

Feasibility study of combined dynamic imaging and lymphaticovenous anastomosis surgery for breast cancer-related lymphoedema

A. A. Khan¹, I. Hernan², J. A. Adamthwaite² and K. W. D. Ramsey²

¹Institute of Cancer Research and ²Department of Plastic and Reconstructive Surgery, Royal Marsden Hospital, London, UK

Correspondence to: Mr K. W. D. Ramsey, Department of Plastic Surgery, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK (e-mail: kelvin.ramsey@rmh.nhs.uk)

Background: Breast cancer-related lymphoedema (BCRL) presents a significant healthcare burden and adversely affects quality of life of breast cancer survivors. A prospective feasibility study was performed on lymphaticovenous anastomosis (LVA) for the treatment of BCRL.

Methods: Patients with BCRL underwent near-infrared spectroscopy with indocyanine green lymphatic mapping to identify suitable lymphatic channels for LVA. End-to-end anastomoses to subdermal venules were performed and patient recommenced compression garment therapy (CGT) after surgery. Volumetric assessment of the affected limb was performed at regular intervals using infrared perometry to calculate the excess volume reduction.

Results: Over a 24-month interval, 27 patients with BCRL underwent LVA. The median duration of lymphoedema was 3.5 (range 0.5–18) years, and the median number of LVAs performed was 3 (range 2–5). Twenty-four of the 27 patients completed 12-month follow-up. Patients exhibited three patterns of volumetric response following LVA: sustained response (16 patients), transient response (5) or no response (6). Sustained responders showed an excess volume reduction of –33 per cent at 12 months, and this correlated positively with the number of LVAs performed ($r = -0.56$, $P = 0.034$). Six of these 16 sustained responders were able to downgrade CGT after surgery, and two patients were CGT-free at 12 months.

Conclusion: LVA resulted in a sustained volume reduction in selected patients and may offset the burden of CGT. Further work is required to identify biomarkers that predict a favourable response to LVA surgery.

+A: Introduction

Improvements in local and systemic therapies for breast cancer have heralded a longer phase of breast cancer survivorship for patients; consequently, minimizing the long-term adverse effects of cancer therapies is imperative. One such adverse effect is breast cancer-related lymphoedema (BCRL) as a result of axillary surgery and/or radiotherapy. The incidence of BCRL is reported as approximately 20 per cent at 1 year and as high as 40 per cent at 10 years after breast cancer treatment¹⁻⁴. The impact, both psychological and physiological, on patients is unquestionable⁵⁻⁷, and the complications of BCRL (cellulitis, ulceration) may require prolonged periods of specialist management. The tenets of lymphoedema management include patient education, skin care and control of coexisting medical conditions that may worsen swelling. Control of limb volume itself has been achieved primarily through the use of compression bandaging⁸, manual lymphatic drainage and tailored exercise programmes to reduce limb volume and improve skin condition.

Traditionally, surgical approaches for the management of lymphoedema have been palliative (Homan's operation, Charles' procedure^{9,10} and the use of omental/enteromesenteric flaps¹¹), and are largely obsolete in modern medical practice. Although modern volume reduction techniques, such as circumferential liposuction, have shown efficacy in reducing limb volume, patients are still required to maintain compression therapy regimens^{7,12,13}. Surgical approaches to restore normal lymphatic physiology, such as lymphaticovenous anastomosis (LVA)^{14,15} or lymph node transfer (LNT)¹⁶⁻¹⁹, have gained popularity in recent years as they offer the potential to normalize lymphatic flow and, therefore, reduce the need for compression therapy. No single procedure has, however, yet demonstrated sustainable improvements in limb volume reduction and obviated the need for compression hosiery. In addition, these procedures are not risk-free, with reports of worsening lymphoedema after surgery in some patients undergoing LVA or LNT²⁰, as well as the risk of developing lymphoedema as a result of LNT harvest^{21,22}. Specifically, although the existing body of literature suggests that LVA may offer a volume reduction benefit, the true efficacy of LVA has been difficult to evaluate because of discrepancies between reported series in patient selection and outcome measurement^{14,20}. The recent introduction of dynamic imaging using indocyanine green (ICG) and near-infrared spectroscopy (NIRS)²³⁻²⁶ has improved reported outcomes as it permits preoperative evaluation of lymphatic flow patterns^{23,27} and thus the identification of patients who may benefit from surgery. In summary, the early promise of physiological surgery for lymphoedema has yet to translate

into the body of evidence required to change standard-of-care and allow clinicians to analyse the value of evidence-based interventions in BCRL.

This paper presents the results of a prospective study of performing LVA for BCRL using dynamic imaging as part of a microsurgical lymphoedema service. The findings of this pilot study are being used to inform the design of a prospective randomized study to evaluate the efficacy of LVA in combination with compression garment therapy (CGT) compared with CGT alone.

+A: Methods

+B: Preoperative clinical assessment

All patients underwent dual assessment by the senior author and a lymphoedema therapist within a dedicated lymphoedema clinic. A standard pro forma was used to capture demographic and clinical data including: duration of lymphoedema, symptom status, episodes of cellulitis and previous treatment for lymphoedema. Oncological examination (clinical and/or radiological if indicated) was performed in all patients to exclude recurrence-related lymphoedema. Volumetric evaluation was performed using infrared perometry²⁸ (*Fig. 1*). Excess volume reduction^{29–31} (EVR) was calculated as a percentage using the formula: (postoperative change in limb volume/preoperative difference in volume between limbs) × 100; otherwise stated as:

$$\frac{[(V_{\text{affected limb at time } t}) - (V_{\text{affected limb at baseline}})] / (V_{\text{affected limb at baseline}} - V_{\text{control limb at baseline}})}{\times 100}$$

Negative values for EVR represent volumetric improvements in the affected limb, whereas positive values represent further increases in limb volume.

+b: Lymphatic mapping

NIRS using ICG was employed to image, dynamically, the lymphatic drainage of the affected and unaffected limb. Under local anaesthetic (1 per cent lidocaine without adrenaline (epinephrine)), an intradermal/subdermal injection of 0.1–0.2 ml ICG (25 mg in 5 ml sterile water) was performed in the second web space of the hand and the ulnar border of the hand (*Fig. 2*). NIRS was performed immediately after injection and at serial time points thereafter using a hand-held near-infrared camera (PDE System; Hamamatsu Photonics UK, Welwyn Garden City, UK). Functioning lymphatic vessels were identified by selecting those displaying appropriate structure and propulsion and marked (*Fig. 2c,d*). LVA was offered only to patients with suitable functional lymphatics on dynamic imaging, in the

context of compression-refractory lymphoedema. Patients were maintained at their preoperative level of compression immediately before surgery and afterwards.

+B: Technique of lymphaticovenous anastomosis

Before induction of anaesthesia ICG was injected as described above under local anaesthetic block. Under general anaesthetic, lymphatic mapping was performed and suitable lymphatic channels were identified and their course marked. Multiple sites for LVA were identified along the course of suitable lymphatic channels, and small incisions were made at each LVA location. Subdermal venules lying juxtaposed to the identified lymphatic channels were identified (*Fig. 3*) and dissected under magnification (39×, Zeiss OPMI Vario/S88 microscope with Zeiss foldable tube f170/f260 attachment (Carl Zeiss AG, Oberkochen, Germany) using supermicrosurgical instruments (S&T AG, Neuhausen, Switzerland). LVA was carried out in an end-to-end^{32,33}, hand-sewn manner using a 12/0 S&T[®] suture on a 50-µm needle (*Fig. 4 and 5*).

Anastomoses were performed between the proximal lymphatic and distal venule to minimize the risk of size discrepancy and with the aim of performing between three and five LVAs per limb. Anastomotic patency was demonstrated by visualization of ICG flow across the anastomosis. Incisions were closed with non-absorbable sutures and skin glue, and the limb dressed with wool and crepe.

Patients were given intravenous antibiotics at induction of anaesthesia and a 5-day course of oral antibiotics after surgery. The limb was elevated for 3 days after surgery using a high-arm sling, and a wound check was performed in the clinic at 1 week. Sutures and bandages were removed at 2 weeks, and compression therapy was recommenced at the same level as before surgery.

Perometry assessments were performed by lymphoedema therapists at 1, 3, 6 and 12 months after surgery, and patients were also reviewed by the senior surgeon at these times. Perometry assessments were used to guide changes to CGT in combination with clinical assessment and discussion with the patient.

+B: Study design and statistical analysis

The objective of this study was to evaluate the volume reduction attributable to LVA in patients with BCRL. The primary endpoint of the study was limb volume as measured by infrared perometry, and the secondary endpoint was grade of compression therapy. The intention of this study was to inform the subsequent design of a randomized trial and,

therefore, a formal sample size calculation was not performed. Institutional review of the protocol was undertaken, and approval was gained before commencement.

Comparison of mean values between groups was performed using Student's *t* test (unpaired), and one-way ANOVA with Bonferroni *post hoc* correction) was carried out for multiple groups. χ^2 contingency analyses were performed to evaluate categorical data. Correlations were evaluated using Pearson's *r* statistic. Significance was attributed to *P* values of less than 0.050 and all analyses were performed using Graphpad Prism version 7 (GraphPad Software, La Jolla, California, USA).

+A: Results

,Between October 2012 and May 2014, 118 patients were referred to the lymphoedema clinic of whom 82 (69 per cent) had BCRL. Of these 82 patients referred for assessment, 27 (33 per cent) underwent LVA surgery. Of the final cohort, five patients were referred with new-onset lymphoedema following axillary dissection (at less than 12 months) and 22 were referred with established lymphoedema to assess the feasibility of LVA. Their mean BMI was 24.8 (range 20.0–38.4) kg/m² (*Table 1*). All patients were non-smokers. The mean duration of lymphoedema before LVA surgery was 3.5 (range 0.5–18) years. The mean number of LVAs performed was 3 (range 2–5).

+B: Previous treatments for lymphoedema

All patients who underwent LVA wore compression garments before surgery (grade 1, 3; grade 2, 21; grade 3, 3). Twenty-two of the 27 patients were receiving ongoing manual lymphatic drainage, and 11 had undergone intensive treatment with multilayer bandaging at some time (*Table 1*).

+B: Previous breast cancer treatment

Eleven of the 27 patients with BCRL had undergone breast-conserving surgery (BCS) as part of their breast cancer treatment, and the other 16 had had a mastectomy. Twelve patients had undergone immediate autologous reconstruction (free transverse rectus abdominis myocutaneous flap, deep inferior epigastric artery perforator flap, or latissimus dorsi flap with implant) at the time of mastectomy. All 27 patients had undergone axillary node dissection with a mean of 2 (range 0–24) positive nodes of a mean harvest of 17 (range 10–27) axillary nodes. Twenty-five patients had received radiotherapy (chest wall, supraclavicular fossa or internal mammary chain), and two had an axillary boost. Twenty-six patients had received either neoadjuvant or adjuvant chemotherapy, and 19 were being treated with hormonal therapy (*Table 1*).

+B: Lymphaticovenous anastomosis

All patients were operated on under general anaesthesia as planned day-case procedures. The mean duration of surgery was 3.3 (s.d.=0.45) h. Patients were recovered in a ward environment for 6 h after surgery before discharge later the same day.

+B: Volumetric outcomes

Twenty-four of the 27 patients who underwent LVA were followed up for 12 months after surgery.

The mean(s.e.m.) EVR across all patients was -14.0(8.0) per cent at 1 month, 2.9(13.7) per cent at 3 months, -0.6(9.9) per cent at 6 months and 9.2(14.7) per cent at 12 months.

Subgroup analysis of the overall cohort found three different patterns of response: sustained responders (16 patients), transient responders (5) and non-responders (6) (figures 7A-C). Sustained responders exhibited significantly greater mean (s.d.) EVR compared with non-responders at all time points ($P=0.014$), and compared with transient responders at 12 months only (-33.2(34.9) *versus* 102.0(75.8) per cent respectively; $P=0.002$) (figures 6 and 8 and *Table 2*). Transient responders showed early volumetric improvements (at 1 and 3 months) before relapsing. Of particular note, two of the five patients who had a transient response developed postoperative cellulitis. Both episodes were delayed in onset (4 and 9 months after LVA), and in one patient was secondary to a thumb laceration. All six non-responders had a mean increase in excess volume of 51.5 (range 31.4–75.5) per cent at 12 months.

Correlation analyses of sustained responders demonstrated that, at 12 months, greater EVR was significantly associated with the number of LVAs performed ($r = -0.56$, $P = 0.034$) (figure 9).

To identify factors that might predict a poor outcome (transient or no response) following LVA, multiple variables were analysed to investigate how these differed between response subgroups. Transient responders had a significantly greater duration of lymphoedema before LVA surgery (adjusted $P = 0.044$), but non-responders did not. No significant associations were observed between LVA response and BMI ($P = 0.748$), number of positive nodes harvested ($P = 0.458$), total number of axillary nodes harvested ($P = 0.790$), axillary radiotherapy ($P = 0.519$), hormonal therapy ($P = 0.683$) or previous autologous reconstruction ($P = 0.152$), or type of previous breast surgery (BCS *or* mastectomy) ($P = 0.157$) (*Table 3*).

The preoperative distribution of CGT grades in sustained responders was: grade 1, one patient; grade 2, 13 patients; and grade 3, two patients. Following LVA, there were five, 11 and zero patients receiving grade 1, 2 and 3 compression therapy. Contingency analysis demonstrated that these proportions were significantly different ($P = 0.045$) (figure 10). Six of the 16 sustained responders had downgraded CGT after surgery, and two patients in the overall cohort ceased to require compression altogether. The decision to downgrade CGT was made jointly with the patient following clinical and perometry assessment of the affected limb after surgery. No patient who had a reduction in CGT grade experienced rebound swelling of the limb.

With a view to designing a prospective randomized trial, a further subgroup analysis of patients who might be eligible for such a study was performed. In our protocol, we propose to recruit patients prospectively following axillary clearance and, to this end, we sought to investigate whether the duration of lymphoedema might affect volumetric outcomes post-LVA. EVR was compared in patients with a duration of lymphoedema of less than 2 years and those with a duration of greater than 2 years: mean(s.d.) EVR $-26.1(50.2)$ versus $16.5(39.6)$ per cent respectively ($P = 0.041$) (figure 11).

+A: Discussion

BCRL commits patients to a lifelong regimen of CGT and increases the risk of complications such as cellulitis, lymphangitis, lymphadenitis and ulceration. It can impair quality of life significantly^{34,35}, have a profound psychological impact, and be a reminder of cancer diagnosis. In rare instances, it can predispose to developing lymphangiosarcoma³⁶ and retiform lymphangioendothelioma³⁷. Although physiological lymphatic surgery such as LVA may offer a therapeutic benefit, the impetus is on the surgeon to select only those patients who may benefit and, above all, avoid interventions that may worsen BCRL.

Surgical strategies for BCRL have traditionally been associated with poor outcomes and high complication rates. Excisional procedures such as Homans' operation and the Charles procedure, which are now largely obsolete, had disastrous cosmetic results and a questionable impact on lymphoedema. Similarly, omental and enteromesenteric flaps¹¹ were used as a way of bridging damaged lymphatics, but were associated with poor volumetric outcomes and unacceptable complication profiles. Liposuction, which is effective in reducing limb volume, does not address the underlying disease process and is limited to patients in whom there is a significant adipose component. It does not obviate the need for ongoing CGT, and concern remains over liposuction worsening the fibrotic component of

lymphoedema^{7,12,13}. Although LNT may offer the possibility of anatomical lymphatic reconstruction, evaluating its true efficacy is difficult and donor site morbidity remains a concern^{22,39,40}; however, a comprehensive discussion of its value is beyond the remit of the present study. Recent preclinical reports^{41,42} of LNT in combination with vascular endothelial growth factor C gene therapy are encouraging, and clinical trial data from translation of this strategy are awaited. Preclinical efficacy for leukotriene antagonists has been reported recently⁴³, and these are currently being evaluated in a phase 2 clinical trial.

LVA offers the opportunity for lymphatic reconstruction with relatively less morbidity and, although LVA has been introduced cautiously into routine clinical practice in the UK, it is now offered in several UK centres. We present the first UK series of LVA in combination with NIRS imaging for BCRL in the UK, with data collected from a clinical LVA service. It is the experience of the present authors that setting up a lymphoedema surgery service requires significant investment in infrastructure, equipment and, perhaps most importantly, capacity and training for specialist lymphoedema therapists. Such expenditure has to be justifiable with regard to outcome, and thus the focus has been on standardizing the processes using validated methods of assessment and treatment to ensure robust and reliable outcome data. Specifically, the postoperative compression regimen employs the same degree of compression as was used before surgery. Adoption of the International Society of Lymphology consensus document⁴⁴ to enable standardization of data collection is advocated for evaluation of all therapeutic interventions for lymphoedema.

In the present series, one-third of patients referred with BCRL were identified as suitable candidates for LVA on the basis of clinical evaluation in combination with favourable NIRS imaging using ICG. The patient population was highly heterogeneous with regard to breast cancer treatment, breast reconstruction, duration of lymphoedema (range 0.5–18 years) and previous treatments for lymphoedema. A mean number of three LVAs were performed per affected limb, and patients recommenced CGT 2 weeks after surgery at the same level as before the operation.

Twenty-four of the 27 patients achieved 12-month follow-up. No response to LVA was observed in six patients, whereas a transient response was achieved in five and a sustained volume reduction in 16. Sustained responders had a 33 per cent reduction in excess volume at 12 months, which was correlated with the number of LVA procedures performed and associated with a downgrading of CGT in six of the 16 patients in this group. Transient responders exhibited early volumetric improvements following LVA, but ultimately

relapsed; of note, two of these five patients had postoperative cellulitis. It is likely that infection adversely affected the LVA, although there are few published data on the impact of postoperative cellulitis on the efficacy of LVA. Although it is not possible to demonstrate causality between infection and adverse volumetric outcomes after LVA, recent evidence⁴⁵ suggests that methicillin-resistant *Staphylococcus aureus* infection results in lymphatic muscle dysfunction that persists long after the infection has been cleared.

In the present study, a mean 51.5 per cent increase in excess volume was observed in non-responders at 12 months. Other published series have reported no change, or a deterioration, in lymphoedema in up to 40 per cent of patients treated with LVA⁴⁶, compared with the 22 per cent (6 of 27) non-response rate in the present series. Although the numbers in the no-response group are too small to demonstrate causality between non-response to LVA and worsening limb volume, further data are required to differentiate between increases in limb volume attributable to LVA failure and the natural evolution of volume changes in lymphoedema. It is likely that this might be shown only in suitably powered studies with large control arms of similar patients. The present analysis showed that longer duration of lymphoedema before LVA was associated with worse volume outcomes, but no associations were observed between volume and breast cancer treatment variables, including axillary radiotherapy and the number of axillary nodes removed.

This feasibility study has highlighted the natural learning curve involved in introducing a LVA service. Performing LVA under general anaesthetic is advocated both for patient comfort and to ensure that the anastomosis is not jeopardized by movement. Ideally, surgery should be performed by surgeons operating in parallel, which would allow for a greater number of LVAs per patient and reduce operating time. The optimal number of LVAs to perform per limb remains debated. In a previous study¹⁵, three LVAs per limb were performed, and in the present study patients with greater volume reductions had a higher number of LVAs. However, identification of these patients *a priori* is currently not possible.

The timing of intervention with LVA remains much debated, but the available literature supports earlier intervention, before the development of adipose tissue proliferation or fibrotic change. The present comparison of volumetric outcomes in patients with long-standing lymphoedema (more than 2 years) with those in patients with a shorter duration (less than 2 years) suggested that earlier intervention was associated with significant improvements in EVR following LVA. Newer approaches advocate for immediate LVA at the time of axillary dissection^{47,48}, although the benefit of this remains to be established, as

only a proportion of patients undergoing axillary dissection will ultimately develop lymphoedema.

Data from this series have been used to inform the design of a prospective randomized trial of LVA with CGT *versus* CGT alone in patients with BCRL (*Fig. S1*, supporting information). That study will aim to randomize patients to LVA early after the diagnosis of BCRL and evaluate the impact LVA in this group. The study protocol for the randomized study aims to follow all patients having axillary dissection and recruit patients who exhibit persistent limb swelling (duration longer than 1 month). Identifying patients who may not benefit from LVA is paramount, and the authors hypothesize that relevant biomarkers may aid in the stratification of patients and facilitate the prospective identification of LVA non-responders. The future trial platform will allow formal evaluation of a panel of biomarkers against volumetric outcomes.

This first UK series of LVA for BCRL demonstrates that the procedure may offer a volume reduction benefit in some patients; however, prospective identification of these patients remains difficult. The surgery itself was associated with relatively low morbidity, but postoperative infections may compromise the efficacy of LVA and worsen lymphoedema. The efficacy of LVA in BCRL will be analysed within the framework of a prospective randomized trial.

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+A: References

- 1 DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol* 2013; **14**: 500–515.
- 2 Ugur S, Arıcı C, Yaprak M, Mesci A, Arıcı GA, Dolay K *et al*. Risk factors of breast cancer-related lymphedema. *Lymphat Res Biol* 2013; **11**: 72–75.
- 3 Menezes MM, Bello MA, Millen E, Lucas FA, Carvalho FN, Andrade MF *et al*. Breast reconstruction and risk of lymphedema after mastectomy: a prospective cohort study with 10 years of follow-up. *J Plast Reconstr Aesthet Surg* 2016; **69**: 1218–1226.
- 4 Ribeiro Pereira ACP, Koifman RJ, Bergmann A. Incidence and risk factors of lymphedema after breast cancer treatment: 10 years of follow-up. *Breast* 2017; **36**: 67–73.

- 5 Leung N, Furniss D, Giele H. Modern surgical management of breast cancer therapy related upper limb and breast lymphoedema. *Maturitas* 2015; **80**: 384–390.
- 6 Kwan W, Jackson J, Weir LM, Dingee C, McGregor G, Olivotto IA. Chronic arm morbidity after curative breast cancer treatment: prevalence and impact on quality of life. *J Clin Oncol* 2002; **20**: 4242–4248.
- 7 Hoffner M, Bagheri S, Hansson E, Manjer J, Troëng T, Brorson H. SF-36 shows increased quality of life following complete reduction of postmastectomy lymphedema with liposuction. *Lymphat Res Biol* 2017; **15**: 87–98.
- 8 Badger CM, Peacock JL, Mortimer PS. A randomized, controlled, parallel-group clinical trial comparing multilayer bandaging followed by hosiery versus hosiery alone in the treatment of patients with lymphedema of the limb. *Cancer* 2000; **88**: 2832–2837.
- 9 Karri V, Yang MC, Lee IJ, Chen SH, Hong JP, Xu ES *et al*. Optimizing outcome of Charles procedure for chronic lower extremity lymphoedema. *Ann Plast Surg* 2011; **66**: 393–402.
- 10 Allen RJ Jr, Cheng MH. Lymphedema surgery: patient selection and an overview of surgical techniques. *J Surg Oncol* 2016; **113**: 923–931.
- 11 Nguyen AT, Suami H. Laparoscopic free omental lymphatic flap for the treatment of lymphedema. *Plast Reconstr Surg* 2015; **136**: 114–118.
- 12 Damstra RJ, Voesten HG, Klinkert P, Brorson H. Circumferential suction-assisted lipectomy for lymphoedema after surgery for breast cancer. *Br J Surg* 2009; **96**: 859–864.
- 13 Boyages J, Kastanias K, Koelmeyer LA, Winch CJ, Lam TC, Sherman KA *et al*. Liposuction for advanced lymphedema: a multidisciplinary approach for complete reduction of arm and leg swelling. *Ann Surg Oncol* 2015; **22**(Suppl 3): S1263–S1270.
- 14 Campisi C, Bellini C, Campisi C, Accogli S, Bonioli E, Boccardo F. Microsurgery for lymphedema: clinical research and long-term results. *Microsurgery* 2010; **30**: 256–260.
- 15 Chang DW. Lymphaticovenular bypass for lymphedema management in breast cancer patients: a prospective study. *Plast Reconstr Surg* 2010; **126**: 752–758.
- 16 Raju A, Chang DW. Vascularized lymph node transfer for treatment of lymphedema: a comprehensive literature review. *Ann Surg* 2015; **261**: 1013–1023.
- 17 Becker C. Autologous lymph node transfers. *J Reconstr Microsurg* 2016; **32**: 28–33.
- 18 Tourani SS, Taylor GI, Ashton MW. Vascularized lymph node transfer: a review of the current evidence. *Plast Reconstr Surg* 2016; **137**: 985–993.
- 19 Ozturk CN, Ozturk C, Glasgow M, Platek M, Ashary Z, Kuhn J *et al*. Free vascularized lymph node transfer for treatment of lymphedema: a systematic evidence based review. *J Plast Reconstr Aesthet Surg* 2016; **69**: 1234–1247.

- 20 **Basta** MN, **Gao** LL, **Wu** LC. Operative treatment of peripheral lymphedema: a systematic meta-analysis of the efficacy and safety of lymphovenous microsurgery and tissue transplantation. *Plast Reconstr Surg* 2014; **133**: 905–913.
- 21 **Azuma** S, **Yamamoto** T, **Koshima** I. Donor-site lymphatic function after microvascular lymph node transfer should be followed using indocyanine green lymphography. *Plast Reconstr Surg* 2013; **131**: 443e–444e.
- 22 **Ciudad** P, Manrique OJ, Date S, Sacak B, Chang WL, Kiranantawat K *et al*. A head-to-head comparison among donor site morbidity after vascularized lymph node transfer: pearls and pitfalls of a 6-year single center experience. *J Surg Oncol* 2017; **115**: 37–42.
- 23 **Mihara** M, Hara H, Araki J, Kikuchi K, Narushima M, Yamamoto T *et al*. Indocyanine green (ICG) lymphography is superior to lymphoscintigraphy for diagnostic imaging of early lymphedema of the upper limbs. *PLoS One* 2012; **7**: e38182.
- 24 **Mihara** M, Hara H, Hayashi Y, Iida T, Araki J, Yamamoto T *et al*. Upper-limb lymphedema treated aesthetically with lymphaticovenous anastomosis using indocyanine green lymphography and noncontact vein visualization. *J Reconstr Microsurg* 2012; **28**: 327–332.
- 25 **Mihara** M, Murai N, Hayashi Y, Hara H, Iida T, Narushima M *et al*. Using indocyanine green fluorescent lymphography and lymphatic-venous anastomosis for cancer-related lymphedema. *Ann Vasc Surg* 2012; **26**: 278.e1–e6.
- 26 **Chowdhry** M, **Rozen** WM, **Griffiths** M. Lymphatic mapping and preoperative imaging in the management of post-mastectomy lymphoedema. *Gland Surg* 2016; **5**: 187–196.
- 27 **Akita** S, Mitsukawa N, Kazama T, Kuriyama M, Kubota Y, Omori N *et al*. Comparison of lymphoscintigraphy and indocyanine green lymphography for the diagnosis of extremity lymphoedema. *J Plast Reconstr Aesthet Surg* 2013; **66**: 792–798.
- 28 **Batista** BN, **Baiocchi** JMT, **Campanholi** LL, **Bergmann** A, **Duprat** JP. Agreement between perometry and sequential arm circumference measurements in objective determination of arm volume. *J Reconstr Microsurg* 2018; **34**: 29–34.
- 29 **Lanza** M, Bergmann A, Ferreira MG, de Aguiar SS, Dias Rde A, Abrahão Kde S *et al*. Quality of life and volume reduction in women with secondary lymphoedema related to breast cancer. *Int J Breast Cancer* 2015; **2015**: 586827.
- 30 **Stewart** CJ, **Munnoch** DA. Liposuction as an effective treatment for lower extremity lymphoedema: a single surgeon’s experience over nine years. *J Plast Reconstr Aesthet Surg* 2018; **71**: 239–245.
- 31 <JCIT>**Ezzo** J, Manheimer E, McNeely ML, Howell DM, Weiss R, Johansson KI *et al*. Manual lymphatic drainage for lymphedema following breast cancer treatment. *Cochrane Database Syst Rev* 2015; (5)CD003475.

- 32 **Ayestaray B, Bekara F, Andreoletti JB.** π -shaped lymphaticovenular anastomosis for head and neck lymphoedema: a preliminary study. *J Plast Reconstr Aesthet Surg* 2013; **66**: 201–206.
- 33 **Yamamoto T,** Narushima M, Kikuchi K, Yoshimatsu H, Todokoro T, Mihara M *et al.* Lambda-shaped anastomosis with intravascular stenting method for safe and effective lymphaticovenular anastomosis. *Plast Reconstr Surg* 2011; **127**: 1987–1992.
- 34 **Vassard D,** Olsen MH, Zinckernagel L, Vibe-Petersen J, Dalton SO, Johansen C. Psychological consequences of lymphoedema associated with breast cancer: a prospective cohort study. *Eur J Cancer* 2010; **46**: 3211–3218.
- 35 **Passik SD, McDonald MV.** Psychosocial aspects of upper extremity lymphedema in women treated for breast carcinoma. *Cancer* 1998; **83**(Suppl): 2817–2820.
- 36 **Tomita K, Yokogawa A, Oda Y, Terahata S.** Lymphangiosarcoma in postmastectomy lymphedema (Stewart–Treves syndrome): ultrastructural and immunohistologic characteristics. *J Surg Oncol* 1988; **38**: 275–282.
- 37 **Yamada S,** Yamada Y, Kobayashi M, Hino R, Nawata A, Noguchi H *et al.* Post-mastectomy benign lymphangioendothelioma of the skin following chronic lymphedema for breast carcinoma: a teaching case mimicking low-grade angiosarcoma and masquerading as Stewart–Treves syndrome. *Diagn Pathol* 2014; **9**: 197.
- 38 **Abbas Khan MA,** Mohan A, Hardwicke J, Srinivasan K, Billingham R, Taylor C *et al.* Objective improvement in upper limb lymphoedema following ipsilateral latissimus dorsi pedicled flap breast reconstruction – a case series and review of literature. *J Plast Reconstr Aesthet Surg* 2011; **64**: 680–684.
- 39 **Sulo E,** Hartiala P, Viitanen T, Mäki M, Seppänen M, Saarikko A. Risk of donor-site lymphatic vessel dysfunction after microvascular lymph node transfer. *J Plast Reconstr Aesthet Surg* 2015; **68**: 551–558.
- 40 **Massey MF, Gupta DK.** The incidence of donor-site morbidity after transverse cervical artery vascularized lymph node transfers: the need for a lymphatic surgery national registry. *Plast Reconstr Surg* 2015; **135**: 939e–940e.
- 41 **Tammela T, Saaristo A, Holopainen T, Lyytikä J,** Kotronen A, Pitkonen M *et al.* Therapeutic differentiation and maturation of lymphatic vessels after lymph node dissection and transplantation. *Nat Med* 2007; **13**: 1458–1466.
- 42 **Lähteenvuo M,** Honkonen K, Tervala T, Tammela T, Suominen E, Lähteenvuo J *et al.* Growth factor therapy and autologous lymph node transfer in lymphedema. *Circulation* 2011; **123**: 613–620.
- 43 **Tian W,** Rockson SG, Jiang X, Kim J, Begaye A, Shuffle EM *et al.* Leukotriene B4 antagonism ameliorates experimental lymphedema. *Sci Transl Med* 2017; **9**: pii: eaal3920.

- 44 International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. *Lymphology* 2013; **46**: 1–11.
- 45 Jones D, Meijer EFJ, Blatter C, Liao S, Pereira ER, Bouta EM *et al*. Methicillin-resistant *Staphylococcus aureus* causes sustained collecting lymphatic vessel dysfunction. *Sci Transl Med* 2018; **10**: pii: eaam7964.
- 46 Mihara M, Hara H, Tange S, Zhou HP, Kawahara M, Shimizu Y *et al*. Multisite lymphaticovenular bypass using supermicrosurgery technique for lymphedema management in lower lymphedema cases. *Plast Reconstr Surg* 2016; **138**: 262–272.
- 47 Boccardo F, Casabona F, De Cian F, Friedman D, Murelli F, Puglisi M *et al*. Lymphatic Microsurgical Preventing Healing Approach (LYMPHA) for primary surgical prevention of breast cancer-related lymphedema: over 4 years follow-up. *Microsurgery* 2014; **34**: 421–424.
- 48 Boccardo F, Valenzano M, Costantini S, Casabona F, Morotti M, Sala P *et al*. LYMPHA technique to prevent secondary lower limb lymphedema. *Ann Surg Oncol* 2016; **23**: 3558–3563.

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article

<TYPESETTER: PLEASE FOLLOW MARK-UPS OF FIGS 1-11>

Fig. 1 Infrared perometry limb volume measurement being performed by a lymphoedema therapist

Fig. 2 a Injection of indocyanine green (ICG) (0.1 ml of 5-mg/ml solution) into the left hand (normal limb) under local anaesthetic. Injections are typically performed in the second web space and along the ulnar border. **b** Near-infrared spectroscopy (NIRS) immediately after injection of ICG, demonstrating early uptake along lymphatic channels. **c** Surface markings demonstrate the course of the basilic vein (arrow). **d** NIRS view of basilic vein (black arrow) with prominent uptake into adjacent lymphatic channels (white arrows), confirming feasibility of lymphaticovenous anastomosis (LVA). **e** Dermal backflow ‘stardust’ appearance of lymphatic flow caused by reflux of ICG into dermal lymphatics, and an absence of linear lymphatic channels suggesting that LVA will not be feasible due to lymphoedema progression

Fig. 3 Intraoperative photograph of lymphatic channel (L) (containing indocyanine green) dissection and adjacent venule (V)

Fig. 4 Microsurgical setup for anastomosis, demonstrating proximity of lymphatic channel (L) and venule (V) to facilitate tension-free anastomosis

Fig. 5 a Photograph of a completed lymphaticovenous anastomosis (LVA) at the time of removal of distal microvascular clamps. **b** Demonstration of LVA patency as shown by indocyanine green flow into the distal limb of the LVA

Fig. 6 a Preoperative photograph of a patient with left-sided upper limb lymphoedema; **b** postoperative photograph of the same patient 12 months after lymphaticovenous anastomosis

Fig. 7 Changes in excess volume reduction (EVR) at 1, 3, 6 and 12 months after lymphaticovenous anastomosis (LVA) in **a** sustained responders, **b** transient responders and **c** non-responders. Values are mean(s.d.)

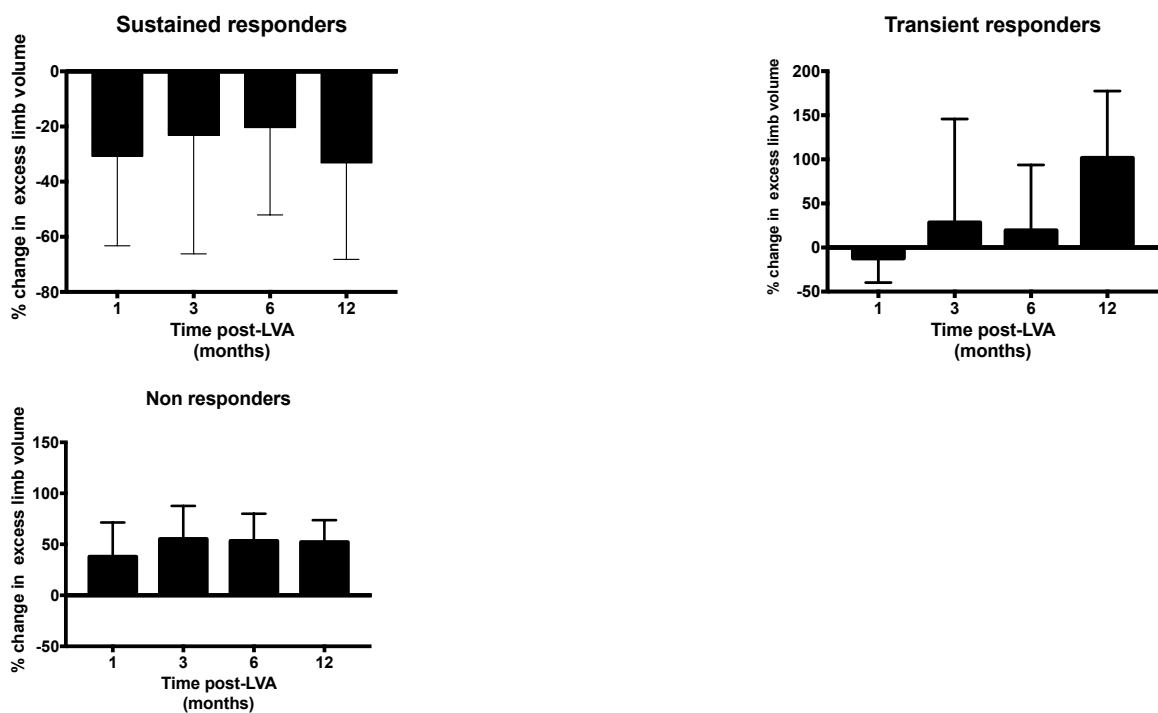


Fig. 8 Comparison of excess volume reduction (EVR) in sustained responders (SR), transient responders (TR) and non-responders (NR) at 12 months after lymphaticovenous anastomosis. Values are mean(s.d.). * $P < 0.050$, † $P < 0.010$ (one-way ANOVA)

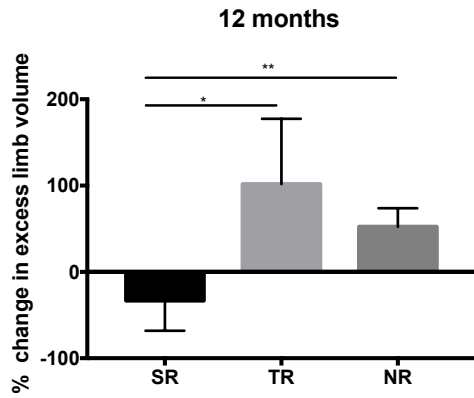


Fig. 9 Correlation between mean excess volume reduction (EVR) at 12 months in sustained responders and the number of lymphaticovenous anastomoses (LVAs) performed. Pearson's $r = -0.56$, $P = 0.034$

Fig. 10 Compression garment therapy (CGT) grade in sustained responders before and after lymphaticovenous anastomosis (LVA). * $P = 0.045$ (χ^2 contingency analysis)

Changes in CGT grade pre- and post-LVA

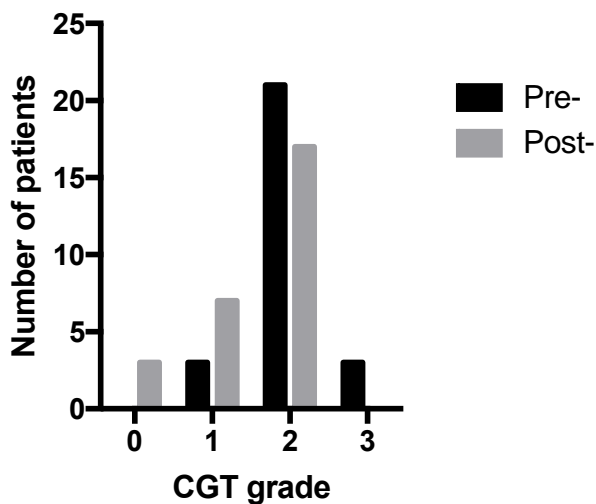


Fig. 11 Comparison of excess volume reduction (EVR) in sustained responders with duration of lymphoedema from diagnosis of less than 2 years and those with duration greater than 2 years. Values are mean(s.d.). $P < 0.050$ (Student's unpaired t test)

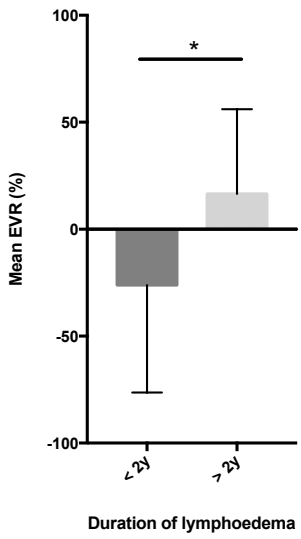


Table 1 Demographics, previous breast cancer treatment and previous treatments for lymphoedema

	No. of patients* (<i>n</i> = 27)
Duration of lymphoedema (years)†	3.5 (0.5–18)
BMI (kg/m ²)†	24.8 (20.0–38.4)
Smoker	0
Diabetes mellitus	0
Previous breast cancer treatment	
Breast-conserving surgery	11
Mastectomy	16
Immediate autologous reconstruction‡ before development of lymphoedema	12
Axillary node dissection	27
No. of positive nodes†	2 (0–24)
No. of harvested nodes†	17 (10–27)
Radiotherapy	
Any (breast, SCF, axilla)	25
Axilla	2
Any chemotherapy (neoadjuvant or adjuvant)	26
Hormonal therapy	19
Previous lymphoedema treatment	
Compression therapy	
Grade 1	3
Grade 2	21
Grade 3	3
Manual lymphatic drainage	22
Intensive treatment with wrapping	11

*Unless indicated otherwise; †values are mean (range). ‡Muscle-sparing transverse rectus abdominis myocutaneous, deep inferior epigastric artery perforator, or latimssimus dorsi plus implant flaps. SCF, supraclavicular fossa.

Table 2 Volumetric outcomes as measured by perometry across subgroups

	Excess volume reduction (%)		
	Sustained response	Transient response	No response
Time after LVA (months)			
1	-30.8(8.1)	-12.3(12.3)	37.9(14.9)
3	-23.2(11.1)	28.4(52.4)	55.3(56.7)
6	-20.4(7.9)	19.5(32.2)	53.4(13.3)
12	-33.2(9.0)	102.0(33.9)	52.3(10.7)

Values are mean(s.e.m.). LVA, lymphaticovenous anastomosis.

Table 3 Analysis of potential clinicopathological variables affecting volumetric outcomes following lymphaticovenous anastomosis

	Sustained response (<i>n</i> = 16)	Transient response (<i>n</i> = 5)	No response (<i>n</i> = 6)	<i>P</i> †
Duration of lymphoedema (years)*	2.8 (0.5–8)	7.5* (1.1–18)	4.4 (1–7)	0.047‡
No. of LVAs*	3.0 (2.0–4.0)	3.6 (2.0–5.0)	3.0 (2.0–5.0)	0.409‡
BMI (kg/m ²)*	26.2 (20.0–38.1)	27.6 (23.2–33.2)	25.8 (21.6–34.2)	0.748‡
Previous BCS	8	2	1	0.241
Previous mastectomy	8	3	5	0.241
No. of positive nodes*	6.0 (0–24)	2.0 (0–6)	1.7 (0–3)	0.458‡
No. of nodes harvested*	17.2 (7–27)	17.5 (13–22)	20.0 (15–25)	0.790‡
Any radiotherapy	15	5	5	0.617
Radiotherapy to axilla	2	0	0	0.519
Hormonal therapy	11	3	5	0.683
Previous autologous reconstruction	5	4	3	0.152

*Values are mean (range). LVA, lymphaticovenous anastomosis; BCS, breast-conserving surgery. † χ^2 contingency analysis, except one-way ANOVA.