphedema who underwent vascularized submental lymph node flaps.

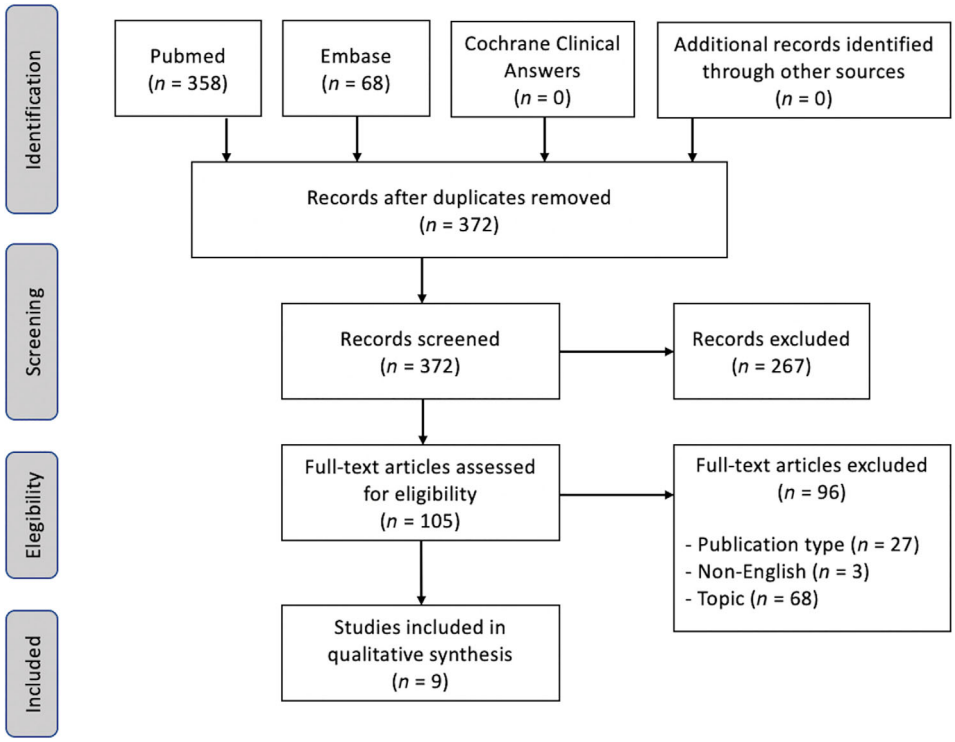

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (*PRISMA*) diagram

Preoperative MRL allowed the identification of 7.2 ± 2.4 submental lymph nodes, which was greater than preoperative ultrasound doppler (3.2 ± 1.1) and intraoperative finding (3.1 ± 0.6) (Asuncion et al., 2018). Zeltzer et al. (2018) conducted a prospective on 25 patients with upper extremity lymphedema where MRL allowed the identification of lymphatic circulation in 18 patients. They reported that LVA was successfully performed in 16 patients from their cohort (Zeltzer et al., 2018). Lohrmann et al. (2008) used MRL to preoperatively and postoperatively (LVA or Lymph vessel transplant) evaluate lymphedema grade and lymphatic channel characteristics. Four patients with unilateral lower-extremity lymphedema participated in the study. The authors compared preoperative and postoperative MRI findings and observed improvement of collateral lymphatic vessels and dermal backflow in two patients. Moreover, MRL identified contrast media extravasation in one patient with a lymphocutaneous fistula (Lohrmann et al., 2008).

Studies compared findings of preoperative MRL and other examinations (Asuncion et al., 2018; Notohamiprodjo et al., 2012; Pons et al., 2019). Notohamiprodjo et al. (2012) conducted a prospective study comparing MRL and lymphoscintigraphy. Thirty patients with unilateral or bilateral lower-extremity lymphedema were enrolled. Correlation between MRL findings and lymphoscintigraphy findings was excellent for delay ($\kappa = 0.93$) and pattern of drainage ($\kappa = 0.84$), good for delineation of lymph nodes ($\kappa = 0.67$) and degree of contrast/radiotracer ascension ($\kappa = 0.77$), and moderate for delineation of lymphatic vessels ($\kappa = 0.50$). They noted that MRL had a higher sensitivity for the visualization of lymphatic vessel abnormalities (100% for MRL vs. 79% for lymphoscintigraphy) and had a lower sensitivity for the visualization of lymph node abnormalities (78% for MRL vs. 100% for lymphoscintigraphy) (Notohamiprodjo et al., 2012).

Pons et al. (2019) conducted a prospective study using MRL and ICG-L to optimize LVA preoperative planning for 82 lymphedema patients. They noted that MRL data allowed intraoperative identification of functional lymphatic vessels more often than ICG-L (mean number of lymphatic locations per limb determined with MRL, 6.87; mean number of locations per limb suitable for LVA, 4.04). When the location for LVA was based on only MRL data, lymphatic vessels were found in 69.7% of the locations and LVA was successfully performed in 57.1%. Interestingly, when both studies are done and there is agreement, then there is the highest chance of finding lymphatics and performing LVAs ($p < .001$). When the results of both examinations agreed, functional lymphatic vessels were found in 96.9% of the locations and LVA was successfully performed in 91.4% (Pons et al., 2019).

Two studies investigated whether MRL is able to distinguish lymphatic vessels from adjacent veins. Mazzei et al. (2017) conducted a prospective study on 30 patients with lower limb lymphedema where they demonstrated through immunohistochemical analysis that MRL is able to distinguish lymphatic vessels from veins. Their findings were corroborated by a study conducted by Gennaro et al. (2017) on 25 patients with upper extremity lymphedema who underwent LVA.

4 | DISCUSSION

The use of MRL for preoperative planning of lymphedema surgery is summarized in this systematic review consisting of nine studies, in

TABLE 1 Summary of the studies investigating the use of magnetic resonance imaging lymphangiography for preoperative planning in lymphedema surgery

Authors	Year	Country	Study type	Level of evidence	Patients N	Lymphedema location	Procedure	MRI	Other examination utilized	Adverse effects to MRL
Pons et al. (Pons et al., 2019)	2019	Spain	Case series	III	82	Upper or lower extremities	LVA, LNT, or DIEP-LNT	3 T	ICG-L	None
Zeltzer et al. (Zeltzer et al., 2018)	2018	Belgium	Prospective study	IV	25	Upper extremity	LVA	3 T	-	None
Asuncion et al. (Asuncion et al., 2018)	2018	Taiwan	Case series	III	15	Upper or lower extremities	VSLN		Ultrasound Doppler	None
Mazzei et al. (Mazzei et al., 2017)	2017	Italy	Prospective study	III	30	17 lower extremity; 6 primary lymphedema	LVA	1.5 T	Immunohistochemistry	None
Long et al. (Long et al., 2017)	2017	China	Case series	III	11	Lower extremity	LVA and/or liposuction		Lymphoscintigraphy	None
Gennaro et al. (Gennaro et al., 2017)	2017	Italy	Case series	III	20	15 upper extremity, 5 lower extremity	LVA	1.5 T	Immunohistochemistry	None
Dayan et al. (Dayan et al., 2014)	2014	USA	Case series	IV	117	-	VGLNT	-	-	None
Notohamiprodjo et al. (Notohamiprodjo et al., 2012)	2012	Germany	Prospective study	II	30	-	-	3 T	Lymphoscintigraphy	None
Lohrmann et al. (Lohrmann et al., 2008)	2008	Germany	Case series	IV	4	Lower extremity	LVT (3 patients); LVA (1 patient)	1.5 T	-	None

Abbreviations: DIEP-LNT, deep inferior perforator lymph node transfer; ICG-L, indocianin green lymphangiography; LVA, lymphovenous anastomosis; LVT, lymphatic vessel transplantation; VGLNT, vascularized groin lymph node transfer; VSLN, vascularized submental lymp.

which a total of 334 lymphedema patients were included (Asuncion et al., 2018; Dayan et al., 2014; Gennaro et al., 2017; Lohrmann et al., 2008; Long et al., 2017; Mazzei et al., 2017; Notohamiprodjo et al., 2012; Pons et al., 2019; Zeltzer et al., 2018). Lymphatic channel assessment was performed with three-dimensional T1-weighted gradient-echo sequences with spectral fat suppression. The studies that compared MRL data to other conventional methods of lymphatic evaluation (i.e., ICG-L and lymphoscintigraphy) revealed that MRL provides valuable information before lymphedema surgery (Notohamiprodjo et al., 2012; Pons et al., 2019). MRL had a higher sensitivity for the detection of lymphatic vessel abnormalities compared to lymphoscintigraphy (Notohamiprodjo et al., 2012). Moreover, a study showed that concordant MRL and ICG-L findings correlated with a higher probability of successful LVA ($p < .001$) (Pons et al., 2019). Although the literature reports adverse events of perivascular injection of gadolinium-based contrast agents such as edema, hemorrhage, and necrosis, none of the studies who investigated the use of MRL reported adverse events (Lohrmann et al., 2008; Notohamiprodjo et al., 2012; Pons et al., 2019).

ICG-L for preoperative planning of lymphedema surgery is considered a standard approach. It was first introduced by Unno et al. (2007)) in 2007, and it has transformed the field of lymphedema surgery dramatically. Before ICG-L, information for lymphatic vessel location was insufficient, and LVA incisions were planned randomly or on the basis of proximity to large veins (Koshima et al., 2004). Therefore, multiple incisions were necessary, the probability of identifying functional lymphatic vessels was low, and worse lymphedema was possible owing to the risk of inadvertent injury to intact lymphatic vessels (Pons et al., 2019).

ICG-L can be used preoperatively and intraoperatively and has several advantages. Because indocyanine green is directly absorbed by lymphatic cells, ICG-L provides precise information about lymphatic vessel location and function, collateral lymphatic circulation, and dermal backflow (Chang, Chu, & Chang, 2018; Pons et al., 2019). ICG-L provides real-time imaging and is considered simple, accurate, highly sensitive, and minimally invasive (Chang, Chu, & Chang, 2018). Furthermore, it can maximize lymphaticovenular anastomosis efficacy by verifying the patency of lymphatic anastomosis as well as detect and predict lymphosclerosis (Chang, Skoracki, & Chang, 2018; Yamamoto et al., 2017; Yamamoto, Narushima, & Koshima, 2018; Yamamoto, Yamamoto, et al., 2018). Nonetheless, a major limitation of ICG-L is that it cannot identify lymphatic circulation located deeper than 1.5 to 2.0 cm from the skin surface (Chang, Chu, & Chang, 2018).

MRL has been proposed as a method for preoperative assessment of lymphatic channels due to several perceived advantages. Its high resolution allows for the depiction of small lymphatic channels beyond the resolution of traditional lymphoscintigraphy. This allows for a more complete assessment of lymphatic channel morphology, provides information about lymphatic channel number, depth, trajectory, and precisely delineates regions of dermal backflow (Pons et al., 2019). Pons et al. (2019) provided evidence in their study that MRL can be used to identify lymphatic vessels not seen with the standard ICG-L approach, namely vessels deep below the skin surface (>2 cm deep). Interestingly, when the findings of MRL and ICG-L agreed, functional lymphatic vessels were found in 96.9% of the LVA incisions, and was anastomoses were successfully performed in 91.4% of instances. Agreement between MRL and ICG-L significantly increased the chance of successful LVA ($p < .001$), providing evidence that the use of both imaging techniques benefits preoperative planning (Pons et al., 2019).

MRL has disadvantages that must be considered before widespread implementation into lymphedema surgery protocols. Venous uptake of gadolinium-based contrast agents is common after intracutaneous injection leading to images contaminated with venous enhancement (Notohamiprodjo et al., 2009). As a solution for this, some groups have advocated the use of ferumoxytol to mask the unwanted signal from intravascular uptake of gadolinium-based contrast (Mitsumori et al., 2015; Neligan et al., 2017). Additionally, intracutaneous injection of gadolinium-based contrast agents required for MRL is considered off-label (Notohamiprodjo et al., 2012). While all the studies included in this systematic review reported no adverse events after the examination, the literature describes several adverse events related to perivascular injection of gadolinium-based contrast agents, such as edema, hemorrhage, and necrosis (Notohamiprodjo et al., 2012). Lastly, MRL is an expensive examination compared to ICG-L, which could substantially increase the cost of treatment and be economically unfeasible in some situations (Pons et al., 2019).

Limitations of this systematic review include the limited number of studies and limited ability to generalize findings. Moreover, there is also a possibility of bias in the analysis of information from each article. Nonetheless, we were able to summarize and discuss the relevance of MRL for preoperative planning of lymphedema surgery, which is relevant to the development of a definitive surgical therapy for lymphedema in appropriate patients. Certainly, cost analysis studies are necessary to support the use of MRL as the standard of care for preoperative planning before performing lymphedema surgery.

In summary, the use of MRL for preoperative planning of lymphedema surgery may improve lymphedema surgery outcomes. A total of 334 lymphedema patients were enrolled in studies identified in the literature and no complications related to the examination were reported. MRL had higher sensitivity to detect lymphatic vessel abnormalities than lymphoscintigraphy, ICG-L, and Ultrasound Doppler. Moreover, when combined with ICG-L, MRL may increase the likelihood of successful LVA. Larger studies assessing the accuracy and cost-effectiveness of MRL are needed as this novel examination is incorporated into lymphedema surgical protocols.

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DISCLOSURE OF INTERESTS

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Pubmed and Embase.

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