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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. Primary outcome was the examination capacity to identify lymphatic anatomy and secondary outcome was 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 to lymphoscintigraphy and a statistically higher chance of successful lymphovenous anastomosis 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.

INTRODUCTION

Lymphedema is chronic condition that occurs secondarily to cancer treatment, such as lymph node dissection and radiotherapy [1-5]. It is estimated that lymphedema will develop in as many as 65% of patients undergoing breast cancer treatment [5-7]. In recent years, advances in imaging and microsurgery have allowed surgeons to pursue surgical treatment for lymphedema [8]. 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 [9].

Multiple advances in radiographic imaging have been implemented to enhance the field of plastic and reconstructive surgery [10, 11]. 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 [11]. For example, virtual planning with 3-dimensional models can be integrated into complex surgical care, such as in composite tissue head and neck reconstruction [12]. Surgical flaps can now be planned with high precision to optimize aesthetic and functional outcomes [12]. Similarly, high-quality imaging is important for lymphatic microsurgery because outcomes depend on the accurate identification of functional lymphatic vessels for anastomosis [13].

Lymphedema treatment has advanced considerably due to the development of physiologic surgeries such as LVA and VLNT that seek to restore lymphatic function [9]. One of the most challenging and burdensome parts of these procedures is locating functional lymphatic vessels and lymph nodes [13]. 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 [14]. However, this technqiue has limitations, such as its inability to visualize deep lymphatic circulation [13]. Magnetic resonance imaging lymphangiography (MRL) is done with 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 [15]. 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.

MATERIALS AND METHODS

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.

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.

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. Primary outcome was the examination capacity to identify lymphatic anatomy and secondary outcome was 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.

RESULTS

Study Characteristics

Of 372 potential articles identified with the search, nine fulfilled the eligibility criteria (Figure 1 and Table 1). In total, the 9 studies evaluated 334 lymphedema patients. Use of MRL for preoperative planning of lymphedema surgery was addressed in studies that used 1.5-T 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 [16] 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 [16]. Asuncion et al [17] conducted a retrospective study on fifteen patients with upper or lower limb lymphedema who underwent vascularized submental lymph node flaps. Preoperative MRL allowed identification of 7.2±2.4 submental lymph nodes, which was a greater than preoperative ultrasound doppler (3.2±1.1) and intraoperative finding (3.1±0.6) [17]. Zeltzer et al[18] conducted a prospective on 25 patients with upper extremity lymphedema where MRL allowed identification of lymphatic circulation in eighteen patients. They reported that LVA was successfully performed in sixteen patients from their cohort [18]. Lohrmann et al[19] 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 [19].

Studies compared findings of preoperative MRL and other examinations [13, 17, 20]. Notohamiprodjo et al[20] 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 (κ=0.93) and pattern of drainage (κ=0.84), good for delineation of lymph nodes (κ=0.67) and degree of contrast/radiotracer ascension (κ=0.77), and moderate for delineation of lymphatic vessels (κ=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) [20].

Pons et al[13] 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% [13].

Two studies investigated whether MRL is able to distinguish lymphatic vessels from adjacent veins. Mazzei et al[21] 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[22] on 25 patients with upper extremity lymphedema who underwent LVA.

DISCUSSION

The use of MRL for preoperative planning of lymphedema surgery is summarized in this systematic review consisting of nine studies, in which a total of 334 lymphedema patients were included [13, 16-23]. 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 prior to lymphedema surgery [13, 20]. MRL had a higher sensitivity for the detection of lymphatic vessel abnormalities compared to lymphoscintigraphy [20]. Moreover, a study shown that concordant MRL and ICG-L findings correlated with a higher probability of successful LVA ($P < .001$) [13]. 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 [13, 19, 20].

ICG-L for preoperative planning of lymphedema surgery is considered a standard approach. It was first introduced by Unno et al[14] 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 [24]. 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 [13].

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 [11, 13]. ICG-L provides real-time imaging and is considered simple, accurate, highly sensitive, and minimally invasive [11]. Furthermore, it can maximize lymphaticovenular anastomosis efficacy by verifying patency of lymphatic anastomosis as well as detect and predict lymphosclerosis [25-28]. 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 [11].

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 [13]. Pons et al[13] 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 use of both imaging techniques benefits preoperative planning [13].

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 [29]. As a solution for this, some groups have advocated use of ferumoxytol to mask the unwanted signal from intravascular uptake of gadolinium-based contrast [30, 31]. Additionally, intracutaneous injection of gadolinium-based contrast agents required for MRL is considered off-label [20]. 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 [20]. 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 [13].

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 prior to 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 vessels 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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ABBREVIATIONS LIST

Lymphovenous anastomosis (LVA); Vascularized lymph node transplant (VLNT); Indocyanine green lymphography (ICG-L); Magnetic resonance imaging lymphangiography (MRL); Magnetic resonance imaging (MRI).

DATA AVAILABILITY STATEMENT

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

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FIGURE LEGENDS

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (*PRISMA*) Diagram.

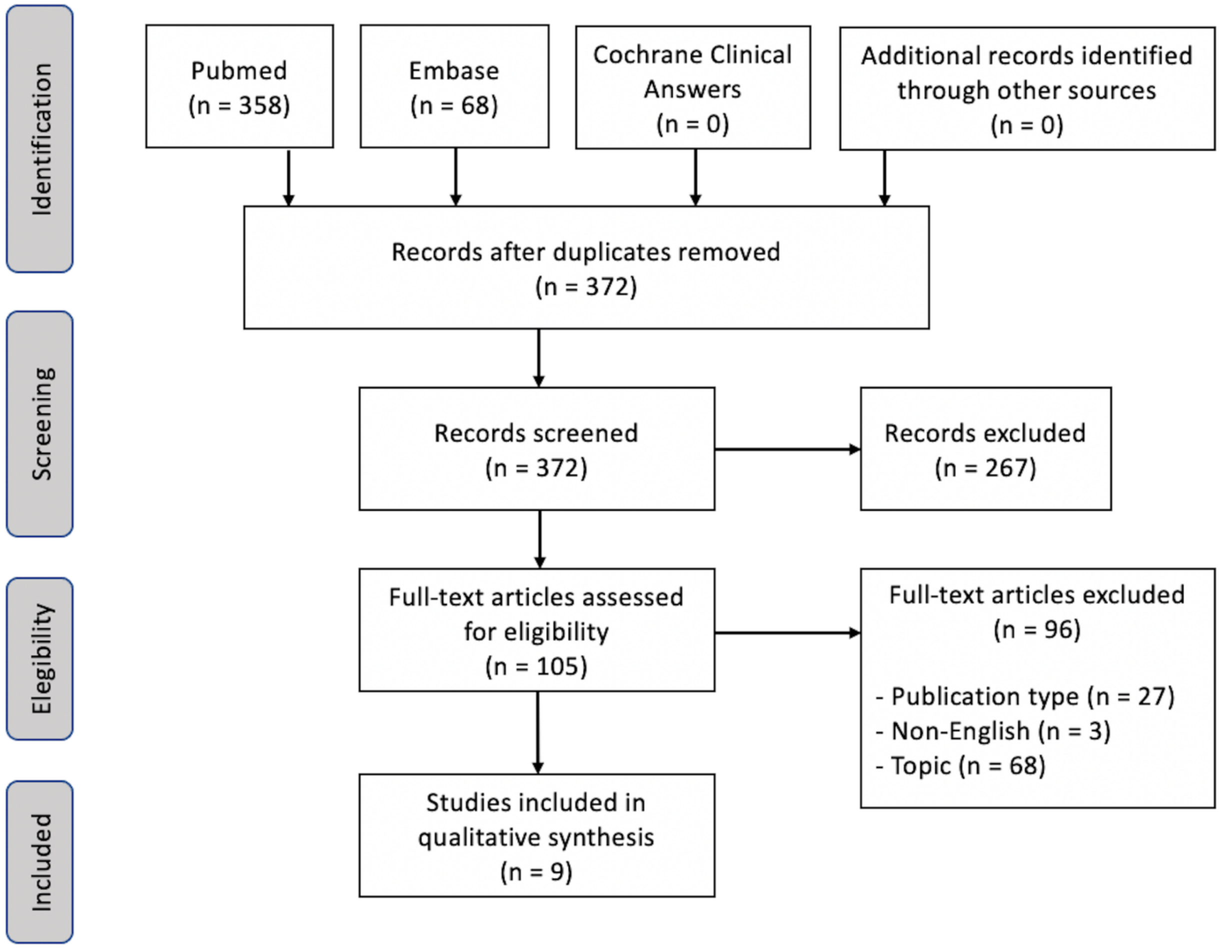
Identification
Screening
Elegibility
Included
Pubmed (n = 358)
Embase (n = 68)
Cochrane Clinical Answers (n = 0)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 372)
Records screened (n = 372)
Records excluded (n = 267)
Full-text articles assessed for eligibility (n = 105)
Full-text articles excluded (n = 96)
- Publication type (n = 27)
- Non-English (n = 3)
- Topic (n = 68)
Studies included in qualitative synthesis (n = 9)

Table I. 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. [13]	2019	Spain	Case series	III	82	Upper or lower extremities	LVA, LNT, or DIEP-LNT	3T	ICG-L	None
Zeltzer et al. [18]	2018	Belgium	Prospective study	IV	25	Upper extremity	LVA	3T	-	None
Asuncion et al. [17]	2018	Taiwan	Case series	III	15	Upper or lower extremities	VSLN		Ultrasound Doppler	None
Mazzei et al. [21]	2017	Italy	Prospective study	III	30	17 lower extremity; 6 primary lymphedema	LVA	1.5T	Immunohistochemistry	None
Long et al. [23]	2017	China	Case series	III	11	Lower extremity	LVA and/or liposuction		Lymphoscintigraphy	None
Gennaro et al. [22]	2017	Italy	Case series	III	20	15 upper extremity, 5 lower extremity	LVA	1.5T	Immunohistochemistry	None
Dayan et al. [16]	2014	USA	Case series	IV	117	-	VGLNT	-	-	None
Notohamiprodjo et al. [20]	2012	Germany	Prospective study	II	30	-	-	3T	Lymphoscintigraphy	None
Lohrmann et al. [19]	2008	Germany	Case series	IV	4	Lower extremity	LVT (3 patients); LVA (1 patient)	1.5T	-	None

Legends: LVA, Lymphovenous anastomosis; DIEP-LNT, Deep Inferior Perforator Lymph Node Transfer; VSLN, Vascularized submental lymph node; VGLNT, Vascularized groin lymph node transfer; LVT, Lymphatic vessel transplantation; ICG-L, Indocianin Green Lymphangiography