

# Review of Non-Contrast MR-Lymphography Techniques and Findings: Challenges and Opportunities

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## Abstract

Lymphedema is a major disorder of lymphatic system that occurs primarily due to lymphatic system disorders or secondary lymphedema which is caused by radiation therapy involving lymph nodes or surgical operation dissection. Magnetic resonance lymphography (MRL) has been used to effectively examine the lymph vessels and identify their morphology. This review study intended to evaluate the role of non MR-lymphographic for the diagnosis assessment of lymphedema and to provide comprehensive review on clinical outcome of non-contrast MRI compared to MRI with contrast medium. In this study, scientific publications published in languages other than English were excluded. A systematic review was done in international databases including PubMed, Scopus, web of sciences, conference proceedings published till 2019. Non contrast MRI lymphography has strong capability to be the main imaging procedure of choice in the diagnosis lymphedema with accuracy up to 90%.

## Keywords

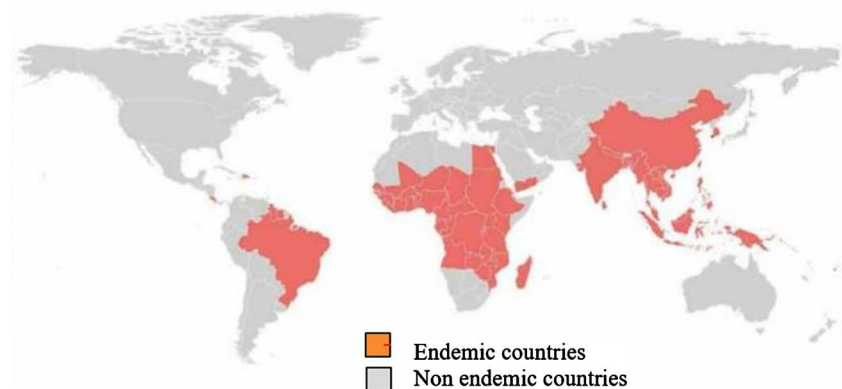
Noncontrast MR Lymphography, Lymphedema, Magnetic Resonance Lymphangiography, Lymphatic Imaging

## 1. Introduction

Lymphatic system disorders are one of the common pathologic conditions that affect a wide range of population worldwide [1]. Lymphatic system, which is a part of circulatory system, has various functions including immunity, fat absorption and fluid homeostasis. Lymphedema or also known as elephantiasis is a lymphatic system chronic disorder caused by accumulation of lymph (protein

rich fluid), the interstitial space which diminishes lymphatic return, resulting in swelling of one or more regions of the body, is one of the common diseases worldwide [1] [2]. Lymphedema responds dynamically when presented with infection, inflammation, altered hemodynamics, and cancer. Lymphedema symptoms include in addition to swelling, skin atrophy, pain and infection [3] [4]. It was estimated that the incidence of this disease ranges from 140.0 to 250.0 million people globally (1 in 30 people) [5] [6] [7]. Lymphedema can affect all body parts and organs but more common in certain organs such as lower limbs, upper limbs with incidence of 99% of total affected organs or regions [1]. Lymphedema can be classified into primary and secondary types according to the cause of the disease whether it's congenital or acquired. Primary lymphedema is caused by congenital abnormalities (incidence  $\approx$  1.15 to 100000), whereas secondary lymphedema is caused by infection (filariasis), trauma, surgery, or radiation due to cancer treatment [2] [4]. The causes of lymphedema depend on the economic level of a country. *i.e.* in developed countries such as the United States and Europe, the lymphedema incidence is 1.4 per 1000 persons, typically secondary due to cancer treatment (8% after mastectomy, 38% after radiotherapy and axillary lymph node surgical removal) or cancer itself due to blockage of lymph vessels by metastasis. The main cause of lymphedema in developing countries is infection due to the parasite *Wuchereria bancrofti* (filariasis) in developing countries in southern part of the globe. Furthermore, It was estimated that almost 1.2 billion people are at risk for contraction of lymphatic filariasis in these countries (Figure 1) [8]. Currently, more than 120 million people are affected by lymphatic filariasis. Other risk factors of lymphedema include patient age, body mass index (BMI > 59, obese class III) is high risk for spontaneous development of lower limb lymphedema, extremity infections and trauma, chronic venous insufficiency.

The lymphatic system plays an important role in human health. It composed of huge network of vessels, nodes and lymphatic organs. Diagnostic and therapeutic intervention with various imaging modalities is required to obtain accurate diagnosis. Medical imaging is imperative to for accurate diagnosis with quantitative



**Figure 1.** Lymphatic filariasis endemic countries (approximately 18% of the population worldwide) [8].

and qualitative data. However, the lymphatic system is physically complex and challenging to obtain diagnostic image [9]. Non-invasive imaging modalities with no radiation exposure is preferred for repeated procedures for close follow-up of treatment outcome.

Imaging of lymphatic systems (lymphangiography) was first introduced to clinical practice in 1951 using an oil-based contrast medium [10] (Figure 2). The procedure is an invasive, complex and causing patient discomfort and is no longer performed due to its severe complications. Nuclear medicine scintigraphy of the lymph system (Lymphoscintigraphy (LS)) is frequently used for the diagnosis of the system disorders. The main drawback of this technique is the low image resolution and the procedure accompanied of ionizing radiation for patient. More recently, magnetic resonance lymphography (MRL) has been used to effectively examine the lymph vessels and identify their morphology [11] [12]. Different imaging techniques are used to diagnose lymphatic disorders (lymphangiography, lymphoscintigraphy, computed tomography (CT), MRL, positron emission tomography (PET)/CT and ultrasound imaging). Non-invasive measurements are also used for diagnosis of lymphedema such as tonometry (tissue resistance assessment), bioimpedance analysis spectroscopy (extracellular fluid assessment), fluorescence imaging and near-infrared fluorescence (NIRF) lymphatic imaging may be useful in early onset of the disease to obtain accurate diagnosis [2]. However, all these techniques have different limitations [13]. Contrast agent is used to create informative radiographic images by direct or indirect injection of contrast in the vessel. Direct injection may induce sever complications, which lead to elimination of this technique. On the other hand, indirect injection conducted by injection the contrast interstitially. Other techniques were developed to overcome the limitation of conventional ones. These techniques include scintigraphy, PET, single photon emission computed tomography (SPECT), CT and



**Figure 2.** lymphogram of the thoracic canal [9].

MRI. Currently, MRI and PET MRI are the best imaging modalities to assess the pathology. Contrast MRI is used usually to alter relaxation time (Shorten the T1 or T2 relaxation time, thereby causing increased signal intensity on T1-weighted images or reduce signal intensity on T2-weighted images) to enable accurate visualization of the anatomy and pathology (gadolinium compounds) [13] [14]. However, MRI contrast media has side effects that can be classified into three categories minor (nausea, vomiting, sneezing), mild (persistent headache, hypotension with bradycardia and severe side effects (Laryngeal edema and cardiac arrest) according to the patients and contrast volume and contrast type. Non contrast MRL is promising technique that provides accurate diagnosis without contrast medium, thus protect patients from these adverse side effects. Furthermore, non-contrast MRL is an emerging technique for noninvasive diagnosis of Lymphedema and limited literature is available in this field. Therefore, we conducted this study to evaluate the existing scientific literature to evaluate whether non-contrast MRL is capable to provide precise and accurate diagnosis of lymphedema. This review study intended to evaluate the role of non MR-lymphographic for the diagnosis assessment of lymphedema and to provide comprehensive review on clinical outcome of non-contrast MRI compared to MRI with contrast medium.

## 2. Materials and Methods

In this study included scientific articles published in English languages journals regarding non contrast MRI for diagnosis lymphedema. A systematic review was done in international databases including PubMed, Scopus, web of sciences, conference proceedings published till 2019.

### MR lymphographic Imaging

Early diagnosis positive affect the treatment outcome which results in prompt progress of treatment and may prevent complications such as secondary fibrosis [15]. It is well documented that MRL provides useful anatomical and physiological data, thus enabling accurate diagnosis of the disease. It was reported that the sensitively and specificity of the procedure is 90% and 94% respectively [16]. Many authors reported the advantages of contrast studies and others attempt to acquire images without contrast medium [11] [13] [14] [16]. (Table 1) MRL consists of two sequences. The first is a 3D heavily T2-weighted sequence to depict the severity and extent of the lymphedema. The second is a fat-suppressed 3D spoiled gradient-echo sequence performed after the intra-cutaneous injection of an extracellular gadolinium-based MR contrast agent [16]. In addition to that, the authors reported that as venous enhancement almost always occurs, one of the interpretative challenges is differentiating enhancing lymphatic channels from superficial veins. Magnetic resonance imaging (MRI), which is chemically sensitive *in-vivo* imaging technique, is a medical noninvasive imaging technique that produce a three dimensional (3D) images of human body using magnet and

**Table 1.** Advantages and drawbacks of various imaging modalities.

Imaging modality	Drawbacks	Advantages
Lymphangiography	Fever, Infection and lymph vessels inflammation, contrast medium remain for up to 2 years in lymph nodes	Demonstrate disorders of the internal tissues of lymph nodes
Lymphoscintigraphy	Low image resolution, prolonged procedure time cost, radiation dose	Lymphatic function
Indo cyanine green-lymphography (ICG-L)	Cannot detect deep lymphatic vessels ( $\leq 2$ cm)	insignificantly invasive, simple, Real-time imaging and sensitive
Computed Tomography	Limited contrast resolution Radiation risk	Cheap, low cost
Magnetic resonance lymphangiography (MRL)	Contrast medium can not differentiate benign and cancer tumors	Excellent anatomy high spatial resolution No radiation exposure 3D image physiological information high soft tissue contrast
Non-contrast Magnetic Resonance Lymphangiography (NCMRL)	Suspension the lymphatic drainage for 48 h. Elastic stockings or bandages for 24 h	No contract medium illustrate static fluid-filled lymphatic vessels, safe and feasible

magnetic characteristics of human body tissues and organs. Since its introduction to clinical use in 1977 [16] MRI systems developed very rapidly to meet the requirements of high diagnostic yield with minimal discomfort and short time.

### 3. MRI Sequences and Equipment Setting

The preferred MR equipment includes a 1.5-Tesla or more MR unit. In our experience, all MR examinations were performed by a General Electric Healthcare Signa Twin Speed HDxt, with a maximum gradient strength value of 23 mT/m and a slew rate of 80 mT/m/ms (software release 15.0-0947A). A multi element body coil is fundamental for this type of examination. For our purposes, we used a receiving phased-array peripheral vascular coil for the study of the lower extremities (Flow 7000 phased-array peripheral vascular, USA Instruments) and an 8-channel body array coil for the upper extremities, with both a large anatomical coverage and a good signal-to-noise ratio.

### 4. MR Lymphographic Imaging

Noncontrast MRL has substantial benefits compared to other imaging techniques. In this context, Arrive *et al.* in their recent studies [17] [18] and Derhy *et al.* [19] reported that Noncontrast MRL can be performed using heavily T2-weighted fast spin echo sequences (to demonstrate the location of edema) with a long T2 relaxation time. Derhy *et al.* [19] *et al.* stated that 3D MRL demonstrates that retroperitoneal lymphatic aneurysmal dilatation exhibits a continuous spectrum of change from normal variants to lymphatic aneurysmal dilatation. The authors reported that this technique was useful to diagnose many clinical

condition. In another recent study, Arrivé *et al.* [18] used noncontrast MRL for evaluation of lymph node for Secondary upper limb lymphedema. The authors used a free-breathing three-dimensional fast spin-echo sequence evaluate the results of axillary lymph node transplantation with noncontrast MRL in 15 patients with secondary upper limb lymphedema. The study recommended that Noncontrast magnetic resonance lymphography may be used as an objective technique to analyze the results of lymph node before and after surgery. MR lymphography with very heavily T2-weighted MR images provides an excellent analysis of both lymphatics vessels and lymph nodes without need of any contrast media. Kim *et al.* [20] assessed the thoracic duct using coronal and axial images of heavily T2-weighted sequences without contrast medium. Nonenhanced MR lymphangiography is a safe and effective method for imaging the central lymphatic system, and can contribute to differential diagnosis and appropriate preoperative evaluation of pathologic lymphatic problems. The main limitations to noncontrast T2 imaging are that it does not provide information about lymphatic flow and the lack of a contrast medium makes it difficult to visualize small lymphatic ducts. Consequently, its use in diagnostic and interventional lymphangiography is limited [19]. Recently, Cellina *et al.* [1] reviewed a non-contrast magnetic resonance lymphangiography as an emerging technique for the study of lymphedema. The authors concluded that non-contrast magnetic resonance lymphangiography, a relatively new technique for the diagnosis, assessment and management of lymphedema. Cellina *et al.* [1] reported that non contrast is useful for the lymphography evaluation and surgical arrangement and provides morphological information regarding size, site of lymph nodes thus can be used for nodal transplantation.

#### **4.1 Non-Contrast MRL Technique**

##### **4.1.1. Patient Preparation and Positioning**

MRL without contrast can be performed using MRI system with magnet strength 1.5 or 3.0 T. Before positioning, it is important to explain in detail the diagnostic procedure and the need to maintain the position throughout the duration of the examination. According to the patient's size, the acquisition is usually performed in 3 or 4 steps to cover all the anatomical stations for both lower and upper extremities. In literature, the acquisition techniques described in the literature have provided for the acquisition of the entire limb also in secondary lymphedema, to accurately define the extent and severity of the disorder and to perform an optimal post-treatment follow-up.

##### **4.1.2. Image Acquisition Protocol**

Non contrast MRL technique is still evolving, but the principle of this examination is based on heavily T2-weighted sequences, resulting in a signal loss in tissue background, with highlighting of static fluids in lymphatic vessels with a very long TR/TE, similar to that used in cholangiopancreatography or in MR urography. Acquisition parameters of non-contrast T2 MR Lymphography se-

quences according to different authors. Arrivé *et al.* [18], applied at the end of the echo train a restore pulse to flip the transverse magnetization to the longitudinal direction to reduce the acquisition time. Other sequences can be associated in the examination: axial HASTE without fat suppression (TR: 1200 ms, TE: 114 ms, matrix:  $176 \times 256$ , flip angle:  $180^\circ$ , slice thickness: 6 mm) or Iterative Decomposition of water and fat with Echo asymmetry and Least-squares estimation (IDEAL; acquisition plane: axial, TR: 4233 ms, TE: 76 ms, slice thickness: 6 mm, matrix:  $320 \times 192$ , FOV:  $380 \times 380$ ), this sequence, based on fat/water separation technique, provides contrasts of water and fat, in phase and out of phase and is used for the analysis of lymphedema characteristics [17] [18] [21]-[27] (Table 2).

## 5. NCMRL Technique Limitations

Because lymphedema is common in obese patients, therefore obese patients

**Table 2.** Image acquisition protocols for MRL in Literature.

Author	Country	No of Patients	Organ of interest	Protocol
Young <i>et al.</i> [6]	Korea	10	Thoracic ducts	3T MR system (MAGNETOM Skyra, Siemens)
Mazzei <i>et al.</i> [12]	Italy	30	Review	1.5 T, Gd-BOPTA heavily T2-weighted sequence 3D fast spoiled gradient-echo T1-weighted sequence with a fat-saturation technique
Xiong <i>et al.</i> [13]	China	Review	All	Lymphoscintigraphy, Lymphangiography SPECT/CT, SPECT, US, MRL
Mitsumori <i>et al.</i> [16]	USA	NA	Peripheral lymphedema	GE, 1.5 T or 3.0 T, (Gd-BOPTA), Multi Hance The MR examination consists of 2 primary sequences. The first is a 3D heavily T2-weighted sequence
Chavhan <i>et al.</i> [21]	USA	Review	MRL	gadolinium-based contrast material T2-weighted imaging plays a complementary role to DCE MR lymphangiography in the assessment of CCLs
Lu <i>et al.</i> [22]	China	37	Male Genital Lymphedema	Preoperative and postoperative MRL Philips 3.0-T, Gd-BOPTA. 3D fast spoiled gradient recalled echo T1-weighted images with a fat saturation technique (TR/TE: 3.5/1.7, flip angle: 25)
White <i>et al.</i> [23]	UK	NA	Lower limb lymphoedema	T Siemens, T2-weighted sequences and coronal FLASH (fast low-angles hot) T1-weighted spoiled gradient-echo sequences
Lu <i>et al.</i> [24]	China	10	whole-body	For MR lymphangiography, a 3D THRIVE sequence (T1 high-resolution isotropic volume excitation, THRIVE) was performed. Pre- and post-contrast injection was done using the following parameters: TR/TE 23/2.1 ms; Flip angle $15^\circ$ ; FOV $38 \times 36 \text{ cm}^2$ ; matrix size $760 \times 720$
Dori <i>et al.</i> [25]	USA	NA	Animal	T2-weighted MR sequence, bilateral inguinal lymph node injection of 2 mL of undiluted gadopentetate at a rate of 1 mL/min, and 60 minutes of MR imaging with T1-weighted high-spatial- and high-temporal-resolution MR angiography
Liu <i>et al.</i> [26]	China	39	whole-body	3D MRI was performed with a 1.5-T whole-body scanner (Magnetom Vision Plus; Siemens) Patients were examined in a body array coil with a flip angle of $150^\circ$
Chen <i>et al.</i> [27]	China	19	Thorax	3-0T MRI system with the imaging sequence of magnetic resonance cholangiopancreatography. TD MRL images were obtained from subjects following an overnight fast and from the same subjects 3 - 4 h after ingestion of a high fat meal

grade three cannot examine in close magnet bore due to their weight and non-contrast MRI is usually performed on 1.5 T magnet or above [1]. Therefore, open magnet cannot be used which one of the limitations of this technique.

## 6. Conclusion

Early Lymphedema stages diagnosis represents great challenges. Non contrast MRL is used to diagnose accurately the lymphatic system disorder. From studies, the researchers have found non contrast MRL is a promising methodology in the diagnosis of lymphatic system disorders with accuracy up to 90%. The study revealed that non-contrast MRL imaging technique can increase the accuracy of lymphedema diagnosis, improve disease prognostication, and provide a more robust marker of treatment response.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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