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Original Scientific Paper

LYMPHOSCINTIGRAPHY IN LYMPHEDEMA

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SUMMARY – Lymphedema is a chronic, progressive condition caused by impaired lymphatic transport, leading to edema in the lower and/or upper extremities, depending on the underlying cause. The diagnosis is based on clinical examination, ultrasound findings, and imaging tests. Treatment is mostly conservative, usually long-term, and often yielding unsatisfactory results. Recently, surgical options have also become available. Lymphoscintigraphy, a non-invasive and simple nuclear medicine imaging technique, is considered the method of choice in diagnostic workup. It consists of intracutaneous or subcutaneous application of colloidal particles labelled with radioactive technetium-99m and two-dimensional or three-dimensional gamma camera imaging. Lymphoscintigraphy helps differentiate lymphedema from edema of another origin, assess disease severity, and evaluate surgery outcome. However, the procedure is not fully standardized, especially in terms of semiquantitative methods, which are additionally used in disease staging; however, their implementation varies depending on local experience and expertise.

Keywords: *Lymphedema; lymphoscintigraphy; technetium Tc 99m-nanocolloid*

Introduction

Lymphedema is a chronic disease characterized by tissue swelling caused by impaired transport of lymphatic fluid (1-3). It is estimated that 90-200 million people worldwide have lymphoedema (4). Primary lymphedema occurs in less than 0.5% of general population, with prevalence of 1.2 per 100 000 patients in pediatric population (5). It results from developmental abnormalities of the lymphatic system. In contrast, secondary lymphedema occurs due to injury, infection, or other damage to the lymphatic tissue (1, 3). Primary lymphedema is a hereditary condition, appearing congenitally (*Mb Milroy*), around puberty (*l. praecox*), or later in life (*l. tardum*). Secondary lymphedema, which is far more common, has various causes: in developed countries, it is mainly iatrogenic, caused by damage to lymphatic tissue mainly by radical dissection of the axillary or pelvic lymph nodes as part of cancer treatment (3-6). In developing countries, it is mostly associated with infectious diseases, such as filariasis (3, 6).

According to the International Society of Lymphology, lymphedema is classified into three stages (Table 1), with additional Stage 0 that refers to a clinically normal extremity despite already confirmed abnormal lymph transport (7, 8). Edema usually starts at the dorsum of the hand or foot but recovers during rest

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Table 1. Clinical staging of lymphedema

STAGE 0	Clinically normal extremity with confirmed lymph transport impairment
STAGE 1	Early edema that subsides with elevation of extremity
STAGE 2	Pitting edema that rarely subsides with elevation of extremity; in late stage 2, pitting may not be present
STAGE 3	Lymphostatic elephantiasis, usually without pitting, accompanied by trophic skin changes

(Stage 1). As it progresses to the proximal parts of the extremity, it becomes pitting and does not resolve with overnight rest (early Stage 2). Later on (late Stage 2), the tissue fibrosis develops and swelling cannot be reduced without therapy. In Stage 3, chronic trophic skin changes, such as hyperpigmentation, keratosis, and papillomatosis may occur, along with skin ulcerations and lymph leakage.

Patients with lymphedema can also have recurring infections.

Treatment is typically long-term and conservative, with moderate success, which consists of slowing down the natural progression of the disease. Recently, there have been some advances in surgical methods, such as lymphovenous anastomosis and free functional lymphatic transfer, which include different flap procedures (9).

Diagnosis of lymphedema

In most cases, an accurate diagnosis of lymphedema can be made based on the clinical history and physical examination of the patient (4). However, many other clinical entities (e.g., systemic diseases, vascular anomalies, lipedema, etc.) can also cause swelling and/or enlargement of extremities, so it is often difficult to establish a proper diagnosis only by clinical examination (1, 4). As a result, many patients with lymphedema are often diagnosed at later stages, which leads to a significant decline in their quality of life, delays in appropriate treatment, and secondary pathological processes, such as fibrosis and lipid deposition, which further worsen their condition (6, 9).

Therefore, lymphedema should be accurately diagnosed as soon as possible. If clinical presentation is not reliable enough, ultrasound examination should be performed as the first step in the diagnostic process, with color Doppler to exclude vascular abnormalities. Radiological lymphography using direct injection of oil-based contrast into lymph vessels is now considered obsolete.

Magnetic resonance imaging (MRI) and/or computerized tomography (CT) are used as additional diagnostic methods (7, 8, 10). MR imaging reveals special features of lymphedema, and a gadolinium-based contrast can also be injected intradermally in the dorsum of the feet (7, 10). CT shows characteristic edematous tissue, but it is usually restricted to examining smaller parts of the body (7, 10).

A more recent diagnostic method, fluorescence lymphography, includes subcutaneous injection of the combination of fluorescent sodium and indocyanine green (ICG). ICG activation by infrared emission causes fluorescence, which can be detected with infrared camera (4, 10).

Lymphoscintigraphy

The most valuable and definitive diagnostic test for lymphedema is lymphoscintigraphy (1-4). It is a minimally invasive procedure, first described in the 1950s, used for visualization of both deep and superficial lymphatic vasculature and lymph nodes and for semiquantitative analysis of lymphatic transport (1-4, 6-8). Although the procedure is not completely standardized and there are differences among diagnostic centers (different radiotracers, radioactivity doses, type/site/number of injections, static and/or dynamic acquisition of images, and/or acquisition times), nanocolloid technetium (^{99m}Tc)-labelled radiotracers with particle sizes from 2 to 1000 nm are predominantly used (1-4, 6-8, 11). These radiotracers tend to accumulate in regional lymph nodes after subcutaneous or intradermal injection, which provides a very good visualization of lymphatic vasculature between the injection site and nearby lymph node basin (6, 11). The volume of radiopharmaceutical is equally important as its activity, because higher volume could potentially disrupt small lymph vessels and jeopardize the physiological visualization of lymphatic paths.

The procedure

Patient preparation is not needed. Lymphoscintigraphy of lower extremities is usually performed with human serum albumin (HSA) nanocolloid particles radiolabeled with ^{99m}Tc, with average particle size of 80 nm, prepared according to the manufacturer's instructions. Patient is in a recumbent position on the gamma camera bed with both feet uncovered. The rest of the legs are covered with absorbing paper, and all the clothes potentially compromising lymphatic flow are removed before the injection (jewelry, belts, etc.).

The procedure used in our institution involves two separate syringes, each containing 0.2-0.3 mL of around 37 MBq of technetium-labelled nanocolloid, which are simultaneously injected subcutaneously into the first interdigital space (between the first and second toes) of each foot (Fig. 1). Dynamic acquisition (1 frame/minute) starts immediately after the administration of radiopharmaceutical, with the gamma-camera field of view being adjusted as the radiotracer travels proximally. If there is no visualization of lymphatic transport from the injection site within 10–15 minutes after the radiotracer administration, patients are advised to walk or use a cycle ergometer for 5–15 minutes, after which the acquisition process is restarted. Once the lymph vessels become visible, the lymphatic transport of the radiotracer can be observed up to the inguinal lymph nodes, which should appear within 20 minutes. A static image (5 minutes) of inguinal/pelvic region should then be acquired, followed by a whole-body scan. Within one hour, activity in the liver should be detected on a planar image of the abdomen as proof of the preserved communication between lymphatic and venous system (Fig. 2). If the liver is not visualized in a timely manner, abdominal and whole-body imaging is repeated.

When lymphedema of arms is suspected, the tracer is injected in the first interdigital space of each hand and lymphatic flow is followed by adjusting gamma camera field of view. It can start with both arms beside the body or laid on the collimator (Fig. 3). Whole body images and additional oblique images of both axillar regions are also acquired.

The imaging is usually completed within 2–3 hours.

Single-photon emission computed tomography/computed tomography (SPECT/CT) of a specific region is performed when nanocolloid accumulation

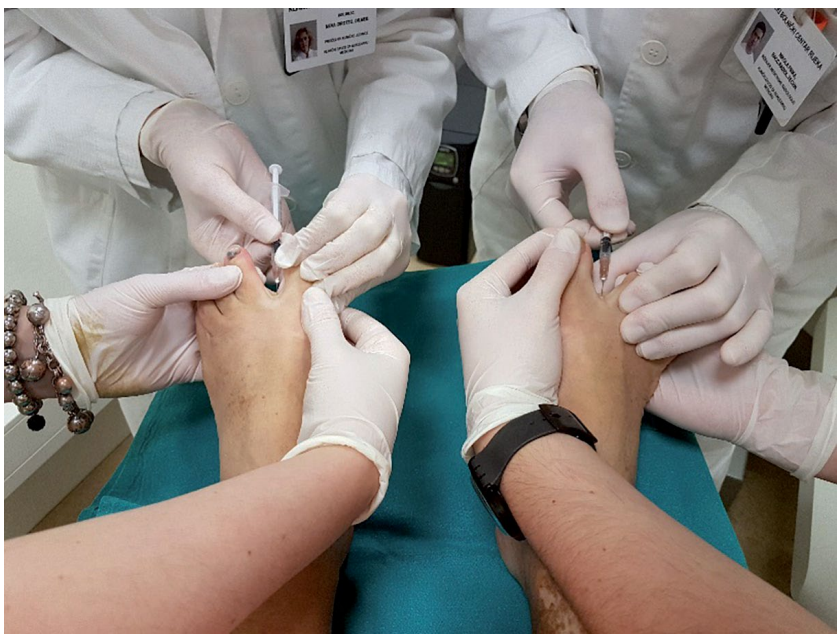

Fig. 1. Subcutaneous administration of 99mTc-nanocolloid in the first interdigital space of each foot.

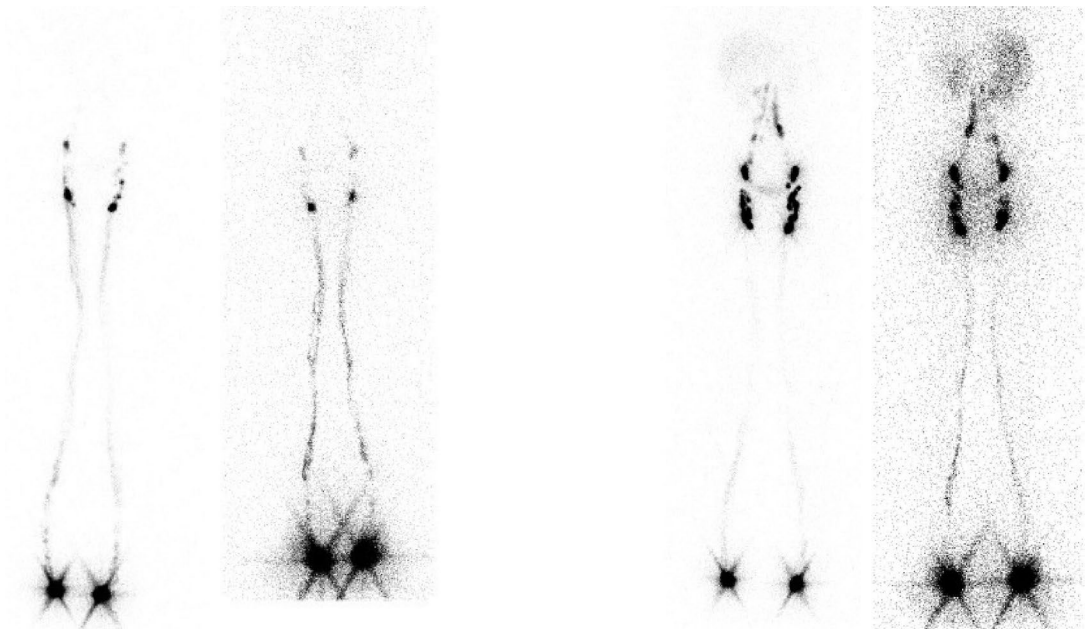

Fig. 2. Lymphoscintigraphy – normal findings: whole body images in anterior and posterior projection 30 and 60 minutes after the subcutaneous administration of 99mTc nanocolloid in the first interdigital space of each foot. At 30 minutes (A), symmetrical lymph paths through both legs and bilateral accumulation of 99mTc nanocolloid in the inguinal lymph nodes is registered. At 60 minutes (B), accumulation in the iliac and abdominal lymph nodes and liver can be seen.

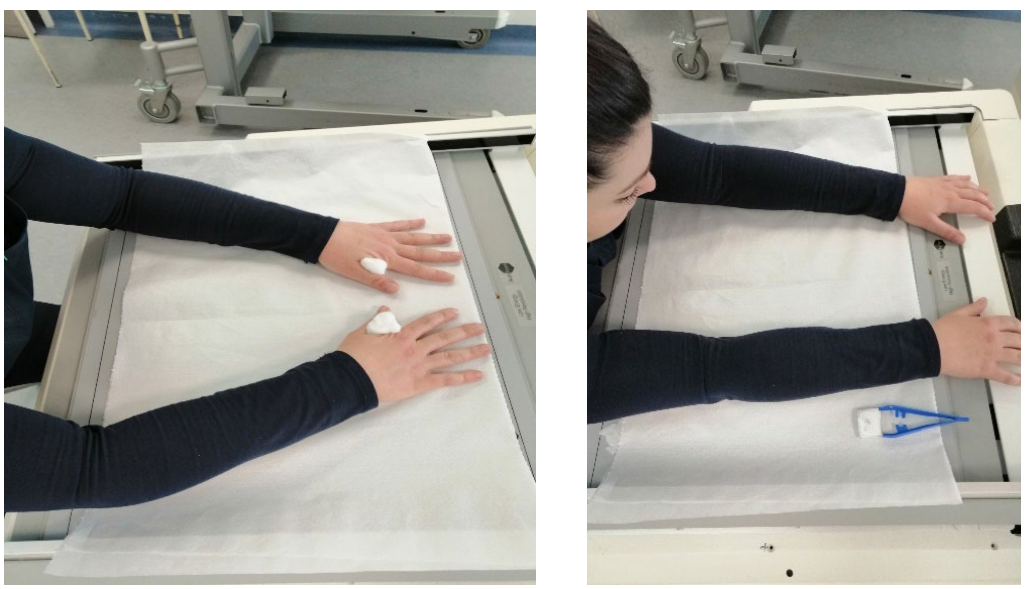

Fig. 3. Positioning of the patient for lymphoscintigraphy of the upper extremities after the subcutaneous administration of 99mTc nanocolloid in the first interdigital space of each hand.

shows unusual pattern to check for possible morphological changes.

The interpretation

If lymphatic anatomy and function are normal, lymphatic transport of radiotracer should be symmetrical and lymphatic vessels should be visualized as a single path throughout the leg, leading to the respective femoral/inguinal regions. Femoral and inguinal lymph nodes on each side should be visible within 20 minutes from injection. Their number and appearance should be symmetrical, with iliac and abdominal nodes seen in continuation (12). The presence of radioactivity in the liver, which indicates the patency between lymphatic and venous system, should be visualized within 60 minutes (12).

In patients with primary lymphedema, mostly bilateral poor or non-visualization of lymph vessels, and/or lymph nodes can be noted (Fig. 4), and sometimes even extravasation of the radiopharmaceutical into body cavities (chylothorax, ascites). In a secondary lymphedema, the absent or poor lymph node visualization is mostly unilateral, and there are many other pathological findings including the visualization of popliteal lymph nodes, presence of collateral lymphatic vessels, delayed transport of radiotracer relative to the normal side, visualization of deeper lymphatic structures, and so-called dermal backflow – a phenomenon in which

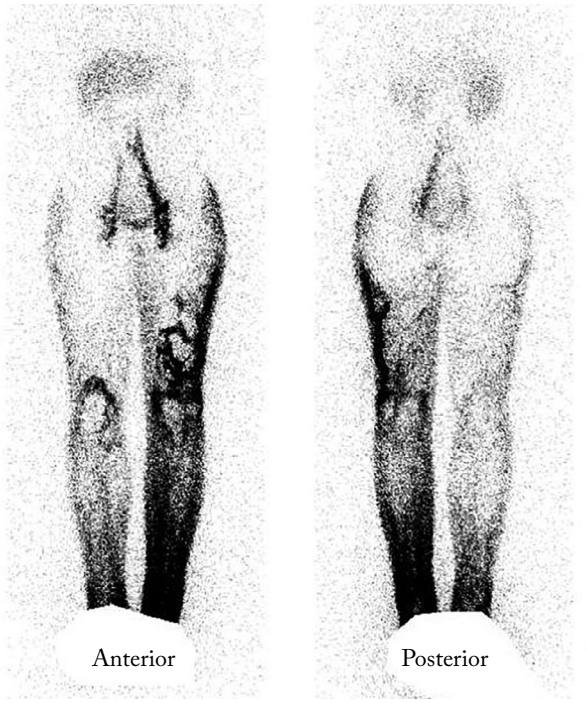

Fig. 4. Lymphoscintigraphy: Whole body images in anterior and posterior projection of an 18-year-old girl with a history of repetitive pleural effusions (chylothorax) and persistent edema of both legs few years after surgical ligation of the thoracic duct (22). The main lymph vessels are not visualized. There is a very pale and scarce visualization of pelvic and abdominal lymph nodes and the diffuse radiopharmaceutical uptake along both legs, enhancing body contours, consistent with extensive dermal backflow due to primary lymphedema – congenital lymphangiomatosis.

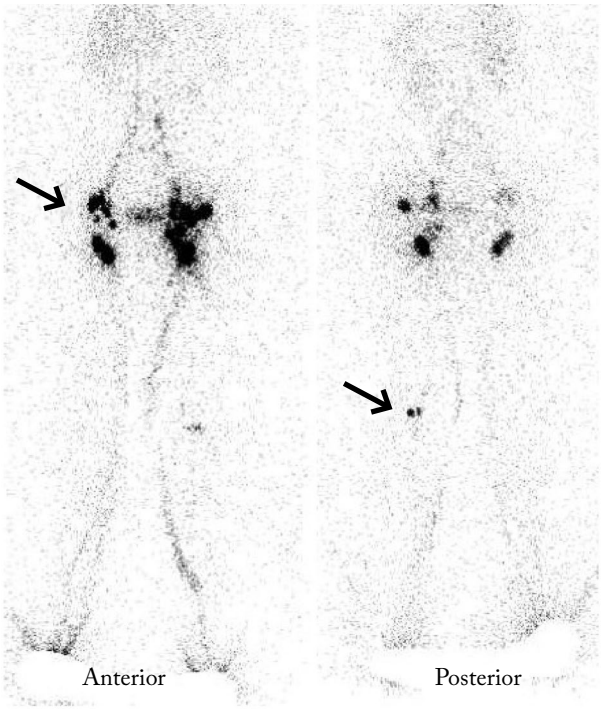

Fig. 5. Lymphoscintigraphy: Whole body images in anterior and posterior projection of a 64-year-old woman with a history of the right leg swelling, skin changes, and recurrence of erysipelas of the right foot. Previously she had trauma of the right leg and implantation of endoprostheses in the left hip and right knee. At the time of imaging, she was free of symptoms on the left side. Lymph vessels and nodes are poorly visualized on the right side, and a popliteal lymph node on the left side can be seen due to bilateral secondary lymphedema.

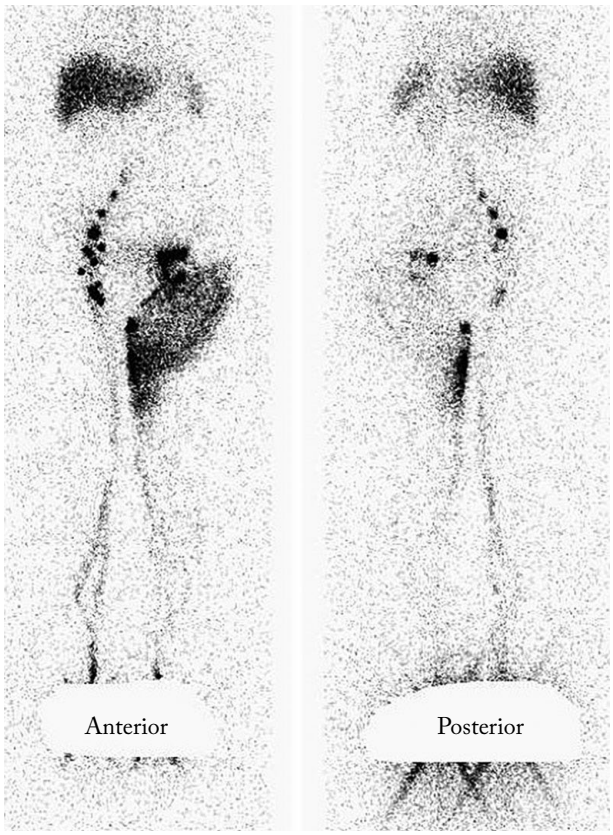

Fig. 6. Lymphoscintigraphy: Whole body images in anterior and posterior projection of a 70-year-old woman with two years of history of left leg swelling, major pelvic surgery 10 years ago, and left thigh trauma in childhood (possible muscle rupture). Lymph vessels and nodes are poorly visualized on the left side, with extensive dermal backflow in the left thigh due to unilateral secondary lymphedema.

radiotracer from deep lymphatic structures reaches subdermal tissue (Fig. 5 and Fig. 6) (2-4, 6, 8, 11, 12).

To facilitate the evaluation of lymphoscintigraphy findings, several staging and scoring systems have been proposed (Table 2). These are summarized in a recent Pappalardo and Cheng's editorial (4). Transport index (13), later modified by Cambria *et al.* (14), included mathematical formula considering visualization of lymph nodes and vessels, transport kinetics, distribution of tracer, and time to lymph node visualization. The scoring system by Szuba *et al.* (6) included the ratio of radioactivity in affected versus normal axillary lymph nodes and was primarily developed for breast surgery patients. Lee and Bergan (15) proposed the method combining imaging with clinical staging where the degree of lymph node uptake, presence of dermal backflow, visualization of main/collateral lymphatics, and clearance from the injection site are evaluated, with a minimum of two or more findings required for staging.

The methods proposed by Pecking (16) and Megawa (17) used mainly qualitative parameters, such as visualization of lymph nodes, lymph stasis, and dermal backflow. Pecking (16) also introduced a quantitative aspect by distinguishing between fast and slow transport efficacy. Ebrahim *et al.* (18) proposed a simple scoring system with a good interobserver compliance.

The authors of editorial, Pappalardo and Cheng (4), proposed a staging system named Taiwan Lymphoscintigraphy Staging (TLS), which includes visualization of proximal/intermediate lymph nodes, linear lymphatic ducts, and dermal backflow, and helps differentiate between normal drainage, partial obstruction, and total obstruction. Combining the TLS data with clinical information (extremity circumference, cellulitis episodes) and indocyanine green lymphography findings, they also proposed a grading system called Cheng's Lymphedema Grade, which consists of five grades (0-IV), and treatment options appropriate for each stage. Although these scoring systems can be applied in most lymphoscintigraphic examinations, they are not always used in practice because of complexity and the lack of clear correlation to disease severity and clinical prognosis.

Discussion

Lymphedema is a chronic and debilitating condition manifesting as unilateral or bilateral limb swelling, which can be congenital or acquired. Initially, edema resolves with rest, but as it progresses to proximal parts of the extremity, it remains present to some degree. Later, swelling cannot be reduced without treatment. Finally, irreversible, chronic skin changes develop and patients suffer from repeated infections. Management of lymphedema is difficult, requires multidisciplinary approach, and is frequently unrewarding.

The diagnosis is based on patient history, physical examination, and diagnostic test results.

Table 2. Examples of lymphoscintigraphy staging: A – Lymphoscintigraphy staging from Lee and Bergan (15), B – Evaluation of transport index (13), C – Taiwan lymphoscintigraphy staging (4)

A Lymphoscintigraphy staging by Lee and Bergan					
	Degree of lymph node uptake	Presence of dermal backflow	Visualization of collateral lymphatics	Visualization of main lymphatics	Clearance of tracer from injection site
Grade I	/	none	good	decreased	decreased
Grade IIa	none	< half of each limb	decreased	poor or no visualization	greater decrease
Grade IIb	none	> half of each limb	decreased	poor or no visualization	greater decrease
Grade III	none	present	poor	none visualized	no clearance
Grade IV	none	poor or no visualization	none visualized	none visualized	no clearance
NB: A minimum of two or more findings are required for staging					
B Evaluation of Transport index (TI) on lymphoscintigrams					
	K (lymphatic transport kinetics)	*D* (distribution pattern)	*T* (time to appearance of lymph nodes)	*N* (assessment of lymph nodes)	*V* (assessment of lymph vessels)
0 points	no delay	normal distribution	*n* time (minutes) to the first appearance of regional lymph nodes	clearly demonstrated	clearly demonstrated
3 points	low-grade delay	partially diffuse		faint visualization	faint visualization
5 points	extreme delay	diffuse		hardly recognizable	hardly recognizable
9 points	no transport	transport stop	no appearance	no visualization	no visualization
TI = K + D + 0.04xT + N + V NB: Higher TI indicates worse lymphatic function					
C Taiwan lymphoscintigraphy staging					
L-0	normal lymphatic drainage				
P-1	decreased linear lymphatic ducts without dermal backflow				
P-2	dilated distal lymphatic ducts with proximal or distal dermal backflow				
P-3	entire dermal backflow				
T-4	no lymphatic ducts visible and presence of distal dermal backflow				
T-5	no lymphatic ducts visible and presence of entire dermal backflow				
T-6	no movement of injected radiotracer				
L-0: normal lymphatic drainage; P-1, P-2, P-3: partial obstruction; T-4, T-5, T-6: total obstruction					

Lymphoscintigraphy is a simple, non-invasive nuclear medicine procedure used to differentiate extremity lymphedema from edema of another origin, assess lymphatic drainage, identify patients at high risk of developing lymphedema after lymph node dissection, and semi-quantify lymphatic flow. The presence of specific features, such as absent radiotracer progression from the injection site, absent lymph node visualization, dermal backflow, or visualization of collateral lymphatics, can be considered specific for lymphedema.

Lymphoscintigraphy can also help in assessing the number and functional status of regional lymph nodes and patent communication between lymphatic and venous system.

Its sensitivity is 70%–96%, but when combined with quantitative data, it may reach 100%. Specificity even without quantification analysis reaches 100% (11, 19, 20). However, it can be lower if patients with similar pathologies are referred to lymphoscintigraphy by a less experienced clinician (1). Therefore, careful selection of patients is important. SPECT/CT, as a 3D imaging method combining morphological (CT) and functional (SPECT) information, additionally helps to identify possible pathological processes or anatomic malformations and precise localization of dermal backflow (21).

Other diagnostic imaging procedures have lower diagnostic sensitivity and specificity in lymphedema, but they can provide additional data on morphology and vasculature (4). There are several occasions when lymphoscintigraphy can yield false-negative results. It usually occurs in patients with early stage of the disease or results from technical issues (inappropriate injection technique, injection site). In the case of negative findings combined with high clinical suspicion of lymphedema, the procedure should be repeated after a year, with interim conservative treatment (1).

Quantification methods listed in this article can increase the sensitivity and are a helpful tool in some equivocal cases; however, their implementation depends on physician's individual experience and expertise (4). Nuclear medicine physicians mostly rely on visual criteria and clinical parameters when evaluating lymphoscintigraphic results, with abnormal lymph node radiotracer uptake and dermal backflow being the most important indicators of severe lymphatic dysfunction (4, 13).

Conclusion

Lymphoscintigraphy is a non-invasive nuclear medicine procedure with an excellent safety profile, which makes it acceptable even in newborns and infants. It should be the first-choice procedure for lymphedema evaluation because it is easy to perform and has high sensitivity and specificity. However, the procedure has not been standardized, and the use of semiquantitative methods, which could improve specificity, depends on local experience and expertise.

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Sažetak

ULOGA LIMFOSCINTIGRAFIJE U DIJAGNOSTICI LIMFEDEMA

I. Iskra, T. Bogović Crnčić i *N. Girotto*

Limfedem je kronična bolest progresivnog tijeka koju uzrokuje poremećaj transporta limfe, a manifestira se oticanjem češće donjih, a ponekad i gornjih ekstremiteta, ovisno o etiologiji. Dijagnoza se postavlja na temelju kliničke slike, pregleda ultrazvukom i slikovnih pretraga, a liječenje je uglavnom konzervativno, dugotrajno i nezadovoljavajuće, no u novije se vrijeme uvode i kirurške metode. Limfoscintigrafija, nuklearno medicinska slikovna pretraga koja je jednostavna i neinvazivna, smatra se metodom izbora u dijagnostici. Uključuje intrakutanu/subkutanu primjenu radiofarmaka u obliku koloidnih čestica obilježenih radioaktivnim tehnecijem – 99m te dvodimenzijsko ili trodimenzijsko snimanje gama kamerom. Omogućuje razlikovanje limfedema od edema druge etiologije, procjenu ozbiljnosti bolesti te uspješnosti kirurškog zahvata. Postupak ipak nije u potpunosti standardiziran, a korištenje semikvantitativnih metoda koje bi trebale pridonijeti procjeni ozbiljnosti limfedema ovisi o lokalnom iskustvu i znanju.

Ključne riječi: *Limfedem; limfoscintigrafija; technetium Tc 99m – nanocolloid*