Lymphaticovenular anastomosis improves quality of life and limb volume in patients with secondary lymphoedema after breast cancer treatment

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Abstract

Secondary lymphoedema is a common side effect of breast cancer treatment, with significant impact on patients' physical and psychological wellbeing. Conservative therapies are the gold standard treatment, however surgical options are becoming more popular. Lymphaticovenular anastomosis (LVA) is a supermicrosurgical procedure that aims to restore lymphatic flow by anastomosing damaged lymphatics to subcutaneous venules. We aimed to assess the effects of LVA on patients' limb volume and quality of life.

Pre and post-operative limb volumes and LYMQOL scores were collected for patients undergoing LVA for lymphoedema secondary to breast cancer. Thirty-seven patients underwent LVA. A significant reduction was seen in median excess limb volume post operatively (13.3% to 6.6%, $p<0.005$), with volumetric improvement seen in 78% of patients. Thirteen patients were

able to discontinue compression garment use. Eighty six percent of patients reported improved quality of life post-operatively with median LYMQOL score increasing from 90 to 104 points ($p < 0.005$).

LVA is a minimally invasive surgical option for patients with early stage lymphoedema. It can lead to significant volumetric improvements and in select patients freedom from compression therapy. LVA can also lead to significant improvements in quality of life, in particular patients' mood and perception of their appearance.

Keywords

Secondary Lymphoedema, Lymhaticovenular Anastomosis, LVA, Breast Cancer, LYMQOL, Quality of Life

Highlights

- LVA is a supermicrosurgical treatment for lymphoedema
- It is minimally invasive and performed under local anesthetic
- 78% of patients achieve volumetric improvement
- 86% of patients report improved quality of life
- Greatest improvements achieved in patients' rating of mood and appearance

Introduction

Breast cancer is the most common cancer in the UK, with 50,000 new cases diagnosed every year (1). The mainstay of treatment involves surgical removal of the tumour with lymph node biopsy or excision. This is frequently followed by adjuvant chemotherapy, radiotherapy or hormonal treatment (2). Five-year survival is now over 85% (1), resulting in an increasing number of women living with long term side effects of treatment and an increased emphasis being placed on quality of life after cancer(3).

Surgery and radiotherapy can damage the lymphatics (4), and one in five women develop lymphoedema after breast cancer treatment (5). Lymphoedema is a disabling condition whereby damage to lymphatic channels causes accumulation of protein-rich lymphatic fluid within the subcutaneous tissues of the arm (4). It affects patients' psychosocial wellbeing, causes swelling and discomfort of the limb, and increases the risk of recurrent cellulitis (4,6).

Although there is no cure for lymphoedema, several conservative and surgical therapies exist, aiming to alleviate symptoms by limiting fluid accumulation. Lymphoedema has traditionally been managed conservatively, using labour-intensive, time-consuming methods such as complex decongestive physiotherapy, skin care and compression sleeves (4,7,8). When conservative treatment fails, surgical options include reductive methods or physiological treatments, such as lymph node transfer and lymphatico-lymphatic bypass (7,9) – these are significant operations requiring general anesthetic.

Lymphaticovenular anastomosis (LVA) is a minimally invasive supermicrosurgical procedure that aims to restore lymphatic flow by anastomosing lymphatic channels to subcutaneous venules with a diameter less then 0.8mm, in order to bypass areas of lymphatic damage. It is a viable treatment option for selected patients with proximal lymphatic obstruction but patent distal vessels. It is performed under local anaesthetic, making it a good option for a wide range of patients, including the elderly and those with significant co-morbidities (10) . LVA has also been performed prophylactically at the time of axillary dissection (3), when subclinical lymphoedema is detected (11), or when conservative methods have failed.

We aimed to assess the effects of LVA on volumetric measurements and quality of life in a cohort of women with secondary lymphoedema after breast cancer treatment.

Methods

Data was collected prospectively for all patients undergoing LVA to treat lymphoedema secondary to breast cancer treatment between September 2013 and December 2016.

Patient selection

Patients with upper limb lymphoedema self-referred or were referred for consideration of LVA by their general practitioner, surgeon or lymphoedema practitioner. Indocyanine Green (ICG) Lymphography was performed on all patients. Patients were selected for LVA surgery if Indocyanine Green (ICG) Lymphography confirmed the presence of lymphoedema, or demonstrated patterns of dermal backflow considered high risk for the development of clinically apparent lymphedema (11). Additionally, patients were required to have adequate functional lymphatic channels, as evidenced by passage of ICG dye from a subcutaneous injection point at the wrist to at least the level of the elbow within 45 minutes.

Procedure

All patients underwent repeat pre-operative ICG lymphography on the day of surgery to determine the location of functioning lymphatics (12,13) . All procedures were performed under local anaesthetic by two consultant microsurgeons operating simultaneously. An average of four transverse incisions between two and five centimeters were made in the arm, typically one in the upper medial arm and three in the forearm. Suitable lymphatic vessels were anastomosed to subdermal venules using 11/0 Ethilon (Figure 1). An average operation lasted four hours. Post-operatively patients were advised to elevate the limb and massage from distal

to proximal towards the scars. Patients were followed up at 3, 6 and 12 months.

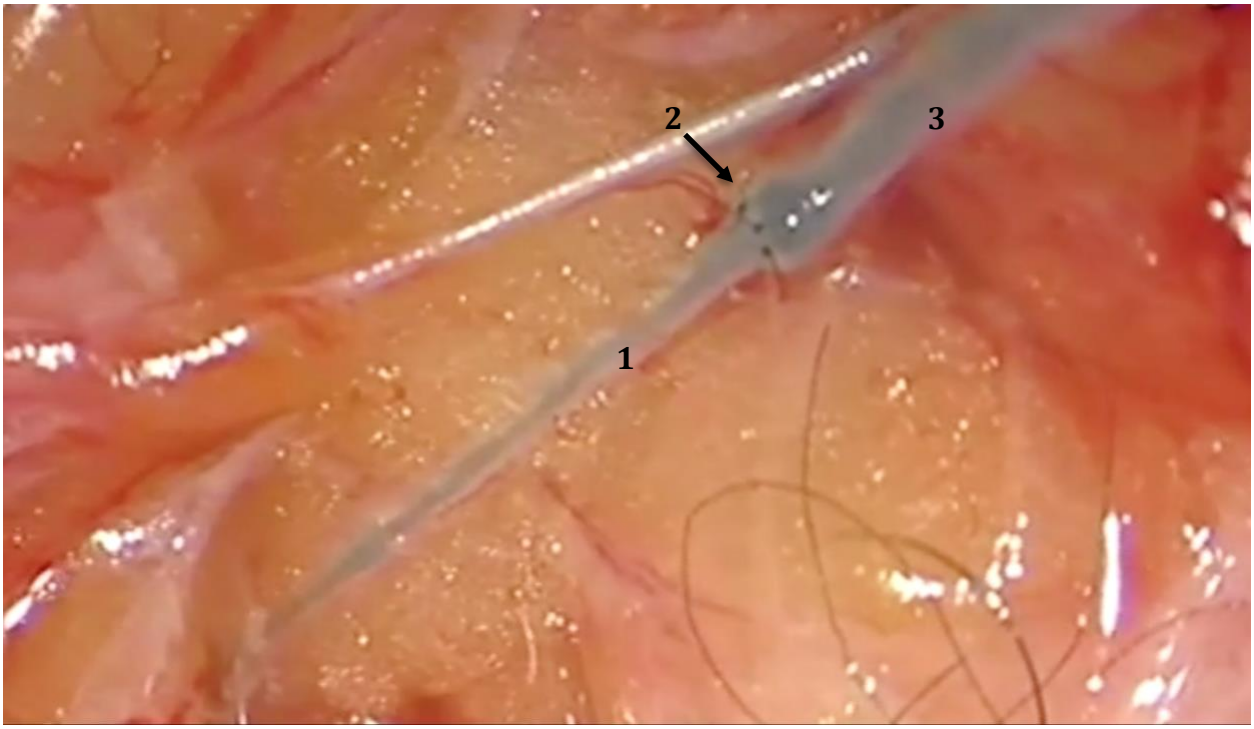


Figure 1

Lymphaticovenular anastomosis involves anastomosing multiple functioning distal lymphatics to small subcutaneous venules in order to restore lymphatic flow. (1) Lymphatic Vessel containing patent blue dye, (2) Anastomosis with 11/0 Ethilon, (3) Venule containing patent blue stained lymphatic fluid.

Quality of life

Quality of life was measured pre-operatively and at every appointment post-operatively using the Lymphoedema Quality of Life Questionaire (LYMQOL). This is a validated quality of life

assessment tool for patients with lymphoedema. Patients are asked 24 questions falling into the following domains; symptoms, body image/appearance, function and mood (14) . The highest total score is 118, with a higher score indicating better quality of life.

Volumetric Measurements

Volumetric measurements were recorded from both limbs pre-operatively and at all post-operative appointments. Measurements were taken using a perometer.

Statistics

Descriptive statistics were used to calculate change in quality of life and limb volumetric measurements. The paired t-test was used to evaluate statistical significance.

Results

Demographics

Thirty-eight patients with unilateral lymphoedema secondary to breast cancer treatment underwent LVA surgery. Median follow up was 6.5 months (range 3 – 33 months).

Volume reduction

The median pre-operative excess volume was 13.3% (range -0.8-59.5%). Twenty-eight out of 38 patients (78%) showed a reduced limb volume post-operatively (Figure 2). The median post-operative excess was 6.6% (range 3.5-36.4%, $p < 0.005$). The median relative volume reduction across all patients was 23%.

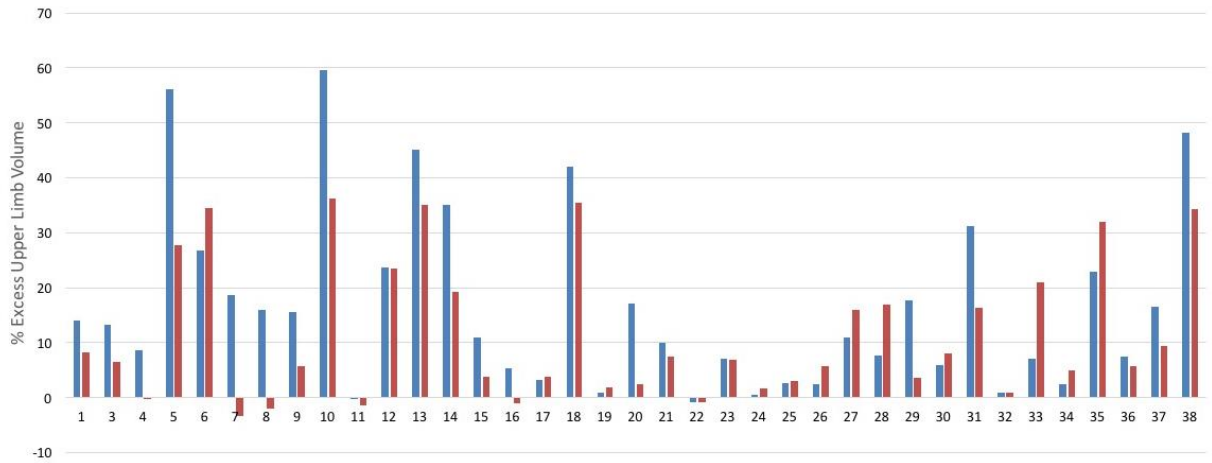
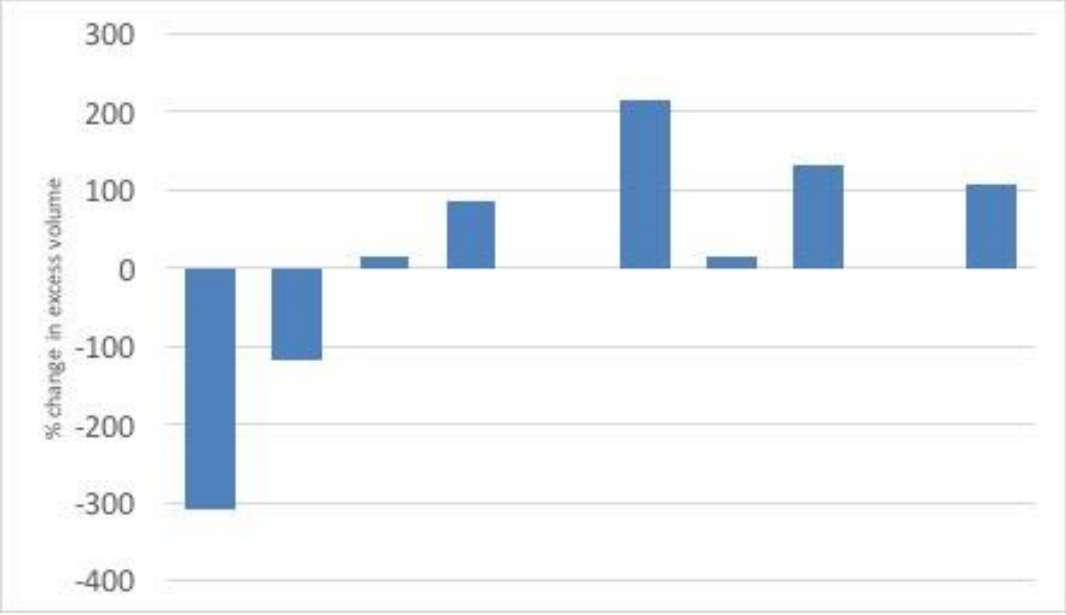


Figure 2

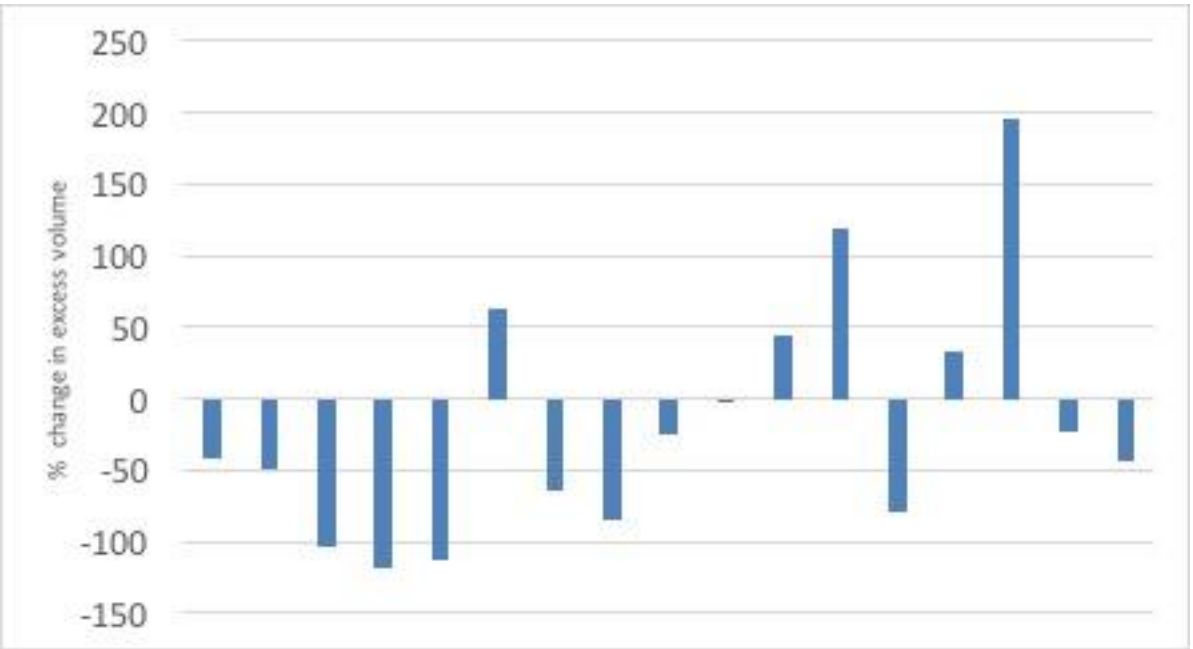
Pre- and post-operative percentage excess limb volume of each patient undergoing LVA. Each bar represents one arm: pre-op (blue) and post-op (red). Post-op excess volume was measured at the most recent clinic follow-up appointment.

There was a clear difference in change in volume between groups depending on the starting volume difference between arms. Volumetric improvement was seen in three of the nine patients with a starting excess volume less than five percent, whereas in patients with an initial excess of 5-20%, 12 out of 17 patients (71%) achieved improvement. In patients with a starting excess of over 20%, 7 out of 8 (88%) showed a volumetric improvement. Patients with an initial excess volume of 5-20% and greater than 20% achieved a median 47% and 29% reduction respectively in excess volume (Figure 3).

(a)



(b)


250
200
150
100
50
0
-50
-100
-150
% change in excess volume

(c)

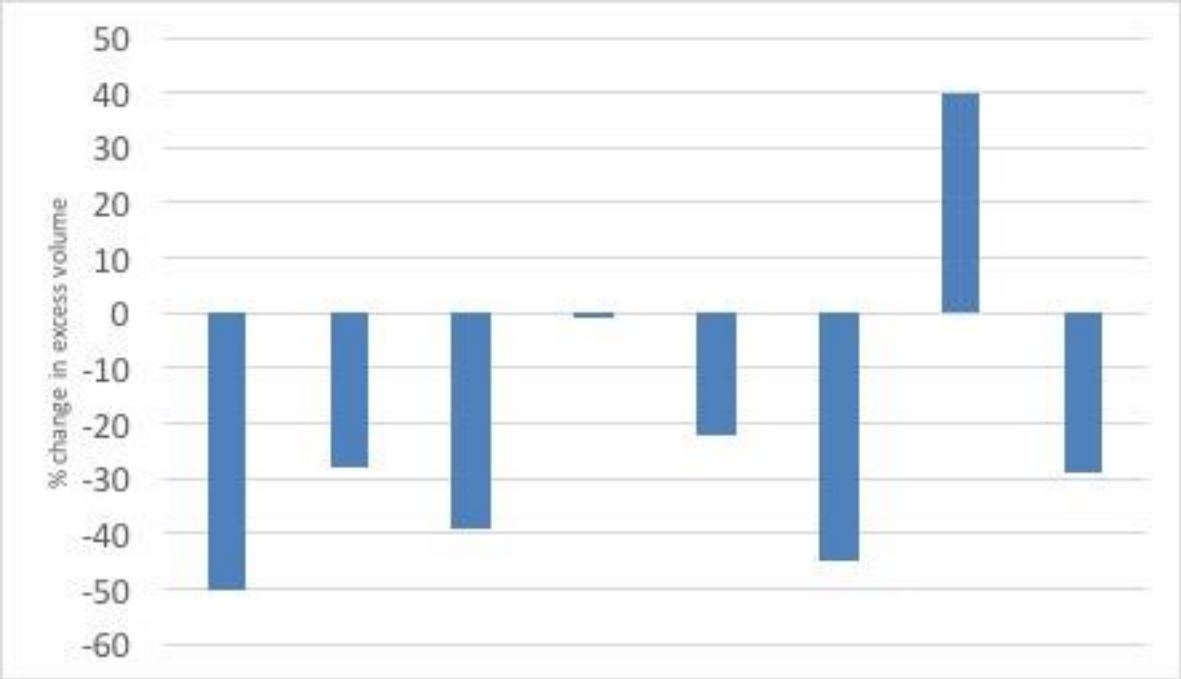

50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
% change in excess volume

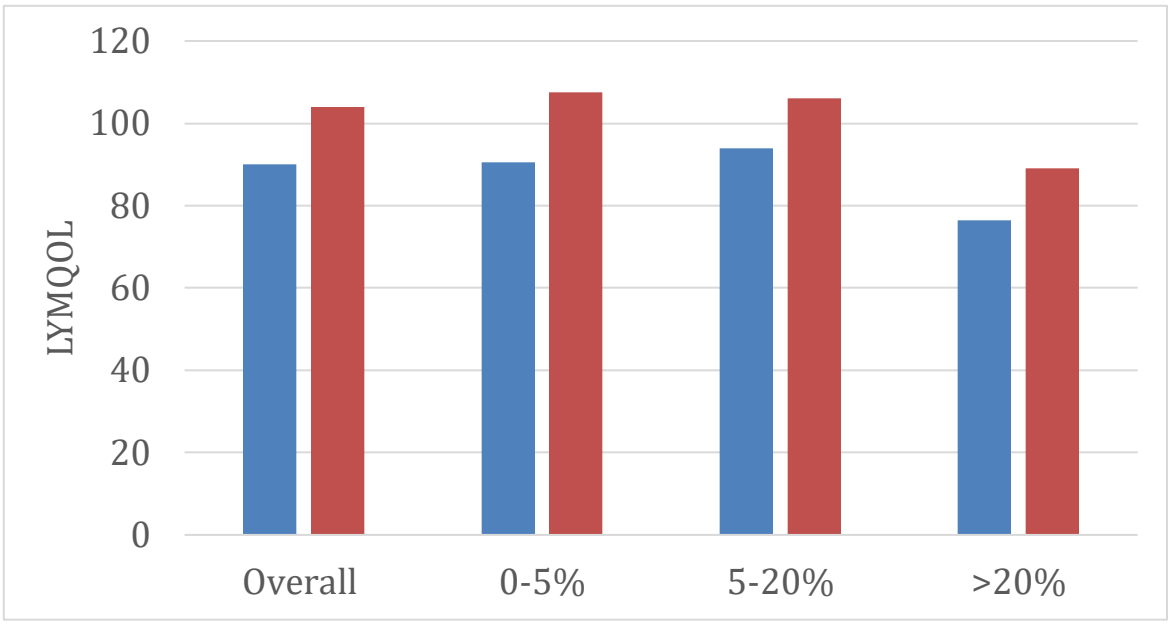
Figure 3

Percentage change in excess volume for each patient dependent on patient's initial (pre-operative) percentage excess volume. (a) Initial excess volume less than 5%. (b) Initial excess volume between 5 and 20%. (c) Initial excess volume greater than 20%. Each bar represents one arm.

Quality of Life

The median pre-op LYMQOL was 90 points (range 46-116), which improved to 104 points (range 45-113) post-operatively ($p < 0.005$) (Figure 4a). The median improvement in quality of life was 9% with 32 of 37 patients (86%) reporting improved quality of life post-operatively. Improvement in quality of life was greatest in patients with the smallest differential volume between arms lymphoedema (Figure 4a). When analysing the LYMQOL domains separately, the greatest improvements were in patients' perception of mood and appearance (Table 1). Improvements were seen in all LYMQOL domains irrespective of initial excess volume except limb function in patients with greater than 20% excess volume (Figure 4b).

a)


120
100
80
60
40
20
0
LYMQOL
Overall
0-5%
5-20%
>20%

b)

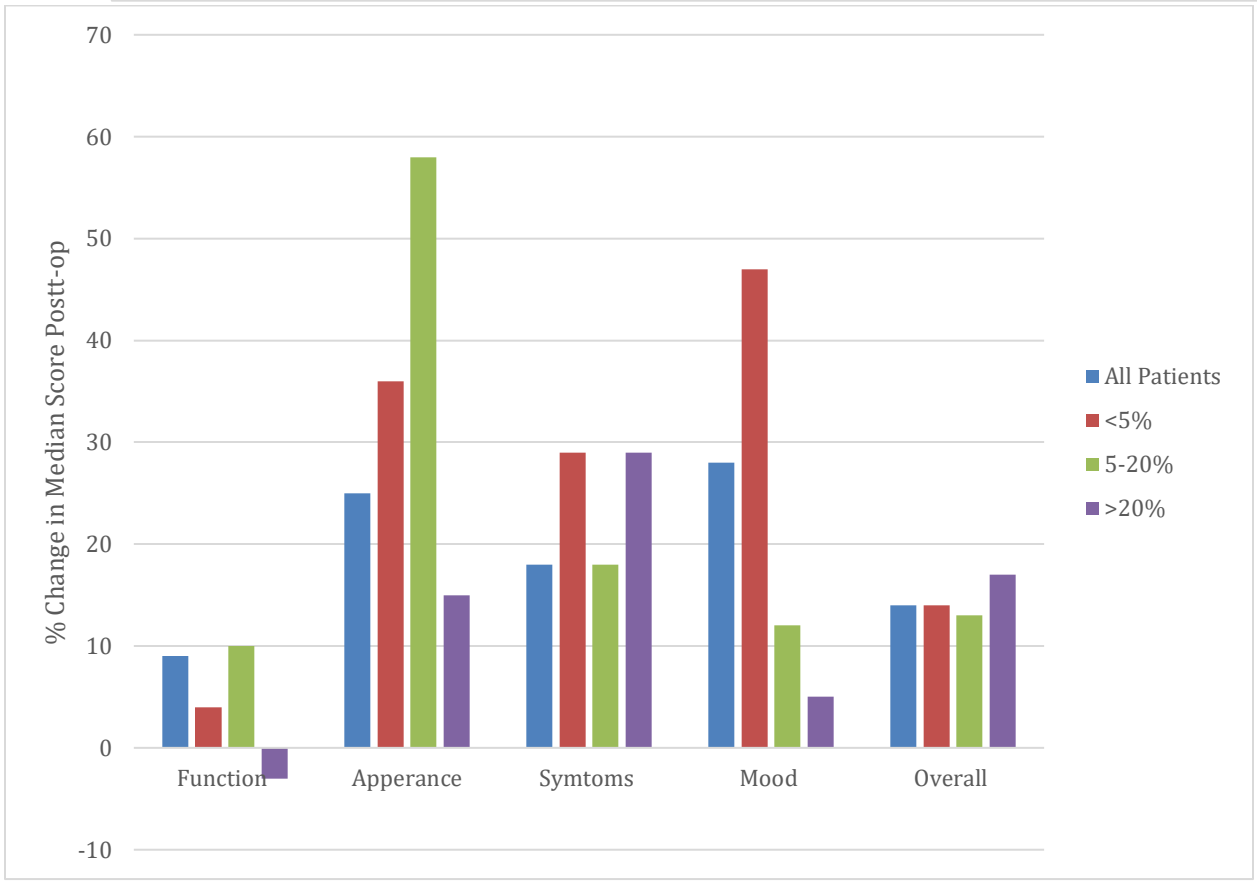

70
60
50
40
30
20
10
0
-10
% Change in Median Score Postt-op
Function
Apperance
Symtoms
Mood
Overall
All Patients
<5%
5-20%
>20%

Figure 4

Median pre and post-operative LYMQOL. a) Median score shown for all patients and dependent on initial excess volume. Blue bar is pre-operative LYMQOL and red is post-operative LYMQOL. b) Median percentage improvement in LYMQOL domains post-operatively dependent on pre-operative excess volume.

Table 1 ***Median percentage improvement in LYMQOL score for each domain in all patients post-operatively.***

Domain	% Improvement in LYMQOL score	p-value
Function	9	0.01
Appearance	25	0.02
Symptoms	18	<0.005
Mood	28	0.001
Overall	14	0.02

Compression Therapy

Of the 37 patients in this study, 13 have been able to discontinue wearing a compression sleeve. Six of nine patients with an initial excess volume less than 5% were able to discontinue wearing a compression sleeve, compared to seven of the 17 with a pre-operative excess volume between 5 and 20%. All patients with an initial excess volume greater than 20% have required ongoing compression therapy.

Complications

There were no complications in this cohort of patients. In particular we did not observe persistent lymphatic leak, wound infection, or cellulitis following surgery.

Discussion

Here we have demonstrated that minimally invasive LVA surgery improved both quality of life and volumetric measurements in patients with stable lymphoedema. Overall, the median reduction in excess volume was 23%, but results varied depending on the volumetric discrepancy pre-operatively. Results have been variable in the literature (15), however surgeons experienced in the procedure achieve similar degrees of volume reduction, dependent on the lymphoedema stage (7).

Although more substantial volumetric improvements are achieved with reductive techniques (16,17) , they require a greater degree of conservative management post-operatively, often with compression garments being worn for 23 hours per day. LVA has the benefit of being minimally invasive and performed under local anaesthetic. In addition, LVA reduced the need for compression therapy in a significant number of patients: 34 % of patients were able to discontinue compression therapy. When analysed by starting volume discrepancy 70% of those with less than 5% initial excess volume, and 38% of those with between 5 and 20% excess volume were able to stop compression. The majority of other patients achieved improved limb volumes and were able to reduce the frequency or strength of compression garments without adverse effects. Our aim is for patients with up to 15% excess volume pre-operatively to no longer be reliant on compression garments post operatively. In comparison, following liposuction, patients must continue lifelong compression therapy (16). Furthermore, unlike LVA reductive procedures can damage and further compromise the remaining functional lymphatics

(17). Improving lymphatic drainage and reducing lymphatic stasis has also been shown to significantly reduce the incidence of cellulitis in patients with lymphoedema, though our study was not designed to test this outcome (6,18).

Our results are skewed by the apparent increase in limb volume in patients with low grade lymphoedema and an initial excess volume of less than 5%. It should be highlighted that in this cohort an apparent 200% increase in excess volume seen in one patient (Figure 3a) actually represents a change from 10ml excess volume to 32ml excess volume from pre-op to 11 months follow up. This is a tiny absolute volume increase, and within the measurement error of the perometer (19). Furthermore, the LYMQOL for this patient increased from 94 to 111, mainly because she felt the arm was less tight, and she no longer wore a compression sleeve or undertook any other forms of conservative therapy. In our experience, the improvement in quality of life reported by patients with early lymphoedema and minimal preoperative excess limb volume, is explained by the reduced need for compression wear and an improvement in the heaviness and discomfort associated with poorly functioning lymphatics.

It should also be noted that all patients in this study have stable or worsening lymphoedema despite conservative therapy and so without surgical treatment limb volume would be expected to worsen or at best remain static.

There are difficulties in measuring successful outcomes in patients presenting with very early stage lymphoedema. These patients may already have a high quality of life and minimal excess

limb volume and little improvement in these values may be achieved post-operatively. However, a successful outcome is prevention of the development of clinically significant lymphoedema and removing the reliance on compression sleeves. Interestingly, the greatest improvements in quality of life are seen in patients within this group. This is likely due to the fact that a large number of these women are able to maintain low excess volumes without use of compression therapy post operatively.

Independent of their initial excess volume, the majority of patients reported improved quality of life post-operatively. Lymphoedema is known to have significant impact on patients' psychosocial wellbeing (20). The greatest improvements we observed were in patients' mood and perception of their appearance.

LVA is a technically demanding operation requiring specialist training but can be performed safely under local anesthetic as a day case, making it a treatment option for patients with multiple co-morbidities (21) . Supermicrosurgical LVA was preceded by microsurgical LVA which anastomosed the lymphatics to venules greater than 2mm rather than the smaller subdermal venules. The use of smaller venules with a lower pressure reduces the risk of anastomosis site thrombosis and improves patency (17) . LVA is a safe procedure. In this cohort, we report no complications, though we have observed minor complications such as wound healing problems and wound infection in other patients in our practice whose lymphoedema was secondary to gynaecological malignancy, or primary lymphoedema.

Due to the latent onset of lymphoedema there is wide variation in when the procedure is performed. Some groups have used LVA as an effective preventative measure at the time of axillary dissection for breast cancer (3), whilst others detect subclinical lymphoedema using ICG lymphography and intervene to prevent lymphoedema development (11). Other groups use LVA in those who have tried but failed conservative treatment (22). In patients with established lymphoedema, LVA is a treatment option for patients with stage I-II, after which fibrosclerotic changes to lymphatic vessels prevent successful functioning of a lymphaticovenular anastomosis. As a result, our group offers LVA to patients with ICG proven subclinical and clinical lymphoedema up to and including stage II. Disease stage rather than duration of lymphoedema is the determining factor in patient selection as the distal lymphatic channels must be patent and free of fibrosclerotic changes.

Conclusion

LVA is a minimally invasive technique providing significant volumetric reduction and improvement in quality of life for lymphoedema after breast cancer treatment and should be considered as a first surgical intervention in patients with lymphoedema not responding to conservative management.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding

None.

Ethical Approval

Study carried out in accordance with the Declaration of Helsinki.

References

1. Cancer Research UK. Breast cancer statistics | Cancer Research UK [Internet]. [cited 2017 Jun 15]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer
2. National Institute for Health and Care Excellence. Early and localised advanced breast cancer overview [Internet]. 2016 [cited 2016 Jul 19]. Available from: https://pathways.nice.org.uk/pathways/early-and-locally-advanced-breast-cancer#content=view-node%253Anodes-surgery-with-or-without-breast-reconstruction
3. Boccardo FM, Casabona F, Friedman D, Puglisi M, De Cian F, Ansaldi F, et al. Surgical Prevention of Arm Lymphedema After Breast Cancer Treatment. Ann Surg Oncol [Internet]. 2011 Sep 3 [cited 2017 Jun 5];18(9):2500–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21369739
4. Tiwari P, Coriddi M, Salani R, Povoski SP, Ellis S, Warren A, et al. Breast and gynecologic cancer-related extremity lymphedema: a review of diagnostic modalities and management options. World J Surg Oncol [Internet]. BioMed Central; 2013 [cited 2016 Jun 14];11(1):237. Available from: http://wjso.biomedcentral.com/articles/10.1186/1477-7819-11-237

5. DiSipio T, Rye S, Newman B, Hayes S. Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. Lancet Oncol [Internet]. Elsevier; 2013 May 1 [cited 2017 Oct 18];14(6):500–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23540561

6. Sharkey AR, King SW, Ramsden AJ, Furniss D. Do surgical interventions for limb lymphoedema reduce cellulitis attack frequency? Microsurgery [Internet]. 2017 May [cited 2017 Jun 5];37(4):348–53. Available from: http://doi.wiley.com/10.1002/micr.30115

7. Leung N, Furniss D, Giele H. Modern surgical management of breast cancer therapy related upper limb and breast lymphoedema. Maturitas [Internet]. 2015 Apr [cited 2017 Jun 5];80(4):384–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25747119

8. BEST PRACTICE FOR THE MANAGEMENT OF LYMPHOEDEMA. [cited 2017 Jun 15]; Available from: http://www.woundsinternational.com/media/issues/210/files/content_175.pdf

9. Foldi E. The treatment of lymphedema. Cancer [Internet]. John Wiley & Sons, Inc.; 1998 Dec 15 [cited 2016 Jul 21];83(S12B):2833–4. Available from: http://doi.wiley.com/10.1002/%2528SICI%25291097-0142%252819981215%252983%253A12B%252B%253C2833%253A%253AAID-CNCR35%253E3.0.CO%253B2-3

10. Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Itoh S. Long-term follow-up after lymphaticovenular anastomosis for lymphedema in the leg. J Reconstr Microsurg [Internet]. 2003 May [cited 2016 Jul 21];19(4):209–15. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/12858242

11. Akita S, Mitsukawa N, Kuriyama M, Hasegawa M, Kubota Y, Tokumoto H, et al. Suitable therapy options for sub-clinical and early-stage lymphoedema patients. J Plast Reconstr Aesthet Surg [Internet]. 2014 Apr [cited 2017 Jun 5];67(4):520–5. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1748681513007389

12. 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 [Internet]. Public Library of Science; 2012 [cited 2016 Jul 22];7(6):e38182. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22675520

13. Mihara M, Seki Y, Hara H, Iida T, Oka A, Kikuchi K, et al. Predictive lymphatic mapping: a method for mapping lymphatic channels in patients with advanced unilateral lymphedema using indocyanine green lymphography. Ann Plast Surg [Internet]. 2014 Jun [cited 2017 Jun 5];72(6):706–10. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000637-201406000-00020

14. Keeley, Vaughan, Crooks, Sue, Locke, Jane, et al. A quality of life measure for limb lymphoedema (LYMQOL). J Lymphoedema [Internet]. 2010 [cited 2016 Jul 21];5(1):26–37. Available from: http://www.lymphormation.org/journal/content/0501

15. Damstra RJ, Voesten HGJ, van Schelven WD, van der Lei B. Lymphatic venous anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11 LVA procedures in 10 patients with breast cancer related lymphedema and a critical

review of the literature. Breast Cancer Res Treat [Internet]. 2009 Jan 13 [cited 2017 Jun 5];113(2):199–206. Available from: http://link.springer.com/10.1007/s10549-008-9932-5

16. Damstra RJ, Voesten HGJM, Klinkert P, Brorson H. Circumferential suction-assisted lipectomy for lymphoedema after surgery for breast cancer. Br J Surg [Internet]. John Wiley & Sons, Ltd.; 2009 Aug [cited 2016 Jul 22];96(8):859–64. Available from: http://doi.wiley.com/10.1002/bjs.6658

17. Tiwari P, Coriddi M, Salani R, Povoski SP. Breast and gynecologic cancer-related extremity lymphedema: a review of diagnostic modalities and management options. World J Surg Oncol [Internet]. 2013 Sep 22 [cited 2017 Jun 5];11(1):237. Available from: http://wjso.biomedcentral.com/articles/10.1186/1477-7819-11-237

18. Mihara M, Hara H, Furniss D, Narushima M, Iida T, Kikuchi K, et al. Lymphaticovenular anastomosis to prevent cellulitis associated with lymphoedema. Br J Surg [Internet]. 2014 Oct [cited 2016 Jul 22];101(11):1391–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25116167

19. Sharkey AR, King SW, Kuo RY, Bickerton SB, Ramsden AJ, Furniss D. Measuring Limb Volume: Accuracy and Reliability of Tape Measurement Versus Perometer Measurement. Lymphat Res Biol [Internet]. 2017 Sep 28 [cited 2017 Oct 18];lrb.2017.0039. Available from: http://online.liebertpub.com/doi/10.1089/lrb.2017.0039

20. Moffatt CJ, Franks PJ, Doherty DC, Williams AF, Badger C, Jeffs E, et al. Lymphoedema: an underestimated health problem. QJM [Internet]. The Oxford University Press; 2003 Oct [cited 2016 Jul 21];96(10):731–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14500859

21. Koshima I, Nanba Y, Tsutsui T, Takahashi Y, Itoh S, Fujitsu M. Minimal invasive lymphaticovenular anastomosis under local anesthesia for leg lymphedema: is it effective for stage III and IV? Ann Plast Surg [Internet]. 2004 Sep [cited 2017 Jun 5];53(3):261–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15480014

22. Campisi C, Bellini C, Campisi C, Accogli S, Bonioli E, Boccardo F. Microsurgery for lymphedema: Clinical research and long-term results. Microsurgery [Internet]. 2010 [cited 2017 Jun 5];NA-NA. Available from: http://doi.wiley.com/10.1002/micr.20737