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Current advances in lymphoedema management

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Abstract

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

Key words: Liposuction; Lymph node transfer; Lymphatic vessels; Lymphaticovenous anastomoses; Lymphoedema

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Introduction

Lymphoedema is the accumulation of protein-rich interstitial fluid within subcutaneous tissue and skin as a result of dysfunction of the lymphatic system. It is a chronic condition without a cure. Despite affecting at least 200 000–420 000 people in the UK, this health problem remains widely unrecognised (Moffatt et al, 2017; 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 for individuals, but also the economic burden on healthcare systems (The National Lymphoedema Partnership, 2019). This article gives an overview of lymphoedema, focusing 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, and plays a key role in tissue fluid homeostasis, immune cell surveillance and trafficking, and lipid absorption.

Filarial infection is the most common cause of lymphoedema 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 ageing and expanding population, together with a significant improvement in cancer survival, means more patients are facing the sequelae of cancer treatment such as

Table 1. Causes of lymphoedema

Primary (rare)		
Secondary	Cancer treatment	Radiotherapy
		Lymph node surgery
	Infection	
	Trauma	
	Surgery	
	Body mass index >50 kg/m^2	

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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 or Noonan syndrome		
Progressive enlargement of area affected by lymphoedema		
Complications	Cellulitis, infection	
	Lymphorrhoea, lymphostatic blisters	
Family history		
Depression, social isolation, frustration		

Table 3. Risk factors for development of lymphoedema

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

lymphoedema. For example, breast cancer is the most common cancer in women worldwide and accounted for 15% of all new cancer cases in UK in 2015 (Cancer Research UK, 2020). Breast cancer-related lymphoedema is estimated to affect 21% of patients treated for breast cancer (DiSipio et al, 2013).

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

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.

The British Lymphology Society recognises different groups affected by lymphoedema (Table 6). They have also described a minimum lymphoedema plan (Table 7; British Lymphology Society, 2016) with further management dictated by the differing presentation, severity and functional detriment of the lymphoedema.

Imaging

Lymphatic imaging is rapidly advancing and is a key aspect of assessment for surgical management. Lymphoscintigraphy is widely available and has been used for many years.

Table 4. Physical examination findings associated with lymphoedema
Limbs most commonly affected
Oedema (pitting or non-pitting; Table 5)
Positive Stemmer's sign (inability to pinch a fold of skin at base of second toe or a finger)
Circumferential (not axial) overgrowth
Scars from lymph node surgery (axilla or inguinal)
Skin changes (hyperkeratosis, acanthosis, warts)
Lymphatic vesicles or lymphorrhoea
Body mass index >50 kg/m^2

Table 5. International Society of Lymphology staging of lymphoedema

Stage	Symptoms
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)

From Executive Committee (2016)

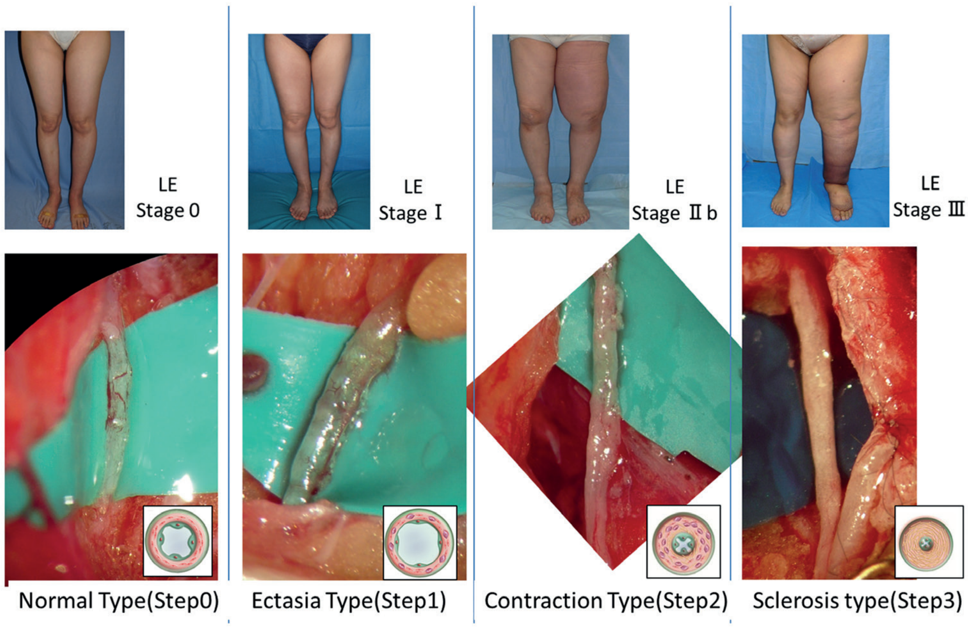

Figure 1. Staging of lymphoedema (LE) and the macroscopic anatomical findings in the collecting lymphatic vessels associated with the stages. In the normal type (stage 0), microvascular networks were found to nourish the largely developed walls of the collecting lymphatic vessels. The microvascular networks were gradually lost with the progression of the disease stages. In addition, the lymphatic vessel lumen was found to be dilated in the ectasis type, which was associated with an increase in endolymphatic pressure. Because increases in smooth muscle cells and collagen fibres 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. From Mihara et al (2012a). (https://doi.org/10.1371/journal.pone.0041126.g002)

Table 6. 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 as a result of advanced cancer and oedema at the end of life

From British Lymphology Society (2016)

Table 7. 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 regimens
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	

From British Lymphology Society (2016)

This technique involves subdermal injection of technetium-99m before scanning (Partsch, 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 sensitivity (96%) and specificity (100%)(Hassanein et al, 2017), 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, more useful imaging methods for assessment and surgical planning have been developed, including indocyanine green lymphangiography and magnetic resonance lymphangiography.

Indocyanine green lymphangiography

Indocyanine green lymphangiography is the gold standard for identifying functional lymphatic channels. It allows real-time fluorescent visualisation of subdermal lymphatic flow using a near infra-red camera and is the single most useful investigation for planning lymphatic surgery. Different patterns of indocyanine green 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.

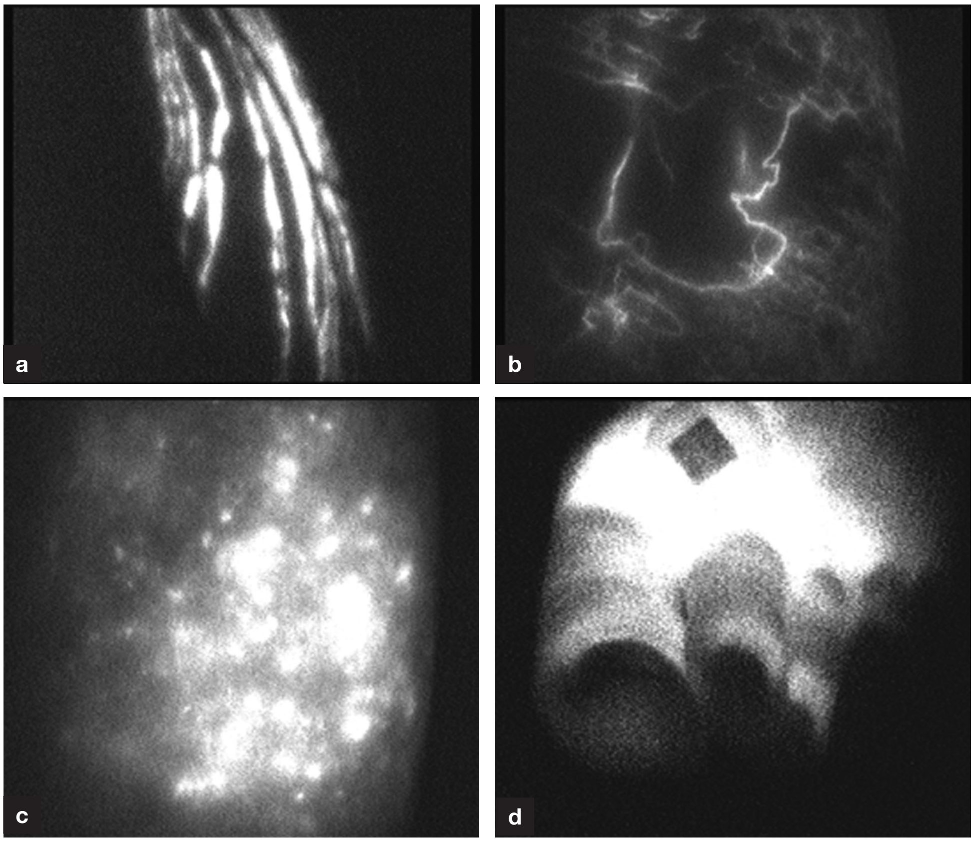

Figure 2. Indocyanine green lymphangiography images showing (a) linear, (b) splash, (c) stardust and (d) diffuse patterns.

Magnetic resonance lymphangiography

More recently, magnetic resonance lymphangiography 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 magnetic resonance lymphangiography has yet to gain widespread acceptance and use.

Non-surgical management

Lymphoedema is traditionally managed conservatively with complete decongestive therapy, which consists of 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 movement of lymph away from the affected area. Complete decongestive therapy initially focuses on volume reduction and requires regular involvement of lymphoedema therapists to perform the above components while also educating patients. This then transitions to phase two, which focuses on maintenance with an emphasis on patient-directed care. Complete decongestive therapy is the standard treatment for lymphoedema with evidence supporting its effectiveness (Lasinski et al, 2012), although the evidence is contradictory as to how the effectiveness of complete decongestive therapy compares to that of one or more of its individual components (McNeely et al, 2004; Dayes et al, 2013; Javid and Anderson, 2013; 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 provide 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.

Reductive approaches

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 as a result of 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; Brorson, 2015a, b; Lamprou et al, 2017).

Physiological approaches

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

O'Brien et al (1977) popularised the concept of lymphaticovenous anastomoses, which involve anastomosing lymphatic channels to veins, thereby providing a physiological bypass of the disrupted lymphatic system. Improvements of microsurgical equipment have allowed the development of supermicrosurgery techniques to anastomose vessels ranging from 0.3 to 0.8 mm diameter. 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 lymphaticovenous anastomosis 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** and **4**).

Lymphaticovenous anastomoses are indicated when there are still some functional lymph channels. Indocyanine green lymphography is therefore important for preoperative assessment to identify potential candidates for lymphaticovenous anastomosis surgery (**Figure 5**). In appropriately selected patients, lymphaticovenous anastomoses have demonstrated objective and subjective improvements (Leung et al, 2015; Scaglioni et al, 2017). Lymphaticovenous anastomoses have promising potential, and reproducible results have led this procedure to be considered one of the gold standard treatments for lymphoedema (Chang et al, 2018).

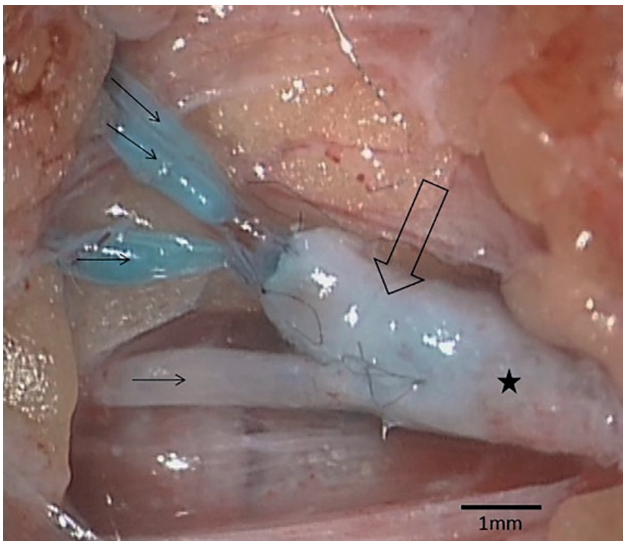

Figure 3. A peripheral sleeve and an end-to-side lymphaticovenous anastomosis. At a peripheral site in the limb, several small lymphatics marked by patent blue staining of the lymphatic fluid and filled arrows have been parachuted inside a vein (asterisk), and an additional lymphatic marked by a filled 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).

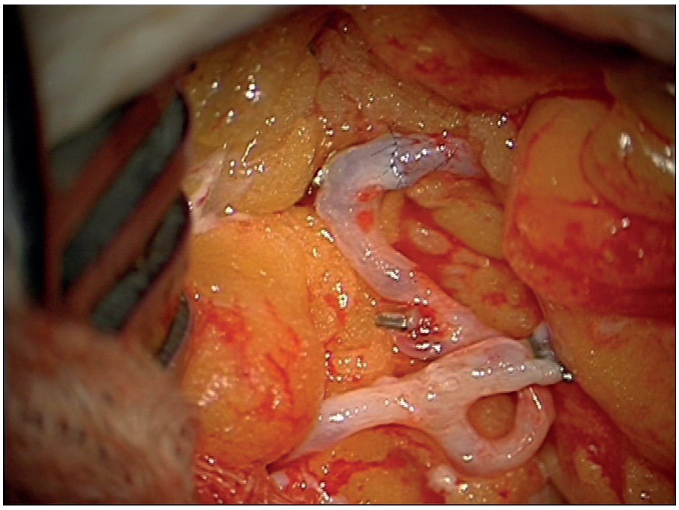

Figure 4. End to end lymphaticovenous anastomosis

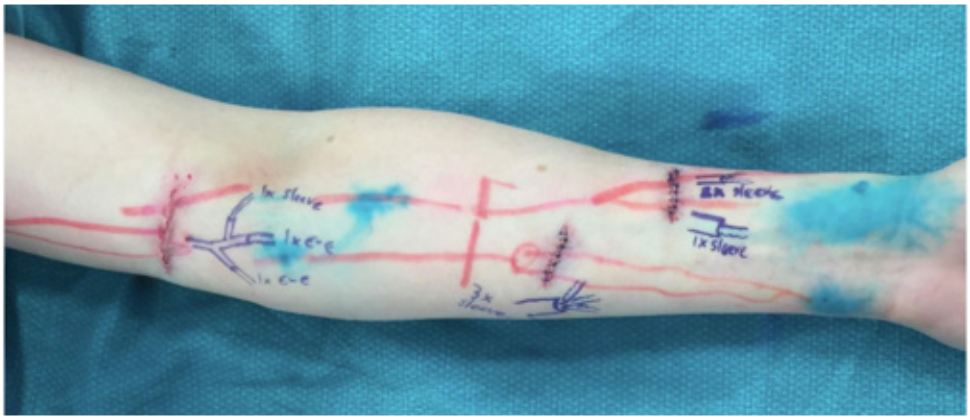

Figure 5. Lymphatic channels identified preoperatively (red lines) with indocyanine green lymphography. Three transverse incisions were subsequently used under a local anaesthetic in the left forearm to perform nine lymphaticovenous anastomoses: three proximal (one sleeve, two end-to-end), three middle (three sleeve) and three distal (three 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.

Despite the significant improvements reported, lymphaticovenous anastomoses do not cure lymphoedema, although patients who no longer suffer from swelling and do not need to wear compression garments may consider themselves cured.

Lymphaticovenous anastomoses 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 breast cancer-related lymphoedema. This lymphatic microsurgical preventive healing approach has demonstrated significant results (Jørgensen et al, 2018). In a randomised study of 46 patients, Boccardo et al (2011) found this approach reduced the incidence of breast cancer-related lymphoedema 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 patency of the lymphaticovenous anastomosis, particularly with regard to the effect of radiation and chemotherapy. The lymphatic microsurgical preventive healing approach is not currently offered on the NHS.

Vascularised lymph node transfer 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 vascularised lymph node transfer 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

Key points

- Lymphoedema is an underestimated and widely neglected chronic debilitating condition.
- Complete decongestive therapy has been the mainstay treatment of lymphoedema, but modern surgical treatments offer the opportunity to reduce morbidity.
- Lymphaticovenous anastomoses and liposuction are the most established surgical treatments.
- Indocyanine green 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.

Curriculum checklist

This article addresses the following requirements from the plastic surgery curriculum

- Should demonstrate knowledge of lymphoedema including surgical management
- Understands principles of microsurgery.

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 neck lymph nodes has been advocated to minimise lymphatic impairment. Although initial reports are promising, there is 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 four domains (function, appearance, symptoms and mood), as well as an overall quality of life score.

Conclusions

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.

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Conflicts of interest

DF performs lymphoedema surgery in the private healthcare sector as co-director of the Oxford Lymphoedema Practice at the Manor Hospital, Oxford. KYW declares no conflicts of interest.

Acknowledgement
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