5 Key Topic: Multimodal Evaluation of the Lymphedema Patient

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Introduction

There are a plethora of etiologies for extremity swelling, each with different treatment algorithms, and around a quarter of patients presenting with suspected lymphedema do not have the condition. Patients with limb swelling present a significant challenge to exclude other causes including lipedema, venous insufficiency, obesity, posttraumatic edema, systemic diseases (including cardiac, renal, hepatic, or rheumatological conditions), lymphovascular malformations, or congenital syndromes [1]. A multimodal structured approach is therefore necessary for accurate diagnosis. Around 90% of patients with lymphedema can be correctly diagnosed by focused clinical history and physical examination [2]; limb measurements and imaging modalities, where indicated, will confirm a lymphedema diagnosis, exclude comorbid conditions, and accurately stage the lymphedema [3–5]. This information informs an algorithmic approach to optimally treat the patient [6]. In patients with acute onset lymphedema (especially if the presentation is delayed) or acute-on-chronic worsening, venous thrombosis or locoregional cancer recurrence must be excluded with appropriate imaging.

Diagnostic modalities can be categorized into objective measurements of volume or extracellular fluid and subjective measures of physiological lymphatic vessel function: these include limb circumference measurements and formulae derived from these, infrared optoelectronic volumetry (perometer), bioimpedance spectroscopy (BIS), lymphoscintigraphy, indocyanine green (ICG) fluorescent lymphography, magnetic resonance imaging/lymphangiography (MRI/MRL), and computed tomographic (CT) imaging [7] (Table 5.1). The use of validated lymphedema-specific patient-reported outcome (PRO) questionnaires and those that evaluate limb function may support a lymphedema diagnosis. A range of consultative services should be available through a multidisciplinary referral framework to manage these complex and diverse presentations, including lymphedema-specialist physical therapy, occupational therapy, radiology, interventional radiology, vascular surgery,

Table 5.1 Assessment tools available for the evaluation of patients presenting with limb swelling

Limb volume measurement	Perometer; tape measure circumference (truncated cone; extremity lymphedema index); water displacement plethysmography; volumetric CT
Extracellular fluid measurement	Bioimpedance spectroscopy (LDex score)
Clinical staging	ISL; Campisi; Cheng Lymphedema Grading; Taiwan Lymphoscintographic Staging
Physiological diagnostic/staging imaging	ICG lymphography (dermal backflow staging scale; MDACC ICG lymphedema staging scale); lymphoscintigraphy (including transport index); MRL
Patient-reported outcomes	LLIS; LYMQOL; ULL-27; LyQLI; FLQA-1; Lymph-ICF-LL; LYMPH-Q.
Limb functional assessment instrument	DASH/ Quick-DASH; LEFS; UEFI; ULDQ.
Assessment of venous system (if suspicion of DVT/venous insufficiency)	Comparative Duplex ultrasound; direct contrast venography; CT venography; MR venography

CT computed tomographic, *ISL* International Society of Lymphology, *ICG* indocyanine green, *MDACC* MD Anderson Cancer Center, *MRL* magnetic resonance lymphangiography, *DVT* deep vein thrombosis, *LLIS* Lymphedema Life Impact Scale, *LYMQOL* Lymphedema Quality of Life, *ULL27* Upper Limb Lymphedema 27, *LyQLI* Lymphedema Quality of Life Inventory, *FLQA-L* Freiburg Life Quality Assessment for Lymphedema, *Lymph-ICF-LL* Lymphedema Functioning, Disability and Health Questionnaire for Lower Limb Lymphedema, *DASH/Quick-DASH* Disabilities of the Arm, Shoulder, and Hand Questionnaire, *LEFS* Lower Extremity Functional Scale, *UEFI* Upper Extremity Functional Index, *ULDQ* Upper Limb Disability Questionnaire

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cardiology, internal medicine, medical and surgical oncology, orthopedics, rheumatology, and nutrition, among others.

At present there is lack of clear consensus regarding how patients presenting with suspected lymphedema should be evaluated, and this complicates comparison of outcomes between different centers performing surgery for lymphedema [8, 9]. This chapter presents an evidence-based practical approach to evaluation of patients with limb swelling suspected to be lymphedema (Table 5.2).

Focused Clinical History

Secondary lymphedema results from injury to a normally developed lymphatic system and accounts for almost all adult cases of lymphedema. A history of axillary or inguinal lymphadenectomy, in particular with regional nodal irradiation, places patients at the highest risk for developing lymphedema. Upper extremity lymphedema following breast cancer treatment is the most common etiology in the United States, and gynecologic/genitourinary malignancies are the most frequent cause of lower extremity lymphedema [10].

There is typically a delay before the onset of symptoms, with the majority developing lymphedema within 3 years [11]. Once clinically evident, lymphedema is usually a chronic condition characterized by progression, and spontaneous intermittent swelling is atypical for lymphedema. The risk is greater in obese patients [12], and severely obese patients can develop obesity-induced lymphedema or massive localized extremity lymphedema, without a history of lymphatic injury [13]. Patients of African-American ethnicity are at higher risk of developing breast cancer-related lymphedema (BCRL). In adults with acquired unilateral lower extremity lymphedema without causative factors, a history of travel to areas where filariasis is prevalent should be sought. The patient population with lymphedema is among the highest risk for cancer recurrence – in those with acute onset lymphedema, especially if the presentation is delayed, or with acute-on-chronic worsening, venous thrombosis (Duplex ultrasonography) and locoregional cancer recurrence (CT or MRI) must be excluded.

In adults presenting with limb swelling, obesity, lipedema, and venous insufficiency are in the differential diagnosis; patients are also queried about systemic diseases, such as congestive heart failure, renal failure, hepatic dysfunction, and rheumatological disorders, as well as a history of extremity trauma. Venous insufficiency is the most common cause of lower extremity swelling in the adult population, predominantly affecting older females and characterized by varicose veins, edema, and trophic skin changes – lymphatic function though is normal. Severe lipedema can create skin folds that result in obstruction of the lymphatic vessels, secondarily resulting in lymphedema.

Primary lymphedema is idiopathic and rare, resulting from an error in lymphatic development. It usually presents prior to adulthood, most commonly during infancy in males and at adolescence in females. Incidence is similar in males and females, and it affects the lower extremities in over 90% of cases, with equal distribution between unilateral and bilateral presentations [14]. Typically, the swelling commences in the distal lower extremity and then progresses proximally. Trauma may precipitate the features of primary lymphedema. A history of parental lymphedema should be sought (although 90% have no family history), and associated con-

Table 5.2 Recommended evidence-based evaluation of the patient presenting with lymphedema

<table>
<tr><td colspan="2">Focused history</td><td>History of surgery/radiation therapy to regional lymph node basin; duration; time to onset; history of cellulitis and number of episodes; treatment history/compliance; reversibility; exacerbating factors; fluctuation during day</td></tr>
<tr><td colspan="2">Lymphedema symptoms</td><td>Swelling; heaviness</td></tr>
<tr><td colspan="2">Lymphedema signs</td><td>Pitting edema; Stemmer sign; chronic lymphedema skin changes</td></tr>
<tr><td colspan="2">Clinical staging</td><td>ISL staging</td></tr>
<tr><td colspan="2">Physiological diagnostic/staging imaging</td><td>ICG lymphography (dermal backflow staging scale; MDACC ICG lymphedema staging scale); and/or MRL/MRA</td></tr>
<tr><td colspan="2">Limb volume measurement</td><td>Perometer; or limb circumferential measurements with truncated cone volume.</td></tr>
<tr><td colspan="2">Extracellular fluid measurement</td><td>LDex score</td></tr>
<tr><td colspan="2">Patient-reported outcome measures</td><td>LLIS (version 2); LYMQoL; or ULL-27</td></tr>
<tr><td rowspan="3">Additional investigations as required:</td><td>Clinical signs of venous insufficiency</td><td>Comparative Duplex ultrasound; direct contrast venography; CTV or MRV</td></tr>
<tr><td>Recipient site assessment prior to orthotopic VLNT</td><td>Lymphoscintigraphy/SPECT</td></tr>
<tr><td>Donor site assessment prior to inguinal/axillary VLNT</td><td>Lymphoscintigraphy/SPECT</td></tr>
</table>

ISL International Society of Lymphology, *ICG* indocyanine green, *MRA* magnetic resonance angiography, *MRL* magnetic resonance lymphangiography, *LLIS* Lymphedema Life Impact Scale, *MRV* magnetic resonance venography, *CTV* computed tomographic venography, *VLNT* vascularized lymph node transplant, *SPECT* single-photon emission computerized tomography genital syndromes (in particular Turner or Noonan syndrome) should be excluded. In the pediatric population, the differential diagnosis includes capillary/venous/lymphatic malformations, infantile hemangioma, kaposiform hemangioendothelioma, CLOVES (Congenital Lipomatosis, Overgrowth, Vascular malformations, Epidermal nevi, and Scoliosis/Skeletal/Spinal anomalies) syndrome, Klippel–Trenaunay syndrome, and Parkes Weber syndrome. Where primary lymphedema is suspected, patients should be referred to a specialist genetic clinic for testing and counseling, and patients with combined vascular malformations should be managed in a specialist center.

It is important to record an accurate history of the lymphedema duration, which relates to severity, as well as a detailed treatment history including complete decongestive therapy (CDT), noting the time between onset and instituting these, and most importantly compliance with these treatments. A history of cellulitis episodes in the affected extremity and whether intravenous antibiotics were required should be sought, together with frequency and timing; infectious episodes are related to more severe lymphedema pathologies. Improvement of the lymphedema when instituting compression or elevation, or overnight, should be ascertained to indicate physiological reversibility, as well as aggravating factors and fluctuations during the day.

Extremity Lymphedema Symptoms

Regardless of whether the lymphedema is congenital or acquired, the subsequent pathophysiology of the condition is similar. Symptoms include limb swelling, truncal swelling, heaviness, tightness, numbness, tenderness, pain, aching, tingling (paresthesia), and impaired limb mobility [15]. The most common of these symptoms reported in patients presenting with lymphedema are swelling and heaviness, and a self-report of arm swelling is sensitive for diagnosing lymphedema [8]. Reporting of multiple symptoms improves the accuracy in diagnosis, with a diagnostic cutoff of three symptoms found to discriminate breast cancer survivors with lymphedema from healthy women with a sensitivity of 94% and a specificity of 97% [16]. A history of time of day and activities that cause/exacerbate or alleviate swelling should also be sought. While pain is not an unusual symptom, a complaint of significant pain is atypical and should prompt further investigation to exclude recurrence, etc.

Physical Examination Findings

The presence of pitting edema comparing the affected with the unaffected extremity is assessed by pressing the examiner's thumb into consistent locations for 60 s; the degree of pitting edema can be expressed using the Pitting Edema Scale [17]. Significant pitting signifies a fluid dominant limb and its presence corresponds to dermal backflow on lymphatic imaging [18]; the degree of pitting edema correlates with the LDex score but not the limb volume difference (LVD)/excess, likely due to the associated fibrosis that characterizes advanced lymphedema [4]. The presence of significant pitting edema should prompt timely referral to lymphedema therapy for reductive CDT. Significant reversibility of pitting edema may indicate suitability for a physiological surgical procedure; patients with minimal or no pitting and significant adipose soft tissue excess may be candidates for a debulking procedure. The degree of fibrosis of the tissues should also be evaluated, as well as the presence of other skin stigmata of chronic advanced stage lymphedema, including dermal lymphedema, hyperkeratosis, and lymphorrhea. The (Kaposi-)Stemmer sign is a sign of distal fibrosis, and therefore advanced stage lymphedema, and is positive if the examiner is unable to pinch the skin on the dorsum of the hand or foot [19, 20].

The degree of fibrosis and skin tethering at the lymphadenectomy surgical site should also be assessed to determine the need for surgical intervention, as well as signs of venous insufficiency distally such as skin color changes and varicose veins. Venous insufficiency may be a contraindication to a physiological surgical procedure. New onset varicosities may indicate deep vein thrombosis, such as prominent chest wall veins in axillary vein thrombosis. It is important to note that in patients with positive clinic signs but normal lymphatic imaging, venous insufficiency is the most common cause of swelling and work-up should include evaluation of cardiac function [19]. Body mass index (BMI) should be evaluated at each clinic visit.

Lymphedema Clinical Staging Scales

The clinical history and physical examination findings inform the International Society of Lymphology (ISL) staging scale [21]. This is the most commonly used system to classify the severity of the lymphedema, describing progression through four stages:

Stage 0 describes latent or subclinical lymphedema without swelling but with impaired lymph transport, subtle alterations in tissue fluid/composition, and changes in subjective symptoms; Stage I lymphedema is characterized by swelling which subsides with limb elevation, and pitting edema may occur. Stage II lymphedema is characterized by subcutaneous fat accumulation – limb elevation alone rarely reduces tissue swelling, and pitting edema is evident – later on the limb may not pit as soft tissue fibrosis develops. Stage III is advanced lymphedema where pitting can be absent and there are trophic skin changes such as hyperkeratosis and acanthosis. A limb may exhibit more than one stage. Several studies however have found that the ISL stage correlates poorly with other lymphedema measures, including LVD and the LDex score [8], likely due to the highly subjective nature of the staging system, with each stage representing a broad spectrum of phenotypes (majority Stage II), and it does not link with surgical treatment decisions. The Campisi lymphedema staging expanded this scale to six stages: Stage I includes latent (A) and initial (B) lymphedema; Stage II includes increasing lymphedema (A) and column-shaped limb fibrolymphedema (B); and Stage III is elephantiasis [22]. The Cheng Lymphedema Grading scale and the Taiwan Lymphoscintographic Staging system utilize lymphoscintigraphy and/or limb circumferential difference to provide additional objective measures of lymphedema for staging [23]. Physiological staging scales utilizing ICG lymphography (see below) allow for surgical decision-making and are the current mainstay for lymphedema staging.

Limb Volume Measurements

Limb measurements are the most commonly used modality for diagnosis and evaluation of lymphedema and can be used to define severity; these include circumferential measurements, volumetry using a perometer, or water displacement.

Tape measurements are well-established and may be used to derive limb volumes using truncated cone formulae from measurements taken at 4 cm intervals for the length of the extremity, or to calculate the upper or lower extremity lymphedema indices [24]. There is significant inter- and intra-rater variability due to difficulty replicating both the exact reference points and the tension applied to the tape measure. Information regarding the localization of the swelling is provided, though the hand and foot volumes cannot be calculated. An increase of ≥2 cm in circumference measurements has been used as a simple means of diagnosis [15]. For limb volume, diagnostic thresholds include limb volume change (LVC) ≥5% or ≥200 ml absolute difference [25]. When compared with limb volume measurements, circumferential measurements have a relatively low sensitivity, specificity, and positive predictive value, suggesting that the use of circumference measurements alone results in underdiagnosis and underestimation of the degree of lymphedema [8, 26].

The perometer, which uses mobile infrared optoelectronic volumetry, is fast, valid, and reliable for limb volume measurements [5, 27]; however, it is expensive and portability can be problematic. Perometer measurements correlate closely with volume measures derived from circumferential measurements using the truncated cone formula, although manual measurements underestimate the total limb volume. Horizontally configured perometers are specifically designed for the upper extremity (Fig. 5.1a), and upright perometers are used for measurement of lower extremity volumes (Fig. 5.1b); it may be possible to use these interchangeably with adaptations. To decrease variance, it is important that the device is regularly recalibrated, operated by consistent trained staff, and that measurements are taken from defined and reproducible points with the same limb length used for each measurement and for each limb. Multiple bilateral measurements may improve the reliability, and variance, particularly of the unaffected limb, should be a benchmark – ideally less than 1% – while accounting for variations in BMI, etc.

The differences between the affected and unaffected limbs are expressed as relative and absolute limb volume excess ratios; in bilateral lymphedema, the excess volume cannot be determined and so the percentage change in volume for each limb is reported. LVC ≥3% based on the preoperative measurement is a diagnostic threshold [28], with LVC ≥5% classified as mild lymphedema, and ≥10% as moderate to severe [29]. As limb volume excess is a significant feature of lymphedema that surgery aims to improve, limb volume measurements, preferably using a perometer to reduce variability, should be used for diagnosis and in longitudinal assessment [4].

Although limb volume measurement using water displacement plethysmography is highly accurate, there are significant practical limitations to its use in the clinical setting, particularly as the water needs to be changed for successive patients, and it is rarely used.

Bioimpedance Spectroscopy (BIS)

BIS provides rapid and reliable noninvasive measurement of extracellular water in an extremity by calculating the resistance at 0 Hz frequency (R0), at which the cell membrane acts as an insulator [5, 27, 30]. The LDex® U400 (Impedimed, Carlsbad, CA), a portable adhesive electrode and lead-based system, has been the most studied BIS device for lymphedema; however, both a significant amount of training and standardization are required for consistent results. The SOZO® can be used in the office setting where the contact electrode pads are built into a fixed system to improve usability and reliability by standardizing palm, sole, and patient positioning (Fig. 5.2). The ratio of the impedance values between the affected and unaffected limb is calculated after adjusting for sex, upper/lower limb, and right/left dominance, to give the LDex score [31]. An LDex score of −10 to +10 has been considered normal (LDex score of 0 represents the mean impedance ratio, and 10 is equal to a linear change of approximately three standard deviations), and above 10 is diagnostic for lymphedema [30, 32]. A growing evidence-base supports the use of an LDex score of ≥7 to be a more accurate diagnostic threshold for lymphedema of the upper

Fig. 5.1 (**a**) Limb volumetric measurements can be taken using a perometer, a mobile infrared optoelectronic volumeter, that is fast, valid, and reliable. A horizontally configured perometer, as shown here, is specifically designed for measurement of the upper extremity. (**b**) The upright perometer shown here is used for measurement of lower extremity limb volume, although it may also be used for measurement of the upper extremity with adaptations. A standardized technique should be used to reduce variance as well as the use of the mean value of multiple bilateral measurements

extremity (≥6.5 for subclinical lymphedema) [30, 33]. Using a cutoff of LDex ratio ≥+7.1 has an 80% sensitivity and 90% specificity to discriminate between at-risk breast cancer survivors and those with lymphedema, and it is therefore important for clinicians to integrate the LDex score with other assessment methods to ensure accurate diagnosis [30]. For patients with preoperative measurements, a change in the LDex score of >10 units is diagnostic [25]. The LDex score is sensitive for the early detection of lymphedema [33], and significantly correlates with lymphedema severity stage and limb volume excess [4, 34]; it is also highly responsive to nonsurgical and surgical interventions [4, 8].

When compared with limb circumference measurements for the upper extremity, one study found that the LDex score was more sensitive in diagnosing lymphedema and had a higher positive predictive value when using an LVD of >10% as the diagnostic threshold [8]. A significant limitation of BIS remains the ability to independently and reliably measure bilateral extremity lymphedema.

Magnetic Resonance Imaging/Angiography

MRI enables high-resolution imaging of the soft tissues which can be used to assess the relative fluid and lymphedema-related fat hypertrophy compositions of an extremity using T1-weighted imaging with and without fat saturation gradient echo images. Gadolinium contrast-enhanced imaging with delayed-phase vascular imaging can be used to evaluate for venous stenosis or thrombosis. Alternatively, T2-weighted fast spin-echo sequences can also visualize the lymphatic vessels without the need for contrast [35].

MRI has a similar sensitivity to ICG lymphography in diagnosing lymphedema, and is superior to lymphoscintigra-

Fig. 5.2 Bioimpedance spectroscopy (BIS) provides rapid and reliable noninvasive measurement of extracellular water in an extremity. The SOZO® device shown here can be used in the office setting where the contact electrode pads are built into a fixed system to standardize palm, sole, and patient positioning, and improve reliability

phy [36]. Fluid accumulation or fat hypertrophy on MRI is highly sensitive for the diagnosis of lymphedema as defined by a limb volume excess ≥10%, with both high negative and positive predictive values for evidence of fluid accumulation. MRI is not only helpful in confirming the diagnosis of lymphedema but also in excluding other etiologies of limb swelling; in lipedema, for example, the fat accumulation typically occurs without signs of fluid accumulation, or there is subcutaneous infiltration of soft tissue with a classical reticular appearance [37]. MRA has the added advantage of imaging of the venous system; one study found that evidence of narrowing or stenosis in the axillary vein was found in around 15% of patients, which may result in venous insufficiency and contribute to the lymphedema pathology, as well as reducing the effectiveness of physiological lymphedema surgeries [8]. Where concordant venous insufficiency is suspected, additional venous investigations, including comparative duplex ultrasonography, CT venography, or direct contrast venography, may be indicated. Occult metastatic disease contributing to lymphedema by venous compression/stenosis can also be excluded.

Computed Tomography/Venography

Although MRI is the preferred modality for assessing lymphedema, CT imaging demonstrates the characteristic reticular pattern and thickening of the subcutaneous tissue in lymphedema, as well as anatomic localization of the edema. Volumetric CT measurements also significantly correlate with limb circumference measures [38]. CT venography can assess for venous stenosis/thrombosis.

Lymphoscintigraphy

Radionuclide lymphoscintigraphy has been extensively studied for the investigation of lymphatic physiological function, allowing for evaluation of both the deep and superficial lymphatic systems and their draining lymph nodes, lymphatic collateralization, and dermal backflow, as well as lymphatic transport using transit times [39]. It may also assist in the adjunctive classification of the degree of lymphatic dysfunction. Intradermal injection of technetium-99m-colloidal albumin into the digit webspaces of both the affected and unaffected extremities is performed, with serial hemi-body radioscintigraphic imaging of the transit of the radioisotope through the lymphatic system typically at 10 min and then at 30-min intervals up to 3 h post-injection [39]. Asymmetric lymphatic drainage with delayed transit time to the regional lymph nodes and visualization of collateral lymphatic channels is suggestive of lymphedema, and the presence of dermal backflow is diagnostic.

The transport index (TI) evaluates several parameters in serial scans, including lymphatic transport kinetics, radiocontrast distribution pattern, time to appearance of lymph nodes, and assessment of lymph nodes and lymph vessels. It is valid for measuring dynamic lymphatic function with high interobserver reliability [40], and staging scales using the dermal backflow pattern and severity have been described and validated [39]. The Taiwan Lymphoscintigraphy Staging system evaluates the lymph nodes, lymphatic ducts, and presence and distribution of dermal backflow [23].

Studies are inconsistent regarding the reliability of lymphoscintigraphy for the diagnosis of lymphedema [39, 41], and results are likely affected by the definitions used, as well as the experience of the radiologist and interpreter. One study found that the sensitivity and specificity with a minimum limb volume excess of 10% were 88% and 41.4%, respectively, and the positive and negative predictive values were 72.1% and 66.7%, respectively [8].

Lymphoscintigraphy enables evaluation of the presence of residual functional axillary lymph nodes, which may imply a better prognosis, in those planned for orthotopic vascularized lymph node transplantation (VLNT) so that they can be preserved during axillary scar release. It also has great utility in reverse lymphatic mapping [8], and can be combined with CT imaging to produce a SPECT/CT for three-dimensional localizations of the sentinel lymph nodes in the superficial inguinal or axillary regional lymphatic basins to reduce the risk of donor-extremity lymphedema after groin or lateral thoracic VLN flap harvest, respectively [42, 43]. It can also be used for follow-up to determine the function of transplanted lymph nodes, although in proximal lymph node transfer the contrast needs to transit from the webspaces to the transplant to be visualized on lymphoscintigraphy.

Indocyanine Green (ICG) Fluorescent Lymphography

ICG fluorescent lymphography is the primary tool for physiological lymphedema staging and enables decision-making between the available surgical options. It allows for detailed visualization of the superficial lymphatic system and is primarily used for intraoperative lymphatic mapping for lymphovenous bypass (LVB). It enables sites of dermal backflow and their "feeding" vessels to be identified, assessment of lymphatic valvular competence by anterograde or retrograde "milking" of the lymphatics to help determine the optimal lymphatic-venous anastomosis configuration, and localization of venules as "shadows" over the lymphatic vessels (Fig. 5.3) – adjunctive use of a vein imager allows identification of nearby venules and assessment of their valvular competence for selection for anastomosis (Fig. 5.4). The comparative transit time between affected and unaffected extremities can also be measured. Dermal backflow severity and distribution correlate closely with the pathological condition of the lymphatic vessels [44].

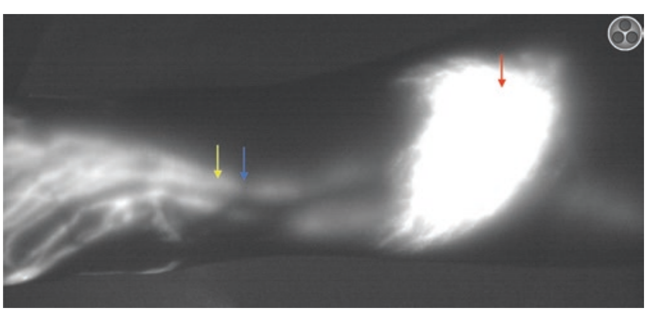

Fig. 5.3 Indocyanine green (ICG) fluorescent lymphography allows for detailed visualization of the superficial lymphatic system and is used for staging and surgical planning. Sites of dermal backflow (*red arrow*) and their linear lymphatic "feeding" vessels (*yellow arrow*) can be identified, as well as localization of venules as "shadows" over the lymphatic vessels (*blue arrow*)

Fig. 5.4 Commercial devices for indocyanine green (ICG) fluorescent lymphography include the PhotoDynamic Eye (PDE, Hamamatsu Inc., Japan) and the SPY Phi (Stryker Inc., USA) (*right*). For surgical planning, the adjunctive use of a vein imager can aid in identification of nearby venules and assessment of their valvular competence for selection for anastomosis (*left*)

Physiological staging systems utilizing ICG lymphography evaluate the following: lymphatic transport, presence of functional lymphatic vessels, and pattern and distribution of dermal backflow. These include the dermal backflow staging scale, a 12-subtype scale, and the MD Anderson Cancer Centre (MDACC) ICG lymphedema staging scale, a five-stage scale [45, 46]. The dermal backflow pattern is additionally characterized as splash, stardust, or diffuse pattern representing increasing levels of fibrosis/sclerosis of the lymphatic vessels, ranging from normal to ectatic, then contraction, and finally sclerosis with obliteration of the lymphatic vessel lumen [46]. These physiological staging systems aid in surgical decision-making – for example, the presence of advanced dermal backflow patterns without visualization of linear lymphatic vessels may be an indication for VLNT.

Approximately 0.05–0.1 mL of ICG (0.25–0.5 mg) is injected intradermally into each webspace, in particular the first and the third [8]. Lidocaine (1%) preinjection is helpful in preventing the local discomfort. Images are acquired using a near-infrared (NIR) fluorescent imager, and several commercial systems are available, including the PhotoDynamic Eye (PDE, Hamamatsu Inc., Japan), the SPY systems including the SPY Elite and Phi (Stryker Inc., USA) (Fig. 5.4), FLARE (Curadel LLC, USA), Fluobeam 800 (Fluoptics, France), and the IC-Flow system (Diagnostic Green GmbH, Germany).

ICG lymphography is currently regarded as the most sensitive test for lymphedema, with one study finding that all abnormal upper limbs with a limb volume of >10% had abnormal ICG patterns [8]. When compared with lymphoscintigraphy, ICG lymphography has greater sensitivity in both the upper and lower extremities [36]. It also aids surgical decision-making: the presence of significant segmental dermal backflow with few or no functioning lymphatic vessels on imaging is an indication for VLNT, and its distribution may help in deciding between proximal anatomic (orthotopic) and distal nonanatomic (heterotopic) flap placement.

Magnetic Resonance Lymphangiography (MRL)

MRL is a relatively noninvasive technique in which a gadolinium-based MRI contrast agent (e.g., gadobenate dimeglumine) is injected intradermally into the interdigital webspaces of the hand or foot. This allows the visualization of the anatomical and functional status of lymphatic vessels, lymph nodes, and dermal backflow in patients with lymphedema, in addition to the inherent ability of MR to image interstitial fluid and subcutaneous adipose tissue [47, 48]. Subtraction venography can be used additionally to discriminate between lymphatic vessels and veins, for example, by intravenous administration of gadobenate dimeglumine contrast [48].

Staging scales using MRL are specific for stratifying patients for surgical intervention [35, 48]. In one study, MRL was found to have greater sensitivity and specificity than lymphoscintigraphy across a range of measures [49]. The main disadvantages of this modality are the operator dependence and necessity for a radiologist with expertise in post-processing and in evaluation of patients with lymphedema.

Patient-Reported Outcome Measures (PROMs) and Limb Functional Assessment Instruments

Patient-reported outcomes (PROs) are important for evaluation of the lymphedema patient as well as for longitudinal assessment in response to nonsurgical or surgical intervention. Several scales have been validated for the measurement of PROs specific for lymphedema and are increasingly being used in the routine clinical setting. These scales include the Lymphedema Life Impact Scale (LLIS), the Lymphedema Quality of Life (LYMQoL) questionnaire, and the Upper Limb Lymphedema 27 (ULL-27). Others include the Lymphedema Quality of Life Inventory (LyQLI), the Freiburg Life Quality Assessment for Lymphedema (FLQA-L), the Lymphedema Functioning, Disability and Health Questionnaire for Lower Limb Lymphedema (Lymph-ICF-LL), and most recently the LYMPH-Q. The LLIS (version 2), which includes 18 questions about the past week distributed across physical, functional, and psychological domains [50], was found to correlate highly with the ULL-27 and was more sensitive in measuring physical and functional disability. There was a weak correlation between the physical and functional domains of the LLIS and limb volume excess, suggesting that even minor increases in limb volume can have a significant impact on quality of life measures, with no correlation found for psychological impairment [8]. A study using the LYMQOL found no correlation with the ISL stage or the LDex score for both upper and lower extremity lymphedema [51].

Limb functional assessment instruments validated in other domains can provide complementary information regarding the physical disability resulting from lymphedema. These tools include the Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH/Quick-DASH), Lower Extremity Functional Scale (LEFS), Upper Extremity Functional Index (UEFI), and Upper Limb Disability Questionnaire (ULDQ). One study found no correlation between the DASH and LEFS scores and ISL stage or the LDex score for upper and lower extremities, respectively [51].

Lymphedema Physical Therapy

The availability of lymphedema therapy delivered by certified lymphedema therapists (CLT) is of central importance for the management of patients with lymphedema, as well as for other causes of edema such as venous insufficiency. Consideration should be made to incorporate lymphedema physical therapy at the time of patient assessment in a multidisciplinary clinic for patient education, to enable therapy to be commenced, for patients to be measured for compression garments, for pneumatic compression pumps to be prescribed, and for coordination of care. If noncompliance is diagnosed, then reasons for it need to be elucidated and addressed: for example, patients may complain that their garment is too tight at the upper arm or wrist, that they feel it is not making a difference, or that it causes their hand to swell. This may be due to their garment being measured at a garment shop without the necessary specialist expertise – custom garments should ideally be measured by an experienced lymphedema therapist or manufacturer representative. During periods of reduced compliance, the limb may become more edematous which adversely affects the garment fitment, and a short course of bandaging may be required, in particular if a new compression garment has been ordered.

Multidisciplinary Lymphedema Team

A comprehensive range of consultative services is important through a multidisciplinary referral framework for the combined management of complex patients with non-lymphedema etiologies or comorbid conditions. In addition to lymphedema-specialist plastic surgery and lymphedema-specialist physical therapy, these include occupational therapy, vascular surgery, diagnostic/interventional radiology with capability for venoplasty/stenting for management of concomitant venous insufficiency, medical and surgical oncology, dieticians/nutritionists (for management of obesity), internal medicine, bariatric specialists, dermatology, orthopedics, rheumatology, physical medicine and rehabilitation, researchers, and geneticists (for primary lymphedema) [52].

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