THE USE OF LYMPHOSCINTIGRAPHY IN THE MANAGEMENT OF CHRONIC OEDEMA

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Lymphoscintigraphy is widely considered to be the main investigation to establish the diagnosis of lymphoedema and visualise peripheral lymphatics. However, there is no internationally agreed standardised technique. This article considers technical aspects of lymphoscintigraphy (radiotracers used, sites of injection, qualitative and quantitative methods and the sensitivity and specificity of the technique) and its clinical application, including the indications for its use, the interpretation of the results obtained and clinical examples from the Derby lymphoedema service.

Key Words

Chronic oedema
Clinical indications
Lymphoedema
Lymphoscintigraphy
Radiotracers

Lymphoscintigraphy (also known as isotope or radionuclide lymphangiography) is widely considered to be the main investigation to establish the diagnosis of lymphoedema and visualise peripheral lymphatics (International Society of Lymphology, 2003; Società Italiana di Linfangiologia, 2006).

However, the indications for its use vary throughout the world. In some centres it is advocated for virtually all patients with lymphoedema, whereas in others it is rarely, if ever, used. On the one hand it is argued that it should be a routine part of the diagnosis and full assessment of lymphatic abnormality, but, on the other, it is argued that the diagnosis is largely based on clinical examination and that lymphoscintigraphy is unlikely to alter the management plan.

Where lymphoscintigraphy is employed, there is no internationally agreed standardised technique and thus results are varied and difficult to compare. This article looks at various technical aspects of lymphoscintigraphy and considers where it may be of value in the assessment and management of patients with chronic oedema.

Lymphoscintigraphy: general principles and uses

Lymphoscintigraphy relies on one of the essential functions of the lymphatic system, i.e. to transport large molecules from the interstitial space back to the vascular compartment. Therefore, if a large molecule such as a protein or colloid with a radioactive label (e.g. technetium [^{99m}Tc]) is injected into the interstitial space, its transport through the initial lymphatics, the collectors and region lymph nodes, can be followed using an external gamma camera to detect the radioactivity. This provides a picture of lymphatic function and pathways but does not give the degree of fine anatomical detail, which may be seen with direct X-ray lymphography (Partsch, 1995).

In clinical work it is used in the assessment of patients with chronic oedema and in the identification of 'sentinel nodes', e.g. in breast cancer treatment. The latter will not be covered in detail in this article; however, the technique has relevance to those managing patients with lymphoedema, as it should help to reduce the incidence of breast cancer treatment-related lymphoedema, perhaps to as low as 3% in those undergoing sentinel lymphadenectomy alone (Sener et al, 2001).

In research, lymphoscintigraphy can further the understanding of the pathophysiology of lymphoedema and its response to treatment (e.g. Rosbotham et al, 2000; Stanton et al, 2003; Szczensny et al, 2005; Kafejian-Haddad et al, 2006).

Technical aspects

Radiotracers

Although the technique relies upon the normal function of the lymphatic system in removing macromolecules from the interstitial space, different molecules are handled in different ways and this can therefore affect the appearances of the lymphoscintigram. There are two main types of preparation used: macromolecules and colloidal suspensions (Kramer,

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2004). The radiolabel attached to these to make them detectable is usually ^{99m}Tc.

Macromolecules

Substances that have been used include (Szuba et al, 2003):

- ^{99m}Tc-HSA (human serum albumin)
- ^{99m}Tc-labelled dextran
- ^{99m}Tc-HIG (human immunoglobulin).

Macromolecules are cleared faster than colloids and produce better images of the lymph vessels. However, they do not produce as good images of lymph nodes, as they are not trapped there as well as colloids. There is also a risk that smaller molecules will enter the blood capillaries (Szuba et al, 2003).

Colloidal suspensions

These are cleared more slowly from the injection site than macromolecules and therefore do not show the lymphatic vessels as clearly. They are, however, trapped more effectively in the lymph nodes and make them more visible on the scan. Examples of colloids used in lymphoscintigraphy include (Szuba et al, 2003):

- ^{99m}Tc-antimony sulphide colloid
- ^{99m}Tc-sulphur colloid
- ^{99m}Tc-albumin colloid (nanocolloid).

The size of the particles in the colloid will determine how well the tracer is removed from the injection site. Particles may be removed by direct entry into the lymphatics, or through phagocytosis by macrophages, which then enter the lymphatics. Massage at the site of injection has been shown to enhance the uptake of the particles into the lymphatics substantially (Ikomi et al, 1995).

Estimates of the 'pore size' through which the molecules have to pass from the interstitial space to the lymphatics range from about 15 nanometers (nm) to several micrometers (Szuba et al, 2003). Particles smaller than a few nanometers in diameter tend to leak into blood capillaries, and larger particles (up to approximately 100 nm) enter the lymphatics. It has been estimated that the optimal particle size for lymphoscintigraphy is 50–70 nm. Particles larger than 100 nm may be trapped in the interstitial space for a prolonged period (Szuba et al, 2003).

To demonstrate the complete anatomy of the lymphatic system, enough tracer must pass through successive lymph nodes, e.g. inguinal to iliac to para-aortic, without being trapped to enable them to be visualised in sequence (Bourgeois, 1997).

However, even large molecules (e.g. human immunoglobulin G) injected subcutaneously have been shown to enter the blood vascular system locally in both healthy subjects and women with breast cancer-related lymphoedema, either through lymphaticovenous communications or direct transendothelial transport (Pain et al, 2004).

Once in the lymphatic system the colloid particles are transported to the lymph nodes where they may become trapped. Here, the uptake of particles does not just depend upon size, as colloids of a similar size may be taken up differentially, depending upon the surface properties of the colloid particles, e.g. their charge. Other factors include whether they are hydrophobic and the presence of ligands (Szuba et al, 2003).

Furthermore, to demonstrate the complete anatomy of the lymphatic system, enough tracer must pass through successive lymph nodes, e.g. inguinal to iliac to para-aortic, without being trapped to enable them to be visualised in sequence (Bourgeois, 1997). If this does not occur, failure of the tracer to show up more proximal lymph nodes may suggest that the pathway is obstructed (Bourgeois, 1997).

Thus, the appearances of the lymphoscintigram will be dependent upon the colloid used and the particle size. ^{99m}Tc-albumin nanocolloid has a particle size of < 80 nm (95% of particles) and is cleared rapidly from the injection site. It has also been argued that this is more 'physiological' than some of the other colloids, as it is similar to the normal gel-like nature of the subcutaneous interstitial space (Bourgeois, 1997).

Choice of radiotracer

The radiotracer used may be determined by what is available in different countries (in the US only ^{99m}Tc-filtered sulphur colloid [through 0.22 micron filter] or ^{99m}Tc-sulphur colloid is available, whereas in the UK, ^{99m}Tc-albumin nanocolloid is usually used) (Kramer, 2004), but may also be affected by whether the lymphoscintigram is intended to be qualitative or quantitative in nature. Qualitative studies primarily aim to demonstrate the morphology of the lymphatic system and so a colloidal preparation, which will outline the lymph nodes and vessels, may be the best choice. However, for quantitative studies, which aim to measure how quickly the lymphatics transport the tracer, a macromolecule, which is removed more rapidly from the tissues, may be the better option (Szuba et al, 2003; Kramer, 2004).

It has also been argued that the choice of tracer may be influenced by the underlying pathology being studied. For example, the use of a colloid to demonstrate lymph nodes may be less important in lymphoedemas caused by surgical lymphadenectomy (O'Mahony et al, 2004).

Volume and quantity of tracer

The rate of uptake of the radiotracer may be influenced by the volume injected, as well as the amount/concentration of the tracer. These may affect the local tissue hydrostatic and oncotic pressures at the site

of injection. The usual volume recommended for subcutaneous injection is about 0.2 ml (Bourgeois, 1997).

Obesity of the subject

The radioactivity emitted from the tracer may be absorbed by fat before it is detected by the gamma camera. This attenuation can lead to poor visualisation of deep lymph nodes (e.g. intra-abdominal), and may suggest that they are poorly or non-functioning (Bourgeois, 1997). Such attenuation can be a significant issue in quantitative lymphoscintigraphy and has to be taken into account (see below).

Stability of the radiotracer

It is important that for the duration of the study the radiolabel remains attached to the macromolecule/colloid. This has been shown to be a problem with some compounds, e.g. ^{111}In-HIgG (indium labelled polyclonal human immunoglobulin G), where the label may become detached and enter the venous system (Pain et al, 2004).

With more stable compounds, once it has travelled through the peripheral lymphatic system, the tracer is carried into the venous system via the normal anatomical connections (e.g. the thoracic duct). It is then carried to the liver where it is trapped. Thus, in the later images of lymphoscintigrams, the liver is outlined under normal circumstances. Also, in late images the urinary bladder may be outlined, as the radiolabel is excreted in the urine (Weissleder and Weissleder, 2003; Kramer, 2004).

Site of injection of tracer

In the limbs there are two levels of the lymphatic system: the superficial (epifascial), which primarily drains the skin and subcutaneous tissues, and the deep (subfascial), which mainly drains the musculature. In the normal limb, transport of lymph through the deep system is slower and smaller in quantity than the superficial system (Szuba et al, 2003). To demonstrate lymphatic drainage in each system, different sites of injection are used (*Table 1*).

There is, however, debate in the literature about the best method for routine lymphoscintigraphy in clinical diagnosis. Many centres, especially in the UK, use the subcutaneous route at the sites described in *Table 1*. It has been argued that this usually reflects the clinical pathology where oedema is mainly present in the subcutaneous tissues in the periphery of the limb and, therefore, it is the drainage from this area that is of most interest. In some centres, especially in continental Europe, proximal areas of oedema may be injected directly (Bourgeois, 1997). However, even with distal injections, proximal abnormalities may be demonstrated, e.g. 'dermal backflow' (see below).

Intradermal injections are more difficult to carry out than subcutaneous ones and there is a risk that some tracer will enter the subcutaneous space, thereby altering the results of the investigation.

Single injections into each periphery are usually given but some centres use multiple injections (Bourgeois, 1997). In the case of the latter, care may be needed in the interpretation of the results, as different lymphatic pathways may be taken by the tracer, e.g. the normal drainage of a subcutaneous injection into the first interdigital space in the foot is via the superficial system, whereas the fourth interdigital space drains via the deep system. Similarly, if large volumes are injected, diffusion may result in the imaging of both superficial and deep systems from a single injection site. As 're-routing' of lymph through the deep system may be a sign of abnormality in the superficial system, it is important that the two systems can be examined separately.

It is usual to inject both limbs even if one is apparently unaffected by lymphoedema. This limb can either act as a control or, indeed, unexpected abnormalities may appear on the scan.

Superficial system

Both subcutaneous and intradermal injections may be used to examine the superficial lymphatic system. However, these may lead to different results depending upon the underlying pathology. Different centres prefer different routes.

Intradermal injections

The intradermal injection of macromolecules (e.g. ^{99m}Tc-HSA) is followed by rapid lymphatic transport and good visualisation of the lymphatic vessels. It can be useful in quantitative studies (Szuba et al, 2003). However, the intradermal injection of colloidal preparations may not be associated with the same degree of uptake and transport.

Table 1

Sites of injection used to examine different elements of the lymphatic system

Lymphatic system	Site of injection
Superficial	Subcutaneous or intradermal: typically into the first interdigital space in the foot for studies of the lower limb, or second interdigital space in the hand for studies of the upper limb
Deep	Intramuscular, e.g. in the lateral part of the foot pad for studies of the lower limb

Nevertheless, when compared with subcutaneous injection, the intradermal injection of colloids, e.g. ^{99m}Tc-HSA nanocolloid, results in more rapid uptake and appearance at the regional lymph nodes, e.g. reaching its peak in the axillary nodes by 40 minutes after injection in the forearm (Bourgeois, 1997).

It is suggested that intradermal injection, which raises a papule in the skin, results in an increase in local interstitial pressure, which facilitates entry into the initial lymphatics. There is also a high concentration of lymphatic vessels in the dermis, giving a large surface area for the uptake of tracer. In subcutaneous injections, the pressure increase is less and the diffusion distance to the nearest lymphatic may be greater, thus leading to a slower uptake.

Intradermal injections are more difficult to carry out than subcutaneous ones and there is a risk that some tracer will enter the subcutaneous space, thereby altering the results of the investigation. It has also been argued that intradermal injections may lead to significant uptake by blood vessels (Weissleder and Weissleder, 1988).

A recent study aimed at defining an optimal method for imaging the lymphatic vessels of the upper limb recommended the use of intradermal ^{99m}Tc-HIG, or intradermal ^{99m}Tc-nanocolloid, with the former producing marginally superior results in terms of image quality (O'Mahony et al, 2004). By comparison, the images obtained after subcutaneous injection were judged to be inferior. The rate of disappearance of tracer from the injection site was three times higher after intradermal injection than after subcutaneous injection.

Others have argued that intradermal injections do not replicate the situation in the subcutaneous space where oedema accumulates (Weissleder and Weissleder, 1988). Instead, they may give results similar to those achieved by direct intralymphatic injection (O'Mahony et al, 2004).

In a quantitative study, Partsch (1995) found that intradermal injections of tracer (^{99m}Tc-microcolloid) in general did not allow the differentiation of the normal situation from that in lymphoedema (*Table 2*). However, there were differences in different types of lymphoedema. For example, pathological values of uptake were found in primary lymphoedema with both proximal and distal involvement of the leg, whereas the values were normal in patients with primary lymphoedema with distal involvement alone and in patients with secondary lymphoedema. This may reflect the comparatively normal (collateral) functioning of dermal lymphatics in the latter conditions.

In contrast, in the same study, the subcutaneous injection of the radiocolloid led to a clear distinction between normal subjects and those with lymphoedema, including those with subclinical lymphoedema. In five patients with clinically unilateral primary lymphoedema, a low uptake was also demonstrated in the apparently uninvolved limb.

Subcutaneous injection

In light of the findings described in the previous section, the subcutaneous route of administration for the assessment of swollen limbs is recommended by a number of authors (e.g. Partsch, 1995; Weissleder and Weissleder, 1988). This can be used for both qualitative and quantitative studies.

Subcutaneous injection is usually relatively straightforward, but can occasionally be difficult in certain sites and individuals where the tissue distensibility may be less (Bourgeois, 1997). The subcutaneous route may be the optimal route for the injection of colloids (Szuba et al, 2003).

The deep system

The deep system can be demonstrated by the subfascial injection of radiotracers. This may be achieved, for example, by intramuscular injection, subfascial injection in the lateral retromalleolar region, and even intraperiosteal injection (Bourgeois, 1997). It is not commonly used for the routine assessment of chronically oedematous limbs. However, it can demonstrate specific abnormalities in different clinical situations. In a quantitative study using intramuscular injection to the posterior lower leg of ^{99m}Tc-microcolloid, Partsch (1995) reported that subfascial lymph transport was lower than epifascial transport in normal individuals, and was extremely reduced in post-thrombotic syndrome. Variable results were obtained in patients with lymphoedema.

Two-compartment lymphoscintigraphy

This technique uses both epifascial and subfascial administration

Table 2

Lymph node uptake expressed as percentage of administered dose (D%-=±SD) after subcutaneous and intradermal injections in normal subjects and patients with lymphoedema

	Subcutaneous		Intradermal	
	Normal	Lymphoedema	Normal	Lymphoedema
D%	14.3 (±4.2)	2.0 (±2.5)	17.4 (±11.8)	11.5 (±9.7)
n	25	25	9	25
p		<0.001	Not significant	

Source: Partsch, 1995

of radiotracer in an attempt to demonstrate the functioning of both compartments in the assessment of different types of oedema.

Bräutigam et al (1998) used such a technique in 55 patients with a variety of leg oedemas. They used a combination of a semi-quantitative estimation of radiotracer transport and qualitative visual assessment of the lymphatics. The subfascial compartment was examined using an injection of ^{99m}Tc-human albumin nanocolloid into the dorsolateral muscles of the sole of the foot. Whole body scintigrams were recorded after 20 minutes of low-level intensity exercise using a bicycle ergometer, and again after a further 30 minutes of exercise. The study was repeated at least two days later but using a subcutaneous injection between the first and third toes.

The quantitative element of the study assessed uptake into the lymph nodes by comparing 'regions of interest' (ROIs) over the inguinal and parailiac nodes and over the injection site and lymph vessels. The epifascial and subfascial lymph transport in various oedemas is shown in *Table 3*.

Qualitative and quantitative lymphoscintigraphy

In the UK, most centres carry out qualitative lymphoscintigraphy, which aims to image the morphology of the lymphatic system. Quantitative lymphoscintigraphy aims to measure lymphatic flow and may be a more sensitive way of diagnosing lymphatic impairment. Weissleder and Weissleder (1988) reported that the sensitivity of qualitative lymphoscintigraphy in diagnosing lymphoedema was 70.1%. This was increased to 100% when quantitative studies were added. However, by taking a sequence of images at different times following the injection of radiotracer, even qualitative images can be used to demonstrate when lymphatic drainage is delayed, e.g. by examining the time taken after the injection until the regional lymph nodes are imaged.

It is well known that exercise accelerates lymphatic drainage by the extrinsic compression of the valved lymphatic vessels contracting skeletal muscles. Thus, the amount of exercise carried out during the course of imaging can affect both qualitative and quantitative results. Unfortunately, there are no internationally agreed protocols for either qualitative or quantitative lymphoscintigraphy using standardised exercise and imaging regimens. Nevertheless, a number of protocols have been reported in the literature. Most of these combine qualitative images with some form of quantitative estimation. Some of these are shown in *Table 4* to illustrate the variety of approaches. The term 'stress lymphoscintigraphy' is sometimes used in the literature to describe the technique of examining the response of lymphatic flow to an intervention, e.g. exercise (Szuba et al, 2003).

Interestingly, a diagnostic protocol for lymphoscintigraphy in newborns has recently been proposed (Bellini et al, 2005).

Qualitative lymphoscintigraphy

The features of the lymphatic system which qualitative lymphoscintigraphy can describe are shown in *Table 5*. However, in the absence of standardised regimens, e.g. when images are taken and whether/how much the patient exercises during the study, it is difficult to compare the results of one centre with another and, indeed, one patient with another. There is even disagreement in the literature on the normality or otherwise of some of the features listed in *Table 5*. For example, most sources regard the visualisation of popliteal nodes following a subcutaneous injection of radiotracer into the first interdigital space of the foot as abnormal, suggesting re-routing of lymph from the superficial to the deep system (Szuba et al, 2003; Kramer, 2004). However, Weissleder and Weissleder (1988) described the presence of one to three popliteal nodes in their 'normal' subjects following the subcutaneous injection of tracer into the first and second interdigital spaces in the feet.

Similar appearances may be seen in upper limb studies. The visualisation of epitrochlear nodes is said not to be associated with abnormality (Kramer, 2004), although like with the foot, this may depend upon the site of injection.

Table 3

Lymph transport in various oedemas using two-compartment lymphoscintigraphy

Condition	Lymph transport	
	Epifascial	Subfascial
Cyclic idiopathic oedema	Increased	Increased
Venous oedemas (with patent deep veins)	Increased	Normal
Post-thrombotic syndrome	Increased/normal	Decreased
Post-thrombotic syndrome with lipodermatosclerosis and skin ulceration	Decreased	Decreased
Lipoedema	Normal	Normal
Lymphoedema	Decreased*	Decreased

* In early lymphoedema this may be normal

Table 4

Lymphoscintigraphy protocols

Authors	Tracer	Route	Qualitative	Quantitative	Exercise regimen	Images	Comments
Weissleder and Weissleder, 1988	^{99m}Tc-HSA microcolloid	s.c.	✓	✓	1. Passive electric foot ergometer at 30 cycles per minute for two hours 2. Climb five flights of stairs (150 steps)	1. Dynamic: injection site + regional nodes 2. Static after exercises 1 and 2 3. Uptake by regional nodes as % of administered dose, after exercises 1 and 2	Correction for background, soft tissue thickness and decay
Partsch, 1995	^{99m}Tc-microcolloid	s.c.	–	✓	Horizontal treadmill at 3.2 km/hour for 15 minutes	1. After exercise 2. Lymph node uptake as % of administered dose	Correction for regional absorption/distance between source and detector
Bourgeois et al, 1997	^{99m}Tc-HSA nanocolloid	s.c.	✓	✓	Phase 1: supine — no movement for 30 minutes Phase 2: move feet/toes for five minutes Phase 3: walking one hour	1. Initial over phase 1 (injection sites, inguinal nodes, legs) 2. During and after phase 2 (plus additional images of chest/abdomen if necessary) 3. Walking (phase 3) 4. Extraction at level of injection sites as % injected activity (E) 5. Time-acuity curves of visualised regional nodes	Correction for decay and background 'Normal': first inguinal node visible by 30 minutes; E≥30%
Suga et al, 2001	^{99m}Tc-HSA	i.d.	–	✓	1. Supine 15 minutes 2. Standing 15 minutes	1. Dynamic images during exercises 1 and 2 2. Time activity curves	Standing activates transport in normal lymphatic system but not in lymphoedema
Proby et al, 1990	^{99m}Tc-antimony sulphide colloid	s.c.	–	✓	Normal walking 20 minutes (20–40 minutes after injection)	1. Rate of clearance from site of injection by decay corrected time-activity curves for injection site 2. % uptake in inguinal nodes at one hour and two hours, using time activity curves as % of administered dose	1. Rate of clearance did not confer any additional advantage over % uptake by regional nodes 2. % uptake at two hours gave a more clinically helpful measurement
Ketterings and Zedderman, 1997	^{99m}Tc-nanocolloid	i.d.	✓	✓	'Walk around and return in three hours'	1. One image at three hours (whole body) 2. ROI analysis expressed as total activity counted	1. Liver scanned after injection to detect accidental intravenous injection 2. Patterns of different ROI uptake related to different types of oedema
Tiedjen et al, 2003	^{99m}Tc-nanocolloid	s.c.	✓	✓	Legs: one hour walking Arms: hand grip 30 times per minute for three five-minute periods, separated by five minutes of rest	1. Qualitative 2. Regional node storage rate after exercise	Transport ratio (Q)* caclulated. For legs only: Q < 10 = normal Q > 15 = lymphoedema Q 10–15 = borderline

Key

$$*Q = \frac{100\% \text{ (injected dose)} - \% \text{ flowing from injection depot}}{\% \text{ flowing into the lymph nodes}}$$

HSA = human serum albumin
s.c. = subcutaneous
i.d. = intradermal

Table 5

Features of the lymphatic system demonstrated by qualitative lymphoscintigraphy

- The number and course of lymphatic vessels
- The symmetry and intensity of uptake and number of regional nodes visualised
- The timing of appearance of regional nodes. This may be delayed or faster than normal, or there may be failure to visualise the nodes at all
- The presence of 'dermal backflow', or dermal collateral flow (an abnormal feature)
- The presence of abnormal deep collateral flow, e.g. the appearance of popliteal nodes following a subcutaneous injection of radiotracer into the first interdigital space in the foot
- Malformations and lymphocoeles which connect with the lymphatic system
- 'Extravasation' at tracer sites of lymphatic damage, e.g. following cellulitis
- Thoracic duct obstruction/leaks
- Reflux flow down lymphatic vessels (valvular incompetence)

Source: Bourgeois, 1997; Szuba et al, 2003; Kramer, 2004

Table 6

Sensitivity and specificity for qualitative, quantitative and combined lyphoscintigraphy

Type of study	Sensitivity	Specificity
Qualitative	70–78%	100%
Quantitative	90–98%	83–100%
Combined qualitative and quantitative	66*–100%	83.5–99%

*NB: the study with 66% sensitivity used intradermal labelled albumin as the radiotracer.

Source: Bourgeois, 1997

In addition, there is variation in interpretation of the timing of the appearance of regional nodes. For example, Burnand et al (2003) suggest that it is 'normal' in their centre for radiotracer to reach the inguinal lymph glands following a subcutaneous injection into an interdigital space in the foot in less than 40 minutes. However, Howarth (1997) in a similar situation judges 'normal' to be between 15 and 60 minutes, with delay beyond 60 minutes being considered abnormal, and the appearance of tracer at the inguinal nodes in less than 15 minutes being abnormally rapid (the latter occurring in venous disease and in some cases of lymphoedema for reasons which are not entirely clear). In Howarth's study, immediately after the injection the patient undertook five minutes of exercise using a foot ergometer and then for a further one minute every 10 minutes in the first hour. Again, without standardisation of the exercise regime, it is difficult to compare results in different centres.

It is also clear that early images (up to one hour) alone may give false negative results. In a qualitative study, Larcos and Foster (1995) found that delayed images (2–24 hours post-injection) showed abnormalities (mainly localised dermal backflow but also a lymphocoele) in 32% of their patients with lymphoedema in whom the images taken at one hour had shown normal transit of the tracer and normal appearance of the regional nodes. However, Bourgeois (1997) points out that the half-life ($t^1/_2$) of ^{99m}Tc is relatively short (about six hours) and, therefore, to capture satisfactory results at 24 hours the imaging time has to be lengthened. Finally, the interpretation of images can be affected by the age of the patient, since it is known that lymphatic function declines with age (Burnand et al, 2003).

Many centres image patients undergoing lymphoscintigraphy of the legs from the feet to the diaphragm (the latter to include the liver). However, it has been argued that thoracic imaging should be included as this may demonstrate thoracic duct abnormalities, e.g. mediastinal and retroclavicular nodes, as a result of backflow from the thoracic duct and collateral flow to axillary nodes (Bourgeois, 1997). In arm lymphoscintigraphy, thoracic views may show collaterals such as the Mascagni pathway to the contralateral axilla.

Quantitative lymphoscintigraphy

As suggested above, the use of quantitative studies has been shown to increase the diagnostic sensitivity of lymphoscintigraphy. However, the need for the standardisation of the method and exercise regime is even more important than in qualitative studies to enable the establishment of 'normal' values and define abnormalities. It is also important that any such exercise regimen is manageable for patients whose mobility is limited by their lymphoedema.

Partsch (1995) made the following recommendations:

- A standardised stress test (exercise regimen)
- The use of subcutaneous injection of tracer to study the epifascial compartment (as normal values can be obtained with intradermal injections in lymphoedematous limbs because of the presence of collaterals in the skin)
- The use of intramuscular injections to study subfascial transport.

Partsch also found that: the measurement of clearance rate from the injection site alone does not necessarily distinguish healthy subjects from those with lymphoedema; and the quantification of storage rates (uptake) by the regional nodes is not reliable without taking into account the individual variation in tissue depth (i.e. distance from lymph node to detector).

Sensitivity and specificity

Bourgeois (1997) reviewed the sensitivity (i.e. the percentage of abnormal studies in patients with lymphoedema) and specificity (i.e. the percentage of normal studies in a normal population) of both qualitative, quantitative and combined qualitative and quantitative studies; total of nine studies. The results are summarised in *Table 6*.

Clinical application of lymphoscintigraphy

With the background of the uncertainties of the technique described above, this section will consider the current clinical application of lymphoscintigraphy. Many centres in the UK do not have easy access to the technique and it can be argued that:

- The results of lymphoscintigraphy do not alter the management of patients with lymphoedema. All are treated with decongestive lymphatic therapy (DLT) (a combination of all or some of the following: compression, manual lymphatic drainage [MLD], exercises and skin care)
- The diagnosis is a clinical one, either made from the history and clinical examination (especially of the oedema and associated skin changes or by exclusion), and having investigated other causes (especially venous disease with techniques such as colour Doppler studies)
- Patients with or at risk of developing lymphoedema are advised against having injections into the affected limb, mainly because of the fear of introducing infection or causing further lymphatic damage. Lymphoscintigraphy involves such injections and therefore may be considered to be an unnecessary risk, if it does not help with the diagnosis or management of the patient.

However, on the contrary:

- The diagnosis of lymphoedema is not always obvious, especially in the early stages where skin changes and the subcutaneous deposition of fibrous and adipose tissue have not yet occurred. With the increasing availability of lymphoedema services and awareness of the problem, especially after treatment for cancer, patients are likely to present earlier, so numerically this is likely to be an increasing issue
- Patients with apparently unilateral (often primary) lower limb lymphoedema may have abnormalities in the 'normal' limb which can be demonstrated with lymphoscintigraphy and affect future management
- Preoperative and postoperative lymphoscintigraphy may help to identify patients more likely to develop lymphoedema following treatment for breast cancer (Bourgeois et al, 1998).

Pecking et al (1996), in a quantitative study of 428 women before surgery for breast cancer, found that the 'functional index' (a measure of lymphatic function) was abnormal in 32 (7.5%) patients and of these 27 (84.4%) had developed clinical lymphoedema within 34 months of surgery and radiotherapy. Preoperative imaging could, therefore,

Table 7

Possible features of qualitative lymphoscintigraphy of the lower limb after breast cancer treatment

- Tracer does not reach the level of both forearms in resting conditions (suggesting pre-existing lymphatic insufficiency)
- Subdermal collateralisation (usually after exercise)
- Dermal backflow at the level of the axilla after initial flow through normal distal lymphatic vessels
- Dermal backflow may be limited to one part of the limb
- Flow of tracer may be blocked at the level of the axilla or more distally
- Axillary and/or supraclavicular nodes receive lymph
- Lymphatic collaterilisation pathways are present and naturally opened at the level of the shoulder: from the axilla towards the contra-lateral axilla (Mascagni pathway); from the axilla to the ipsilateral internal mammary nodes; and through the chest wall

N.B. Some of the proximal features, e.g. collateral pathways, may only be demonstrated if additional intradermal injections of tracer are given at the root of the limb.

Source: Bourgeois et al, 1998

affect subsequent management. Indeed, one group uses this to determine whether patients should have prophylactic lymphovenous anastomosis at the time of axillary surgery for breast cancer in an attempt to prevent the development of lymphoedema (Campisi, 2004).

Findings from qualitative lymphoscintigraphy performed after treatment for breast cancer are shown in *Table 7*.

Quantitative studies (e.g. Bourgeois et al, 1998) have suggested three abnormal patterns in patients with breast cancer treatment-related oedema of the arm:

- Low flow (<50% of contralateral arm) — lymphoedema
- High flow (greater than contralateral arm) — predominantly venous oedema
- Flow 50–100% of contralateral arm — mixed venous and lymphatic oedema.

Bourgeois et al (1998) recommend postoperative lymphoscintigraphy in all patients who have had axillary dissection (partial or complete) as part of the treatment for breast cancer, and also in all patients presenting with upper limb lymphoedema after breast cancer treatment. They feel this will influence management, e.g. MLD technique and the possibility of surgical lymphovenous anastomosis.

The diagnosis of lymphoedema by exclusion is not always safe. In a number of situations, a lymphatic component can coexist with other pathologies such as venous insufficiency, so imaging of both systems will be needed to demonstrate the true pathology (Bourgeois, 1997). Raju et al (2001) reported a group of 26 patients with a diagnosis of lymphoedema of the lower limb made on the basis of lymphoscintigraphy alone who received 'conservative therapy' but who then underwent venous investigations, which demonstrated obstruction. Correction of the venous lesion by balloon dilatation and the placement of stents in the iliac veins led to symptomatic relief which included resolution of the swelling and even normalisation or improvement of the lymphoscintigraphic findings.

Lymphoscintigraphy may be a useful preoperative investigation. For example, Vaqueiro et al (1986) reported the value of lymphoscintigraphy in the selection of patients for microvascular procedures (lymphovenous anastomoses), by demonstrating the patency of major lymph channels suitable for anastomosis, which could not be predicted on clinical grounds.

Lymphoscintigraphy may also be used to predict the outcome of treatment. Lee and Bergan (2005) have developed a staging system based upon lymphoscintigraphic findings. They have used this together with a clinical staging, which includes a simple quality of life measure to predict treatment outcome and decide when additional medical or surgical therapy is indicated (*Tables 8 and 9*).

The scores were retrospectively assessed in 220 patients who were followed up for four years. Clinical staging was assessed every six months and lymphoscintigraphic annually (except in those with recurrent sepsis).

Although the relationship between the two different staging systems was not exact, a more advanced lymphoscintigraphic stage was generally accompanied by the compatible/equivalent clinical stage. The lymphoscintigraphic staging seemed to improve the overall predictability of the outcome of treatment. However, the authors suggest that further evaluation of the systems is necessary to demonstrate their clinical usefulness, especially the role of lymphoscintigraphic staging in follow-up.

Szuba et al (2003) also developed a grading system for the lymphoscintigraphic appearances in women with arm oedema following breast cancer therapy and also calculated the ratio of radioactivity within the affected axilla to that in the normal axilla (ARR). They

Table 8

Lymphoscintigraphy staging as derived from Lee and Bergan (2005)

Feature	Grade I	Grade II	Grade III	Grade IV
Degree of lymph node uptake	Decreased	None	None	None
Presence of dermal backflow	None	Present in: a) <half of each limb b) >half of each limb	Present	Poor or no visualisation
Visualisation of collateral lymphatics	Good	Decreased	Poor	None visualised
Visualisation of the main lymphatics	Decreased	Poor to no visualisation	None visualised	None visualised
Clearance of tracer from the injection site	Decreased	Greater decrease	No clearance	No clearance

NB: A minumum of two or more findings are required for staging

Table 9

Clinical staging as derived from Lee and Bergan (2005)

Feature	Grade I	Grade II	Grade III	Grade IV
Oedema	Mild, easily reversible	Moderate, reversible with effort	Moderate to severe, minimally reversible or irreversible	Severe, irreversible
Skin changes	None, no DFS*	None to minimal No DFS	Moderate with DFS	Severe with advanced DFS
Sepsis	None	None to occasional	<4 times per year	≥4 times per year
Limitation of daily activity	None	Occasional and/or moderate	Frequent and significant	Constant and severe
Quality of life	Good with minimal/ occasional limitation	Fair with moderate limitation	Poor with significant limitation	Bad with severe limitation

* dermatofibrosclerosis

NB A minimum of three or more clinical findings are required for clinical staging

found a correlation between the lymphoscintigraphic score and the initial excess volume in the arm and the duration of swelling. The ARR correlated with the percentage reduction in oedema volume following therapy (DLT). They also concluded that lymphoscintigraphy could be used to predict the outcome of treatment. The ARR reflected the residual axillary lymphatic function.

In a small series, Bourgeois et al (2006) have recently described a progression of lymphoscintigraphic changes in patients with lower limb primary lymphoedema, with repeated investigations. The main finding was the apparent involution of regional lymph nodes. Other findings included reduced extraction from the injection site and extension of dermal collateral flow.

Lymphoscintigraphy can also be helpful in filariasis. In a study of filarial lymphoedema (n = 167), lymphoscintigraphy using intradermal ^{99m}Tc-rhenium sulphide (Shelley et al, 2003) showed:

- Flow in multiple channels (100%)
- Dilated and tortuous channels (51%)
- Delayed visualisation of lymph nodes (34%)
- Flow through the deep system (34%)
- Dermal backflow (71%)
- Subclinical lymphoedema (59%).

Summary of main clinical applications

The main clinical applications of lymphoscintigraphy include:

- Differential diagnosis of extremity oedema
- Assessment of the results of therapeutic interventions, e.g. microsurgery, liposuction
- Prediction of outcome of lymphoedema therapy
- Assessment of the risk of development of lymphoedema (Szuba et al, 2003).

In primary lymphoedema, lymphoscintigraphy may be useful in the:

- Demonstration of the level of obstruction and severity of the abnormality
- Identification of involvement of clinically unaffected limbs
- Planning of therapy, e.g. MLD, by identifying the presence and course of collaterals (Kramer, 2004).

The importance of the standardisation of techniques and the use of quantitative analysis should be emphasised, particularly in the demonstration of mild degrees of lymphatic abnormality. It is exactly in this situation that clinical assessment alone may not be able to make the diagnosis.

Wheatley et al (1996) concluded that the combination of qualitative lymphoscintigraphy and colour Doppler sonography was able to ascertain the cause of unexplained limb oedema in 82% of their study population.

The Derby experience

Qualitative lymphoscintigraphy has been used as part of the investigation of patients presenting with chronic oedema in the lymphoedema service in Derby. The main reasons for its use are shown in *Table 10* and the method employed in *Table 11*.

From July 2001 to May 2005, 75 lymphoscintigrams were carried out in Derby (69 lower limb and 6 upper limb). They have been useful in the diagnosis and management of these patients, especially those with primary lymphoedema and, in a number, unexpected results were found. Patients often reported that seeing the images is helpful in understanding their condition.

The examples given in *Figures 1–7* illustrate the results obtained.

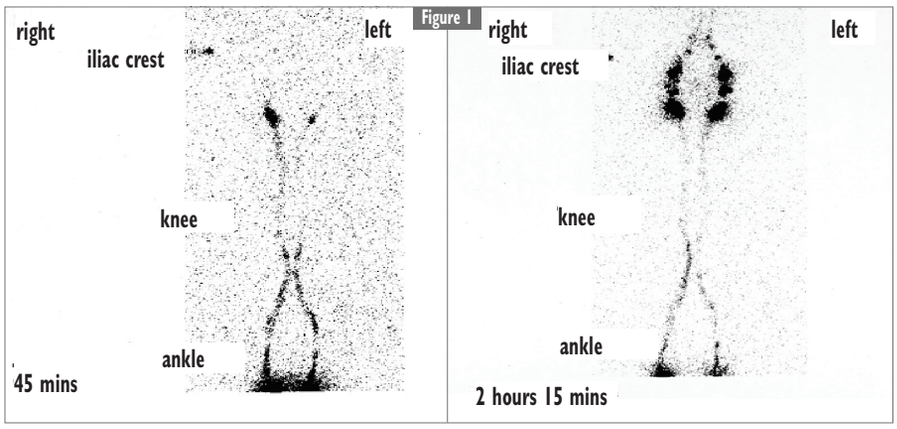

Figure 1. The normal appearance of qualitative lymphoscintigram of lower limbs. Note: appearance of tracer at inguinal nodes by 30–45 minutes; imaging of pelvic nodes and liver in the 2 hour 15 minute scan.

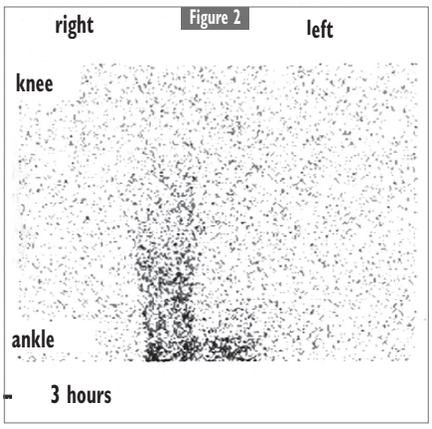

Figure 2. Lymphoscintigram of lower limbs (ankle to knee) in a six-year-old boy with clinical bilateral primary lymphoedema of the lower limbs. The right leg is significantly more swollen than the left; taken at three hours post-injection. Note: dermal backflow on right. There was no flow on the left.

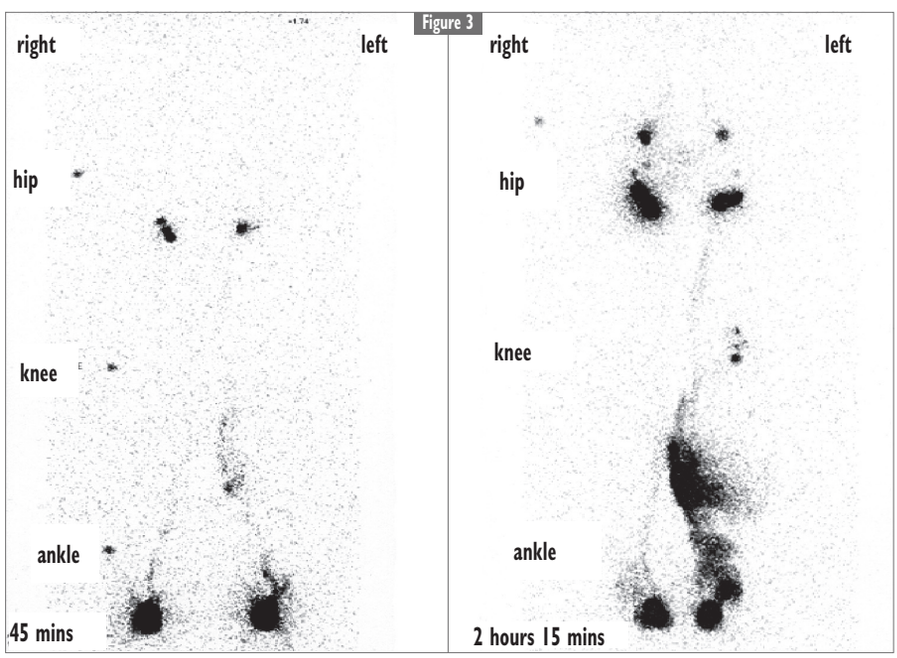

Figure 3. Lymphoscintigram of the lower limbs in a 33-year-old woman with an eight-year history of recurrent cellulitis of the left leg and subsequent swelling in the lower left leg. Clinically there was some right ankle swelling. The Stemmer's sign is negative in both feet. Note: imaging of bilateral inguinal nodes by 45 minutes but the appearance of popliteal nodes and dermal backflow in the left leg at 2 hours 15 minutes. There is also faint dermal backflow in the right foot at 2 hours 15 minutes.

Three years after this lymphoscintigram was carried out, the woman developed cellulitis in the right leg and more overt right leg swelling. At that stage the Stemmer's sign was positive in both feet. It is likely that the patient has an underlying primary lymphoedema.

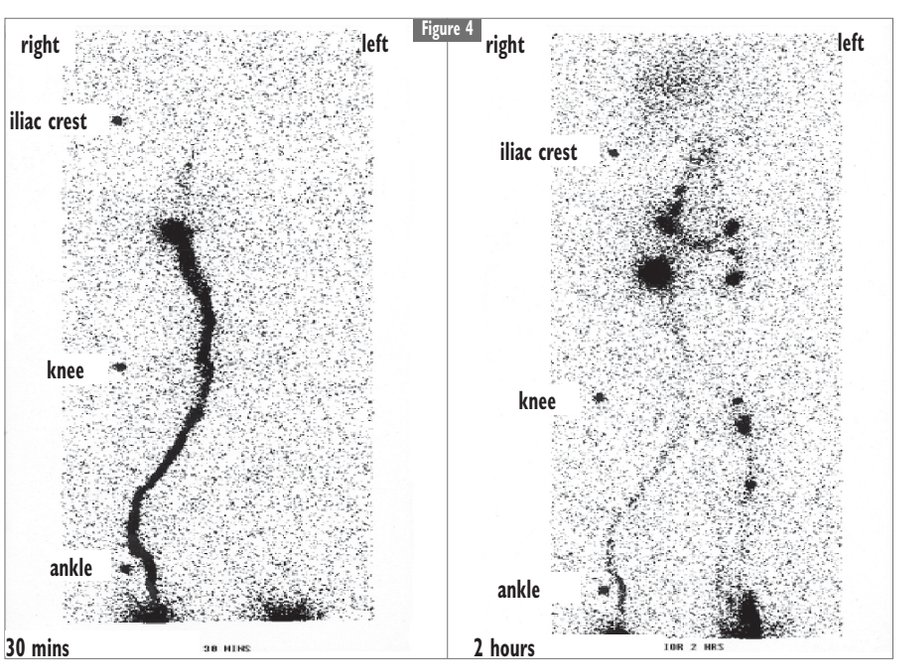

Figure 4. Lymphoscintigram of the lower limbs in a 26-year-old woman with a six-year history of swelling of the left foot. The Stemmer sign is positive on the left. Note: the left leg shows delayed uptake into the inguinal nodes (1 hour 15 minutes) together with popliteal nodes and dermal backflow. The right leg shows rapid filling of what seems to be a dilated lymphatic and a very large inguinal node. Clinically, the patient had primary lymphoedema of the left leg only.

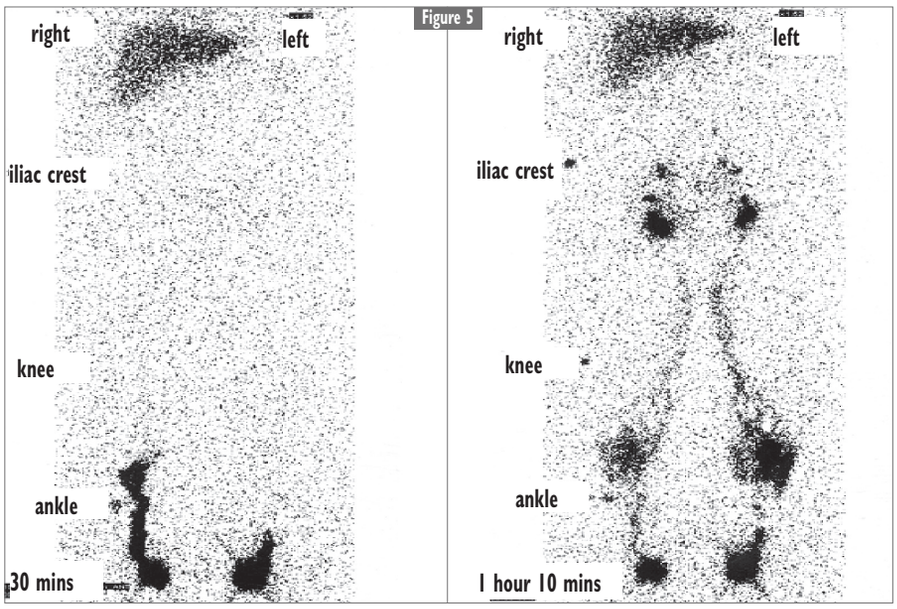

Figure 5. Lymphoscintigram of the lower limbs of a 46-year-old overweight man who presented with a severe cellulitis in the left calf and also subsequent inflammation in the right calf. There may have been a tendency to some ankle swelling before this event. Note: rapid visualisation of the liver, suggesting accidental intravenous injection of some tracer (blood oozed from an injection site). There are appearances of 'extravasation' or dermal backflow in the calves at site of previous cellulitis/ inflammation. These appearances are often seen in patients who have recently had cellulitis.
N.B. A repeat study was done subsequently. This showed no early uptake by the liver, but the appearance of inguinal nodes by 20 minutes and still abnormal tracer distribution in calves, i.e. showed improvement and confirmed that the previous rapid visualisation of the liver was as a result of accidental intravenous injection of tracer.

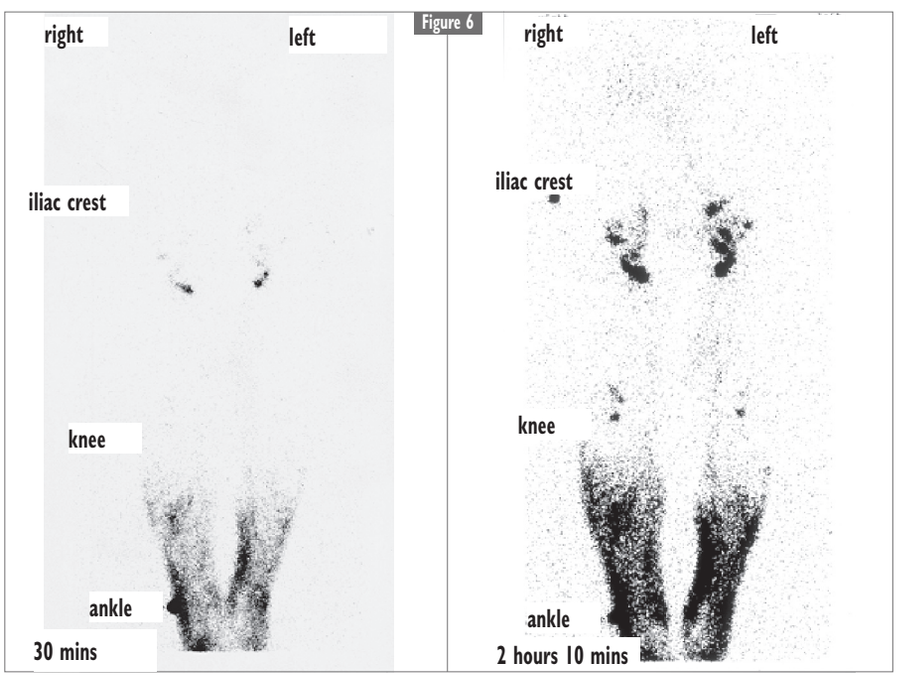

Figure 6. Lymphoscintigram of the lower limbs of a 71-year-old woman with a history of bilateral lymphoedema from the age of 16 years; the right leg was worse than the left. At the time of the study, she had been treated with compression garments (and intermittent bandaging) for about 14 years. Surgery for severe arthritis of the right knee was being considered. Clinically, the swelling of the legs was under reasonable control and she did not have recurrent cellulitis.
Note: visualisation of inguinal nodes by 30 minutes but marked 'dermal backflow' and popliteal nodes bilaterally. It is suggested that the successful compression treatment has encouraged collateral flow of lymph through the skin and deep systems, resulting in 'normal' visualisation of the inguinal nodes.

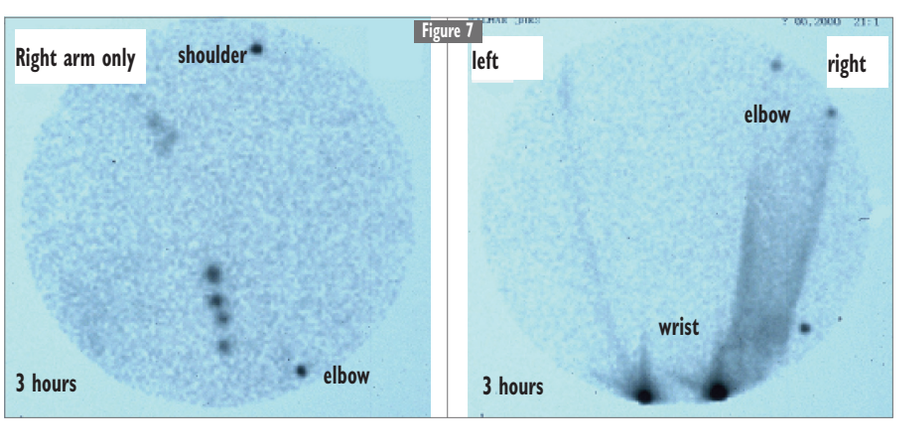

Figure 7. Lymphoscintigram of upper limbs in a 26-year-old woman who developed right forearm swelling after what seemed to be an acute inflammatory episode affecting the forearm. No other limbs were affected. Images at three hour post-injection.
Note: dermal backflow in the right forearm and epitrochlear nodes at the right elbow. It is not clear whether this is a primary or secondary lymphoedema of the forearm.

Table 10

Indications for lymphoscintigraphy in the Derby lymphoedema clinic

- Diagnosis of lower limb oedema of uncertain origin
- Confirmation of the likely clinical diagnosis of primary lymphoedema, particularly in those with apparently unilateral involvement to assess the lymphatic drainage in the 'normal' limb, in all patients with undiagnosed upper limb oedema; and in patients with post-cellulitis lymphoedema to assess lymphatic function of both the affected limb and the apparently unaffected limb (i.e. to determine whether there is evidence of an underlying primary lymphoedema which predisposed to the development of cellulitis)
- Reassessment of patients who initially presented with unilateral leg lymphoedema and later developed bilateral lymphoedema despite previous lymphoscintigraphy which suggested unilateral involvement only
- Assessment of lymphatic function in patients with lymphoedema in whom other surgery is planned, e.g. knee replacement

Table 11

Lymphoscintigraphy of the legs: method used in Derby

- Subcutaneous injection of radiotracer (^{99m}Tc-albumin nanocolloid) usually into the first interdigital space in each foot, injecting the affected limb first in bilateral oedema
- Volume of injection 0.2–0.3 ml
- Dose = approximately 20 MBq per foot
- The lower part of the body is scanned from the liver down to the feet (0–15 minutes). The early scan of the liver is designed to demonstrate early uptake by the liver, which would suggest accidental intravenous injection of tracer (or significant lymphovenous anastomosis). This scan is repeated (at 15–30 minutes)

  After 30 minutes the patient is then asked to walk around for about 30 minutes, although there is no fixed exercise regimen

  Scans are then repeated at half-hourly intervals up to about 2–3 hours depending upon the appearances, i.e. whether regional nodes/liver are visualised

  An external radioactive source is used as a marker for the level of the hips, knees and ankles

N.B. The injections can be painful and patients are warned about this. The dose of radiation received is less than a plain X-ray, e.g. of the chest

Conclusion

In a recent survey of vascular surgeons in the UK, 78% of consultants saw fewer than 10 patients annually with lymphoedema of the leg. Lymphoscintigraphy was used to confirm the diagnosis by 54.5% of the respondents (Tiwari et al, 2006).

In comparison with other European countries, lymphoscintigraphy is not commonly performed in the UK. Despite the uncertainties of the technique, it does have a role to play in the diagnosis and management of patients with chronic oedema, as described above.

Agreement about a standardised approach to the investigation, including standard qualitative and quantitative components, and the indications for its use would facilitate a more appropriate application of this tool.

Other technologies are being developed, including fusion images of lymphoscintigraphy/computerised tomography scans (Pecking, 2005) and interstitial magnetic resonance imaging (MRI) scans, in which a material detectable by MRI is injected subcutaneously and is absorbed into the lymphatics (Ruehm et al, 2001). It is too early to judge where these techniques will fit into the assessment of patients with swollen limbs. In the meantime, lymphoscintigraphy remains an important tool in the diagnosis and management of chronic oedema. JL

References

Bellini C, Boccardo F, Taddei G et al (2005) Diagnostic protocol for lymphoscintigraphy in newborns. *Lymphology* **38(1)**: 9–15

Bourgeois P (1997) Critical analysis of the literature on lymphoscintigraphic investigations of limb edemas. *Eur J Lymphology* **6(21)**: 1–9

Bourgeois P, Leduc O, Leduc A (1998) Imaging techniques in the management and prevention of posttherapeutic upper limb edemas. *Cancer* **83(12 Suppl American)**: 2805–13

Bourgeois P, munck D, Becker C, et al (1997) A three-phase lymphoscintigraphic investigation protocol for the evaluation of lower limb oedemas. *Eur J Lymphology and Related Problems* **6(21)**: 10–21

Bourgeois P, Belgrado JP, Michelini S, et al (2006) Lymphoscintigraphic evolution of primary lower limb lymphedemas: retrospective review of 11 cases. Presented at GEL Congress, Hinterzarten, Germany 12–14 May 2006

Bräutigam P, Földi E, Schaiper I, Krause T, Vanscheidt W, Moser E (1998) Analysis of lymphatic drainage in various forms of leg oedema using two-compartment

lymphoscintigraphy. *Lymphology* **31(2)**: 43–55

Burnand KG, Mortimer PS, Partsch H (2003) Diagnosis and investigation of lymphoedema. In: Browse NL, Burnand KG, Mortimer PS, eds. *Diseases of the Lymphatics*. Arnold, London

Campisi C (2004) Italian Society of Lymphangiology Guidelines. *Eur J Lymphology and Related Problems* **12(40)**: 2–12

Howarth DM (1997) Increased lymphoscintigraphic flow pattern in the lower extremity under evaluation for lymphedema. *Mayo Clin Proc* **72(5)**: 423–9

Ikomi F, Hann GK, Schmid-Schönbein GW (1995) Mechanism of colloidal particle uptake in the lymphatic system: basic study with percutaneous lymphography. *Radiology* **196(1)**: 107–1

International Society of Lymphology (2003) The diagnosis and treatment of peripheral lymphoedema. Consensus Document of the International Society of Lymphology. *Lymphology* **36(2)**: 84–91

Kafejian-Haddad AP, Perez JM, Castiglioni ML, Miranda Junior F, de Figueiredo LF (2006) Lymphoscintigraphic evaluation of manual lymphatic drainage for lower extremity lymphedema. *Lymphology* **39(1)**: 41–8

Ketterings C, Zeddeman S (1997) Use of the C-scan in evaluation of peripheral lymphoedema. *Lymphology* **30(2)**: 49–62

Kramer EL (2004) Lymphoscintigraphy: defining a clinical role. *Lymphat Res Biol* **2(1)**: 32–7

Larcos G, Foster DR (1995) Interpretation of lymphoscintigrams in suspected lymphoedema: contribution of delayed images. *Nuclear Med Comm* **16**: 683–6

Lee BB, Bergan JJ (2005) New clinical and laboratory staging systems to improve management of chronic lymphoedema. *Lymphology* **38(3)**: 122–9

O'Mahony S, Rose SL, Chilvers AJ et al (2004) Finding an optimal method for imaging lymphatic vessels of the upper limb. *Eur J Nucl Med Mol Imaging* **31(4)**: 555–63

Pain SJ, Barber RW, Ballinger JR et al (2004) Local vascular access of radioprotein injected subcutaneously in healthy subjects and patients with breast cancer-related lymphedema. *J Nucl Med* **45(5)**: 789–96

Partsch H (1995) Assessment of abnormal lymph drainage for the diagnosis of lymphoedema by isotopic lymphangiography and by indirect lymphography. *Clin Dermatol* **13(5)**: 445–50

Pecking AP, Floiras JL, Rouessé J (1996) Upper limb lympedema's frequency in patients treated by conservative therapy in breast cancer. *Lymphology* **29(Suppl)**: 293–6

Pecking AP (2005) The fusion of anatomic and functional images: new development in lymphatic imaging. Presented at International Society of Lymphology Congress, Salvador, Brazil: 26 Sept–1 Oct 2005

Proby CM, Gane JN, Joseph AEA, et al (1990) Investigation of the swollen limb with isotope lymphography. *Br J Dermatology* **123**: 29–37

Raju S, Owen S Jr, Neglen P (2001) Reversal of abnormal lymphoscintigraphy after placement of venous stents for correction of associated venous obstruction. *J Vasc Surg* **34(5)**: 779–84

Rosbotham JL, Brice GW, Child AH, Nunan TO, Mortimer PS, Burnand KG (2000) Distichiasis-lymphoedema: clinical features, venous function and lymphoscintigraphy. *Br J Dermatol* **142(1)**: 148–52

Ruehm SG, Schroeder T, Debatin JF (2001) Interstitial MR lymphography with gadoterate meglumine: initial experience in humans. *Radiology* **220(3)**: 816–21

Sener SF, Winchester DJ, Mortz CH et al (2001) Lymphedema after sentinel lymphadenectomy for breast carcinoma. *Cancer* **92(4)**: 748–52

Shelley S, Indironi M, Manokaran G et al (2003) Lymphoscintigraphy in lymphedema — an analysis of 183 cases. Presentation at International Society of Lymphology Congress, Freiburg, Germany: 4–6 September 2003

Società Italiana di Linfangiologia (2006) EBM guidelines on the diagnosis and treatment of lymphoedema. *Eur J Lymphology Related Problems* **16(46)**: 11–21

Stanton AWB, Mellor RH, Cook GJ, Svensson WE, Peters AM (2003) Impairment of lymph drainage in subfascial compartment of forearm in breast cancer-related lymphedema. *Lymphat Res Biol* **1(2)**: 121–32

Suga K, Kume N, Matsunaga N, et al (2001) assessment of leg oedema by dynamic lymphoscintigraphy with intradermal injection of technetium-99m human serum albumin and load produced by standing. *Eur J Nuclear Med* **28(3)**: 294–303

Szczesny G, Olszewski WL, Gorecki A (2005) Lymphoscintigraphic monitoring of the lower limb lymphatic system response to bone fracture and healing. *Lymphat Res Biol* **3(3)**: 137–45

Key Points

- Lymphoscintigraphy is widely considered to be the main investigation to establish the diagnosis of lymphoedema and visualise peripheral lymphatics.
- Different tracers, sites of injection, exercise regimens and imaging times give different results.
- There is no internationally (or nationally) agreed standardised technique for lymphoscintigraphy and so comparisons between results from different centres is difficult.
- Lymphoscintigraphy can be particularly helpful in investigating patients with chronic oedema of uncertain origin and in assessing patients with clinically diagnosed primary lymphoedema.

Szuba A, Shin WS, Strauss W, Rockson S (2003) The third circulation: radionuclide lymphoscintigraphy in the evaluation of lymphedema. *J Nucl Med* **44(1)**: 43–57

Tiedjen KU, Heimann K-D, Knorz S (2003) Chapter 13: Radiological diagnostic procedures in edema of the extremities. In: Földi M, Földi E, Kubik S, eds. *Textbook of Lymphology*. Urgan & Fischer, Munich, Germany: 433–53

Tiwari A, Myint F, Hamilton G (2006) Management of lower limb lymphoedema in the United Kingdom. *Eur J Vasc Endovasc Surg* **31(3)**: 311–15

Vaqueiro M, Gloviczki P, Fisher J, Hollier LH, Schirger A, Wahner HW (1986) Lymphoscintigraphy in lymphedema: an aid to microsurgery. *J Nucl Med* **27(7)**: 1125–30

Weissleder H, Weissleder R (1988) Lymphedema: evaluation of qualitative and quantitative lymphoscintigraphy in 238 patients. *Radiology* **167(3)**: 729–35

Wheatley DC, Wastie ML, Whitaker SC et al (1996) Lymphoscintigraphy and colour Doppler sonography in the assessment of leg oedema of unknown cause. *Br J Radiol* **69(828)**: 1117–24