Lymphoscintigraphy of the Lower Extremities

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1. Introduction

Lymphoedema is a chronic, progressive, and often debilitating condition. Primary lymphoedema is a lymphatic malformation which developsduring the later stage of lymphangiogenesis. Secondary lymphoedema is the result of obstruction or disruption of the lymphatic system, which can occur as a consequence of tumours, surgery, trauma, infection, inflammation, or radiation therapy.

In the extremities, the lymphatic system consists of a superficial (epifascial) system that collects lymph from the skin and subcutaneous tissue. A deeper system drains subfascial structures such as muscle, bone, and deep blood vessels. The superficial and deep systems drain at markedly different rates, subfascial transport is slower and drains less lymph than the epifascial system. The epifascial transport seems to be optimal for routine lymphscintigraphy of the extremities (described below) using colloidal agents, macromolecules and colloids with a particle size between 10 and 50 nm are exclusively cleared from the interstitial space by the lymphatic system. Functional imaging of the lymphatic vessels can be carried out using lymphoscintigraphy. Hereby, the physiological transport of radioactively labelled protein particles (nanocolloid) in the lymphatic system is examined following subcutaneous injection into the affected limb. Alternative lymph routes (collateral routes, dermal backflow) and lymph nodes are also visualised in this manner. Semi-quantitative parameters are often used to aid visual interpretation of the images (qualitative or static lymphoscintigraphy). Quantitation of lymphatic flow (quantitative lymphoscintigraphy) may be a more sensitive approach to the diagnosis of lymphatic impairment. The radiopharmaceutical transit time is evaluated (dynamic study) and the lymphatic transport capacity of the extremity is expressed using a clearance percentage (uptake percentage in the proximal nodes of the extremity in relation to the total injected dose and following correction for decay of the radiopharmaceutical). Quantitative measurements require the extremity to be subjected to standardised stress; the resulting measurements can vary significantly depending on whether or not the muscle pump has been activated. Studies to investigate the different methods of administering the radiopharmaceutical have shown subcutaneous injection to be superior to intracutaneous injection for evaluating the epifascial or superficial lymphatic system. There is no correlation between colloid clearance at the site of injection and functional lymph node uptake.

Lymphoedema can be surprisingly difficult to diagnose, especially in the early stages. Without an established diagnosis, therapy is often delayed, allowing secondary fibrosis and lipid deposition to take place. Early treatment often results in rapid clinical improvement and prevents progression to the chronic phase of disease. Early detection and characterisation of the disorder through lymphscintigraphy leads to earlier and better implementation of therapy, which may improve quality of life.

Table: Staging of lymphoedema

Stage 1:

a. Latent lymphoedema, without clinical evidence of oedema, but with impaired lymph transport capacity (provable by lymphoscintigraphy) and with initial immunohistochemical alterations of lymph nodes, lymph vessels and extracellular matrix.
b. Initial lymphoedema, fully or partially decreasing through rest and draining position, with worsening impairment of lymph transport capacity and of immunohistochemical alterations of lymph nodes and extracellular matrix.

Stage 2:

a. Increasing lymphoedema, with diminishing lymph transport capacity, relapsing lymphangitis, fibroindurative skin changes, and developing disability.
b. Column shaped limb fibrolymphoedema, with lymphostatic skin changes, reduced lymph transport capacity and worsening disability.

Stage 3:

a. Also known as elephantiasis, with scleroindurativepachydermatitis, papillomsatouslymphostaticverrucosis, no lymph transport capacity and life-threatening disability.
b. Extreme elephantiasis with total disability.

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications

Lymphoscintigraphy is indicated for patients:

- With onset of oedema at a young age and requiring confirmation of the diagnosis
- In whom venous or other demonstrable pathology has been excluded and the diagnosis of lymphoedema cannot yet be made on the basis of clinical examination
- With recurrent erysipelas/cellulitis
- With a discrepancy between trauma and persistent swelling, for example following an insect bite, twisted ankle, knee surgery
- With a discrepancy between the subjective symptoms and the degree of swelling in the extremity as measured objectively
- With chronic therapy resistant ulcers and severe chronic venous insufficiency
- With any previously demonstrated lymphatic system fistulas
- With therapy resistant lymphoedema despite optimal treatment
- As yet there is no evidence in the medical literature to prove that lymphoscintigraphy is valuable in distinguishing between risk groups following mastectomy and/or radiotherapy.

4. Relation to other diagnostic procedures

Radiological investigations(CT, MRI, vascular imaging) are useful in diagnosing lymphoedema as they can either illustrate or rule out causal abnormalities (extraluminal/obstructed lymph drainage, oncological abnormalities, vascular abnormalities). Direct

lymphangiography is now obsolete.
Indirect lymphangiography using MRI and optical lymphangiography are currently still in the experimental stage. The main diagnostic imaging method for the lymphatic system is lymphoscintigraphy: a functional, non-invasive and nontraumatic method of investigation.

5. Medical information necessary for planning

a. Past medical history related to the development of oedema.
b. General past medical history including malignancies, surgery, thromboembolic events, radiotherapy, infections (erysipelas, cellulitis), CVI, lipohypertrophy.
c. Results of relevant dermatological and radiological investigations.

6. Radiopharmaceutical

Tracer:	^{99m}Tc-nanocolloid
Nuclide:	Technetium-99m
Activity:	50 MBq per foot in a small volume (approx. 0,2 ml)
Administration:	Subcutaneous injection into the 1st (and 2nd) interdigital space of both feet

7. Radiation safety

a. Pregnancy:
Avoid procedure if possible
b. Lactation:
According to ICRP 106 there is no need to interrupt breastfeeding, but due to possible free ^{99m}Tc pertechnetate it is advisable to interrupt the feeding for 4 h (the effective dose to patients is 0,002 to 0,03 mSv/MBq)
c. Radiation exposure
Very low (the effective dose to patients is 0,002 to 0,03 mSv/MBq)

8. Patient preparation/essentials for procedure

Preparation: Disposable mat, gauze pads, alcohol, gloves.
Procedure: 1 or 2 extremities are investigated depending on the indication. If the indication for scintigraphy is to assess the function of a lymphovenous shunt, it should only be carried out on the affected extremity because, theoretically, the colloid should spread directly via the venous system if the shunt is working and it should appear immediately in the RES (liver, spleen, bone marrow etc.). No evidence to support this indication has been found in the medical literature.

The patient must empty his/her bladder fully before scintigraphic imaging commences.

a. Whilst sitting/lying on the table, the patient receives 1 or 2 subcutaneous injections in the first (and second) interdigital space of each foot.
b. Position feet approximately 10 cm above the camera collimator; measure the depot for 1 min. Record counts and time per foot (t=0).
c. Ask the patient to step on and off a footstool or march on the spot approximately 20 times.
d. Dynamic images: Ask the patient to lie supine on the table. Follow the activity towards the pelvis (inguinal nodes) with the camera in an anterior position. Serial scintigraphy,

30 x 1 min frames to determine the speed of lymph transport (transit time).

e. Follow immediately with static images including the abdomen (liver region), groin/pelvis, upper legs and lower legs, 2 min per image.
f. Instruct the patient to walk for at least 30 min between acquiring the early and late images.
g. Two hours post injection, acquire late static images of the abdomen (liver region), pelvis, upper legs and lower legs (including injection site), 5 min per image. Draw a ROI around the inguinal nodes of each leg and determine the number of counts.

9. Acquisition and processing

Energy:	^{99m}Tc--setting, 140 keV
Window:	15-20%
Collimator:	Use a collimator that produces an active point source image without a star pattern. LEHR or LEAP collimator
Counts:	depends on images required (see procedure)
Computer:	single image: Measure depot immediately following injection (approx. 10 cm distance from the collimator), minimum matrix size of 64x64.
Dynamic series:	0-30 min from feet to groin (anterior)
Images:	At 30 min and 2 hrs p.i. anterior images of feet and groin; 128x128 matrix size for single headed cameras and 128x512 for scanning cameras. Additional SPECT/CT images can be helpful for the interpretation of images

Calculate the *lymph transport capacity (*= lymph node uptake measurements expressed as a percentage or clearance percentage) for each leg according the formula below in which the following data is used:

C_{depot}= counts depot per foot at t=0
T_{corr}= correction factor for imaging time. Suggested time for depot measurement: 1 min; late static image: 5 min. Correction factor: 5
$C_{inguinal}$= counts inguinal nodes of each leg 2 h p.i.
R = correction for radiopharmaceutical decay: $A(t)=A(t=0) \times R$ or $R=e^{\lambda t}$ where $\lambda=0{,}693/T1/2$.

Lymphatic transport capacity (%) = $((C_{inguinal} \times R) : (C_{depot} \times T_{corr})) \times 100\%$
The following normal values for the lower extremities can be used with the formula above:
normal values
Transit time < 10 min
Lymph transport capacity > 15 %
Difference left/right < 7 %

It should be noted that the lymphatic transport capacity gradually reduces with increasing age. Healthy young subjects (< 35 years of age) have a lymphatic transport capacity of > 17%.

10. Interpretation

A standardised protocol (including motor activity) is recommended for the interpretation of visual parameters. A standardised protocol is essential for the interpretation of

quantitative parameters.

a. Normal lymphoscintigram:

- Good visualisation of one or two lymphatic chains localised on the medial aspect of the legs
- Visualisation of the prefascial inguinal lymph nodes within 10 min of subcutaneous injection of the activity.
- Visualisation of multiple para-iliac and para-aortic lymph nodes as well as the liver 2 h after injection
- Symmetry
- Faint, physiological, visualisation of the kidneys and urine activity in the bladder.
- Reference values for quantative parameters: see table 1

b. An abnormal lymphoscintigram indicates abnormal lymph drainage

I. Visual assessment:

- No migration of activity from the site of injection (depot)
- Fragile and/or hypoplastic lymphatic chains
- Little or no visualisation of the lymphatic chains on the medial side of the leg
- Visualisation of several collateral chains (alternative drainage)
- Hyperplastic chains, any excessively tortuous chains (e.g. in lipolymphoedema).
- Presence of dermal backflow, either local (e.g. due to erysipelas) or diffuse (due to obstructed drainage e.g. inguinal node resection)
- Differences between left and right. Slight differences in function are best assessed using late images and with the aid of quantification

II. Quantitative assessment:

- -Reduced lymphatic transport speed (transit time >10 min) unilateral or bilateral.
- Reduced lymphatic transport capacity (percentage of uptake by inguinal nodes)

Lymphoscintigraphy combined with quantitative parameters is preferable to lymphoscintigraphy without these parameters. This applies in particular in the diagnosis of early reversible lymphoedema of the lower extremities, which is often asymptomatic. Scintigraphy alone does not allow for differentiation between the causes of lymphoedema, primary or secondary. It is therefore essential to combine scintigraphy with other clinical information. However, components of lymphogenic oedema can be demonstrated or ruled out using quantitative lymphoscintigraphy, for example in the differential diagnosis of chronic venous insufficiency and lipohypertrophy (lipoedema)

c. Pitfalls:

- Particle sizes >50 nm, such as in ^{99m}Tc-tin-antimony, ^{99m}Tc-tin-antimony/sulphide and ^{99m}Tc-tin-rhenium colloid, result in reduced transport of activity via the lymphatic system, and normal reference values are therefore not applicable. ^{99m}Tc-tin-fluoride has a much smaller particle size and produces non-standard results. A long time-interval between preparation and administration of the colloids listed above results in an increase in particle size and therefore non-standard results. These problems almost never occur when ^{99m}Tc-nanocolloidis used
- Sluggish transport due to inadequate muscle pump stimulation (e.g. bed ridden patients)
- Accidental (partial) intravenous administration (activity is taken up directly by the liver)
- Method of the investigation

11. Report

The report should contain the following information:

a. The degree of visualisation and the course of the lymphatic chains shown on the image (1 chain comprises several lymph vessels), the presence of any collateral chains in the upper and lower extremities, and signs of dermal backflow (collateral cutaneous network).
b. Activity and symmetry in the following lymph node stations: inguinal, para-iliac, para-aortic.
c. Liver activity.
d. Activity outside the lymphatic system.
e. For quantification: a description of the standard procedure followed, the dynamic results (transit time), the calculated lymphatic transport capacity and the differences between left and right.

12. Literature

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