Chapter 20
Duplex Ultrasonography

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Diagnosis of lymphedema (LYM) of upper and lower limbs currently relies upon the clinical assessment and upon lymphoscintigraphy in most cases. Color-duplex ultrasound (CDU) is an extremely reliable diagnostic technology for arterial and venous investigation, and the application of ultrasound investigation in LYM diagnostics has been reported since 1986,[1,2] to complement these imaging modalities. The exploitation of this safe, easily repeatable, quite reproducible, and relatively inexpensive technology for lymphatic disorders has resulted in the possibility of collecting some useful information before, during, and after any LYM treatment.

High-frequency (10–20 MHz) ultrasound probes allow a fine study of the more superficial tissues,[3] including the LYM sites, with regard to both qualitative and quantitative findings on the accumulation of fluid in supra- and subfascial planes, and elucidating the architecture. Similarly, ectatic lymphatic vessels,[4-7] with some degree of complexity, alterations in lymph node morphology/vascularization in particular, and venous or arterial hemodynamics may be visualized (Fig. 20.1); any concomitant anatomical abnormality, such as nodules or cysts that appear in a lymphedematous limb, will be easily imaged with CDU as well. Since the early 1990s,[8-12] an ultrasound semiology has been proposed to exploit the CDU diagnostic proprieties in this new field. More recently, comparison of ultrasound imaging, magnetic resonance imaging, computed tomography, spectroscopy, and histology in LYM cases has revealed a good intercorrelation of the diagnostic findings,[13,14] confirming the usefulness of this inexpensive technology.

By means of repeatable measurements it is possible to monitor the LYM evolution and the therapeutic results. CDU examination may equally detect any venous concomitant disorder with great accuracy and is necessary and sufficient for most of the differential diagnoses of the swollen limb (e.g., deep venous thrombosis, [DVT],

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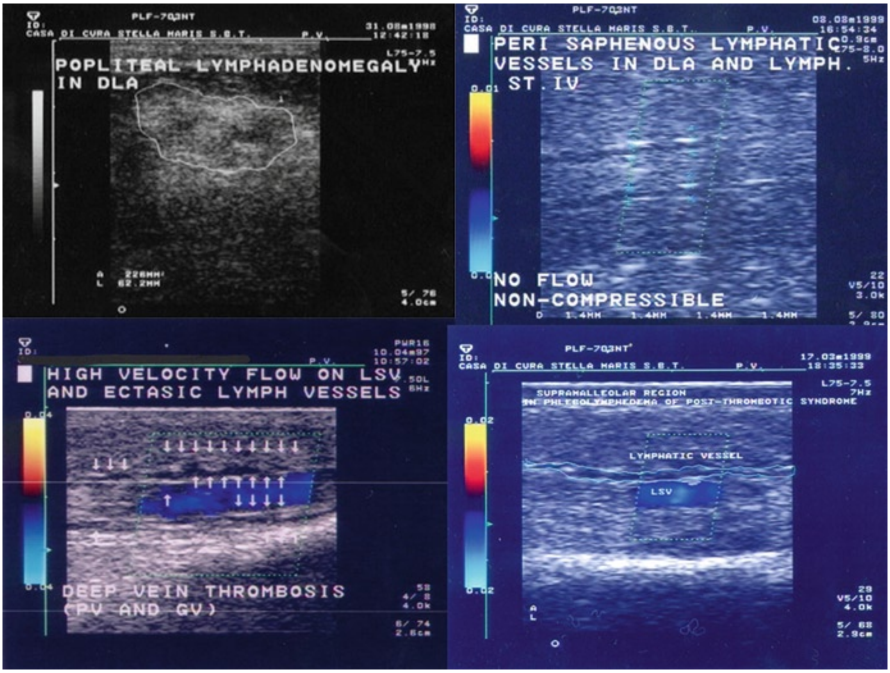

Fig. 20.1 Multiple images of color-duplex ultrasound (CDU) imaging of lymph vessels and nodes

angiodysplasia, postthrombotic syndrome [PTS]). In consideration of the possible role of CDU in identifying venous changes in lymphedematous limbs, a few authors[15] have described the possible dilation of the major deep and superficial venous structures as a consequence of the impaired lymphatic drainage in lymphedematous limbs, with or without acute dermato-lymphangioadenitis. In contrast, several publications have highlighted the possible participation of reduced venous drainage in many cases of “apparently” pure LYM. In fact, impaired subclavian–axillary venous drainage is often present in the edematous arm after mastectomy (in up to 31% of the cases),[16] and some degree of obstruction, or occlusion, of the deep veins has been demonstrated.[17,18] The phlebolymphedema, which may characterize these patients with breast cancer-related arm edema, results in an aggregate of the typical ultrasound findings of LYM (e.g., the so-called lymphatic “lakes,” edematous/fibrotic tissues, etc.) and of CDU signs of a PTS and pathological patterns within the subclavian–axillary veins (Fig. 20.2).

The lower-limb PTS may, of course, represent a concomitant disease in any case of LYM of the lower extremity as well, and the CDU investigation of deep, superficial, and perforating veins in these mixed cases of phlebo-lymphedema of the lower limbs is commonly undertaken and is of great benefit for a more precise diagnostic and therapeutic approach.

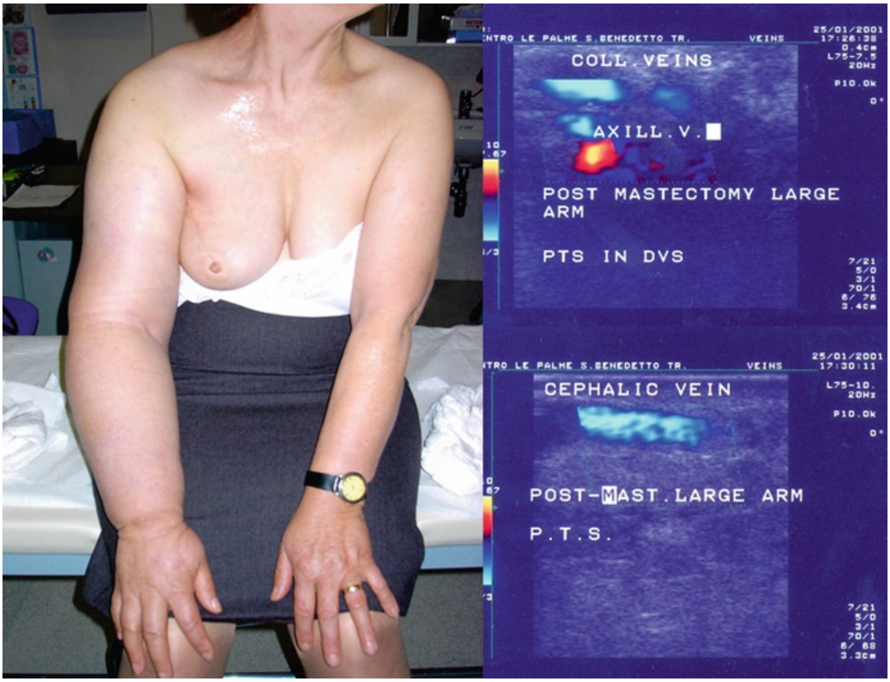

Fig. 20.2 Clinical and CDU pictures of post-mastectomy phlebolymphedema (lymphedema and post-thrombotic syndrome of the upper extremity)

On the arterial side, in 1994, Svensson et al.[19] used CDU to demonstrate increased arterial inflow in arm edema after mastectomy, possibly as a result of altered vasoconstrictor innervations.

Another CDU application relates to vascular malformations involving the lymphatic system. In fact, most "apparently" pure venous angiodysplasias exhibit a relevant lymphatic dysplastic component, and the opposite is also true. Safe and accurate use of CDU in vascular malformations has been proposed by most experts as first-line diagnostic technology, and detection of lymphatic abnormalities may be of help to focus on a proper treatment for these complex diseases.

In cases of posttraumatic or postoperative lymph stasis, CDU once more plays a decisive role: to screen for deep venous thrombosis and to image any serum and blood accumulation and other pathological findings.

With reference to the use of CDU in the investigation of lymphadenomegalias (enlarged lymph node[s]) in the groin or, more rarely, in the popliteal or axillary area, b-mode imaging is usually complemented by color-flow Doppler to highlight possible altered vascularization of the nodes, which usually represent a negative prognostic sign because of its association with neoplasms/metastases.[20] Other possible, quite common findings in CDU imaging of lymphedematous limbs include the ruptured or intact popliteal cyst and/or fluid collection in the knee joint.

The use of CDU investigation was proposed several years ago in specific LYM cases related to filariasis, and a few specific diagnostic markers (such as "the worm dance sign") have been reported.[21-23] Ultrasound imaging may help address local/regional pharmacomechanical treatment for filiariae removal. Monitoring of the infection is facilitated through repeated ultrasound scanning.

It can be argued that the complexity of differential diagnosis and of the therapeutic options available in cases of a swollen limb fully justifies extensive and systematic use of CDU, especially in expert hands.[24]

Specific Details in Ultrasound Investigation of Lymphedema

Ultrasound anatomy of normal skin and deeper layers is generally characterized by:

(a) A first, superficial hyperechogenic layer (the epidermis).
(b) The usually low-echogenicity layer of "papillary" dermis and hyperechogenicity of the deeper reticular dermis.
(c) The mixed-echogenicity of the subcutaneous layer, which is characterized by connective bands and nodule-like (adipose component) images.

At greater depths, the hyperechogenic muscular fascia is easily recognized, and the muscular layer ultrasound image is well defined.

In the case of LYM of the lower or upper limb, several possible modifications may occur in the architecture, echogenicity, and imaging characteristics within the epifascial and subfascial layers. Strict comparison of the same areas in the two limbs, especially in cases of unilateral LYM, and multiplanar transverse and longitudinal scans, together with a bimodal investigation (in the standing and supine positions), are of great help for proper CDU imaging.

A few basic features and findings can be observed through careful technique and proper ultrasound probes. A summary is proposed below.

- The presence of "lymphatic lakes," hypo-echogenic images of fluid collections, which can be located mostly in the epifascial compartment and in the subcutaneous layer, but also, in more advanced cases, in sub-fascial tissues; these fluid extravasations can be distinguished from the collectors because of their "anarchic" disposition, and their abundance and size, although some misinterpretation is always possible; the ultrasound image of the fluid collections, resembling bands of various width, gives the tissues a stratified conformation (Fig. 20.3).
- A dilation of the lymphatic main trunks/collectors is potentially imaged through high-frequency probes (ideally 18 MHz) (Fig. 20.1, 20.4, 20.5); usually the dilated lymphatic vessels are visible in the subcutaneous tissues, mostly along the greater saphenous vein axis for the leg region (where they predominantly lie in normal subjects), or in close proximity to the major lymph nodes (pre-post-lymph node collectors). The visualization of the lymphatic trunks may be more frequent in secondary LYM, because, in primary LYM, the lymphatic vessels may be atretic, hypo-functioning or totally absent; similarly, in cases of acute

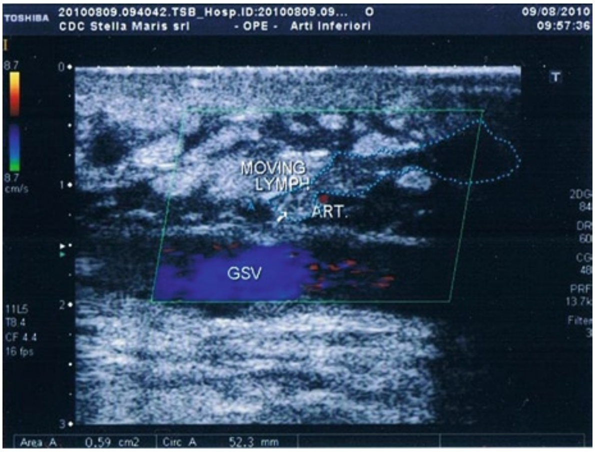

Fig. 20.3 CDU imaging in lymphedema; note the lymph movement in proximity to an arteriole, beside the great saphenous vein (GSV)

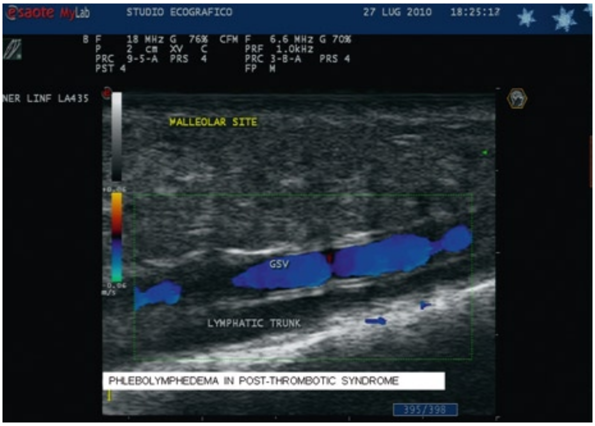

Fig. 20.4 Ectatic lymphatic vessels along the GSV at the malleolar site

Fig. 20.5 Visible lymphatic vessels in lipolymphedema

dermato-lymphangioadenitis or lymphocele, the lymph collectors tend to dilate functionally and are more visible on ultrasound images. The ultrasound appearance of the lymphatic channel is that of a double hyperechogenic walled tube and sometimes even valves, or thrombi[7] are highlighted inside the largest trunks. Because of the extremely small caliber of these vessels and the extremely slow lymphatic flow, CDU cannot objectively detect any "colored" fluid movement and cannot always distinguish these structures from fluid collections (the so-called "lymphatic lakes") that are visible in any edematous condition.[25] Immediately before Duplex ultrasound (DUS) investigation, an injection of (diluted) liquid albumin,[26] a mini-trauma,[7] or even a tourniquet above the edematous region,[7] may enhance the ultrasound visualization of the lymphatic vessels in lymphedematous limbs or, especially, in normal limbs. Matter et al.[7] also confirmed lymph vessel ultrasound imaging through lymphatic fluid aspiration in the detected channel and through the injection of a radiopaque contrast agent within the same structure.

- The degree and location of echogenicity of the tissues, which strictly correlates with the degree of the fibrosis in the affected areas[27]; in greater detail, minimally pitting or non-pitting LYM correlates with the presence of a higher degree of fibrosis or, better, fibroadiposis, which commonly occurs in the late stages of LYM; long-lasting LYM may result in a DUS pattern that is characterized by a lack of fluid collections and by a hyperechogenicity and anarchy of the supra-sub-fascial tissues, with nodule-like images. However, the early stages of LYM, such as the non-swollen upper extremity after breast cancer surgery (which is clinically comparable to the contralateral limb), may also exhibit a pattern of deterioration of the architecture and an increased thickness and/or echogenicity of the epi-fascial layers, not necessarily showing any lymphatic lakes.[28]
- Lymph node visualization, measurement, and investigation with color-Doppler flow, or power Doppler flow, should complement the ultrasound investigation in LYM cases, to differentiate abnormalities of lymph nodes related to infections, neoplasms (metastases), functional overloading, etc.
- The increase in thickness of the dermis (especially in breast cancer-related LYM)[29] and/or of the subcutaneous layer and/or of the subfascial layer is a constant finding; it involves especially the subcutaneous space until LYM frankly deteriorates, then it involves all layers at the later stages.
- The compressibility of the tissues under the ultrasound probe pressure seems to be well-correlated with the degree of fibrosis/echogenicity, at least in the upper extremity.[30,31]

A few authors[4,25,32,33] have described several rules to differentiate pure venous edema (phlebedema), from pure LYM and especially from lipedema (lipodystrophy of the lower limbs with fat deposition and interstitial fluid retention). In the presence of phlebedema most hypo-echogenic collections are visible in the dermal layers, while in cases of lymphostasis, the fluid collections are located in the subcutaneous region and/or in the sub-fascial space. More advanced LYM cases show bands of hyper-echogenic reflection (which represent perilymphangiosclerosis in advanced cases). Finally, lipedema is usually characterized by diffused echoes along the whole

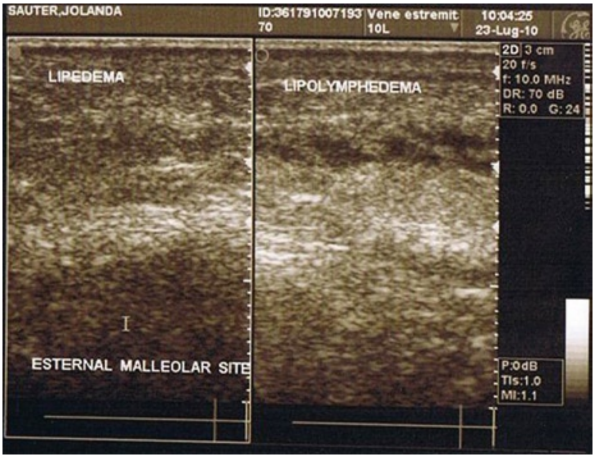

Fig. 20.6 Ultrasound images of lipedema (*left side*) and lipolymphedema (*right side*), with low-echogenicity findings in the latter condition

thickness of the suprafascial tissue, with no noticeable areas of low-reflection intensity (no "lymphatic lakes" are visualized) and no increase in dermal thickness (which, on the contrary, happens in LYM). During the late stages of lipedema, lymphostasis may secondarily intervene because of the progressive deterioration of the lymphatic vessels/nodes within the fat tissues and worsening fibrosis. Thus, CDU highlights the typical low-echogenicity spaces in the areas affected by lipolymphedema (Fig. 20.6).

It should be recalled that whenever edema reflects impaired (overloaded or organically pathological) lymphatic drainage and the common CDU findings pattern of hypoechogenic areas will be seen in several of the non-vascular clinical entities, such as heart/renal/liver failure or hypo-disprotidemia.

The largest lymphatic trunk, i.e., the thoracic duct, may also be the object of investigation through CDU. Franceschi[34] first published on B/W ultrasound imaging of a thrombotic obstruction of the thoracic duct and the corresponding intra-operative findings.

Ultrasound usage during LYM treatment can be based on repeated measurements at fixed locations and different measures can be highlighted (Fig. 20.7):

(a) The thickness of the suprafascial tissue (having the muscular fascia as the basal marker).
(b) The skin-to-bone thickness, in particular at the level of the ankle, the foot, and, above all, the retromalleolar regions for the lower limb and the forearm for the upper limb.

If one of the main superficial veins is included in the picture/measurements, or in the case of inclusion of one or two skin markers, such as nevi or spider veins, CDU imaging reproducibility can be improved; similarly, the inclusion of abundant gel on the skin will, on the one hand, minimize the possibility of interference with the images through unwanted pressure on the skin, while, on the other hand, it will improve imaging of the most superficial layers (Fig. 20.8). A holistic, integrated

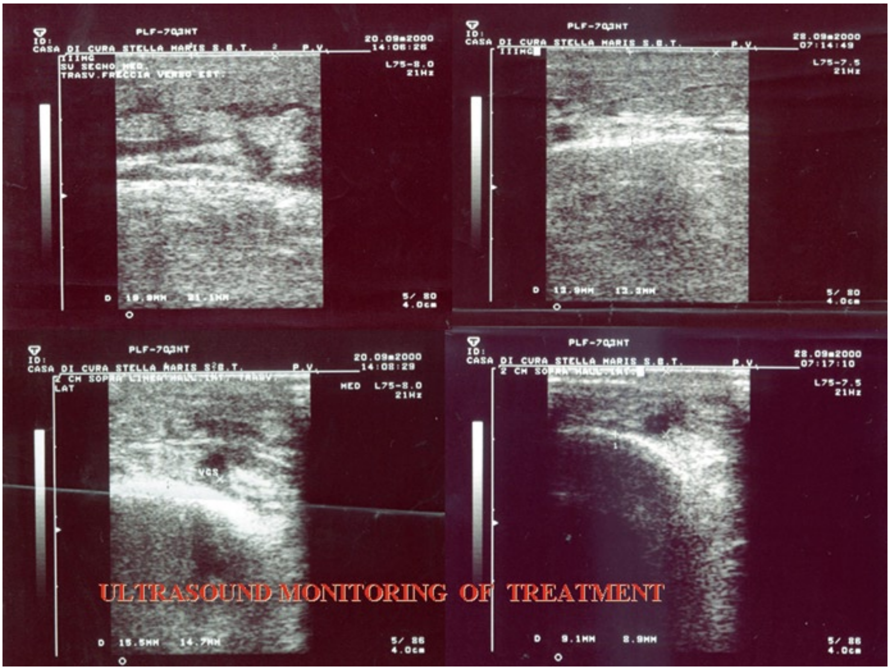

Fig. 20.7 Lymphedema treatment and CDU monitoring of the outcomes

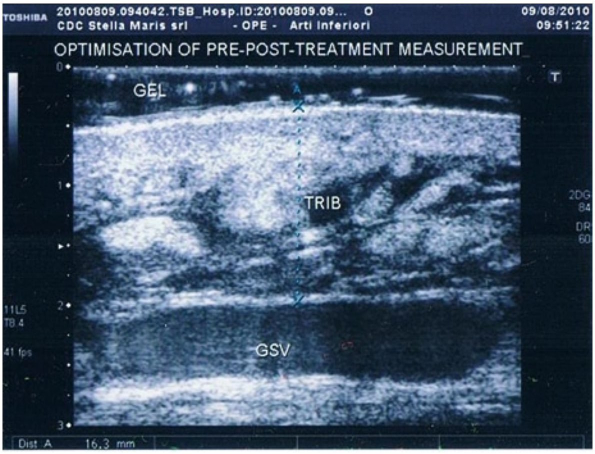

Fig. 20.8 Optimisation of CDU measurement in lymphedema follow-up

therapeutic approach to LYM is often capable of producing results after a few days and this results in a reduction (or disappearance) of extravascular layers of liquid, as well in a decrease in the echogenicity of the tissues, together with a reduction in size of the lymphatic collectors. A further method of applying CDU investigation to LYM is by using the probe to bring out some pitting in the edematous areas,[30]

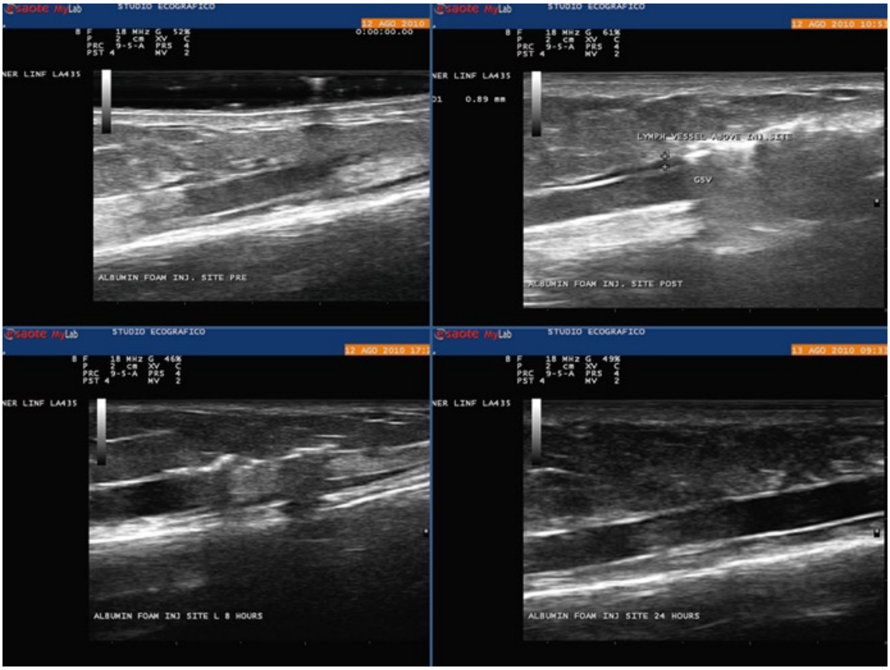

Fig. 20.9 Ultrasound imaging of injections of albumin-based ultrasound contrast agent (UCA) in a normal subject and ultrasound monitoring of UCA distribution within 24 h

highlighting the nature of the edema and its fibrotic component, as well as monitoring the treatment outcomes.

After the introduction of ultrasound contrast agents (UCA) for echocardiography in 1969,[35] the inclusion of albumin or other organic macromolecules in the chemical structure of these agents, led us to investigate the possible usage of UCA in LYM diagnostics.[26] The possibilities and limitations of albumin-based UCA, or of foamy albumin in CDU investigation of LYM, have never been assessed in depth and the few pertinent scientific data that were available from experiments in 2000[26] were not, in fact, conclusive. Several limitations of the older, preliminary experimental studies can be possibly overcome by modern technologies and by the improved knowledge of UCA and of CDU; hence, a reappraisal of those investigations has been undertaken by our group (Fig. 20.9) and some interesting (unpublished) data have been collected in the last few months.

In conclusion, the use of CDU in the field of lymphatic diseases seems to be still in the early stages, but further technological and methodological advancements hopefully will facilitate a broader usage of ultrasound in lymphatic diagnostics and therapeutics. The technical limitations, the dependence of the accuracy on the operator, together with the lack of high-level scientific evidence for CDU investigation in LYM can be counterbalanced by the non-invasive nature and low expense of this diagnostic tool, an approach that is still in its infancy.

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