European Radiology (2020) 30:4686–4694
https://doi.org/10.1007/s00330-020-06790-0

MUSCULOSKELETAL

MRI staging of upper extremity secondary lymphedema: correlation with clinical measurements

Geunwon Kim[1] · Martin P. Smith[1] · Kevin J. Donohoe[1] · Anna Rose Johnson[2] · Dhruv Singhal[2] · Leo L. Tsai[1]

Received: 19 December 2019 / Revised: 17 February 2020 / Accepted: 4 March 2020 / Published online: 27 March 2020
© European Society of Radiology 2020

Abstract

Objectives Staging of upper extremity lymphedema is needed to guide surgical management, but is not standardized due to lack of accessible, quantitative, or precise measures. Here, we established an MRI-based staging system for lymphedema and validate it against existing clinical measures.

Methods Bilateral upper extremity MRI and lymphoscintigraphy were performed on 45 patients with unilateral secondary lymphedema, due to surgical intervention, who were referred to our multidisciplinary lymphedema clinic between March 2017 and October 2018. MRI short-tau inversion recovery (STIR) images were retrospectively reviewed. A grading system was established based on the cross-sectional circumferential extent of subcutaneous fluid infiltration at three locations, labeled MRI stage 0–3, and was compared to L-Dex®, ICG lymphography, volume, lymphedema quality of life (LYMQOL), International Society of Lymphology (ISL) stage, and lymphoscintigraphy. Linear weighted Cohen's kappa was calculated to compare MRI staging by two readers.

Results STIR images on MRI revealed a predictable pattern of fluid infiltration centered on the elbow and extending along the posterior aspect of the upper arm and the ulnar side of the forearm. Patients with higher MRI stage were more likely to be in ISL stage 2 ($p = 0.002$) or to demonstrate dermal backflow on lymphoscintigraphy ($p = 0.0002$). No correlation was found between MRI stages and LYMQOL. Higher MRI stage correlated with abnormal ICG lymphography pattern ($r_s = 0.63$, $p < 0.0001$), larger % difference in limb volume ($r_s = 0.68$, $p < 0.0001$), and higher L-Dex® ratio ($r_s = 0.84$, $p < 0.0001$). Cohen's kappa was 0.92 (95% CI, 0.85–1.00).

Conclusion An MRI staging system for upper extremity lymphedema offers an improved non-invasive precision marker for lymphedema for therapeutic planning.

Key Points

- *Diagnosis and staging of patients with secondary upper extremity lymphedema may be performed with non-contrast MRI, which is non-invasive and more readily accessible compared to lymphoscintigraphy and evaluation by lymphedema specialists.*
- *MRI-based staging of secondary upper extremity lymphedema is highly reproducible and could be used for long-term follow-up of patients.*
- *In patients with borderline clinical measurements, MRI can be used to identify patients with early-stage lymphedema.*

Keywords Lymphedema · Lymphography · Lymphoscintigraphy

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00330-020-06790-0) contains supplementary material, which is available to authorized users.

✉ Geunwon Kim
gkim6@bidmc.harvard.edu

[1] Department of Radiology, Beth Israel Deaconess Medical Center, Shapiro 463, 330 Brookline Ave., Boston, MA 02215, USA

[2] Department of Surgery, Beth Israel Deaconess Medical Center, 330 Brookline Ave., Boston, MA 02215, USA

Abbreviations

ANOVA	Analysis of variance
BMI	Body mass index
DB	Dermal backflow
ICG	Indocyanine green
ISL	International Society of Lymphology
LYMQOL	Lymphedema Quality of Life
MRI	Magnetic resonance imaging
QoL	Quality of life
STIR	Short-tau inversion recovery

Introduction

Upper extremity lymphedema is a chronic disease affecting 3–30% of patients receiving breast cancer therapy depending on the treatment received [1, 2]. There is increasing interest in more accurate and timely diagnoses of secondary lymphedema as well as better characterization of the spatial distribution of fluid infiltration, due to improving microsurgical techniques such as lymphovenous bypass and lymph node transplants that can be tailored for each patient. To date, the diagnosis of lymphedema relies mostly on history and physical examination findings, with limb volume discrepancy as the most quantitative marker [3]. The most widely used staging system by the International Society of Lymphology (ISL) only uses clinical physical exam findings to categorize disease severity [4, 5]. These methods, however, rely on global measures that are imprecise and do not reveal the spatial distribution of fluid infiltration, which the description is required for emerging surgical techniques. Other grading systems, such as lymphedema-specific quality of life questionnaires (LYMQOL) and bioimpedance spectroscopy, lack sensitivity [6–9].

Imaging of lymphedema focuses on the evaluation of lymphatic function, with either radionuclide, MR lymphoscintigraphy, or ICG lymphography, with the diagnosis of lymphedema supported by indicators of lymphatic disruption such as dermal backflow (DB) [10–12]. However, these methods are used in a binary fashion only to diagnose or exclude lymphedema, and prior attempts at staging the severity of disease with lymphoscintigraphy have demonstrated variable results [13–17]. To date, no imaging technique has been widely adopted for the staging of lymphedema.

Non-contrast MRI lymphangiography is being increasingly used in the presurgical evaluation of secondary lymphedema due to its non-invasiveness and its ability to show the distribution of fluid infiltration and fat throughout affected extremities. These capabilities, coupled with the capability to detect small amounts of fluid that are below the sensitivity of existing techniques, make MRI an ideal modality to grade lymphedema severity. Already, MR lymphangiography has demonstrated to be a reliable tool in detecting and grading lymphedema severity in the lower extremity as well as evaluating residual post-surgical follow-up after lymph node transfer in the upper extremity [12, 18, 19]. In this study, we developed a simple, checklist-type MRI-based staging system based on the degree of circumferential subcutaneous fluid infiltration seen on a fluid-sensitive sequence. We have chosen to use the term "fluid infiltration" rather than "edema," which is often used interchangeably. However, "edema" technically refers to swelling secondary to the presence of excess fluid within the tissues, while we are referring specifically to the presence and distribution of abnormal fluid. We hypothesize that this MRI staging system could be used to supplement or replace ISL staging and other existing clinical measures of lymphedema. The purpose of this study was to test the reproducibility of this MRI staging system and validate its performance against established clinical measures in a cohort of patients with secondary upper extremity lymphedema.

Methods

Patient selection

This HIPAA-compliant retrospective study was approved by the institutional review board, which waived requirement for informed consent for review of medical records and images. Patients were first evaluated at our multidisciplinary clinic specializing in lymphatic medicine and surgery. Those who were subsequently clinically diagnosed with secondary upper extremity lymphedema and who were potential candidates for surgical lymphatic repair were referred for imaging.

MRI was performed on consecutive 51 patients (49 women and 2 men) with unilateral upper extremity lymphedema between March 2017 and September 2018. Patients who had both lymphoscintigraphy and MRI within 1 month were included. No new intervention, either surgical or any change to existing conservative treatments, was introduced during the period between MRI and lymphoscintigraphy or other clinical measurements. Five patients did not meet the 30-day imaging window and were excluded. The remaining 45 patients (43 women and 2 men) were included in the final analysis (Fig. 1).

Clinical measures

Clinical history and physical evaluations were performed by a lymphatic surgeon and a lymphatic medicine internist. Evaluation by a lymphedema certified physical therapist included quantitative measurements (limb volume and L-Dex®), and Lymphedema Quality of Life score (LYMQOL), a validated tool consisting of 28 questions evaluating overall quality of life (QoL) and four domains: function, appearance, symptoms, and mood [20]. At the conclusion of the clinical evaluation, International Society of Lymphology (ISL) staging was provided on 36 of 45 patients. Limb volume, L-Dex® ratio (L-Dex®), and lymphography techniques are detailed in Supplement Materials.

MRI

All MRI was performed on a single 1.5-T scanner (Siemens Magnetom Aera) using two 13-channel body array coils. Patients were instructed to remove compression garments for at least 48 h prior to the MRI. Patients were placed supine with arms at the sides, palms facing medially. The target limb was positioned as close to the magnet isocenter as possible and a

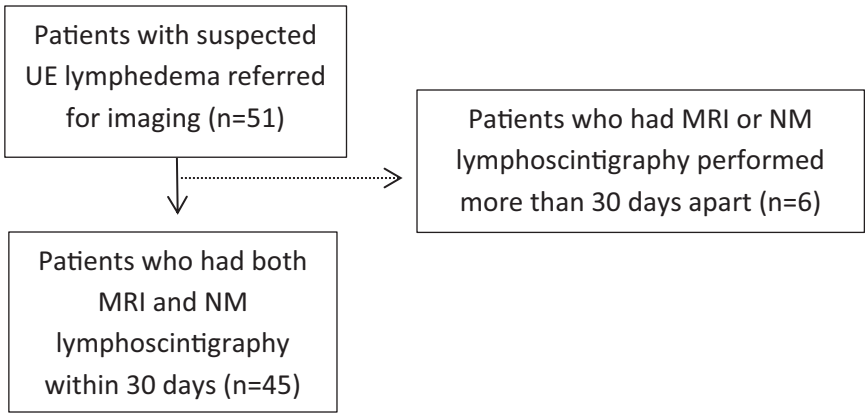

Fig. 1 Flowchart of participants. Upper extremity (UE) MRI was performed on 51 patients who were referred from the lymphedema multidisciplinary group. Six patients were excluded from analysis due to having MRI and lymphoscintigraphy performed more than 30 days apart. The remaining 45 patients were included in this retrospective study

1.5-cm-thick cushion placed between the arm and torso to provide a small gap to reduce the potential for wrap artifacts from the lower abdominal side wall or lateral breast tissue overlapping with the extremity. The unaffected limb was imaged first to serve as a control, then the patient was repositioned to place the second limb at the isocenter. Two imaging stations were acquired for each limb. The first station spanned the upper arm, from shoulder to elbow, and included the ipsilateral upper chest wall and breast. The second station covered the forearm, from the elbow to the dorsum of the hand. Axial short-tau inversion recovery (STIR) sequence images were acquired, with the following base parameters: for the upper station, TR = 7080 ms, TE 53 ms, echo train length 16, field of view 400 × 200 mm, 52 slices, slice thickness 6 mm, matrix size 384 × 192. For the lower station, TR 7150 ms, TE 53 ms, echo train length 16, field of view 160 × 145 mm, 52 slices, slice thickness 6 mm, matrix size 192 × 174. Phase encoding was performed in the anterior-posterior direction for both stations.

Lymphoscintigraphy

Patients were instructed to remove compression garments for at least 48 h prior to lymphoscintigraphy. Please refer to the Supplement Materials for technical details. First, the flow of radiotracer was assessed with images acquired at 30 s/frame for 20 min. The initial static images were acquired at 1 h and the delayed at 2 h or 6 h for 5 min each with transmission images to assess for the presence of dermal backflow [21] and lymphatic flow.

Imaging analysis

A 4th year resident and a board-certified radiologist with 5 years of experience analyzed MRI images using McKesson PACS. A nuclear medicine board-certified expert with 32 years of experience analyzed the lymphoscintigraphy using MIM Software. Imaging analysis was performed independently with each reader blinded to patients' clinical history and all other clinical and imaging data.

MRI staging

The MRI staging system, based on STIR images, is summarized in Table 1 and Figs. 2, 3, and 4. The staging is based on the degree of circumferential subcutaneous fluid infiltration seen along the epifascial regions or infiltrating the subcutaneous fat, evaluated across the axial plane at three points: the elbow, 5–8 cm proximal to the radial head (upper arm), and 5–8 cm distal to the olecranon (forearm). MRI stage 0 is assigned when no fluid infiltration of the subcutaneous tissue is detected, and MRI stage 1–3 reflect increasing severity of disease. In MRI stage 1, which represents the mildest manifestation, there is fluid infiltration of the subcutaneous tissue that does not exceed 50% of the circumference of the upper extremity at any level (Fig. 2). At this stage, fluid is usually first seen along the posterior aspect of the elbow, then along the ulnar aspect of the forearm, and often absent or minimal at the upper arm. MRI stage 2 is defined by the presence of circumferential fluid infiltration exceeding 50% at any level, with the forearm usually worse and occasionally demonstrating complete circumferential involvement, but without all three levels simultaneously exceeding 75% (Fig. 3). Stage 3, the most severe, is assigned when all three regions demonstrate complete or near-complete (> 75%) circumferential fluid infiltration (Fig. 4). Near-complete circumferential fluid infiltration of the upper arm is typically a defining feature of stage 3. The recommended approach is to determine if the patient is MRI stage 0, 1, or 3, with MRI stage 2 not meeting the criteria for the other stages (Table 1).

Statistical analysis

Linear weighted Cohen's kappa was calculated to assess interobserver agreement. In 4 cases where staging classification differed between the two readers by 1 level, consensus

Table 1 Summary of MRI staging. Determination of the degree of circumferential fluid infiltration is determined by a single axial STIR image at the forearm (5–8 cm distal to the olecranon), the elbow, and the upper arm (5–8 cm proximal to the olecranon)

MRI stage	Definition
0	No detectable fluid infiltration at any level (forearm, elbow, or upper arm)
1	Circumferential fluid infiltration does not exceed 50% at forearm, elbow, or upper arm
2	Circumferential fluid infiltration may exceed 50% at any level, but does not meet stage 3 criteria
3	Circumferential fluid infiltration exceeds 75% at all three levels

decision for staging was arrived and used for the remainder of the statistical analyses.

One-way analysis of variance (ANOVA) with post hoc Tukey HSD test was used to analyze the differences in age, symptom duration, and body mass index (BMI) between the MRI stages. Fisher's exact test was used to analyze the relationship between the ISL stage, LYMQOL, DB, and MRI stage. Mann-Whitney *U* test was used to compare the distribution of MRI stage in the conservative and surgical treatment groups. Spearman rank-order correlation and one-way ANOVA with post hoc Tukey HSD tests were used to analyze relationship between MRI stage and L-Dex®, ICG lymphography, and limb volume. The statistical analysis was performed using a software (SAS version 9.4 of the SAS System for Windows; SAS Institute), and free online statistical calculators MedCalc, available at https://www.medcalc.org/calc/, and VassarStats, available at http://vassarstats.net/.

Results

Forty-five patients were included in the analysis (Fig. 1). Patient demographics are summarized in Table 2. Forty-one of 45 (91.1%) patients had a history of breast cancer. Of these, 73% (30/41) had a unilateral or bilateral mastectomy and 27% (11/41) had a lumpectomy (Table 1). Twenty-seven mastectomy patients also underwent axillary lymph node dissection (ALND) on the side that developed lymphedema. The

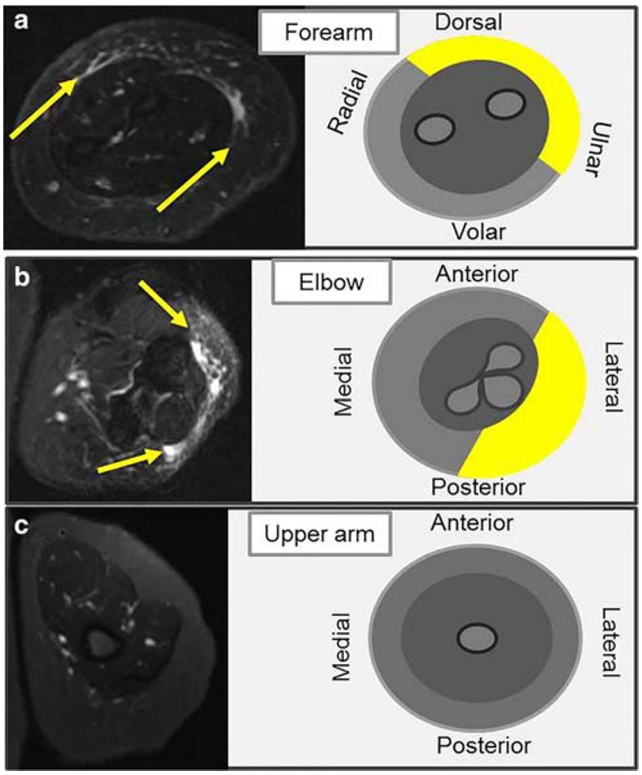

Fig. 2 Axial non-contrast STIR images of the forearm (**a**), elbow (**b**), and upper arm (**c**) of a 40-year-old woman with history of left breast cancer treatment, presenting with MRI stage 1 in the left arm. **a** There is mild fluid infiltration is noted in the dorsal and ulnar aspect of the forearm in this patient (yellow arrows and yellow shading). **b** At the elbow, the fluid infiltration (yellow arrows and yellow shading) is mostly localized to the posterior aspect. **c** No subcutaneous fluid infiltration is seen at the upper arm

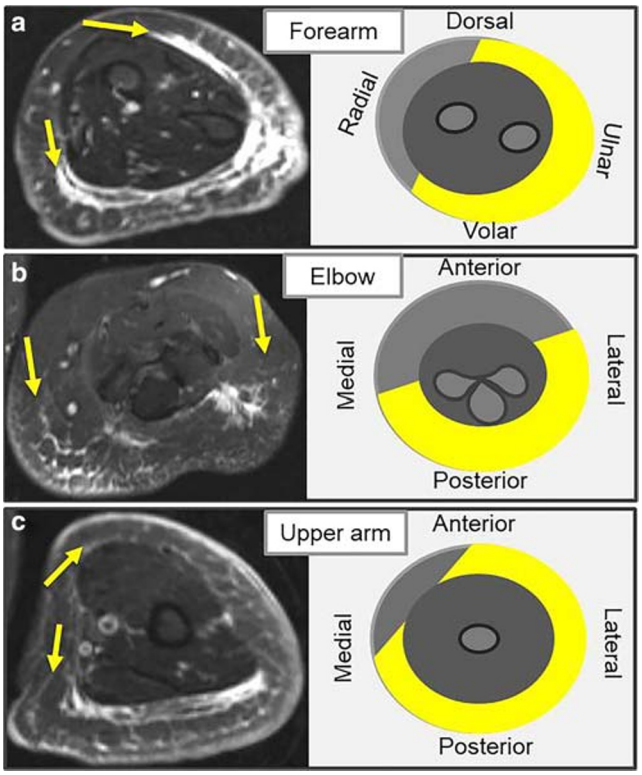

Fig. 3 Axial non-contrast STIR images of the forearm (**a**), elbow (**b**), and upper arm (**c**) of a 69-year-old woman with history of left breast cancer treatment, presenting with MRI stage 2. **a** Fluid infiltration in the forearm extends more than 50% and less than 75%, sparing the radial aspect (yellow arrow and shading). **b** At the elbow, there is approximately 50% circumferential fluid infiltration. **c** Within the upper arm, there is subcutaneous fluid infiltration affecting approximately 75% of the circumference

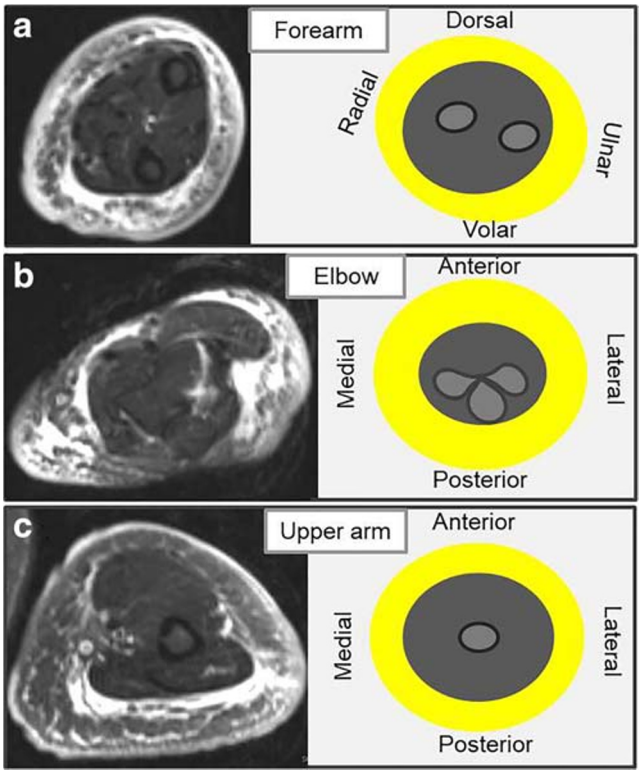

Fig. 4 **a**–**c** Axial non-contrast STIR images of the forearm (**a**), elbow (**b**), and upper arm (**c**) of a 70-year-old woman with history of left breast cancer treatment, presenting with MRI stage 3. Here, the fluid infiltration (yellow shading) exceeds 75% of the circumference throughout the three regions

remainder (3/41) underwent sentinel node biopsies (SLNB). Eight of the 11 lumpectomy patients had ipsilateral axillary node dissection, 2 had sentinel node biopsies, and 1 did not undergo axillary surgery.

Four patients (4/45, 8.9%) reported non-oncologic surgeries and interventions, such as bilateral breast reduction and unilateral brachioplasty and radiation for lymphoma.

There were 8 patients with no discernable fluid infiltration (MRI stage 0), 9 patients with MRI stage 1, 17 with MRI stage 2, and 11 with MRI stage 3. There was no statistical difference between the MRI stages and patient age, symptom duration, or BMI ($p > 0.2$), except in BMI where patients with MRI stage 3 had significantly lower BMI than MRI stage 2 ($p = 0.03$). More patients with higher MRI stages were recommended for surgical treatment compared to conservative treatment ($U = 135$, Z-score $= 2.27$, $p = 0.012$).

MRI stage interobserver variability

There was high degree of agreement between two independent readers on the MRI staging (Cohen's kappa 0.92 ± 0.04, 95% CI, 0.85–1.00). There was no disagreement in MRI stage 0 and 3. Disagreement was noted in 1 out of 9 (11.1%) patients in MRI stage 1, and 3 out of 17 (17.6%) patients in MRI stage 2. All disagreements differed by a single stage.

MRI stage correlation with ISL stage and LYMQOL

There were 5 ISL stage 0 and 31 ISL stage 2 patients; none were ISL stage 1 (Table 2). Patients with ISL stage 2 demonstrated higher MRI stage than patients in ISL stage 0 ($p = 0.002$, Table 2). Two patients with ILS stage 0, which refers to a subclinical stage where swelling is not yet evident, were classified as MRI stage 1. Two ISL stage 2 patients showed no detectable fluid infiltration on STIR images (MRI stage 0).

Baseline LYMQOL was available on 38 of 45 patients. The average Lymphedema Quality of Life (LYMQOL) score was the highest in the MRI stage 0 ($n = 5$, 59.8 ± 13.3) and the lowest in the MRI stage 3 ($n = 9$, 55.1 ± 9.2). However, there was no significant correlation between the MRI stage and LYMQOL ($r_s = -0.19$, $p = 0.25$). Furthermore, no significant

Table 2 Summary of patient characteristics

MRI stage	Patient count	Age	Symptom duration	BMI	ISL stage 0*	ISL stage 2*	Conservative treatment	Surgical treatment
0	8	55.3 ± 8.8	2.4 ± 1.8	30.1 ± 3.8	3	2	6	2
1	9	52.8 ± 13.7	6.3 ± 5.8	30.2 ± 9.8	2	6	4	5
2	17	58.6 ± 9.9	5.1 ± 4.8	33.4 ± 5.8	0	14	5	12
3	11	64.5 ± 9.5	4.8 ± 2.8	26.6 ± 4.1	0	9	2	8
Total	45	58.1 ± 11.0	4.8 ± 4.3	30.5 ± 6.5	5	31	17	27
		$p > 0.2^{\dagger}$	$p > 0.2^{\dagger}$	$p > 0.2^{\dagger}$	$p = 0.002'$		$U = 135$, Z-score $= 2.27$, $p = 0.012^{\ddagger}$	

*ISL stage: International Society of Lymphology Stage. The ISL staging information was available only on 36 out of 45 patients

† p value was obtained from the comparison among the MRI stages

$'$ p value was obtained from the comparison between ISL and MRI stages

‡ p value was obtained from the comparison between the MRI stages and the treatment groups (conservative or surgical). No final treatment decision was available on one patient in MRI stage 3

difference in the average LYMQOL was found between the MRI stages ($F(3,34) = 0.25$, $p = 0.85$ between all levels).

MRI stage correlation with dermal backflow on lymphoscintigraphy

Dermal backflow (DB) on lymphoscintigraphy was observed in in the affected arm of 29 out of the 45 total patients (64.4%). The presence of DB correlated with higher MRI stage ($p = 0.002$, Table 3). One out of 8 MRI stage 0 (12.5%), 4/9 MRI stage 1 (44.4%), 13/17 MRI stage 2 (75.5%), and 11/11 MRI stage 3 (100%) patients demonstrated DB (Table 3). The extent of DB, defined as whether the DB was seen up to the level of the elbow or beyond the elbow, did not correlate with MRI stage ($p = 0.26$ by Fisher exact text, Table 3). In 9 patients where fluid infiltration was present on MRI (5 MRI stage 1 and 4 MRI stage 2), DB was not observed on lymphoscintigraphy.

MRI stage correlation with L-Dex®, limb volume, and ICG lymphography

The L-Dex® was within the normal range (between − 10 and + 10) in 2 out of 9 MRI stage 1 patients (22.2%). There was high positive correlation between the MRI stage and the L-Dex® ($r_s = 0.84$, $p < 0.0001$) (Fig. 5). While the L-Dex® ratios between the MRI stages were statistically significantly different ($F(3,41) = 29.05$, $p < 0.0001$), the post hoc test revealed no significant difference in L-Dex® ratio between MRI stage 0 and 1 ($p = 0.108$, Table 4).

There was moderate positive correlation between the MRI stage and the degree of abnormality on the ICG lymphography ($r_s = 0.63$, $p < 0.0001$, Table 5). However, while the degree of ICG lymphography abnormality is statistically different between MRI stage 0 and 1, no difference was found between MRI stage 1 versus 2 or 2 versus 3.

There was moderate, positive correlation between the MRI stage and the percent volume difference between the affected and the unaffected arms by perometer measurements

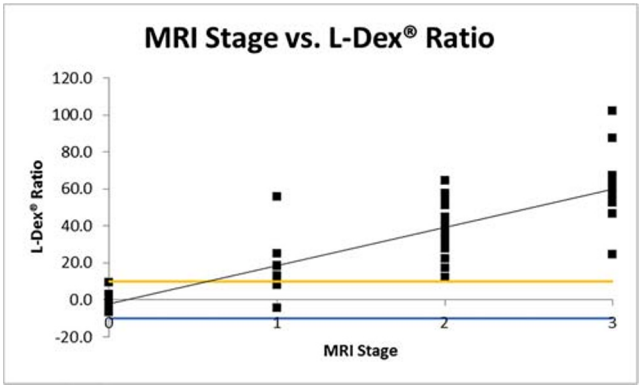

Fig. 5 Scatter plot of L-Dex® ratio against MRI stage demonstrating positive correlation (gray line). Upper (yellow line) and lower (blue line) normal L-Dex range is shown

($r_s = 0.68$, $p < 0.0001$, Table 6 in Supplementary Material). However, there were no significant volume differences between the MRI stages ($p = 0.28$, $p = 0.22$, $p = 0.14$, Table 6 in Supplementary Material). There were 5 patients in MRI stage 1, 1 patient in MRI stage 2, and 1 patient in MRI stage 3 whose limb volume difference was less than the 10% threshold diagnostic for lymphedema [22]. No patient in MRI stage 0 had a limb volume difference greater than 10%.

Discussion

In this study, we developed a highly reliable MRI staging system for upper extremity lymphedema based on the degree of axial circumferential subcutaneous fluid infiltration which does not require any post imaging processing, and only requiring estimates of the extent of fluid at three anatomic locations to assign the staging. To our knowledge, this is the first staging system based on spatial distribution of fluid infiltration of the upper extremity with description of fluid infiltration that is characteristic for the disease process. The staging was reproducible with high degree of agreement. MRI stage correlates with all established clinical parameters, including ICG lymphography, limb volume, and bioimpedance measurements

Table 3 Correlation between MRI stage and dermal backflow on lymphoscintigraphy

MRI Stage ($n = 45$)	DB present ($n = 29$)		DB absent ($n = 16$)
	Up to elbow ($n = 14$)	Beyond elbow ($n = 15$)	
0 ($n = 8$)	1 (12.5%)	0 (0%)	7 (87.5%)
1 (n = 9)	3 (33.3%)	1 (11.1%)	5 (55.6%)
2 ($n = 17$)	4 (11.8%)	9 (52.9%)	4 (23.5%)
3 ($n = 11$)	6 (54.5%)	5 (45.5%)	0 (0%)
DB presence vs. MRI stage, $p = 0.0002$[†]			
DB extent vs. MRI stage, $p = 0.26$[†]			

[†] By two-sided Fisher exact test

DB: dermal backflow on lymphoscintigraphy

Table 4 Correlation with post hoc Tukey HSD test between MRI stages and mean L-Dex® ratio

MRI stage ($n = 45$)	Mean L-Dex® ratio (± SD)	L-Dex® ratio range (min–max)	Post hoc Tukey p value
0	− 0.16 ± 5	− 7.0–9.4	0 vs. 1: $p = 0.108$
1	17.3 ± 16.6	− 4.5–55.7	1 vs. 2: $p = 0.016$
2	37.4 ± 14.5	12.0–64.4	2 vs. 3: $p = 0.001$
3	62.3 ± 20.2	24.7–102.0	
ANOVA: $F(3,41) = 29.05$, $p < 0.0001$			
Spearman: $r_s = 0.84$, $p < 0.0001$, df = 43			

SD: standard deviation

with L-Dex®, which are currently used to assess the severity of lymphedema [4, 7, 9]. In addition, the presence of DB on lymphoscintigraphy correlates with higher MRI stage.

In our study, we noted a pattern of fluid infiltration, which typically begins at the elbow, then involves the forearm. The degree of fluid infiltration in the forearm tends to become near circumferential even in early stages and always present in higher stages. Appearance of fluid infiltration in the upper arm typically lags behind the forearm and is present in more moderate disease. Fluid infiltration in the upper arm usually first appears along the posterior aspect and spreads laterally and anteriorly, mostly sparing the medial aspect of the upper arm.

Since MRI is already playing an increasing role in the evaluation of lymphedema [17–19, 23], our staging method can be incorporated into existing examinations. A MR-based lymphedema staging system was previously proposed in patients with lower extremity primary lymphedema [18]. Arrivé et al described infiltration of fluid within the subcutaneous fat and epifascial fluid collection, similar to what we have seen, and use this as a basis for grading lymphedema severity. However, that study utilized dermal and epifascial fluid collection thickness as part of the criteria for advanced stages, whereas our technique does not utilize thickness measurements. While dermal thickening and epifascial fluid collection were also observed in our study, we found that the degree of circumferential fluid infiltration was easier and faster to assess than other measures.

Table 5 Correlation between MRI stages and mean abnormality on the ICG lymphography

MRI stage ($n = 31$)	Mean ICG (± SD)	Post hoc Tukey p value
0	0.54 ± 0.8	0 vs. 1: $p = 0.03$
1	1.75 ± 1.0	1 vs. 2: $p = 0.48$
2	2.23 ± 0.49	2 vs. 3: $p = 0.87$
3	2.49 ± 0.59	
ANOVA: $F(3,27) = 8.78$, $p = 0.0003$		
Spearman: $r_s = 0.63$, $p < 0.0001$, df = 29		

SD: standard deviation

ICG: indocyanine Green

ICG scores: 0—linear (normal); 1—splash; 2—stardust; 3—diffuse

Franconeri et al recently described a method that also utilizes the extent of fluid infiltration [17]. However, this requires evaluation of six regions per limb, with assessment of the fraction of fluid infiltration of four quadrants per section, or 24 assessments total. In contrast, only a total of three assessments are needed to stage lymphedema severity with our technique. Both studies show excellent correlation with ILS stage; however, our study also incorporated a more comprehensive comparison against multiple clinical and functional measures, including gold-standard lymphoscintigraphy, ICG lymphography, perometry, and bioimpedance.

The two studies by Arrivé et al and Franconeri et al also targeted nearly exclusively different populations, limiting further direct comparison. Our study focused on secondary upper extremity lymphedema primarily in breast cancer patients, while the patient cohort in Francoerni et al were mostly comprised of lower extremity lymphedema cases and a mixture of primary and secondary lymphedema, and specifically excluded breast cancer patients. Given major differences in the anatomy of upper versus lower extremities and the pathophysiology of primary versus secondary lymphedema, it is reasonable to expect that different MR staging techniques may be used for these two different processes. Nevertheless, the studies by Arrivé et al and Franconeri et al show excellent correlation with ILS staging, synergistically supporting the diagnostic utility of non-contrast MRI for lymphedema staging. Future studies can focus on the application of these staging techniques in lower extremity secondary lymphedema and primary lymphedema with comparison to functional studies.

In contrast to MR lymphangiography [24], ICG lymphography [7, 25], and lymphoscintigraphy [10, 12, 26], our MRI staging system does not require exogenous contrast agents and can be performed using an MRI sequence that is widely available. Unlike the recently described non-contrast MR lymphangiography, our MRI staging can be performed as part of the diagnostic interpretation without additional software or segmentation [12].

While the STIR sequence used in this study is not a dynamic study of the lymphatic function and has not been optimized to visualize the lymphatic vessels as in MR lymphangiography, the images provide a map of the culminating effect of a patient's abnormal lymphatics. The STIR sequence is highly sensitive to

fluid and may detect preclinical lymphedema, as evidenced by two patients who were ILS stage 0 and MRI stage 1. Interestingly, even in patients with severe lymphedema, the muscles and myofascia appear spared, a finding also observed in lower extremity lymphedema [18, 26].

Strong, positive correlation between L-Dex® and MRI stage is expected since both measures are directly dependent on the physiologic amount of fluid throughout the limb. There were two patients with normal bioimpedance range that demonstrated lymphedema on MRI, suggesting that the MRI is more sensitive, likely due to its ability to show trace amounts of fluid in regions that may have minimal effect on the overall electrical impedance of the extremity. The patient with the highest L-Dex® ratio of 55.7 in MRI stage 1 demonstrated concentrated lymphedema in the forearm, which was nearly circumferential, but only mild lymphedema about the elbow and no discernable lymphedema in the upper arm. The lowest L-Dex® ratio in MRI stage 2 was 12. This patient demonstrated DB to mid upper arm on the lymphoscintigraphy, where lymphedema was observed on MRI.

Prior studies have noted low sensitivity of bioimpedance spectroscopy in detecting early lymphedema, inability to detect bilateral disease, and variable impedance ratio depending on body fat composition, temperature, or activity [8, 23, 27–29]. MRI is not susceptible to these factors and thus can be used for initial detection of lymphedema and potentially used for follow-up or for primary evaluation.

There are several limitations to the study. Our patient population is a subset of patients who were deemed surgical candidates based on their fitness for surgery upon evaluation with the lymphedema specialists. Therefore, the population studied in our study do not include patients who would be offered conservative treatment due to their inability to undergo a surgical procedure. However, the reasons for referral ranged from unclear clinical presentation needing additional imaging for clarification to those with stigmata of lymphedema needing imaging for surgical planning. This diversity in patient selection is reflected in our analysis showing a wide range of clinical measurements and in imaging characteristics showing large amount to no fluid infiltration. Therefore, we believe that we have captured a large repertoire of disease presentation despite the selected cohort, and our study could be extrapolated and applied to any patient with suspected or known lymphedema.

A second limitation is that our staging study does not address fat deposition or fibrosis, which are chronic changes related to lymphedema [30, 31]. Clinically, these changes pose a diagnostic challenge as there is theoretical possibility of decreased L-Dex® due to decreased resistance with increased fat component and limb volume may decrease over time due to fibrosis. In our study, these changes may result in lower MRI staging. However, our staging system notes even trace amounts of fluid and focuses on the extent of fluid spread rather than discrete volume. Nevertheless, the integration of fat hypertrophy in overall staging of disease severity warrants further investigation.

Lastly, this study focused on the use of the STIR sequence. This sequence was chosen for our study because of its wide availability and small variation between vendors. Other commercially available pulse sequences for fat suppression or the distinction of fat from fluid, for example Dixon-based techniques or alternative long-TR/TE sequences used for MR lymphangiography, may also be used to provide staging but this was not studied here. Further investigation will be needed to compare and validate these sequences.

In summary, we used a distinct pattern of soft tissue fluid infiltration on MRI in patients with secondary upper extremity lymphedema to form an MRI staging system, which showed excellent interpretive reproducibility and correlation with existing clinical measures and demonstrated greater sensitivity for early-stage lymphedema. This staging system can be incorporated into existing MRI examinations as part of lymphedema evaluation in surgical candidates.

Funding information This study has received funding by the RSNA R&E Resident Research Grant RR1820.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Geunwon Kim.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

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

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Retrospective
- Diagnostic or prognostic study
- Performed at one institution

References

1. Nguyen TT, Hoskin TL, Habermann EB, Cheville AL, Boughey JC (2017) Breast cancer-related lymphedema risk is related to multidisciplinary treatment and not surgery alone: results from a large cohort study. Ann Surg Oncol 24(10):2972–2980. https://doi.org/10.1245/s10434-017-5960-x
2. DiSipio T, Rye S, Newman B, Hayes S (2013) Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol 14(6):500–515. https://doi.org/10.1016/S1470-2045(13)70076-7

3. Rockson SG (2018) Lymphedema after breast cancer treatment. N Engl J Med 379(20):1937–1944. https://doi.org/10.1056/NEJMcp1803290
4. Garza RM, Ooi ASH, Falk J, Chang DW (2018) The relationship between clinical and indocyanine green staging in lymphedema. Lymphat Res Biol. https://doi.org/10.1089/lrb.2018.0014
5. Lee TS, Morris CM, Czerniec SA, Mangion AJ (2018) Does lymphedema severity affect quality of life? Simple question. Challenging answers. Lymphat Res Biol 16(1):85–91. https://doi.org/10.1089/lrb.2016.0049
6. Patel KM, Lin C-Y, Cheng M-H (2015) A prospective evaluation of lymphedema-specific quality-of-life outcomes following vascularized lymph node transfer. Ann Surg Oncol 22(7):2424–2430. https://doi.org/10.1245/s10434-014-4276-3
7. Narushima M, Yamamoto T, Ogata F, Yoshimatsu H, Mihara M, Koshima I (2016) Indocyanine green lymphography findings in limb lymphedema. J Reconstr Microsurg 32(1):72–79. https://doi.org/10.1055/s-0035-1564608
8. Qin ES, Bowen MJ, Chen WF (2018) Diagnostic accuracy of bioimpedance spectroscopy in patients with lymphedema: a retrospective cohort analysis. J Plast Reconstr Aesthetic Surg 71(7):1041–1050. https://doi.org/10.1016/j.bjps.2018.02.012
9. Coroneos CJ, Wong FC, DeSnyder SM, Shaitelman SF, Schaverien MV (2018) Correlation of L-Dex bioimpedance spectroscopy with limb volume and lymphatic function in lymphedema. Lymphat Res Biol. https://doi.org/10.1089/lrb.2018.0028
10. Lohrmann C, Foeldi E, Speck O, Langer M (2006) High-resolution MR lymphangiography in patients with primary and secondary lymphedema. AJR Am J Roentgenol 187(2):556–561. https://doi.org/10.2214/AJR.05.1750
11. Notohamiprodjo M, Weiss M, Baumeister RG et al (2012) MR lymphangiography at 3.0 T: correlation with lymphoscintigraphy. Radiology 264(1):78–87. https://doi.org/10.1148/radiol.12110229
12. Cellina M, Oliva G, Menozzi A, Soresina M, Martinenghi C, Gibelli D (2019) Non-contrast magnetic resonance lymphangiography: an emerging technique for the study of lymphedema. Clin Imaging 53:126–133. https://doi.org/10.1016/j.clinimag.2018.10.006
13. Pappalardo M, Cheng M-H (2018) Abstract: a new lymphoscintigraphy staging for unilateral extremity lymphedema. Plast Reconstr Surg Glob Open 6:74–75. https://doi.org/10.1097/01.GOX.0000546918.33068.82
14. Hassanein AH, Maclellan RA, Grant FD, Greene AK (2017) Diagnostic accuracy of lymphoscintigraphy for lymphedema and analysis of false-negative tests. Plast Reconstr Surg Glob Open 5(7):e1396. https://doi.org/10.1097/GOX.0000000000001396
15. Dylke ES, McEntee MF, Schembri GP et al (2013) Reliability of a radiological grading system for dermal backflow in lymphoscintigraphy imaging. Acad Radiol 20(6):758–763. https://doi.org/10.1016/j.acra.2013.01.018
16. Yamamoto T, Yamamoto N, Doi K et al (2011) Indocyanine green–enhanced lymphography for upper extremity lymphedema: a novel severity staging system using dermal backflow patterns. Plast Reconstr Surg 128(4):941–947. https://doi.org/10.1097/PRS.0b013e3182268cd9
17. Franconeri A, Ballati F, Panzuto F et al (2020) A proposal for a semiquantitative scoring system for lymphedema using non-contrast magnetic resonance lymphography (NMRL): reproducibility among readers and correlation with clinical grading. Magn Reson Imaging 68:158–166. https://doi.org/10.1016/j.mri.2020.02.004
18. Arrivé L, Derhy S, Dahan B et al (2018) Primary lower limb lymphoedema: classification with non-contrast MR lymphography. Eur Radiol 28(1):291–300. https://doi.org/10.1007/s00330-017-4948-z
19. Arrivé L, Derhy S, Dlimi C, El Mouhadi S, Monnier-Cholley L, Becker C (2017) Noncontrast magnetic resonance lymphography for evaluation of lymph node transfer for secondary upper limb lymphedema. Plast Reconstr Surg 140(6):806e–811e. https://doi.org/10.1097/PRS.0000000000003862
20. van de Pas CB, Biemans AA, Boonen RS, Viehoff PB, Neumann HA (2016) Validation of the lymphoedema quality-of-life questionnaire (LYMQOL) in Dutch patients diagnosed with lymphoedema of the lower limbs. Phlebology 31(4):257–263. https://doi.org/10.1177/0268355515586312
21. Sty JR, Boedecker RA, Scanlon GT, Babbitt DP (1979) Radionuclide "dermal backflow" in lymphatic obstruction. J Nucl Med 20(8):905–906
22. Armer JM, Stewart BR (2005) A comparison of four diagnostic criteria for lymphedema in a post-breast cancer population. Lymphat Res Biol 3(4):208–217. https://doi.org/10.1089/lrb.2005.3.208
23. Sanders JE, Allyn KJ, Harrison DS, Myers TR, Ciol MA, Tsai EC (2012) Preliminary investigation of residual-limb fluid volume changes within one day. J Rehabil Res Dev 49(10):1467–1478
24. Mitsumori LM, McDonald ES, Neligan PC, Maki JH (2016) Peripheral magnetic resonance lymphangiography: techniques and applications. Tech Vasc Interv Radiol 19(4):262–272. https://doi.org/10.1053/j.tvir.2016.10.007
25. Mihara M, Hara H, Araki J et al (2012) Indocyanine green (ICG) lymphography is superior to lymphoscintigraphy for diagnostic imaging of early lymphedema of the upper limbs. PLoS One 7(6):e38182. https://doi.org/10.1371/journal.pone.0038182
26. Case TC, Witte CL, Witte MH, Unger EC, Williams WH (1992) Magnetic resonance imaging in human lymphedema: comparison with lymphangioscintigraphy. Magn Reson Imaging 10(4):549–558
27. Czerniec SA, Ward LC, Kilbreath SL (2016) Breast cancer-related arm lymphedema: fluctuation over six months and the effect of the weather. Lymphat Res Biol 14(3):148–155. https://doi.org/10.1089/lrb.2015.0030
28. Ridner SH, Dietrich MS, Stewart BR, Armer JM (2011) Body mass index and breast cancer treatment-related lymphedema. Support Care Cancer 19(6):853–857. https://doi.org/10.1007/s00520-011-1089-9
29. Fu MR, Cleland CM, Guth AA et al (2013) L-dex ratio in detecting breast cancer-related lymphedema: reliability, sensitivity, and specificity. Lymphology 46(2):85–96
30. Mehrara BJ, Greene AK (2014) Lymphedema and obesity: is there a link? Plast Reconstr Surg 134(1):154e–160e. https://doi.org/10.1097/PRS.0000000000000268
31. Zampell JC, Aschen S, Weitman ES et al (2012) Regulation of adipogenesis by lymphatic fluid stasis: part I. Adipogenesis, fibrosis, and inflammation. Plast Reconstr Surg 129(4):825–834. https://doi.org/10.1097/PRS.0b013e3182450b2d

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.