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Lymphatic Intervention, the Frontline of Modern Lymphatic Medicine: Part I. History, Anatomy, Physiology, and Diagnostic Imaging of the Lymphatic System

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Recent advances in lymphatic imaging have provided novel insights into the lymphatic system. Interventional radiology has played a significant role in the development of lymphatic imaging techniques and modalities. Radiologists should be familiar with the basic physiology and anatomy of the lymphatic system to understand the imaging features of lymphatic disorders, which reflect their pathophysiology. This study comprehensively reviews the physiological and anatomical aspects of the human lymphatic system as well as the latest lymphatic imaging techniques.

Keywords: *Lymph; Lymphatic; Intervention; Lymphangiography; Radiology*

INTRODUCTION

Despite being functionally integrated into the circulatory system, the lymphatic system has historically received less attention than its arterial or venous counterparts. A milestone in lymphatic imaging was pedal lymphangiography, which was first described by Kinmonth in 1952 [1]. This was followed by the development of intranodal lymphangiography, which has gained popularity among radiologists because of its technical ease. Dynamic contrast-enhanced MR lymphangiography is a novel imaging modality that utilizes the intranodal injection technique to administer gadolinium contrast media. Thus, this modality may play a significant role in the diagnosis of lymphatic disorders. Such advances in radiological imaging would not have been possible without an understanding of the lymphatic system's anatomy and physiology. This article reviews the basic anatomy and physiology of the lymphatic system, as well as the technical details, indications, and clinical applications of lymphatic imaging.

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Physiology and Anatomy

Plasma, Interstitial Fluid, and Lymphatic Fluid

The primary role of the cardiovascular system is to distribute oxygen and nutrients to the peripheral tissues. Once oxygenated blood from the heart reaches the capillaries, the fluid and low-molecular components of plasma traverse the capillary walls to form interstitial fluid [2]. According to Starling's model, fluid movement across the capillary wall is governed by the balance between hydrostatic and oncotic pressure gradients (primarily defined by the presence of albumin) in the capillary and interstitial tissues. In this model, plasma fluid and small molecular components on the arterial side of the capillaries (where hydrostatic pressure is higher) are filtered outwards to form interstitial fluid and are reabsorbed into the circulation on the venous side. Traditionally, only a small portion of this interstitial fluid was believed to remain during this process [3]. However, this hypothesis has been challenged in recent years after fluid resorption on the venous side of

capillaries was identified as only occurring in exceptional circumstances. Contrary to earlier beliefs, growing evidence suggests the lymphatic system plays a significant role in returning a large amount of interstitial fluid to the systemic circulation [4]. The lymphatic system is now believed to serve as a major route through which 8–12 L of interstitial fluid produced daily is returned to systemic circulation.

Anatomy

Lymphatic capillaries converge to form a complex network of lymphatic vessels distributed along the course of major blood vessels. Numerous lymph nodes are found in this network. Lymph in the soft tissue, mesentery, and organs, such as the liver, drain into the central lymphatic system, otherwise known as central conducting lymphatics [5]. Lymphatic fluid from the peripheral soft tissues of the lower extremities flows into the lumbar trunks, which converge to form the cisterna chyli situated between the levels of the T12 and L2 vertebrae. The cisterna chyli is the largest lymphatic structure in the human body, with an average of 6.7 mm in diameter and a length of 1–2 cm. However, many anatomical variations are observed in its size and shape. Lymph from the mesentery and liver also flows into the cisterna chyli. The thoracic duct starts at the cisterna chyli and courses cranially through the diaphragmatic crus between the aorta and azygous vein. It continues posteriorly to the pericardium and esophagus and courses along the right side of the thoracic aorta until it crosses behind the aorta, to its left side at the level of the T5 vertebra. The thoracic duct courses further left behind the left common carotid artery, after which it turns downwards at the level of the C7 vertebra to join the confluence of the left internal jugular and subclavian veins. Numerous bicuspid valves are located in the distal thoracic duct, which prevent the reflux of blood from the central venous system. Meanwhile, lymphatic fluid from the right side of the head and neck, upper limbs, and right thoracic cage, as well as most of the lymphatic fluid from both lungs flows into a separate right lymphatic duct, which in turn drains into the central venous system between the right internal jugular and subclavian veins (Fig. 1) [6,7].

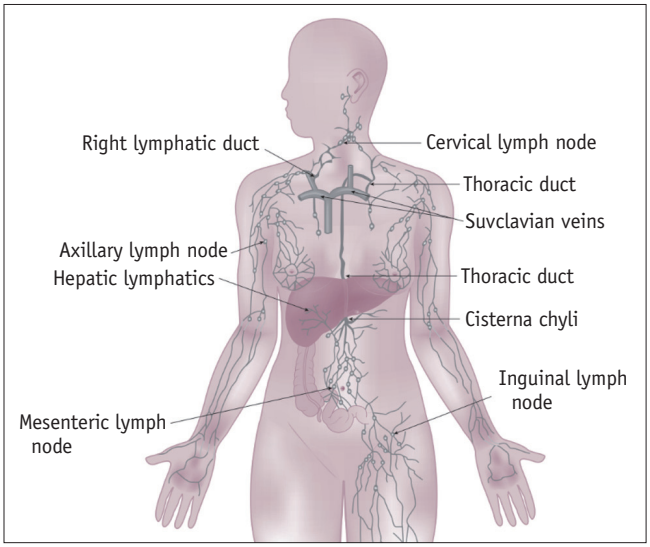

Fig. 1. A schematic diagram of the human lymphatic system. Lymphatic fluid from the peripheral soft tissues of the lower extremities flows into lymphatic vessels of the lumbar trunk and converges with lymph from the mesentery and liver to form the cisterna chyli. Meanwhile, lymphatic fluid from the right side of the head and neck, upper limbs, right thoracic cage, and most of the lymph from both lungs flows into a separate right lymphatic duct. Reprinted from Hur et al. Ilchokak; 2022. p.543, with permission of Korean Society of Inverventional Radiology [6].

Lymph Nodes

The human body possesses approximately 450 lymph nodes. The peripheral lymphatic vessels converge to form collective lymphatic ducts, each connected to at least one lymph node. A single lymph node may contain numerous afferent ducts, resulting in a complex network of lymphatic channels. Inside the lymph node, lymph from the afferent duct passes through the subcapsular sinus, follicles (or superficial cortex), deep cortical unit (or deep cortex), medullary sinus, and hilum. Eventually, it exits the lymph node through the efferent duct (Fig. 2) [7]. During this process, foreign antigens and pathogens are filtered and exposed to immunocytes, triggering the body's immune response. Meanwhile, the lymph nodes receive their blood supply through blood vessels in the hilum, distributed throughout the medulla. Up to 4 L of lymphatic fluid is purportedly shunted through lymphovenous connections within the lymph nodes [8]. Lymphovenous connections may become evident during intranodal injection of contrast medium during lymphangiography. Excessive shunting of the contrast media into the systemic vein during intranodal lymphangiography reportedly results from needle placement in the medullary vein.

Mesenteric Lymphatics

The anatomy of the mesenteric lymphatics starts at the lymphatic capillary (termed "lacteal"), situated in the small intestinal villi. Lymph from the lacteal courses through the submucosal lymphatic network and drains into the

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Korean Journal of Radiology
KJR

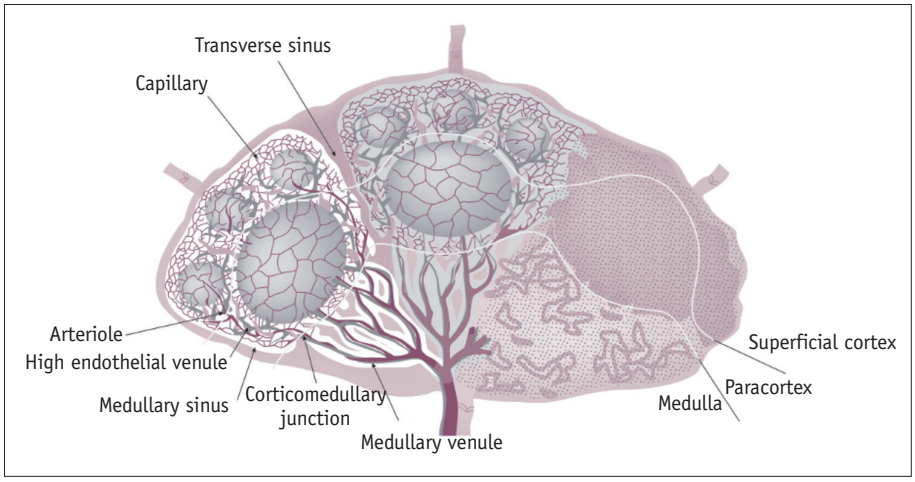

Fig. 2. A schematic diagram of a lymph node. Lymph from the afferent duct passes through the subcapsular sinus, follicles (or superficial cortex), deep cortical unit (or deep cortex), medullary sinus, and hilum, and eventually exits the lymph node through the efferent duct. Reprinted from Hur et al. Ilchokak; 2022. p.543, with permission of Korean Society of Inverventional Radiology [6].

mesenteric collecting lymphatics, interconnected with numerous mesenteric lymph nodes. Thereon, mesenteric lymph flows through the intestinal trunks to reach the cisterna chyli or through other communications with the retroperitoneal lymphatic network. The mesenteric lymphatic system participates in lipid absorption in the intestinal tract. Ingested lipids are hydrolyzed into fatty acids and monoglycerides, which are resorbed by enterocytes. While short- and medium-chain fatty acids are primarily absorbed through the portal vein, long-chain fatty acids are re-esterified inside the enterocytes to form triglycerides that are packaged with lipoproteins, cholesterol, and other lipids to form chylomicrons. Chylomicrons are exocytosed from the enterocytes to enter the mesenteric lymphatic stream. Chylomicrons are the reason for the characteristic "milky" color of lymphatic fluid, known as chyle. The chyle comprises up to 40% of the body's lymph. However, its amount varies significantly according to diet. Chylous ascites usually results from lymphatic leakage occurring either in the mesenteric lymphatics or in the central conducting lymphatics at or above the confluence of mesenteric lymphatic inflow.

Liver Lymphatics

The liver is the predominant source of lymph, contributing up to 50% of the lymph flow in the thoracic duct [9]. Lymph production begins in the hepatic lobule, the smallest functional unit in the liver. Inside the lobule are sinusoids lined with fenestrated endothelia that allow free passage of plasma fluid from the sinusoid into the Space of Disse between hepatocytes and sinusoids. The lymph then flows into the lymphatic plexus around the portal tract and drains along the porta hepatis, passing through the lymph nodes around the hepatic artery and the celiac trunk. This pathway constitutes deep lymphatic drainage of the liver, which ultimately joins the central conducting lymphatics at the cisterna chyli [10]. Superficial lymphatic drainage also occurs at the surface of the liver beneath the capsule. However, its contribution to lymphatic clearance from the liver is smaller than that of the deep lymphatic pathway unless drainage through the latter is hindered.

Imaging of the Lymphatic System

Conventional Imaging Modalities

The role of cross-sectional modalities, such as CT, MRI, and ultrasound, is limited owing to the small size and inconsistent anatomy of the lymphatic network. the thoracic duct is not always distinguishable from the adjacent vessels and surrounding structures. Therefore, the application of such modalities has been restricted to the identification of lymphoceles, lymphatic malformations, and lymph nodes [11].

Heavily T2-Weighted MR Lymphangiography

The cisterna chyli and thoracic duct can be identified on heavily T2-weighted MR sequences. The sequence is similar to that used in MR cholangiography, in which static or slow-flowing lymph appears bright, whereas the signal from flowing blood is suppressed. Ideally, images should be acquired with a slice thickness of less than 2 mm and

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overlapping sections, considering the small caliber of the lymphatic ducts. Respiratory gating helps reduce motion artifacts related to breathing. Fasting reduces lymph flow and may cause the collapse of central lymphatic structures, making their identification even more difficult. Meanwhile, feeding the subject a fatty meal 30–60 minutes before the examination may help acquire better images [12,13]. A major advantage of the heavily T2-weighted sequence over the contrast-enhanced T1-weighted sequence is that it demonstrates lymphatic structures or lymph collections that lie outside the path of the contrast medium used in the latter sequence. However, this sequence lacks specificity, which may lead to misinterpretation of other fluid-filled structures, such as lymphatic ducts or vice versa. Another drawback is the lack of information regarding the direction of the lymphatic flow.

Nuclear Lymphoscintigraphy

Nuclear lymphoscintigraphy is a traditional modality for assessing lymphatic flow and lymph node mapping. The mechanism is based on the physiology of colloidal agents, which, after intradermal injection, enter the peripheral lymphatic channels together with interstitial fluid. When combined with radiotracers that emit gamma rays, the movement of these agents can be detected using a gamma camera. One commonly used agent is Tc-99m filtered sulfur colloid (> 50 nm), which is usually injected intradermally into the web space between the toes. Sequential or continuous images are acquired immediately after injection. Delayed images may be obtained from 1 to 3 hours or even longer following injection, depending on the purpose of the study [14]. The radiation dose is relatively low, and there are no known risks. Lymphoscintigraphy has maintained its position as the primary imaging modality in the clinical setting of lymphedema. Despite its ability to provide information on flow dynamics, lymphoscintigraphy is limited by its low resolution and the lack of anatomical information. SPECT/CT may compensate for these limitations.

Pedal Lymphangiography

The original technique described by Kinmonth in 1952 [1] starts with an injection of dye (usually approximately 0.5 mL), such as isosulfan blue 1%, into the subcutaneous layer of one or more toe web spaces [1,15]. Once the lymphatic channels became visible in the dorsum of the foot, a small incision is made in the skin, and the lymphatic channel is carefully dissected from the surrounding tissue. The lymphatic channel is cannulated with a 30-gauge needle, and a silk suture is tied around the needle and cannulated to secure the needle in place. An automated injector filled with Lipiodol (Guerbet) was then connected to the needle and set to the following injection protocol: injection rate, 8–12 mL/hour; total injection volume, 10 mL per extremity; and pressure, 150 psi [14]. A low injection speed should be maintained to prevent rupture of the lymphatic channel, which can result from forceful injection. The injection site and slow injection rate are significant drawbacks of pedal lymphangiography because Lipiodol takes several hours to ascend into the central conducting lymphatics. For this reason, pedal lymphangiography has recently been replaced with intranodal lymphangiography. However, pedal lymphangiography retains its value in the management of infrainguinal lymphatic leaks.

Ultrasound-Guided Intranodal Lymphangiography

Ultrasound-guided intranodal lymphangiography was first described in 2011 as a more recent and significant development in lymphatic intervention [16]. The technique involves needle placement in the inguinal lymph nodes using ultrasound guidance, followed by the injection of contrast media. Intranodal lymphangiography addresses the main drawbacks of pedal lymphangiography and has now completely replaced the older technique. Since the introduction of intranodal lymphangiography, many institutions have seen significant growth in the demand for lymphatic procedures. Intriguingly, even before the application of ultrasound in medicine, documentation existed on intranodal Lipiodol injection (named "lymphadenography" at the time) describing percutaneous needle access into large, palpable lymph nodes, such as those found in lymphoma. Given the developments in ultrasound-guided procedures, it took a surprisingly long time to develop the current intranodal lymphangiography technique [17,18]. The method is relatively simple, and requires the ability to puncture a lymph node under ultrasound guidance, awareness of the equipment required for the procedure, and a few straightforward technical steps.

Indication

The procedure is indicated for the assessment of patients with leakage of lymphatic fluid (chylothorax or chylous ascites), which may be iatrogenic or related to underlying pathology affecting the lymphatic system;

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Korean Journal of Radiology
KJR

assessment of patients with primary lymphatic disorders to outline the anatomy of the central lymphatic system; and a preliminary step to guide minimally invasive (interventional radiological) or surgical intervention of the lymphatic system. Several studies have demonstrated the therapeutic benefit of Lipiodol lymphangiography in patients with lymphatic leakage. This effect is attributed to an inflammatory reaction induced by Lipiodol at the site of leakage after aqueous hydrolysis and saponification of the surrounding fat tissue. In a study of 43 patients with lymphatic leaks, Lipiodol lymphangiography was therapeutic in stopping the leakage in up to 70% of patients with < 500 mL of lymphatic fluid drainage per day and in up to 35% of patients with drainage of > 500 mL of fluid per day. The overall therapeutic success rate of Lipiodol lymphangiography, regardless of the leakage volume, was 51% [19].

Equipment

Fine needle: 21–26 gauge; plastic component must be Lipiodol-compatible.

Lipiodol: 10–20 mL in total

Lipiodol-compatible syringe with Lipiodol-compatible connecting tubing or pressure insufflator

Ultrasound: linear transducer 7.5 MHz or more

Local anesthesia

Procedure

The target lymph nodes should be identified in the inguinal or femoral regions. Any lymph node can be targeted; larger lymph nodes are easier to puncture. Nodes should be targeted in the longitudinal plane. Ideally, when identifying a node, the target node should be away from the groin crease to enable easy access and secure fixation of the needle with dressings after puncture. Additionally, if possible, a node with an easily identifiable cortex and medulla should be selected.

Once the lymph node has been identified, it should be punctured via a shallow trajectory. The target lymph nodes are invariably superficial; thus, a long, shallow track is important to facilitate a stable needle position with support from the surrounding soft tissues. This approach also enables securing the needle to the patient's thigh with adhesive without displacing the needle once it is in position.

The use of a needle with a sharp bevel is helpful for puncturing lymph nodes. Despite local anesthesia, most patients experience transgression of the lymph node with a needle, and it may be worth warning them about this. After penetrating the lymph node capsule, the target zone for needle placement is the corticomedullary junction of the lymph node.

Once the needle is in position, a small amount of Lipiodol is injected under fluoroscopy. Initially, a small focal pooling of contrast can be seen with filling of the medullary sinus with contrast. This should be followed by a characteristic beaded appearance with small globules of Lipiodol traveling cranially if the needle is correctly positioned. If the needle is not correctly positioned, extravasation of contrast medium in the soft tissues around the node can be observed. Occasionally, venous or arterial filling can also be identified, and if this occurs, repositioning may be required to obtain a more favorable position.

Given the viscous nature of Lipiodol, warming it prior to injection may be beneficial. This can be performed either in a contrast warmer or in a water bath. The warmed Lipiodol enables injection to be performed more easily. The injection rate should not exceed 0.5 mL/min, which equates to a total of 20 minutes to inject 10 mL of Lipiodol. A slow injection rate is important to avoid the rupture of the lymph node sinus. A pressure insufflator is useful for slow injection and comes with a connecting tube at the end of the insufflator syringe, thus enabling injection without moving the needle once it has been connected. Given the precarious nature of needle placement in small lymph nodes, care must be taken to ensure that the needle is not displaced when connecting the pressure insufflator or the connecting tubing. Additionally, during the procedure, the target node should be visualized either continuously, or when imaging the chest, occasional checks of the puncture site should be carried out with continued injection to ensure that the needle has not become displaced and that the lymph node has not ruptured.

Imaging Acquisition

Digital subtraction angiography is unnecessary. Images can be obtained using spot fluoroscopy views following the passage of contrast from the injection sites in the groins to the termination of the thoracic duct in the venous angle on the left side of the neck. Using collimation and fluoroscopy a low dose should be maintained in a potentially prolonged examination. Passage of contrast media is observed under fluoroscopy as it ascends from the inguinal nodes to the cisterna chyli and then into the thoracic duct to finally

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reach the termination of the thoracic duct at its confluence with the subclavian vein (Fig. 3). Pathological reflux of contrast media may be visualized during this process.

Complications

At the end of the procedure, most patients report minor discomfort at the injection site. This usually does not require any treatment or is managed well with simple analgesia. Potential complications of Lipiodol injection include allergic reactions to Lipiodol which are uncommon. Extravasation into the soft tissue is frequent, but has no adverse outcomes besides relatively short-lived discomfort at the inguinal extravasation site. The most concerning risk of the procedure is the risk of Lipiodol embolization to the pulmonary vasculature and intra-alveolar hemorrhage. Because of the potential risk of this occurrence, the procedure is contraindicated in patients with significant underlying respiratory disorders, as the occurrence of Lipiodol emboli could cause them to decompensate, as well as in those with a known right-to-left cardiac shunt due to the risk of cerebral embolization of any embolic material from the pulmonary arteries [19-21]. The risk of pulmonary embolization increases significantly when volumes greater than 20 mL of Lipiodol are utilized; hence, this is stated as

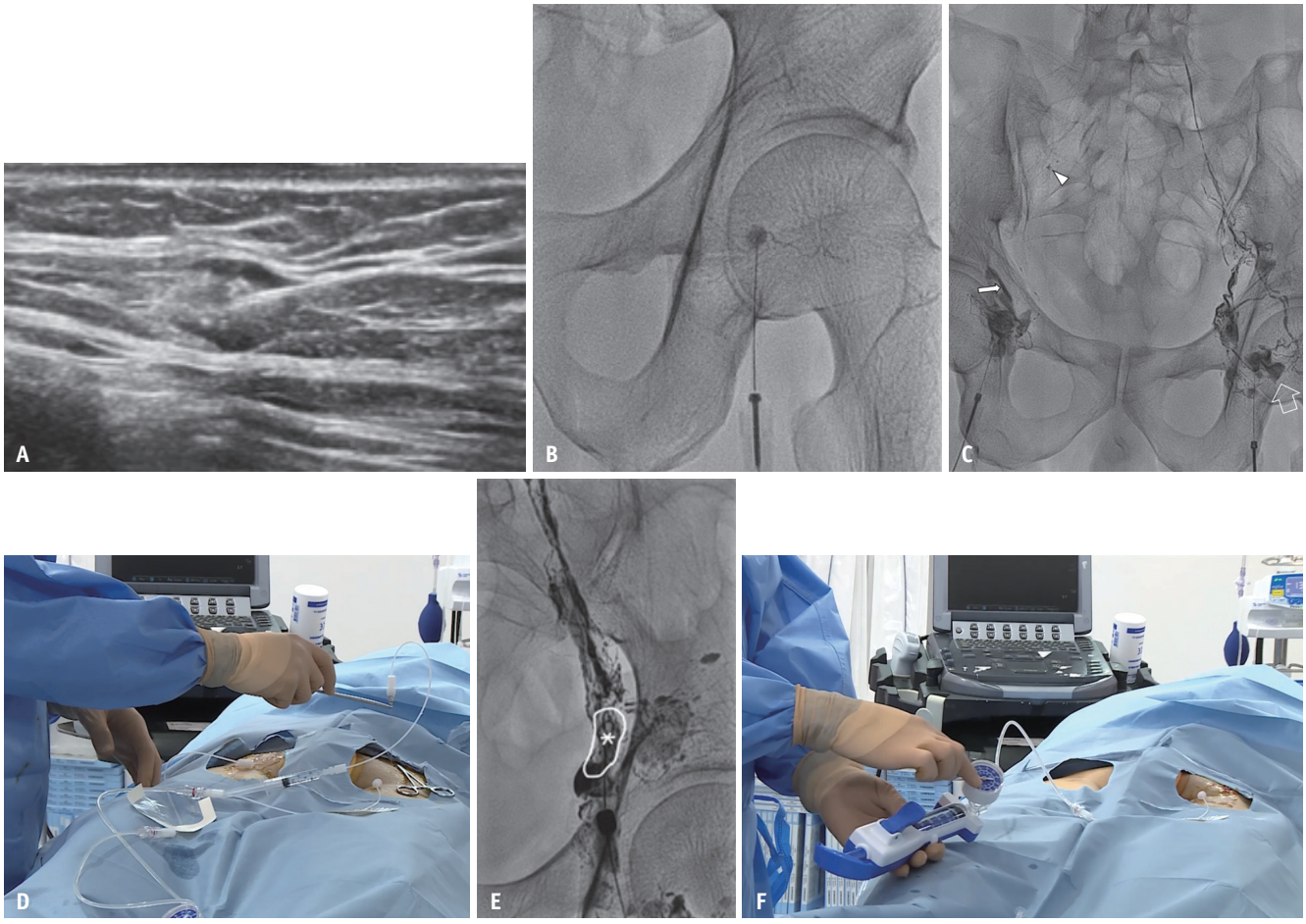

Fig. 3. A 46-year-old male with chylothorax after thymectomy and pleural metastectomy for thymoma.
A. Under ultrasound guidance, a fine needle is used to access the corticomedullary junction of an inguinal lymph node, where the medullary sinuses are mainly distributed. **B.** Reticular staining of the medullary sinus and flow of contrast media through efferent lymphatic vessels observed immediately after injection of contrast media. Lipiodol is preferred over water-soluble contrast media, especially when used to opacify the thoracic duct, because it does not dissipate from dilution. **C.** Left inguinal and iliac lymphatic channels of the lymph nodes and vessels are well-visualized. Pressure during injection caused by the viscosity of Lipiodol may result in minor extravasation at the injection site (open arrow). On the right side, Lipiodol droplets rapidly traverse the iliac vein (arrowhead) owing to a lymphovenous shunt within the lymph node. Perinodal extravasation of Lipiodol is also observed (arrow). Under such circumstances, the needle tip should be repositioned. **D, E.** A deep-seated iliac lymph node (asterisk) stained with contrast media can be accessed under fluoroscopic guidance using a longer needle. Iliac lymph nodes generally have better contrast medium conductance than that of inguinal lymph nodes. **F.** Lipiodol-compatible insufflator can be used for Lipiodol injection. Using the gauge on the insufflator device, consistent pressure can be applied during injection, with a lower likelihood of inadvertent, forceful injection.

https://doi.org/10.3348/kjr.2022.0688

Korean Journal of Radiology
KJR

the upper limit of the recommended injection volume [10].

Delayed Non-Contrast CT after Lipiodol Injection

An additional CT scan may help identify the site of contrast leakage and its relationship to anatomical structures, as well as to identify potential puncture sites for further intervention. If the site of leakage is in the inguinal or pelvic region, the procedure can be performed immediately. If the site of leakage is the abdomen or thorax, a CT scan can be performed 4–5 hours after the initial procedure [21-23].

Liver Lymphangiography

Liver lymphatics may be incidentally demonstrated during percutaneous procedures such as cholangiography [24]. Previously, liver lymphangiography was occasionally performed to determine the extent of nodal involvement in malignancies [25]. Liver lymphangiography was first described in 2000 as a means of diagnosing lymphatic leakage [26]. With its ability to demonstrate hepatic connections and provide information on the direction of flow, liver lymphangiography has since been used to diagnose various clinical conditions, ranging from postoperative hepatic lymphorrhea to protein-losing enteropathy [27].

To perform liver lymphangiography, a needle is directed to the hyperechoic band around the portal vein under ultrasound guidance. Water-soluble contrast media are slowly injected to opacify the liver lymphatics, which appear as thread-like channels directed toward the hepatic hilum. A similar technique may be used to inject gadolinium-based contrast agents into the liver lymphatics for intrahepatic MR lymphangiography [28]. The learning curve for liver lymphangiography is not too steep. The procedure is technically easier in the presence of periportal edema, which represents dilated periportal lymphatic ducts (Fig. 4). The lymphatic system in the liver is segmented and therefore composed of multiple draining routes. The site of injection determines which part of the liver lymphatic system is opacified, which may result in false-negative results [10].

Mesenteric Lymphangiography

Chylous ascites is a common manifestation of lymphatic leakage and may be attributed to chyle leakage from the mesenteric lymphatics. Owing to the direction of lymph flow, where lymph from the mesentery flows into the central conducting lymphatics, the mesenteric lymphatic system is a potential "blind spot" during pedal or intranodal lymphangiography. In the absence of pathological lymph reflux from the central conducting lymphatics to the mesentery, lymphatic leakage in the mesentery cannot be demonstrated using these techniques. Mesenteric lymphangiography was performed to expose this anatomical region for imaging and treatment. An animal study described the use of explorative laparotomy

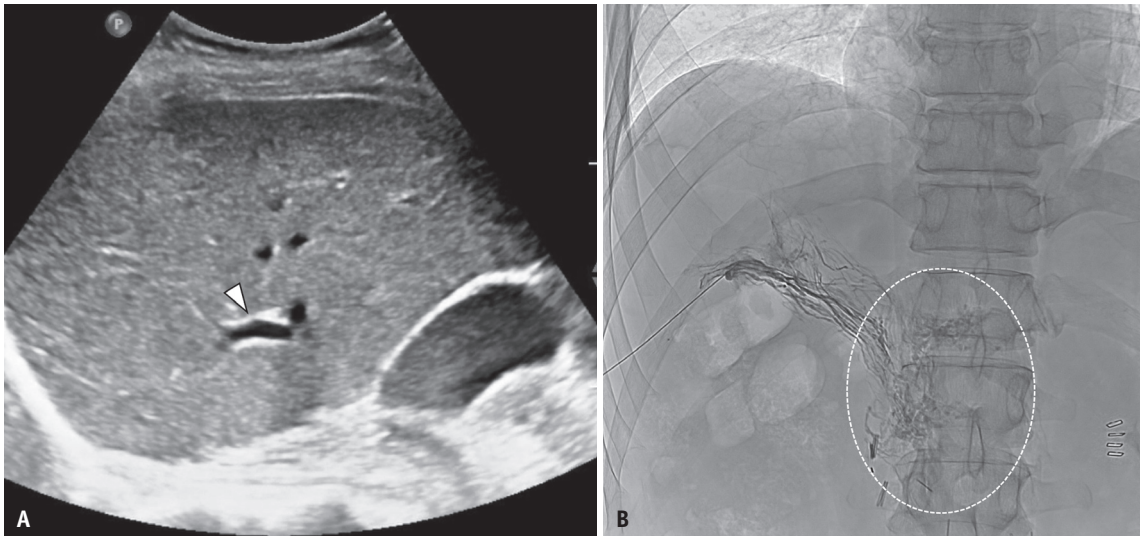

Fig. 4. A 60-year-old male with bladder cancer who developed chylous ascites following cystectomy with paraaortic and aortocaval lymph node dissection.
A. Periportal lymphatic vessels are distributed along the portal vein, appearing as a hyperechoic band around the portal vein on ultrasound (arrowhead). **B.** Liver lymphangiography reveals abundant lymphatic channels coursing toward the surgical field around the aorta (dashed circle).

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to locate mesenteric lymph nodes, which were then punctured for intranodal lymphangiography (Fig. 5). The clinical application of this technique in human subjects with chylous ascites was restricted by its invasiveness and the lack of scientific evidence on its safety and efficacy. Literature is limited to a series of case reports, including one from the 1970s and another that recently described the application of mesenteric lymphangiography through surgical exploration in a patient with recalcitrant chylous ascites [29,30].

Intranodal DCMRL

Intranodal dynamic contrast-enhanced MR lymphangiography (DCMRL) is performed using the intranodal lymphangiography technique described above, combined with MRI and gadolinium-based MR contrast media instead of Lipiodol. This technique was first described in 2014, leading to a revolution in lymphatic imaging. The ability to opacify the central lymphatic system while concurrently performing cross-sectional imaging has opened up a wide range of possibilities in terms of diagnostic and therapeutic options [31,32].

Equipment

A 21 gauge MRI-compatible fine needle
Syringe for contrast and connecting tubing
Gadolinium contrast – 5 mL per node
Ultrasound – linear transducer 7.5 MHz or more
Ultrasound contrast
Local anesthesia

Procedure

The initial steps of the procedure are identical to those of intranodal Lipiodol lymphangiography. Additionally, the procedure involves injecting MR contrast inside the MRI scanner; therefore, the needle placement should be carried out either in the MR scanner if there is an MR procedural suite; alternatively, it should ideally be carried out on an MR-compatible table in order to wheel the patient directly into the MRI scanner without requiring transfer of the patient. This minimizes the risk of needle displacement. If an MR table is used, the required coils should be placed under the patient before needle placement.

If there are no contraindications (e.g., severe lymphedema in any groin regions or absence of lymph nodes in the groin regions due to prior surgery), bilateral groin lymph nodes are targeted. Needle placement is more critical than in conventional intranodal lymphangiography. This is because once the scanning is commenced, there is usually no option to reposition the needles due to limitations of moving the patient into the scanner and time constraints. Therefore, when possible, more than two lymph nodes can be targeted to increase the chances of successful opacification of the lymphatic system, even if one or more needles are displaced.

Once the needle is in the lymph node, its placement cannot be confirmed fluoroscopically. The needle position was confirmed using ultrasound contrast [33]. A mixture of 2 mL of SonoVue (sulfur hexafluoride microbubbles) (Bracco SpA) and 1 mL of 1% Chirocaine (levobupivacaine) (Abbott Laboratories) was used. A small amount of the mixture is then injected. If the needle is appropriately placed, the contrast will only demonstrate enhancement of the node. If contrast extravasates outside the node, the needle placement is incorrect. The use of local anesthesia is important, as most patients find subsequent injection

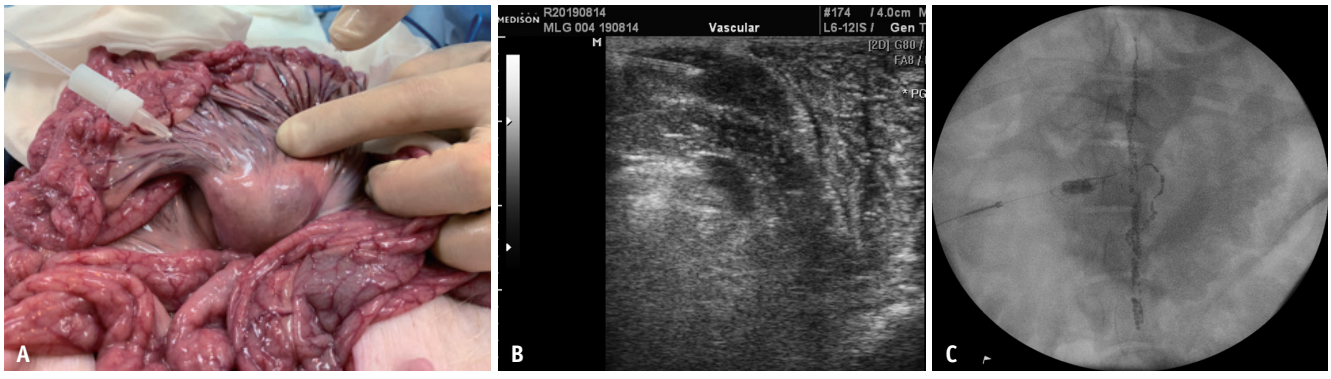

Fig. 5. A porcine model.
A. A mesenteric lymph node is exposed during explorative laparotomy. **B.** The mesenteric lymph node is accessed with a fine needle under ultrasound guidance. **C.** Mesenteric lymphangiography using Lipiodol shows the mesenteric lymphatic trunk, cisterna chyli, and thoracic duct.

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Korean Journal of Radiology
KJR

of gadolinium into the lymph node painful. The use of this mixture of local anesthetic and ultrasound contrast addresses the issues of confirmation of appropriate needle placement, as well as the analgesic component. If there is no access to ultrasound contrast, a small amount of saline can be injected. Once again, if the needle placement is correct, the node is seen to swell; whereas misplacement of the needle results in saline leakage around the node and into the perinodal space.

Once the needles are in place and appropriate placement is confirmed, they are secured with adhesives to the patient's thigh. The use of connecting tubing is advised, as injection of contrast when the patient is inside the MR scanner is difficult, as you will have to reach the scanner. The tubing should be primed with contrast. Once the needles and tubing are secured, the top of the coil is placed on the patient to ensure that they were not displaced. The table is then moved to the MRI scanner (Fig. 6) [5].

A phased array torso/anterior coil is placed, and baseline scans are acquired before intranodal contrast injection, usually consisting of T2-weighted fast spin echo and 3D gradient echo T1-weighted sequences in the axial and coronal planes [12,34-37]. Table 1 shows the protocol used at our institution. The purpose of a heavily T2-weighted non-contrast scan is to assess fluid (for example, soft tissue edema, ascites, and pleural or pericardial effusions) and to identify any lymphatic channels prior to injection of contrast. Once the non-contrast acquisition is complete, approximately 4–6 mL of contrast is injected into each needle over approximately 3–5 minutes. Any gadolinium-based contrast agent can be used, and its dose is equivalent to that of intravenous administration in widely used contrast-enhanced MR sequences. Although dilution of the contrast agent is not generally required, its dilution may help to visualize abnormalities near the injection site because high concentrations of gadolinium-based agents result in signal loss from the T2* effect.

Once the injection is commenced, fast T1 weighted coronal imaging is repeated continuously every 1–3 minutes and assessed while the contrast moves up the lymphatic system. Axial scans may be acquired once every 5–10 coronal scans to obtain information on cross-sectional anatomy. Once the contrast reaches the upper limit of the abdomen, the coil can be moved up to the thorax. If a neck-to-groin coil is utilized, imaging of the thorax and abdomen can be performed without moving the coil. Needles were removed at this stage. Scanning is continued until the contrast medium reaches the terminal thoracic duct. Patients presenting with lymphedema of the limbs or genital lymphedema may require delayed scans of the lower abdomen and pelvis. In this case, the coil is usually moved back down to re-image the abdomen to assess for delayed leakage of lymphatic fluid, after which the coil is moved to image the upper thighs and genital region to assess reflux or dermal backflow of lymphatic fluid.

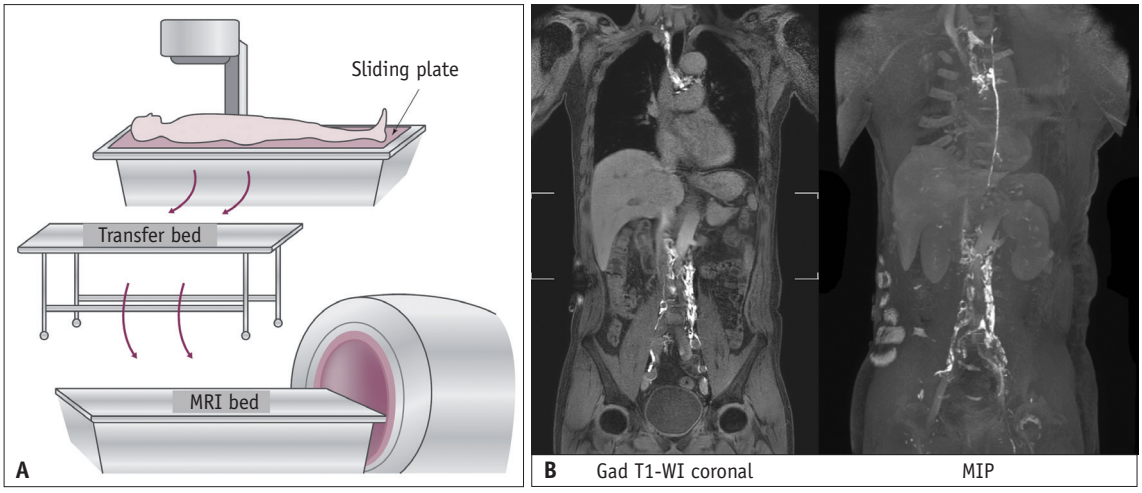

Fig. 6. Intranodal DCMRL.
A. An illustration of a patient being transferred from the angiography table to the MR scanner after inguinal lymph node access. The risk of needle dislodgement can be minimized by utilizing a sliding plate compatible with the angiography and MR equipment. **B.** MR lymphangiography provides anatomical and functional information on the central lymphatic system. Reprinted from Hur et al. Ilchokak; 2022. p.543, with permission of Korean Society of Inverventional Radiology [6]. DCMRL = dynamic contrast-enhanced MR lymphangiography, MIP = minimum intensity projection

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Table 1. Dynamic Contrast-Enhanced MR Lymphangiography Protocol

No.	Sequence	Plane	TR/TE (ms)	Flip angle (°)	Matrix	Slice Thickness (mm)	ETL	Band-Width	Time (sec)
1	T2WI BLADE TSE with FS	Axial	4700/101	140	320 x 320	5	25	260	180
2	3D GRE T1WI (Radial VIBE) with FS	Axial	3.7/1.8	11	280 x 280	3	1	501	180
3	3D GRE T1WI (VIBE) with FS	Coronal	3.4/1.3	30	360 x 360	1	1	504	40
	GBCM 7.5 cc in lymph node on each side of the groin, slowly hand injected (approximately 0.5–1 mL/min)								
4	3D GRE T1WI (VIBE) with FS every minute	Coronal	3.4/1.3	30	360 x 360	1	1	504	40
5	Post-contrast 3D GRE T1WI (Radial VIBE) with FS	Axial	3.7/1.8	11	280 x 280	3	1	501	180
6	3D respiratory gating SPACE T2WI with FS	Coronal	3572/306	150	384 x 384	1	119	200	900

A pre-contrast image is acquired and used for comparison. Thereafter, images are obtained every minute from the commencement of contrast material injection, until ten times. The dynamic coronal images are reformatted using maximum intensity projection. Sequences 4 and 5 were repeated up to three times. If the radiologist wished to confirm other collateral channels, additional SPACE T2WI coronal images were obtained in only two patients. BLADE = T2WI radial k-space sampling MRI pulse sequence, ETL = echo train length, FS = fat saturation, FSE = fast spin-echo, GBCM = gadolinium-based contrast medium, GRE = gradient echo, SPACE = sampling perfection with application optimized contrasts, TE = echo time, TR = repetition time, TSE = turbo spin echo, T1WI = T1 weighted image, T2WI = T2 weighted image, VIBE = T1WI volumetric interpolated breath-hold sequence, 3D = three-dimensional

Complications

Intranodal DCMRL is more likely to result in a non-diagnostic study, given the precarious position of the needles within very small lymph nodes and the inability to reposition them in the same way as in a fluoroscopic study. However, other than the rare likelihood of contrast allergy, it is a safe procedure.

Contraindications

Contraindications include contraindications for MRI, gadolinium allergy, and severe claustrophobia.

Pedal Interstitial DCMRL

Interstitial pedal DCMRL relies on the same technique as intranodal DCMRL, except that gadolinium contrast is injected into the web spaces between toes. However, this requires far less experience and training than lymph node targeting. This technique is identical to that traditionally used to inject radiotracers. Historically, this was primarily utilized for the assessment of lymph node metastasis and the lymphatic system of the lower extremities [38,39]. The main indications for use are the assessment of patients with refractory lymphatic leakage, but can also be utilized for assessment of the central lymphatic system in patients with primary lymphedema (Fig. 7) [40].

The injected mixture at the author's institution comprises a dilution of 0.2 mL of gadolinium-based contrast Dotarem (gadoterate meglumine) (Guerbet), 1.8 mL of 1% lidocaine and 8.8 mL of sodium chloride made up to 10 mL in total. This mixture is then mixed, and eight 1 mL syringes of this

Fig. 7. Pedal interstitial DCMRL.
A. A picture of a foot showing the dermal injection sites for MR contrast agent. **B.** Patient with unilateral lymphedema. Lymphatic channels in the legs are demonstrated with some venous contamination. DCMRL = dynamic contrast-enhanced MR lymphangiography

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Korean Journal of Radiology
KJR

mixture are aspirated from the 10 mL syringe. Then, 1 mL is injected into each interdigital space, resulting in a total of four injection sites in each foot.

Prior to the injection, an axial T1-weighted non-contrast image is acquired. The injection is then administered intradermally to avoid the subcutaneous layer. Patients are then requested to exercise by walking or performing knee bends for approximately 5 minutes with subsequent immediate T1-weighted fat-suppressed sequence imaging. Imaging is then repeated at least five times at 5-minutes intervals to identify lymphatic flow until contrast excretion into the kidney is observed and wash-out of contrast from the central lymphatic system is observed. If no contrast is observed within 30 minutes of injection, the examination should be aborted [40]. Subsequently, axial post-contrast T1w m-Dixon images are acquired.

Contrast injection in the interdigital web spaces is well-tolerated by patients with no significant complications reported. Image quality is generally felt to be good, with issues in imaging quality mostly attributed to motion artifacts (for example, shortness of breath in patients with pleural effusions).

Following injection, contrast is visualized within 5 minutes in a large number of patients (hence the need to image immediately post injection) and up to 15 minutes later. Once the central lymphatic system is visualized, washout of contrast medium occurs within approximately 25 minutes.

Potential causes of failure of this technique include poor timing, as there is a narrow window of 10–50 minutes after injection when adequate enhancement is observed, starting within 5–15 minutes after injection of contrast [40]. Venous contamination can occur, which makes it difficult to differentiate between venous and lymphatic channels. This can be overcome by using water-only multi-echo gradient echo images [41], thus eliminating the requirement for image subtraction.

The importance of performing MR-based lymphangiography prior to proceeding to fluoroscopic intranodal Lipiodol lymphangiography is to identify anatomical variations and other underlying pathologies and to aid treatment planning [42]. This information can be obtained before planning definitive treatment and does not incur a radiation dose that may be pertinent in younger patients or in those requiring subsequent treatment, which may result in prolonged procedures with attendant high radiation doses [40,43]. The authors reported a high rate of success in the identification of anatomic variations, lymphatic pathological abnormalities, and access routes for planning intervention [40].

This remains an off-label use for gadolinium, and patients must therefore consent specifically for this purpose. Local infections and reactions to contrast agents are risks for which counselling must be provided. Antibiotic prophylaxis should be administered in patients with lymphedema who are prone to cellulitis.

The requirement for active exercise of the leg muscles means that it cannot be performed under general anesthesia in frail elderly patients or the very young, which is a limiting factor.

Intranodal CT Lymphangiography (ICTL)

Despite the clinical benefits of DCMRL and pedal lymphangiography, the logistical hurdles of MRI scanners have limited their widespread use. Unlike MRI, CT scanners are much more accessible in most facilities, and thus have great potential to fulfill the increasing clinical demand for lymphatic imaging. Traditionally, the term "CT lymphangiography" describes an additional CT scan after intranodal lymphangiography using Lipiodol [44-47]. However, the hydrophobicity of Lipiodol causes discrete and non-physiological distribution within lymphatic vessels, which limits its diagnostic potential. More recently, a report described intranodal CT lymphangiography (ICTL), in which water-soluble, iodine-based contrast media are injected through the inguinal lymph nodes, followed by CT scanning [48]. Unlike MR lymphangiography, ultrasound-guided lymph node access can be performed safely within the CT scanning room. This means that there is no need for the patient to be transported and, as a result, the needle is less likely to be displaced. The contrast media injected via the inguinal lymph node reached the level of the thoracic duct in 5–15 minutes. Such variability in the contrast arrival time may make it difficult to determine the timing of image acquisition. In one study, CT fluoroscopy was performed intermittently at the level of the upper abdomen approximately 5 minutes after the injection. Once the arrival of contrast media was confirmed, images were acquired 1–2 minutes later, and scanning was repeated until the thoracic duct was adequately visualized [48]. Unlike DCMRL, the examiner must consider escalating the radiation dose resulting from multiple CT scans.

Despite the drawbacks of ICTL over DCMRL, such as radiation hazard or inferior sensitivity of contrast media, ICTL has multiple potential benefits over DCMRL. First, CT

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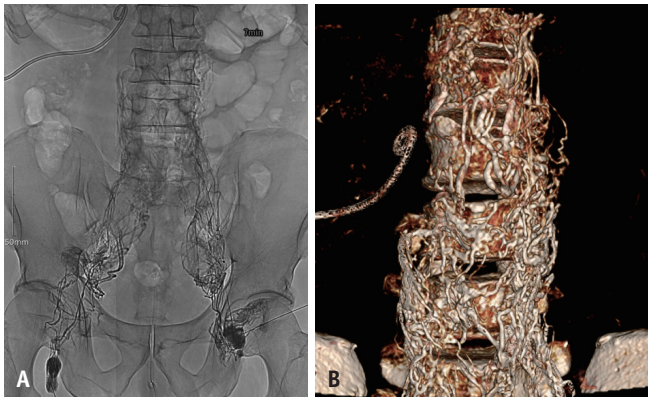

Fig. 8. A 63-year-old male with renal cell carcinoma who developed chylous ascites following right radical nephrectomy.
A. Under ultrasound guidance, bilateral inguinal lymph nodes were accessed, and 20 mL of CT contrast medium was injected via both accesses at a rate of 3 mL/min. The fluoroscopic spot image 7 minutes after the start of contrast injection showed dense pelvic lymphatic vessels and relatively faint para-aortic lymphatic vessels. **B.** C-arm CT lymphangiography clearly depicts dilated and abundant para-aortic retroperitoneal lymphatic vessels, suggesting underlying lymphangiectasia even when contrast staining is faint on fluoroscopy.

scanners are more accessible than MRI scanners at most facilities. Second, it is easier to standardize the scanning parameters for ICTL than DCMRL. Third, the scanning time is shorter and the spatial resolution is higher. Fourth, the use of CT is not limited to patients with implanted cardiac defibrillators or claustrophobia. The combination of a fluoroscopy unit with a CT scanner—such as the AngioCT equipment—can maximize the benefits of ICTL. However, even without such sophisticated equipment, ICTL may be performed using conventional MDCT or cone-beam CT in the angiography suite (Fig. 8).

CONCLUSION

Significant progress has been made in lymphatic imaging, evolving from conventional modalities such as nuclear scintigraphy to DCMRL, which represents one of the latest developments in lymphatic imaging. Furthermore, the development of imaging techniques that allow radiological assessment of the liver and mesenteric lymphatics has provided further insight into the pathophysiology of some lymphatic disorders that are likely to have been overlooked in the past. The widespread application of these novel imaging modalities will aid in the diagnosis and treatment of various lymphatic disorders.

Availability of Data and Material

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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