MRI of Lymphedema

Betsa Parsai Salehi, MD,[1] Robert Carson Sibley, MD,[2] Rosie Friedman, BS,[3] Geunwon Kim, MD, PhD,[4] Dhruv Singhal, MD,[3] Andreas Markus Loening, MD, PhD,[2] and Leo L. Tsai, MD, PhD, MSc[1*]

Lymphedema is a devastating disease that has no cure. Management of lymphedema has evolved rapidly over the past two decades with the advent of surgeries that can ameliorate symptoms. MRI has played an increasingly important role in the diagnosis and evaluation of lymphedema, as it provides high spatial resolution of the distribution and severity of soft tissue edema, characterizes diseased lymphatic channels, and assesses secondary effects such as fat hypertrophy. Many different MR techniques have been developed for the evaluation of lymphedema, and the modality can be tailored to suit the needs of a lymphatic clinic. In this review article we provide an overview of lymphedema, current management options, and the current role of MRI in lymphedema diagnosis and management.
Evidence Level: 5
Technical Efficacy: Stage 5

J. MAGN. RESON. IMAGING 2023;57:977–991.

Lymphedema affects 3–5 million Americans and 200 million people worldwide.[1] This chronic disease occurs from impaired transport of lymph, resulting in accumulation of proteinaceous fluid in the interstitial compartment and a cycle of T-cell-mediated inflammation, fibrosis of lymphatic vessels, and adipose deposition.[2–4] This may be further complicated by episodic cellulitis, lymphangitis, and, infrequently, secondary cutaneous angiosarcoma.[5,6]

Lymphedema onset is insidious and is characterized by progressive swelling, typically in one or more extremities (Fig. 1).[7] Hallmark symptoms include discomfort, heaviness, numbness, skin thickening, disfigurement, and functional deficits, which can have a devastating impact to patients' physical, functional, and psychosocial well-being.[8,9] There is a high financial cost as well; lymphedema-related US hospitalizations from 2012 to 2017 resulted in greater than $1 billion of reimbursed costs, with most patients facing additional out-of-pocket costs.[10–12]

There is currently no cure for lymphedema. Current treatments aim to slow the inevitable progression of the disease and to improve the function of the part of the body burdened with lymphedema. Given the complex pathophysiology and manifestation of their disease, patients with lymphedema benefit from a multidisciplinary approach to management, driven primarily by certified lymphedema physical therapists, vascular medicine, lymphatic surgery, and, increasingly, imaging specialists.[13] Conservative strategies, such as manual lymphatic drainage and use of compression garments or pneumatic devices, are aimed at reducing limb volume and slowing disease progression.[14–16] Other nonoperative management strategies include skin care to prevent cellulitis, and, if necessary, lifestyle and dietary habits to reduce body mass index.

Surgical interventions for the treatment of lymphedema have gained popularity in recent decades with the advancements of microsurgical techniques (Fig. 2).[17] Physiologic procedures such as vascularized lymph node transfer and lymphovenous bypass are aimed at correcting the underlying disease process. These techniques are particularly useful for patients with earlier-staged lymphedema, as they rely on identifiable and functional lymphatic vessels prior to adipose hypertrophy and fibrosis. For patients with chronic lymphedema, debulking procedures such as suction lipectomy of the affected extremity reduce limb volume by removing excess adipose tissue.[14,18]

View this article online at wileyonlinelibrary.com. DOI: 10.1002/jmri.28496

Received Jul 5, 2022, Accepted for publication Oct 7, 2022.

*Address reprint requests to: L.L.T., 330 Brookline Avenue, ANSIN 230, Boston, Massachusetts 02215, USA. E-mail: ltsai1@bidmc.harvard.edu
Betsa Parsai Salehi and Robert Carson Sibley are co-first authors.

From the [1]Department of Radiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; [2]Department of Radiology, Stanford Medical Center, Stanford, California, USA; [3]Division of Plastic and Reconstructive Surgery, Department of Surgery, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; and [4]Atrius Health, Newton, Massachusetts, USA

Moreover, debulking procedures can be performed as a first-stage step in surgical management prior to vascularized lymph node transplant.[19–21] As disease severity, manifestations, and response to treatment often vary between patients, a tailored approach to care is often necessary to achieve maximum disease control and align with patient goals.

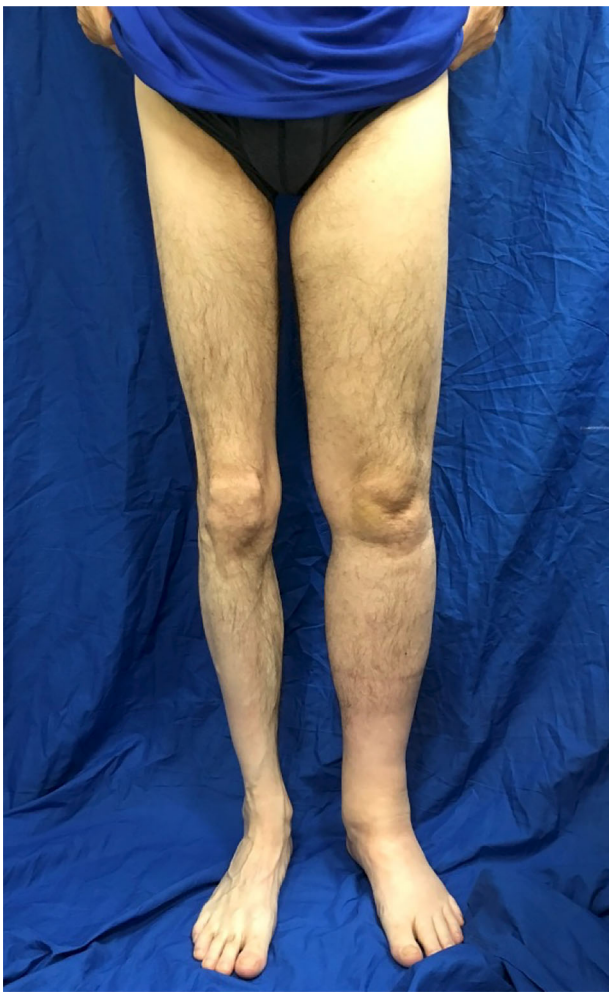

FIGURE 1: Patient with left lower extremity lymphedema with a 56% volume difference between right and left leg.

Lymphatic Imaging

One of the main challenges in imaging lymphedema is the difficulty in directly visualizing the lymphatic system. Lymph vessels are nearly an order of magnitude smaller than the blood vasculature, measuring 0.4–0.8 mm in diameter, and lymphatic flow is 1–2 orders of magnitude slower than venous or arterial flow. The thoracic duct, the largest lymph vessel, measures only 5 mm in diameter. Unlike blood vessels, lymphatic system also contains lymph nodes that serve as focal collectors for afferent vessels (Fig. 3). Cannulation of lymphatic vessels other than the thoracic duct is often not possible unless they are abnormally (typically congenitally) enlarged. Injection into lymph nodes is limited by anatomy to evaluation of central lymphatics as lymph does not flow peripherally. Peripheral vessel assessment, therefore, relies on absorption and transport of contrast from intradermal/subcutaneous capillary beds into the vessels.

Imaging can detail other features of lymphedema in addition to direct assessment of the lymphatic vessels, for example, fluid accumulation in the soft tissues, fat hypertrophy, and skin thickening. This is beneficial for treatment planning as the main physical exam findings for lymphedema, swelling and edema, are nonspecific, as reflected by the International Society of Lymphology (ISL) grade, which is currently the only universal staging system in use (Table 1). Imaging-based evaluation of lymphedema is now used routinely for diagnostic confirmation and the evaluation of disease severity and distribution for treatment planning and response assessment.[23–25] Here, we will review the different ways by which MRI is used for the evaluation of lymphedema.

MRI of Lymphedema: Background and Techniques

Multiple imaging modalities have been used to characterize the lymphatic system. These are summarized in Table 2. MRI offers several advantages by providing high-resolution anatomical detail and soft tissue contrast with pulse sequences that can be adjusted to highlight edema, fat, or contrast agents, while avoiding exposure to ionizing radiation. MR

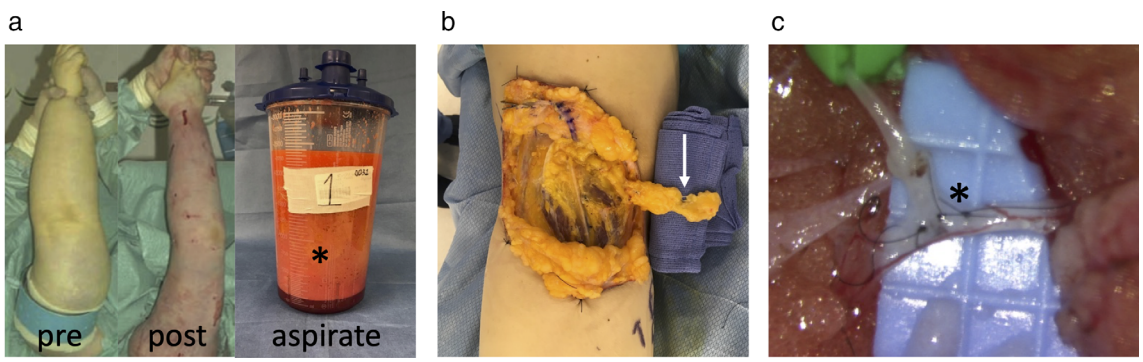

FIGURE 2: Examples of different surgical approaches to lymphedema treatment. (a) Pre and post images of an upper extremity debulking with the collection canister showing total fat (*) removed. (b) Lymph node transplant (arrow) into a lower extremity. (c) Lymphovenous bypass showing the anastomosis (*); each etched square on the blue backplate measures 1 mm.

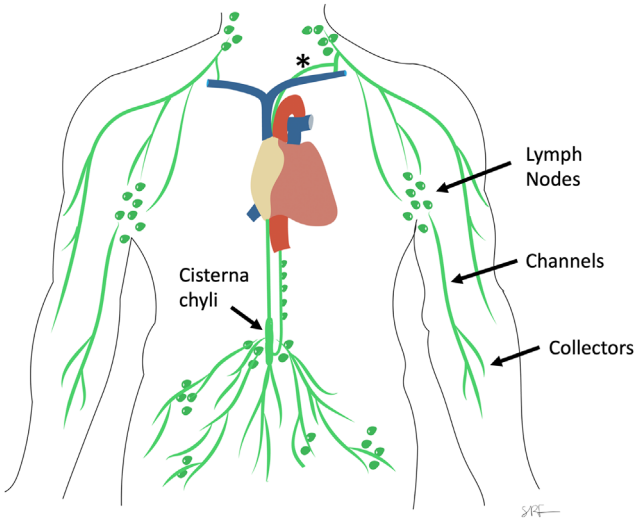

FIGURE 3: Diagram of lymphatic drainage. Lymphatic channels from the extremities drain into lymph nodes at the axilla and inguinal regions, which can resorb lymph and send efferent channels more centrally. Central lymphatics drain primarily into the thoracic duct (*), which directly communicates with the left subclavian vein.

TABLE 1. International Society of Lymphology Staging System for Extremity Lymphedema[22]

Stage	Description
Stage 0	Subclinical or latent condition in which swelling is not yet observable despite underlying impairment in lymphatic transport; may involve subtle tissue changes and subjective symptoms. This stage may exist for months or years prior to presence of overt edema
Stage I	Early accumulation of proteinaceous fluid that improves or temporarily resolves with limb elevation. Pitting is variably present. An increase in various types of proliferating cells may be observed
Stage II	Edema with pitting that does not subside with limb elevation alone
Stage III	Lymphostatic elephantiasis involving skin changes, including thickening, acanthosis, and warty over growths. This may occur with or without pitting

lymphangiography (MRL) offers superior resolution to lymphoscintigraphy and can resolve lymphatic channels like ICG and high-resolution US without depth limitations.[45–48] Additionally, MRI can image large portions of the body within a single imaging session, for example, covering from the feet to the termination of the thoracic duct at the left subclavian vein.

The flexibility of MR pulse sequences allows MRI to be used in many ways to assess lymphedema. This ranges from direct visualization of lymphatic channels to assessment of secondary effects such as fat hypertrophy (Table 3).

MR lymphangiography techniques can be divided into two categories: contrast-enhanced and noncontrast. Lymph has an inherently high T2 relaxation time of ~600 msec at 3.0 T,[49] and most protocols employ a version of a heavily T2-weighted sequence to image the lymphatic channels or to assess for edema.[50,51] Sequences that directly image the lymphatic vessels without exogenous contrast have been termed noncontrast MR lymphography (NCMRL). NCMRL typically relies on 3D T2 fast/turbo spin echo sequences (FSE/TSE) with a TR/TE of at least 3000/600.[52] Fat suppression by short tau inversion recovery (STIR) or fat separation with Dixon technique is typically used. The images are acquired in stations to cover the desired anatomy. Although lymph vessels are typically on a submillimeter scale,[53] the degree of soft tissue edema can be characterized at an order of magnitude lower resolution (~2–3 mm). From our experience, axial orientation allows for optimal interpretation of edema degree and distribution, while acquiring 3D acquisitions in the coronal orientation is more efficient for covering large anatomic fields of view.

For contrast-enhanced MRL, gadolinium-based agents can be introduced intradermally, subcutaneously, or intranodally.[48,54,55] Detection of contrast is performed typically with fat-saturated T1-weighted spoiled gradient recalled echo (SPGR)-based sequences.[56,57] Spatial resolutions on the order of ~1 mm^3 are typically used.[58] Contrast-enhanced MRI techniques can also be combined with noncontrast techniques for a more comprehensive assessment.

Skin injections are necessary to introduce contrast into the peripheral lymphatics. When MR contrast agents are injected intradermally or subcutaneously into the skin, these agents will enter dermal lymphatic capillaries, which drain into lymphatic collecting vessels and subsequently into lymph nodes. As lymphatic function decreases, the amount of contrast moved per unit time decreases. Massage of the injection site and activation of muscle activity can speed the distribution of contrast throughout the peripheral lymphatic vessels.[59–63]

Multiple extracellular MR contrast agents have been safely used for MR lymphangiography including gadopentetate dimeglumine (Magnevist, GD-DTPA),[32,64] gadoterate meglumine (Dotarem, Gd-DOTA),[60] gadobutrol (Gadavist, Gd-DO3A-butrol)[65–67] gadoteridol (Prohance, Gd-HPDO3A),[57,68,69] gadodiamide (Omniscan, Gd-DTPA-BMA),[59,63] and gadobenate dimeglumin (MultiHance, Gd-BOPTA).[70] A 1:1 contrast to saline dilution will yield an approximately isotonic mixture. The injection volume per site ranges from 0.5 mL to 2 mL with greater injection volumes used for intranodal administration.[58] Use of small gauge (28–32 G) needles, mixing of contrast agents with local anesthetic,

TABLE 2. Comparison of Lymphatic Imaging Modalities

Modality	Description	Advantage(s)	Disadvantage(s)
Conventional (direct) lymphangiography	Lymphangiography is one of the oldest diagnostic techniques for the evaluation of lymphatic system.[26,27] Ethiodized oil is injected directly into lymphatic channels or lymph nodes and tracked by real-time fluoroscopy[28,29]	Provides excellent resolution and enables the evaluation of both peripheral and central lymphatics Direct cannulation of the larger ducts also offers the opportunity for interventions such as angioplasty[30]	Invasive imaging technique that exposes the patient to ionizing radiation and requires contrast agent Ethiodized oil is viscous and may require hours to track throughout the central lymphatics
Lymphoscintigraphy	Lymphoscintigraphy is performed by intradermal injection of radioactive agents such as ^{99m}Technetium (Tc99m) albumin or sulfur colloid. In this technique, the radiotracer is taken up by lymphatic vessels and flows through the lymphatic system[31]	In addition to anatomic depiction, lymphoscintigraphy is a great tool for evaluation of lymphodynamics and can demonstrate lymphatic flow disorders[32,33] The hallmark feature of dermal backflow[a] is considered a diagnostic gold standard for lymphedema	Poor resolution limits the use of this method for treatment planning. Even though SPECT-CT has improved the spatial resolution, it is still not sufficient to guide interventional procedures[26]
Optical imaging (ICG)	Near-infrared fluorescence (NIRF) optical imaging uses intradermally injected indocyanine green (ICG) to delineate both the anatomy and function of superficial lymphatics	Light emitted by this fluorescent agent enables the visualization of lymphatics and detection of dermal backflow[a34,35] Intraoperative ICG is used to identify potential lymphatic vessels for lymphatic-venous bypass[36,37]	ICG is limited by photon scatter and absorption in the tissue which restricts imaging to a depth of 1–3 cm.[38,39]
Ultrasound	Duplex ultrasound can be used to stage lower extremity edema by assessment of different tissue layers characteristics including skin thickness, subcutaneous thickness as well as subcutaneous echogenicity. Subcutaneous echogenicity has been shown to correlate with ISL stage with a high sensitivity and specificity[40,41]	Ultrasound is a noninvasive imaging and relatively inexpensive technique that needs no exogenous contrast medium or radiation exposure	Limiting factors include operator dependency and limited depth of assessment[42]

[a]Dermal backflow: Abnormal filing of lymphatic capillaries in the dermis which suggests lymphatic reflux as result of valve insufficiency caused by anatomical or functional obstruction of lymphatic pathways.[43,44]

TABLE 3. Example MRI Sequences Utilized in the Evaluation of Lymphedema at the Authors' Institutions (Two Separate Sites) Highlighting Some of the Sequences Used. These May be Acquired in Multiple Bed Positions to Cover the Anatomy of Interest

Type of Sequence	Purpose	Example Sequence Parameters	Notes
T2-weighted imaging with fat suppression	Assess degree and distribution of edema	For Upper extremity: 2D STIR Upper station (shoulder and ipsilateral breast to elbow): Axial orientation 40 × 20 cm FOV 384 × 192 matrix slice thickness 6 mm TE 52, TR = 7080 msec echo train length 16 Lower station (elbow to hand): 16 × 14 cm FOV 192 × 174 matrix. Other parameters are the same as with the upper station Acquisition time: ~ 3 min/station	Widely available, less prone to artifacts Heavily T2-weighted sequences, as used in MRCP sequences, can also be used
T2-weighted imaging with fat separation	Assess degree and distribution of edema Visualize dilated lymphatic channels	3D FSE Coronal orientation 40 cm FOV Matrix 320 × 320 × 200 Isometric voxels ~1.3 mm Dixon fat separation Acceleration 3 × 2 TE 200, TR 2000 msec Acquisition time ~4 min/station	In the chest and abdomen, either respiratory triggered or single shot technique is preferred
T1-weighted imaging with fat separation	Assess the degree of subcutaneous fat hypertrophy Intradermal contrast agent can be used to assess speed of lymphatic flow, level of central contrast agent migration, and areas of dermal backflow. Smaller lymphatic vessels can be visualized than what are evident with T2-weighted technique	3D SPGR Coronal orientation 40 cm FOV. Matrix 320 × 320 × 200 Isometric voxels ~1.3 mm Dixon fat separation Acceleration 3 × 1 TE 1.3/2.2 msec, TR 4 msec Acquisition time ~2 min/station	Standard clinical 3D SPGR sequences are acceptable, although these should be configured for high-resolution acquisitions

STIR = short tau inversion recovery; FOV = field of view; FSE = fast echo; SPGR = spoiled gradient recalled echo.

and premedication of injection sites with topical anesthetic are techniques that may be used to mitigate the pain associated with injection.

One challenge of intradermal and subcutaneous contrast agent injection is venous contamination, whereby contrast agents are taken up by both lymphatic channels and slow-flowing superficial veins at similar concentrations (Fig. 4).[32,59,71] Subcutaneous injections allow a greater volume of contrast delivery but are associated with greater venous contamination.[71] Veins are relatively larger than lymphatic channels with smooth walls, while lymphatic vessels are often more tortuous in patients with lymphedema, features that can help distinguish the two.

Venous contamination can be mitigated with a technique called dual agent relaxivity contrast (DARC) MRL.[72] In this technique, a gadolinium-based agent is injected

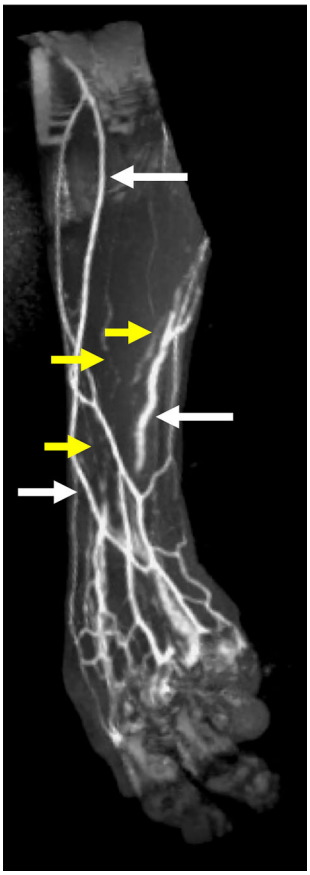

FIGURE 4: MIP image from an MRL following subcutaneous injection of gadobutrol at three locations along the dorsum of the left hand. While lymphatic channels are demonstrated (yellow arrows), there is substantial contamination from superficial veins (white arrows) which demonstrate relatively greater signal intensity which obscures the lymphatics.

intradermally or subcutaneously, similar to conventional MR lymphangiography. Ferumoxytol (iron nanoparticles) is then infused intravenously at 5 mg/kg or at 510 mg (diluted with normal saline to a total volume of 60 mL). Dynamic imaging is first performed using a short-echo T1-weighted SPGR sequence that allows gadolinium and ferumoxytol enhanced structures to be seen. Then multiecho T1w SPGR acquisitions with progressively lengthened TE combinations are obtained until complete venous suppression is achieved due to the enhanced r2* relaxation of water molecules in the blood pool from ferumoxytol. T1-weighted SPGR sequences are then obtained at this optimized TE, leaving only signal contribution from the lymphatic channels (Fig. 5). Although Dixon-based fat separation is generally favored at 3 T due to more homogenous fat saturation, vendor 3D SPGR implementations do not allow specifying longer in-phase/out of phase echo times. Also, per FDA guidelines, blood pressure and cardiac electrophysiology should be monitored for 30 minutes after injection of ferumoxytol due to a small risk of hypersensitivity reactions.

Visualization of the central lymphatic system is typically performed with intranodal contrast injections that bypass the peripheral lymphatic system.[73] Cannulation of the inguinal lymph nodes is performed under ultrasound guidance and contrast is injected directly into the nodes. The dosing for intranodal injections is typically weight based.[74,75] The enhancement of central lymphatics occurs over a timescale of several minutes and dynamic T1-weighted imaging is typically acquired in the coronal plane. Fat-separation, fat-saturation, or subtraction techniques (eg time-resolved MR angiography) can be used for the dynamic images that are

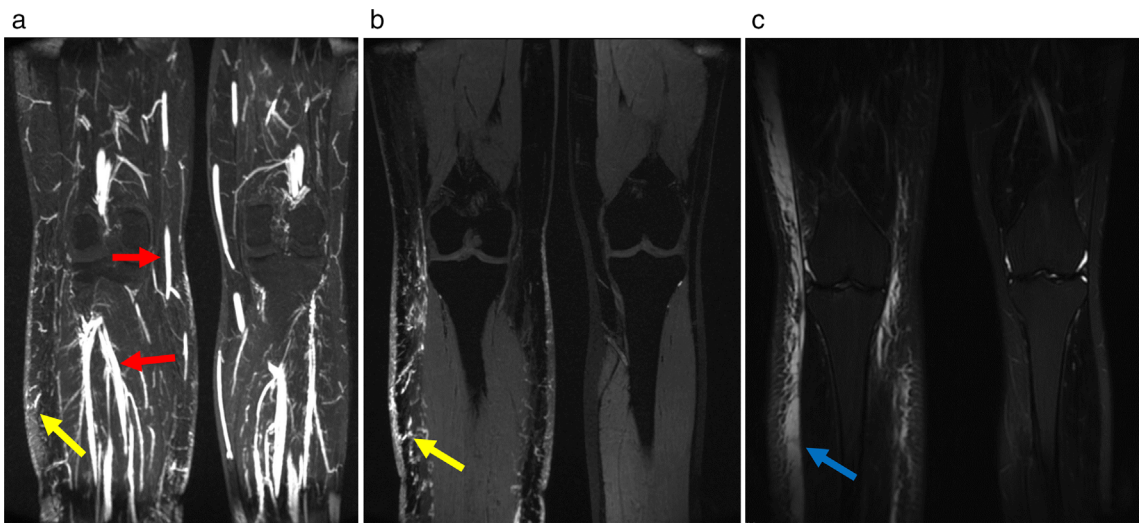

FIGURE 5: DARC MRL in 32-year-old female with right lower extremity lymphedema. (a) Coronal 3D SPGR TE 0.9 msec MIP angiographic image shows enhancement of blood vasculature (red arrows) and lymphatic vasculature (yellow arrow). (b) Coronal 3D SPGR TE 4.4 msec MIP lymphangiographic image with enhancement of lymphatic vessels (yellow arrow) and suppression of venous signal. (c) Cor 3D T2w image with increased subcutaneous thickness and prominent epifascial edema (blue arrow).

typically acquired with a temporal resolution on the order of 1 minute and the series acquired over ~10 minutes. Static T1-weighted imaging can be acquired at higher resolution focusing on areas of interest, for example, an area of stenosis, suspected leak, retrograde flow into pulmonary lymphatics, or retrograde flow into mesenteric lymphatics.[74]

The following sections detail these different techniques and their applications in lymphedema imaging, with a focus on the extremities. Examples of pulse sequences and sequence parameters are provided in Table 3, and technical-specific reviews are also available.[58]

MRI of Peripheral Lymphedema

NONCONTRAST MRI. Noncontrast MRI of peripheral (upper or lower extremity) lymphedema is used to locate dilated lymphatic channels, to demonstrate the spatial distribution of edema throughout the soft tissues and to characterize the amount of fat or muscle throughout a limb. Additional noncontrast MRI sequences are used to comprehensively assess the adjacent soft tissues, in particular fat and muscle, which can be used for therapeutic planning. For example, assessment of the degree of fat hypertrophy can help decide whether debulking (liposuction) would be considered as an initial treatment step prior to consideration of a lymph node transplant or lymphovenous bypass.

Extremity imaging can be performed at 1.5 T or 3.0 T, using body/torso array coils. Imaging of the lower extremities can also be performed using a vascular run-off coil. For lower extremity lymphedema, both legs are usually imaged, as even though one leg may be more effected, both can be involved. Since both lower extremities are covered by the coil arrays, imaging the contralateral extremity comes without a time penalty. In the upper extremity, secondary lymphedema is most associated with breast cancer treatment and is thus usually unilateral. However, comparisons to the unaffected side are helpful for surgical planning, for example, in determining the severity of fat hypertrophy. Upper extremity imaging is more challenging given the width of most patients' shoulders. Coverage of the entire upper extremity is often obtained using the "superman" position, with the patient in a decubitus lay, with the extremity of interest extended above the head and covered by coils, and with the contralateral extremity in neutral position along the patient's side. This position optimizes imaging, but the impact of this position on lymphatic function is unknown and patients with moderate-to-severe disease or arthritic shoulders may have difficulty with maintaining a raised arm position for the study duration. Imaging with the arms in a neutral position maximizes comfort but may necessitate moving the patient to keep each arm near the isocenter of the magnet to optimize scan quality.[76]

NCMRL sequences, akin to magnetic resonance cholangiopancreatography (MRCP), have been used to assess dilated lymphatic channels and to characterize edema patterns in extremities.[23,77] It has also been used to assess the degree of edema improvement and to detect lymph nodes following lymph node transplant.[78] Patients should be requested to refrain from compression for at least 48 hours prior to MRI to avoid underestimation of the burden of lymphedema.[76,79] Normal peripheral lymphatic channels are usually too small to be clearly resolved with these techniques; rather, NCMRL is used to detect dilated vessels, which are typically the most pronounced in primary lymphedema.[77] One challenge using NCMRL is its inability to distinguish lymphatic channels from superficial veins, where blood flow may be slow enough to yield a similar signal intensity as lymph. Another disadvantage is the lack of functional information provided.

STIR sequences are used to obtain T2-weighted fat-suppressed images that show the distribution and pattern of edema, which include honeycombing, dermal thickening, and epifascial fluid (Fig. 6). STIR and NCLMRL have been used to characterize secondary upper and lower lymphedema in cancer patients, correlating well with clinical lymphedema staging and functional studies such as lymphoscintigraphy.[23,76,79,80]

Fat hypertrophy can be assessed on T2-fat-suppressed sequences, but a large amount of edema may obscure underlying fat. The use of Dixon fat-separating sequences can be incorporated to better assess the amount of fat hypertrophy (Fig. 7). The degree of fat deposition in the axilla has been shown to be altered in the axilla of patients with breast cancer treatment-related lymphedema.[81] Muscle atrophy is not typically directly related to lymphedema but can be associated with decreased activity due to symptoms or direct damage from surgery or radiotherapy. Significant muscle atrophy in the effected limb may mask volumetric differences due to

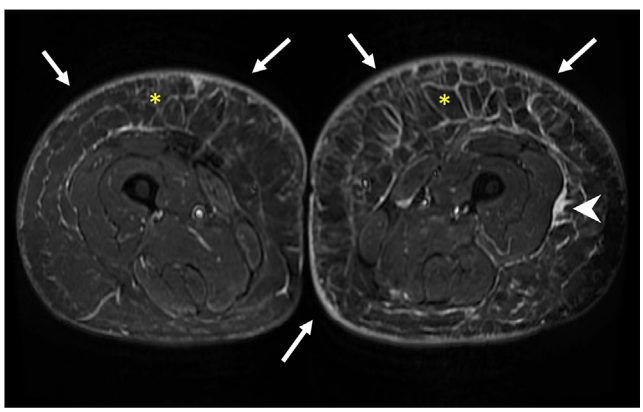

FIGURE 6: Axial T2-weighted fat-nulled STIR image across the mid thighs of a 46-year-old female with chronic bilateral lower extremity lymphedema demonstrates three hallmark features: honeycombing (*), dermal thickening (arrows) and epifascial fluid (arrowhead).

edema and fat hypertrophy when comparing against the contralateral limb using conventional perometry or circumferential measurements.

Noncontrast MRI provides static information and is thus unable to relay dynamic processes, for example active chyle leaks.[25] In moderate and severe cases of lymphedema, the lymphatic channels can be obscured by adjacent and overlying soft tissue edema. Lastly, the resolution of noncontrast sequences is generally lower than that of 3D gradient-echo-based sequences used in contrast-enhanced studies.

CONTRAST-ENHANCED MR LYMPHANGIOGRAPHY. Contrast-enhanced MR lymphangiography essentially builds on NCMRL as a foundation. MR contrast agents injected into the dermis are taken up by the lymphatic system. When the MR contrast agent is in the lymphatic system, the lymphatic vessel anatomy and basic flow characteristics can be determined. Dermal backflow, classically described in lymphoscintigraphy and pathognomonic for lymphedema, can be seen on contrast-enhanced MR lymphangiography.[82] Dermal backflow occurs when a contrast agent enters the collecting lymphatics then flow retrograde through the precollecting lymphatics and into the initial dermal collecting lymphatics. This occurs because pressure gradients and valve failure promote lymph drainage toward the dermis. The initial dermal lymphatics, which are inherently leaky then dilate releasing lymph into the dermis.[83]

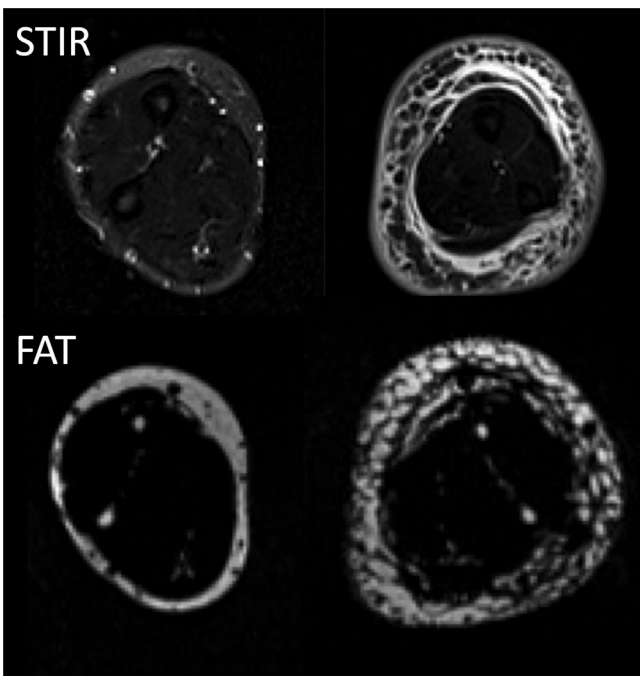

FIGURE 7: Axial STIR (top) and DIXON-fat (bottom) images of the mid forearms in a 43-year-old male with chronic left upper extremity lymphedema. There is extensive confluent subcutaneous fluid and dermal thickening highlighted on STIR; however, DIXON-fat images reveal a substantial amount of fat hypertrophy relative to the right forearm, which is not as conspicuous on STIR.

In addition to dermal backflow, contrast-enhanced MR lymphangiography allows for the characterization of both deep and superficial lymphatic vessels. In extremities with a healthy lymphatic system, the lymphatic vessels may not be visualized indicating normal small diameter vessels with quick transit of contrast agent. This can be confirmed by uptake in proximal lymph nodes. In extremities with lymphedema, the location, degree of dilation, and relative timing of contrast agent opacification of lymphatic vessels can be described. The proximal lymph nodes in the extremity with lymphedema can be characterized by number, contrast enhancement pattern, and relative timing of contrast enhancement.

MRI Staging Systems and Reporting for Lymphedema

Management of lymphedema has become more complex with the advent of surgical options. Lymphatic clinics that offer both medical and surgical approaches are relying increasingly more on quantitative information, for example, volumetrics and bioimpedance. Imaging has similarly evolved to help determine the optimal surgery or non-surgical therapy to pursue and to track post-treatment change and becoming standard of care for all chronic lymphedema patients. For example, the patient shown in Fig. 7 demonstrates both significant epifascial/subcutaneous edema as well as fat hypertrophy. For this reason, the patient's care would be optimized by manual compression followed by debulking.

Several MRI-based staging systems and interpretative guidelines have been developed and proposed (Table 4). Patterns of edema correlate with the severity of lymphedema, in particular the characteristic honeycomb pattern of fluid interdigitating throughout subcutaneous fat lobules and dermal thickening, characteristics also seen in CT.[80,88] These MRI features have been shown to correlate with dermal backflow seen on lymphoscintigraphy.[89] Similar patterns are also seen in MRL (Fig. 8). These features seen on imaging exams allow for differentiation from other conditions like phlebedema or lipidema, which can be clinically challenging.[90–92] Grading systems that take into account the degree of fat and fluid contributions to extremity swelling in chronic lymphedema would assist in determining whether a patient could undergo debulking vs. direct lymphatic repair.[86]

Microreconstruction planning can require a detailed assessment of regional lymph node characteristics and precise depiction of the lymphatic system including number, diameter, and location.[47,57] Patients with lower extremity edema from a hypoplastic lymphatics benefit from lymph node transfer, while lymphovenous bypass may be preferred for patients with dilated lymphatic vessels.[93–95]

The severity of lymphedema has been shown to correlate with abnormal morphology and a smaller number of

TABLE 4. Summary of Select MR Lymphangiography Grading, Staging, and Severity Systems in Lymphedema

Patient Population	Technique	Grading, Staging, and Severity Systems	Correlation	References
Lower limb lymphedema	Noncontrast T2w 3D FSE	Iliac and Inguinal Trunk Grading Aplastic: no trunks Hypoplastic: <3 trunks Normal: 3–6 trunks Hyperplastic: >6 trunks Lymphedema Severity Mild: superior margin of edema below knee, no subcutaneous fat increase, epifascial fluid <5 mm Severe: edema of entire limb, increase subcutaneous fat, epifascial fluid >15 mm Moderate: intermediate between mild and severe Honeycombing—more common in severe Dermal thickness >2 mm Absent Muscular edema Reduced muscular trophism Dilated distal leg lymph vessels >2 mm	ISL Stage Dermal backflow on Lymphoscintigraphy	77,84
Upper extremity lymphedema	Non-contrast T2w FSE	MRI Stage 0: no detectable fluid infiltration at any level 1: Fluid infiltration does not exceed 50% circumference at forearm, elbow, or upper arm 2: Not stage 1 or stage 3 3: Fluid infiltration exceeds 75% of the circumference at all three levels	ISL Stage LYMQOL Limb volume L-Dex	76
Suspected Upper extremity lymphedema	Non-contrast T2w FSE	Dermal Rim Sign • honeycombing • hyperintense signal of overlying thickened skin • fluid signal within the subcutaneous tissue	ISL Stage Dermal Backflow on Lymphoscintigraphy L-Dex	80
Lower Extremity lymphedema	Post-contrast T1w 3D SPGR	Inguinal node contrast ratio (SI postcontrast/SI precontrast) at 5 minutes	ISL Stage	85
Lower Extremity lymphedema	T1 GRE	*Fluid accumulation grade* 0 = no fluid 1 = honeycombing/reticular pattern of fluid within the subcutaneous fat 2 = continuous visible stripe of fluid between the fat and investing muscle fascia. *Fat Accumulation Grade* 0 = no excess fat	ISL Stage	86

TABLE 4. Continued

Patient Population	Technique	Grading, Staging, and Severity Systems	Correlation	References
		1 = fat accumulation less than twice the width of the widest fat stripe on the unaffected side 2 = fat accumulation greater than twice the width of the widest fat stripe on the unaffected side		
Lower Extremity lymphedema	Postcontrast 3D Dixon	MRL Stage 1: no DBF, and lymph vessels are visible above the knee joint. Normal, nondilated lymphatic vessels can be seen above the knee joint and are slightly visible in the groin. 2: no DBF, and lymph vessels above the knee joint are not visible. Normal, nondilated lymphatic vessels can be seen below the knee joint. 3: DBF appears below the knee joint, and lymph vessels are seen above the knee joint. 4: Both DBF and lymph vessels are seen below the knee joint. 5: DBF and lymph vessels are seen above the knee joint. 6: DBF is seen above the knee joint, lymph vessels are observed below the knee joint. 7: DBF appears only in the foot, and lymph vessels are not visualized proximal to the foot	ISL Stage	87

FIGURE 8: A 65-year-old-female with history of breast cancer and right arm lymphedema. Cor 3D SPGR lymphangiography demonstrates contrast flowing along prominent collecting vessels (yellow arrows) with retrograde flow of contrast into the dermis (yellow arrow heads). It is unclear what component of this contrast is within a dilated lymphatic system vs. extravasated out of the lymphatic vasculature.

inguinal lymph nodes, as well as the degree of dilation of iliac lymphatic trunks.[77,84,95,96] Dilated lower extremity lymphatic vessels more than 2 mm have shown significant correlation with ISL stage.[51,84] Dilatation of distal lymphatic vessels is seen more in hyperplasic lymphatic patterns.[77] An MR lymphangiogram staging system that groups postcontrast lymphatic enhancement patterns into seven stages has been demonstrated to correlate with ISL stage.[87]

While we highlight several staging systems that can be tailored to suit the needs of a specific clinic, MRI reports for extremity lymphedema should nonetheless include several core descriptions. These include an evaluation of the distribution and severity of subcutaneous edema and skin thickening, the presence of fat hypertrophy (typically compared to the contralateral limb at the same levels), the presence of any dilated lymphatic channels if detectable, the presence of any vascular (arterial or venous) anomalies, or any other incidental findings that may contribute to similar symptoms as lymphedema (eg hematoma). Anatomic description of fat and edema distribution can also be tailored to the needs of the surgeon and therapist. For example, if there is uneven distribution of edema along a forearm with lymphedema, a surgeon deciding on an ulnar versus radial placement of a lymph node transplant may elect to target the area with worse edema.

MRI of the Central Lymphatics in the Assessment of Lymphedema

The role of central lymphatic imaging is growing particularly in the pediatric hospital setting. Central MRL can identify

central lymphatic disorders often associated with congenital heart disease such as pulmonary lymphatic perfusion syndrome and protein losing enteropathy, as well as primary lymphedema. This technique may have a role for evaluating intrapelvic lymphatic pathophysiology in patients with secondary lower extremity lymphedema following lymph node dissection and/or radiation for pelvic malignancies.[97,98]

Dynamic central MRL is particularly useful for evaluation for chylous ascites or chylothorax. In addition to intranodal injection, intrahepatic and intramesenteric injections have been used to evaluate central lymphatic disorders.[99,100] Pedal intradermal/subcutaneous contrast agent injections can also be used to obtain central lymphangiograms[101] and as it is technically less complex than intranodal contrast agent injection. It is used at some centers as a preliminary study as the results can often answer targeted questions regarding lymphatic continuity (eg confirming thoracic duct continuity following spinal surgery). However, central lymphangiograms from a transpedal contrast agent injection approach can be expected to have much less contrast agent available in the central lymphatics than a direct intranodal approach and have a limited role in lymphedema patients with impaired lymphatic flow that would limit or prevent the contrast agent from reaching the central channels. T2-weighted imaging, including fat-saturated 3D FSE and MRCP sequences like that used in NCMRL, can also be obtained in central MRL prior to contrast injection.

MRI of Genital Lymphedema

Genital lymphedema is rare and is typically seen concurrently with lower extremity lymphedema. Like lower extremity lymphedema, it can be classified as primary or secondary. Symptoms may include swelling, heaviness, urinary incontinence, and lymphorrhea from lymphatic vesicles, a condition also known as acquired cutaneous lymphangectasia.[102] Scrotal MR lymphangiography (Fig. 9) may be performed with intradermal injections at the base[103] but is more commonly done with pedal or intranodal injections.

MR findings of scrotal lymphedema include scrotal thickening and lymphatic hyperplasia. Scoring systems have been developed for ICG lymphangiography and lymphoscintigraphy but not yet for MRI.[104,105] MR lymphangiography has been used to guide lipiodol embolization of lymphatic vasculature that refluxes into the genital region.[106]

MRI of Head and Neck Lymphedema

Lymphedema can develop following head and neck cancer treatments (Fig. 10).[107] Two patterns of lymphedema have been described: External (head and face) and internal (pharynx and larynx).[108] External head and neck lymphedema can be assessed by using standardized toxicity criteria and tape measurement systems.[109,110] Near-infrared fluorescence lymphatic imaging and sonography are conventional imaging methods that have been used in conjugation with clinical assessment. Head and neck lymphatic drainage patterns have been revealed using MRL with scalp and submucosal oral cavity injections.[111] MRI currently has a relatively limited role in the workup of head and neck lymphedema as treatment options remain much more limited than for peripheral lymphedema.

Limitations of MRI

Limitations of MRI include artifacts from implants, for example, orthopedic hardware, or patient motion, which may obscure areas of interest.[112] There may also be restrictions on sequences or even overall access from implants that require reduced electromagnetic field exposures or are incompatible with the MRI environment.[113,114] Patient claustrophobia can also limit feasibility. Lastly, MRI is more costly and less accessible than other modalities such as US or ICG.

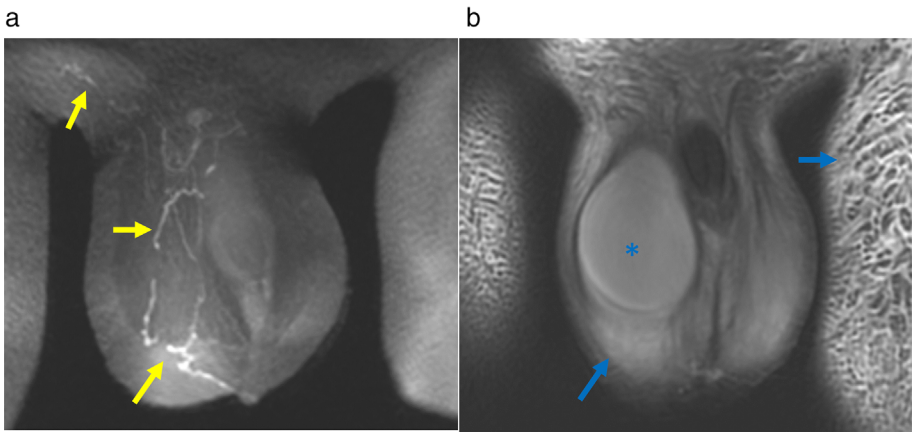

FIGURE 9: MR lymphangiography in 27-year-old male with scrotal and lower extremity lymphedema. (a) Coronal 3D SPGR MIP angiographic image shows lymphatic vessels draining from the right inguinal lymph node (not shown) into the scrotum (yellow arrows). (b) Cor 3D T2 w image with scrotal wall edema and honeycombing of the left thigh (blue arrows).

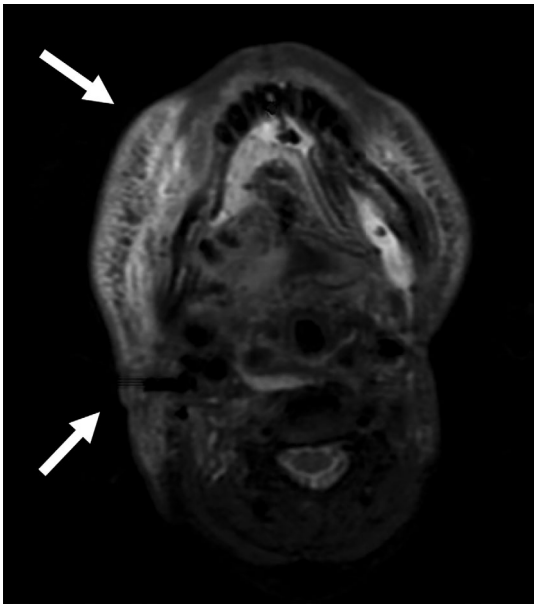

FIGURE 10: Axial T2-weighted image at the upper neck of a 38-year-old with persistent facial swelling following right hemiglossectomy and radiation for squamous cell carcinoma. Extensive edema overlies the mandibles bilaterally, worse on the right with extension to the upper right neck (arrows).

Current Needs and Future Directions

MRI offers the ability to obtain high-resolution anatomic detail of both superficial and deep lymphatic vasculature necessary for surgical planning and is well positioned to become the next imaging gold standard for the diagnosis of lymphedema and for therapeutic tracking. Although many systems for diagnosing and grading lymphedema severity have been proposed, as detailed above, most are based on single-institutional studies based on small patient cohorts, and none have been adopted into widespread use. Structured reporting and standardization of nomenclature of MRI descriptors will also be of benefit to the lymphatic community.

Current use of MRI in lymphedema has focused more on the distribution of disease or lymphatic anatomy, rather than lymphatic function. Lymphoscintigraphy has long offered the ability to quantitate lymphatic transit, but MRI can potentially offer a similar capability along with the added advantages of avoidance of ionizing radiation and the ability to characterize other secondary features such as fat hypertrophy. The ability of MRI to potentially resolve functional difference across different vessels may provide surgeons and therapists with a way to select specific targets to prioritize treatment or repair, or, equally important, if function has been compromised too severely for repair to be beneficial. Measurement of central lymphatic flow rates using MRI has been recently performed, demonstrating its ability to quantify function.[115] Iron-oxide nanoparticle MRL (ION-MRL), which uses subcutaneous injections of ferumoxytol to image the lymphatic system, exploits the inability of interstitial ferumoxytol to diffuse into the venous system, resulting in selective lymphatic uptake.[116] R2* methods have been described for iron quantification and can thus be used to quantitate lymphatic transit with ION-MRL.[117–120]

Conclusion

Lymphatic anatomy and pathology present unique challenges for diagnostic imaging, but MRI currently provides information crucial for lymphedema treatment planning. There remain many avenues of improvement in MR techniques and reporting that will ultimately translate into better and standardized tools to aid surgeons and therapists in the management of lymphedema.

References

1. Cemal Y, Pusic A, Mehrara BJ. Preventative measures for lymphedema: Separating fact from fiction. J Am Coll Surg 2011;213(4):543-551. https://doi.org/10.1016/j.jamcollsurg.2011.07.001.
2. Suami H, Pan WR, Taylor GI. Changes in the lymph structure of the upper limb after axillary dissection: Radiographic and anatomical study in a human cadaver. Plast Reconstr Surg 2007;120(4):982-991. https://doi.org/10.1097/01.prs.0000277995.25009.3e.
3. Hespe G, Nitti M, Mehrara B. Pathophysiology of lymphedema. *Lymphedema*. Cham: Springer International Publishing; 2015. p 9-18.
4. Szuba A, Rockson SG. Lymphedema: Anatomy, physiology and pathogenesis. Vasc Med 1997;2:321-326.
5. Farzaliyev F, Hamacher R, Steinau Professor HU, Bertram S, Podleska LE. Secondary angiosarcoma: A fatal complication of chronic lymphedema. J Surg Oncol 2020;121(1):85-90. https://doi.org/10.1002/jso.25598.
6. Grada AA, Phillips TJ. Lymphedema: Pathophysiology and clinical manifestations. J Am Acad Dermatol 2017;77(6):1009-1020. https://doi.org/10.1016/j.jaad.2017.03.022.
7. Goss JA, Maclellan RA, Greene AK. Adult-onset primary lymphedema: A clinical-lymphoscintigraphic study of 26 patients. Lymphat Res Biol 2019;17(6):620-623. https://doi.org/10.1089/lrb.2018.0032.
8. Fu MR, Ridner SH, Hu SH, Stewart BR, Cormier JN, Armer JM. Psychosocial impact of lymphedema: A systematic review of literature from 2004 to 2011. Psychooncology 2013;22(7):1466-1484. https://doi.org/10.1002/pon.3201.
9. McWayne J, Heiney SP. Psychologic and social sequelae of secondary lymphedema: A review. Cancer 2005;104(3):457-466. https://doi.org/10.1002/cncr.21195.
10. Dean LT, Ransome Y, Frasso-Jaramillo L, et al. Drivers of cost differences between US breast cancer survivors with or without lymphedema. J Cancer Surviv 2019;13(5):804-814. https://doi.org/10.1007/s11764-019-00799-1.
11. Finkelstein ER, Ha M, Hanwright P, et al. A review of American insurance coverage and criteria for the conservative management of lymphedema. J Vasc Surg Venous Lymphat Disord 2022;10:929-936. https://doi.org/10.1016/j.jvsv.2022.03.008.
12. Roberson ML, Strassle PD, Fasehun LKO, Erim DO, Deune EG, Ogunleye AA. Financial burden of lymphedema hospitalizations in the United States. JAMA Oncol 2021;7(4):630-632. https://doi.org/10.1001/jamaoncol.2020.7891.
13. Johnson AR, Fleishman A, Tran BNN, et al. Developing a lymphatic surgery program: A first-year review. Plast Reconstr Surg 2019;144(6):975e-985e. https://doi.org/10.1097/PRS.0000000000006223.
14. Brorson H, Svensson H. Liposuction combined with controlled compression therapy reduces arm lymphedema more effectively than

controlled compression therapy alone. Plast Reconstr Surg 1998; 102(4):1058-1067.

15. Yasuhara H, Shigematsu H, Muto T. A study of the advantages of elastic stockings for leg lymphedema. Int Angiol. 1996;15(3):272-7.

16. Zaleska M, Olszewski WL, Durlik M. The effectiveness of intermittent pneumatic compression in long-term therapy of lymphedema of lower limbs. Lymphat Res Biol 2014;12(2):103-109. https://doi.org/10.1089/lrb.2013.0033.

17. Bamba R, Chu A, Gallegos J, Herrera FA, Hassanein AH. Outcomes analysis of microsurgical physiologic lymphatic procedures for the upper extremity from the United States National Surgical Quality Improvement Program. Microsurgery 2021;42:305-311. https://doi.org/10.1002/micr.30844.

18. Greene AK, Slavin SA, Brorson H. *Lymphedema: Presentation, diagnosis, and treatment*. Heidelberg, Germany: Springer International Publishing; 2015.

19. Granoff MD, Pardo J, Singhal D. Power-assisted liposuction: An important tool in the surgical management of lymphedema patients. Lymphat Res Biol 2021;19(1):20-22. https://doi.org/10.1089/lrb.2020.0115.

20. Granoff MD, Johnson AR, Shillue K, et al. A single institution multidisciplinary approach to power-assisted liposuction for the management of lymphedema. Ann Surg 2020;276:e613-e621. https://doi.org/10.1097/SLA.0000000000004588.

21. Granzow JW, Soderberg JM, Dauphine C. A novel two-stage surgical approach to treat chronic lymphedema. Breast J 2014;20(4):420-422. https://doi.org/10.1111/tbj.12282.

22. Executive Committee of the International Society of lymphology. The diagnosis and treatment of peripheral lymphedema: 2020 consensus document of the International Society of Lymphology. Lymphology 2020;53(3):141-151.

23. Cellina M, Oliva G, Menozzi A, Soresina M, Martinenghi C, Gibelli D. Non-contrast magnetic resonance lymphangiography: an emerging technique for the study of lymphedema. Clin Imaging 2019;53:126-133. https://doi.org/10.1016/j.clinimag.2018.10.006.

24. International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. Lymphology 2013;46(1):1-11.

25. Lee E, Biko DM, Sherk W, Masch WR, Ladino-Torres M, Agarwal PP. Understanding lymphatic anatomy and abnormalities at imaging. Radiographics 2022;42(2):487-505. https://doi.org/10.1148/rg.210104.

26. Dori Y. Novel lymphatic imaging techniques. Tech Vasc Interv Radiol 2016;19(4):255-261. https://doi.org/10.1053/j.tvir.2016.10.002.

27. Rakow PL. Perspective on contact lenses: Profile of a researcher. J Ophthalmic Nurs Technol 2019;5(3):111-113.

28. Nadolski GJ, Itkin M. Feasibility of ultrasound-guided intranodal lymphangiogram for thoracic duct embolization. J Vasc Interv Radiol 2012;23(5):613-616. https://doi.org/10.1016/j.jvir.2012.01.078.

29. Nadolski GJ, Itkin M. Thoracic duct embolization for nontraumatic chylous effusion: Experience in 34 patients. Chest 2013;143(1):158-163. https://doi.org/10.1378/chest.12-0526.

30. Guermazi A, Brice P, Hennequin C, Sarfati E. Lymphography: An old technique retains its usefulness. Radiographics 2003;23(6):1541-1558; discussion 1559-60. https://doi.org/10.1148/rg.236035704.

31. Yoshida RY, Kariya S, Ha-Kawa S, Tanigawa N. Lymphoscintigraphy for imaging of the lymphatic flow disorders. Tech Vasc Interv Radiol 2016;19(4):273-276. https://doi.org/10.1053/j.tvir.2016.10.009.

32. Notohamiprodjo M, Weiss M, Baumeister RG, et al. MR lymphangiography at 3.0 T: Correlation with lymphoscintigraphy. Radiology 2012; 264(1):78-87. https://doi.org/10.1148/radiol.12110229.

33. Bellini C, Villa G, Sambuceti G, et al. Lymphoscintigraphy patterns in newborns and children with congenital lymphatic dysplasia. Lymphology 2014;47(1):28-39.

34. Kajita H, Kishi K. High-resolution imaging of lymphatic vessels with photoacoustic lymphangiography. Radiology 2019;292(1):35. https://doi.org/10.1148/radiol.2019190241.

35. Yamamoto T, Narushima M, Doi K, et al. Characteristic indocyanine green lymphography findings in lower extremity lymphedema: The generation of a novel lymphedema severity staging system using dermal backflow patterns. Plast Reconstr Surg 2011;127(5):1979-1986. https://doi.org/10.1097/PRS.0b013e31820cf5df.

36. Chang EI, Skoracki RJ, Chang DW. Lymphovenous anastomosis bypass surgery. Semin Plast Surg 2018;32(1):22-27. https://doi.org/10.1055/s-0038-1636510.

37. Mihara M, Hara H, Araki J, et al. Indocyanine green (ICG) lymphography is superior to lymphoscintigraphy for diagnostic imaging of early lymphedema of the upper limbs. PLoS One 2012;7(6):e38182. https://doi.org/10.1371/journal.pone.0038182.

38. Partsch H. Practical aspects of indirect lymphography and lymphoscintigraphy. Lymphat Res Biol 2003;1(1):71-73; discussion 73–4. https://doi.org/10.1089/15396850360495727.

39. Sevick-Muraca EM, Kwon S, Rasmussen JC. Emerging lymphatic imaging technologies for mouse and man. J Clin Invest 2014;124(3):905-914. https://doi.org/10.1172/JCI71612.

40. O'Donnell TF, Rasmussen JC, Sevick-Muraca EM. New diagnostic modalities in the evaluation of lymphedema. J Vasc Surg Venous Lymphat Disord 2017;5(2):261-273. https://doi.org/10.1016/j.jvsv.2016.10.083.

41. Suehiro K, Morikage N, Murakami M, Yamashita O, Samura M, Hamano K. Significance of ultrasound examination of skin and subcutaneous tissue in secondary lower extremity lymphedema. Ann Vasc Dis 2013;6(2):180-188. https://doi.org/10.3400/avd.oa.12.00102.

42. Clément O, Luciani A. Imaging the lymphatic system: Possibilities and clinical applications. Eur Radiol 2004;14(8):1498-1507. https://doi.org/10.1007/s00330-004-2265-9.

43. Dylke ES, McEntee MF, Schembri GP, et al. Reliability of a radiological grading system for dermal backflow in lymphoscintigraphy imaging. Acad Radiol 2013;20(6):758-763. https://doi.org/10.1016/j.acra.2013.01.018.

44. Unno N, Inuzuka K, Suzuki M, et al. Preliminary experience with a novel fluorescence lymphography using indocyanine green in patients with secondary lymphedema. J Vasc Surg 2007;45(5):1016-1021. https://doi.org/10.1016/j.jvs.2007.01.023.

45. Case TC, Witte CL, Witte MH, Unger EC, Williams WH. Magnetic resonance imaging in human lymphedema: Comparison with lymphangioscintigraphy. Magn Reson Imaging 1992;10(4):549-558. https://doi.org/10.1016/0730-725x(92)90006-l.

46. Liu N, Wang C, Sun M. Noncontrast three-dimensional magnetic resonance imaging vs lymphoscintigraphy in the evaluation of lymph circulation disorders: A comparative study. J Vasc Surg 2005;41(1):69-75. https://doi.org/10.1016/j.jvs.2004.11.013.

47. Liu NF, Lu Q, Jiang ZH, Wang CG, Zhou JG. Anatomic and functional evaluation of the lymphatics and lymph nodes in diagnosis of lymphatic circulation disorders with contrast magnetic resonance lymphangiography. J Vasc Surg 2009;49(4):980-987. https://doi.org/10.1016/j.jvs.2008.11.029.

48. Mazzei FG, Gentili F, Guerrini S, et al. MR lymphangiography: A practical guide to perform it and a brief review of the literature from a technical point of view. Biomed Res Int 2017;2017:2598358. https://doi.org/10.1155/2017/2598358.

49. 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 assessment. Radiology 2013; 269(3):893-902. https://doi.org/10.1148/radiol.13120145.

50. Crescenzi R, Donahue PMC, Hartley KG, et al. Lymphedema evaluation using noninvasive 3T MR lymphangiography. J Magn Reson Imaging 2017;46(5):1349-1360. https://doi.org/10.1002/jmri.25670.

51. Arrivé L, Derhy S, el Mouhadi S, Monnier-Cholley L, Menu Y, Becker C. Noncontrast magnetic resonance lymphography. J Reconstr Microsurg 2016;32(1):80-86. https://doi.org/10.1055/s-0035-1549133.

52. Cellina M, Gibelli D, Martinenghi C, et al. Non-contrast magnetic resonance lymphography (NCMRL) in cancer-related secondary lymphedema: Acquisition technique and imaging findings. Radiol Med 2021;126(11):1477-1486. https://doi.org/10.1007/s11547-021-01410-3.

53. Margaris KN, Black RA. Modelling the lymphatic system: Challenges and opportunities. J R Soc Interface 2012;9(69):601-612. https://doi.org/10.1098/rsif.2011.0751.

54. Chavhan GB, Amaral JG, Temple M, Itkin M. MR lymphangiography in children: Technique and potential applications. Radiographics 2017;37(6):1775-1790. https://doi.org/10.1148/rg.2017170014.

55. Pieper CC, Feisst A, Schild HH. Contrast-enhanced interstitial transpedal MR lymphangiography for thoracic chylous effusions. Radiology 2020;295(2):458-466. https://doi.org/10.1148/radiol.2020191593.

56. Ripley B, Wilson GJ, Lalwani N, Briller N, Neligan PC, Maki JH. Initial clinical experience with dual-agent relaxation contrast for isolated lymphatic channel mapping. Radiology 2018;286(2):705-714. https://doi.org/10.1148/radiol.2017170241.

57. Lohrmann C, Felmerer G, Foeldi E, Bartholomä JP, Langer M. MR lymphangiography for the assessment of the lymphatic system in patients undergoing microsurgical reconstructions of lymphatic vessels. Microvasc Res 2008;76(1):42-45. https://doi.org/10.1016/j.mvr.2008.03.003.

58. Mills M, van Zanten M, Borri M, et al. Systematic review of magnetic resonance lymphangiography from a technical perspective. J Magn Reson Imaging 2021;53(6):1766-1790. https://doi.org/10.1002/jmri.27542.

59. Lohrmann C, Foeldi E, Speck O, Langer M. High-resolution MR lymphangiography in patients with primary and secondary lymphedema. AJR Am J Roentgenol 2006;187(2):556-561. https://doi.org/10.2214/AJR.05.1750.

60. Ruehm SG, Schroeder T, Debatin JF. Interstitial MR lymphography with gadoterate meglumine: Initial experience in humans. Radiology 2001;220(3):816-821. https://doi.org/10.1148/radiol.2203010090.

61. Pan D, Suzuki Y, Yang PC, Rockson SG. Indirect magnetic resonance lymphangiography to assess lymphatic function in experimental murine lymphedema. Lymphat Res Biol 2006;4(4):211-216. https://doi.org/10.1089/lrb.2006.4405.

62. Lohrmann C, Foeldi E, Bartholomä JP, Langer M. Interstitial MR lymphangiography - A diagnostic imaging method for the evaluation of patients with clinically advanced stages of lymphedema. Acta Trop 2007;104(1):8-15. https://doi.org/10.1016/j.actatropica.2007.07.001.

63. Lohrmann C, Foeldi E, Langer M. Indirect magnetic resonance lymphangiography in patients with lymphedema preliminary results in humans. Eur J Radiol 2006;59(3):401-406. https://doi.org/10.1016/j.ejrad.2006.02.012.

64. Lu Q, Delproposto Z, Hu A, et al. MR lymphography of lymphatic vessels in lower extremity with gynecologic oncology-related lymphedema. PLoS One. 2012;7(11):e50319. https://doi.org/10.1371/journal.pone.0050319.

65. Dimakakos E, Koureas A, Koutoulidis V, et al. Interstitial magnetic resonance lymphography: The clinical effectiveness of a new method. Lymphology 2008;41(3):116-125.

66. Jeon JY, Lee SH, Shin MJ, Chung HW, Lee MH. Three-dimensional isotropic fast spin-echo MR lymphangiography of T1-weighted and intermediate-weighted pulse sequences in patients with lymphoedema. Clin Radiol 2016;71(1):e56-e63. https://doi.org/10.1016/j.crad.2015.10.015.

67. Lohrmann C, Pache G, Felmerer G, Foeldi E, Schaefer O, Langer M. Posttraumatic edema of the lower extremities: Evaluation of the lymphatic vessels with magnetic resonance lymphangiography. J Vasc Surg 2009;49(2):417-423. https://doi.org/10.1016/j.jvs.2008.08.069.

68. Lohrmann C, Foeldi E, Langer M. Assessment of the lymphatic system in patients with diffuse lymphangiomatosis by magnetic resonance imaging. Eur J Radiol 2011;80(2):576-581. https://doi.org/10.1016/j.ejrad.2009.10.021.

69. Felmerer G, Sattler T, Lohrmann C, Tobbia D. Treatment of various secondary lymphedemas by microsurgical lymph vessel transplantation. Microsurgery 2012;32(3):171-177. https://doi.org/10.1002/micr.20968.

70. Mitsumori LM, McDonald ES, Neligan PC, Maki JH. Peripheral magnetic resonance lymphangiography: Techniques and applications. Tech Vasc Interv Radiol 2016;19(4):262-272. https://doi.org/10.1053/j.tvir.2016.10.007.

71. Notohamiprodjo M, Baumeister RGH, Jakobs TF, et al. MR-lymphangiography at 3.0 T--a feasibility study. Eur Radiol 2009;19(11):2771-2778. https://doi.org/10.1007/s00330-009-1461-z.

72. Maki JH, Neligan PC, Briller N, Mitsumori LM, Wilson GJ. Dark blood magnetic resonance lymphangiography using dual-agent relaxivity contrast (DARC-MRL): A novel method combining gadolinium and iron contrast agents. Curr Probl Diagn Radiol 2016;45(3):174-179. https://doi.org/10.1067/j.cpradiol.2015.08.003.

73. Pamarthi V, Pabon-Ramos WM, Marnell V, Hurwitz LM. MRI of the central lymphatic system: Indications, imaging technique, and preprocedural planning. Top Magn Reson Imaging 2017;26(4):175-180. https://doi.org/10.1097/RMR.0000000000000130.

74. 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):871-878. https://doi.org/10.1148/radiol.14131399.

75. 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):1689-1696. https://doi.org/10.1513/AnnalsATS.201604-292OC.

76. Kim G, Smith MP, Donohoe KJ, Johnson AR, Singhal D, Tsai LL. MRI staging of upper extremity secondary lymphedema: Correlation with clinical measurements. Eur Radiol 2020;30(8):4686-4694. https://doi.org/10.1007/s00330-020-06790-0.

77. Arrivé L, Derhy S, Dahan B, et al. Primary lower limb lymphoedema: Classification with non-contrast MR lymphography. Eur Radiol 2018;28(1):291-300. https://doi.org/10.1007/s00330-017-4948-z.

78. Arrivé L, Derhy S, Dlimi C, el Mouhadi S, Monnier-Cholley L, Becker C. Noncontrast magnetic resonance lymphography for evaluation of lymph node transfer for secondary upper limb lymphedema. Plast Reconstr Surg 2017;140(6):806e-811e. https://doi.org/10.1097/PRS.0000000000003862.

79. Cellina M, Gibelli D, Martinenghi C, et al. Noncontrast magnetic resonance lymphography in secondary lymphedema due to prostate cancer. Lymphat Res Biol 2021;19(4):355-361. https://doi.org/10.1089/lrb.2020.0034.

80. Kim G, Donohoe K, Smith MP, et al. Use of non-contrast MR in diagnosing secondary lymphedema of the upper extremities. Clin Imaging 2021;80:80-405. https://doi.org/10.1016/j.clinimag.2021.08.018.

81. Crescenzi R, Donahue PMC, Garza M, et al. Elevated magnetic resonance imaging measures of adipose tissue deposition in women with breast cancer treatment-related lymphedema. Breast Cancer Res Treat 2022;191(1):115-124. https://doi.org/10.1007/s10549-021-06419-w.

82. Szuba A, Shin WS, Strauss HW, Rockson S. The third circulation: Radionuclide lymphoscintigraphy in the evaluation of lymphedema. J Nucl Med 2003;44(1):43-57.

83. Olszewski WL, Zaleska MT, Jakimowicz-Cakala M. *Pathology and histochemistry*. Heidelberg, Germany: Springer International Publishing; 2018. p 125-138. https://doi.org/10.1007/978-3-319-52423-8_10.

84. Cellina M, Martinenghi C, Panzeri M, et al. Noncontrast MR lymphography in secondary lower limb lymphedema. J Magn Reson Imaging 2021;53(2):458-466. https://doi.org/10.1002/jmri.27328.

85. Xing ZG, Chen X, Hua ZJ, Qi ZJ, Bin WY, Qiu WZ. MR lymphangiography at 3.0 tesla to assess the function of inguinal lymph node in low

extremity lymphedema. J Magn Reson Imaging 2014;40(6):1430-1436. https://doi.org/10.1002/jmri.24499.

86. Dayan JH, Wiser I, Verma R, et al. Regional patterns of fluid and fat accumulation in patients with lower extremity lymphedema using magnetic resonance angiography. Plast Reconstr Surg 2020;145(2):555-563. https://doi.org/10.1097/PRS.0000000000006520.

87. Soga S, Onishi F, Mikoshi A, Okuda S, Jinzaki M, Shinmoto H. Lower limb lymphedema staging based on magnetic resonance lymphangiography. J Vasc Surg Venous Lymphat Disord 2022;10(2):445-453.e3. https://doi.org/10.1016/j.jvsv.2021.06.006.

88. Hadjis NS, Carr DH, Banks L, Pflug JJ. The role of CT in the diagnosis of primary lymphedema of the lower limb. AJR Am J Roentgenol 1985;144(2):361-364. https://doi.org/10.2214/ajr.144.2.361.

89. Kim G, Tsai LL. Use of non-contrast MR in diagnosing secondary lymphedema of the upper extremities (reply to a letter to the Editor). Clin Imaging 2022;82:171. https://doi.org/10.1016/j.clinimag.2021.11.020.

90. Duewell S, Hagspiel KD, Zuber J, von Schulthess GK, Bollinger A, Fuchs WA. Swollen lower extremity: Role of MR imaging. Radiology 1992;184(1):227-231. https://doi.org/10.1148/radiology.184.1.1609085.

91. Crescenzi R, Donahue PMC, Garza M, et al. Subcutaneous adipose tissue edema in lipedema revealed by noninvasive 3T MR lymphangiography. J Magn Reson Imaging 2022;3. https://doi.org/10.1002/jmri.28281.

92. Duhon BH, Phan TT, Taylor SL, Crescenzi RL, Rutkowski JM. Current mechanistic understandings of lymphedema and lipedema: Tales of fluid, fat, and fibrosis. Int J Mol Sci 2022;23(12):6621. https://doi.org/10.3390/ijms23126621.

93. Ciudad P, Sabbagh MD, Agko M, et al. Surgical management of lower extremity Llymphedema: A comprehensive review. Indian J Plast Surg 2019;52(1):81-92. https://doi.org/10.1055/s-0039-1688537.

94. Garza R, Skoracki R, Hock K, Povoski SP. A comprehensive overview on the surgical management of secondary lymphedema of the upper and lower extremities related to prior oncologic therapies. BMC Cancer 2017;17(1):468. https://doi.org/10.1186/s12885-017-3444-9.

95. Gould DJ, Mehrara BJ, Neligan P, Cheng MH, Patel KM. Lymph node transplantation for the treatment of lymphedema. J Surg Oncol 2018;118(5):736-742. https://doi.org/10.1002/jso.25180.

96. Becker C, Assouad J, Riquet M, Hidden G. Postmastectomy lymphedema: Long-term results following microsurgical lymph node transplantation. Ann Surg 2006;243(3):313-315. https://doi.org/10.1097/01.sla.0000201258.10304.16.

97. Bakar Y, Tuğral A. Lower extremity lymphedema management after gynecologic cancer surgery: A review of current management strategies. Ann Vasc Surg 2017;44:442-450. https://doi.org/10.1016/j.avsg.2017.03.197.

98. Dessources K, Aviki E, Leitao MM. Lower extremity lymphedema in patients with gynecologic malignancies. Int J Gynecol Cancer 2020;30(2):252-260. https://doi.org/10.1136/ijgc-2019-001032.

99. Biko DM, Smith CL, Otero HJ, et al. Intrahepatic dynamic contrast MR lymphangiography: Initial experience with a new technique for the assessment of liver lymphatics. Eur Radiol 2019;29(10):5190-5196. https://doi.org/10.1007/s00330-019-06112-z.

100. Dori Y, Smith CL, DeWitt AG, et al. Intramesenteric dynamic contrast pediatric MR lymphangiography: Initial experience and comparison with intranodal and intrahepatic MR lymphangiography. Eur Radiol 2020;30(10):5777-5784. https://doi.org/10.1007/s00330-020-06949-9.

101. Pieper CC. Nodal and pedal MR lymphangiography of the central lymphatic system: Techniques and applications. Semin Intervent Radiol 2020;37(3):250-262. https://doi.org/10.1055/s-0040-1713442.

102. Guiotto M, Bramhall RJ, Campisi C, Raffoul W, di Summa PG. A systematic review of outcomes after genital lymphedema surgery: Microsurgical reconstruction versus excisional procedures. Ann Plast Surg 2019;83(6):e85-e91. https://doi.org/10.1097/SAP.0000000000001875.

103. Lu Q, Jiang Z, Zhao Z, et al. Assessment of the lymphatic system of the genitalia using magnetic resonance lymphography before and after treatment of male genital lymphedema. Medicine 2016;95(21):e3755. https://doi.org/10.1097/MD.0000000000003755.

104. Hara H, Mihara M. Indocyanine green lymphographic and lymphoscintigraphic findings in genital lymphedema-genital pathway score. Lymphat Res Biol 2017;15(4):356-359. https://doi.org/10.1089/lrb.2017.0025.

105. Yamamoto T, Yamamoto N, Furuya M, Hayashi A, Koshima I. Genital lymphedema score: Genital lymphedema severity scoring system based on subjective symptoms. Ann Plast Surg 2016;77(1):119-121. https://doi.org/10.1097/SAP.0000000000000360.

106. Kwon LM, Hur S, Kim KM, Im YJ, Ha J, Chung JW. Lymphatic embolization for primary Chylous reflux of genitalia in 2 cases. J Vasc Interv Radiol 2019;30(7):1140-1143. https://doi.org/10.1016/j.jvir.2018.12.706.

107. Ridner SH, Dietrich MS, Niermann K, Cmelak A, Mannion K, Murphy B. A prospective study of the lymphedema and fibrosis continuum in patients with head and neck cancer. Lymphat Res Biol 2016;14(4):198-205. https://doi.org/10.1089/lrb.2016.0001.

108. Deng J, Ridner SH, Dietrich MS, et al. Factors associated with external and internal lymphedema in patients with head-and-neck cancer. Int J Radiat Oncol Biol Phys 2012;84(3):e319-e328. https://doi.org/10.1016/j.ijrobp.2012.04.013.

109. Smith BG, Lewin JS. Lymphedema management in head and neck cancer. Curr Opin Otolaryngol Head Neck Surg 2010;18(3):153-158. https://doi.org/10.1097/MOO.0b013e32833aac21.

110. Purcell A, Nixon J, Fleming J, McCann A, Porceddu S. Measuring head and neck lymphedema: The "ALOHA" trial. Head Neck 2016;38(1):79-84. https://doi.org/10.1002/hed.23853.

111. Loo BW, Draney MT, Sivanandan R, et al. Indirect MR lymphangiography of the head and neck using conventional gadolinium contrast: A pilot study in humans. Int J Radiat Oncol Biol Phys 2006;66(2):462-468. https://doi.org/10.1016/j.ijrobp.2006.05.045.

112. Graves MJ, Mitchell DG. Body MRI artifacts in clinical practice: A physicist's and radiologist's perspective. J Magn Reson Imaging 2013;38(2):269-287. https://doi.org/10.1002/jmri.24288.

113. Sammet S. Magnetic resonance safety. Abdom Radiol (NY) 2016;41(3):444-451. https://doi.org/10.1007/s00261-016-0680-4.

114. Tsai LL, Grant AK, Mortele KJ, Kung JW, Smith MP. A practical guide to MR imaging safety: What radiologists need to know. Radiographics 2015;35(6):1722-1737. https://doi.org/10.1148/rg.2015150108.

115. Zheng Q, Itkin M, Fan Y. Quantification of thoracic lymphatic flow patterns using dynamic contrast-enhanced MR lymphangiography. Radiology 2020;296(1):202-207. https://doi.org/10.1148/radiol.2020192337.

116. Sibley R, Moroz M, Vasanawala S, Loenig A, Agarwal N, Hargreaves BA. Iron oxide nanoparticle magnetic resonance lymphangiography (ION-MRL): A simplified technique for evaluating the peripheral and central lymphatic system. *Joint Annual Meeting ISMRM-ESMRMB & ISMRT 31st Annual Meeting*. Berkeley, California, USA; 2022.

117. Vasanawala SS, Yu H, Shimakawa A, Jeng M, Brittain JH. Estimation of liver T_2 in transfusion-related iron overload in patients with weighted least squares T_2 IDEAL. Magn Reson Med 2012;67(1):183-190. https://doi.org/10.1002/mrm.22986.

118. Sharma SD, Fischer R, Schoennagel BP, et al. MRI-based quantitative susceptibility mapping (QSM) and R2* mapping of liver iron overload: Comparison with SQUID-based biomagnetic liver susceptometry. Magn Reson Med 2017;78(1):264-270. https://doi.org/10.1002/mrm.26358.

119. Magnitsky S, Zhang J, Idiyatullin D, et al. Positive contrast from cells labeled with iron oxide nanoparticles: Quantitation of imaging data. Magn Reson Med 2017;78(5):1900-1910. https://doi.org/10.1002/mrm.26585.

120. Liu W, Dahnke H, Rahmer J, Jordan EK, Frank JA. Ultrashort T2* relaxometry for quantitation of highly concentrated superparamagnetic iron oxide (SPIO) nanoparticle labeled cells. Magn Reson Med 2009;61(4):761-766. https://doi.org/10.1002/mrm.21923.