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LYMPHEDEMA AND PERIPHERAL LYMPHOSCINTIGRAPHY

LENFÖDEM VE PERİFERİK LENFOSİNTİGRAFİ

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ABSTRACT

Peripheral lymphedema occurs because of mechanical or functional obstruction of the lymphatic system. Accurate diagnosis is important for the appropriate management of patients with lymphedema. Lymphoscintigraphy is a useful technique among the first-choice methods to detect lymphedema. Factors affecting the outcome of the test and different test protocols can make it difficult to interpret. The aim of this review is to provide a literature-based overview of the aetiology and diagnostic methods of extremity lymphedema and to summarise the current knowledge on lymphoscintigraphy protocols and interpretation.

Keywords: Peripheral lymphedema, lymphoscintigraphy, scintigraphy protocols

ÖZET

Periferik ekstremite lenfödemi lenfatik sistemin mekanik veya fonksiyonel obstrüksiyonu sonucunda oluşur. Lenfödemli hastaların uygun şekilde yönetilebilmesi için doğru tanı konulması önemlidir. Lenödemin saptanması için ilk tercih edilecek yöntemler arasında lenfosintigrafi önemli bir yer tutar. Testin sonucunu etkileyen faktörler, farklı test protokollerinin yorumlanmasını zorlaştırabilir. Bu derlemenin amacı, alt ekstremite lenfödeminin etiyolojisi ve tanı yöntemleri hakkında literatüre dayalı bir bakış sağlamak ve lenfosintigrafi protokolleri ve yorumlaması hakkındaki güncel bilgileri özetlemektir.

Anahtar Kelimeler: Periferik lenfödem, lenfosintigrafi, sintigrafi protokolleri

INTRODUCTION

Powerful diagnostic methods are needed for the definitive diagnosis and appropriate treatment of peripheral lymphedema, which is manifested by the deterioration of lymphatic drainage in the extremities due to various aetiologies. Peripheral lymphoscintigraphy, which has been used for many years in imaging lymphatic ducts and nodes, is a useful method for both differential diagnosis and clarification of the aetiology of lymphedema. In this review, a brief history of lymphoscintigraphy, anatomy and physiology of peripheral lymphatic ducts, aetiology of lymphedema, and other imaging methods will be discussed. Radiopharmaceuticals used, application techniques, interpretation, advantages and disadvantages, and clinical indications of lymphoscintigraphy will also be mentioned.

History

Walker was the first to report the activity observed in regional lymph nodes after radioactive Gold-198 colloid injection (1). In a study conducted by Sherman and Ter-Pogossian in 1953, subcutaneous radioactive colloid gold was injected into the right and left sides of the anterior abdominal wall of rabbits, and it was shown that the colloid quickly drained into the regional lymph nodes (2) . Threefoot and his colleagues used this method to demonstrate lymphaticovenous and lymphaticolymphatic communication in humans in 1963 (3). Radioactive gold-198 colloid was not used in later years because of its high beta radiation, but lymphoscintigraphy has taken its place as a valuable method in the diagnosis of lymphedema with the development of new and various radiopharmaceuticals. Peripheral lymphoscintigraphy is most commonly performed to investigate extremity lymphedema.

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Anatomy and physiology

The lymphatic system comprises two parts in the extremities: superficial and deep. While the superficial (epifascial) system collects the lymphatic flow of the skin and subcutaneous tissues, the deep (subfascial) system drains lymph from muscle, bone tissues, and deep blood vessels. This lymphatic drainage is directed to the pelvic lymph nodes in the lower extremities and the axillary lymph nodes in the upper extremities (4, 5).

In contrast to the closed systemic circulation, the lymphatic system is open. It transports macromolecules and immune and excess interstitial fluids in tissues through lymphatic channels and delivers them to cells and systemic circulation through the subclavian vein. The lymphatic vascular structure initially consists of subunits called lymphangion. These structures form lymphatic microcapillaries, starting with blunt ends under the epidermis in the extremities and in the tunica adventitia of the vessels. By regular contraction, lymph reaches the systemic circulation. Initially, there is no basement membrane in this structure. It comprises lymphatic endothelial cells with spaces between them. These cells have filamentous extensions that attach to the surrounding tissues. Endothelial cells are in relationship with the extracellular matrix and move away from each other and come closer with the oncotic and hydrostatic pressure difference, taking fluid and other molecules into this microcapillary structure and providing drainage. The lymph fluid formed in this manner moves passively. Meanwhile, the lymphatic microcapillaries grow a little more and become a conducting vessel or channel structure with a basement membrane and peripheral smooth muscle. Because of the one-way-opening valves, lymph fluid does not flow backwards but is pumped to the next vascular segment. Any mechanical or other cause that disrupts this function causes accumulation of lymph fluid and lymphedema (6, 7).

LYMPHEDEMA

Lymphedema may occur because of local or systemic reasons (8, 9). Systemic diseases such as congestive heart failure, renal failure, hypoalbuminemia, and nephropathies that cause protein loss can induce lymphedema. Local causes include primary and secondary lymphedema, lipedema, deep vein thrombosis, chronic venous diseases, postoperative complications, and cellulitis.

Lymphedema can be divided into two groups; primary and secondary.

Primary lymphedema occurs congenitally in the lymphatic system. There are three different types depending on the age of emergence. Primary congenital lymphedema usually occurs under 1-2 years of age. It may be sporadic or familial. It may be a symptom of some genetic diseases, such as Milroy disease. Primary lymphedema precocial is the most common type. It usually occurs between the ages of 1 and 35. It is more common in women and occurs most commonly during puberty. It usually becomes evident when the compensated lymphatic structure is decompensated after a minor trauma. Primary lymphedema tarda occurs after the age of 35 (9).

Secondary lymphedema is lymphedema that occurs later in the lymphatic system because of infection, cancer, trauma, and other reasons. Secondary lymphedema is most common in developing countries due to filariasis infection and in developed countries in patients who undergo axillary or inguinal lymph surgery and radiotherapy due to breast and pelvic cancers (4). Again, surgeries performed in the inguinal region and any type of lymph node excision may cause secondary lymphedema. Lymphedema occurs within 1 to 3 years in approximately 20-30% of breast cancer patients who undergo axillary surgery (10, 11).

Lymphedema is generally a slowly progressing disease. At first, the oedema is soft and leaves a pit when pressed with a finger, but over time it hardens and does not leave a pit. As the process progresses, skin thickening (hyperkeratosis) and coarsening (papillamotosis) develop. Disruption of skin integrity causes recurrent infections, cellulitis, and lymphangitis. Lymphatic drainage deteriorates further and enters a vicious cycle if left untreated (9). Therefore, early diagnosis and a correct treatment approach are important. In treatment, conservative or surgical approaches are applied depending on the stage of the disease. The conservative approach, namely, decongestant lymphatic therapy, includes methods such as skin hygiene, massage, manual lymphatic drainage, extremity compression, and exercise. Surgical methods such as subcutaneous tissue resection, lymphovenous microanastomoses between lymphatic vessels and the venous system, and vascularised lymph node transfer are used (12, 13).

IMAGING METHODS

Lymphangiography

Before lymphoscintigraphy, lymphangiography was used to show lymphatic pathways and investigate lymphedema. Kinmoth introduced traditional lymphangiography (14). In this method, following the intradermal injection of blue dye, the lymph channels are stained blue and become visible through an incision made in the foot skin. After the fat-soluble iodine contrast agent is injected into the visible lymph channels with a thin cannula, serial imaging is taken with X-ray or computed tomography at the 60., 90., minutes and 24. h. It is a quite invasive method. Because it requires incision and cannulation, it is susceptible to infection and local inflammation. It is a technically difficult procedure. It has not been a widely used method because of reasons such as being painful, the procedure taking time, allergy to contrast material or embolisation (6, 7, 9, 15, 16).

Ultrasonography

Ultrasonography (USG) and Doppler USG provide information about the lymph nodes but do not show the lymphatic channels and vascular structure. In the evaluation of lymphedema in the extremities, USG helps to exclude venous aetiologies by showing the presence of obstruction or reflux in the venous system (6). With USG, volumetric features, such as thickening of the dermis, thickening of the subcutaneous tissue, and changes in muscle mass, as well as structural features, such as changes in the echogenicity of the dermis and subcutaneous tissues, can be evaluated in the extremities with lymphedema (17).

Computed tomography

In lymphedema, computed tomography (CT) like USG, shows skin and subcutaneous tissue thickening, increased fat density, and anatomical changes around the muscle. In tomography, there is often a honeycomb appearance in the subcutaneous tissue, but it is not a specific finding because it is also seen in cellulitis and generalised oedema. In addition, as an anatomical imaging modality, it also provides information about the morphology and number of lymph nodes (18). Because it cannot differentiate between lymphedema and oedema, it plays a supportive role in lymphedema diagnostics.

Magnetic resonance imaging

Anatomical evaluation of the lymphatic system can be made with standard magnetic resonance imaging (MRI) images, and information about deep lymphatic vessels can be obtained. MRI provides the extent of oedema and adipose tissue deposition (19). Non-contrast MRI is non-invasive but has not been widely used because of image degradation. Using contrast-enhanced MR Lymphangiography, information is obtained about the anatomical and functional status of the lymphatic vascular structure in the extremities. In lymphedema, volume changes in the extremities, as in USG and CT, show structural changes in the skin and subcutaneous tissue. Its advantages are that it is radiation-free, shows the entire extremity, and allows 3D reconstruction (19, 20). However, prolonged use reduces patient comfort, has low sensitivity in distinguishing lymphatic-venous vessels, has no standard protocol or reporting, and gadolinium contrast material allergy may occur.

Indocianine green lymphography

This is a simple, sensitive, and precise method that does not involve radiation and is used in the diagnosis of lymphedema and in the planning of lymphaticovenous anastomosis treatment. For the first time, in 2008, Unno et al. used near infrared fluorescence (NIRF) imaging with Indocyanine green to make the lymph channels visible in the diagnosis of lymphedema in 2008 (21). When an indocyanine green substance is injected into the vein, lymphatic channels become visible and their location and functions can be determined. Usually injected perioperatively, the vessels are visible with good resolution. It can demonstrate superficial lymphatic flow and areas of congestion with high resolution (19). Its disadvantage is that it is insufficient to show lymphatics deeper than 1- 2 cm. The risk of allergy to contrast medium should also be considered. Indocyanine green is also used with near-infrared fluorescence imaging. Near-infrared fluorescence imaging with indocyanine green is a minimally invasive, reliable, and reproducible method that has emerged in recent years. It is performed especially for evaluation in terms of plastic surgery before lymphovascular anastomosis. However, it is not yet widely available in every clinic. There is limited experience and availability (19). However, it is one of the most promising methods in the future.

PERIPHERAL LYMPHOSCINTIGRAPHY

Radiopharmaceuticals

Unfortunately, there is no ideal radiopharmaceutical for lymphoscintigraphy today. Gold-198 colloid, which has historical importance, could not be used much because of its high beta radiation. The most standard radiopharmaceuticals used today are nanocolloids labelled Technetium 99m (Tc99m). However, colloids marked with Tc99m do not have a worldwide standard because they have different diameters. For example, because nanocolloid is not licenced in the United States, sulphur colloid, which was formerly used in liver scintigraphy, is filtered through 0.1 micrometer philtres to obtain colloids smaller than 100 nm. In Europe, Rhenium sulphide colloid and albumin nanocolloids marked with Tc99m are mostly used. Once radioactive colloids are injected into the interstitial tissue, they are absorbed slowly, with most of the activity remaining at the injected site. Progression occurs slowly in the lymph channels (4).

Unlike colloids, non-colloidal substances such as human serum albumin, dextran, and human immunoglobulin labelled with Tc99m have also been used for lymphoscintigraphy. When injected, they are rapidly absorbed and lymph vessels become immediately visible. For this reason, they are preferred for quantitative analyses, but different criteria may be required when interpreting due to differences in absorption mechanisms (22-24).

Today, the most commonly used colloids in lymphoscintigraphy are Tc99m nanocolloids with a diameter of less than 100 nanomicrons, which are also used in our clinic.

Imaging protocol

There is no single globally accepted methodology for peripheral lymphoscintigraphy. As with radiopharmaceuticals, the injection method and protocols may vary slightly from country to country and from department to department. No special patient preparation is required, such as fasting or stopping medications before scanning.

Injection: Injection is made intradermally or subdermally into the space between the first and second finger roots of both normal and oedematous extremities. After intradermal injection, lymphatic channels appear immediately; however, with subdermal injection, they appear more slowly. In lymphedema, the results of the test using subdermal injection are more reliable than those using intradermal injection (25, 26). In our department, 200-300 microCurie of Tc99m-nanocolloid is injected subdermally in approximately 0.5 ml volume. The nanocolloid has a slight burning effect at the injection site. The diffusion of the radioactive material can be increased by gently massaging the area after injection. In addition, after early dynamic imaging, the patient can be mobilised and encouraged to walk, and if it is upper extremity oedema, lymph flow can be stimulated with a light exercise for the arm muscles. Then, delayed images can be obtained.

Instrumentation: Although imaging varies depending on the facilities in the Nuclear Medicine Department, a double-headed SPECT-CT (Single Photon Emission Computerised Tomography) hybrid gamma camera with high-resolution parallel hole collimators is used in our department. For Tc99m gamma rays, a 140 keV photopeak and 20% window are set in the camera.

Positioning: Depending on the location of the lymphedema, the patient is placed in the supine position so that the injection sites on both lower extremities or both arms and the parts of the extremities that can enter the camera field.

Imaging: There is no complete consensus on imaging protocols. In some clinics, they start with dynamic imaging, whereas in some departments, imaging starts by scanning the extremities. In scanning mode, the extremities are scanned immediately after injection, with the camera moving 10 cm/min. In dynamic imaging, after the injection sites are placed at the bottom of the camera field, 20 images of 10 s are taken, then the camera is moved to the knee or elbow area and another 20 images of 10 s are obtained, and finally it is shifted to the pelvic or axillary region, continuing and ending the dynamic images in the same way. A 300-s static acquisition of the lymph nodes in the axillary or pelvic area is taken immediately after the scan mode or dynamic images are finished and at 1, 2, and 3 h and later if necessary. If the regional lymph nodes are not visible, images can be taken after the patient is mobilised and walked for a while. SPECT-CT study may also be recommended if lymphedema occurs, especially in the pelvis, abdomen, and thoracic regions (27). Late images are particularly useful in demonstrating dermal reflux, and the visualisation of liver uptake indicates that the radiopharmaceutical has reached the hepatic circulation (28). Late imaging is also essential for assessing dermal backflow or post-traumatic stagnation. If available in the clinic, a Cobalt-57 flood phantom source is placed between the patient and the gamma camera during imaging to determine the patient's body contours.

Greater sensitivity and better three-dimensional spatial resolution can be achieved by acquiring single-photon emission computed tomography (SPECT) by combining LS with single-photon emission computed tomography. SPECT/CT study is recommended when lymphedema concerns the pelvic-abdominal-thoracic districts (29). Yoon et al. developed a hybrid SPECT/CT classification using dermal backflow of SPECT and honeycomb pattern of CT and compared it with lymphoscintigraphic staging and clinical severity (30). In this study, the addition of SPECT/CT to planar scintigraphy showed a 15.4% modification rate in lymphoscintigraphic staging (30).

Normal distribution and Interpretation

Qualitative and visual assessment

In people with normal lymphatic anatomy and function, the radiopharmaceutical flows symmetrically through the lymphatic channels (usually 3-5 vessels in the calf, 1-2 vessels in the thigh) and drains simultaneously into the regional lymph nodes in about 30-60 minutes (Figure 1) (31). When qualitatively interpreting peripheral lymphoscintigraphy, the symmetry of the two extremities is examined (4,9). The number and time of appearance of lymphatic drainage channels and vessels in both extremities is another criterion. The time of appearance of regional lymph nodes and whether there is a delay or not are noted (Figure 2). After these findings, the secondary findings are evaluated. Whether there is a sudden interruption in the continuation of lymphatic vessels or channels, collateral vessel development, and the presence of backflow in the skin were evaluated (Figure 3). Lymph nodes in the popliteal or epitrochlear region are usually

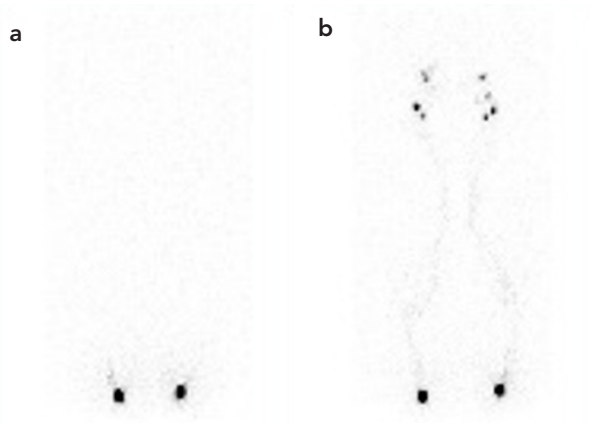

Figure 1: Lower extremity lymphoscintigraphy; normal findings. a) Immediate post-injection image: Injection sites on both feet. b) Static image at 1 h. Bilateral symmetrical and similar numbers of ilioinguinal lymph nodes are visualised.

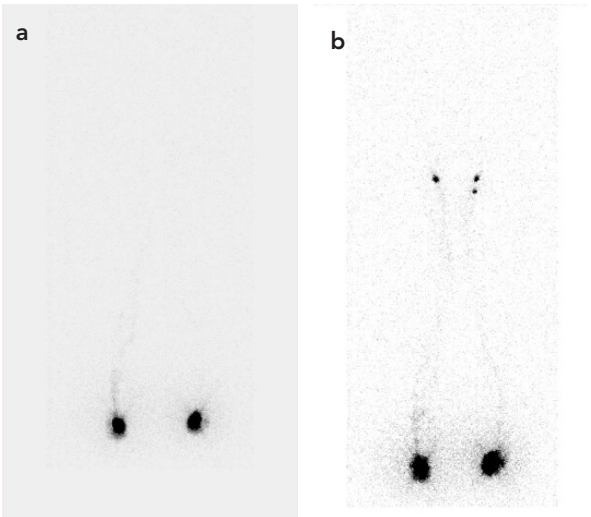

Figure 2: Lower extremity lymphoscintigraphy; a patient with bilateral lower extremity oedema. a) Immediate post-injection image: Injection sites on both feet. b) Delayed static whole-body image at 2. hour; there is delayed visualisation and decreased number of pelvic lymph nodes bilaterally but more prominent on the right side.

not seen, but when they are seen, it indicates that the lymph flow passes through the deep lymphatic system (4, 9). A semi-quantitative scoring system has also been developed using these qualitative evaluation criteria (26). Although there are no definitive findings distinguishing primary and secondary lymphedema, delay or interruption in the transport of the radiopharmaceutical is more common in primary lymphedema. Regional lymph nodes may be reduced in number or not seen at all. In advanced cases, reflux is observed on the skin. In secondary lymphedema, prominence and enlargement of lymphatic channels, delay in activity transport, presence of collateral channels, and skin reflux and lymphatic leakage are more common in late images (26, 31) (Table 1).

Quantitative evaluation

Quantitative evaluation may increase the sensitivity of the test compared with qualitative visual evaluation. However, there is no full consensus on this issue. Various researchers have used different measurement criteria with different radiopharmaceuticals and protocols. Different quantitative criteria, such as the clearance rate and time of the substance from the injection site, the remaining activity rate at the injection site, the time of the substance to reach the lymph node from the injection site (transport time or index), and the retention rate in the lymph node, etc., have been applied (32-34). In a study by Weissleder et al., 70% of 238 patients were diagnosed with lymphedema by visual evaluation, whereas this rate increased to 100% with quantitative analysis. It has been stated that quantitative evaluation increases the sensitivity in detecting new-onset lymphedema (35). However, there is no standard method for quantitative evaluation as in visual evaluation.

Table 1: Criteria for qualitative interpretation of lymphoscintigraphy

Interpretation of lymphoscintigraphy
1. Primary findings:
Symmetry
Appearance time of lymph vessels and nodes
Number of lymph nodes
2. Secondary findings:
Sudden interrruption of the lymphatic channels
Presence of collateral lymphatic vessels
Backflow activity in the skin

Advantages and disadvantages of lymphoscintigraphy

Lymphoscintigraphy, as a nuclear medicine method, has low resolution compared with other modalities and cannot show anatomical contours. Lymph nodes and large vessels appear with low resolution and may not indicate low-level lymph leakage in small lymphatic channels (6). Anatomical imaging can be improved with SPECT-CT hybrid imaging, and additional information can be obtained, especially regarding the typical honeycomb appearance due to lymphedema (27). Another disadvantage is the lack of a standard in terms of both the radiopharmaceutical used and the application of the test, that is, the injection site, volume, and acquisition protocol (6). This does not allow obtaining standard results in the meta-analytic evaluation of studies in which the test is used. However, lymphoscintigraphy is a non-invasive, easily applicable method for the diagnosis of lymphedema, and is accessible for clinical follow-up and pre/post-treatment evaluations.

The visual evaluation of lymphoscintigraphy in patients with lymphedema, Alavi et al. found that the test was 73% sensitive and 100% specific (36). The low sensitivity was due to three false negative cases, and pathology could not be detected in these cases because early imaging was not performed. In late images, the findings were evaluated as normal.

Hassanein et al. qualitatively evaluated lymphoscintigaphy studies performed in 227 patients with lymphedema and showed that the test was 96% sensitive and 100% specific (37). It was observed that the seven cases with false negative results were due to reasons such as misdiagnosis, new-onset disease, and not having enough delayed images. They reported that lymphoscintigraphy is successful in revealing the diagnosis in patients with borderline clinical findings, confirming people with normal lymphatic function, and indicating the severity of the disease (37).

Clinical Indications

1- Lymphoscintigraphy is an appropriate test for the evaluation of primary lymphedema or limb oedema of unclear aetiology. Lymphoscintigraphy can also be appropriate

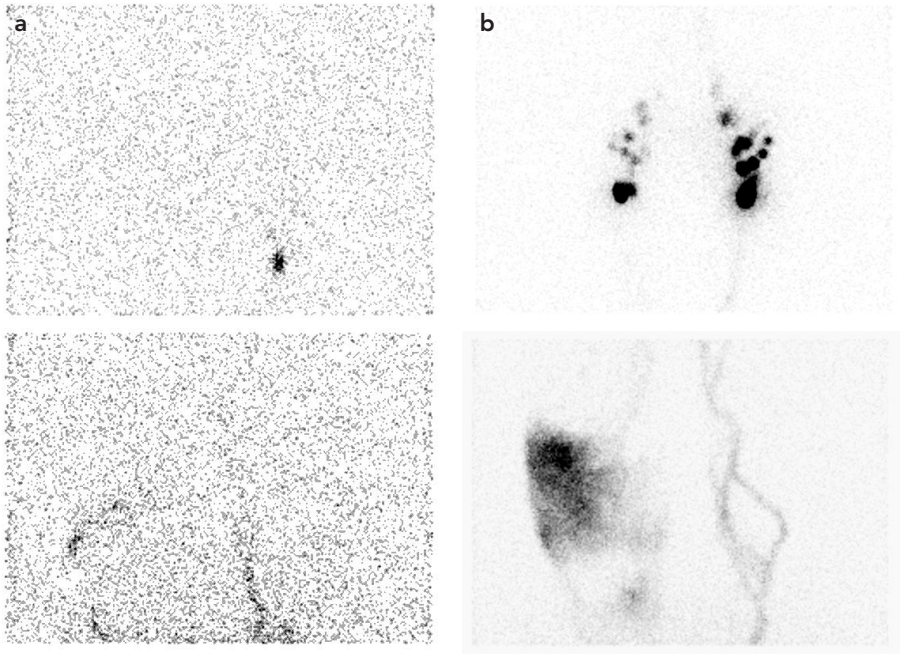

Figure 3: Lower extremity lymphoscintigraphy; a patient with bilateral lower extremity oedema. a) Early static images: Lower: Just above the injection sites and knee region, lymphatic channels are visualised asymmetrically; Upper: No inguinal lymph nodes are seen on the right and only one lymph node is seen on the left. b) Delayed static images at 4 h; lower: knee region, increased subcutaneous activity indicates dermal backflow on the right; upper: pelvic region, decreased number of lymph nodes on the right side indicates the presence of an obstruction on the right side of the extremities.

for patients with suspicion of secondary lymphedema, particularly if the clinical history or examination is not definitive for the diagnosis of lymphedema (38). It plays a role in the differential diagnosis of nonlymphomatous oedema of the extremities. Lymphoscintigraphy is usually normal in nonlymphomatous oedema. Lipedema (dense fat storage under the skin), deep vein thrombosis, and oedema developing after femoropopliteal bypass should be considered in the differential diagnosis. In these cases, lymphoscintigraphy will give normal results (9).

2- Lymphoscintigraphy can be performed to determine the severity and degree of the disease. In a study evaluated using the scoring criteria developed by Papalardo and Cheng, it was shown that lymphoscintigraphic findings were compatible with the clinical findings of lymphedema (26).

3- It is performed to evaluate the presence of lymphatic drainage after axillary surgery. Lymphatic drainage of the axilla after surgery in breast cancer has been evaluated in various studies. In a study of 313 patients who underwent axillary lymph node dissection, axillary lymph nodes were not seen in 35.8% of the patients, whereas lymphatic drainage was observed in the others (39). Szuba et al. showed that axillary lymph nodes were visible with lymphoscintigraphy in 86.7% of patients who had breast cancer and underwent axillary surgery (40). These studies show that lymphatic drainage is restored after surgery in most cases.

Table 2: Indications for lymphoscintigraphy

Indications
1. Evaluation of primary lymphedema or limb oedema of unclear aetiology.
2. Evaluation of secondary lymphedema, particularly if the clinical history or examination is not definitive for the diagnosis of lymphedema .
3. Differential diagnosis of nonlymphatic oedema of the extremities (lipedema (dense fat storage under the skin), deep vein thrombosis, and oedema developing after femoropopliteal bypass should, etc.)
4. Understanding the severity and degree lymphedema.
5. To evaluate the presence of lymphatic drainage after axillary surgery (i.e.in breast cancer).
6. To confirm lymphatic dysfunction before lymphatic surgery.
7. To demonstrate the effectiveness of the treatment.

4- Lymphoscintigraphy can be helpful in confirming lymphatic dysfunction before lymphatic surgery (38).

5- Lymphoscintigraphy is used to show the effectiveness of the treatment in patients receiving lymphedema treatment. For example, in patients who have undergone lymph node or vein transfer for treatment, the function of the new transplant and the status of lymphatic drainage were investigated. Complications at the donor site where the lymph node was removed were examined. Lymphoscintigraphy reveals the prognostic value of treatment.

Studies have shown that lymphoscintigraphy findings are compatible with clinical findings (41).

However, although guidelines recommend lymphoscintigraphy, in a recent study of 57,000 patients, only 2.5% of patients underwent lymphoscintigraphy. Most patients undergoing lymphoscintigraphy are diagnosed with melanoma or breast cancer (42).

In addition, according to the expert opinion consensus report published in 2022 consisting of The American Venous Forum, American Vein and Lymphatic Society, and the Society for Vascular Medicine in the diagnosis and treatment of lymphedema, no consensus was reached regarding routine clinical practice use of radionuclide lymphoscintigraphy as a mandatory diagnostic tool in lymphedema (43).

CONCLUSION

Lymphoscintigraphy is a very sensitive and specific method for the diagnosis, treatment, and monitoring of lymphedema when it is easily accessible. It is easy to apply, reliable, has a low radiation dose, and does not depend on the operator when performed in experienced clinics. Although its low resolution limits anatomical evaluation, it provides information about lymphatic drainage and function. The lack of a single standard application method is a disadvantage. Expert representatives from 11 professional societies, as part of an autonomous work group, researched and developed appropriate use criteria (AUC) for lymphoscintigraphy in sentinel lymph node mapping and lymphedema (38).

Further studies with a larger number of patients are required on this subject. Although lymphoscintigraphy is a widely used method, contrast-enhanced MR Lymphangiography and Indocyanine Green Near Infrared Lymphangiography are also used more and more frequently in recent years and are promising methods in the future.

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