Lymphaticovenular anastomosis in the treatment of secondary lymphoedema of the legs after cancer treatment

Georgina S A Phillips[1], Sinclair Gore[2,3], Alex Ramsden[2,3], Dominic Furniss[2,3]

1. Oxford University Clinical Academic Graduate School, John Radcliffe Hospital, Oxford, UK, OX3 9DU
2. Plastic and Reconstructive Surgery Department, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, UK, OX3 9DU
3. Oxford Lymphoedema Practice, Nuffield Health, The Manor Hospital, Beech Road, Oxford, OX3 7RP

Corresponding Author

Dominic Furniss

Address: Oxford Lymphoedema Practice, Nuffield Health, The Manor Hospital, Beech Road, Oxford, OX3 7RP

Tel: ++44 1869351300

Running title: LVA for leg lymphedema after cancer treatment

Funding: None

Acknowledgements: The data in this manuscript has been presented at the British Lymphology Society Conference, Birmingham, October 2016.

Précis

In selected patients with early stage lymphedema, LVA offers a minimally invasive surgical option that can achieve significant volumetric and quality of life improvements.

Abstract

Objective

As survival from cancer continues to improve, greater importance is placed on quality of life after surgery. Lymphoedema is a common and disabling complication of cancer treatment. Lymphaticovenular anastomosis (LVA) is a supermicrosurgical treatment option for lower limb lymphoedema. The aim of this study was to assess the effectiveness of LVA in reducing limb volume and its effect on quality of life of patients with secondary leg lymphoedema following treatment for cancer, including gynaecological cancers.

Methods

Limb volume and patient rated quality of life were collected prospectively pre-operatively and at every post-operative appointment. All patients presenting to the clinic with stable or progressive leg lymphedema despite conservative therapy who were suitable candidates for LVA over a three-year period were included.

Results

Twenty-nine patients were treated with LVA, 19 for unilateral lymphoedema and 10 for bilateral. In unilateral cases median limb excess volume reduced from 27% to 16% post operatively ($p < 0.005$) and in bilateral cases a median 9% reduction in absolute limb volume was achieved. Significant improvement in patient-reported quality of life was demonstrated, as measured by the LYMQOL: 23% improvement in unilateral and 14% improvement in bilateral patients (both $p < 0.05$).

Conclusions

In selected patients with early stage lymphedema secondary to cancer treatment, LVA offers a minimally invasive surgical option that can achieve significant volumetric and quality of life improvements.

Introduction

Gynecological cancers affect over 13,000 women in the UK each year (1–3). Surgery and radiotherapy play an important role in treatment. As survival continues to improve (1–3) an increasing number of women are living with side effects of treatment and a greater emphasis is being placed on quality of life after cancer.

The lymphatics regulate the removal of fluid from the interstitium (4), transporting lymph back into the venous system. Surgery and radiotherapy can damage the lymphatics and depending on the treatment modality and type of gynecological cancer up to 51% (5) of women will develop secondary lymphoedema. Lymphoedema is caused by inadequate lymph return to the venous system and the subsequent accumulation of protein-rich exudate within subcutaneous tissue in the limb (6). Lymphoedema is a serious and progressive condition and without careful management causes functional impairment with significant effects on patients' quality of life. Patients report leg heaviness and discomfort, a reduced ability to work, to carry out normal daily activities, and reduced self-confidence. Patients are also at increased risk of recurrent cellulitis (5,7–9).

There is no cure for lymphoedema; it is a chronic progressive condition. Early diagnosis and therapy is important to control and slow progression. Complex decongestive physiotherapy is the current gold standard treatment consisting of a combination of manual lymphatic drainage, skin care and compression therapy (10).

Although this may achieve adequate control, in the majority of patients it is labour-intensive, time-consuming and as a result patients struggle with compliance. In addition, in some patients lymphoedema will progress despite maximal conservative therapy.

Surgery is an option when conservative measures fail to achieve adequate volume control, and if implemented early in disease it may reduce or eliminate the need for continued conservative treatment. Surgical options include physiological reconstructive techniques such as lymphaticovenular anastomosis (LVA) and lymph node transfer, or reductive techniques such as debulking and liposuction (11). LVA is a supermicrosurgical operation using high power operating microscopes to anastomose distal functioning lymphatic channels to small subdermal venules less than 0.8 mm in diameter, thereby creating a physiological bypass of damaged lymphatics. It can be performed under local anesthetic (12) making it an attractive treatment option for all patients, including the elderly or those with multiple co-morbidities.

The aim of this study was to assess the effectiveness of LVA in reducing limb volume and its effect on quality of life of patients with secondary leg lymphoedema following cancer treatment.

Materials and Methods

Data was collected prospectively for all patients who underwent LVA to treat lymphoedema of the legs secondary to cancer treatment between November 2013 and November 2016.

Patient selection

Patients are referred by their GP or specialist, or self-refer to our clinic. LVA was offered to patients with stable or worsening symptoms on maximal conservative therapy in whom Indocyanine Green Lymphography (ICG) confirmed the presence of lymphoedema or subclinical lymphoedema as demonstrated by specific patterns of dermal backflow (13,14). Pre-operatively patients are assessed to ensure adequate underlying distal lymphatic function, defined by us as transport of dye from a subcutaneous injection in the first webspace of the foot to the level of the knee or more proximal within 45 minutes. Patients who did not fulfill our criteria were not offered LVA surgery.

Procedure

Pre-operatively lymphatic channels were marked using ICG lymphography (13). LVA was performed under local anesthetic. Two consultant plastic surgeons operated simultaneously on all patients, allowing two separate sets of anastomoses to be

performed simultaneously, thereby limiting operative time. These results reflect the work of the three consultant microsurgeons working in our practice. All procedures were performed under the operating microscope from initial incision to skin closure. Four transverse incisions were made in the limb, guided by findings of linear lymphatic channels on ICG lymphography - typically in the upper thigh, lower thigh, proximal medial calf, and above the ankle. Lymphatics and veins were identified in the subcutaneous tissue, and anastomosed using 11/0 Ethilon® Nylon sutures (Ethicon Inc, US) (Figure 1). A typical procedure lasted four hours. Post-operatively patients were encouraged to elevate their legs and perform simple massage from distal to proximal towards the scars. Compression garments were re-started at seven days post-op, and a full return to normal activities was encouraged from four weeks. Outpatient follow-up was routinely undertaken at three, six and 12 months, however some patients opt out of extended follow-up as they travel long distances to our clinic.

Volume measurement

Limb volume was measured pre-operatively and at every post-operative appointment. To reduce inter-observer variability measurements were taken using a perometer (15). For patients with unilateral lymphoedema excess volume was calculated using the unaffected leg as a control. In patients with bilateral lymphoedema change in absolute limb volume from baseline for each limb was used as no “normal” limb is available for comparison.

Quality of life

Quality of life was measured pre-operatively and at every post-operative appointment using the Lymphoedema Quality of Life Questionnaire (LYMQOL). This is a validated tool for the assessment of the impact of lymphoedema on patients' quality of life, with specific questions to assess the impact of lymphoedema in terms of symptoms, appearance, function and mood (16). The maximum LYMQOL score is 114, with a higher score after intervention representing improved quality of life at the time of measurement.

Statistics

We used simple descriptive statistics to analyse change in limb volume and quality of life following LVA surgery. To compare pre- and post-operative scores we used the Wilcoxon test.

Results

Demographics

Our cohort consisted of 29 women, with an average age of 50 years (range 28-76). The underlying diagnosis was cervical cancer in 17, endometrial in 4, melanoma in 3, leiomyosarcoma in 2, and the remaining three patients had diagnosis' of ovarian cancer, synovial sarcoma and rhabdomyosarcoma. Twenty-six (90%) patient's had lymphadenectomy, 14 (48%) radiotherapy and 5 (17%) chemotherapy. The mean time from cancer treatment to LVA was 9 years (range 1-22). Pre-operatively all patients wore compression garments, 21 (72%) used manual lymphatic drainage and 14 (48%) other conservative therapies. Nineteen patients had unilateral lymphoedema and ten had bilateral lymphoedema. Median follow up was eight months for unilateral and 10 months for bilateral patients. Quality of life and volumetric data is from the most recent post-operative appointment.

Volume reduction

In unilateral cases, the median pre-operative excess volume was 27% (range 1.4 – 85%). Fifteen out of 19 patients (79%) showed reduced limb volume post-operatively (Figure 2a). The median post-operative excess was 16% (range -2.3 – 63%). The median relative percentage volume reduction was 26% (range -46.9 – 267.9, $p < 0.005$).

In bilateral cases, absolute volumetric improvement was seen in 19/20 limbs (95%)

(Figure 2b). Post-operative median absolute percentage improvement in limb volume was 9% (range -3.4 – 29.1%).

Quality of Life

The median pre-op LYMQOL was 71 (range 31-95). This improved to a median of 90 (range 43-108) post-operatively. The median improvement in quality of life was 22% (range -34.8 – 164.5, $p < 0.005$). Improved quality of life was seen in 23/28 (82%) patients. Post-operative LYMQOL scores were not available for one patient.

In the unilateral cohort statistically significant improvements were seen in patients' overall rating of quality of life, function and appearance ($p < 0.05$) (Figure 3). While in bilateral cases, a statistically significant improvement in quality of life was reported in patient's perception of overall quality of life, mood and symptoms ($p < 0.05$).

Compression Therapy

Of the 29 patients in this study, four (2 unilateral, 2 bilateral) have discontinued compression therapy after LVA and three have reduced their use of compression garments.

Complications

There were no surgical complications in this cohort of patients.

Discussion

Main Findings

These results demonstrate that LVA, a minimally invasive operation performed under local anaesthetic, can significantly reduce limb volume and improve quality of life in cancer survivors with secondary lymphoedema of the legs. A reduction in limb volume was seen in 83% of patients overall and improved quality of life was reported in 82% of patients. Combined results for unilateral and bilateral cases demonstrated significant improvements were seen in patient's rating of limb function, symptoms, mood, appearance and overall quality of life post LVA. In addition, four of 29 patients were to discontinue compression while maintaining volumetric improvement. A further three patients were able to reduce use of compression therapy.

Strengths and Limitations

Our results demonstrate the potential benefits in terms of significant improvements in limb volume and quality of life that can be achieved by LVA. LVA is a highly complex procedure requiring specialized training, as such it is not widely available in the UK, as a result this is a single centre study, reflecting the work of three microsurgical consultants. However, our volumetric outcomes are in line with the international literature (12,17,18).

Median patient follow-up was 7 months for unilateral and 9 months for bilateral cases, post-operative data was taken from the most recent post-operative appointment. Although we routinely see patients at 3, 6, 12 months patients, length of follow-up is dependent on patient's wishes and those that achieve either good or disappointing results may not perceive long-term follow-up appointments to be necessary.

Lymphedema is a progressive disease (19) characterized by lymphatic scarring, lymphatic vessel sclerosis and loss of smooth muscle cells (6). All patients included in this study had stable or worsening lymphoedema on maximal conservative therapy, with dermal backflow patterns confirmed on ICG lymphography; without surgery we would expect their lymphoedema to remain static or progress, and as such a control group is not included in this study. There were no changes to conservative therapies received by patients post-operatively, therefore any improvement in limb volume can be considered due to surgery. An increased limb volume was seen in a few of our patients, given the natural history of lymphedema this is likely to be the result of lymphoedema progression despite surgery rather than surgery itself worsening symptoms.

Interpretation

LVA is technically demanding surgery, our results combined with international literature demonstrate that specialist surgery can significantly improve patients'

symptoms and limb volume (12,20). Boccardo et al achieved significant volumetric improvement in 83% of patients treated with LVA with an average reduction of 67% (20), Koshima achieved volumetric reduction in 82.5% of patients with an average 41.8% reduction in excess volume (12).

Cellulitis is troublesome complication of chronic lymphedema often requiring hospitalization (9). Although not measured in this study, our unit and others have reported a reduction of up to 87% in the incidence of cellulitis post LVA (9,20,21). Interestingly, volumetric improvement does not correlate with improvement in LYMQOL score. In our experience many patients report a subjective improvement in limb discomfort post operatively despite not achieving a statistically significant improvement in limb volume, and we perceive this to be one of the main benefits of LVA in patients with low initial excess volumes. This subjective improvement was not directly addressed in this study.

Within our practice, LVA is offered only to patients with early stage (I-II) lymphedema, we feel treatment is most effective at this stage before lymphatic vessels become fibrotic and lose smooth muscle function (6). Volumeteric improvement can be difficult to detect in early disease, and the greatest improvements in limb volume are typically seen in stage II-III disease (17). Boccardo et al have successfully reduced the proportion of women developing arm lymphoedema from 30% to 4% by performing LVA at the time of axillary dissection (22). However, conservative therapies remain the gold-standard of care, and within

our practice LVA is offered only to women with intrusive lymphoedema despite maximal conservative therapies, due to the morbidity associated with operating on patients without disease. Reductive techniques such as liposuction are the most appropriate treatment options for patients with more advanced disease and achieve greater volumetric reduction than that typically seen after LVA and are not reliant on the patency of lymphatic vessels (23,24). Mihara et al recommend treatment options such as liposuction in patients where no lymphatic function is maintained, as patients must wear lifelong compression therapy 24 hours a day (19,24). In contrast, LVA can offer the opportunity of freedom from compression garments (20). Within our cohort 4/29 patients were able to discontinue compression therapy. Another series with 10 year follow-up reported 85% of patients are able to stop conservative therapies post-operatively (20). Additionally, in patients with early stage disease LVA has other benefits over reductive methods: it is a physiological reconstruction with little risk of further damage to lymphatics, it can be performed under local anesthetic as a day case making it more accessible to patients with multiple co-morbidities, and it has a low complication rate.

Conclusion – practical and research recommendations

Our results suggest that LVA can offer both volumetric reduction and improvement in quality of life in selected patients with early stage lymphoedema secondary to cancer. Patients with early symptoms or signs of lymphoedema, or whose lymphoedema is progressing despite maximal conservative therapy, may benefit

from surgical assessment as to their suitability for LVA. Further research should look at the longer term multi-centre outcomes of LVA.

Conflicts of Interest

None

Ethical approval

As this was a service evaluation, ethical approval was not required.

Funding

None

References

1. Cancer Research UK. Ovarian cancer statistics | Cancer Research UK [Internet]. 2014 [cited 2017 Jun 15]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer
2. Cancer Research UK. Vaginal cancer statistics | Cancer Research UK [Internet]. 2014 [cited 2017 Jun 15]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/vaginal-cancer
3. Cancer Research UK. Cervical cancer statistics | Cancer Research UK [Internet]. 2014 [cited 2017 Jun 15]. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer
4. Ellis S. Structure and function of the lymphatic system: an overview. Br J Community Nurs [Internet]. 2006 Dec [cited 2017 Jun 15];11(Sup6):S4–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16739286
5. Beesley V, Janda M, Eakin E, Obermair A, Battistutta D. Lymphedema after gynecological cancer treatment : prevalence, correlates, and supportive care needs. Cancer [Internet]. 2007 Jun 15 [cited 2017 Jun 5];109(12):2607–14. Available from: http://doi.wiley.com/10.1002/cncr.22684
6. Nagase T, Gonda K, Inoue K, Higashino T, Fukuda N, Gorai K, et al. Treatment of lymphedema with lymphaticovenular anastomoses. Int J Clin Oncol [Internet]. 2005 Oct 25 [cited 2017 Jun 5];10(5):304–10. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/16247656

7. 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 [cited 2017 Jun 5];11(1):237. Available from: http://wjso.biomedcentral.com/articles/10.1186/1477-7819-11-237

8. Ryan M, Stainton MC, Jaconelli C, Watts S, MacKenzie P, Mansberg T. The experience of lower limb lymphedema for women after treatment for gynecologic cancer. Oncol Nurs Forum [Internet]. [cited 2016 Jun 14];30(3):417–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12719742

9. 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

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

11. Cormier JN, Rourke L, Crosby M, Chang D, Armer J. The Surgical Treatment of Lymphedema: A Systematic Review of the Contemporary Literature (2004–2010). Ann Surg Oncol [Internet]. 2012 Feb 24 [cited 2017 Jun 5];19(2):642–

51. Available from: http://www.springerlink.com/index/10.1245/s10434-011-2017-4

12. 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

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. 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

15. 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

16. 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

17. 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 [Internet]. 2016 Jul [cited 2017 Dec 15];138(1):262–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27348659

18. 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

19. 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

20. 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

21. 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 [Internet]. 2016 Jul [cited 2017 Dec 20];138(1):262–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27348659

22. 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

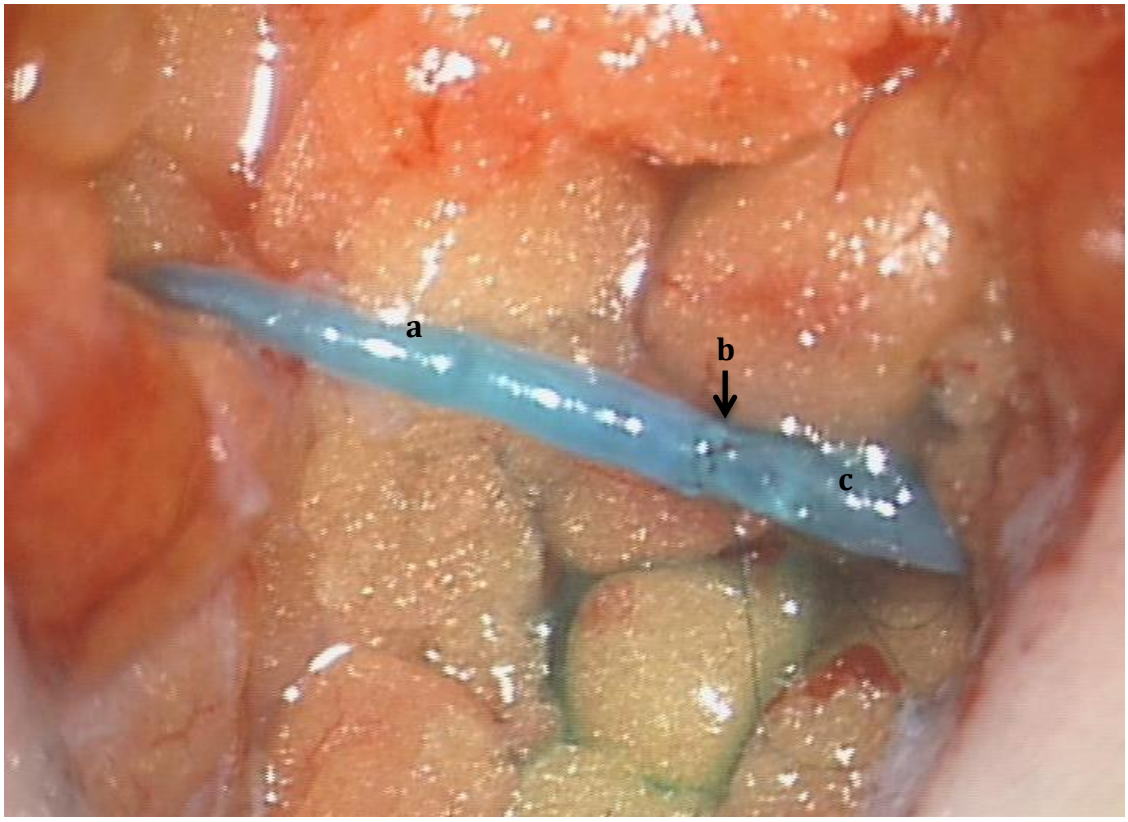
23. Leung N, Furniss D, Giele H. Modern surgical management of breast cancer therapy related upper limb and breast lymphoedema. Maturitas [Internet]. 2015 Apr [cited 2017 Jun 5];80(4):384–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25747119

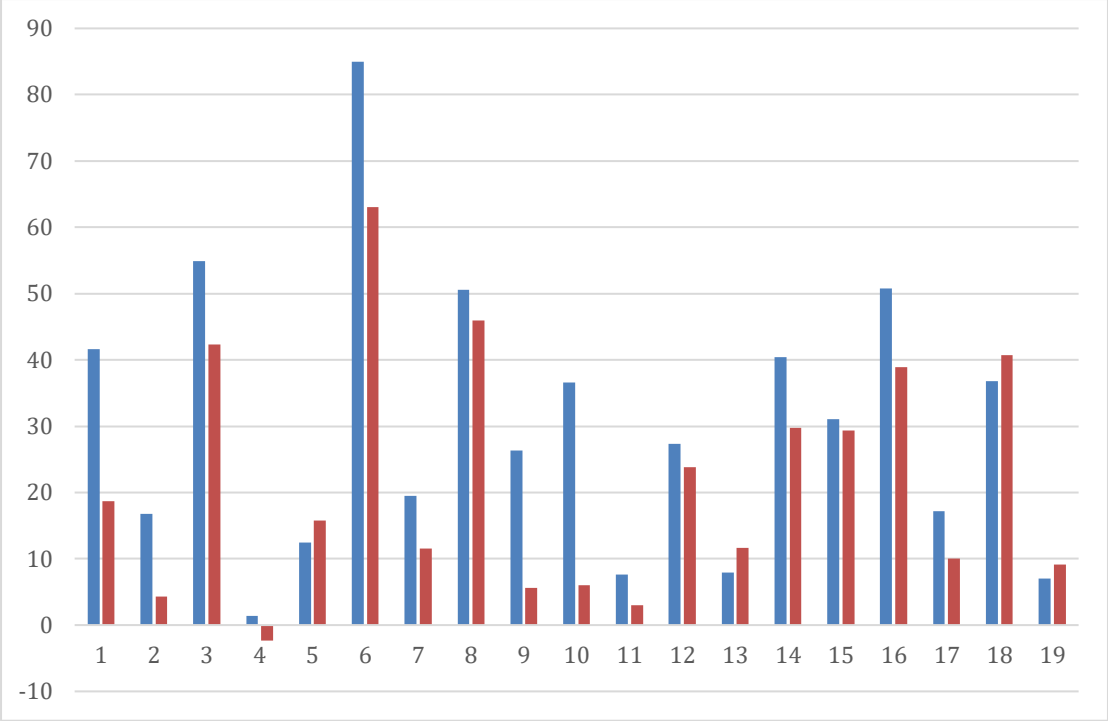
24. Damstra RJ, Voesten HGJM, Klinkert P, Brorson H. Circumferential suction-assisted lipectomy for lymphoedema after surgery for breast cancer. Br J Surg [Internet]. John Wiley & Sons, Ltd.; 2009 Aug [cited 2016 Jul 22];96(8):859–64. Available from: http://doi.wiley.com/10.1002/bjs.6658

Figures

Figure 1

Lymphaticovenular anastomosis involves anastomosing multiple functioning distal lymphatics to small subcutaneous venules in order to restore lymphatic flow. (a) Lymphatic Vessel containing patent blue dye, (b) Anastomosis with 11/0 Ethilon sutures, (c) Venule also contains patent blue, indicating a functioning anastomosis.





b) Percentage reduction in absolute limb volume for each limb in patients with bilateral lymphoedema who underwent LVA. Each bar represents a single leg.

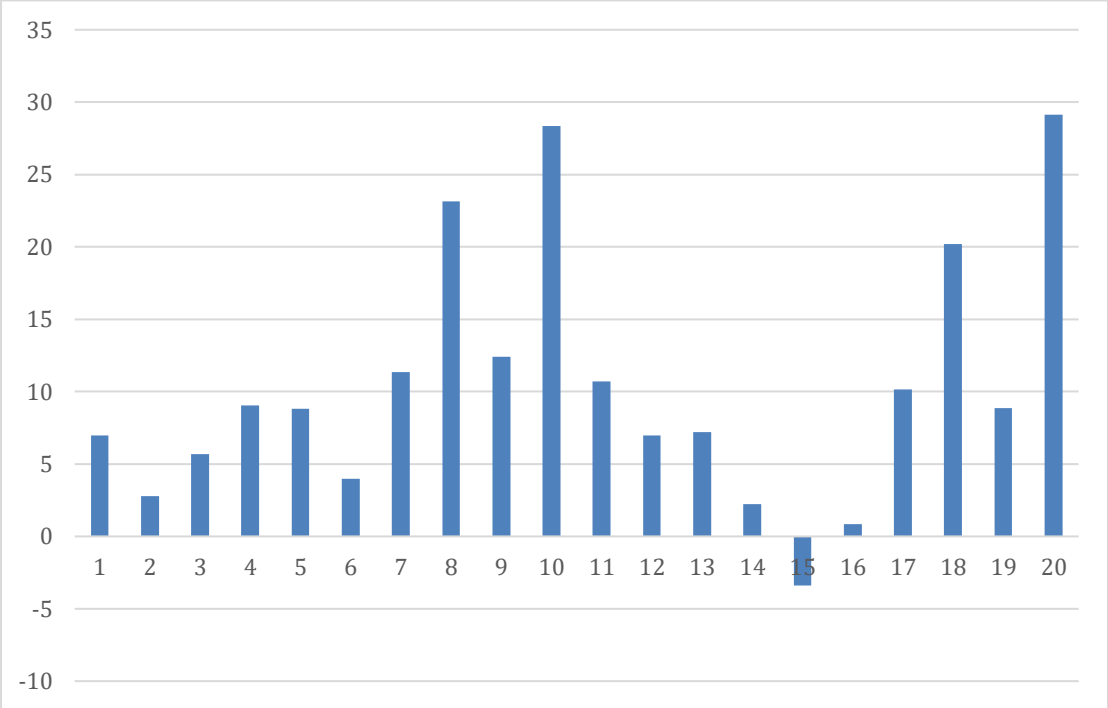
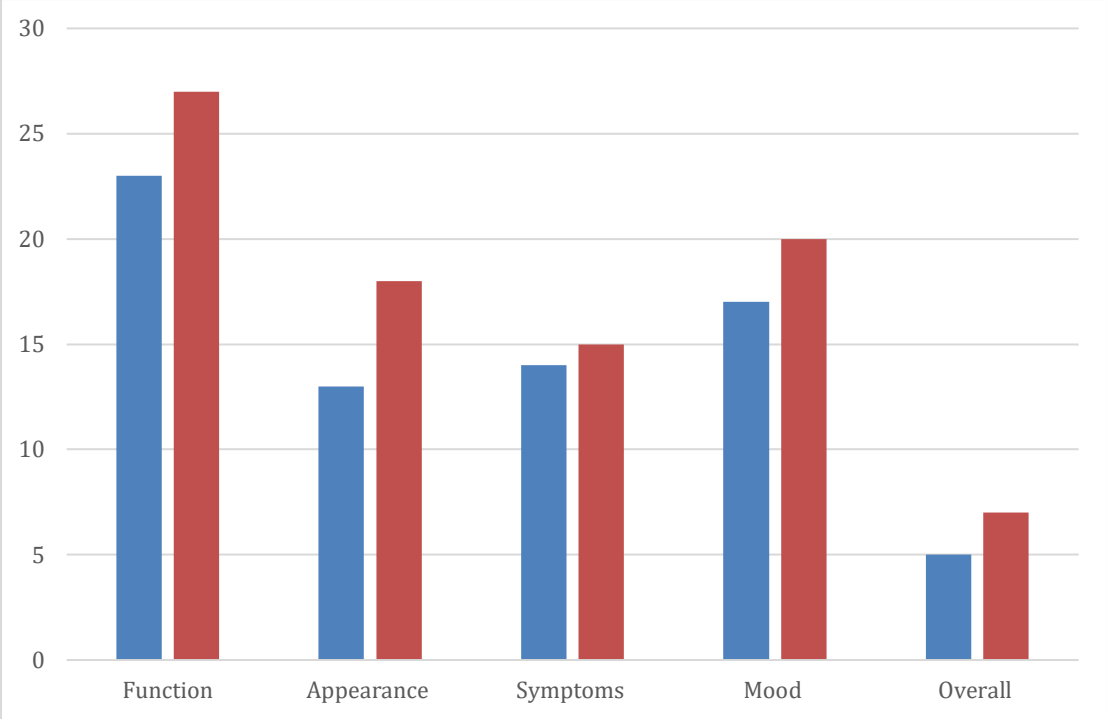


Figure 3

Quality of life before and after LVA surgery

Median LYMQOL score for each domain for patients with unilateral and bilateral lower limb lymphoedema combined. Maximum score varied per domain. All changes are significantly significant ($p<0.05$). Blue bars are pre-operative scores and red post-operative.


30
25
20
15
10
5
0
Function
Appearance
Symptoms
Mood
Overall