Intranodal lymphangiography characteristics of primary lymphedema

<u>Charissa Kim</u>⁽¹⁾ - Hamza Ali⁽¹⁾ - Julie Bulman⁽¹⁾ - Leo Tsai⁽¹⁾ - Dhruv Singhal⁽²⁾ - Brett Carroll⁽³⁾ - Muneeb Ahmed⁽¹⁾ - Jeffrey Weinstein⁽¹⁾

Beth Israel Deaconess Medical Center, Radiology, Boston, United States Of America⁽¹⁾ - Beth Israel Deaconess Medical Center, Plastic Surgery, Boston, United States Of America⁽²⁾ - Beth Israel Deaconess Medical Center, Cardiology, Boston, United States Of America⁽³⁾

Lymphedema (LED) is the accumulation of lymphatic fluid in soft tissues due to impaired lymphatic drainage, resulting in inflammatory changes, fat hypertrophy, and fibrosis(1). It negatively impacts quality of life, affecting approximately 140–200 million patients worldwide(1). However, there is limited existing data on the lymphatic anatomy of patients with primary LED, which is caused by inherent abnormalities in lymphatic system development(1). Transpedal and intranodal lymphangiography (IL) are methods that provide detailed images of lymphatic vessels and the opportunity for intervention, with IL as the less invasive option(2).

This single-center, IRB-approved study compared the IL presence of lymphovenous anatomic anastomoses, contralateral collateral connections, and transit to the central upper abdominal lymphatics in 17 patients with clinically diagnosed primary LED to 17 patients without LED who underwent IL for other indications in the same time period. Procedure reports for the LED patients were searched for the above findings, while non-LED images were reviewed by a blinded, fellowship-trained interventional radiologist to determine if the findings noted in LED patients were present. The percentage of each finding was calculated, and statistical comparisons were made with Fisher's exact test; p-value <0.05 was considered significant.

There was a higher percentage of lymphovenous anatomic anastomoses in the LED group compared to the non-LED group (47% versus 0%, p=0.003). Similarly, LED patients demonstrated higher rates of contrast passage past midline to the contralateral lymphatics (47% versus 0%, p=0.003). LED patients also failed to opacify central lymphatics on their initial lymphangiograms when compared to non-LED patients (29% LED central opacification to the renal vein versus 75% in non-LED, p=0.01). Delayed CT of 3 primary LED patients showed eventual central lymphatic opacification up to the renal veins, but none showed central opacification to the thorax.

The finding of delayed/non-opacification of the central lymphatics may be due to pre-existing developmental lymphatic aberrations(*3*) or inherent malfunction of lymphatic channels(*4*) in primary LED. In our study, primary LED patients demonstrated higher rates of lymphovenous anatomic anastomoses, concordant with prior findings(*5-7*).

Lymphovenous anatomic anastomoses may represent compensatory decompression of an abnormal high-pressure lymphatic system into the lower-pressure venous system(8). Cross-emptying into the contralateral lymphatics may similarly represent compensatory decompression into less stenosed, lower-pressure lymphatic channels. Future evaluation of flow dynamics in primary LED may impact location of lymph node transfer and benefits of lymphovenous bypass(9). These findings may also help with prognostication of future lymphedema in the contralateral side(7) in the context of lymphangiographic anatomic findings.

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Correlation of Inguinal Lymph Node Number and Volume with Lower Extremity Lymphedema Severity

Hamza Ali⁽¹⁾ - Michael Adondakis⁽¹⁾ - Betsa Parsai Salehi⁽¹⁾ - Rosie Friedman⁽²⁾ - Weiliang Sun⁽¹⁾ - Kevin Donohoe⁽¹⁾ - Geunwon Kim⁽¹⁾ - Dhruv Singhal⁽²⁾ - Brett Carroll⁽³⁾ - Jeffrey Weinstein⁽¹⁾ - Leo Tsai⁽¹⁾

Beth Israel Deaconess Medical Center, Department of Radiology, Boston, United States Of America ⁽¹⁾ - Beth Israel Deaconess Medical Center, Department of Surgery, Boston, United States Of America ⁽²⁾ - Beth Israel Deaconess Medical Center, Department of Internal Medicine, Boston, United States Of America ⁽³⁾

Correlation of Inguinal Lymph Node Number and Volume with Lower Extremity Lymphedema Severity Rationale and Objectives

Inguinal lymph node access for lymphangiography can be challenging in patients with chronic lower extremity lymphedema, presumably from atrophy related to chronic lymphatic dysfunction. In this study we looked for correlation between inguinal lymph node number and volume with lower extremity lymphedema presence, severity, and chronicity.

Materials and Methods

A waiver of informed consent was obtained by the institutional review board for this single-institution retrospective study. Patients with lower extremity lymphedema who obtained a lower extremity MRI from 1/2018–12/2021 were included. The exclusion criteria were patients who had any inguinal lymph node resection or history of lower extremity lymphatic surgery (debulking, lymph node transplant, or lymphovenous bypass). The number and volume of inguinal lymph nodes on each side were measured from the MRI examinations. Fat and fluid scores for each lower

extremity were also obtained using a validated MRI-based grading system. Patient demographics, limb volumes by perometer, and the International Society of Lymphology score were also collected. Wilcoxon signed-rank tests compared the greater-affected limbs with the lesser-affected limbs. Correlation analysis using the Spearman-Rank method was performed first on a 'per limb' basis for MRI-based scoring and clinical parameters with ipsilateral lymph node number and volume. An 'analysis of difference' was then done to analyze the correlation of radiological and clinical parameters with the difference in lymph node number and volume between the greater and the lesser-affected limb. The level for statistical significance (α) was set at 0.05, and the Benjamini-Hochberg method was used to control the false discovery rate.

Results

A total of 32 patients (mean age \pm SD = 53 \pm 16 years, 88% (n =28/32) females) met the inclusion criteria. Lower extremity edema was unilateral in most patients (n = 20/32; 62%), and almost all patients were graded as ISL stage II (n = 30/32; 93%). The average duration of lymphedema was 12 \pm 13 years. The greater-affected limb had higher MRI fluid scores (median (interquartile range) = 3 (3 - 3) vs. 0 (0 - 1), p < 0.01) relative to the contralateral limb and had a median fat asymmetry score of 2 (1 - 3). On the per-limb analysis, lymph node number and volume inversely correlated with total MRI scores (node number: ρ = -0.47, p < 0.01; node volume: ρ = -0.47, p < 0.0). On the analysis of difference, the difference of lymph node number and volume correlated with MRI score difference (node number: ρ = -0.66, p < 0.01; node volume: ρ = -0.64, p < 0.01) and perometer difference (node number: ρ = -0.58, p < 0.01; node volume: ρ = -0.59, p < 0.01). No correlation was found between lymph node number and volume number and volume number numb

Conclusion

Inguinal lymph node number and volume inversely correlate with lower extremity edema presence and severity.

Near -Infrared Fluorescence Imaging in Lymphatic/Chylous Diseases

Pablo Castro⁽¹⁾ - Miguel Amore⁽¹⁾

Military Central Hospital, Palermo, Ciudad Autonoma de Buenos Aires, Argentina⁽¹⁾

Near-Infrared Fluorescence Imaging in Chylous Diseases

Amore.M^{1,2},Castro.P¹, Salvia.S,¹Bengoa.G¹, Marcovecchio.L¹, Gerez.N Phlebology and Lymphology Unit. Cardiovascular Surgery Division. Central Military Hospital. Buenos Aires. Argentine.¹ Phlebology and Lymphology Unit. Favaloro Foundation University Hospital.²

Background: Near-Infrared (NIR) Fluorescence imaging is being used increasingly more intraoperative applications, providing more anatomic and functional data on the chylous - lymph system.

Aim/purpose: to assess the usefulness of NIR imaging for diagnosis and treatment of primary lymphatic/chylous malformations and secondary chylous diseases.

Material & Methods: We have evaluated and treated 3 (N=3) patients with primary lymphatics-chylousmalformations and 3 (N=3) patients with secondary chylous diseases. We perform indocyanine green (ICG) lymphography by trans nodal inguinal injection, preoperative endoscopy and ICG stomach injection and ICG + cream oral infusion 12 hs preoperative. In every case we performed a fluorescent guided laparoscopic surgery as a tool for diagnosis and eventual therapeutic management.

Results: With the guidance of real-time fluorescence lymphography, the lymphatic/chylous malformations and eventual leaks of secondary chylous diseases were successfully identified and treated by surgical or conservative treatments.

Conclusion: Near-infrared fluorescence imaging with ICG provided highly sensitive and real-time imaging of lymph-chylous malformations, that allowed for the interpretation of the pathophysiology of the lesion, enabling a targeted and specific management.

Edematous Dermal Thickening as a Biomarker for Lymphatic Surgical Outcomes

JacqueLyn Kinney ⁽¹⁾ - Sara Babapour ⁽²⁾ - Erin Kim ⁽¹⁾ - Rosie Friedman ⁽¹⁾ - Bernard Lee ⁽¹⁾ - Dhruv Singhal ⁽¹⁾ - Leo Tsai ⁽²⁾

Beth Israel Deaconess Medical Center, Surgery, Boston, United States Of America ⁽¹⁾ - *Beth Israel Deaconess Medical Center, Radiology, Boston, United States Of America* ⁽²⁾

Edematous Dermal Thickening as a Biomarker for Lymphatic Surgical Outcomes

Background:

Surgical treatments for breast cancer-related lymphedema (BCRL) include vascularized lymph node transplant (VLNT) and debulking lipectomy. Clinical outcomes are assessed using subjective patient questionnaires (LYMPH-Q), bioimpedance scores (L-dex), and relative volume change in the limb of interest. However, these scores often do not correlate well with each other. There are unexplored quantitative imaging biomarkers with the potential to be more accurate assessments of clinical outcomes. Our clinical experience suggests that dermal thickness, measurable on MRI, may correlate with BCRL severity. Therefore, the aim of this study is to investigate whether dermal thickness could be utilized as an objective indicator of postoperative changes following VLNT and debulking.

Methods:

A retrospective review identified patients with BCRL treated with debulking lipectomy. Patients were included if they had both preand postoperative MRIs. Dermal thicknesses were measured by two separate readers (JK and SB) at 4 points (medial/ulnar, lateral/radial, posterior/dorsal and anterior/ventral), at 2 different regions of the upper arm and 2 different regions of the forearm (total 16 sites per arm). The area of the largest measurement per arm was designated as the maximum dermal thickness. Data was compared across two groups: changes to the arm that received debulking treatment and the contralateral control arm without treatment. Wilcoxon rank sum test was used to compare changes to the affected arm with the control arm. Univariate linear regression was used to assess the relationship between dermal thickness reduction with changes to LYMPH-Q scores, L-dex scores, and relative volume change.

Results:

17 patients met the inclusion criteria. There was a median dermal thickness change of 0 mm across all regions in the control (unaffected) arm following debulking, while there was a significant reduction in 8/16 limb compartments in the affected arm. The overall maximal dermal thicknesses significantly decreased in the treatment group (p<0.05). Maximum dermal thickness in the upper arm tended to favor the dorsal and lateral portions, whereas in the lower arm it tended to favor the ventral and ulnar portions. Change to dermal thicknesses significantly correlated with changes to LYMPH-Q, L-dex, and relative volume change in 5/16 and 3/16 limb compartments, per respective reader.

Conclusion:

Dermal thickness may be used to track post-operative outcomes in BCRL after debulking, but further understanding of variations due to anatomical location and the selection of the optimal imaging technique require further exploration. Future studies with greater power are necessary to confirm our preliminary findings.

Non-Symmetric Lymphatic Drainage Patterns in the Upper Extremities

Angela Chen⁽¹⁾ - Rosie Friedman⁽¹⁾ - Leo Tsai⁽²⁾ - Aaron Fleishman⁽¹⁾ - Dhruv Singhal⁽¹⁾ - Kevin Donohoe⁽²⁾

Beth Israel Deaconess Medical Center, Plastic and Reconstructive Surgery, Boston, United States Of America ⁽¹⁾ - *Beth Israel Deaconess Medical Center, Radiology, Boston, United States Of America* ⁽²⁾

Background

Prior investigations of lymphatic anatomy have reported conflicting results regarding the symmetry of lymphatic drainage patterns between the upper extremities in individual subjects. In this investigation, we conducted lymphoscintigraphy with single-photon emission computed tomography/computed tomography (SPECT/CT) of the bilateral upper extremities in healthy individuals to evaluate the symmetry of lymphatic drainage patterns.

Methods

Lymphoscintigraphy with SPECT/CT was performed in healthy female adult volunteers between May 2022 and May 2023 following staged intradermal injection of Tc-99m sulfur colloid: over the cephalic vein, 4 cm proximal to the antecubital crease on Study Visit 1, and 4 injections on Study Visit 2 located just proximal to the first and fourth web spaces of the dorsal hand and over the radial and ulnar arteries at the wrist. At 2 hours planar images and SPECT/CT images were obtained of the neck, chest, upper abdomen, and arms. Lymph node regions were defined according to prior anatomic studies. Symmetry was defined as the presence or absence of tracer accumulation in corresponding left and right lymph node groups at 2 hours.

Results

Twenty-six participants completed both study visits. All participants (100%, n=26) demonstrated lymph nodes in right and left Axillary Level I. In Axillary Level II, 5 of 26 subjects had at least one node on one side with none on the contralateral side (19%). Of the Axillary Level III region, 15 of 26 subjects (58%) had lymph nodes on only one side. In the infraclavicular region, 13 of 26 subjects (50%) had a node on only one side. Also noted was asymmetry in drainage seen following the cephalic vein through the deltopectoral groove to the axillary vein. In this region 10 of the 26 subjects (42%) did not show symmetric drainage on both sides. Similar discrepancies were seen in the humeral, epitrochlear, and supraclavicular levels IV & Vb groups.

Conclusion

Previous publications have suggested upper arm lymphatic drainage shows right/left symmetry. Our results in normal subjects show variability in the number and presence of lymph nodes when comparing right and left upper extremities. Asymmetric lymphatic drainage may have important implications for surgical planning of axillary node dissection and in the management of patients with lymphedema.

Lymphatic remapping by intradermal lymphoscintigraphy in breast cancer survivors.

<u>Girolamo Tartaglione</u>⁽¹⁾ - Marco Pagan⁽¹⁾ - Francesco Pio Ieria⁽¹⁾ - Emilia Covello⁽²⁾ - Luigi Maria Pio Marino Cosentino⁽³⁾ - Simona Di Filippo⁽²⁾ - Rosella Marsico⁽³⁾ - Sabrina Ghinassi⁽³⁾ - Leonardo Leone⁽³⁾ - Maria Rosaria Limiti⁽⁴⁾ - Roberto Bartoletti⁽⁵⁾ - Pier Luigi Bonatti⁽²⁾

Cristo Re Hospital, Nuclear Medicine, Rome, Italy ⁽¹⁾ - Santo Spirito Hospital, Breast Unit ASL Roma 1, Rome, Italy ⁽²⁾ - San Filippo Neri Hospital, Breast Unit ASL Roma 1, Rome, Italy ⁽³⁾ - Santo Spirito Hospital, Pathology, Rome, Italy ⁽⁴⁾ - IDI IRCCS, Oncological Rehabilitation, Rome, Italy ⁽⁵⁾

Aim: Axillary Lymph Nodes Dissection (ALND) and radiation treatment in breast cancer patients may alter lymphatic drainage of cancer's area. We proposed intradermal lymphoscintigraphy for lymphatic remapping after ALND, in breast cancer survivors.
Materials and Methods: We conducted a review of patients who received previous treatments for breast cancer between February 2018 and December 2022.
Forty-one patients (40 f, 1 m) median age 70.5 years (range 41-95) underwent a lymphatic remapping on the ipsilateral side an average of 160 months after their first ALND. Thirty-three out of forty-one patients underwent to a reoperative sentinel node for breast cancer recurrence, while eight out of forty-one patients underwent lymphatic imaging for an armpit and chest area breast cancer related lymphedema. We injected intradermally a dose of 99mTc-nanocolloids, 50 MBq, 0.4 mL, dividing the dose in the four quadrants of breast. We acquired a planar scan in anterior view immediately after tracer injections. In recurrent breast cancer we performed a radioguided sentinel node biopsy 3-18 hours later.

Results: in twenty-six patients the scan showed a lymph path that crossed the midline and a draining lymph node located in contralateral axilla (in 5 out of 26 patients we also observed an unexpected lymph node uptake in internal mammary chain); while in fifteen patients the scan showed a draining lymph node located in internal mammary chain. In the group of 33 patients with breast cancer relapse, three patients had been upstaged to pN1mi(sn), and one patient to pN2a from cN0 based on One Step Nuclear Amplification results. In the group of 8 patients with chest area and armpit breast cancer related lymphedema we imaged a lymphatic path and a draining lymph node in contralateral axilla in all cases.

Conclusion: lymphatic remapping in previously treated breast cancer patients is feasible using nuclear imaging procedure. The intradermal lymphoscintigraphy showed in all patients an unusual lymphatic pathway from breast area to an extra axillary draining lymph node. Pathological evaluation of involved sentinel nodes improved staging in breast cancer relapse. The nuclear imaging supports that lymph node metastases in the contralateral axilla represents a locoregional spread

of the tumor from the breast via lymphatics. In all patients with armpit and chest area lymphedema, the intradermal lymphoscintigraphy showed an unexpected draining lymph node in contralateral axilla, this finding may be helpful for physiotherapist in decision making process.

Quantitative microscopy of kidney lymphatics in health and acute kidney injury (AKI)

<u>Gelare Ghajar-Rahimi</u>⁽¹⁾ - Daria Barwinska⁽²⁾ - Malgorzata Kamocka⁽²⁾ - Tarek Ashkar⁽²⁾ - James George⁽³⁾ - Anupam Agarwal

University of Alabama at Birmingham, Medicine, Birmingham, United States Of America ⁽¹⁾ - Indiana University, Medicine, Indianapolis, United States Of America ⁽²⁾ - University of Alabama at Birmingham, Surgery, Birmingham, United States Of America ⁽³⁾

Until the discovery of key lymphatic cell markers three decades ago, the lymphatic system had historically been overlooked due to the difficulty of distinguishing it from the blood vasculature. Within the kidney, the blood and lymphatic endothelial vascular systems work in concert to maintain homeostasis. While the blood vasculature supplies oxygen and carries blood to be filtered, the lymphatics aid in maintaining fluid homeostasis, trafficking immune cells, and clearing debris. Both systems respond dynamically to injury. In the setting of acute kidney injury (AKI), the lymphatic system undergoes a process of expansion termed lymphangiogenesis. Evidence suggests an expanded network of kidney lymphatics is protective against AKI. Transgenic mice with expanded lymphatics secondary to kidney-specific VEGF-D overexpression are more resistant to ischemia. Blocking lymphangiogenesis through inhibition of VEGF-R3 worsens renal function in cisplatin-induced AKI. The current treatment options of dialysis and supportive care inadequately address the complex clinical consequences of AKI and manipulating kidney endothelia to prevent augmenting lymphangiogenesis holds great promise as a therapeutic strategy for AKI of multiple etiologies. A current barrier in the advancement of lymphatic-modulating therapies is our ability to comprehensively examine the structural and functional integrity of kidney lymphatics in pre-clinical models such as mice. Lymphatic vasculature can be quite sparse through the kidney, so there can be significant variability in observed vessel density when using traditional sectioning and immunolabeling. Here, we describe a methodology to allow visualization of intact lymphatic vessel architecture at the organ level providing a more comprehensive analysis of the lymphatic system within the kidney. The solvent-based iDISCO tissue clearing pipeline was adapted for visualization of endothelial structures in kidney tissue specimens up to 3000

micrometers thick using confocal microscopy combining image stitching and z-stacks. Three-dimensional reconstruction of lymphatic vasculature and computational analysis returns readouts of lymphatic vasculature including total contiguous vessel length, and branch point density. Applied to murine kidneys subjected to a bilateral ischemia reperfusion model of AKI, this methodology identified quantifiable changes in the lymphatic architecture of injured kidneys compared to sham-operated controls. This approach enables a robust and quantitative method for interrogating the kidney lymphatic system in response to injury and therapeutic intervention.

02. Anatomy and Pathology of the Lymphatic Circulation for Clinical Practice

05. 05. Imaging of the Lymphatic System & Role of Lymphoscintigraphy

Lymphatic Anatomy Is Not Symmetrical Between the Upper Extremities on Indocyanine Green Lymphography

<u>Rosie Friedman</u>⁽¹⁾ - Angela Chen⁽¹⁾ - Aaron Fleishman⁽¹⁾ - Valeria Bustos⁽¹⁾ - Mohamed Ismail Ali⁽¹⁾ - Kevin Donohoe⁽¹⁾ - Leo Tsai⁽¹⁾ - Dhruv Singhal⁽¹⁾

Beth Israel Deaconess Medical Center, Division of Plastic and Reconstructive Surgery, Boston, United States Of America⁽¹⁾

Lymphatic Anatomy Is Not Symmetrical Between the Upper Extremities on Indocyanine Green Lymphography

Purpose

Upper extremity lymphatic anatomy is an underrecognized risk factor for breast cancer related lymphedema (BCRL). While our understanding of lymphatic anatomy has evolved, symmetry of the lymphatic anatomy between the upper extremities has not yet been established. The aim of this study was to characterize symmetry and asymmetry present in lymphatic anatomy of the upper extremities in healthy volunteers using Indocyanine Green (ICG) Lymphography.

Methods

In this retrospective study, bilateral upper extremity ICG lymphography was performed in healthy adult female volunteers between May and October 2022. In order to visualize all major lymphosomes within the extremity, serial ICG injections were placed at the first and fourth dorsal hand webspaces, radial and ulnar wrist crease, in the peri-olecranon region, and over the cephalic vein which was visualized using ultrasound guidance. Lymphatic channels in the upper extremity were visualized and mapped systematically immediately following each injection by two independent readers. For the lateral upper arm and tricipital channels, long bundles were defined as pathways that could be visualized continuously from forearm channels and short bundles were defined as pathways only visualized after upper arm injections. To assess for symmetry, findings were compared within the bilateral extremities within individuals. For the forearm channels, symmetry between the extremities of a single participant was defined as whether the dorsal or volar forearm channels remained in the dorsal or volar aspect of the forearm, respectively, on bilateral extremities. For the upper arm channels, symmetry was defined as consistency in bundle phenotype in bilateral extremities.

Results

In this cohort of 16 individuals, the superficial lymphatic anatomy of the upper extremities was symmetric in the upper extremities in 50% (n=8) of the participants. The anterior radial and ulnar forearm channels were symmetric in all participants (n=16, 100%), whereas the posterior radial and ulnar channels were symmetric in 94% (n=15) and 69% (n=11), respectively. In terms long and short bundle phenotypes, the lateral upper arm channel was symmetric in 69% (n=11) of participants and the tricipital channel was symmetric in 81% (n=13) of participants.

Conclusions

There is significant asymmetry in baseline lymphatic anatomy of the upper extremities. The notable asymmetry observed in the posterior ulnar forearm channel may be clinically significant in the development of lymphedema, which is characterized by fluid accumulation in the ulnar forearm in early stages. Additionally, findings from this investigation are important to consider for studies in which the unaffected extremity is used as a control to which the anatomy of the lymphedematous extremity is compared. When investigating the role of lymphatic anatomy in the risk of BCRL development, it is important to consider the lymphatic anatomy of each extremity individually and independently.

Scintigraphic Mapping of Cephalic Pathway Lymphatic Drainage in Normal Subjects

Kevin Donohoe⁽¹⁾ - Valeria Bustos⁽²⁾ - Rosie Friedman⁽²⁾ - Angela Chen⁽²⁾ - Dhruv Singhal⁽³⁾

Beth Israel Deaconess Medical Center, Radiology/Nuclear Medicine, Boston, United States Of America ⁽¹⁾ - Beth Israel Deaconess Medical Center, Lymphatic Center, Boston, United States Of America ⁽²⁾ - Beth Israel Deaconess Medical Center, Plastic Surgery, Boston, United States Of America ⁽³⁾

Variations in lymphatic anatomy in the upper extremity may protect some patients from lymphedema following axillary node dissection. One variant that has been suggested to decrease the risk of lymphedema is the Mascagni-Sappey (M-S), cephalic or lateral pathway, previously described as predominantly draining the arm to cervical and supraclavicular nodes, by-passing the axilla. Our preliminary experience with mapping lymphatic drainage in the upper extremities of normal female subjects has demonstrated lymphatic drainage from the upper arm along the cephalic pathway more commonly enters the axilla than the cervical and supraclavicular node beds.

Methods: 26 women >18 years of age without a history of lymphatic abnormality, trauma to the lymphatic system or surgery were injected with 99mTc sulfur colloid followed by Imaging with planar and SPECT/CT on two different dates. The first imaging session followed intradermal injection over the cephalic vein and the second followed intradermal injections over the hand and wrist.

Results: SPECT/CT allowed localization of tracer uptake to specific lymph nodes in the upper extremity and neck. Our preliminary findings show injection over the cephalic vein most commonly drains to the axilla, often to the same nodes that drain injections on the dorsum of the hand and the wrist. Drainage exclusively from the cephalic injection site along the cephalic pathway to nodes in the delto-pectoral groove is rare. Drainage to the posterior scapular nodes was not seen in any subject. Drainage to axillary level III, infraclavicular, and cervical levels IV and Vb was more commonly seen from wrist injections than from injections over the cephalic vein in the upper arm.

Conclusion: Drainage over the cephalic dermatome more commonly enters the axilla as opposed to supraclavicular, scapular or cervical lymph nodes. Lymph nodes draining the cephalic dermatome also often receive drainage from hand and wrist dermatomes. Drainage patterns show substantial variation between normal subjects. These data may help to differentiate patients prone to lymphedema following axillary node dissection.

Technical Challenges of Scintigraphic Mapping of Lymphatic Drainage

Kevin Donohoe⁽¹⁾ - Angela Chen⁽²⁾ - Rosie Friedman⁽²⁾ - Valeria Bustos⁽²⁾ - Dhruv Singhal⁽³⁾

Beth Israel Deaconess Medical Center, Radiology/Nuclear Medicine, Boston, United States Of America ⁽¹⁾ - Beth Israel Deaconess Medical Center, Lymphatic Center, Boston, United States Of America ⁽²⁾ - Beth Israel Deaconess Medical Center, Plastic Surgery, Boston, United States Of America ⁽³⁾

Mapping lymphatic drainage of the upper extremity is essential for understanding variations in anatomy that may predispose some patients to lymphedema following axillary surgery. Indocyanine green (ICG) mapping is helpful in mapping superficial lymphatic drainage but ICG is not useful for mapping lymphatic channels deeper than 2 cm. Other anatomic imaging methods such as magnetic resonance lymphangiography or contrast lymphangiography can also demonstrate lymphatic channels, but these methods are less physiologic than scintigraphic imaging. Despite the long history of scintigraphic imaging of the lymphatic system, changes in imaging technology, regional practice and radiotracer availability have resulted in literature describing a variety of methods used for lymphoscintigraphy. Our experience and modifications of several methods have helped us standardize our imaging, yet challenges remain that prevent us from fully mapping lymphatic drainage.

Methods: 26 women >18 years of age without a history of lymphatic abnormality, trauma to the lymphatic system or surgery were injected with 99mTc sulfur colloid followed by Imaging with planar and SPECT/CT on two different dates. Axillary regions were defined based on prior published information. The first imaging session followed intradermal injection over the cephalic vein and the second followed intradermal injections over the hand and wrist.

Results: Normal subjects showed as many as many as 32 and as few as 10 lymph nodes in both axillary and cervical regions combined. Localization to each axillary region was challenging secondary to node size and configuration of each node, the amount of tracer concentrating in each node, overlap of nodes into more than one region, movement of the subject between SPECT and CT portions of the SPECT/CT, and changes in nodal positioning between imaging sessions.

Conclusion: SPECT/CT has added the ability to more precisely localize nodes involved in upper extremity lymphatic drainage, yet variations in lymph node architecture and localization present problems for precise mapping of upper extremity lymphatic drainage patterns. However, SPECT/CT documentation of upper extremity lymphatic drainage has already revealed new insights into regional and inter-individual differences in lymphatic drainage. These insights into lymphatic drainage may be helpful to guide surgical lymphadenectomy, particularly in the prevention of lymphedema.

Visualizing vividly the chains of lymphangions in health and disease simply by non-contrast MRI

WICHAI EKATAKSIN⁽¹⁾

Lymphology Institute of Thailand, Day Care Center for People with Poor Lymph Disorder, Nontaburi, Thailand ⁽¹⁾

Background: The concept of organ functional unit is common in basic medical and clinical science. Starting with the neuron, there followed the nephron, osteon, chondrion, enteron, gastron, pancreon, hepaton, choleon, choleohepaton, stellon, et cetera, to state, but a few. In the lymphatic system, the lymphangion has been proposed, but with little acceptance. Patients-Materials and Methods: We found that the presence of lymphangions can be demonstrated on magnetic resonance imaging which we routinely used at Thailand Academy for People with Poor Lymph Disorder to assess the lymph congestion condition. All visualized structures were based mostly on serial images of T2W short Tau inversion recovery (STIR) to null signal from fat, and viewed with OsiriX MD DICOM viewer under MIP and VR modes. Results and Discussion: The series of non-contrast T2W STIR fat suppression, which normally depicted the existence of non-flowing or slowly-moving fluid, when switched to MIP/VR at different stack thicknesses came to reveal beautifully the presence of valves, delineating the textbook-described morphology of lymphangions. Unlike the veins, whose calibers were apparently larger, valves placed widely apart, 3~6 cm, and courses as described in the Anatomy, the lymphatics were very much slenderer with valves located in close series like a bead chain. The latter could be straight, curved, or serpentine, seen traversing a distance of several centimeters. The bead-

to-bead intervals measured 6~12 mm, with a miniature fine strand connecting them. However, the filamentous strand could range longer than one or two lymphangions, suggesting that lymph did not fill in that particular segment. Bead chains were sighted most often in the intercostal, supraclavicular, cervical, axillary, mammary, forearm, and proximal femoral regions; we were not successful in visualizing the anterior thoracic/abdominal walls, back, and visceral organs. Interestingly, some bead chains abruptly changed to fully congested columns in a disto-proximal manner as in the medial segment of costal lymphatics; the distended conduits were usually straightened, but could also be found surprisingly undulate. Individuals with lung cancer and other lymph-congestive disorders were especially drastic. Cellulite sites especially in thigh regions were also illustrative. In conclusion, the lymphangions were demonstrable by ordinary MRI. Since the simple method without gadolinium-based contrast agent injection, could result in excellent visualization, we expect to see more studies analyzing the significance of lymph and lymphatics. Their full presence, partial presence, and/or absence could be interpreted according to disease states.

The Staging and Clinical Correlation of Lymphoscintigraphic Findings in Extremity Lymphedema

<u>Pinar Borman</u>⁽¹⁾ - Sibel Unsal Delialioğlu⁽¹⁾ - Berna Okudan Tekin⁽²⁾ - Ayşegül Yaman⁽³⁾ - Ahmet Kılıçarslan⁽²⁾ - Bihter Altunay⁽¹⁾ - Meltem Dalyan⁽¹⁾ - Busem Atar⁽⁴⁾

University of Health Sciences Ankara City Hospital, Dept of Physical Medicine and Rehabilitation, Ankara, Turkey ⁽¹⁾ - University of Health Sciences Ankara City Hospital, Department of Nuclear Medicine, Ankara, Turkey ⁽²⁾ - Ankara Etlik City Hospital, Department of Physical Medicine and Rehabilitation, Ankara, Turkey ⁽³⁾ - Ankara Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Ankara, Turkey ⁽⁴⁾

Background/Aim: Appropriate diagnosis, staging, and selection of the best treatment of patients with extremity lymphedema (LE) are essential for patient management. Lymphoscintigraphy (LS), which was defined 60 years ago for this purpose, is still accepted as the gold standard imaging method for the diagnosis of lymphedema. The qualitative and quantitative lymphoscintigraphic analysis and staging are sensitive approaches to diagnose lymphedema. The aim of this study was to retrospectively evaluate LS findings and LE staging and their compatibility with clinical findings.

Methods: The data of 131 patients who underwent lymphoscintigraphy imaging in our clinic in the last 9 months were included in the study. The demographic and clinical variables comprising; age, BMI, etiology, duration, site and staging) were recorded from the patient files. Lymphoscintigraphic images were evaluated according to normal lymphatic flow, number of multi and/or dilated channels, transition to proximal lymph nodes, presence of deep lymph nodes and dermal-backflow. Lymphoscintigraphies were classified as normal and Grade I-IV by 2 independent readers according to 'An Atlas of Clinical Nuclear Medicine' criteria who were blind to clinical information. The results of LS and clinical evaluation were compared. Statistical analysis was performed using Chi-Square and Kendalls tau tests in the IBM SPSS 26 program.

Results: 59 male (45.1%) and 72 female (59.9%) with a total of 131 patients (123 lower and 8 upper extremity LE), with a mean age of 51.53+17.14 years were included to the analysis. Majority of the patients had primary lymphedema (76.3%) and the median duration of lymphedema was 43 months. In clinical

staging, 41 (31.2%) of the patients were stage 1, 66 (50.4) stage 2, and 24 (18.4) stage 3. In the LS evaluation, 41 (31%) of the patients were found to be lymphoscintigraphically normal. 38 (29%) were stage 1; 18 (13.7%) were stage 2; 20 (15.3%) were stage 3 and 14 (10.7%) were stage 4. The most common LS findings were; dilatation of lymphatic vessels and decreased passage to proximal lymph nodes, followed by dermal backflow. A positive correlation was found between both readers (intraclass correlation Coefficient for right and left: 0.87; 0.89, respectively) in lymphoscintigraphy staging (p<0.05). Among the readers, a positive correlation was found between reduced penetration to proximal lymph nodes, multichannel lymphatic flow, and dermal-backflow, and the clinical stages (p<0.05). However, no correlation was detected between deep lymph nodes and clinical stages (p>0.05).

Conclusion: According to our results, the presence of decreased passage to proximal lymph nodes, multichannel and/or dilated lymphatic duct, and dermalbackflow were common and correlated with clinical stages of LE; but the presence of deep lymph node did not correlated with clinical staging. LS, as the gold standard in the diagnosis of LE, is an important auxiliary technique which is correlated with clinical stages of lymphedema however further studies are needed for standardized protocols and interpretation of images in diagnosis and staging of the extremity lymphedema.

Refining a Large Animal Model Assessing Real-Time Lymphatic Function: Progress Towards Clinical Translation

Valeria P Bustos ⁽¹⁾ - Rosie Friedman ⁽¹⁾ - Jason Dinh ⁽²⁾ - Hajin Joanne Kim ⁽²⁾ - Rita Laurence ⁽¹⁾ - <u>James E Fanning</u> ⁽¹⁾ - Satoshi Kashiwagi ⁽²⁾ - Bernard T Lee ⁽¹⁾ - Hak Soo Choi ⁽²⁾ - Dhruv Singhal ⁽¹⁾

Beth Israel Deaconess Medical Center, Division of Plastic and Reconstructive Surgery, Boston, United States Of America ⁽¹⁾ - *Massachussetts General Hospital, Department of Radiology, Boston, United States Of America* ⁽²⁾

Background: Developing a method to evaluate real-time lymphatic function will have profound implications for the diagnosis, surveillance, and treatment of lymphatic diseases. Currently, no accurate and reproducible method of measuring direct lymphatic flow exists. Our team has been working on a large animal model to develop a method for evaluating real-time lymphatic function utilizing optical dyes.^{1,2} We will present our most recent modifications aimed at delivering a model which is clinically translatable.

Methods: Two optical dyes were injected into the respective hind limbs of nine female swine, and their transit was simultaneously assessed. Specifically, near-infrared imaging of blood and urine samples was performed after subcutaneous injection of 700 nm and 800 nm emitting fluorophores at set time points. Continuous imaging was also performed of the superficial epigastric vein and adjacent skin. The pharmacokinetics, biodistribution, and clearance of the two dyes were evaluated.

Results: Inconsistent pharmacokinetics of the two dyes led to refinement in both fluorophore delivery and composition. Reproducible fluorophore delivery into the dermis was achieved utilizing a novel delivery platform VAX-ID [®] that provides standardized, accurate, and user-friendly intradermal injections. Moreover, we modified our fluorophore by removing human serum albumin, thereby optimizing the pharmacokinetics of the optical dye for ultimate clinical translation.

Conclusion: Developing a model for noninvasive measures of direct lymphatic flow in real-time remains a critical unmet need in the field of lymphatics. We continue to focus on the clinical translatability of our model with the goal of human translation in the near future.

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Primary Lower Extremity Lymphedema Classification based on Non-Contrast MR Lymphography Findings

Toko Miyazaki⁽¹⁾

National Center for Global Health and Medicine, Plastic and Reconstructive Surgery, Tokyo, Japan⁽¹⁾

Primary Lower Extremity Lymphedema Classification based on Non-Contrast MR Lymphography Findings

Toko Miyazaki.¹, Hayahito Sakai.¹, Reiko Tsukuura.¹, Takumi Yamamoto.¹

1. Department of Plastic and Reconstructive Surgery, National Center for Global Health and Medicine, Tokyo, Japan

Objective: Non-contrast magnetic resonance lymphography (NMRL) has been reported useful for lymphedema evaluation, but little is known on NRML findings of primary lower extremity lymphedema (LEL). This study aimed to clarify characteristic NMRL patterns and to develop a new classification for primary LEL.

Method: This retrospective observational study included primary LEL patients who underwent indocyanine green lymphography (ICGL) and NMRL from August 2017 to August 2021. NMRL findings of lymphedematous and non-lymphedematous limbs were evaluated, and categorized in 4 types according to the number of layers in subcutaneous tissues on NMRL. Clinical demographics were compared with categorized MRL patterns.

Results: Eighteen patients were included in this study. ICGL revealed that 27 limbs were lymphedematous with abnormal ICGL findings and 9 limbs were non-lymphedematous. NMRL patterns could be classified into 4 types: no layer pattern (type 1, n = 11), mono-layer pattern (type 2, n = 15), dual-layer pattern (type 3, n = 8) and multi-layer pattern (type 4, n = 2). According to the NRML types (type 1 vs. type 2 vs. type 3 vs. type 4), there were significant differences in lymphedematous volume (3314.0 ± 938.2 vs. 4203.9 ± 1129.3 vs. 5155.8 ± 1856.2 vs. 6389.0 ± 3799 , P = 0.014).

Conclusions: NMRL findings could be classified into 4 types with different clinical characteristics. Further studies are warranted to confirm usefulness of the NMRL classification for management of primary LEL.

Introduction

Lymphoscintigraphy is the gold standard for the diagnosis of lymphedema. In our experience, lymphoscintigraphy is required for: prognostic evaluation in established clinical diagnosis; differential diagnosis in edema of uncertain origin; early detection of lymphatic disorder in lipedema A complete lymphoscintigraphic study includes the investigation of both the superficial and the deep circulation. The alterations can affect both networks at the same time or even just one. Since 2013 at the Nuclear Medicine Institute of the Udine University Hospital, the exam involves the study of superficial and deep networks on different days. All combinations of superficial and/or deep, uni- or bilateral damage were found. The object of our study was the identification of clinical pictures related to the damage of the deep circulation only.

Materials and methods

A retrospective survey was performed on lymphoscintigraphies performed from 2013 to 2021 at the University Hospital of Udine (Italy). The examinations were performed with a first session for the visualization of the superficial system and, after 2-4 days, a second one for the deep circulation. After taking static images, performed immediately after the radionuclide injection, continuous segmental motor activity was performed for 45 minutes; images of the lower limbs and also of the trunk were taken one hour and two hours after inoculation.

Results

Of 313 examinations performed (248 on the lower limbs and 65 on the upper limbs), we selected those showing a damage to the deep circulation, interesting one or both limbs. In 120 cases the impairment in one limb was associated with deficit of superficial and deep circulations of the other side. There were 42 cases with bilateral deep circulation damage, of which 9 were male and 33 were female. The median age is 57 years (12-90). The damage was found in 14 lipedemas in various stages, 13 edemas of unclear nature, in 10 cases of overt primary or secondary lymphedema, in 3 markedly obese subjects and in two cases of posttraumatic lymphedema.

There were 17 cases with unilateral damage to the deep circulation, 4 of which were male and 13 female. The median age is 48 years (28-74). The damage was found in 2 lipedemas in various stages, 7 edemas of an indeterminate nature, in 5 cases of overt primary or secondary lymphedema, in 3 markedly obese subjects.

In 6 cases the involvement of the deep circulation of one limb was associated with damage of the superficial circulation of the contralateral limb.

Discussion

Few Nuclear Medicine services carry out the study of the deep circulation, in the case of lymphoscintigraphy of the limbs. As demonstrated by recent literature, this lack leads to a possible misdiagnosis, especially in cases where the damage affects only the deep network. A correlation between the damage of deep lymphatics alone and their clinical manifestations has not been performed so far. This type of study, which we performed on a large number of cases, allowed us to identify various corresponding clinical pictures, represented in a greater percentage by cases of edema of clinically unclear origin.

15. Indocyanine Green – ICG Lymphography

Primary Lymphedema Classification based on Indocyanine Green Lymphography Findings

Hayahito Sakai⁽¹⁾ - Toko Miyazaki⁽¹⁾ - Reiko Tsukuura⁽¹⁾ - Nana Yamamoto⁽¹⁾ - Takumi Yamamoto⁽¹⁾

National Center for Global Health and Medicine, Department of Plastic and Reconstructive Surgery, Tokyo, Japan⁽¹⁾

Primary Lymphedema Classification based on Indocyanine Green Lymphography Findings

Hayahito Sakai, Toko Miyazaki, Reiko Tsukuura, Nana Yamamoto, Takumi Yamamoto

Department of Plastic and Reconstructive Surgery, National Center for Global Health and Medicine, Tokyo, Japan

Objective: Primary lower extremity lymphedema (LEL) has a wide variety of etiologies. Indocyanine green (ICG) lymphography has been applied in secondary lymphedema evaluation, and is considered useful also for primary lymphedema evaluation. This study aimed to evaluate feasibility of ICG lymphography for primary LEL evaluation.

Methods: Medical charts of primary LEL patients who underwent ICG lymphography were reviewed. ICG lymphography findings were classified according to visibility of Linear pattern and distribution of dermal backflow (DB) patterns. Clinical characteristics and postoperative outcomes of lymphaticovenular anastomosis (LVA) were compared according to the developed ICG lymphography classification.

Results: ICG lymphography showed 100% sensitivity and 100% specificity for lymphedema diagnosis. Primary LEL could be classified into 4 types based on ICG lymphography findings; proximal DB (PDB), distal DB (DDB), less enhancement (LE), and no enhancement (NE) types. There were significant differences in age, laterality, cellulitis history, lymphedema onset, and lymphedematous volume among the types (all P < 0.05). Postoperative volume reduction after LVA surgery was significantly lower in patients with NE type than those with PDB type (P < 0.05)

Conclusions: ICG lymphography is useful for primary lymphedema diagnosis and evaluation. Primary LEL can be classified into 4 types with different clinical characteristics and prognosis. LVA surgery is not recommended for NE type primary LEL.

15. Indocyanine Green – ICG Lymphography

Relation between characteristics of ICG lymphography and the development of breast cancer-related lymphedema

Sarah Thomis⁽¹⁾ - Sophie Ronse⁽¹⁾

University Hospitals Leuven, Vascular surgery, Leuven, Belgium⁽¹⁾

Relation between characteristics of ICG lymphography and the development of breast cancer-related lymphedema

Background. Breast cancer related lymphedema (BCRL) is a disabling condition affecting 14 to 40% of the patients that underwent breast cancer treatment. To date, the pathophysiology of BCRL has not been fully understood, making it difficult to understand why some patients develop BCRL and others do not. Studying lymph anatomy by means of indocyanine green (ICG) lymphography is one promising tool to help in better understanding BCRL. The aim of this study is to determine if there is a relation between ICG lymphography characteristics and the risk of developing BCRL.

Methods. This study was a retrospective cohort study with a prospectively constructed database of patients scheduled for breast surgery with either unilateral axillary lymph node dissection (ALND) or sentinel node biopsy (SNB) in the Multidisciplinary Breast Clinic at the University Hospitals Leuven between November 2017 and May 2019. Patients were assessed at baseline and at 1, 3, 6, 9, 12, 18, 24 and 36 months post-operatively. BCRL was defined as a \geq 5% relative arm volume difference increase compared to preoperative measurement. The ICG lymphography characteristics visualized in this study were the number of lymph vessels and the presence of lymph nodes.

Results. 128 patients were included in this study. 45 patients (35.2%) developed BCRL in the course of 36 months after surgery. The number of lymph vessels visualized by ICG lymphography before surgery was not a statistically significant predictor of the risk of developing BCRL. Also the presence of visual lymph

nodes and the change in presence of lymph nodes compared to baseline cannot be used as predictors of the risk of BCRL. However, an increase in number of lymph vessels compared to baseline measurement turned out to be a statistically significant protective factor for developing BCRL (OR=0.8). An increase of one lymph vessel corresponds to a 19% relative risk reduction of developing BCRL.

Conclusion. ICG lymphography can be used to visualize lymph anatomy of the upper limb before and after breast cancer surgery. An increase in number of lymph vessels compared to baseline is a protective factor for developing BCRL. Therapies with the ability to increase the number of lymph vessels can thus possibly decrease the risk of developing BCRL

15. Indocyanine Green – ICG Lymphography

PREVALENCE OF SUBCLINICAL LYMPHOEDEMA IN PATIENTS WITH LYMPHONODAL BIOPSY OR AXILLARY LYMPHADENECTOMY IN BREAST CANCER SURGERY

<u>Sofía Alexia Salvia</u>⁽¹⁾ - Luis Daniel Marcovecchio⁽¹⁾ - Pablo Nahuel Castro⁽¹⁾ - Maria Guadalupe Bengoa⁽¹⁾ - Sandra Nelly Gerez⁽¹⁾ - Marianela Ramirez⁽¹⁾ - Carolina Laplace⁽¹⁾ - Maria Esther Locatti⁽¹⁾ - Monica Avila⁽¹⁾ - Miguel Angel Amore⁽¹⁾

Military Central Hospital, Phlebology and Lymphology Service, Buenos Aires, Argentina ⁽¹⁾

Work submitted to be considered for the presidential award

PREVALENCE OF SUBCLINICAL LYMPHOEDEMA IN PATIENTS WITH LYMPHONODAL BIOPSY OR AXILLARY LYMPHADENECTOMY IN BREAST CANCER SURGERY

Sofia Alexia Salvia , Luis Daniel Marcovecchio, Pablo Nahuel Castro, Maria Guadalupe Bengoa, Lorena Rodriguez, Sandra Nelly Gerez, Marianela Ramirez, Carolina Laplace, Maria Esther Locatti, Monica Avila, Miguel Angel Amore

Phlebology and Lymphology Service – Breast Pathology Service. Military Central Hospital Grl 601, Buenos Aires, Argentina

INTRODUCTION

The main cause of secondary lymphoedema in our country is due to the treatment of breast cancer. It is estimated that after axillary lymphnode dissection, the incidence of lymphoedema ranges from 7-49%; and even after sentinel node biopsy the estimated incidence is 13%.

Stage 0 lymphoedema represents a latent or subclinical condition in which oedema is not yet evident despite mechanical impairment in lymphatic transport.

The high prevalence of the disease, the high health care cost and the efficacy of timely treatment make the need for early detection relevant.

OBJECTIVE

Purpose of this work is to detect early changes in the superficial lymphatic system using fluorescence lymphography in patients who have undergone axillary lymphadenectomy or lymphonodal biopsy in the context of breast cancer surgery.

MATERIALS AND METHODS

The investigation was carried out from January 2022 to January 2023 in the Phlebology and Lymphology Service and Breast Pathology Service of the Military Central Hospital. A total of 63 (n=63) upper limbs were evaluated, corresponding to 60 patients (57 women and 3 men), with axillary lymphadenectomy or sentinel lymph node biopsy performed between 5 and 90 days prior to the study, and absence of clinical signs and subjective symptomatology of lymphoedema in the upper limb.

For the study, 1 ml of indocyanine green was injected subcutaneously in theweb spaces.

An IC flow camera was used to evaluate the lymphatic pattern and the images were recorded. Results were contrasted with body mass index and number of resected nodes (sentinel node, sentinel node protocol (biopsy of 3 lymph nodes), and axillary lymphadenectomy).

RESULTS

A total of 63 (n=63) upper limbs were evaluated, corresponding to 60 patients (53 females and 7 males).

According to the type of surgical procedure (amount number of resected lymph nodes), the results obtained were: in 24 patients with sentinel lymph node biopsy: 9 patients presented normal pattern, and 15 showed alterations in the lymphography; in 16 patients with sentinel lymph node protocol : 7 patients presented normal study, and 9 showed alterations in the same; and regarding the 23 patients with axillary lymphadenectomy: 6 presented normal pattern and 17 presente different dermal backflow pattern.

The relationship between the ICG lymphography findings and the body mass index (BMI) of the patients was established. On the 23 overweight patients, 15 had abnormal pattern in the lymphography; on the 10 patients with grade I obesity, 7 had dermal backflow pattern on the study; and on the 6 patients with grade II obesity and the 8 patients with grade III obesity, all had backflow and reflux pattern on lymphography.

CONCLUSIONS

Indocyanine green lymphography allowed a quick and simple evaluation of the lymphatic system, with early detection of lymphoedema stage 0, in order to carry out early rehabilitation, directed and oriented to each patient with the final objective of preventing the progression of lymphoedema. Those patients with axillary lymphadenectomy and grade II and III obesity had a high prevalence of dermal backflow pattern in fluorescence lymphography, demonstrating subclinical lymphoedema.