European Radiology (2019) 29:5190–5196
https://doi.org/10.1007/s00330-019-06112-z

MAGNETIC RESONANCE

Intrahepatic dynamic contrast MR lymphangiography: initial experience with a new technique for the assessment of liver lymphatics

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Received: 11 September 2018 / Revised: 7 February 2019 / Accepted: 14 February 2019 / Published online: 18 March 2019

Abstract

Objectives To describe the technique and report on our initial experience with the use of intrahepatic dynamic contrast magnetic resonance lymphangiography (IH-DCMRL) for evaluation of the lymphatics in patients with hepatic lymphatic flow disorders.

Methods This is a retrospective review of the imaging and clinical findings in six consecutive patients undergoing IH-DCMRL. The technique involves injection of a gadolinium contrast agent into the intrahepatic lymphatic ducts followed by imaging of the abdomen and chest with both heavily T2-weighted imaging and dynamic time-resolved imaging.

Results In six consecutive patients, IH-DCMRL was technically successful. There were four patients with protein-losing enteropathy (PLE) and two with ascites in this study. In the four patients with PLE, IH-DCMRL demonstrated hepatoduodenal connections with leak of contrast into the duodenal lumen not seen by conventional lymphangiography. In one patient with ascites, IH-DCMRL demonstrated lymphatic leakage into the peritoneal cavity not seen by intranodal lymphangiography. In the second patient with ascites, retrograde lymphatic perfusion of mesenteric lymphatic networks and nodes was seen. Venous contamination was seen in two patients. No biliary contamination was identified. There were no short-term complications.

Conclusions IH-DCMRL is a cross-sectional technique which successfully evaluated hepatic lymphatic flow disorders and warrants further investigation.

Key Points

- *Intrahepatic dynamic contrast magnetic resonance lymphangiography (IH-DCMRL) is a new imaging technique to evaluate hepatic lymphatic flow disorders such as protein-losing enteropathy.*
- *In comparison to conventional liver lymphangiography, IH-DCMRL offers a 3D imaging technique and better distal lymphatic contrast distribution and does not use ionizing radiation.*

Keywords Magnetic resonance imaging · Lymphatic system · Protein-losing enteropathies

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Abbreviations

IH-DCMRL	Intrahepatic dynamic contrast magnetic resonance lymphangiography
PLE	Protein-losing enteropathy
TD	Thoracic duct
TWIST	Time-resolved imaging with interleaved stochastic trajectories

Introduction

The liver lymphatic system plays a key role in several disease processes, including ascites, protein-losing enteropathy (PLE), and heart failure. Recently, it has been

demonstrated by conventional liver lymphangiography that Fontan-associated PLE is a result of abnormal hepatoduodenal connections. Leak of liver lymphatic fluid into the duodenal lumen was demonstrated in these patients by duodenoscopy with blue dye injection into the liver lymphatics [1]. Conventional liver lymphangiography has also shown abnormal liver lymphatic flow in patients with ascites [2]. However, conventional fluoroscopic liver lymphangiography has certain limitations. First, it is 2D and has limited evaluation of adjacent anatomical structures. Second, with conventional hepatic lymphangiography, the distribution of the contrast is limited. Water-soluble contrast injected intrahepatically opacifies the liver lymphatic system, but the thoracic duct (TD) and other distal structures are rarely seen during imaging. In patients with PLE, lymphatic leakage into the duodenal lumen is also not well seen during conventional hepatic lymphangiography. Confirmation of pathology is therefore performed with the injection of isosulfan blue in conjunction with duodenoscopy [1]. Due to the importance of the liver lymphatic system and the potential role in the etiology of several diseases, including PLE, it would be beneficial to have a cross-sectional imaging method to evaluate the liver lymphatic system. MRI has been described as an excellent technique for imaging the central lymphatic system with good spatial and temporal resolution [3]. The application of MRI to evaluate the liver lymphatic system has not been described. The purpose of this article is to describe the technique and our initial experience using an intrahepatic dynamic contrast magnetic resonance lymphangiography (IH-DCMRL) to evaluate the liver lymphatic system in patients with abnormal liver lymphatic flow disorders.

Methods

With IRB approval, a retrospective evaluation of six consecutive patients who had IH-DCMRL was performed. Patients were evaluated with this technique as clinically indicated following request for evaluation of PLE or ascites not controlled with conservative treatment.

For liver access, a 3.5-in. 25-gauge spinal needle (Becton Dickinson) is placed adjacent to a branch of the portal vein under ultrasound guidance [4] by our interventional lymphatic team, which includes an interventional cardiologist and an interventional radiologist. This typically takes approximately 5–10 min to obtain access and confirm under fluoroscopy by slowly injecting a water-soluble contrast agent (Optiray 350, Guerbet) [1, 2]. The needles are then secured with Tegaderm™ (3M), and the patient was transferred to MRI. MRI was performed using a 1.5-T magnet (Magnetom Avanto, Siemens Healthineers).

Contrast agent preparation

Undiluted gadobutrol (Gadavist, Bayer Healthcare) at a dose of 0.1–0.2 mmol/kg was injected by hand at an approximate rate of 0.5 mL/min to 1 mL/min.

Imaging protocol

All studies imaged the neck, chest, and abdomen as caudally as possible. All but one patient initially had a heavily T2-weighted imaging (T2-weighted sampling perfection with application-optimized contrasts using different flip angle evolutions (SPACE)) (Siemens Healthineers; matrix 320 × 264 to 284 × 342, FOV 400–500, TR 2500, TE 670, flip angle 140, slice thickness 1.2 mm to 1.5 mm, voxel size 1.2 mm × 1.1 mm × 1.3 mm to 1.5 mm × 1.2 mm × 1.8 mm). Following the injection of contrast into the intrahepatic lymphatics, time-resolved imaging with interleaved stochastic trajectories (TWIST) (Siemens Healthineers; matrix 320 × 264 to 352 × 308, FOV 370–500, TR 3, TE 1, flip angle 25, slice thickness 1.2 mm to 1.4 mm, voxel size 1.2 mm × 1.1 mm × 1.3 mm to 1.4 mm × 1.3 mm × 1.6 mm) with a temporal resolution of 8–12 s was performed over 6–7 min. This was followed by a high-resolution respiratory-navigated 3D IR T1 gradient echo sequence (matrix 352 × 234 to 352 × 315, FOV 370–500, TR 300, TE 1.5, TI 220, flip angle 20, slice thickness 1.1 mm to 1.4 mm, voxel size 1.1 mm × 1.1 mm × 1.3 mm to 1.4 mm × 1.1 mm × 2.1 mm). Acquisition time for this sequence is approximately 2–5 min depending on patient size and efficiency of the respiratory navigation (see Table 1).

Analysis of imaging

Images were evaluated by two radiologists (DMB and DS) using multiplanar reformats and maximum intensity projections for the quality and timing of visualization of lymphatic perfusion (good, moderate, and poor, qualitatively based on the quality of imaging) of the deep liver lymphatics, hepatoduodenal lymphatics, duodenum, mesentery, and thoracic duct. The presence or absence of biliary and/or venous contamination was also evaluated. Short-term complication rates were recorded. Findings were correlated with duodenoscopy following injection of isosulfan blue 1% into the intrahepatic lymphatics (if applicable and when performed).

Results

The patients are summarized in Table 2. The technique was successful in all six patients (100%). In all six patients, IH-DCMRL demonstrated enhancement of the liver lymphatics with lymphatic flow medially through the liver hilum via the

Table 1 MR imaging protocol for intrahepatic dynamic contrast lymphangiography (IH-DCMRL)

Sequence	Matrix	FOV	TR	TE	TI	Flip angle	Slice thickness (mm)	Voxel size (mm)	Acquisition time (varies)
T2-weighted sampling perfection with application optimized contrasts using different flip angle evolutions	320 × 264 to 284 × 342	400–500	2500	670	N/A	140	1.2 to 1.5	1.2 × 1.1 × 1.3 to 1.5 × 1.2 × 1.8	5–6 min
Time-resolved imaging with stochastic trajectories (TWIST)	320 × 264 to 308 × 352	370–500	3	1	N/A	25	1.2 to 1.4	1.2 × 1.1 × 1.3 to 1.4 × 1.3 × 1.6	Every 8–12 s for 6–7 min
Respiratory-navigated 3D inversion recovery T1 gradient echo	234 × 352 to 315 × 352	370–500	300	1.5	220	20	1.1 to 1.4	1.1 × 1.1 × 1.3 to 1.4 × 1.1 × 2.1	2–5 min

periportal lymphatics (Fig. 1). A comparison between T2-weighted imaging and contrast-enhanced IH-DCMRL is shown in Fig. 2. Five patients had enhancement of the TD (absent in patient with a history of TD embolization). In all four patients with a history of PLE, IH-DCMRL demonstrated hepatoduodenal connections with perfusion of the duodenal wall and leak of contrast into the duodenal lumen (Fig. 1). Leak was not seen in any of these patients with conventional lymphangiography (Fig. 1g). In three patients that underwent lymphatic intervention, leak into the duodenal lumen was confirmed by endoscopy with injection of isosulfan blue 1% into the liver lymphatics (Fig. 1h). The fourth patient with PLE did not undergo an intervention so endoscopy was not performed. Two patients presented with ascites, one congenital where IH-DCMRL demonstrated a leak of lymphatic fluid originating from the liver into the peritoneum not seen by intranodal DCMRL (Fig. 3). In the patient who had ascites due to liver cirrhosis, there was a retrograde flow of lymphatic contrast to the mesentery and mesenteric lymph nodes via the porta hepatis. Again, this was not seen on conventional lymphangiogram.

Following injection of the liver lymphatics, contrast was seen passing into the hilar periportal lymphatics in less than 45 s in four of the six cases. The TD was not seen by conventional lymphangiography but was seen by IH-DCMRL in five of the six cases. In two cases, the TD was visualized within 30 s of injection of MRI contrast. In a single PLE patient, there was a prior intranodal DCMRL, resulting in partial opacification of the TD. In this patient, intranodal DCMRL failed to demonstrate the lymphatic flow abnormality (Fig. 4). In the patient with a history of cirrhosis, the TD was not visualized until 3.5 min following injection.

Image quality for visualization of the periportal lymphatics was good for both readers in five of the six cases. In the single case where an inguinal intranodal DCMRL was performed just prior to the IH-DCMRL, the visualization was moderate. In the four cases with PLE, visualization of the lymphatic perfusion of the duodenum was good. Visualization of the TD was good in four cases with the TD not visualized in one case post TD embolization and only partially visualized in another case. Venous contamination with enhancement of the middle hepatic vein was present in two cases. No biliary contamination was seen. In all cases, there was pericholecystic lymphatic perfusion without evidence of gallbladder wall thickening. There were no short-term complications.

Table 2 Summary of characteristics and findings in patients undergoing intrahepatic dynamic contrast MR lymphangiography (IH-DCMRL)

	Age (years)	Clinical presentation	Oral contrast (Y/N)	Visualization of the thoracic duct (Y/N)	Lymphatic perfusion of the duodenum (Y/N)	Lymphatic leak into the peritoneal cavity (Y/N)	Endoscopy confirmation of lymphatic spillage into the duodenum	Short-term complications (Y/N)
1	14	Fontan-associated PLE	N	Y	Y	N	Y	N
2	15	Non-Fontan-associated PLE	Y	N, previously embolized	Y	N	Y	N
3	22	Fontan-associated PLE	N	Y	Y	N	Not performed	N
4	1.2	Congenital chylous ascites	N	Y	N	Y	Not performed	N
5	27	Non-Fontan-associated PLE	Y	Y	Y	N	Y	N
6	11	Ascites secondary to liver cirrhosis	N	Y	N	N	Not performed	N

PLE protein-losing enteropathy, *Y* yes, *N* no

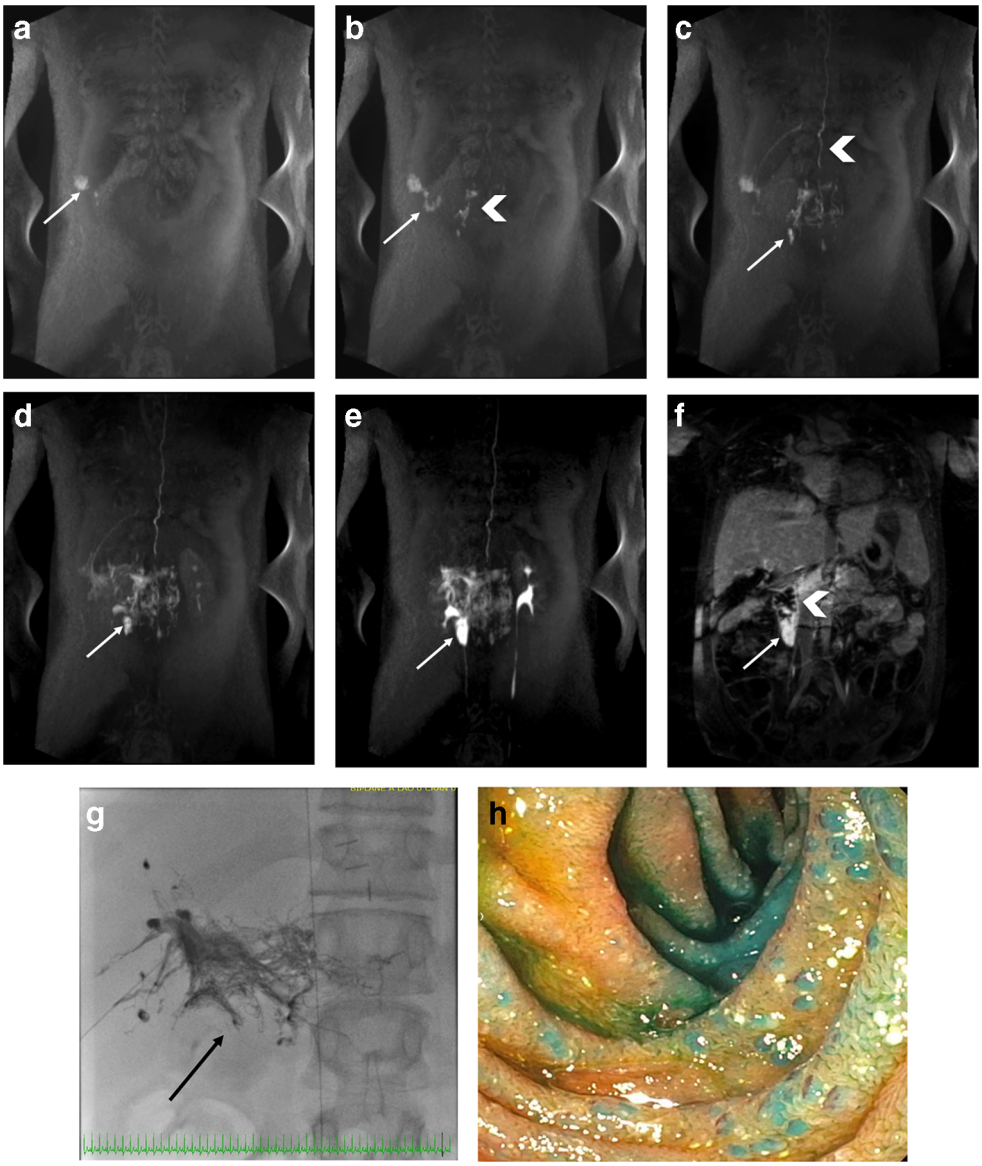

Fig. 1 A 22-year-old female with a history of hypoplastic left heart syndrome post Fontan palliation who presents with protein-losing enteropathy (PLE). **a**–**f** Time series of intrahepatic dynamic contrast magnetic resonance lymphangiography (IH-DCMRL) showing coronal maximum intensity projections of the abdomen and chest. **a** At the time of the start of injection ($t = 0$) showing the site of injection (arrow). **b** At 2 min after injection demonstrating contrast moving along the hepatic lymphatic system (arrow) and exiting into the hepatic hilum (arrowhead). **c** At 3 min after injection showing contrast beginning to leak into the duodenum (arrow) and opacifying the thoracic duct (TD) (arrowhead). **d** At 4.5 min after injection demonstrating further filling of the duodenum and hilar lymphatic channels (arrow). **e** At 8.5 min after injection where there is complete filling of the first portion of the duodenum (arrow) as well as hepatic, hilar, retroperitoneal lymphatics, and the TD. **f** A more delayed coronal image obtained 12 min after injection shows enhancement of the duodenal wall (arrowhead) and filling of the duodenal lumen with contrast. **g** Oblique image from a conventional hepatic lymphangiography performed 1 h after the IH-DCMRL demonstrates opacification of the hepatic lymphatics and hepatoduodenal connections (arrow) but no visualization of the TD or leak into the duodenal lumen. **h** Confirmation of the MRI findings was demonstrated by intrahepatic injection of blue dye with endoscopy showing a leak into the duodenal lumen

Discussion

The liver lymphatic system is a major contributor to central lymphatic flow especially in patients with elevated central venous pressure such as in heart failure patients. A better understanding of liver lymphatic flow is needed to better understand the role of the liver lymphatic system in certain disease processes such as PLE. In this manuscript, we describe our initial experience with IH-DCMRL. This is a new imaging modality for liver lymphatic anatomy and flow that has several potential advantages over conventional liver lymphangiography. The technique is 3D, offers good tissue contrast to adjacent anatomical structures, has good distal contrast distribution, and does not use ionizing radiation during lymphangiography. When dilated, the intrahepatic

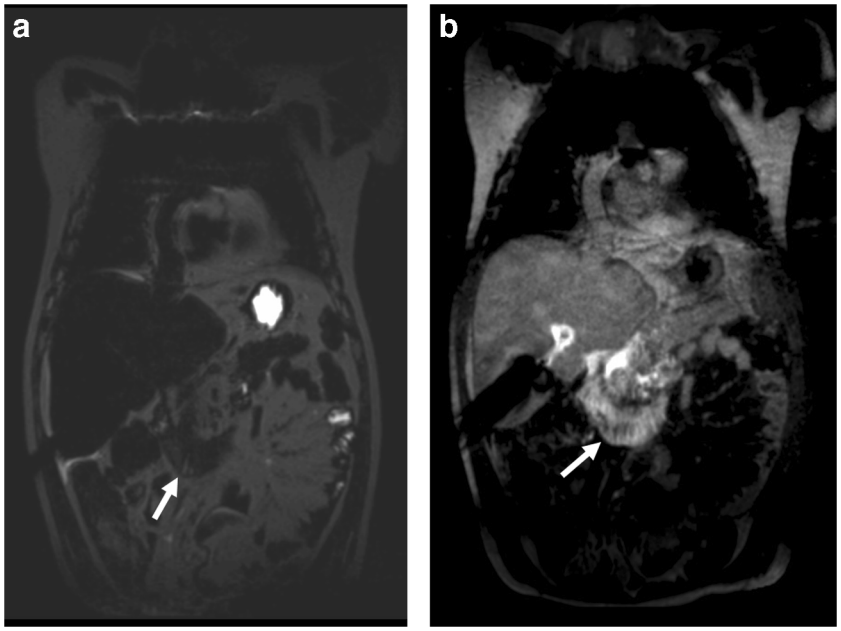

Fig. 2 A 14-year-old male with a history of hypoplastic left heart syndrome post Fontan palliation who presents with protein-losing enteropathy (PLE). **a** Coronal plane of T2-weighted imaging of the abdomen and chest in a patient with PLE showing the duodenum (arrow) with minimal fluid and no significant T2 signal. **b** In a coronal plane at the same location as **a**, a high-resolution contrast-enhanced T1 sequence shows enhancement of the duodenum (arrow) consistent with PLE

lymphatics could be visualized with T2-weighted imaging as hyperintense signal or CT as hypoattenuation, but the drainage of the hepatic lymphatics could only be visualized with conventional lymphangiography [1, 2, 5]. In this study, leak of contrast into the duodenal lumen in patients with PLE was only visualized by IH-DCMRL and not seen in patients by intranodal DCMRL. Additionally, in two patients with intranodal imaging, IH-DCMRL was able to demonstrate the abnormality which was not visualized by intranodal DCMRL. Normally, the liver lymphatic system will not be opacified via intranodal DCMRL. In our patients with ascites, one of which was congenital and the other was acquired, IH-DCMRL was able to also assess the mesenteric lymphatic channels.

Our protocol involves both dynamic time-resolved imaging and a static respiratory-navigated 3D IR T1 gradient echo sequence. The dynamic imaging is essential in following the time course and distribution of lymphatic flow from the liver and is performed by sampling central *k*-space in order to

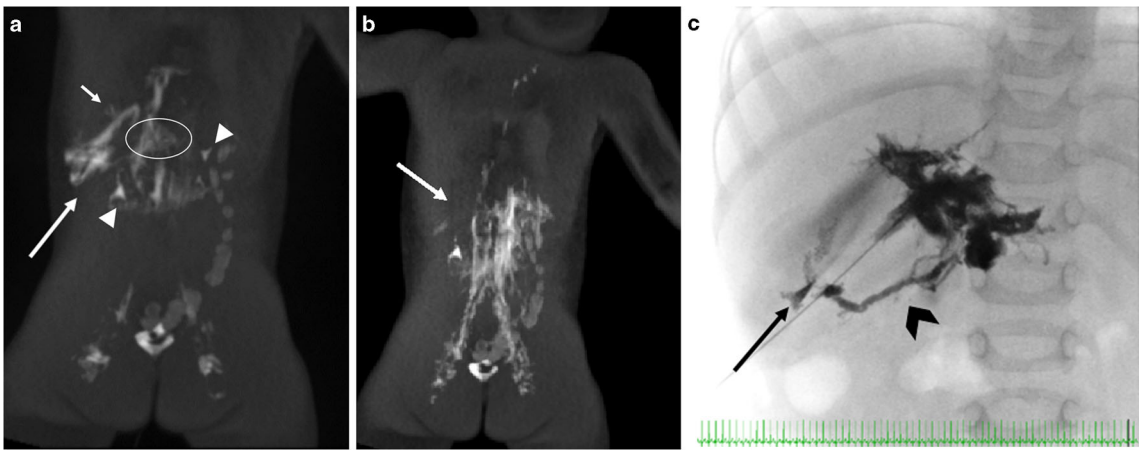

Fig. 3 A 14-month-old female with a history of congenital chylous ascites. **a** Coronal maximum intensity projection (MIP) image of intrahepatic dynamic contrast magnetic resonance lymphangiography (IH-DCMRL) demonstrating a leak of contrast into the peritoneum (long arrow). Also seen is a branch of the intrahepatic lymphatics (short arrow) and the retroperitoneal lymphatics (circle). There is filling of the renal collecting system (arrowheads) by excreted contrast confirming that there is a connection between the lymphatic and venous systems. Contrast overlying the right and left groin is from earlier intranodal dynamic contrast MR lymphangiography. **b** Coronal MIP image of intranodal DCMRL demonstrating the central lymphatic system without demonstrating the leak (arrow). **c** Frontal image from a conventional intrahepatic lymphangiogram demonstrates a dilated lymphatic duct exiting the liver (arrowhead) and leakage of lymphatic contrast into the peritoneum within the right upper quadrant of the abdomen (arrow) confirming the MRI finding

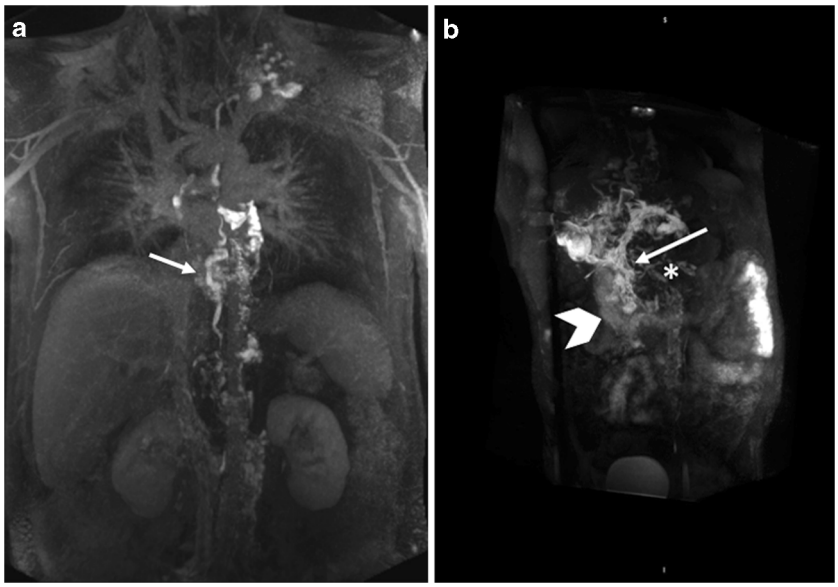

Fig. 4 A 27-year-old male with a history of KRAS mutation and a neurofibromatosis-like syndrome who presents with multiple neurogenic paraspinal masses. **a** Coronal MIP of intranodal lymphangiogram demonstrating tortuous dilated central lymphatic ducts (arrow) without flow towards the duodenum. **b** Coronal MIP of an intrahepatic dynamic contrast magnetic resonance lymphangiography (IH-DCMRL) demonstrating hepatoduodenal connections (arrow) surrounding a mass (asterisk) and leakage into the duodenal lumen (arrowhead) with forward flow of contrast into multiple distal bowel loops

obtain more contrast and allow for rapid acquisition [6]. This sequence provides more limited spatial resolution particularly since we perform it without breath-holding. The high-resolution respiratory-navigated 3D IR T1 gradient echo sequence is a complement to the dynamic sequence as it does not provide the temporal resolution but provides higher spatial resolution particularly given the respiratory navigation.

During this retrospective evaluation, there were no short-term complications. However, with penetration of the skin and liver parenchyma, there may be associated complications. Complication rates of percutaneous biopsy of the liver is reported to be 0.2%, but biopsy needles are much larger than the 25-gauge needles we used so complication rates could be lower [7]. Further studies are needed to determine if this is the case. Additionally, there is a risk of contamination of the biliary system or venous system potentially causing false positives. In two cases, there was contamination of a hepatic vein which was easily distinguished from the lymphatics. No biliary tree contamination was seen, and there were no short-term complications.

The contrast dose used in this study (0.1–0.2 mmol/kg) of undiluted gadobutrol is the standard dose used in our institution for DCMRL as well as other contrast studies such as cardiac imaging. It is possible that lower diluted doses of contrast could also be used but further studies would need to be conducted to determine whether lower contrast doses will result in the same imaging outcome.

The main limitation of this study is that it is a retrospective review of a small number of patients undergoing IH-DCMRL. Given the selection bias in patients chosen, we cannot make any conclusions about the safety and efficacy of this technique.

In conclusion, this study is an initial description of the technique and our initial experience with IH-DCMRL for evaluation of the liver lymphatics. This is a cross-sectional technique to evaluate liver lymphatic flow and can be helpful for assessment of certain conditions involving abnormal liver lymphatic flow, such as PLE. Further studies should be conducted to evaluate the safety and utility of this technique.

Funding The authors state that this work has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Yoav Dori.

Conflict of interest The authors declare that they have no conflict of interest.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional review board approval was obtained.

Methodology
- retrospective
- observational
- performed at one institution

References

1. Itkin M, Piccoli DA, Nadolski G et al (2017) Protein-losing enteropathy in patients with congenital heart disease. J Am Coll Cardiol 69: 2929–2937. https://doi.org/10.1016/j.jacc.2017.04.023
2. Guez D, Nadolski GJ, Pukenas BA, Itkin M (2014) Transhepatic lymphatic embolization of intractable hepatic lymphorrhea. J Vasc Interv Radiol 25:149–150. https://doi.org/10.1016/j.jvir.2013.09.002
3. Dori Y (2016) Novel lymphatic imaging techniques. Tech Vasc Interv Radiol 19:255–261. https://doi.org/10.1053/j.tvir.2016.10.002
4. Matsumoto S, Mori H, Tada I (2000) Successful demonstration of post-operative lymphatic fistula by percutaneous transhepatic lymphography. Clin Radiol 55:485–486. https://doi.org/10.1053/crad.2000.0123
5. Pupulim LF, Vilgrain V, Ronot M et al (2015) Hepatic lymphatics: anatomy and related diseases. Abdom Imaging 40:1997–2011. https://doi.org/10.1007/s00261-015-0350-y
6. Herrmann KH, Baltzer PA, Dietzel M et al (2011) Resolving arterial phase and temporal enhancement characteristics in DCE MRM at high spatial resolution with TWIST acquisition. J Magn Reson Imaging 34:973–982. https://doi.org/10.1002/jmri.22689
7. Piccinino F, Sagnelli E, Pasquale G et al (1986) Complications following percutaneous liver biopsy. A multicentre retrospective study on 68,276 biopsies. J Hepatol 2:165–173. https://doi.org/10.1016/S0168-8278(86)80075-7