

## DIAGNOSTIC IMAGING OF LYMPHOEDEMA – THE ROLE OF LYMPHOSCINTIGRAPHY

### DIAGNOSTYKA OBRAZOWA OBRZĘKU LIMFATYCZNEGO – ROLA LIMFOCYNTYGRAFII

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*Słowa kluczowe:* ????

#### SUMMARY

The paper overviews the problem of pathology in diagnostic imaging of lymphoedema, including direct and indirect lymphography, MRI, CT and ultrasound imaging. Particular emphasis is put on lymphoscintigraphy, which is currently considered to be a leading technique in this field. This paper discusses performing the lymphoscintigraphy, normal and abnormal findings, the role in the primary diagnostics of lymphoedema and its follow-up.

#### STRESZCZENIE

Celem pracy było przedstawienie podstaw patofizjologicznych i obrazowych metod diagnostycznych obrzęku limfatycznego. Szczególny nacisk jest położony na zastosowania diagnostyczne limfoscyntygrafii z omówieniem sposobu wykonania, wyników prawidłowych i patologicznych oraz jej roli w wyjściowej diagnostyce obrzęku limfatycznego oraz oceny postępów terapii.

#### INTRODUCTION

##### *Clinical basics*

Lymphoedema is the painless progressive accumulation of protein-rich fluid in the interstitial spaces of the skin, resulting from an anatomic or functional obstruction of the lymphatic system [1].

Lymphoedema of the lower or upper extremities is typically a chronic condition that has several possible causes and that presents considerable physical as well as psychological difficulties for patients. Patients with lymphoedema experience extremity

swelling, decreased coordination and mobility, and secondary infections [2]. The disorder typically affects the dermis and spares the deeper compartments. At the initial medical evaluation of patients with suspected extremity lymphoedema, it is highly desirable for physicians to define the abnormality; to determine whether the suspected abnormality is, in fact, a lymphatic one before instituting a therapeutic plan; and to establish an objective baseline [3, 4]. The differential diagnosis of suspected extremity lymphoedema includes obesity, venous disease, and systemic disease (e.g., hypoalbuminemia) [2].

Lymphatic oedema or lymphoedema may be primary or secondary to the presence of other disease and/or to the consequences of surgery. Primary lymphoedema may occur at any phase of life but it most commonly appears at puberty. Secondary lymphoedema is encountered more often. The most prevalent worldwide cause of lymphoedema is filariasis, which is particularly common in south-east Asia. In the USA, postsurgical lymphoedema of the extremity prevails. Lymphoedema is a quite a prevalent disease. Worldwide, about 90 million of people have lymphoedema, primarily because of parasitic infections. Approximately 10 million people have lymphoedema secondary to breast and pelvic cancer therapy, recurrent infections, injuries or vascular surgery. When chronic venous insufficiency is added as a case, there may be as many as 300 million cases [5, 6]. The reported incidence of secondary lymphoedema after mastectomy varies amongst different published series from 5.5 to 80% reviewed by Szuba and Rockson [2], in the other studies studies from 24–49% [7, 8]. Complications of chronic limb lymphoedema include recurrent cellulitis and lymphangiosarcoma. Most patients are treated conservatively, by means of various forms of compression therapy, including complex physical therapy, pneumatic pumps and compressive garments. Volume reducing surgery is performed rarely. Lymphatic microsurgery is still in an experimental stage, although a few centers consistently report favorable outcomes.

This disease is often able to be diagnosed by its characteristic clinical presentation, yet, in some cases, ancillary tests might be necessary to establish the diagnosis, particularly in the early stages of the disease and in oedemas of mixed etiology [2].

Frequently used measures of lymphoedema include circumferential measures of limbs at various points (usually at bony landmarks); volumetric measures using limb submersion in water; recording deformation of tissue by a mass (tonometry) and the step compression method, measurement of impedance (amount of extracellular water and total water content) and diagnostic imaging to which this paper is devoted. Circumferential measures with calculations designed to compute limb volumes and volumetric measures are used most frequently, but these have some difficulty with reliability [9].

### **Diagnostic imaging of lymphoedema**

Available modalities include contrast lymphography, indirect lymphography, lymphoscintigraphy, lymphatic capillaroscopy, magnetic resonance imaging, computed tomography and ultrasonography [2]. Lymphatic capillaroscopy is available only in specialised centres [2].

### ***Contrast lymphography***

Contrast lymphography is accomplished through the direct injection of iodine based, lipid-soluble contrast media into subcutaneous lymphatic vessels, identified prior the study by subcutaneous injection of blue dye. It is an old technique, introduced in

1944 [10] and refined in fifties of XX century [11]. Its use has declined recently, superseded by lymphoscintigraphy as a primary diagnostic tool, although it is still useful in visualizing lymphatic anatomy prior to lymphatic reconstructive surgery [2]. It is also carried out in patients, when the lymphoscintigraphy results are thought to be misleading [12].

Some authors still strongly advocate this technique [13]. They argue that the unique ability of lymphography to demonstrate derangements of the internal architecture of normal-sized lymph nodes can be valuable and makes it more accurate than CT in evaluation of some lymphomas (especially Hodgkin disease) and genitourinary malignancies. They believe, that lymphography and CT are complementary rather than mutually exclusive techniques for the staging of some lymphomas and genitourinary malignancies. In addition, lymphography opacifies the lymphatic channels and therefore may be a valuable tool for detection of lymphatic fistulas or lymphatic leakage. Finally, the authors believe that lymphography helps to guide subsequent therapy in patients with lymphomas, genitourinary malignancies, or disorders of lymphatic flow [13]. This may be correct, but rather in secondary, not primary lymphoedemas.

Additionally, this technique presents many technical difficulties and may exacerbate lymphoedema by pooling and accumulation of oil-based contrast media.

### ***Indirect lymphography***

Indirect lymphography is based upon an intradermal infusion of water-soluble iodinated contrast media [14]. It is particularly useful in imaging skin lymphatics and lymphatic trunks. It is useful both as a primary diagnostic tool and prior to lymphatic reconstructive surgery.

### **Magnetic resonance imaging**

Magnetic resonance imaging is a useful tool in differential diagnosis of limb oedema. In lymphatic oedema there is a characteristic MRI image of honeycomb pattern within the epifascial compartment along with thickening of the skin. In venous oedema both the epifascial compartments are affected. In lipoedema there is a fat accumulation without fluid [15, 16]. Another typical findings are trabecular structures suggesting dilated collateral lymphatic vessels in the swollen subcutis [17]. Magnetic resonance imaging is also useful in lymph nodes imaging, visualising enlarged lymphatic trunks and identifying the underlying cases of secondary lymphoedema. Magnetic resonance imaging of lymphatic vessels may be enhanced with tissue-specific iron contrast media [18].

### **Computed tomography**

Computed tomography (CT) usefulness in diagnosis lymphoedema is rather limited. It provides defining of oedema localisation (subfascial vs. epifascial), identifies skin thickening as well as the characteristic honeycomb pattern of the subcutaneous tissue [2, 19]. CT may be useful in monitoring the outcomes of compression therapy [20]. Edema accumulation is readily demonstrated with plain CT scan and is not present in lipoedema. Specific CT features of the subcutaneous fat and muscle compartments also allow accurate differentiation between lymphoedema and deep vein thrombosis.

### **Ultrasound examination**

Ultrasound examination (US) plays an ancillary role in non-invasive diagnosis of lymphoedema. It shows the thickening of the cutaneous, epifascial and subfascial tissue compartments, interstitial fluid accumulation, sometimes it allows to evaluate the degree of fibrosis. High frequency ultrasound reveals characteristic patterns of cutaneous fluid localisation in various types of oedema [16, 21].

Balzarini et al. showed by US fluid accumulation in 35%, fibrosis in 26% and a mixed picture (fibrosis and fluid) in 40%. Correlation with clinical information (“soft,” “medium,” “hard,” and “pitting” oedema) demonstrated that US documented interstitial fluid in 68.4% of soft oedema, mixed fluid and fibrosis in 64.2% of medium oedema, and fibrosis in 76.9% of hard oedema. Ultrasonography also showed that in soft and medium oedema, fibrosis might already have formed [22].

Colour Doppler ultrasound augments the findings of lymphoscintigraphy, when performed together [23]. There is an influence of development of fibrosis on US results – subcutaneous tissue is more echogenic on the oedematous side, with significant hyperechogenicity at the fascial subcutaneous layer, which indicates that fibrotic tissue develops distally in the forearm [24].

Some findings substantiate the unique role of this modality in the evaluation of filariasis in secondary lymphoedema. With use of a standard transducer, Amaral et al [25] were able to detect indwelling motile adult nematodes in the groins of patients in Recife, Brazil, an endemic area for those parasites.

### **Fluorescein microlymphangiography**

Intradermal injection of fluorescein isothiocyanate dextran allows visualization of the superficial peripheral microvasculature, including the contractility, permeability, and diffusion characteristics of local blood and lymph capillaries [26, 27]. Diameters of lymph capillaries can be determined from sequential video-recorded images of the injected field. Findings indicate that patients who have had lymphoedema since childhood have aplasia of lymphatic microvessels, whereas those in whom lymphoedema first appears during puberty (lymphoedema precox) have intact lymphatic capillaries (initial lymphatic vessels) in conjunction with hypoplastic lymph trunks more proximally [27].

### **Lymphoscintigraphy**

Lymphoscintigraphy is today the primary imaging modality used in determining a diagnosis in patients with suspected extremity lymphoedema. Lymph nodes evaluation with radiotracers dates back to 1950s [28]. This method has largely replaced the more invasive and technically difficult technique of lymphography [29]. Lymphoscintigraphy has been refined over the past few decades and has proved reliable and reproducible [2]. The study is non-invasive with no known adverse effects. In addition, the radiation dose received during the examination is low, and the study can be repeated after therapy [3]. Some authors underline the high sensitivity, but – at least in some cases – not sufficient specificity – which may mistakenly classify some normal legs as lymphoedematous [30].

## **Performing lymphoscintigraphy**

### ***Radiotracers***

First studies were performed utilising the colloidal gold-198 [28]. Due to the high radiation burden this was subsequently replaced by technetium-99m agents: sulphur, rhenium, stannous sulphur colloids, antimony sulphide colloid, albumin colloid, microaggregated albumin, human serum albumin [31, 32]. Today, probably millipore filtered technetium-99m sulphur colloid is the most commonly used radiotracer for lymphoscintigraphy, as inexpensive, with a very good safety profile and demonstrated clinical value, although some authors believe that (99m)Tc-HIG is marginally superior to nanocolloid and sulphur colloid for this purpose [32].

### ***Imaging***

Most often 74-296 MBq of <sup>99m</sup>Tc sulphur colloid suspended in 0.10 ml of saline is injected into the interdigital web spaces between the first and second digits on the patient's right and left lower (or upper) extremities. Intradermal injection is superior to the subcutaneous [32]. Both of the feet (or hands) are massaged for 2 min immediately after the injection. A high-resolution collimator is always used, the camera speed is set at 8 cm/min, and images of at least 300.000 counts are acquired. Images should be recorded with a dual-head gamma camera, using high-resolution collimators, the whole-body scanning mode, using a scan speed of 10 cm/min [33]. A flow study is performed, and the arrival of radionuclide delivery to the knees and groin (or to the elbows and axillary regions for the arms) is timed. Spot and whole-body images are obtained for up to 3-4 hr; the study may be also tailored to the need for individual findings [34]. Quantitative or semi-quantitative approach to lymphoscintigraphy may improve the results of the study [2, 14]. Quantitation of the regional lymph node accumulation of radiotracer is preferred [14].

### ***Normal findings***

In patients with normal lymphatic anatomy and function, a predictable sequence should be seen on lymphoscintigraphy. In the lower extremities, symmetric migration of the radionuclide should be seen through discrete lymph vessels (three to five lymph vessels per calf and one to two per thigh). Then bilateral visualization of ilioinguinal lymph nodes should occur within 1 hr, as should visualization of the liver because of the systemic circulation of the radiocolloid [1, 32, 34]. Typically, approximately one to three popliteal nodes and two to 10 ilioinguinal nodes are visualized [29]. A parallel sequence should be seen in the upper extremities.

### ***Abnormal findings***

On lymphoscintigrams with abnormal findings, a variety of findings can be identified, including interruption of lymphatic flow, collateral lymph vessels, dermal backflow, delayed flow, delayed visualization or nonvisualization of lymph nodes, a reduced number of lymph nodes, dilated lymphatics, and in severe cases, no visualization of the lymphatic system at all [1, 4, 29]. Purely qualitative analysis has been reported to be very accurate for confirming or excluding the diagnosis of lymphoedema, with a sensitivity as high as 92% and a specificity as high as 100% [1].

Despite earlier reports, most authors believe that primary lymphoedema cannot be reliably differentiated from secondary lymphoedema on the basis of lymphoscintigraphic findings alone [1, 4, 29]. Some authors have reported that lymphoscintigrams of patients with primary lymphoedema tend to show a lack of lymphatic vessels and absent or delayed transport, whereas those of patients with secondary lymphoedema tend to show obstruction with visualization of discrete lymphatic trunks and slow transport [3]. In both primary and secondary lymphoedema, however, both dermal backflow and a decreased number of lymph nodes can be identified [17].

### *The role of lymphoscintigraphy in the follow-up of therapy of lymphoedema*

Lymphoedema is notoriously difficult to treat. Surgical procedures have been attempted, but none have proven to be particularly successful [2]. At present, the most successful conservative therapy is a 4–6 week regime known as complex lymphoedema therapy [34, 35]. This labor-intensive therapy requires as many as 4 hr per day [34, 35]. In a report by Boris et al. [1994], 30 patients whose progress was followed up for as long as 1 year after complex lymphoedema therapy had an average 86% decrease in their initial extremity volume. Alternatively a muscular-venous by-pass associated with ultrasound liposuction may be performed [36].

Lymphoscintigraphy can be repeated after therapy to provide an objective measure of the disease status in patients [3]. The other authors, however, found no changes in lymphatic flow in patients treated by Sequential Intermittent Pneumatic Compression (SIPC) and assessed by lymphoscintigraphy. The authors argued that that compression increased transport of lymph fluid (i.e., water) without comparable transport of macromolecules (i.e., protein). Alternatively, SIPC reduced lymphoedema by decreasing blood capillary filtration (lymph formation) rather than by accelerating lymph return [38].

Lymphoscintigraphy has been also reported in follow-up for a period of 8 years after microsurgical treatment of lymphatic vessels of an upper extremity. In 11 of 12 patients, lymphatic function improved after autologous lymphatic vessel transplantation compared with preoperative findings. This could be verified by a statistically significant decrease of the transport index ( $< 0.01$ ), clear demonstration of lymph nodes, and a less diffuse distribution pattern of the Tc-99m-labeled nanocolloids [39].

## CONCLUSIONS

There is a hope for decreased morbidity of lymphatic oedema due to the increasing role of selective surgery of lymph nodes, following the sentinel node concept.

However, the role of lymphoscintigraphy in lymphoedema will be probably growing for two reasons:

- growing morbidity of breast carcinoma,
- declining role of direct lymphography.

Therefore, imaging of lymphatic oedema will remain an interesting meeting-point of diagnosing imaging specialists, surgeons and physiotherapists.

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