The utility of Dynamic Contrast Enhanced Intranodal MR Lymphangiography in the investigation of primary lymphatic anomalies.

Ratnam L.A., Mills M., Wale A., Howroyd L.R., Itkin M., Howe F.A., Gordon K., Mansour S., Ostergaard P., Mortimer P.S.

PII: S0009-9260(24)00298-8

DOI: https://doi.org/10.1016/j.crad.2024.06.009

Reference: YCRAD 6629

To appear in: Clinical Radiology

Received Date: 24 January 2024

Revised Date: 18 May 2024

Accepted Date: 1 June 2024

Please cite this article as: Ratnam L, Mills M, Wale A, Howroyd L, Itkin M, Howe F, Gordon K, Mansour S, Ostergaard P, Mortimer P, The utility of Dynamic Contrast Enhanced Intranodal MR Lymphangiography in the investigation of primary lymphatic anomalies., *Clinical Radiology*, https://doi.org/10.1016/j.crad.2024.06.009.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2024 Published by Elsevier Ltd on behalf of The Royal College of Radiologists.



Author Contributions:

1 guarantor of integrity of the entire study. Ratnam

2 study concepts and design. Ratnam, Mills, Wale, Itkin, Howe.

3 literature research. Ratnam, Wale, Mills, Howroyd

- 4 clinical studies. Ratnam, Howroyd, Mills
- 5 experimental studies / data analysis. Ratnam, Mills, Wale, Howroyd
- 6 statistical analysi. Ratnam
- 7 manuscript preparation. Ratnam, Mills, Wale, Howroyd

8 manuscript editing. Ratnam, Mills, Wale, Howroyd, Howe, Gordon, Mansour, Ostergaard,

Mortimer

Jonungi bred

TITLE PAGE

Manuscript Title

The utility of Dynamic Contrast Enhanced Intranodal MR Lymphangiography in the investigation of primary lymphatic anomalies.

Manuscript Type: Technical report

Authors

Ratnam LA^{1,2}, Mills M², Wale A^{1,2}, Howroyd LR^{1,2}, Itkin, M⁵, Howe FA², Gordon K^{2,3}, Mansour S^{2,4}, Ostergaard P², Mortimer PS^{2,3}

1 Department of Radiology, St George's University Hospitals NHS Foundation Trust, London SW17 0QT, UK

2 Molecular and Clinical Sciences Research Institute, St George's University of London, London SW17 0RE, UK

3 Dermatology and Lymphovascular Medicine, St George's University Hospitals NHS Foundation Trust, London SW17 0QT, UK

4 South West Thames Centre for Genomics, St George's University Hospitals NHS Foundation Trust, London, UK

5 Department of Radiology, University of Pennsylvania Health System, Philadelphia, USA.

Corresponding authors

Dr LA Ratnam, <u>lakshmi.ratnam@stgeorges.nhs.uk</u>, for technical correspondence and Prof S Mansour, <u>smansour@sgul.ac.uk</u>, for clinical queries.

Acknowledgements

We would like to thank Professor Robert Morgan for his advice and assistance in the submission of this manuscript. We would also like to thank Professor Vaughan Keeley and Dr Katie Riches from Derby Hospitals NHS Foundation Trust for their support with the patient identification stage of the project.

Funding information:

- This paper has been supported by a joint grant from the Medical Research Council (MRC) and the British Heart Foundation (BHF) (MR/P011543/1 and RG/17/7/33217), with no direct involvement of these sponsors.
- 2. The authors declare that they have no conflict of interest.

Abbreviations:

- CNR Contrast-to-noise ratio
- DCMRL Dynamic Contrast Enhanced Intranodal Magnetic Resonance Lymphangiography
- MIP Maximum Intensity Projection
- MR Magnetic resonance
- MRA Magnetic Resonance Angiography
- MRL Magnetic Resonance Lymphangiography
- SCID Severe combined immunodeficiency
- SPGR Spoiled Gradient Echo

TD - Thoracic Duct

<u>The utility of Dynamic Contrast Enhanced Intranodal MR Lymphangiography in the</u> <u>investigation of primary lymphatic anomalies.</u>

Abstract

Background: Primary lymphatic anomalies are often complicated by central lymphatic abnormalities. Intranodal dynamic contrast enhanced MR lymphangiography (DCMRL) is a relatively new technique for imaging the central lymphatic system. Historically, the only method of imaging the central lymphatics well was with pedal lymphangiography, which is technically challenging, time consuming, involves the use of ionising radiation and has risks associated with the use of lipiodol. The treatment options for primary lymphatic disorders have also been limited to symptomatic management.

Purpose: To describe the technique of DCMRL to identify central lymphatic abnormalities in patients with primary lymphatic anomalies and discuss utility of the findings.

Materials and Methods: 28 patients with primary lymphatic abnormalities underwent dynamic MR imaging following injection of gadolinium directly into inguinal lymph nodes at a tertiary lymphovascular referral centre.

Results: Technical success was achieved in 23 patients (82.1%). Pathological imaging findings included obstructed, hypoplastic or absent lymphatic channels with collateralisation/rerouting or reflux of flow, lymphangiectasia, lymphatic pseudoaneurysms and lymph leaks. Protocol modifications for improved imaging are highlighted including technical aspects of lymph node injection, image acquisition and MRI parameters. In two patients, imaging findings warranted embolization of the abnormal lymphatic channels with subsequent symptomatic improvement.

Conclusion: DCMRL has been shown to be a safe, reproducible technique in patients with primary lymphatic anomalies enabling imaging of the central lymphatic system.

<u>The utility of Dynamic Contrast Enhanced Intranodal MR Lymphangiography in the</u> investigation of primary lymphatic anomalies.

3 Introduction

Intranodal dynamic contrast enhanced MR lymphangiography (DCMRL) is a relatively new technique 4 5 enabling imaging of the central lymphatics via injection of contrast directly into inguinal lymph 6 nodes. Lymphoscintigraphy remains the investigation of choice for diagnosis in lymphatic disorders 7 but does not give detailed imaging of the central lymphatics.1–3 Pedal lymphangiography with Lipiodol whereby contrast was injected directly into lymphatics in the foot which had been surgically 8 9 exposed is invasive, very time consuming, involves ionising radiation, and can result in lipiodol 10 embolization.4 XXXXXX NHS Foundation Trust is recognised as a national referral centre in the UK 11 for Primary Lymphatic Anomalies. Many of these genetically determined forms of primary lymphatic 12 anomalies have central lymphatic abnormalities associated with (or causing) peripheral 13 lymphoedema.5–8 These lymphatic abnormalities may not be clinically obvious yet are important to 14 diagnose both for correct phenotyping and for ongoing management.9 Although described for other 15 indications, there remains a paucity of data exploring DCMRL's utility in patients with primary 16 lymphatic anomalies.10–12 The purpose of this paper is to describe the method and utility of this 17 technique in imaging central lymphatic abnormalities in patients with primary lymphatic anomalies.

18 Materials and Methods

19 <u>Patients</u>

Patients were referred for DCMRL if they had a diagnosis of a primary lymphatic anomaly (chylous
reflux, significant lymphoedema with a suggestion of obstruction on lymphoscintigraphy,

22 chylothorax, chylopericardium or chylous ascites).

23 DCMRL technique

24 Inguinal lymph node puncture was carried out under ultrasound guidance using a shallow angle of

entry with a long subcutaneous tract to obtain a stable needle position with a 23G spinal needle (BD,

26 Franklin Lakes, NJ). Ideally, a minimum of one needle was sited in each groin. Where nodes were

easily visualised and patients tolerated placement well, a third needle was sited to increase likelihood
of contrast uptake. Satisfactory position within the lymph node was then confirmed using injection of
1ml of SonoVue (sulphur hexafluoride microbubbles) ultrasound contrast (Bracco Spa, Milan, Italy)
mixed with 2ml of 0.25% Chirocaine (levobupivacaine) for local anaesthesia. The needles were then
secured in place with dressings and connecting tubing attached with syringes primed with Gadoteric
acid (Dotarem®; Guerbet, France).

33 <u>Magnetic Resonance Imaging</u>

For all studies, MR imaging was performed using a clinical 3.0T MRI system Philips Achieva 3.0T TX
and a 16-element phased array torso coil for signal reception. The imaging protocol (Table 1) consists
of initial non-contrast sequences followed by dynamic contrast enhanced imaging.

37 Non-contrast imaging of the abdomen and pelvis begins with a 2D T₂-weighted breath-held turbo spin 38 echo (TSE) acquisition for identification of gross abnormalities (e.g., fluid accumulations), 3D image 39 planning, and allows for the identification of incidental findings. A 3D heavily T₂-weighted TSE sequence follows, for which only very long T₂ compartments retain reasonable signal intensity. Finally, 40 41 a pre-contrast 3D T₁-weighted spoiled gradient echo (SPGR) image was acquired. The non-contrast T2-42 weighted images were assessed for the presence or absence of ascites, pleural and pericardial effusions, oedema in the soft tissues and the presence of masses of lymphatic nature, and for how well the 43 44 lymphatics were visualised.

Slow injection (over 1-2 minutes) of 4 - 9ml of undiluted 279.32 mg/ml Gadoteric acid (Dotarem®; 45 Guerbet, France) was then carried out simultaneously via each needle placed in an inguinal lymph node, 46 followed by dynamic T₁-weighted imaging post-injection to depict contrast dispersion over time (each 47 48 acquisition lasted 0.5 minutes). A maximum of 3 needles were placed and maximum total dose of 18ml 49 of Gadoteric acid injected. In cases where contrast was initially difficult to visualise, T₁-weighted 50 Dixon images, of higher spatial resolution and larger field of view than the spoiled gradient echo 51 sequences, were acquired. Imaging initially focussed on the pelvis and lower abdomen until contrast 52 was seen to leave this region (variable), at which point the coil was repositioned to continue imaging to

53 the thoracic duct termination. The post-contrast T1weighted images were evaluated for presence or 54 absence of lymphatic vessels, anatomical distribution of the contrast (normal or abnormal), reflux, lymphatic pseudoaneurysms, leakage of lymphatic fluid, rerouting/ collateralisation, and the presence 55 56 of dermal backflow of contrast. All image volumes were reformatted as maximum intensity projections 57 (MIPs) for review, coronal projections for T₁-weighted image series and radial projections for the T₂-58 weighted images. Total imaging time ranged from approx. 30-90 minutes, however an hour was typical (average \pm standard deviation = 53 \pm 13 min), variability was secondary to individual variation in the 59 60 post-contrast acquisition time.

61

62 **Results**

From January 2018 to December 2022, 28 patients were imaged. A summary of the results and
underlying primary lymphatic diagnosis is provided in **Table 2**. The imaging findings are described
below. No contrast reactions were observed and no patients terminated the examination due to pain,
no delayed complications were reported during post procedure follow-up.

67

68 <u>Non contrast:</u>

From the T2 non-contrast imaging, central lymphatic channels could not be identified in 10 of the 28
patients. Of the remaining 18 patients, the lymphatic channels could be seen but were faint and not
deemed to be sufficiently visualised to be diagnostically helpful in 16 patients [Figure 1]. The
lymphatic channels were seen well in only two patients [Figure 2a].

73

74 <u>Post contrast:</u>

75 Technical success visualising the central lymphatics was achieved in 23 patients (82.1%). In five
76 patients, injection was performed unilaterally due to absence/ inability to identify targetable lymph

77	nodes on the contralateral groin either due to previous surgical removal of nodes or extensive oedema								
78	[Table 2]. Central lymphatics were successfully visualised in all five patients with contrast noted on								
79	the non-injected side signifying reflux (Cases 10, 26 and 28) [Figure 2b], normal unilateral uptake								
80	with normal thoracic duct (Case 20), and superficial re-routing indicating obstructed main drainage								
81	routes	(Case 13).							
82	In the r	remaining 23 patients, bilateral injections were performed. Of these,							
83	a)	In 5 patients (Cases 1, 2, 9, 15 and 17), no propagation of contrast was seen bilaterally. These							
84		were considered technical failures.							
85	b)	In 3 patients (Cases 5, 16, and 19), bilateral uptake of contrast was noted, and the imaging							
86		showed normal central lymphatics.							
87	c)	In 6 patients (Cases 3, 6, 7, 8, 11, and 25), bilateral uptake of contrast was noted with							
88		abnormalities detected (termination of the thoracic duct (TD), absent filling of TD,							
89		lymphopseudoaneurysms, lymphangiectasia, obstructed or absent lymphatic channels with							
90		collateralisation).							
91	d)	In 9 patients, propagation of contrast was absent on one of the injected sides in the groin							
92		(bilateral injections performed). Of these, 2 patients (Cases 21 and 22) showed normal lumbar							
93		and iliac lymphatics on the side with contrast propagation with normal appearances of the TD.							
94		The remaining 7 had a range of abnormalities including reflux into the ipsilateral pelvis and							
95		limb which was the limb affected with lymphoedema (Case 23), collateralisation with re-							
96		routing of the lymphatic fluid to the distal lymphatic channels (Cases 14, 18 and 27) and							
97		lymphopseudoaneurysms (Cases 12 and 24) and a patient with Noonan syndrome with							
98		abnormal mediastinal and pulmonary lymphatic perfusion and rapid flow of contrast to the							
99		terminal TD (Case 4).							

100 Discussion

The ability to image the central lymphatic system in this group of patients has led to an understanding
of the anatomy of their central lymphatics which was previously unknown. The discussion is divided
into technical factors and the lymphatic findings.

104 <u>1. Review of DCMRL procedures</u>

Selection of lymph node for contrast injection: Subjectively abnormal, absent and hypoplastic
lymph nodes are more common in patients with primary lymphatic disorders with target nodes
frequently < 1cm in size. Ideal needle tip positioning is at the corticomedullary junction. Lymph node
enhancement and efferent flow after injection of ultrasound contrast confirms good positioning. 13–15
The chirocaine alleviates pain that is otherwise experienced on injection of Gadoteric acid
intranodally.

111 Securing the needles in position: We noted ease of needle displacement in our initial studies (loss of position between placement and fixation, extravasation noted in the groin) with no uptake of contrast 112 on the displaced side. Thus, if patients tolerated needle placement well, up to 3 needles in one groin 113 were placed to maximise chances of introducing contrast into lymph nodes. This was only carried out 114 in 3 patients. Initial studies had an attempted injection of 9 ml of Gadoteric acid into each node, 115 116 however reduction to 4 ml injected into each node was found to still provide satisfactory contrast visualisation with improved tolerance from patients. We found that avoiding placement of needles in 117 the groin crease, positioning the coil above the tip of the needles and the use of connecting tubing 118 119 primed with contrast and attached at needle placement also stops the needles becoming displaced 120 when connecting a syringe to the needle for injection in the MRI scanner.

121 Non-contrast T_2 weighted Magnetic Resonance Imaging: Unlike most bodily tissues, lymph can be 122 expected to retain reasonable signal in long echo time scans given its T_2 time of approx. 610 msec at 123 3T16. These images provide a high contrast-to-noise ratio (CNR) for fluid containing regions and are 124 thus especially useful for identifying areas of lymphatic fluid accumulation [Figure 3]. Despite a 125 reduced CNR, moderately T_2 -weighted 2D sequences were also found to be beneficial as the fluid

126 accumulations could be observed in the context of the underlying anatomy. Sites setting up their own 127 MRL protocols may wish to consider whether two acquisitions are required in their context, 128 particularly if scanner time is limited. Acceleration techniques such as partial Fourier reconstruction 129 can also be applied to reduce imaging time but can reduce image SNR and introduce artefacts.17 130 Other non-contrast approaches have been described to assess the lymphatics in the abdomen 131 including a recent attempt using balanced steady state free-process (bSSFP).18 In this paper, cardiac 132 triggered and respiratory navigated bSSFP images facilitated improved visualisation of the lymphatics compared to respiratory triggered heavily T_2 weighted TSE. bSSFP sequences exhibit a 133 134 complex T_2/T_1 weighting in which fluids (lymph, CSF, blood) are high signal. We therefore chose not to employ bSSFP over TSE given the t high blood signal which could cause confusion in differentiating 135 lymphatic from the vascular structures. 136

137 Contrast-enhanced T₁-weighted Magnetic Resonance Imaging: Administration of Gadoteric acid 138 into the lymphatics reduces the long T₁ time of lymph sufficiently to be observed in dynamic T₁-139 weighted images where the passage of contrast agent within the lymphatics needs to be observed over 140 time [Figure 3].16. We employed Gadoteric acid due to a combination of local availability and its 141 strong safety profile.19 Similar enhancement with a reduced volume of contrast agent may be possible 142 using a similarly safe agent with greater r₁ relaxivity such as Gadoteridol or Gadobutrol20 but 143 requires *in-vivo* validation for lymphatic applications.

With high spatial and temporal resolution [**Table 1**], the spoiled gradient echo sequence was the default sequence for our dynamic imaging, Dixon based images are less affected by inhomogeneities outside the scanner isocentre but maintain high quality fat suppression, DIXON imaging was acquired in several cases and were particularly useful for cases in which contrast agent was seen to re-route via superficial lymphatic vessels [**Figure 4**]. A spoiled gradient echo sequence was chosen as the standard sequence for the dynamic post-contrast imaging as DIXON imaging takes longer to reconstruct and therefore limits the ability for on-table evaluation of the findings.

Some sites performing DCMRL have employed keyhole imaging to accelerate their T₁-weighted dynamic imaging21. However, care must be taken to ensure sufficient high spatial frequency data is captured to appropriately reconstruct small structures such as lymphatics and further work in this area is required. Additionally, methods of motion artefact reduction have been employed by several centres (breath-held T₁-weighted contrast enhanced scans, and respiratory or cardiac gating/triggering T₂ scans) to reduce motion artefacts and improve image quality, at the expense of extend imaging times and can be considered if time is not a limiting factor.22–29

158 <u>2. Observation of Lymphatic Abnormalities</u>

Absence of contrast uptake: 5 patients with absent bilateral contrast uptake were also found to have 159 160 no uptake beyond the ilioinguinal nodes on pedal lymphoscintigraphy. Thus, although considered technical failures, this may in fact be a true finding. It appears possible that those with no uptake on 161 pedal lymphoscintigraphy may be unlikely to show uptake with DCMRL although numbers are too 162 small to make definitive conclusions. Of the 9 patients in whom contrast uptake was absent on one 163 side, this may be due to an absence, functional aplasia or hypoplasia of the lymphatic system, 164 technical failure to access the lymph nodes, or needle displacement. Hypoplastic or absent lymphatics 165 166 has been shown to be useful for confirming or completing the clinical diagnosis in conditions with primary lymphatic anomalies.30 167

168 Dynamic aspect of DCMRL allows for more detailed study of flow in the lymphatics and

therapy compared to non-contrast MR imaging and lymphoscintigraphy. For example, 3 of the patients found to have reflux into the contralateral side was not known about prior to DCMRL. Two of these patients subsequently underwent glue embolization [Figure 5] with improvement in number of lymphatic blisters and volume of chylous leak, and no further episodes of infection on the affected side in both patients.31

174 5 patients demonstrated superficial re-routing of the lymphatics confirming obstruction of their

175 normal lymphatic pathways [Figure 6 and Table 2]. Confirmation of central lymphatic obstruction

176 can then lead to exploration of surgical options such as lymphovenous anastomosis.32,33

177 An inherent difficulty arising from investigating rare diseases is the relatively small numbers of

178 patients with each condition, however the imaging has led to improved understanding of the

179 mechanisms behind lymphatic anomalies and changes in patient management. The development of the

180 technique has resulted in refinements over time which has made the data more heterogenous. Our

181 experience is presented here to facilitate the development of DCMRL services elsewhere within the

182 UK.

183 Conclusion

184 DCMRL has proven to be a safe technique for imaging the central lymphatic anatomy of patients with

185 primary lymphatic anomalies without any adverse effects that were observed with lipiodol

186 lymphangiography. Increased uptake of this imaging modality will be invaluable in the phenotyping,

187 classification, and management of patients with primary lymphatic anomalies.

188

189 References

190 191 192	1.	Ramirez-Suarez KI, Tierradentro-Garcia LO, Smith CL, <i>et al</i> . Dynamic contrast-enhanced magnetic resonance lymphangiography. Pediatr Radiol 2022; 52 (2):285–94. https://doi.org/10.1007/s00247-021-05051-6.
193 194 195	2.	Bordonaro V, Ciancarella P, Ciliberti P, <i>et al.</i> Dynamic contrast-enhanced magnetic resonance lymphangiography in pediatric patients with central lymphatic system disorders. Radiol Med 2021; 126 (5):737–43. https://doi.org/10.1007/s11547-020-01309-5.
196 197 198	3.	Chavhan GB, Lam CZ, Greer MLC, Temple M, Amaral J, Grosse-Wortmann L. Magnetic Resonance Lymphangiography. Radiol Clin North Am 2020; 58 (4):693–706. https://doi.org/10.1016/j.rcl.2020.02.002.
199 200	4.	Browse NL, Burnand KG, Mortimer PS. Diseases of the lymphatics. 1. publ. London: Arnold; 2003.
201 202 203	5.	Li D, Wenger TL, Seiler C, <i>et al</i> . Pathogenic variant in EPHB4 results in central conducting lymphatic anomaly. Hum Mol Genet 2018; 27 (18):3233–45. https://doi.org/10.1093/hmg/ddy218.
204 205 206	6.	Liu M, Smith CL, Biko DM, <i>et al.</i> Genetics etiologies and genotype phenotype correlations in a cohort of individuals with central conducting lymphatic anomaly. Eur J Hum Genet 2022; 30 (9):1022–8. https://doi.org/10.1038/s41431-022-01123-9.
207 208 209	7.	Byrne AB, Brouillard P, Sutton DL, <i>et al.</i> Pathogenic variants in <i>MDFIC</i> cause recessive central conducting lymphatic anomaly with lymphedema. Sci Transl Med 2022; 14 (634). https://doi.org/10.1126/scitranslmed.abm4869.
210 211	8.	Biko DM, Reisen B, Otero HJ, <i>et al.</i> Imaging of central lymphatic abnormalities in Noonan syndrome. Pediatr Radiol 2019; 49 (5):586–92. https://doi.org/10.1007/s00247-018-04337-6.
212 213 214	9.	Gordon K, Varney R, Keeley V, <i>et al.</i> Update and audit of the St George's classification algorithm of primary lymphatic anomalies: A clinical and molecular approach to diagnosis. J Med Genet 2020; 57 (10):653–9. https://doi.org/10.1136/jmedgenet-2019-106084.
215 216 217	10.	Patel S, Hur S, Khaddash T, Simpson S, Itkin M. Intranodal CT Lymphangiography with Water- soluble Iodinated Contrast Medium for Imaging of the Central Lymphatic System. Radiology 2022; 302 (1):228–33. https://doi.org/10.1148/radiol.2021210294.
218 219 220 221	11.	Rabinowitz D, Dysart K, Itkin M. Neonatal lymphatic flow disorders: central lymphatic flow disorder and isolated chylothorax, diagnosis and treatment using novel lymphatic imaging and interventions technique. Curr Opin Pediatr 2022; 34 (2):191–6. https://doi.org/10.1097/MOP.000000000001109.
222 223 224	12.	Pieper CC, Wagenpfeil J, Henkel A, <i>et al.</i> MR lymphangiography of lymphatic abnormalities in children and adults with Noonan syndrome. Sci Rep 2022; 12 (1). https://doi.org/10.1038/s41598-022-13806-w.

225 13. Nadolski GJ, Itkin M. Feasibility of Ultrasound-guided Intranodal Lymphangiogram for 226 Thoracic Duct Embolization. Journal of Vascular and Interventional Radiology 227 2012;**23**(5):613–6. https://doi.org/10.1016/j.jvir.2012.01.078. 228 14. Nadolski GJ, Ponce-Dorrego MD, Darge K, Biko DM, Itkin M. Validation of the Position of 229 Injection Needles with Contrast-Enhanced Ultrasound for Dynamic Contract-Enhanced MR 230 Lymphangiography. Journal of Vascular and Interventional Radiology 2018;29(7):1028–30. 231 https://doi.org/10.1016/j.jvir.2018.02.034. 232 15. Hur S, Kim J, Ratnam L, Itkin M. Lymphatic Intervention, the Frontline of Modern Lymphatic 233 Medicine: Part I. History, Anatomy, Physiology, and Diagnostic Imaging of the Lymphatic 234 System. Korean J Radiol 2023;24(2):95–108. https://doi.org/10.3348/kjr.2022.0688. 235 16. Rane S, Donahue PMC, Towse T, et al. Clinical Feasibility of Noninvasive Visualization of Lymphatic Flow with Principles of Spin Labeling MR Imaging: Implications for Lymphedema 236 237 Assessment. Radiology 2013;269(3):893–902. https://doi.org/10.1148/radiol.13120145. 238 17. Bernstein MA, King KF, Zhou XJ. COMMON IMAGE RECONSTRUCTION TECHNIQUES. 239 Handbook of MRI Pulse Sequences. Elsevier; 2004;491–571. https://doi.org/10.1016/B978-240 012092861-3/50019-4. Gooty VD, Veeram Reddy SR, Greer JS, et al. Lymphatic pathway evaluation in congenital 241 18. 242 heart disease using 3D whole-heart balanced steady state free precession and T2-weighted cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2021;23(1):16. 243 244 https://doi.org/10.1186/s12968-021-00707-6. 19. 245 The Royal College of Radiologists. Guidance on gadolinium-based contrast 246 agent administration to adult patients. The Royal College of Radiologists 2019. Retrieved 247 from https://www.rcr.ac.uk/our-services/all-our-publications/clinical-radiology-248 publications/guidance-on-gadolinium-based-contrast-agent-administration-to-adult-patients 249 20. Rohrer M, Bauer H, Mintorovitch J, Requardt M, Weinmann H-J. Comparison of magnetic 250 properties of MRI contrast media solutions at different magnetic field strengths. Invest Radiol 251 2005;**40**(11):715–24. https://doi.org/10.1097/01.rli.0000184756.66360.d3. 21. Biko DM, Smith CL, Otero HJ, et al. Intrahepatic dynamic contrast MR lymphangiography: 252 253 initial experience with a new technique for the assessment of liver lymphatics. Eur Radiol 254 2019;29(10):5190-6. https://doi.org/10.1007/s00330-019-06112-z. 22. 255 Mills M, van Zanten M, Borri M, et al. Systematic Review of Magnetic Resonance 256 Lymphangiography From a Technical Perspective. Journal of Magnetic Resonance Imaging 257 2021;53(6):1766-90. https://doi.org/10.1002/jmri.27542. Mazzei MA, Gentili F, Mazzei FG, et al. High-resolution MR lymphangiography for planning 258 23. 259 lymphaticovenous anastomosis treatment: a single-centre experience. Radiol Med 260 2017;**122**(12):918–27. https://doi.org/10.1007/s11547-017-0795-x.

261 262 263	24.	Krishnamurthy R, Hernandez A, Kavuk S, Annam A, Pimpalwar S. Imaging the central conducting lymphatics: Initial experience with dynamic MR lymphangiography. Radiology 2015; 274 (3):871–8. https://doi.org/10.1148/radiol.14131399.
264 265 266	25.	Itkin MG, McCormack FX, Dori Y. Diagnosis and treatment of lymphatic plastic bronchitis in adults using advanced lymphatic imaging and percutaneous embolization. Ann Am Thorac Soc 2016; 13 (10):1689–96. https://doi.org/10.1513/AnnalsATS.201604-292OC.
267 268 269	26.	Dori Y, Keller MS, Fogel MA, <i>et al.</i> MRI of lymphatic abnormalities after functional single- ventricle palliation surgery. American Journal of Roentgenology 2014; 203 (2):426–31. https://doi.org/10.2214/AJR.13.11797.
270 271 272	27.	Mohanakumar S, Telinius N, Kelly B, <i>et al.</i> Morphology and Function of the Lymphatic Vasculature in Patients With a Fontan Circulation. Circ Cardiovasc Imaging 2019; 12 (4):e008074. https://doi.org/10.1161/CIRCIMAGING.118.008074.
273 274 275 276	28.	Dori Y, Keller MS, Rome JJ, <i>et al.</i> Percutaneous lymphatic embolization of abnormal pulmonary lymphatic flow as treatment of plastic bronchitis in patients with congenital heart disease. Circulation 2016; 133 (12):1160–70. https://doi.org/10.1161/CIRCULATIONAHA.115.019710.
277 278 279	29.	Suga K, Yuan Y, Ogasawara N, Okada M, Matsunaga N. Localization of breast sentinel lymph nodes by MR lymphography with a conventional gadolinium contrast agent. Preliminary observations in dogs and humans. Acta Radiol 2003; 44 (1):35–42.
280 281 282	30.	Uchida T, Uchida Y, Takahashi M, <i>et al.</i> Yellow nail syndrome in which intranodal lymphangiography contributed to the diagnosis. Internal Medicine 2021; 60 (22):3599–603. https://doi.org/10.2169/internalmedicine.6499-20.
283 284	31.	Pieper CC, Hur S, Sommer C-M, <i>et al.</i> Back to the Future. Invest Radiol 2019; 54 (9):600–15. https://doi.org/10.1097/RLI.000000000000578.
285 286 287	32.	Othman S, Azoury SC, Klifto K, Toyoda Y, Itkin M, Kovach SJ. Microsurgical Thoracic Duct Lymphovenous Bypass in the Adult Population. Plast Reconstr Surg Glob Open 2021; 9 (10):e3875. https://doi.org/10.1097/gox.000000000003875.
288 289 290	33.	Weissler JM, Cho EH, Koltz PF, <i>et al.</i> Lymphovenous anastomosis for the treatment of chylothorax in infants: A novel microsurgical approach to a devastating problem. Plast Reconstr Surg 2018; 141 (6):1502–7. https://doi.org/10.1097/PRS.000000000004424.
291		

292

293 Figures

Figure 1. Comparison of non contrast and DCMRL images of the iliac and lumbar lymphatics in a 30-year-old female patient (Case 19) with unilateral right leg lymphoedema. Images shown are over the abdomen and pelvis from the lower lumbar vertebrae to the level of the femoral heads. The lymphatics (white arrows) are faintly visualised on the T_2 weighted non-contrast imaging, with a central slice of the 3D acquisition shown here (1a) and seen much more clearly on the post contrast T_1 -weighted imaging, as demonstrated in this MIP SPOILED GRADIENT ECHO image (1b). DCMRL showed normal central lymphatics with good bilateral drainage.

300

301

Journal Prevention

302

Figure 2. One of two patients in whom lymphatics were visualised on non-contrast imaging is a 64-year old male patient (Case 28) with chylous reflux into right thigh and genitalia, and right thigh and genital
 lumphoedame. The first image anonymous the lower therew to the lower of the famoral heads. Markedly dilated

305 lymphoedema. The first image encompasses the lower thorax to the level of the femoral heads. Markedly dilated 306 lymphatics (white arrow) are reasonably well seen on the non-contrast T_2 images, as can be seen in the single

central slice of the 3D acquisition shown (2a) The same dilated lymphatic channel is shown in the post

308 contrast image (black arrow). Contrast was only injected from left groin as nodes had been surgically

- 309 removed on the right. However, significant reflux into the right side was identified (white arrow) on post
- 110 contrast T₁-weighted SPRG image, displayed in MIP form here (2b). Dynamic imaging demonstrated the
- 311 opacification of the right sided channels after injection of contrast from the left.
- 312
- 313

Journal

314 Figure 3. T₂ weighted images of a patient (25-year-old female, Case 8), with enlarged inguinal lymphatic vessels. (3a) shows the MIP resulting from the 2D T₂-weighted TSE sequences, while (3b) is a mid-image slice 315 316 from this sequence. (3c) and (3d) are the equivalent from the 3D heavily T2-weighted sequence. Note that while 317 more of the anatomy is visible in a-b, the reduced background signal improves lymphatic vessels and fluid 318 pooling visibility with the 3D acquisition (c-d). Note too that visualisation of lymphatic vessels is rarer in the 319 more moderately 2D T₂-weighted images (a-b) than the 3D (c-d). The arrows highlight lymphatics in the upper 320 thigh on the patient's left.

321	
322	
323	
324	
325	
326	
327	
328	
329	
330	
331	
332	
333	
224	

334

335	
000	

Figure 4. Post contrast T₁ weighted Dixon maximum-intensity projection (MIP) of a 24-year-old male patient (Case 14) with no drainage into normal lymphatic vessels showing superficial rerouting of contrast injected into a right groin lymph node (thick white arrow shows contrast partially extravasated around the right groin lymph

node) up the right flank (thin white arrow showing contrast re-routing along right flank). ournal proposition

- 349 Figure 5. Glue embolization carried out on a patient with reflux (Case 28 from Figure 2). Lipiodol
- 350 lymphangiogram first carried out with injection from left groin lymph node. Refluxing channels targeted
- fluoroscopically and glue embolization (thin white arrow shows glue cast in embolized lymphatics) carried out
- after microcatheter (white arrow) catheterisation of the lymphatic vessels.

353

354

Journal Presson

355

Figure 6. 66-year-old male patient (Case 28) with right leg and genital lymphoedema. Previous surgery with
 removal of right groin lymph nodes thus only the left was injected. Post contrast maximum-intensity projection

(MIP) shows contrast injected from left groin node (black arrow) has refluxed to the right, then rerouting around

the right flank (white arrow shows refluxed contrast starting to track up right flank) (**6a**). Delayed imaging

360 showed the contrast from the right flank tracking up the chest wall (white arrow) before draining via further

collaterals into the TD (black arrow) (6b). Images shown were acquired with the Dixon technique.

362

363

364

Journal Pre-proof

Table 1. Typical imaging parameters for magnetic resonance lymphangiography at 3.0 T. Note that field of view and acquisition matrix varied from participant to participant based on the anatomy. Image acquisition times varied based on the field of view required for adequate anatomical coverage but were generally between 6 - 10 minutes for the heavily T₂-weighted and 0.5-1 minutes per volume for the dynamic T₁-weighted series.

TR: repetition time, TE: echo time, FA: flip angle, NSA: number of signal averages, SENSE factor: SENSitivity Encoding

	TR / TE (ms)	FA (⁰)	Reconstructed Voxel Size (mm)	NSA	Fat Suppression	Motion Reduction	SENSE Factor (Direction)	Typical acquisition time	Features of interest
Pre-contrast:						0	· · · · · · · · · · · · · · · · · · ·		
Coronal 2D T ₂ -weighted TSE	'shortest' * / 80 ms	90	0.78 x 0.78 x 4.00	1	SPAIR	Breath-held	2.0 (RL)	5 min	Fluid accumulations (e.g., ascites), anatomy, incidental findings
Coronal 3D heavily T ₂ - weighted TSE	3200 / 740	90	0.90 x 0.90 x 1.50	2	SPAIR	N/A	1.6 (RL) 1.6 (AP)	9 min	Fluid accumulations, occasionally LV
Coronal 3D T ₁ -weighted SPOILED GRADIENT ECHO	'shortest' /'shortest' *	30	0.76 x 0.76 x 1.50	JI)	N/A	N/A	3.0 (RL)	0.5 min	Baseline prior to contrast injection
Post-contrast:		-					· · · · · · · · · · · · · · · · · · ·		
Coronal 3D T ₁ -weighted SPOILED GRADIENT ECHO	'shortest' /'shortest' *	30	0.76 x 0.76 x 1.50	1	N/A	N/A	3.0 (RL)	0.5 min / dynamic	Enhancing LV, and contrast leakage/pooling
Coronal 3D T ₁ -weighted Dixon	4.36 / 1.41/ 2.60 [†]	10	0.71 x 0.71 x 1.00	1	Dixon	N/A	1.6 (RL) 1.6 (AP)	2 min	Enhancing LV, and contrast leakage/pooling

* 'shortest' TR for the Coronal 2D T₂-weighted TSE was approx. 2000ms; 'shortest' TR / TE for the Coronal 3D T₁-weighted spoiled gradient echo were approx. 5 / 2 ms.

[†] $TE_1 = 1.41 ms$, $TE_2 = 2.60 ms$.

RL: Right – Left; AP: Anterior – Posterior; LV: lymphatic vessels

Table 2. Summary of patients and DCMRL findings

Patient No	Sex	Age at time of study (years)	Lymphatic Diagnosis	Unilateral Injection	Bilateral injection with no uptake	Bilateral injection with bilateral uptake	Bilateral injection with unilateral uptake
1	М	18	WILD syndrome [22]	0	х		
2	М	38	WILD syndrome		Х		
3	М	31	RASopathy (Noonan syndrome)			TD terminates at ligation.	
4	F	39	RASopathy (Noonan syndrome)				Mediastinal, pleural & pericardial leak.
5	F	50	YNS			Normal central lymphatics.	
6	М	61	YNS			Absent TD, collateral filling, LPSA.	
7	F	47	GLD			Dilated lymphatic vessels.	
8	F	25	GLD			Absent TD, collateral filling.	
9	М	46	GLD		Х		
10	М	19	GLD	CL severe oedema. CL contrast- reflux.			

11	F	70	GLD			Obstruction with rerouting and filling of distal TD.	
12	М	31	GLD				LPSA, absent lower TD (ligated). Distal filling via collaterals.
13	М	42	GLD	CL severe oedema. Superficial rerouting.			
14	М	24	ERG-related GLD [23]		ð		Obstruction with rerouting to TD.
15	F	41	ERG-related GLD		x		
16	М	29	SCIDS		2	Normal central lymphatics.	
17	М	38	Unilateral leg lymphoedema (R)	NO.	x		
18	F	16	Unilateral leg lymphoedema (L)				Absent TD, collateral filling.
19	F	30	Unilateral leg lymphoedema (R)			Normal central lymphatics.	
20	F	39	Unilateral leg lymphoedema (L)	CL severe oedema. Normal on side of uptake and centrally.			
21	F	25	Unilateral leg lymphoedema (L)				Normal on side of uptake and centrally.
22	М	29	Left perineal lymphovascular malformation				Normal on side of uptake and centrally.
23	M	33	Left hindquarter lymphovascular malformation, chylous reflux, lymph leakage				Ipsilateral reflux to pelvis and leg.
24	F	52	Bilateral lower limb and abdominal wall lymphoedema, chylous				LPSA, dilated TD with distal TD obstruction.

			ascites & pleural effusions.				
25	М	34	Unilateral leg lymphoedema (L), chylous ascites & pleural effusions			Absent distal TD, LPSA.	
26	М	62	Genital and right leg lymphoedema, chylous reflux, lymph leakage	CL surgery. CL contrast- reflux.	4		
27	М	17	Genital and bilateral lower limb lymphoedema		. (OOT		Obstruction with rerouting to CC.
28	М	64	Genital and right leg lymphoedema, chylous reflux, lymph leakage	CL surgery. CL contrast- reflux.	R		

Abbreviation Key

CC - Cisterna chylii

CL - Contralateral

GLD - Generalised Lymphatic Dysplasia

L – left

LPSA - Lymphopseudoaneurysm

R - right

SCIDS - Severe combined immunodeficiency syndrome

TD - Thoracic duct

WILD - Warts, Immunodeficiency, Lymphoedema and anogenital Dysplasia

YNS - Yellow Nail Syndrome



b













Journal Preservo

Highlights:

- 1. Central lymphatics visualised in 82.1% with DCMRL
- 2. Optimising imaging parameters and needle placement technique are critical
- 3. DCMRL enables dynamic assessment of central lymphatics with anatomical correlation

Journal Prevention

Declaration of interests

 The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☑ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

L A Ratnam reports financial support was provided by UKRI Medical Research Council. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.