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THE ROLE OF LYMPHOSCINTIGRAPHY IN THE DIAGNOSIS OF LYMPHEDEMA

ULOGA LIMFOSCINTIGRAFIJE U DIJAGNOSTICI LIMFEDEMA

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Summary

Introduction. Lymphedema is a chronic disease of the lymphatic system that often remains undiagnosed or poorly diagnosed and can lead to severe and disabling swelling of the extremities. The aim of this paper was to review the literature on lymphoscintigraphy as a nuclear medicine imaging technique in the diagnosis of lymphedema, as well as to present clinical cases where lymphoscintigraphy was performed due to edema of unknown origin. **Material and Methods.** A literature review was performed using PubMed and manual search. Additionally, characteristics of diagnostic radiopharmaceuticals, methodological aspects of lymphoscintigraphy and interpretation criteria used in our department were presented in two clinical cases. **Results.** Literature data analysis showed that in the diagnosis of lymphedema, lymphoscintigraphy is a reliable diagnostic method in evaluation of the functional capacity of the lymphatic system, with a sensitivity of up to 96% and a specificity of 100%. In the presented clinical cases, lymphoscintigraphy diagnosed functional dysfunction/obstruction of the lymphatic pathways in the lower extremities. **Conclusion.** Lymphoscintigraphy is a safe and reliable method in the diagnostic algorithm of patients with lymphedema, also valuable in monitoring the condition after the applied therapeutic modalities.

Key words: Lymphedema; Lymphoscintigraphy; Diagnostic Imaging; Risk Factors; Lymphatic Vessels; Edema

Sažetak

Uvod. Limfedem je hronična bolest limfnog sistema koja često ostaje nedijagnostifikovana ili nedovoljno dijagnostifikovana i može dovesti do ozbiljnog i onesposobljavajućeg otoka ekstremiteta. Cilj ovog rada bio je pregled literature o limfoscintigrafiji kao nuklearno medicinskoj imidžing metodi u dijagnostici limfedema kao i prikaz kliničkih slučajeva gde je limfoscintigrafija urađena zbog edema nepoznatog porekla. **Materijal i metode.** Izvršen je pregled literature korišćenjem PubMed-a i drugih baza podataka. Pored toga, karakteristike radioobeleživa ča, metodološki aspekti limfoscintigrafije i kriterijumi za interpretaciju na našem odeljenju predstavljeni su kroz dva prikaza slučaja. **Rezultati.** Podaci iz literature potvrđuju limfoscintigrafiju kao pouzdanu dijagnostičku metodu u proceni funkcionalne sposobnosti limfnog sistema, sa senzitivnošću do 96% i specifičnošću od 100% u dijagnozi limfedema. U prikazanim kliničkim slučajevima limfoscintigrafijom je dijagnostifikovana funkcionalna disfunkcija/opstrukcija limfnih puteva u donjim ekstremitetima. **Zaključak.** Limfoscintigrafija je sigurna i pouzdana metoda u dijagnostičkom algoritmu pacijenata sa limfedemom, takođe je dragocena u praćenju stanja nakon primenjenih terapijskih modaliteta.

Ključne reči: limfedem; limfoscintigrafija; dijagnostički imidžing; faktori rizika; limfni sudovi; edem

Introduction

Lymphedema is a chronic disease characterized by reduced lymph transport, usually with swelling of one or more extremities and sporadically of the trunk and genitals [1]. Lymphedema is a chronic disease of the lymphatic system that often remains undiagnosed or poorly diagnosed potentially leading to severe and disabling swelling of the extremities. Fluid accumulates in the interstitial space as a result of the imbalance between the formation and reabsorption of lymph. Due to the insufficiency of the lymphatic system, there is an increase in osmotic pressure in the tissue and the consequent accumulation of fluid, which leads to swelling. Although the disease is not associated with pain, it can have a great impact on the quality of life of patients [2].

Swelling is associated with a feeling of heaviness, discomfort and reduced mobility of the extremities and they are initially pitting, but due to the longer duration of the disease there is an inflammatory and immune response of the body which is characterized by tissue infiltration with mononuclear cells, fibroblasts and adipocytes, which eventually leads to fibrosis of the skin and subcutaneous tissue and formation of hard edema [1]. If the treatment of the disease is not started on time it progresses and affects the skin, which becomes hyperkera-

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Abbreviations

99mTc-SbSC	– Technetium-99m-antimony sulfide colloid
99mTc-SC	– Technetium-99mTc-sulfur colloid
99mTc-HSA	– Technetium-99mTc-human serum albumin
LEHR	– low-energy high-resolution collimator
MBq	– megabecquerels
AP	– anterior-posterior

totic, hyperpigmented, papillomatous or verrucous with increased turgor. In the end, the skin is at risk of developing ulcerations and infections, which additionally affects the quality of life. Lymphedema may be primary or secondary.

The prevalence of primary edema is approximately 1.15 per 100,000 people under the age of 20, with a higher incidence in females [3]. Primary lymphedema may be caused by agenesis, hypoplasia, hyperplasia, or lymphatic obstruction. There are three clinical subtypes of primary lymphedema: congenital lymphedema, which occurs immediately after birth, lymphedema praecox, which occurs around puberty, and lymphedema tarda, which usually begins after the age of 35. At least 20 genes are associated with an inherited form of lymphedema [5].

Secondary lymphedema is an acquired condition that occurs because of injury or obstruction of lymph vessels that were previously normal. The most common cause of secondary lymphedema in the world is lymphatic filariasis [1]. In developed countries, the most common cause of secondary lymphedema is surgical excision or irradiation of axillary or inguinal lymph nodes in the treatment of cancers such as breast, endometrial, cervical, prostate cancer, sarcoma and melanoma. Lymphedema of the arms occurs in 14–40% of patients with breast cancer after surgery or completed radiotherapy [3, 4].

Advanced stages of lymphedema are most often diagnosed clinically, and earlier stages of the disease often require additional diagnostic procedures such as: lymphoscintigraphy, direct and indirect lymphography, magnetic resonance imaging, computed tomography and ultrasonography [1].

The aim of this paper was literature review on lymphoscintigraphy as a diagnostic method in the diagnosis of lymphedema, as well as presentation of two cases where lymphoscintigraphy was performed due to lymphedema.

Material and Methods

A literature review was performed using PubMed and manual search. Two cases were presented, as well as a lymphoscintigraphy protocol and findings with criteria for interpretation.

Results

Lymphoscintigraphy is a reliable method in diagnosing lymphedema, and due to low amounts of radioactivity, it can be relatively safely repeated several times [7–9]. In this diagnostic procedure, a radiotracer is injected into the soft tissue of the re-

Table 1. Primary and secondary lymphedema (clinical classification) (1)
Tabela 1. *Primarni i sekundarni limfedem (klinička klasifikacija) (1)*

Primary lymphedema/*Primarni limfedem*	**Secondary lymphedema/*Sekundarni limfedem***
Sporadic lymphedema (cause unknown)	Infection/*Infekcija*
Sporadični limfedem (uzrok nepoznat)	Bacterial lymphanginitis/*Bakterijski limfanginitis*
Genetic disorders/*Genetski poremećaji*	Lymphogranuloma venereum
Milroy's disease/*Milrojeva bolest*	*Limfogranuloma venereum*
Meige's disease/*Meova bolest*	Filariasis/*Filarijaza*
Cholestasis lymphedema/*Holestazni limfedem*	Tuberculosis/*Tuberkuloza*
Henakam's lymphangiectasia	Malignant lymph node infiltration
Henekamova limfangiektazija	*Maligna infiltracija limfnih čvorova*
Emberger's syndrome/*Embergerov sindrom*	Lymphoma/*Limfom*
Microcephaly-lymphedema syndrome	Prostate cancer/*Karcinom prostate*
Mikrocefalija-limfedem sindrom	Other cancers/*Drugi karcinomi*
Hypotrichosis-lymphedema-telangiectasia	Surgical or radiotherapy of axillary or inguinal lymph
Hipotrihoza-limfedem-teleangiektazija	nodes in the treatment of cancer/*Operativna ili radioterapija aksilarnih ili ingvinalnih limfnih čvorova u lečenju karcinoma*
Chromosomal aneuploidies	Iatrogenic (most often during vascular surgery or saphenous vein preparation)/*Jatrogeno (najčešće u toku vaskularnih operacija ili preparacije vene safena)*
Hromozomske aneuploidije	Diverse/*Raznovrsno*
Turner syndrome/*Tarnerov sindorm*	Contact dermatitis/*Kontaktni dermatitis*
Klinefelter's syndrome/*Klinefelterov sindrom*	Podoconiosis/*Podokonioza*
Trisomy 13,18 or 21 chromosomes	Rheumatoid arthritis/*Reumatoidni artritis*
Trizomija 13, 18 ili 21. hromozoma	Pregnancy/*Trudnoća*
Other disorders associated with primary lymphedema	
Drugi poremećaji u vezi sa primarnim limfedemom	
Noonan's syndrome/*Nunanov sindrom*	
Parker Weber syndrome/*Parker Veberov sindrom*	
Yellow nail syndrome/*Sindrom žutih noktiju*	
Intestinal lymphangiectasia syndrome	
Sindrom crevne limfangiektazije	
Neurofibromatosis type 1/*Neurofibromatoza tip 1*	

gion of interest and then the lymphatic pathways and lymph nodes are evaluated. Lymphoscintigraphy can be both quantitative and qualitative. Quantitative lymphoscintigraphy is based on the measurement of various quantitative parameters in the diagnosis of lymphedema, while qualitative lymphoscintigraphy provides insight into the morphology of the lymphatic system. Currently, there are no standardized guidelines for lymphoscintigraphy of lymphedemas. Consequently, each institution has its own protocol, adapted to available radiotracers, imaging systems and their strategic system.

Several radiotracers can be used for lymphoscintigraphy, and some of them are: Technetium-99m-antimony sulfide colloid (99mTc-SbSC), 99mTc-sulfur colloid (99mTc-SC) filtered or unfiltered, 99mTc-human serum albumin (99mTc-HSA), and 99mTc-dextran. The main difference between these radiotracers is the size of their particles. Smaller particles can enter the blood vessels and increase the background activity, and on the other hand, large particles cannot enter the lymphatic system at all [10]. It is believed that the best size of the particles is between 50 – 70 nm [11]. The particle size of 99mTc-SC is larger than other radiotracers and this can lead to a delayed transit through the lymphatic system and to non-visualization of lymphatic pathways [12]. Smaller particles of 99mTc-SbSC and 99mTc-HAS allow faster study and better display

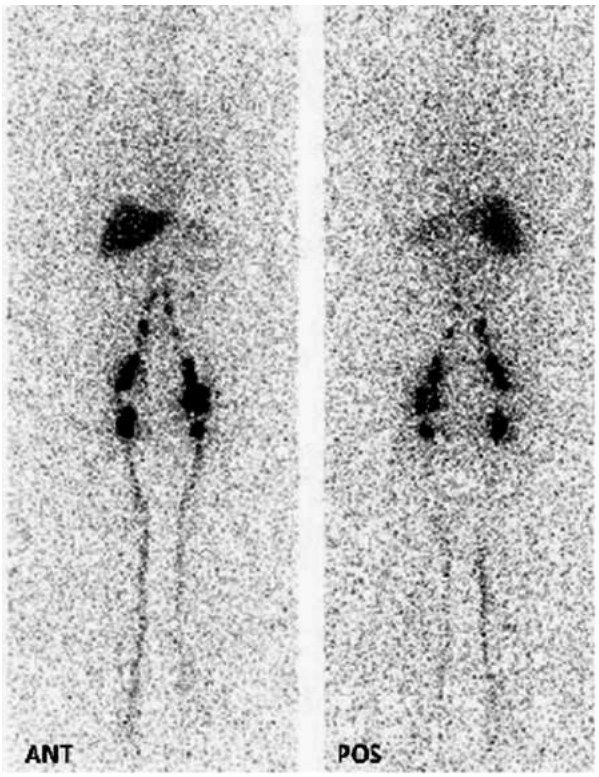

Figure 1. Normal lymphoscintigraphic finding 4h after administration of radiotracer [17]
Slika 1. *Normalan limfoscintigrafski nalaz 4 h nakon aplikacije radioobeleživa*č*a [17]*

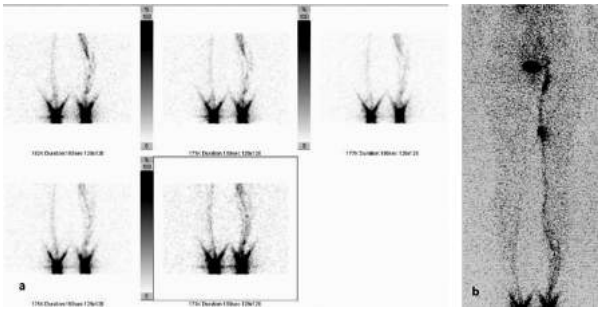

Figure 2. Anterior-posterior (AP) image, early dynamic study of lower legs (a) and early whole body image (b) showing reduced number of lymph vessels in the right lower leg and slowed flow of radiotracer in the right leg
Slika 2. *Anteriorni i posteriorni snimak, rana dinamička studija potkolenica (a) i rani snimak celog tela (b) koji pokazuju smanjen broj limfnih sudova u desnoj potkolenici i usporen protok radioobeleživa*č*a u desnoj nozi*

of lymphatic pathways [10, 13]. Radiotracer application may be subcutaneous, intradermal, or subfascial. It is debatable which method of application is the best. Some authors emphasize the need for the application of radiotracers both subcutaneously and subfascially, in order to examine both superficial and deep lymphatic pathways during the same study [14]. Also, the amount of administered activity varies from institution to institution and the type of performed study. In the vast majority of cases of limb lymphedema, the radiotracer is administered in both extremities. Exceptionally, in cases with chylous reflux, the radiotracer is administered to the healthy limb. Regarding the procedure, some authors recommend a dynamic study after the administration of the radiotracer, while others practice the whole body scanning at different time intervals from the administration of the radiotracer. It is recommended to perform recording using a low-energy high-resolution collimator (LEHR) and the whole body scan speed during acquisition is 10 cm/min. In case when early images do not show lymphatic pathways, stress activities such as walking, limb massage or pressing the ball are recommended. Changes in lymphoscintigraphy after stress activity may predict a good response to physical treatment in patients with lymphedema [15]. The sensitivity of qualitative lymphoscintigraphy in the diagnosis of lymphedema is 70%, and if quantitative parameters are included, sensitivity can go up to 100% [16]. Qualitative lymphoscintigraphy in the diagnosis of lymphedema is performed at our Department of Nuclear Medicine of the Clinical Center of Vojvodina. The 99mTc-SbSC is the most commonly used radiotracer, due to optimal characteristics (particle size) and long standing experience in preparation. The radiotracer is administered subcutaneously in the area of the dorsum of the foot (dorsum of the hand) between the roots of the first and second toe bilaterally and simultaneously. The administered amount of radioactivity is 30 – 50 megabecquerels (MBq). After the application of the radiotracer, a dynamic study is

Table 2. Stages of lymphedema (6)
Tabela 2. *Stadijumi limfedema (6)*

Stage 0 (or Ia) *Stadijum 0 (ili Ia)*	Latent or subclinical stage of the disease without swelling, despite slow lymph transport. This condition can last for months or years before the swelling occurs/*Latentni ili supklinički stadijum bolesti bez prisustva otoka uprkos usporenom transportu limfe. Ovakvo stanje može da traje mesecima ili godinama pre javljanja otoka*
Stage I *Stadijum I*	Early accumulation of fluid that is relatively full of proteins and the formation of swelling that passes during the elevation of the extremities. An increased number of proliferative cells can be observed/*Rano nakupljanje tečnosti koja je relativno puna proteina i stvaranje otoka koji prolazi prilikom elevacije ekstremiteta. Može da se uoči povećan broj proliferativnih ćelija*
Stage II *Stadijum II*	Elevation of the extremities rarely leads to a reduction in swelling, a clear presence of pitting edema, while in the late second stage pitting edema is not so pronounced due to the accumulation of fat and the formation of connective tissue/*Elevacija ekstremiteta retko dovodi do smanjenja otoka, jasno prisustvo testastog edema, dok u kasnom II stadijumu testasti edem nije toliko izražen zbog nakupljanja masti i stvaranja vezivnog tkiva*
Stage III *Stadijum III*	Lymphatic elephantiasis, the presence of trophic changes in the skin, presence of deposits of adipose tissue and connective tissue, the skin becomes papillomatous or verrucous *Limfatična elefantijaza, prisustvo trofičkih promena kože, prisustvo depozita masnog tkiva i vezivnog tkiva, koža postaje papilomatozno ili verukozno izmenjena*

performed for 30 minutes, covering the region from the application site to the inguinal regions for the lower extremities, i.e. axillary regions for the upper extremities, followed by static images of the region of thighs (upper arms) and inguinal regions (axillary regions) at intervals of 45 min, 90 min, 4h and 24h after the administration of radiotracer, as well as static imaging of the liver. We must note that the time intervals of static image acquisition time of the regions of interest vary in accordance with clinical needs, but also from patient to patient. If there is no visualization of lymphatic pathway during the early dynamic study, the patient is advised to take a short walk or to massage

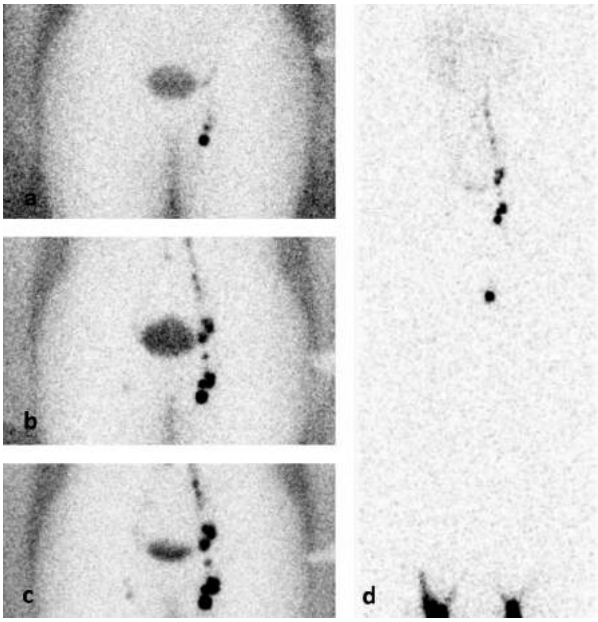

Figure 3. Static images at 45 min (a), 90 min (b), 4h (c) and a late whole body image after 24h
Slika 3. *Statički snimci nakon 45 minuta (a), 90 minuta (b), 4 h (c) i kasni snimak celo tela nakon 24 h*

the extremity. Normal lymphoscintigraphic finding represents symmetrical movement of radiotracer in the extremities, visualization of discrete lymphatic pathways; early visualization of regional lymph nodes usually within 15 – 20 minutes [14] as well as visualization of the liver within one hour **(Figure 1)** [17, 18]. Some studies suggest that visualization of popliteal lymph nodes is normal in the lower extremities [16], while other studies consider that visualization of popliteal lymph nodes is a sign of lymphatic system dysfunction [19]. Pathological finding of lymphoscintigraphy represents: asymmetric presentation of regional lymph nodes, or non-visualization of lymph nodes in severe cases of the disease, dermal backflow of radiotracer that occurs due to the existence of smaller collateral lymphatic pathways [14], interrupted or blocked flow of radiotracer, dilated or collateral lymphatic pathways as well as reduced number of regional lymph nodes.

Although some authors believe that lymphoscintigraphic findings are different in primary and secondary lymphedema [14], most studies claim that these two entities cannot be distinguished by lymphoscintigraphy [18]. Before lymphoscintigraphy, it is necessary to exclude the most common causes of extremity swelling such as renal failure, nephrotic syndrome, hypoalbuminemia, congestive heart failure, pulmonary hypertension, iatrogenic edema caused by drugs, obesity and pregnancy.

Case 1.

Figure 2 shows a lymphoscintigraphic finding indicating a reduced number of lymph vessels in the right lower leg and delayed kinetics of radiotracer in the right leg in a 35-year-old female patient referred due to stage I lymphedema of the right lower leg. Vascular etiology of the swelling was ruled out by the vascular surgeon and by color Doppler examination of lower extremities; laboratory findings and ultrasound examination of the abdomen excluded liver and kidney pathology, whereas gynecological examination excluded the possibility of

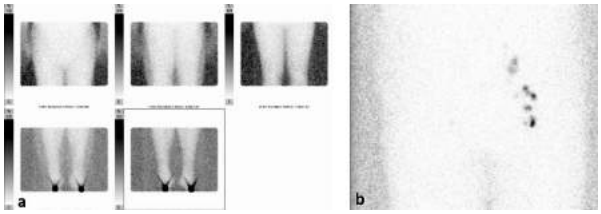

Figure 4. Early dynamic study indicating the absence of radiotracer kinetics on both sides (a) and delayed static image 3h after radiotracer administration, without showing inguinal lymph nodes on the right side (b)
Slika 4. *Rana dinamička studija koja ukazuje na odsustvo kinetike radioobeleživa*č*a obostrano (a) i odloženi statitčki snimak 3 h nakon aplikacije radioobeleživa*č*a, bez prikazivanja ingvinalnih limfnih čvorova desno (b)*

gynecological pathology and pregnancy. The patient has been an athlete for many years, and the internist's examination ruled out the possibility of heart failure and pulmonary hypertension.

Figure 3 shows delayed static images after physical activity in the same patient at 45, 90 min, and 4 h after radiotracer administration, as well as a late whole body imaging after 24 h. These images showed a slow and late visualization of lymph nodes in the right inguinum, and a reduced number of right inguinal lymph nodes. The finding on the left was timely and orderly.

Case 2.

Figure 4 shows a lymphoscintigraphic finding indicating delayed radiotracer kinetics bilaterally, more to the right in a 55-year-old male patient referred for stage II lymohedema of the right lower leg. The patient was controlled by a hematologist for 25 years due to suspected myeloproliferative syndrome, although it was not confirmed by histopathological examination of the bone marrow. Vascular cause of swelling was ruled out by color Doppler and vascular surgeon examination, laboratory analysis ruled out liver and kidney pathology, internist examination revealed cardiac pathology which was not the cause of unilateral leg swelling. The patient was using a selective beta blocker, torasemide, and a combination of antiplatelet therapy. He also had a history of right ankel fracture.

Figure 4 (b) shows a delayed static image after physical activity in the same patient. The finding on the right indicates practical absence of a radiotracer in the right inguinal region, while in the left inguinal region visualization of normal number of lymph nodes is delayed.

Discussion

Lymphoscintigraphy is considered to be one of the main diagnostic methods in the diagnosis of lymphedema and visualization of lymphatic pathways [20, 21]. However, the use of lymphoscintigraphy for diagnostic purposes varies worldwide from being used in some centers for each lymphedema, while in some centers it is rarely used. Lymphoscintigraphy is a method based on the transport role of the lymphatic system by which interstitial fluid with molecules is transported from the interstitial space to the vascular compartment. The radiotracer injected into the interstitial space is transported by lymphatic pathways and through the lymph nodes, all of which is monitored using a gamma camera that registers radioactivity. In this way, an image of the lymphatic system is obtained. The speed of movement of the radiotracer through the lymphatic system depends on the particle size of the radiotracer itself. It is best to use a radiotracer that has particle size of 50 – 70 nm [12] such as 99mTc-SbSC and 99mTc-HAS. Also, the kinetics of radiotracer is affected by physical activity, and therefore patients should be encouraged to walk or massage the extremities in case there is no visualization of lymphatic pathways after a dynamic study lasting 30 minutes. Our department of nuclear medicine performs qualitative lymphoscintigraphy, which aims to show the morphology of the lymphatic system. Scintigraphic findings from these two cases imply different degrees of lymphatic dysfunction. In our first case we observed unilateral presentation of lymphatic dysfunction. The patient had reduced number of lymphatic vessels in the right lower extremity, delayed kinetics of radiotracer with consequent delayed visualization of inguinal lymph nodes, as well as reduced number of inguinal lymph nodes. Clinical presentation was in correlation with the scintigraphic finding. On the contrary, bilateral presentation of lymphatic dysfunction and lack of correlation between scintigraphy and clinical sings were observed in the second case. This patient showed absence of kinetic radiotracer in the right lower extremity and delayed radiotracer kinetics in the left lower extremity. Due to no clinical sings of edema on the left leg, this scintigraphic findings were important for visualization of dysfunction. The sensitivity of qualitative lymphoscintigraphy in the diagnosis of lymphedema is 70% [16]. Some studies claim that the sensitivity of qualitative lymphoscintigraphy in the diagnosis of lymphedema is 96% and the specificity 100% in centers that have years of experience in the diagnosis of lymphedema; however, lower sensitivity has been previously reported due to lack of knowlede about the diseases that lead to limb swelling and some studies included patients who would not be considered to have lymphedema according to today's clinical criteria It is also extremely important to note that the clinical stage of lymphedema does not correlate with lymphoscintigraphic findings, which means that patients with severe lymphedema may have delayed transit of radiotracer or that patients with clinically mild lymphedema may have markedly delayed transit in the region of lymph nodes [23]. There are also papers suggesting that quantitative data obtained by measuring radioactive decay are often inconsistent or that it is often not possible to adequately perform such measurements [24]. We have already discussed the pathological findings of qualitative lymphoscintigraphy, however some authors believe that the lym-

phoscintigraphic findings are different in primary and secondary lymphedemas [14], but most studies claim that these two entities cannot be distinguished by lymphoscintigraphy [18]. Some studies report that primary lymphedema is lymphoscintigraphically characterized by delayed or absent transport of radiotracer or absence of lymphatic pathways followed by poor visualization or lack of regional lymph nodes and occasional dermal backflow on early imaging, but this finding may correspond to primary lymphedema when there is no clinical data suggesting lymphedema of secondary cause. The lymphoscintigram in patients with secondary lymphedema shows dilated lymphatic pathways, collateral lymphatic pathways, lymphatic pathway disruption, delayed transport of radiotracer, and dermal backflow on delayed imaging [25].

Lymphoscintigraphy may be useful preoperatively; Vaqueiro et al. point to the benefit of lymphoscintigraphy in the selection of patients for microvascular procedures, lymphatic-venous anastomosis, by showing the passabel lymphatic pathways that are suitable for making an anastomosis [26].

These types of surgeries have recently gained more popularity and are most effective in the early stages of the disease and in patients with secondary lymphedema compared to patients with primary lymphedema. This is because in patients with primary lymphedema the lymph vessels are structurally damaged and cannot be used as good permeable grafts. These surgeries have so far shown better results on the upper extremities compared to the lower extremities [27].

Lee and Bergan emphasize the use of lymphoscintigraphy in predicting the outcome of lymphedema treatment. They devised a lymphedema grading system based on lymphoscintigraphic findings and used it with the clinical lymphedema grading system to predict the outcome of treatment as well as to determine if additional drug or surgical treatment of lymphedema is needed [28].

Although newer imaging methods may provide additional information on extremity lymphedema, which may be useful in planning surgery [29], they are not as accurate in the diagnosis of lymphedema. Magnetic resonance lymphangiography outlines the lymphatic vessels of the extremities but its sensitivity is 68% in the diagnosis of lymphedema [30]. Lymphangiography with indocyanine highlights subdermal lymphatic pathways, but its specificity in the diagnosis of lymphedema is 55% [31].

Conclusion

Lymphoscintigraphy is reliable in the diagnosis of lymphedema with a sensitivity of up to 96% and a specificity of 100%. The procedure itself is practically painless and requires no special preparation of patients. Lymphoscintigraphy has proven to be a superior method in the diagnosis of lymphedema compared to other diagnostic methods. It is of great importance that this procedure can be repeated several times in one patient in order to monitor the condition after the applied therapeutic modalities, all without fear of additional damage to the lymphatic system. This method can be used preoperatively, in the selection of patients for formation of lymphatic venous anastomosis, as well as a tool for predicting the treatment outcome of patients with lymphedema.

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