Clinical Imaging 53 (2019) 126–133

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag

Body Imaging

Non-contrast Magnetic Resonance Lymphangiography: an emerging technique for the study of lymphedema

Michaela Cellina[a,*], Giancarlo Oliva[a], Andrea Menozzi[b], Massimo Soresina[b], Carlo Martinenghi[c], Daniele Gibelli[d]

[a] *Department of Radiology, ASST Fatebenefratelli Sacco, Piazza Principessa Clotilde 3, 20121 Milan, Italy*
[b] *Department of Plastic and Reconstructive Surgery, ASST Fatebenefratelli Sacco, Piazza Principessa Clotilde 3, 20121 Milan, Italy*
[c] *Department of Radiology, IRCCS San Raffaele Hospital, via Olgettina 60, 20123 Milan, Italy*
[d] *Department of Biomedical Science for Health, Università degli Studi di Milano, via Mangiagalli 31, 20133 Milan, Italy*

ARTICLE INFO

Keywords:
Non-contrast MR lymphography
MR lymphography
Lymphatic vessels
Lymphedema
Lower limb lymphedema
Upper limb lymphedema

ABSTRACT

Lymphedema (LE) is a chronic disabling disease, characterized by the accumulation of macromolecules and liquids in the interstitial space. Patients affected by LE should undergo appropriate imaging to confirm the diagnosis, to evaluate characteristics and the severity of LE and to allow for correct management and treatment plan. However, there is no consensus regarding the best imaging technique to study this disorder. We want to propose an overview of the studies published on Non-contrast Magnetic Resonance Lymphangiography, a relatively new technique for the diagnosis, assessment and management of lymphedema.

1. Introduction

Lymphedema (LE) is a chronic and progressive disease, characterized by the accumulation of macromolecules and liquids in the interstitial space, as a result of the impairment of the lymphatic system with respect to the formation and drainage of lymph [1,2]. It can affect any part of the body, but it is more common in the extremities, and is clinically characterized by chronic gross swelling of the affected limb, localized pain, atrophic skin changes and susceptibility to infections [3].

LE can be primary or secondary [4]; primary LE follows developmental abnormalities of the lymphatic system while secondary LE is the result of lymphatic vessels obstruction due to different conditions such as surgery, radiation treatment, trauma, pathological involvement of lymph nodes and infections [5,6].

Primary LE can be classified in: congenital, which is present at birth with a prevalence of 1.15/100,000 people and a predilection for women [4]; praecox, if LE appears during adolescence; or tarda, in case of late onset (after 35 years) of LE, which is uncommon and most frequent in female.

In developing countries, the most frequent cause of secondary LE is represented by Filariasis, whereas in developed countries the commonest cause of secondary LE are lymphadenectomy and radiation therapy for cancer treatment [5].

LE is rarely fatal, but it is a disabling disorder that hugely affects the patients' quality of life, causes significant morbidity and its management is very difficult.

Traditionally, LE has been commonly treated by a conservative approach, such as physiotherapy, lymphatic massage, wrapping and controlled compression [7].

However, in recent times, the implementation of new surgical techniques: the microsurgical lympho-venous shunts and lymph nodes autologous transfer have changed the therapeutic approach of this disorder. Lympho-venous shunt is the treatment of choice for hyperplastic LE, while lymph nodes transplantation is recommended for patients affected by aplastic or hypoplastic LE [8,9].

Investigation of LE is useful to provide differential diagnosis, to confirm the diagnosis, to assess the severity and extension of LE and to allow an adequate treatment planning.

Few imaging techniques can be used for LE evaluation. Lymphography has been the only available technique to study LE for a long time; it involves the injection of lipiodol ultra-fluid into a previously surgical exposed and cannulated lymphatic vessel. This invasive technique required long acquisition times and was often burdened by allergic reactions and complications like pneumonia, and it was therefore abandoned [10].

Lymphoscintigraphy is performed by injecting intradermal Technetium 99 m sulfur colloid; the progression and the distribution of

* Corresponding author at: Department of Radiology, ASST Fatebenefratelli Sacco, Piazza Principessa Clotilde 3, 20121 Milan, Italy.
E-mail address: michaela.cellina@asst-fbf-sacco.it (M. Cellina).

https://doi.org/10.1016/j.clinimag.2018.10.006
Received 1 June 2018; Received in revised form 13 September 2018; Accepted 4 October 2018
0899-7071/

the radio-labeled particles is evaluated by a gamma camera, but subdermal lymphatics cannot be assessed [11–13].

Another technique to detect lymphatic channels and evaluate patients with LE is indocyanine green (ICG) lymphography: ICG imaging is performed by injecting ICG into the interdigital web spaces; after 4 h, fluorescence images of lymphatic vessels can be obtained with a near-infrared camera device; the fluorescence images are digitalised for real-time display [14]. The main limits are: the long time after the injection needed to mark the lymphatic vessels and difficulty to clearly identify lymphatic vessels course in late-stage lymphedema [15].

Contrast-enhanced Magnetic Resonance Lymphangiography (CEMRL) is performed through subcutaneous injection of gadolinium-based contrast medium in interdigital web spaces of feet or hands [16]. It has been proved to be a safe technique, with high spatial resolution and able to provide a good visualization of the lymphatic drainage [17–20].

However, CEMRL is limited by some issues: first, the procedure of injecting gadolinium chelates in the interdigital spaces is still off-label [21], it can cause patients' discomfort and local reactions; moreover, due to the recent evidence of intracranial gadolinium deposition after contrast-enhanced MR imaging [22–24], the effort to use magnetic resonance imaging techniques that do not involve the administration of any contrast media, especially in younger patients, is increasingly pronounced.

In this scenario, Non-contrast Magnetic Resonance Lymphangiography (NCMRL), a non-invasive imaging technique based on heavily T2-weighted sequences, able to highlight the signal of static or slow-moving fluid-filled structures, like lymphatic vessels, with a suppression of the signal intensity of the background tissues, could be an alternative safe and feasible technique for the diagnosis and treatment planning of LE.

In this article we want to propose a review of the Literature about NCMRL. A search of literature was conducted by searching PubMed (including Medline) and Science Direct to identify articles about lymphatic MRI. The PubMed database and Google search were conducted using the search by key words as follows: lymphatic MRI, lymphatic Magnetic Resonance, MR lymphangiography, Magnetic Resonance Lymphangiography, non-contrast MR lymphangiography, unenhanced MR lymphangiography. Conference papers were outside the scope of the review.

2. NCMRL technique

2.1. MR equipment

NCMRL can be executed on a 3.0 T unit [25] but also on a 1.5 T unit [26–31].

At our Institution, MRI scans for LE assessment are performed with a 1.5-T scanner (Magnetom Avanto, Siemens Medical Solutions).

To study the thoracic duct, Takahashi et al. [26] used a quadrature detection phased-array coil; while a six-channel phased array body coil can be used for imaging the retroperitoneal lymphatic vessels [27,28], lower limb LE [29,30] and for the upper limb LE.

We did not perform imaging of retroperitoneal lymphatic vessels and thoracic duct; for LE of the lower limb, we use a phased-array 36-channel peripheral angiography coil and an 8-channel body coil (Siemens Medical Solutions; Fig. 1A), whereas, for the upper limb we use an 8-channel phased-array body coil (Siemens Medical Solutions; Fig. 1B).

2.2. Patient preparation

Patients are asked to suspend the lymphatic drainage for 48 h and the use of elastic stockings or bandages for 24 h.

To study retroperitoneal lymphatic vessels or lower limb LE, oral administration of pineapple juice 30 min before the examination can be considered to decrease the signal intensity of the bowel content, due to its content of manganese [29,32].

Fasting is not necessary but recommended for those patients who require a study of the upper limbs, in a prone position.

2.3. Patient positioning

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 [29,30] and upper [31] extremities; for lower limbs, the anatomical stations are: 1: feet, ankle, lower leg; 2: knee, upper leg, lower thigh; 3: medial and proximal thigh; 4: inguinal and pelvic region, root of the thigh; while for the upper extremities, the anatomical stations are: 1: hand, wrist and forearm; 2: elbow, arm, shoulder; 3: axillary lymph nodes.

So far, 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. In the future, it will be possible to evaluate, in agreement with the Clinicians, the hypothesis to perform more targeted examinations in patients with LE caused by lymph node dissection, to reduce the acquisition time.

2.4. Acquisition protocol

NCMRL 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 [25–32], with a very long TR/TE, similar to that used in cholangiopancreatography or in MR urography. Acquisition parameters of non-contrast T2 MR lymphography sequences according to different authors and anatomical districts are listed in Table 1. Arrivé et al. 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 [28,29,31].

Other sequences can be associated in the examination: axial HASTE without fat suppression (TR: 1200 ms, TE: 114 ms, matrix: 176 × 256, flip angle: 180°, slice thickness: 6 mm) [28] 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 × 192, FOV: 380 × 380) [29], 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 LE characteristics.

After performing a survey and calibration for all the anatomical stations previously listed, before the acquisition of the T2-lymphangiography sequence, we execute axial and coronal True Fisp sequences to assess the volumes of the affected and healthy extremity and to delineate the extension of LE, and axial T2 TSE to calculate lymph nodes number and size. Acquisition parameters of our protocol are listed in Table 2.

2.5. Post-processing and image analysis

After acquisition, the heavily T2-weighted 3D sequences source images are transferred to a dedicated workstation and elaborated with maximum intensity projection (MIP) reconstruction [26–32].

NCMRL allows the radiologist to obtain information regarding:

1. the symmetry/asymmetry of lower or upper limbs and, in case of asymmetry, if diffuse or segmental
2. the objective measurement of bilateral circumferential diameter of the affected and healthy limbs and of the subcutaneous fat thickness

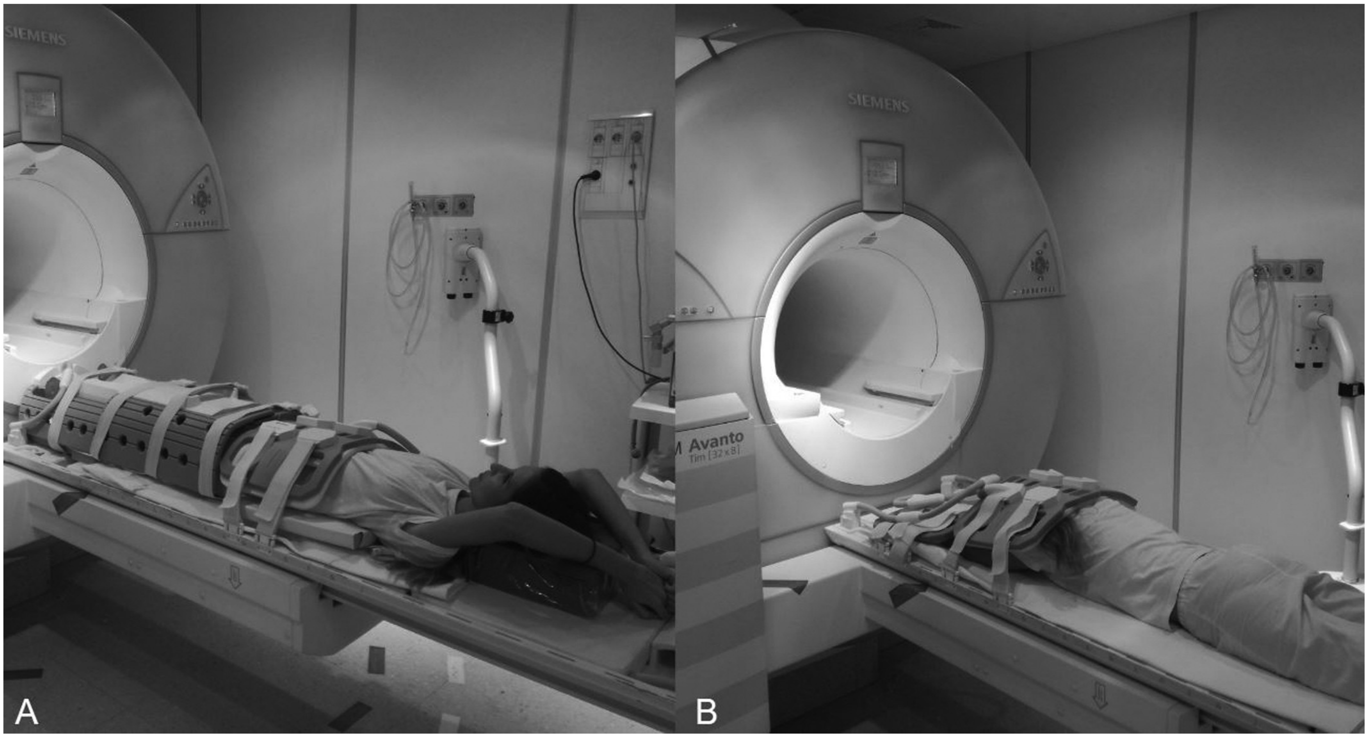

Fig. 1. Patient positioning.
(A) Shows the positioning of the patient for the study of lower limb: the patient is in supine position; a 36-channel peripheral angiography coil is positioned as displayed in the picture; cranially to this coil, a 8-channel body-coil is placed for the study of the inguinal region.
(B) Shows the positioning for the study of upper limb. For the study of upper extremities, the patient is placed in prone position, head first with a body 8-channel body-coil positioned as displayed in the picture.

3. the severity of LE that can be graded as absent, mild, moderate or severe [29,31]. LE was defined mild when: (a) the upper limit of subcutaneous infiltration was below the knee (when studying the lower extremities) of below the elbow (when studying the upper extremities), (b) the fluid infiltration of the subcutaneous tissue does not result in dimensional increase of the subcutaneous fat, (c) minimal epifascial fluid (thickness < 5 mm). LE was described as severe in the following cases: (a) when the subcutaneous infiltration is diffuse to the entire affected limb, (b) profuse fluid infiltration conditioning marked increase of the subcutaneous tissue thickness, (c) epifascial fluid thickness > 15 mm.
4. the presence of the honeycomb pattern [29,31], visible as trabecular/reticular structures in the subcutaneous fat
5. the thickening of dermis (dermis thickness > 2 mm)
6. any abnormalities in the muscle compartment, such as impaired/reduced tropism, atrophy, altered signal, fluid infiltration
7. the number of inguinal/axillary lymph nodes, their location and size
8. the appearance of loco regional lymphatic trunks [29]: aplastic, if no lymphatic trunk is visible; hypoplastic, if < 3 lymphatic trunks are recognizable; normal, when 3–6 lymphatic trunk are identifiable; hyperplastic, if > 6 lymphatic trunks are present or if their caliber is > 3 mm
9. the caliber [26] and dilatation of lymphatic vessels [28], presence of distal dilated lymphatic vessels (diameter > 1 mm) [29,31]

3. NCMRL indications

According to the studies reported in literature, NCMRL can be used with various purposes:

Table 1
Acquisition parameters of NCMRL according to the studies reported in literature.

	Takahashi [26]	Arrivé [28]	Arrivé [29]	Liu [30]	Arrivé [31]
MRI unit	VISART EX, Toshiba	Magnetom Symphony, Siemens	Signa HDxt, GE	Magnetom Vision Plus, Siemens	Signa HDxt, GE
Sequence	3D Half-Fourier TSE	3D TSE	3D TSE	TSE	3D TSE
Plane	Coronal	Coronal	Coronal	Coronal	Coronal
TR ms	7000	1400	4000	2800	4000
TE ms	500	800	884	1100	884
Matrix size	320 × 320	256 × 256	512 × 288	256 × 256	NS
FOV mm	360 × 360	NS	400 × 400	NS	NS
Flip angle	NS	180°	90°	150°	90°
Slice thickness (mm)	2	1	0.8–1.4	3	NS
Anatomical district	Thoracic duct	Retroperitoneal lymphatic vessels	Lower limb	Lower and upper limb External genital	upper limb
Gating	Free breathing and respiratory gating	Free breathing	Free breathing	NS	Free breathing

NS = not specified in the article; TSE = Turbo Spin Echo.

Table 2
Acquisition protocol used in our Institution.

	T2 trufi COR	T2 trufi TRA	T2 space COR FS	T2 TSE TRA
Sequence	GE	GE	TSE	TSE
Plane	Coronal	Axial	Coronal	Axial
Acquisition type	2D	2D	3D	2D
TR (ms)	4.07	4.17	2870	8200
TE (ms)	2.04	2.09	797	102
Flip angle (°)	70°	70°	140°	137°
Average	2	3	2	1
FOV (mm × mm) (RL × AP)	430 × 350	380 × 273	380 × 380	320 × 320
Matrix	156 × 256	138 × 256	358 × 384	314 × 448
Slice thickness (mm)	5	5	1	3.2
GAP (mm)	0	1.5	0	1
Scan time (min:s)	00:45	01:10	04:20	03:50
Fat saturation	–	–	FS	FS
Anatomical coverage	Whole extremities	Whole extremities	Whole extremities	Groin/axilla

trufi = True Fisp; TSE = Turbo Spin Echo; GE = Gradient Echo; FOV = Field of View; RL = right to left; AP = anteroposterior.
This acquisition protocol is the one used at our institute. We acquire NCMRL on a 1.5 Tesla Magnet (Magnetom Avanto, Siemens Healthineers).
The acquisition is performed from distal to proximal, that is from feet to thigh for the lower limbs, and from hands to shoulder for the upper limbs. The last sequence acquired is a T2 TSE on axial plane to assess inguinal and axillary lymph nodes. The Field of View (FOV) can be slightly modified according to the size of the patient and to the entity of lymphedema.

3.1. Evaluation of the thoracic duct

Takahashi et al. [26], in a study on 113 patients affected by liver diseases or malignancy demonstrated that NCMRL with respiratory gating could visualize the whole thoracic ducts in 72.6% of cases and observed a significant dilatation of the thoracic duct in patient with alcoholic liver cirrhosis. The authors stated the utility of this technique for surgical planning, to avoid thoracic duct lesions, to assess its dilatation in case of portal hypertension, to diagnose chylothorax.

3.2. Evaluation of retroperitoneal lymphatic vessels

NCMRL can be used to assess retroperitoneal lymphatic vessels, their anatomical variations or aneurysmal dilatation [27] and to diagnose and characterize abnormal conditions, such as retroperitoneal cystic lymphangioma [27], intestinal lymphangiectasia, lymphangioleiomyomatosis, post-surgical injury or dilatation [28].

Retroperitoneal cystic lymphangioma is a rare disorder, found predominantly in children, represented by uni or multilocular cysts containing lymphatic tissue in the wall [35], usually appearing as a cystic multiseptated mass with thin walls.

Intestinal lymphangiectasia is characterized by tortuous and markedly dilated lymphatic mesenteric vessels that can be well visualized on MR lymphangiography [28]; in lymphangioleiomyomatosis, NCMRL can show dilatation of the abdominal lymphatic vessels with cystic appearance [28]. Another indication is the assessment of post-surgical abnormalities of lymphatic vessels that can be dilated after thoracic duct ligation for gastric or esophageal surgery or can be injured during surgical interventions on pancreas, stomach or esophagus, resulting in small lymphoceles [36].

3.3. LE assessment

The diagnosis is LE is usually clinical, but NCMRL can be used to confirm the presence of a LE, which is visible as a fluid infiltration of the subcutaneous fat tissue, often visualized with a honeycomb pattern, associated with epifascial fluid collection [29], without any involvement of the muscular compartment (Figs. 2-6).

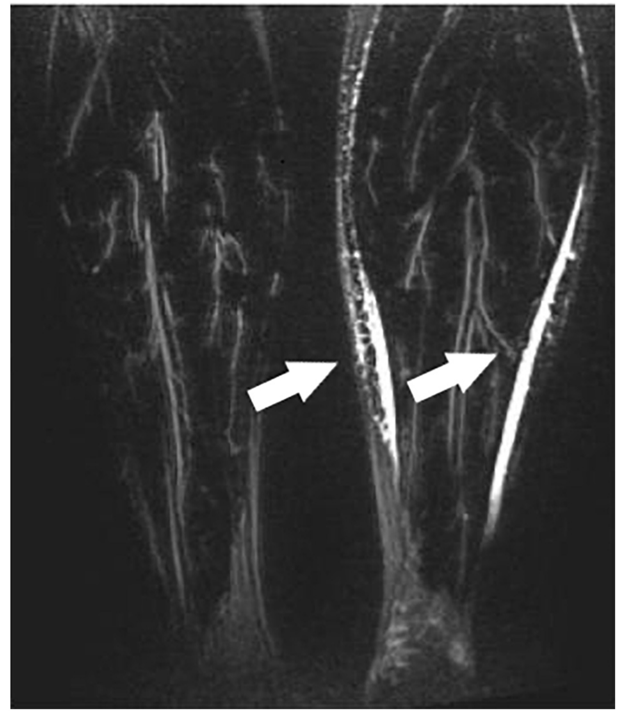

Fig. 2. Left lower extremity congenital LE.
Coronal MIP reconstruction of lymphatic MRI showing left lower extremity congenital LE with characteristic epifascial distribution (arrows).

NCMRL can identify LE, assess its extent and grade its severity [29].

3.4. Differential diagnosis of LE

NCMRL allows a differential diagnosis between LE and fatty infiltration due to morbid obesity or lipoedema [29,33,34] and between LE and phlebedema: phlebedema is characterized by an involvement of the subfascial muscular compartment appearing as dimensional increase, muscle edema or fatty degeneration [34]. LE is a disorder limited to the subcutaneous fat tissue and there is a saving in the involvement of the muscular compartment, also recently confirmed by a case series of 187 lower limbs LE [29] (Fig. 7).

3.5. Treatment planning of LE

There is no consensus about the imaging modality of choice for the evaluation of LE to establish the best treatment. X ray lymphangiography with oil-contrast injection has been abandoned, due to its invasiveness and possible complications [10,11]; lymphoscintigraphy can provide quantitative analysis of the lymph transport, but without a visualization of normal size lymphatic structures [12]. CEMRL demonstrated to have an excellent spatial resolution and can provide information regarding the anatomy of the lymphatic system and dynamic information of contrast medium transportation and nodal uptake [37]. This technique is useful for pre-surgical planning [13,14], but it has also some limitations: the quality of the visualization of larger lymphatic vessels (e.g. iliac trunks) is poorer than that of the distal lymphatic trunks [38] and the injected contrast medium is partially washed out through the circulatory system, thus causing an enhancement of the venous vessels that can be difficult to distinguish from the lymphatic structures [18]. In addition, a comparative study between CEMRL and NCMRL demonstrated a discrepancy in the assessment of number and caliber of lymphatics [39]: the authors hypothesized a reduced uptake of contrast medium in dilated lymphatic vessels caused by the raise in

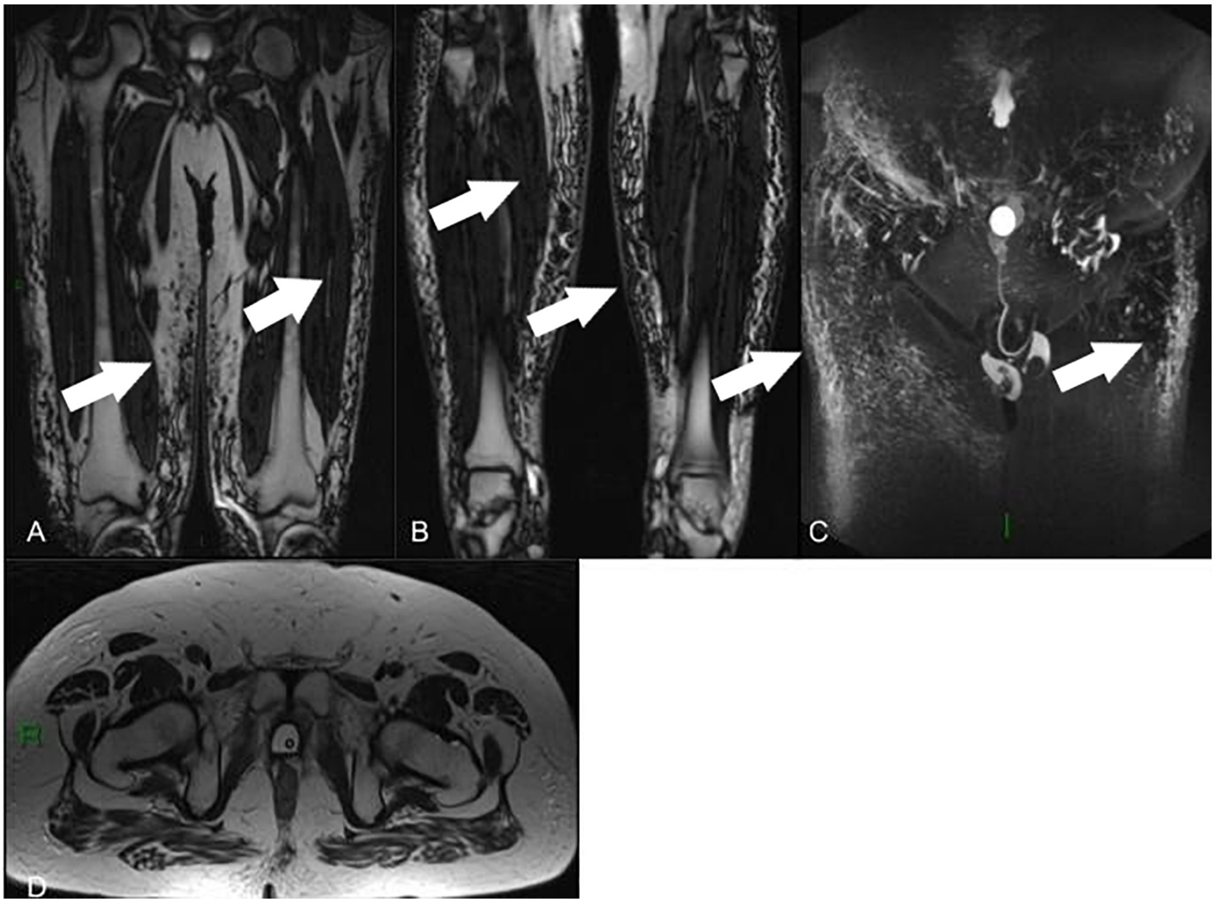

Fig. 3. 70-Year old patient who underwent radical prostatectomy and lymphadenectomy for a carcinoma.
(A) True Fisp of the thighs.
(B) True Fisp of the legs.
(C) coronal MIP reconstruction of lymphatic MRI of the inguinal and iliac regions.
(D) inguinal axial T2 TSE.
Diffuse bilateral honey comb pattern of the subcutaneous fat tissue, which is markedly thickened (A, B, C) (arrows).
In MIP reconstruction (C), bilateral hypoplasia of left and right inguinal and lymphatic vessels; no inguinal lymph node is visible (D).

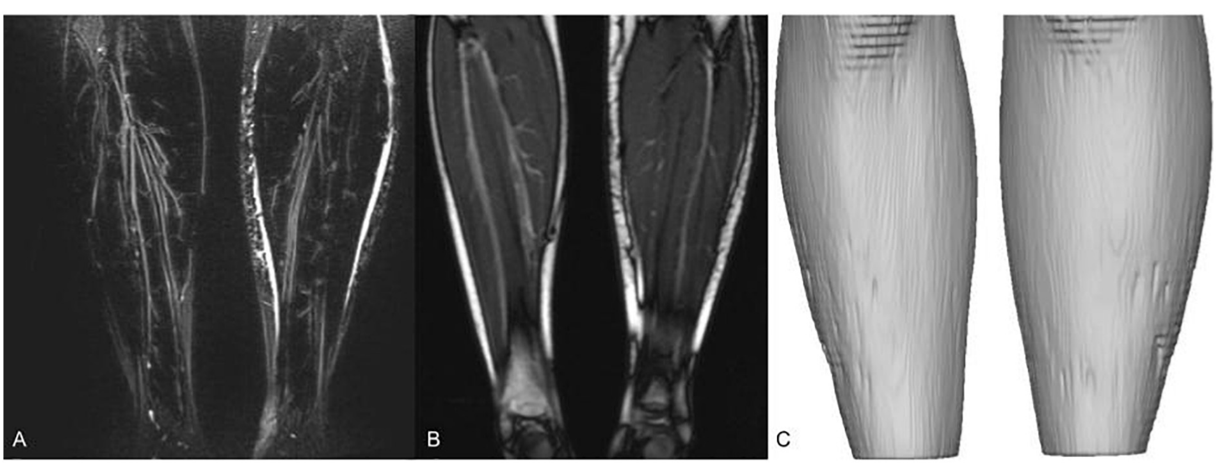

Fig. 4. Left leg congenital LE in a 14-year old girl.
(A) Coronal MIP reconstruction of the lower legs.
(B) Coronal True Fisp of the lower legs.
(C) Volume rendering calculated with ITK SNAP open source software.
Left leg LE with epifascial distribution (A). True Fisp sequence (B) can be automatically segmented through ITK SNAP open source software or other images analysis software to objectively calculate the volumes of healthy and affected limbs and to monitor treatment results.

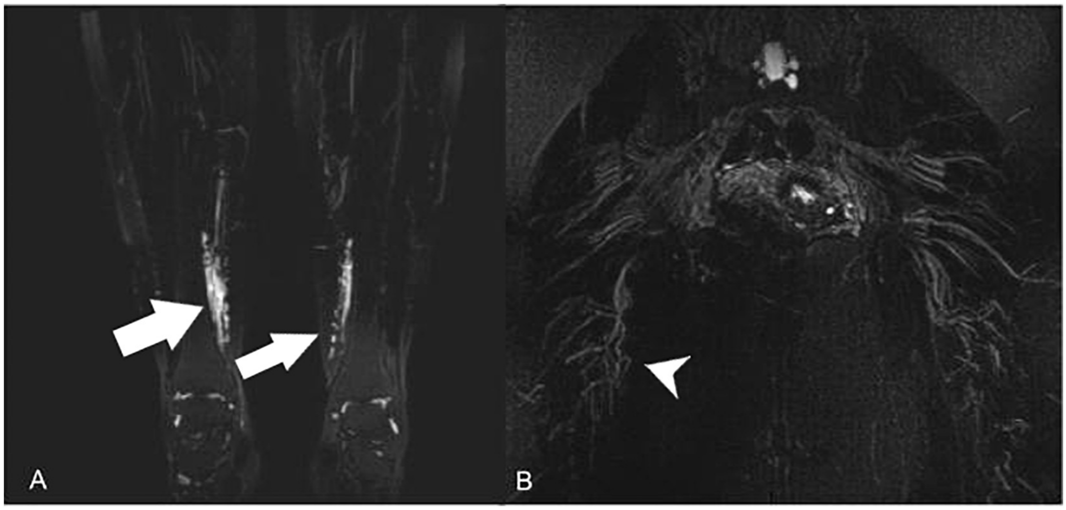

Fig. 5. Primary tarda LE in a 38 year old woman.
Bilateral LE of the lower third of the legs with epifascial distribution (A) (arrows).
Hyperplasia of inguinal lymphatic vessels on both sides (B) (arrow head).

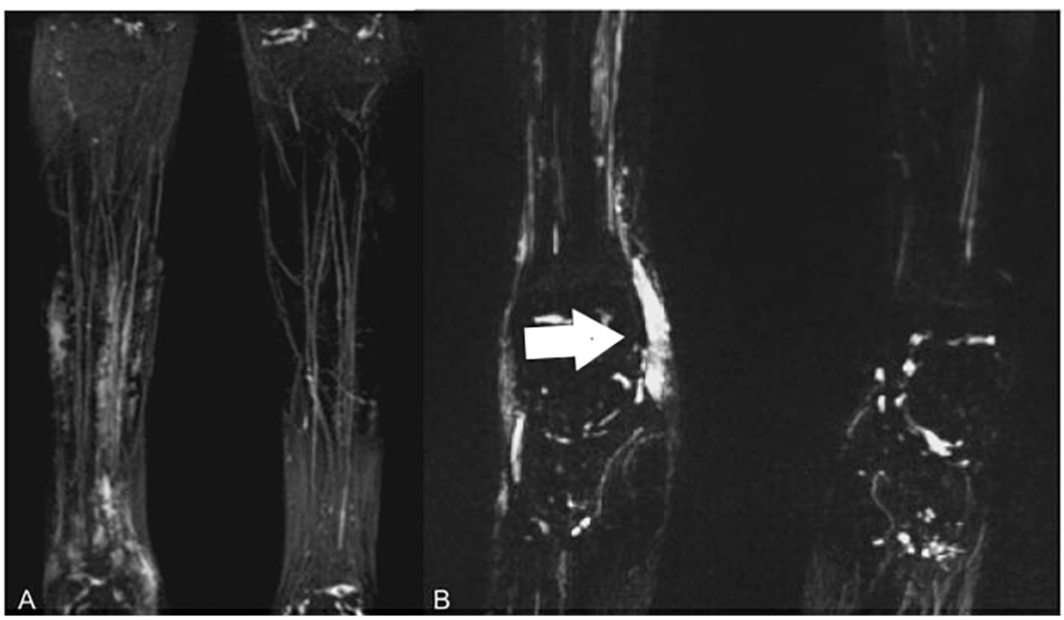

Fig. 6. Primary LE in a 10 year old female child.
LE of the right leg (A), more represented at the ankle level (B) (arrow).

the endolymphatic pressure.

In this context, NCMRL is starting to present itself as an optimal imaging technique for LE treatment planning [32]. In their study on 187 primary lower limb LE, Arrivé et al. [29] demonstrated an excellent correlation between the LE grading and characteristics of lymphatic trunks and the capacity of this examination to differentiate the type of LE in aplastic, hypoplastic or hyperplastic in order to choose the correct surgical strategy.

3.6. Follow up after treatment

There is no reliable method for follow-up LE after treatment. NCMRL, as a noninvasive technique, can be used to objectively evaluate the results of LE therapy. Arrivé et al. [31] reported a first experience on 15 patients affected by secondary LE following breast carcinoma treatment. They performed a pre-treatment NCLMR of the upper limb and a second examination at least 6 months after lymph node transplantation. In the presurgical MR they assessed: the severity of LE, the involvement of the muscular compartment, the evidence of distal dilated lymphatic structures; in the follow-up MR, they evaluated: the visualization of the transplantation site, the visualization of transferred lymph nodes and the LE severity in comparison with the previous MR (stable, reduced or increased). According to their experience, NCMRL can be used as an objective reproducible imaging examination to establish the course of LE after surgery.

4. Limitations and strengths

NCMRL has some limitations. First of all, diagnostic experiences with this relatively new technique are few: more investigations with larger patient case series are still needed to validate the use of this examination, to accurately determine the areas of application, and maybe even to improve the technique.

Secondarily, non-contrast lymphangiography cannot depict normal

Fig. 7. 30-Year old male with congenital lower extremities LE.
Diffuse subcutaneous infiltration with honeycomb pattern (A) (arrows). Presence of anomalous tortuous lymphatic vessels, particularly evident at the ankle region (C) (arrow head).

or hypoplastic lymphatic structures [30], only when the lymphatic fluid is impaired, the vessel is dilated and filled with stagnated lymph, and it becomes visible on NCMRL.

Third, because of the absence of contrast medium, NCMRL does not provide functional information about the timing of the lymphatic drainage or the nodal uptake, unlike CEMRL.

Moreover, NCMRL has limited spatial resolution, therefore CEMRL results to be the best technique for the evaluation of distal lymphatic vessels; however, NCMRL seems to be superior for the analysis of proximal lymphatic trucks, such as inguinal and iliac [29].

Although so far not reported by the studies in the literature, we must also consider as a limitation the possibility of confounding influence of fat; therefore, according to our experience, the sequences without fat saturation are useful for an optimal evaluation of the extension of size increase of the involved limbs and to obtain reproducible measurements, especially useful in the follow-up of treatment. On the other side, the heavily T2-weighted sequences, resulting signal loss in tissue background, with highlighting of static fluids, allow the visualization of epifascial fluid components and lymphatic vessel. The most important advantage of this technique is the non-invasiveness and the non-need to administer contrast medium: this means great benefits for allergic patients and for pediatric patients, who can safely undergo this type of examination, and no risk related to gadolinium deposition. Moreover, the absence of contrast medium results in lower costs, when compared to CEMRL. Another advantage against CEMRL is the short acquisition time: in at least half an hour patient positioning and imaging acquisition of the whole lower limbs are performed, while for CEMRL a total average examination time of 1 h and 15 min for the lower limb is expected [17] and faster acquisition time means further cost reduction.

5. Conclusion

NCMRL is a non-invasive imaging technique, useful for the analysis of LE.

It seems to be a valuable tool in the diagnosis and the surgical planning of LE, providing helpful anatomical information on the type of LE, on the lymph nodes number and the sites suitable for nodal transplantation and LE follow up after surgery.

Further studies with more extensive cases are necessary to validate this technique.

Declarations of interest

None.

References

[1] Lee BB, Antignani PL, Baroncelli TA, Boccardo FM, Brorson H, Campisi C, et al. IUA-ISVI consensus for diagnosis guideline of chronic lymphedema of the limbs. Int Angiol Aug 2015;34(4):311–32.
[2] Damstra RJ, Mortimer PS. Diagnosis and therapy in children with lymphoedema. Phlebology 2008;23(6):276–86. https://doi.org/10.1258/phleb.2008.008010.
[3] Schook CC, Mulliken JB, Fishman SJ, Grant FD, Zurakowski D, Greene AK. Primary lymphedema: clinical features and management in 138 pediatric patients. Plast Reconstr Surg Jun 2011;127(6):2419–31. https://doi.org/10.1097/PRS.0b013e318213a218.
[4] Lee BB, Villavicencio JL. Primary lymphoedema and lymphatic malformation: are they the two sides of the same coin? Eur J Vasc Endovasc Surg May 2010;39(5):646–53. https://doi.org/10.1016/j.ejvs.2010.01.018.
[5] Lim MC, Lee JS, Nam BH, Seo SS, Kang S, Park SY. Lower extremity edema in patients with early ovarian cancer. J Ovarian Res Mar 2014;7(7):28. https://doi.org/10.1186/1757-2215-7-28.
[6] Choi I, Lee S, Hong YK. The new era of the lymphatic system: no longer secondary to the blood vascular system. Cold Spring Harb Perspect Med Apr 2012;2(4):a006445. https://doi.org/10.1101/cshperspect.a006445.
[7] Douglass J, Graves P, Gordon S. Self-care for management of secondary lymphedema: a systematic review. PLoS Negl Trop Dis Jun 8 2016;10(6):e0004740https://doi.org/10.1371/journal.pntd.0004740.
[8] Kayıran O, De La Cruz C, Tane K, Soran A. Lymphedema: from diagnosis to treatment. Turk J Surg Jun 1 2017;33(2):51–7. https://doi.org/10.5152/turkjsurg.2017.3870.
[9] Garza R, Skoracki R, Hock K, Povoski SP. A comprehensive overview on the surgical management of secondary lymphedema of the upper and lower extremities related to prior oncologic therapies. BMC Cancer Jul 5 2017;17(1):468. https://doi.org/10.1186/s12885-017-3444-9.
[10] Husband J. Diagnostic techniques: their strengths and weaknesses. Br J Cancer Suppl Apr 1980;4:21–9.
[11] Yoshida RY, Kariya S, Ha-Kawa S, Tanigawa N. Lymphoscintigraphy for imaging of the lymphatic flow disorders. Tech Vasc Interv Radiol Dec 2016;19(4):273–6. https://doi.org/10.1053/j.tvir.2016.10.009.
[12] O'Donnell Jr. TF, Rasmussen JC, Sevick-Muraca EM. New diagnostic modalities in the evaluation of lymphedema. J Vasc Surg Mar 2017;5(2):261–73. https://doi.org/10.1016/j.jvsv.2016.10.083.
[13] Liu N, Zhang Y. Magnetic resonance lymphangiography for the study of lymphatic system in lymphedema. J Reconstr Microsurg 2016;32:66–71. https://doi.org/10.1055/s-0034-1384213.
[14] Narushima M, Yamamoto T, Ogata F, Yoshimatsu H, Mihara M, Koshima I. Indocyanine green lymphography findings in limb lymphedema. J Reconstr Microsurg Jan 2016;32(1):72–9. https://doi.org/10.1055/s-0035-1564608.
[15] Lee YW, Lee SH, You HJ, Jung JA, Yoon ES, Kim DW. Lymphatic vessel mapping in the upper extremities of a healthy Korean population. Arch Plast Surg Mar 2018;45(2):152–7. https://doi.org/10.5999/aps.2017.00983.
[16] Mazzei MA, Gentili F, Mazzei FG, Gennaro P, Guerrieri D, Nigri A, et al. High-resolution MR lymphangiography for planning lymphaticovenous anastomosis treatment: a single-centre experience. Radiol Med Dec 2017;122(12):918–27. https://doi.org/10.1007/s11547-017-0795-x.
[17] Mazzei FG, Gentili F, Guerrini S, Cioffi Squitieri N, Guerrieri D, Gennaro P, et al. MR lymphangiography: a practical guide to perform it and a brief review of the literature from a technical point of view. Biomed Res Int 2017;2017:2598358https://doi.org/10.1155/2017/2598358.
[18] Mitsumori LM, McDonald ES, Neligan PC, Maki JH. Peripheral magnetic resonance lymphangiography: techniques and applications. Tech Vasc Interv Radiol Dec 2016;19(4):262–72. https://doi.org/10.1053/j.tvir.2016.10.007.

[19] Lohrmann C, Foeldi E, Speck O, Langer M. High-resolution MR lymphangiography in patients with primary and secondary lymphedema. AJR Am J Roentgenol Aug 2006;187(2):556–61.
[20] Dori Y. Novel lymphatic imaging techniques. Tech Vasc Interv Radiol Dec 2016;19(4):255–61. https://doi.org/10.1053/j.tvir.2016.
[21] Weiss M, Burgard C, Baumeister R, Strobl F, Rominger A, Bartenstein P, et al. Magnetic resonance imaging versus lymphoscintigraphy for the assessment of focal lymphatic transport disorders of the lower limb: first experiences. Nuklearmedizin 2014;53(5):190–6. https://doi.org/10.3413/Nukmed-0649-14-03.
[22] McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology Jun 2015;275(3):772–82. https://doi.org/10.1148/radiol.15150025.
[23] Stojanov D, Aracki-Trenkic A, Benedeto-Stojanov D. Gadolinium deposition within the dentate nucleus and globus pallidus after repeated administrations of gadolinium-based contrast agents-current status. Neuroradiology 2016 May;58(5):433–41. https://doi.org/10.1007/s00234-016-1658-1.
[24] Kanda T, Matsuda M, Oba H, Toyoda K, Furui S. Gadolinium deposition after contrast-enhanced MR imaging. Radiology Dec 2015;277(3):924–5. https://doi.org/10.1148/radiol.2015150697.
[25] Crescenzi R, Donahue PMC, Hartley KG, Desai AA, Scott AO, Braxton V, et al. Lymphedema evaluation using noninvasive 3T MR lymphangiography. J Magn Reson Imaging 2017 Nov;46(5):1349–60. https://doi.org/10.1002/jmri.25670.
[26] Takahashi H, Kuboyama S, Abe H, Aoki T, Miyazaki M, Nakata H. Clinical feasibility of noncontrast-enhanced magnetic resonance lymphography of the thoracic duct. Chest Dec 2003;124(6):2136–42.
[27] Derhy S, El Mouhadi S, Ruiz A, Azizi L, Menu Y, Arrivé L. Non-contrast 3D MR lymphography of retroperitoneal lymphatic aneurysmal dilatation: a continuous spectrum of change from normal variants to cystic lymphangioma. Insights Imaging Dec 2013;4(6):753–8. https://doi.org/10.1007/s13244-013-0290-4.
[28] Arrivé L, Azizi L, Lewin M, Hoeffel C, Monnier-Cholley L, Lacombe C, et al. MR lymphography of abdominal and retroperitoneal lymphatic vessels. AJR Am J Roentgenol Nov 2007;189(5):1051–8.
[29] Arrivé L, Derhy S, Dahan B, El Mouhadi S, Monnier-Cholley L, Menu Y, et al. Primary lower limb lymphoedema: classification with non-contrast MR lymphography. Eur Radiol Jan 2018;28(1):291–300. https://doi.org/10.1007/s00330-017-4948-z.
[30] Liu N, Wang C, Sun M. Noncontrast three-dimensional magnetic resonance imaging vs lymphoscintigraphy in the evaluation of lymph circulation disorders: a comparative study. J Vasc Surg Jan 2005;41(1):69–75.
[31] Arrivé L, Derhy S, Dlimi C, El Mouhadi S, Monnier-Cholley L, Becker C. Noncontrast magnetic resonance lymphography for evaluation of lymph node transfer for secondary upper limb lymphedema. Plast Reconstr Surg Dec 2017;140(6):806e–11e. https://doi.org/10.1097/PRS.0000000000003862.
[32] Arrivé L, Derhy S, El Mouhadi S, Monnier-Cholley L, Menu Y, Becker C. Noncontrast magnetic resonance lymphography. J Reconstr Microsurg Jan 2016;32(1):80–6. https://doi.org/10.1055/s-0035-1549133.
[33] Petrek JA, Pressman PI, Smith RA. Lymphedema: current issues in research and management. CA Cancer J Clin Sep–Oct 2000;50(5):292–307.
[34] Case TC, Witte CL, Witte MH, Unger EC, Williams WH. Magnetic resonance imaging in human lymphedema: comparison with lymphangioscintigraphy. Magn Reson Imaging 1992;10(4):549–58.
[35] Wiegand S, Eivazi B, Barth PJ, von Rautenfeld DB, Folz BJ, Mandic R, et al. Pathogenesis of lymphangiomas. Virchows Arch Jul 2008;453(1):1–8. https://doi.org/10.1007/s00428-008-0611-z.
[36] Riddell AM, Davies DC, Allum WH, Wotherspoon AC, Richardson C, Brown G. High-resolution MRI in evaluation of the surgical anatomy of the esophagus and posterior mediastinum. AJR Am J Roentgenol Jan 2007;188(1):W37–43.
[37] Bae JS, Yoo RE, Choi SH, Park SO, Chang H, Suh M, et al. Evaluation of lymphedema in upper extremities by MR lymphangiography: comparison with lymphoscintigraphy. Magn Reson Imaging Jan 3 2018;49:63–70. https://doi.org/10.1016/j.mri.2017.12.024.
[38] Olszewski WL, Liu NF. Magnetic resonance lymphography (MRL): point and counter-point. Lymphology Dec 2013;46(4):202–7.
[39] Lu Q, Xu J, Liu N. Chronic lower extremity lymphedema: a comparative study of high-resolution interstitial MR lymphangiography and heavily T2-weighted MRI. Eur J Radiol Feb 2010;73(2):365–73. https://doi.org/10.1016/j.ejrad.2008.10.041.