

Two Non-gadolinium-based, Innovative Approaches to Preoperative Lymphangiography

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Summary: Most magnetic resonance lymphangiography techniques employ intravenous gadolinium-based contrast agents, which carry a US Food and Drug Administration warning about gadolinium retention in the body when used intravenously. Because of this, there may be reluctance to perform intradermal injections of gadolinium-based contrast agents in patients with obstructed lymphatic drainage due to concerns about gadolinium retention in the skin and soft tissues and potential-related toxicity. The aim of this study was to show proof of concept of 2 preoperative lymphangiographic techniques that do not use gadolinium-based contrast agents. One technique used contrast-enhanced ultrasound with intradermal injections of microbubbles (Lumason) in a patient with stage 3, nonpitting left upper extremity edema. Another technique used magnetic resonance imaging with intradermal injections of 0.03 mg/mL or 0.003% ferumoxytol (Feraheme) in a patient with stage 3, nonpitting right lower extremity edema. Both contrast-enhanced ultrasound with microbubbles and magnetic resonance lymphangiogram with ferumoxytol were able to identify candidates for lymphovenous bypass surgery. These candidates were not identified by conventional indocyanine green injections. The authors conclude that (1) low-dose ferumoxytol is a potentially effective non-gadolinium-based contrast alternative to gadolinium-based contrast agent in magnetic resonance lymphangiography and (2) contrast-enhanced ultrasound can identify candidate lymphatic vessels for anastomosis. (*Plast Reconstr Surg Glob Open* 2020;8:e2805; doi: [10.1097/GOX.0000000000002805](https://doi.org/10.1097/GOX.0000000000002805); Published online 22 April 2020.)

INTRODUCTION

Lymphovenous bypass surgery^{1,2} for patients with stage 3 extremity lymphedema is time consuming, with up to 75% of intraoperative time spent using indocyanine green injection and near-infrared fluorescence imaging searching for viable lymphatic vessels and venules for bypass. Despite multiple cut-downs and supermicrosurgical dissection, functional vessels are not always identified.

Preoperatively mapping the lymphatics with magnetic resonance (MR) lymphangiography³⁻⁶ involves injecting gadolinium-based contrast agent into the skin. The US Food and Drug Administration warns of gadolinium retention in the body with intravenously administered

gadolinium-based contrast agent⁷⁻¹⁰ and of the risk of nephrogenic systemic fibrosis, a debilitating, incurable condition in patients with renal failure. Although adverse effects associated with gadolinium-based contrast agents in patients with lymphedema have not been reported, there may be reluctance to inject gadolinium-based contrast agent intradermally in patients with severely compromised lymphatic drainage.

Ferumoxytol (Feraheme; AMAG Pharmaceuticals, Waltham, Mass.), a carbohydrate-coated, superparamagnetic iron oxide nanoparticle taken up by the mononuclear phagocyte system, is used as an intravenous iron supplement for the treatment of anemia and exhibits a long blood half-life of 14–21 hours.¹¹ The concentration-dependent intrinsic T1-shortening properties of ferumoxytol on magnetic resonance imaging (MRI) are well known and make it appealing for off-label use as a non-gadolinium-based contrast agent for vascular MRI.^{11,12} Because ferumoxytol is not associated with a risk of nephrogenic sclerosis, it may have a safer profile as a contrast agent compared with gadolinium-based contrast agents in some applications.¹³

Contrast-enhanced ultrasound (CEUS) examinations use microbubbles containing a variety of different

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gases covered by a shell. The microbubbles compress and expand when scanned with ultrasound, creating contrast in the image. Intravenous ultrasound contrast agents are most commonly used to characterize lesions or improve lesion detection,^{14,15} and intradermal administration of microbubbles (Lumason; Bracco Suisse SA, Plan-les-Ouates Geneve, Switzerland) has been used for identification of sentinel lymph nodes.^{16,17}

The authors describe 2 preoperative lymphangiographic techniques that do not use gadolinium-based contrast agents. One uses intradermal injections of ferumoxytol followed by MRI. The other uses intradermal injections of microbubbles followed by ultrasound. We show how each technique is able to preoperatively identify candidate lymphatic vessels when current conventional techniques are unsuccessful.

PATIENTS AND METHODS

Ferumoxytol

A 70-year-old woman with stage 3, nonpitting right lower extremity edema was scheduled for lymphovenous bypass surgery. The risks and benefits of off-label use of ferumoxytol as an MRI contrast agent were discussed with the patient. Earlier in vitro MRI scans of serial dilutions of

ferumoxytol with normal saline starting from 0.75% suggested that a 0.03 mg/mL (0.003%) concentration would provide optimal contrast enhancement for T1-weighted images. Ferumoxytol (0.003%) was injected intradermally at 8 different locations (Fig. 1). Each site was massaged for about 5–10 seconds, and skin fiducials were placed at the injection sites. MRI at 1.5T (Signa HDx; GE Healthcare, Waukesha, Wisc.) consisted of multiplanar 3D T1-weighted spoiled gradient echo images (Fig. 2).

Microbubbles

A 53-year-old woman with stage 3, nonpitting left upper extremity lymphedema was scheduled for lymphovenous bypass. Eight intradermal injections of microbubbles were administered with each site massaged following injection.



Fig. 1. Sites and volume of ferumoxytol intradermal injections. Eight different sites were targeted for intradermal injection along the ventral surface of the right lower extremity (n,v) = (injection #, mL of 0.003% ferumoxytol).



Fig. 2. MRI of the distal right calf (injection #5 and #6 in Fig. 1) about 25 minutes after intradermal ferumoxytol injection. Coronal reformatted image shows ferumoxytol contrast within suspected lymphatic vessels (arrows). The highest signaling areas correspond to the areas of injection laterally (*, injection #6) and medially (**, injection #5).

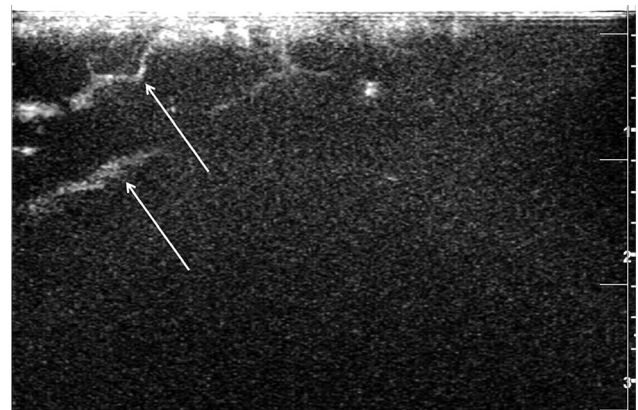


Fig. 3. CEUS examination of the left upper extremity. Microbubble contrast is identified in what is believed to be lymphatic vessels (arrows) in the contrast-specific images. The contrast-specific image is a summation of 7 cine frames near the medial distal arm at the level of the elbow.

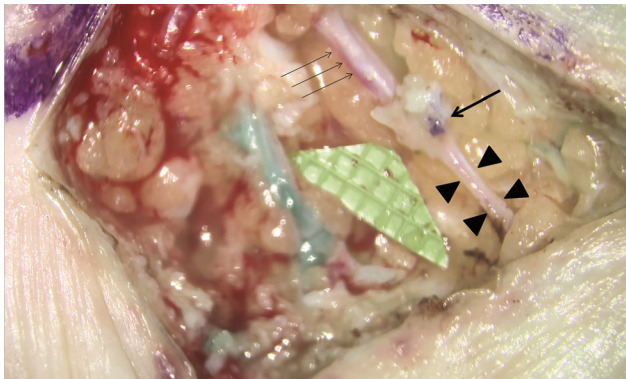


Fig. 4. Intraoperative photograph. In the leg, end vein (triangles) to lymphatic (thin arrows) anastomosis was performed by telescopic technique with 11-0 Nylon sutures at the anastomosis (thick arrows). Thin arrows show the string-like lymphatics. Despite no lumen, copious clear lymph leak exuded from its stump. Image was taken under Mitaka MM51 Series $\times 30$ magnification.

Ultrasound was then performed cephalad from each site to identify possible lymphatics (Fig. 3). The most promising lymphatic vessel was identified in the ventral medial distal arm near the elbow.

For both ferumoxytol MR lymphangiography and CEUS lymphangiography with microbubbles, possible functional lymphatics were marked on the skin with indelible ink after the examination. At the time of surgery, both techniques correctly identified a lymphatic vessel not located intraoperatively by conventional indocyanine green and near-infrared fluorescence imaging. The target lymphatic vessel identified by each technique facilitated straightforward lymphovenous bypass. The techniques were sensitive for detecting fibrotic lymphatic channels that actively drained fluid during surgical exploration. Without true lumen for end-to-end anastomosis, these channels were inserted into a vein lumen as a telescoping lymphovenous anastomosis (Fig. 4).

DISCUSSION

This article presents proof of concept of 2 alternatives to gadolinium-based, contrast-enhanced MR lymphangiography. One method uses intradermal ferumoxytol and MRI, and the other employs intradermal microbubbles and ultrasound.

Updated by the Food and Drug Administration in March 2015, the ferumoxytol prescribing information contains a black box warning for serious hypersensitivity reactions including anaphylaxis.¹⁸ The ferumoxytol used intradermally in our study is diluted to 0.003% with normal saline which is 1,000 times more dilute than the commercial concentration of ferumoxytol (3%) and as much as 280 times more dilute than typically used for intravenous MRI contrast.

In this study, preliminary in vitro scans of serial dilutions of ferumoxytol showed MRI signal suppression for concentrations $>0.3\%$, a result of the dominant T2* (effective T2 or T2-star) shortening effect, whereas at lower dilutions, the T1-shortening effect becomes

predominant, thereby leading to increased signal intensity on T1-weighted images. T2* effects of intravenous ferumoxytol have been used to suppress venous contamination signal.¹⁹ In comparison, the 0.003% dilution used here provided enough T1 signal for contrast conspicuity, while minimizing T2*-associated signal loss.

Intraoperative ultrasound typically uses conventional B-mode imaging.²⁰ The conspicuity of microbubbles in or exuding from lymphatic vessels suggests that contrast-specific ultrasound imaging may provide useful preoperative or even intraoperative information, particularly in patients with metallic prostheses which cause MRI susceptibility artifacts.

Ferumoxytol is commercially supplied as a 510 mg/17 mL vial with a wholesale acquisition cost of \$1,071, considerably more expensive than gadolinium-based contrast agents (\$83–\$166) and microbubbles (\$142). However, the cost may be offset by reduced intraoperative time spent searching for viable lymphatic vessels and venules.

We believe that ferumoxytol injection can be performed 1–2 hours before MR lymphangiography, possibly depending on the degree of lymphatic obstruction. Ferumoxytol MR lymphangiography should be a straightforward examination, consisting of standard 3D T1-weighted images acquired in multiple planes. CEUS lymphangiography should also translate relatively easily from its current use for lesion detection or sentinel lymph node identification.

These 2 novel lymphangiographic techniques could potentially be useful for identifying lymphatic vessels in difficult patient populations where conventional methods have failed. Comparative analysis, longitudinal evaluation, and dose dependence of ferumoxytol for different stages of lymphedema are topics for future investigations.

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