

## **What you need to know about: Current advances in lymphoedema management**

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### **Conflict of interest**

DF performs lymphoedema surgery, in the private healthcare sector as co-director of the Oxford Lymphoedema Practice at the Manor Hospital, Oxford.

### **Abstract**

Lymphoedema is the accumulation of protein rich interstitial fluid within subcutaneous tissue and skin due to dysfunction of the lymphatic system. It is an underestimated and widely neglected chronic debilitating condition. This article presents an overview of lymphoedema and recent advances in its management.

### **Keywords**

Lymphoedema, lymphatic vessels, lymphaticovenous anastomoses, lymph node transfer, liposuction

## **Introduction**

Lymphoedema is the accumulation of protein rich interstitial fluid within subcutaneous tissue and skin due to dysfunction of the lymphatic system. It is a chronic condition without cure. Despite affecting at least 200,000-420,000 people in the United Kingdom, this health problem remains widely unrecognised (Moffatt et al, 2016; Thomas and Morgan, 2017). Lymphoedema is associated with significant physical, functional and psychological morbidity affecting a person's quality of life. It also has wide-ranging financial implications not only to individuals, but also an economic burden on healthcare systems (The National Lymphoedema Partnership, 2019).

This article presents an overview of lymphoedema and focuses on recent advances in its management.

## **Presentation**

Lymphoedema most commonly affects the limbs but can affect any part of the body. It can be classified as primary when there is an intrinsic defect in the lymphatic system, or secondary arising from damage to a normally developed lymphatic system (**Table 1**). The lymphatic system consists of lymph vessels and nodes. The lymphatic system plays a key role in tissue fluid homeostasis, immune cell surveillance and trafficking, and lipid absorption.

Filarial infection is the commonest cause worldwide with approximately 120 million cases. It leads to inflammation and fibrosis of the lymphatic system (Taylor et al, 2010). In the developed world secondary lymphoedema is usually associated with cancer treatment, such as lymph node dissection surgery or radiotherapy. The lymphatic system can also be damaged as a result of infiltration by the cancer itself. Rarely, lymphoedema is caused by trauma or infection.

An aging and growing population, together with a significant improvement in cancer survival, means more patients are facing the sequelae of cancer treatment such as lymphoedema. For example, breast cancer is the commonest cancer in women worldwide and accounted for 15% of all new cancer cases in the United Kingdom in 2015 (Cancer Research UK). Breast cancer related lymphoedema (BCRL) is estimated to affect 21% of patients treated for breast cancer (DiSipio et al, 2013).

A thorough history will help differentiate the causes of lymphoedema (**Table 2**) and highlight any risk factors for developing the condition (**Table 3**). For example, primary lymphoedema almost always affects children with adult onset being uncommon. In addition, clinical examination helps assess severity (**Table 4**).

**Table 1** Causes of lymphoedema

## Primary (rare)

## Secondary

- Cancer treatment
  - Radiotherapy
  - Lymph node surgery
- Infection
- Trauma
- Surgery
- Body mass index > 50

**Table 3** Lymphoedema risk factors

- Age
- Morbid obesity
- Cancer and its treatment
- Infection
- Trauma
- Low physical activity

**Table 2** History associated with lymphoedema

- Age of onset
- Symptoms
  - Discomfort, heaviness
  - Duration, stable/worsening
- Cancer history
  - Lymph node surgery
    - Number of nodes dissected
    - Number of metastatic nodes
  - Radiotherapy
  - Chemotherapy
- Travel to areas endemic for filariasis
- Genetic conditions associated with lymphoedema such as Turner syndrome and Noonan syndrome
- Progressive enlargement of area
- Complications
  - Cellulitis, infection,
  - Lymphorrhoea, lymphostatic blisters
- Family history
- Depression, social isolation, frustration

Lymphoedema worsens over time regardless of the cause. Lymphatic stasis leads to inflammation, lipogenesis, fat deposition and fibrosis. These pathological processes correspond to clinical stages of lymphoedema (**Table 5**). The relationship between the staging of lymphoedema and the macroscopic anatomical findings in collecting lymphatic vessels is well demonstrated by Mihara et al (2012a) and illustrated in **Figure 1**.

**Table 4** Physical examination findings associated with lymphoedema

- Limbs most commonly affected
- Oedema (pitting or non-pitting; see **Table 5**)
- Positive Stemmer's sign is inability to pinch a fold of skin at base of second toe or in a finger
- Circumferential (not axial) overgrowth
- Scars from lymph node surgery (axilla or inguinal)
- Skin changes (hyperkeratosis, acanthosis, warts)
- Lymphatic vesicles or lymphorrhea
- Body mass index > 50

**Table 5** International Society of Lymphology staging of lymphoedema (2016)

- 0 Subclinical lymphoedema without oedema but evidence of impaired lymphatic function. This can exist months or years before overt oedema occurs.
- 1 Reversible pitting oedema. No palpable fibrosis.
- 2a Pitting oedema that is not reduced by elevation.
- 2b Non-pitting oedema secondary to pronounced fibrosis.
- 3 Lymphostatic elephantiasis. Progressive fibrosis, acanthosis (hyperpigmentation), hyperkeratosis and papillomatosis (warty growths).

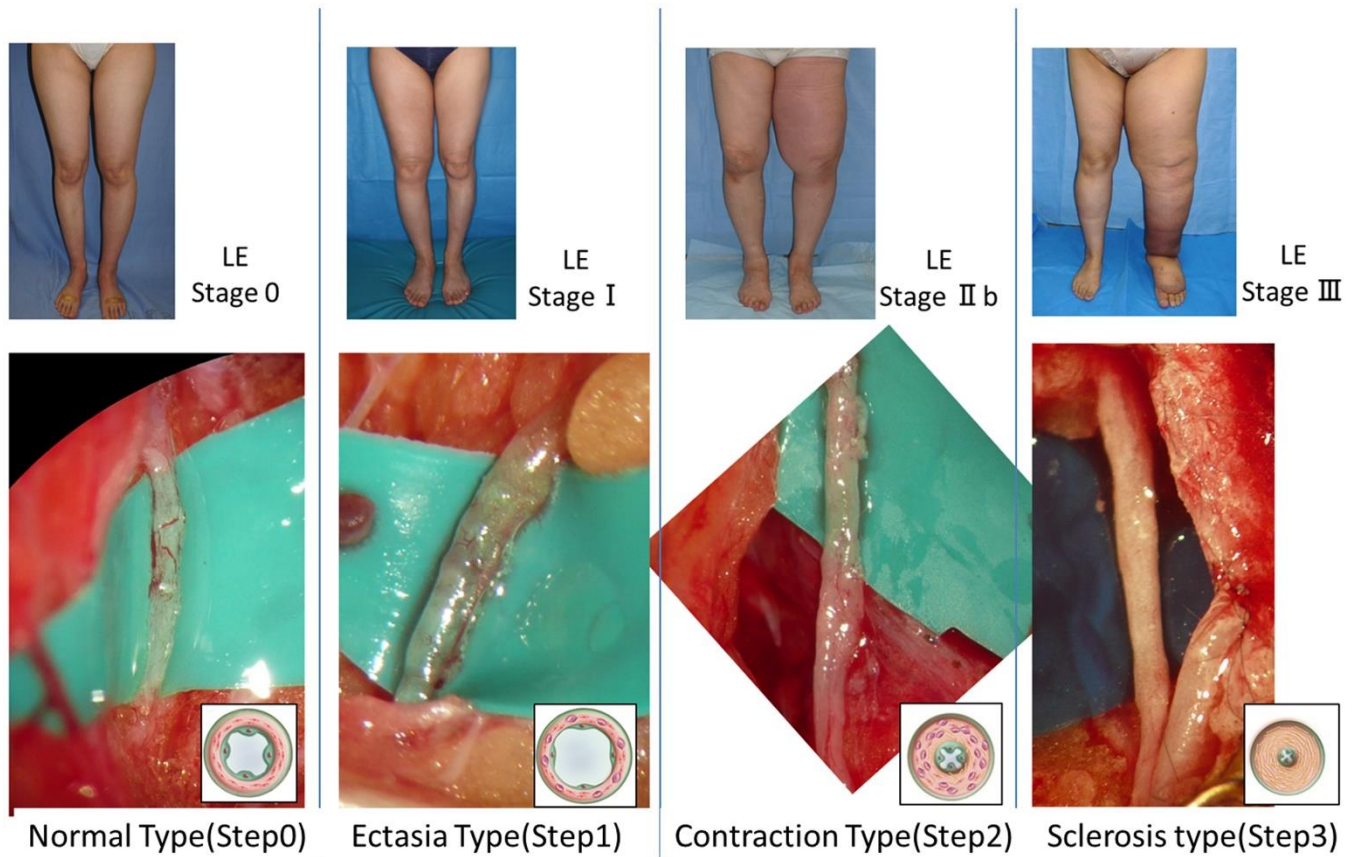
The British Lymphology Society also recognises different groups affected by lymphoedema (**Table 6**). and has described differing needs in their guidelines (**Table 7**; British Lymphology Society, 2016).

**Table 6** British Lymphology Society (2016) recognises different types of lymphoedema:

- At risk or latent lymphoedema
- Mild oedema of a limb or limbs
- Moderate oedema of a limb or limbs
- Complex, resistant, severe oedema
- Lymphoedema due to advanced cancer and oedema at the end of life

**Table 7** British Lymphology Society (2016) describes a minimum lymphoedema plan of care appropriate to needs, lifestyle, abilities and self-goals:

- Education, verbal and written information about:
  - Causes of swelling and risk factors that may exacerbate the swelling
  - Skin hygiene and moisturising, avoidance of trauma, sunburn, insect bites
  - What to do if cellulitis develops
  - Normal use of limb, aerobic exercises or graded exercise regimes
- Provision of compression garments and/or Velcro wraps if appropriate
  - Use and care of compression garments and Velcro wraps
  - Application and removal techniques for compression garments and Velcro wraps
  - Evaluation of garment / Velcro wrap effectiveness
- Weight management advice
- Teaching of firm self-massage techniques
- Referral to appropriate specialists where indicated such as medical specialties, oncology, dermatology, psychology, nutrition, occupational therapy, physiotherapy, lymphoedema, palliative care, podiatry, plastic surgery
- What to do and who to contact if condition deteriorates
- Information on where and how to access further information and support



**Figure 1** Staging of lymphedema and the macroscopic anatomical findings in the collecting lymphatic vessels associated with the stages. Reproduced with permission from Mihara et al (2012a) under CC BY:

*In the normal type, microvascular networks were found to nourish the largely developed walls of the collecting lymphatic vessels. The microvascular networks were gradually lost with the progression of the disease stages. In addition, the lymphatic vessel lumen was found to be dilated in the ectasia type, which was associated with an increase in endolymphatic pressure. Because increases in smooth muscle cells and collagen fibers are the major causes of the cloudiness and thickening of the lymphatic vessel wall, they were found to be prominent in the contraction type and the sclerosis type.*

## **Imaging**

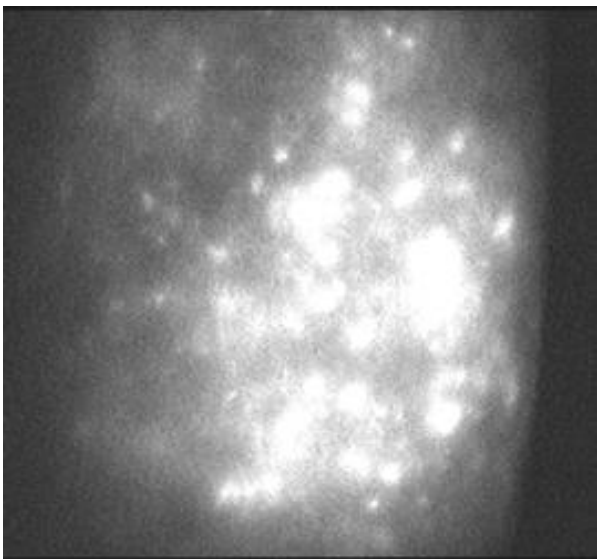
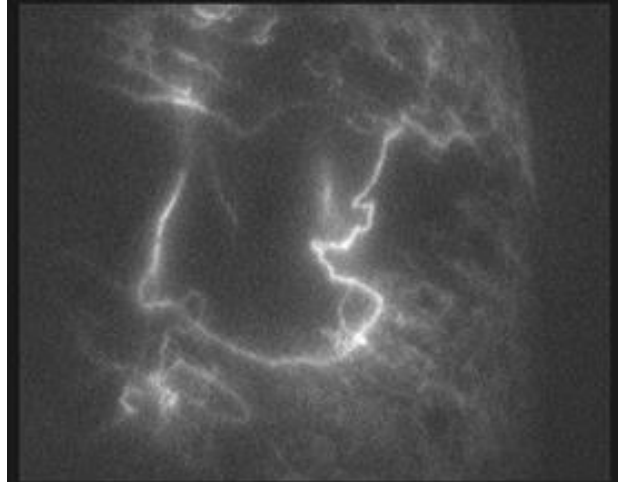
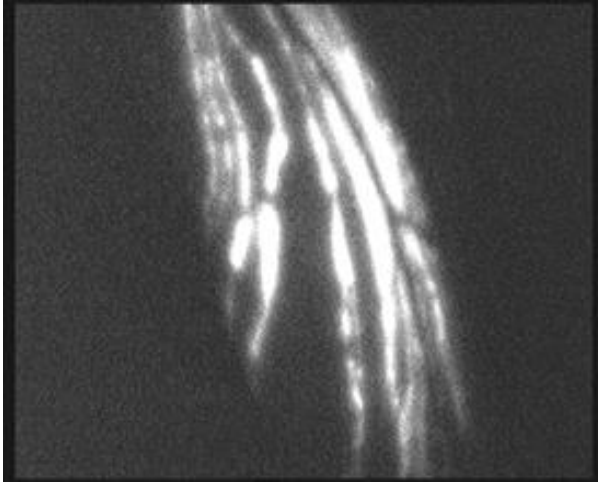
Lymphatic imaging is rapidly advancing and is a key aspect of assessment for surgical management. Lymphoscintigraphy is widely readily available and has been used for many years. This technique involves subdermal injection of Technitium-99 prior to scanning (Partsch II, 2003). This radioisotope is preferentially taken up by the lymphatic system and can help visualise the drainage of the lymph proximally to the draining lymph node basins. Abnormalities or obstruction of the lymphatic system may present as delayed transit time of the radioisotope to the lymph node basins, dermal backflow, reduced number of lymph channels, asymmetric node uptake and/or formation of collateral lymphatic channels.

Although this commonly used imaging modality has a very high reported (Hassanein et al, 2017) sensitivity (96%) and specificity (100%), disadvantages include poor resolution and being a time-consuming procedure, which only provides a static set of images at a given time point. As such, for assessment and surgical planning more useful imaging methods have been developed including indocyanine green (ICG) lymphangiography and magnetic resonance lymphangiography (MRL).

ICG lymphangiography is the gold standard for identifying functional lymphatic channels. It allows real time fluorescent visualisation of subdermal lymphatic flow using a near infrared camera. It is the single most useful investigation for planning lymphatic surgery. Different patterns of ICG can be used to grade lymphoedema severity (**Figure 2**). Linear patterns are normal whereas splash, stardust and diffuse patterns reflect increasing levels of lymphatic vessel fibrosis and lymphoedema severity.

More recently, MRL has been developed to provide much higher resolution imaging of the lymphatic system with the added benefit of characterising the soft tissues such as fat and the degree of oedema and fibrosis (Mitsumori et al, 2015). Various protocols have been described to differentiate between the venous and lymphatic system such as using intravenous injection of ferumoxytol to suppress the veins (Maki et al, 2016), but MRL has yet to gain widespread acceptance and use.

**Figure 2** Indocyanine green lymphangiography images showing linear (top left), splash (top right), stardust (bottom left) and diffuse (bottom right) patterns.





## **Nonsurgical Management**

Lymphoedema is traditionally managed conservatively with complete decongestive therapy (CDT), which consists of four components including manual lymphatic drainage, skin care, compression and remedial exercises (Foldi, 1998). The latter are specific exercises encouraging muscle contraction to increase pressure on the lymph vessels and facilitate their movement away from the affected area. CDT initially focuses on volume reduction and requires regular involvement of lymphoedema therapists to perform the above components whilst also educating patients. This then transitions to phase two, which focuses on maintenance with an emphasis on patient-directed care. CDT is the standard treatment for lymphoedema with evidence supporting its effectiveness (Lasinski et al, 2012). However, the current evidence is contradictory as to the effectiveness of CDT compared to one or more of its individual components (McNeely et al, 2004; Mondry et al, 2004; Dayes et al, 2013; Javid and Anderson, 2013; Buragadda et al, 2015; Zhang et al, 2016). There is no evidence to support the use of pharmacological agents for treating or preventing lymphoedema (Chang et al, 2016).

It is important to remember the importance of providing psychological support to individuals and their families (British Lymphology Society, 2016) as lymphoedema can cause significant physical and psychological distress impacting on activities of daily living.

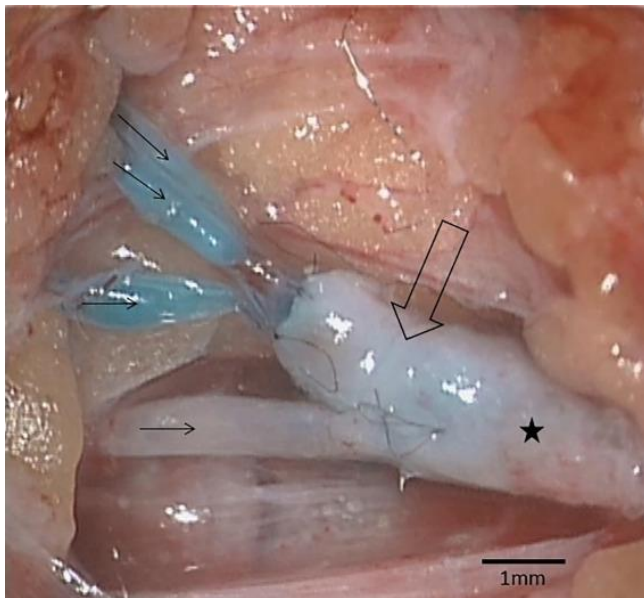
## **Surgical Management**

Historically, various debulking procedures were used to remove tissue affected by lymphoedema such as the Charles procedure (Charles, 1912) and its subsequent modification by Homans (1936). These procedures are now historic. Modern surgical approaches can be categorised as reductive or physiological.

The main reductive technique is liposuction, which has been popularised by Hakan Brorson. Liposuction is indicated in late stage lymphoedema patients with significant volume excess due to hypertrophied adipose tissue. Subsequent lifelong use of compression garments for 24 hours a day is mandatory for preventing recurrence (Schaverien et al, 2018). Long-term favourable and reproducible results have been reported (Damstra et al, 2009; Schaverien et al, 2012; Boyages et al, 2015; Brorson 2015a, 2015b; Lamprou et al, 2017; Stewart and Munnoch, 2017).

The main physiological techniques include lymphaticovenous anastomosis (LVA) and vascularised lymph node transfer (VLNT). These aim to improve lymphatic circulation by augmenting its clearance.

O'Brien et al (1977) popularised the concept of LVAs, which involve anastomosing lymphatic channels to veins thereby providing a physiological bypass of the disrupted lymphatic system. The improvement of microsurgical equipment has allowed the development of supermicrosurgery techniques to anastomose vessels ranging from 0.3 to 0.8mm. Koshima et al (2000) were the first to report using supermicrosurgery to anastomose tiny subdermal lymphatics and venules. They hypothesised that minimal backflow would occur across these superficial connections particularly when the lymphatic pressure is raised in lymphoedema. Numerous LVA techniques and variations have been described such as end-to-end, end-to-side, side-to-end and lambda-shaped (Mihara et al, 2012b; Yamamoto et al, 2013; **Figures 3-4**).



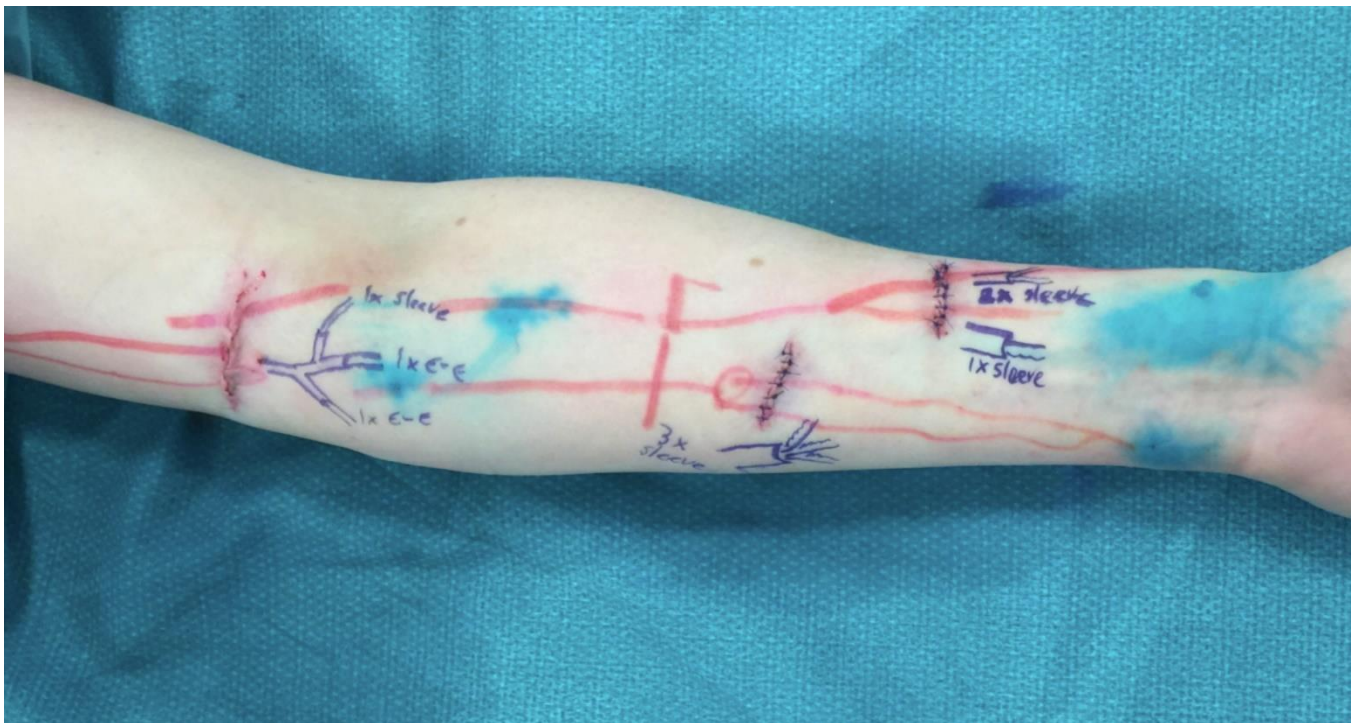
**Figure 3** A peripheral sleeve and an end-to-side lymphaticovenous anastomosis. Reproduced with permission from Sharkey et al (2016).

*At a peripheral site in the limb, several small lymphatics marked by patent blue staining of the lymphatic fluid and filled arrows have been parachuted inside a vein (asterisk), and an additional lymphatic marked by a filled arrow but no patent blue staining has been anastomosed onto the same vein in an end to side fashion. Flow of lymphatic fluid into the venous system is demonstrated by blue staining inside the vein (unfilled arrow).*



**Figure 4** End to end lymphaticovenous anastomosis.

LVAs are indicated when they are still some functional lymph channels. ICG lymphography is therefore important for preoperative assessment to identify potential candidates for LVA surgery (**Figure 5**). In appropriately selected patients, LVAs have demonstrated objective and subjective improvements in most patients (Leung et al, 2015; Scaglioni et al, 2017). LVAs have promising potential and their reproducible results has led it to be considered one of the gold standard treatments for lymphoedema (Chang et al, 2018). Despite the significant improvements reported, LVAs do not cure lymphoedema, though patients who no longer suffer from swelling and do not need to wear compression garments may consider themselves cured.



**Figure 5** Lymphatic channels identified preoperatively (red lines) with indocyanine green lymphography. Three transverse incisions were subsequently used under a local anaesthetic in the left forearm to perform 9 lymphaticovenous anastomoses: 3 proximal (1x sleeve, 2x end-to-end), 3 middle (3x sleeve) and 3 distal (3x sleeve). Note the blue staining of the skin, which is from the use of patent blue intraoperatively to more easily visualise the lymphatic channels identified preoperatively.

LVAs have also been used as a prophylactic procedure performed at the same time as axillary lymph node dissection (Boccardo et al, 2009) to prevent the development of BCRL. This Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) has demonstrated significant results (Jorgensen et al, 2018). In a randomised study of 46 patients, Boccardo et al (2011) found this approach reduced the incidence of BCRL from 30.4% to 4.3% at 18 months follow up (number needed to treat ~4). These

findings have been reinforced with longer follow-up at 4 years (Boccardo et al, 2014). Although these results are promising, questions still remain regarding the long-term LVA patency, particularly with regard to the effect of radiation and chemotherapy. LYMPHA is not currently offered in the UK National Health Service.

VLNT involves microvascular transfer of lymph nodes harvested from a donor site as a free flap to the affected limb. The functional mechanism of this procedure is unclear. One theory is that the VLNT acts as a pump to return the lymphatic fluid into the systemic circulation. The other main theory is that it induces lymphangiogenesis. Various donor sites have been described including groin, thoracic, submental, supraclavicular and omentum. To reduce the risk of donor iatrogenic lymphoedema, reverse lymphatic mapping techniques have been described to avoid harvesting important sentinel nodes in the groin or axilla (Chang et al, 2016). Similarly, the use of the neck lymph nodes has been advocated to minimise lymphatic impairment. Although initial reports are promising, there is currently a low level of evidence to support this technique and long-term well-designed studies are required.

### **Outcomes**

There is no gold standard for monitoring or assessing outcomes of lymphoedema management. Various methods are used including circumference measurements, water displacement, tissue tonometry, perometry and bioimpedance spectroscopy. Tonometry measures the amount of force required to make an indent in the tissue, which relates to the degree of fibrosis. Perometry uses infrared light to measure overall limb volume. Bioimpedance spectroscopy determines the amount of extracellular fluid by measuring resistance of the body's fluid to the flow of electrical current.

LYMQOL is a validated quality of life assessment tool for limb lymphoedema, which is useful for clinical assessment and as an outcome measure (Keeley et al, 2010). It is a self-report questionnaire covering 4 domains including function, appearance, symptoms and mood, as well as an overall quality of life score.

### **Conclusion**

The management of lymphoedema is complex and rapidly evolving. Further research is required and a recent collaborative approach using the James Lind Alliance's methodology is the first to attempt to systematically identify research priorities for lymphoedema management (Underwood et al, 2019).

**Key points**

- Lymphoedema is an underestimated and widely neglected chronic debilitating condition.
- Complete decongestive therapy has been the mainstay treatment of lymphoedema, however, modern surgical treatments offer the opportunity to reduce morbidity.
- LVAs and liposuction are the most established surgical treatments.
- ICG lymphangiography is the gold standard for identifying functional lymphatic channels and is a key investigation for planning lymphatic surgery.
- Effective lymphoedema management will likely involve a combination of non-surgical and surgical modalities.

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