Lymphoscintigraphy of the Upper Extremities

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1. Introduction

Lymphoedema is a chronic, progressive, and often debilitating condition. Primary lymphoedema is a lymphatic malformation which develops during 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, and radiation therapy. Arm lymphoedema is a frequent complication of breast cancer therapy and axillary lymph node dissection, with an estimated frequency of 5-30%.

Macromolecules and colloids with a particle size between 10 and 50 nm are cleared from the interstitial space exclusively by the lymphatic system. Functional imaging of the lymphatic vessels can be carried out using lymphoscintigraphy, in which the physiological transport of radioactively labelled protein particles (nanocolloid) in the lymphatic system is determined following subcutaneous injection into the affected extremity. Alternative lymphatic routes (collateral routes, dermal backflow) and lymphnodes are also visualised. Semi-quantitative parameters are often used to aid visual interpretation of the images (qualitative or static lymphoscintigraphy). 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 that the extremity to be examined is subjected to standardized stress: the measurements can vary significantly depending on whether or not the muscles are used in order to activate a pump function of the lymphatics. Studies to investigate the different methods of administering the radiopharmaceutical have shown that subcutaneous injection is 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 its early stages. Without a confirmed 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 this disease. Lymphoscintigraphy offers an objective and reliable approach to diagnosis and characterisation of the severity of lymphoedema. Therby allowing for the implementation of therapy which may improve quality of life.

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, papillomsatous lymphostatic verrucosis, 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 methods

Radiological examinations (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 non-traumatic 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 extremity in a small volume (approx. 0,2 ml)
Administration:	Subcutaneous injection in the 2nd (and sometimes the 3rd) interdigital space of both hands

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 0,005 mSv/MBq)

c. Radiation exposure

Very low (the effective dose to patients is 0,005 mSv/MBq)

8. Patient preparation/essentials for procedure

Preparation: Alcohol, gauze pads, disposable mat, gloves, squeeze ball/ stress ball.
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.

a. The patient receives 1 or 2 injections in each hand (in the 2nd and the 3rd interdigital space).
b. Place hands on the camera; measure the depot activity for 1 min at approximately 10 cm from the collimator and use this value as a basis for quantification. Record counts and time for each hand (C depot=0).
c. Give the patient a squeeze ball/stress ball to generate motor activity in the lower arm muscles (for at least 15 min) in the period between early and late imaging (2 to 3 h p.i.).
d. Obtain static images (5 min) of the abdomen (liver region), RAO and LAO images of the shoulders, elbows and lower arms. Ensure the entire arm is visible.
e. If necessary, repeat the entire series 6 h following injection.
f. For semi-quantification (optional): Using late images, draw ROIs over axillary nodes and calculate the total number of counts (Caxillary 3 h p.i.). Lymphatic transport capacity is calculated in the same way as for the legs (see lymphoscintigraphy lower extremities).

9. Acquisition and processing

Energy:	^{99m}Tc-setting, 140 keV
Window:	15-20%
Collimator:	Use a collimator that images an active point source without producing a 'star artefact'. This is usually a Low Energy High Resolution collimator although a Low Energy General Purpose collimator is often sufficient to fulfil these requirements.
Counts:	See procedure
Computer:	matrix 128x128
Images:	At 3 h and 6 h p.i.; 128x128 matrix size for single headed cameras and 128x512 for scanning cameras. Additional SPECT/CT images can be helpful for the interpretation of the planar images

10. Interpretation

A standardised investigation protocol (including stress) is recommended for the interpretation of visual parameters. A standardised investigation protocol is essential for the interpretation of quantitative parameters.

a. Normal lymphoscintigram:

- Good visualization of one or two lymphatic chains.
- Visualisation of the axillary lymph nodes within 10 min of subcutaneous injection of the activity.

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
- Visualization of several collateral chains (alternative drainage)
- Hyperplastic chains, any excessively tortuouschains(e.g. as in lymphoedema)
- Presence of dermal backflow, either local (e.g. due to erysipelas) or diffuse (due to obstructed drainage e.g. lymph node resection)

II Quantitative assessment:

Since the use of quantitative parameters for the upper extremities has not been validated in the medical literature, assessment is based primarily on visual parameters (see lymphoscintigraphy of lower extremities). Furthermore, many patients who are referred for lymphoscintigraphy of the upper extremities have undergone an oncological axillary node resection.

If the indication for scintigraphy is to assess the function of a lymphovenous shunt, it should only be carried out on the affected arm. Quantitative liver uptake measurements are not supported in the medical literature.

It is not possible to determine the causes of lymphoedema, primary or secondary, on the basis of scintigraphy alone. It is therefore essential to combine scintigraphy with other clinical information.

However, components of lymph oedema can be shown 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. The 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. bedridden patients).
- Accidental (partial) intravenous administration (activity is taken up directly by the liver).

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. The activity and symmetry in the lymph node stations: axillary and neck.
c. Liver activity.
d. Activity outside the lymphatic system.
e. For quantification (optional): a description of the procedure followed, the dynamic results (transit time), the calculated lymphatic transport capacity and the differences between left and right.

12. Literature

- Bats AS, Nos C, Bensaid C, Le Frere-Belda MA, Collignon MA, Faraggi M, and Lecuru F. 2013. Lower-limb drainage mapping for lymphedema risk reduction after pelvic lymphadenectomy for endometrial cancer. Oncologist. 18(2):174-9.
- Bilancini S, Lucchi M, Tucci S, and Eleuteri P. 1995. Functional lymphatic alterations in patients suffering from lipedema. Angiology. 46 (4):333-9.
- Damstra RJ, van Steensel MA, Boomsma JH, Nelemans P, and Veraart JC. 2008. Erysipelas as a sign of subclinical primary lymphoedema: a prospective quantitative scintigraphic study of 40 patients with unilateral erysipelas of the leg. Br. J. Dermatol. 158 (6):1210-5.
- Dutch Guideline of Lymphoedema 2014 (RichtlijnLymfoedeem CBO 2014).
- Dutch Guideline of Lipoedema (RichtlijnLipoedeem CBO 2014).
- ISL. 2013. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. Lymphology. 46 (1):1-11.
- Jensen MR, Simonsen L, Karlsmark T, Bulow J. 2010. Lymphoedema of the lower extremities-background,pathofysiology and diagnostic considerations. ClinPhysiolFunct Imaging 30:389-98.
- Lucarelli RT, Ogawa M, Kosaka N, Turkbey B, Kobayashi H, and Choyke PL. 2009. New approaches to lymphatic imaging. Lymphat. Res. Biol. 7 (4):205-214.
- Mostbeck A, and Partsch H. 1999. [Isotope lymphography–possibilities and limits in evaluation of lymph transport]. Wien. Med Wochenschr. 149(2-4):87-91.
- Murdaca G, Cagnati P, Gulli R, Spano F, Puppo F, Campisi C, and Boccardo F. 2012. Current views on diagnostic approach and treatment of lymphoedema. Am. J. Med. 125 (2):134-140.

- Partsch H. 1995. Assessment of abnormal lymph drainage for the diagnosis of lymphoedema by isotopic lymphangiography and by indirect lymphography. ClinDermatol. 13 (5):445-50.
- Partsch 2003. Practical aspects of indirect lymphography and lymphoscintigraphy. Lymphat. Res Biol. 1 (1):71-3.
- Reich-Schupke S, Altmeyer P, and Stucker M. 2013. Thick legs - not always lipedema. J Dtsch. Dermatol. Ges. 11 (3):225-33.
- Rockson SG. 2010. Current concepts and future directions in the diagnosis and management of lymphatic vascular disease. Vasc. Med. 15(3):223-31.
- Scarsbrook AF, Ganeshan A, and Bradley KM. 2007. Pearls and pitfalls of radionuclide imaging of the lymphatic system. Part 2: evaluation of extremity lymphoedema. Br J Radiol. 80(951):219-26.
- Szuba A, Shin WS, Strauss HW, and Rockson S. 2003. The third circulation: radionuclide lymphoscintigraphy in the evaluation of lymphoedema. J Nucl Med. 44(1):43-57.
- Szuba A, Strauss W, Sirsikar SP, and Rockson SG. 2002. Quantitative radionuclide lymphoscintigraphy predicts outcome of manual lymphatic therapy in breast cancer-related lymphoedema of the upper extremity. Nucl. Med. Commun. 23(12):1171-5.
- Weissleder H, Brauer JW, Schuchhardt C, and Herpertz U. 1995. [Value of functional lymphoscintigraphy and indirect lymphangiography in lipedema syndrome]. Z. Lymphol. 19(2):38-41.
- Yuan Z, Chen L, Luo Q, Zhu J, Lu H, and Zhu R. 2006. The role of radionuclide lymphoscintigraphy in extremity lymphoedema. Ann Nucl Med 20 (5): 341-4.