

Lymphovenous anastomoses in patients with primary and secondary lymphoedema

Systematic Review



Ludwig Boltzmann Institut
Health Technology Assessment

Decision Support Document No. 110
ISSN online: 1998-0469

Lymphovenous anastomoses in patients with primary and secondary lymphoedema

Systematic Review



Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, March 2018

Project Team

Project leader: Dr.ⁱⁿ med. Katharina Hawlik, MSc

Authors: Katharina Rosian, BSc, MSc
MA Michal Stanak, AKC

Project Support

Systematic literature search: Tarquin Mittermayr, BA (Hons), MA

External Review 1: Univ.-Prof. Dr. Christine Radtke, MBA, FEBOPRAS
University Hospital for Surgery, Department for Plastic and Reconstructive Surgery,
University Hospital Vienna;

External Review 2: Dr. med. Katrin Seidenstücker
Clinic for Plastic Surgery II, Sana Hospital Düsseldorf Benrath;

Internal Review: Dr.ⁱⁿ med. Katharina Hawlik, MSc

Correspondence

Katharina Rosian, BSc, MSc, Katharina.Rosian@hta.lbg.ac.at

This report should be referenced as follows:

Rosian K, Stanak M. Lymphovenous anastomoses in patients with primary and secondary lymphoedema. Decision Support Document No. 110; 2018. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the LBI-HTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the LBI-HTA.

The HTA Core Model[®], developed within EUnethTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. The following version of the Model was used: HTA Core Model Version 4.2. Use of the HTA Core Model does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

CONTENT INFORMATION

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Wien
<https://hta.lbg.ac.at/page/imprint>

Responsible for content:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisonsgasse 7/20, A-1090 Vienna
<https://hta.lbg.ac.at/>

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at <https://eprints.hta.lbg.ac.at>

Decision Support Document No.: 110

ISSN-online: 1998-0469

© 2018 LBI-HTA – All rights reserved

Content

Executive Summary	5
Zusammenfassung	9
1 Scope	15
1.1 PICO question	15
1.2 Inclusion criteria	15
2 Methods	17
2.1 Research questions	17
2.2 Sources.....	18
2.3 Systematic literature search.....	19
2.4 Flow chart of study selection	20
2.5 Analysis	21
2.6 Synthesis.....	21
3 Description and technical characteristics of technology	23
4 Health Problem and Current Use.....	27
5 Clinical effectiveness	33
5.1 Outcomes.....	33
5.2 Included study	33
5.3 Results	34
6 Safety.....	37
6.1 Outcomes.....	37
6.2 Included Studies	37
6.3 Results	39
7 Quality of evidence	41
8 Discussion	43
9 Recommendation	49
10 References.....	51
Appendix	55
Evidence tables of individual studies included for clinical effectiveness and safety	55
Risk of bias tables and GRADE evidence profile	61
Applicability table	65
List of ongoing trials	66
Literature search strategies.....	70
Search strategy for Cochrane	70
Search strategy for CRD (DARE, NHS-EED, HTA).....	70
Search strategy for Embase	71
Search strategy for Medline via Ovid.....	71

List of Figures

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)	20
Figure 3-1: Basic four types of LVA.....	24

List of tables

Table 1-1: Inclusion criteria.....	15
Table 4-1: ISL and Campisi staging of lymphoedema.....	30
Table 7-1: Summary of findings table of LVA.....	42
Table 9-1: Evidence based recommendations.....	49
Table A-1: LVA: Results from one non-randomized controlled study.....	55
Table A-2: LVA: Results from prospective interventional single-arm studies.....	57
Table A-3: RoBANS risk of bias assessment tool for non-randomized controlled studies.....	61
Table A-4: Risk of bias – study level (case series), IHE checklist.....	62
Table A-5: Evidence profile: efficacy and safety of LVA surgical treatment in lymphoedema.....	64
Table A-6: Summary table characterizing the applicability of a body of studies.....	65
Table A-7: List of ongoing randomised controlled trials of LVA.....	66
Table A-8: List of ongoing trials of LVA (parallel non-randomized and single-arm non-randomized studies).....	67

List of abbreviations

AdHopHTA.....	European Project on Hospital-Based Health Technology Assessment
AWMF.....	Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.)
CRD.....	Centre for Review and Dissemination
GRADE.....	Grading of Recommendations Assessment, Development and Evaluation
HTA.....	health technology assessment
ICG.....	indocyanine green
IHE checklist.....	Institute of Health Economics Quality Appraisal of Case Series Studies Checklist
ISL.....	International Society of Lymphology
CDT.....	complex decongestive therapy (komplexe physikalische Entstauungstherapie, KPE)
LVA.....	lymphovenous anastomosis
LVL.....	lymphovenous-lymphatic transplant
NRCT.....	non-randomized controlled trial
n.s.....	not significant
PoP.....	Planned and Ongoing Projects
QoL.....	quality of life
RCT.....	randomized controlled trial
RoB.....	risk of bias
RoBANS.....	Risk of Bias Assessment Tool for Non-randomized Studies
s.s.....	statistical significant
US.....	United States
USA.....	United States of America
VLNT.....	vascularized lymph node transfer
VSLNT.....	vascularized supraclavicular lymph node transfer

Executive Summary

Introduction

Health Problem

In the scope of this assessment, primary and secondary lymphoedema is the condition of interest. Lymphoedema is a chronic disease and requires treatment. It can occur at any age – in childhood, primary forms are more common [1]. Overall, lymphoedema can be congenital or acquired, so-called primary (congenital abnormality or malfunction in the lymphatic system) and secondary lymphoedema (caused by defects to the lymphatic system, usually due to cancer treatment, infection, or trauma) [2-4].

There is no cure for lymphoedema [2, 5, 6]. Without appropriate management, lymphoedema may worsen causing pain and comprise body image disturbances, infections, restrictions in range of motion (functional impairment/restricted mobility), swelling, cellulitis, and a decrease in patients' QoL with functional, aesthetic, and psychic repercussions (e.g., feeling of tightness, heavy feeling, narrowness of clothing, shoes and jewellery, and skin alterations). It may also lead to irreversible changes like fibrosis or the excess of adipose tissue. These patient-reported symptoms can occur individually or in combination [1, 7-11].

Description of Technology

The aim of LVA is to restore lymphatic circulation and bypass obstructions in lymphatics by constructing an alternative lymph drainage pathway [12]. The procedure anastomoses distal subdermal lymphatic vessels and adjacent venules with the diameter of less than 0.8 mm [13, 14]. Therefore, a connection of functioning lymphatic vessels and similarly sized subdermal venules is made to allow unidirectional flow of lymphatic fluid directly into the venous system, meaning that the lymph does not need to pass the damaged lymphatic area to return to the circulation [5, 15, 16].

LVA can be performed in four basic ways: end-to-end, side-to-side, end-to-side, and side-to-end [17, 18]. The procedure is technically demanding, time-consuming, and requires a specialized team with experience in microsurgical techniques [19]. The procedure is performed under microscope with maximum magnification and therefore, specifically designed supermicrosurgical instruments as well as suture material with the size of 11.0 and 12.0 are required. Further, to map healthy and functioning lymphatic vessels and to approve the patency of the anastomosis, one recent technological advance in LVA procedures is the use of indocyanine green (ICG) fluorescence lymphangiography [20]. Ongoing anastomosis patency can be confirmed during follow-up with lymphoscintigraphy or ICG lymphography [16, 20, 21].

Research question

Is lymphovenous anastomosis in comparison to conservative or other surgical treatments (e.g., lymph node transfer/transplantation) in patients with lymphoedema stage I, II and III more effective and safer concerning pain, functionality, quality of life (QoL), recurrence or complications?

focus:
primary and secondary lymphoedema

no cure for lymphoedema, without appropriate management it may be causing pain, comprise body image disturbances, infections, restrictions in range of motion, cellulitis, and decrease in QoL

LVA is supermicrosurgical method, which anastomoses distal subdermal lymphatic vessels and adjacent venules with the diameter of less than 0.8 mm

LVA can be performed in 4 basic ways: end-to-end, side-to-side, end-to-side, and side-to-end

LVA is performed under microscope and with supermicrosurgical instruments

research question

systematic literature search	<p>Methods</p> <p>To answer the research questions on efficacy and safety-related outcomes, a systematic literature search in four databases was conducted. In addition, we performed a manual search and screened information provided by the submitting hospital to identify further relevant studies. The study selection, data extraction, and assessing the methodological quality of the studies was performed by two independent researchers.</p>
crucial outcomes for efficacy ...	<p>Domain effectiveness</p> <p>The following efficacy-related outcomes were used as evidence to derive a recommendation: QoL, pain, functionality, and recurrence.</p>
... and safety	<p>Domain safety</p> <p>The following safety-related outcomes were used as evidence to derive a recommendation: adverse events (procedure-related and not procedure-related).</p>
1 non-randomized controlled study and 4 prospective single-arm studies	<p>Results</p> <p>Available evidence</p> <p>A total of one non-randomized controlled study and four prospective single-arm studies were eligible for inclusion in the current report. A cut-off of more than or even 10 patients was defined as an inclusion criterion for prospective single-arm studies.</p> <p>Overall, data on efficacy and safety was evaluated in 56 and 217 patients, respectively.</p>
only 1 non-randomized controlled study	<p>Clinical effectiveness</p> <p>To assess the effectiveness of LVA for lymphoedema, we could only identify one non-randomized controlled study (NRCT) with a total of 43 patients assessing the effectiveness of LVA compared to 13 patients with vascularized supraclavicular lymph node transfer (VSLNT).</p>
no evidence on crucial outcomes	<p>No evidence was found on the crucial outcomes pain, functionality, and recurrence.</p>
important endpoint "changes in the postoperative volume" in VSLNT-group statistical significant	<p>Only the NRCT assessed the important outcome on changes in the postoperative volume. The comparison was made between the LVA and the VSLNT group using the Lower Extremity Lymphoedema index (LEL). The mean changes of volume compared with preoperative volumes were statistical significant in the VSLNT group [22].</p>
crucial endpoint adverse events:	<p>Safety</p> <p>One NRCT could be identified for the safety assessment of LVA (43 patients) and VSLNT (13 patients). Further, safety outcomes were evaluated in four prospective single-arm studies (161 patients).</p>
in NRCT no adverse events with LVA reported; with VSLNT 3 out of 13 patients (23.1%)	<p>In the LVA group of the NRCT, no adverse events were reported compared to the VSLNT group, where adverse events were reported in three patients who completed the follow-up, out of 13 patients (23.1%), with statistical significance in favor of LVA.</p>

Overall, procedure-related adverse events occurred in two patients who completed the follow-up, out of 161 included patients across the prospective single-arm studies (1.2%).

**in prospective studies:
2 out of overall
161 patients (1.2%)**

None of the studies reported on procedure unrelated adverse events.

Upcoming evidence

Currently, there are three ongoing randomized controlled trials, which might show effects of LVA with a higher quality of evidence: two ongoing RCTs evaluate LVA compared to complex decongestive therapy (NCT02790021 & JPRN-UMIN000025137), and one ongoing pilot study evaluating the efficacy of robot-assisted LVA in comparison to conventional LVA (NTR6465).

3 ongoing RCTs

Furthermore, 8 ongoing parallel non-randomized (n=4) and single-arm non-randomized studies (n=4) could be identified.

**8 further ongoing
studies (4 NRCTs and
4 single-arm studies)**

Reimbursement

At this point in time, the use of LVA for the treatment of lymphoedema is not reimbursed by the Austrian health care system.

**no reimbursement of
the procedure in Austria**

Discussion

Overall, the strength of evidence for the effectiveness and safety of LVA was very low due to high risk of bias in the NRCT, the observational study design, insufficient outcome reporting, and small sample sizes.

**strength of evidence
for effectiveness and
safety “very low”**

The overall risk of bias was considered moderate to high because no randomization or blinding was performed, and because of insufficient reporting on critical outcomes (e.g. QoL), unclear reporting of confounding variables, and patients' consecutive recruitment.

**moderate to
high risk of bias**

The included studies in this report demonstrate mixed results following the LVA procedures and the quality of these studies varies. A major concern of most of the identified prospective interventional single-arm studies is the low number of included patients. In order to identify rare procedure related adverse events, low patient numbers are insufficient. Another essential issue are the follow-up periods in the included studies. Yet, only one study had a longer follow-up period of 12 months [20]. Therefore, reliable data of long-term safety and efficacy outcomes are missing. Another limitation of this review is that the studies included varied in terms of stages of lymphoedema, localisation of lymphoedema (upper or lower extremity), and outcomes were not reported separately on primary and secondary lymphoedema, which may lead to a variation in efficacy and safety of the results.

**studies demonstrate
mixed results and quality
of studies varies**

Nevertheless, LVA seems to be safe for the treatment of primary and secondary lymphoedema. However, no controlled evidence for crucial outcomes could be identified evaluating LVA and a comparator. Patient-relevant outcomes such as QoL were only described in uncontrolled studies and inconsistently reported. Because the included studies showed poor quality of evidence and high risk of bias, it is not possible to draw a reliable conclusion on the clinical effectiveness of LVA.

**LVA could be safe
procedure, but low
quality of evidence
→ reliable conclusion
not possible**

further high-quality studies necessary to confirm outcomes (e.g., QoL) and to determine exact patient group that would benefit most from procedure

Further, there were various methods of LVA performed in the studies, data on upper extremity lymphoedema was reported more frequently, and the estimation of ongoing post-interventional treatments (e.g., compression treatment etc.) is scarce and presented a large variety. Future RCTs and/or prospective NRCTs need to be performed to find the optimal lymphoedema management algorithm and to help determine the exact patient group that would benefit most from the procedure. In addition, these studies need to be conducted to confirm the outcomes, especially on QoL, and to further knowledge of this field.

**evidence insufficient
→ LVA currently not recommended**

Conclusion

On the basis of the available evidence, we cannot conclude if the assessed procedure LVA is at least equally effective and safer as the comparator VLNT or conservative treatment. Due to the methodological shortcomings of the available evidence, no conclusions are made about the effectiveness of the procedure. There is a need for high-quality studies due to consistent positive findings based on observational evidence with respect to limb volume reduction. Concerning safety outcomes, only procedure-related complications were reported based upon data from one NRCT and four prospective interventional single-arm studies. These suggest a relatively safe profile of LVA. New study results based on a high-quality RCT will potentially influence the effect estimate considerably.

re-evaluation after 2021 recommended, if ongoing studies include patient-relevant outcomes

The re-evaluation is recommended after 2021, if the potentially relevant ongoing studies are completed and only if patient-relevant outcomes are included to derive a recommendation. Otherwise, still no conclusions can be drawn on patient-relevant outcomes.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Der Fokus dieser systematischen Übersichtsarbeit liegt auf primären und sekundären Lymphödemen.

Ein Lymphödem ist eine chronische, entzündliche Erkrankung, die eine Behandlung erfordert. Die Erkrankung kann angeboren oder erworben sein, so genannte primäre (kongenitale Fehlbildung oder Fehlfunktion des lymphatischen Systems) und sekundäre Lymphödeme (verursacht durch Defekte des lymphatischen Systems, in der Regel aufgrund von Krebsbehandlungen, Infektion oder Trauma) [2-4]. Lymphödeme können in jedem Alter auftreten – primäre Formen sind in der Kindheit häufiger [1].

Der Krankheitsverlauf ist variabel [23]. Ein Lymphödem entsteht aus einer Zusammensetzung proteinreicher Flüssigkeit im interstitiellen Raum mit anfänglichen Symptomen eines weichen, pitterenden Ödems in der betroffenen Extremität. Dies kann eine Entzündung des Gewebes und eine Stimulation der Fibrose verursachen. Die Verschlechterung der lymphatischen Funktion führt ferner zu Ablagerungen im Unterhautgewebe. Diese Faktoren beeinflussen das Lymphödem, wodurch es zu einer Verschlechterung der Symptome kommt und zu einer dicken, fibrotischen, fettigen, ödematösen und schmerzhaften Extremität fortschreitet, die die täglichen Aktivitäten der PatientInnen beeinträchtigt [23].

Lymphödeme können nicht vollständig geheilt werden [2, 5, 6]. Ohne entsprechende Behandlung kann sich das Lymphödem verschlechtern und Schmerzen verursachen. Dazu gehören Körperbildstörungen, Infektionen, Einschränkungen des Bewegungsumfanges (funktionelle Beeinträchtigung/eingeschränkte Mobilität), Schwellungen, Zellulitis und eine Abnahme der Lebensqualität der PatientInnen mit funktionellen, ästhetischen, und psychischen Auswirkungen (z. B. Engegefühl, Schweregefühl, Enge von Kleidung, Schuhen und Schmuck sowie Hautveränderungen) [1, 7-11].

Beschreibung der Technologie

Das Ziel einer lymphovenösen Anastomose (LVA) ist die Wiederherstellung des lymphatischen Kreislaufs und die Umgehung von Hindernissen in Lymphgefäßen durch den Aufbau eines alternativen Lymphdrainageweges [12]. Das Verfahren anastomosiert distale, subdermale Lymphgefäße und angrenzende Venolen mit einem Durchmesser von weniger als 0,8 mm [13, 14]. Somit wird eine Verbindung von funktionierenden Lymphgefäßen und ähnlich großen subdermalen Venolen hergestellt, um eine unidirektionale Strömung der Lymphflüssigkeit in das Venensystem zu ermöglichen. Die Lymphe muss demnach den beschädigten Lymphbereich nicht passieren, um in den Blutkreislauf zurückzukehren [5, 15, 16]. Um eine dauerhafte Verbesserung des Lymphödems zu erreichen, sind subdermale Venolen vorteilhafter, da der Blutdruck niedriger ist als in den tiefen, größeren Venen, wodurch es zu einem geringeren venösen Rückfluss kommt [24, 25].

Fokus: primäre und sekundäre Lymphödeme

chronische, entzündliche und schwächende Erkrankung verursacht durch beeinträchtigtes Lymphsystem

anfängliche proteinreiche Flüssigkeit im interstitiellen Raum → Entzündung des Gewebes → Verschlechterung der Lymphfunktion führt zu Fettablagerung, Schmerzen und schränkt tägliche Aktivitäten ein

ohne angemessene Behandlung führen Lymphödeme zu Schmerzen, Infektionen, Funktionseinschränkungen, verminderter Lebensqualität etc.

LVA ist supermikrochirurgische Methode, die distale, subdermale Lymphgefäße und benachbarte Venolen mit einem Durchmesser von < 0,8 mm anastomosiert

4 grundlegende Arten der LVA: end-zu-end, seit-zu-seit, seit-zu-end und end-zu-seit

LVA kann auf vier grundlegende Arten durchgeführt werden: End-zu-End, Seit-zu-Seit, End-zu-Seit und Seit-zu-End [17, 18]. Das Verfahren ist technisch anspruchsvoll, zeitaufwendig und erfordert ein spezialisiertes Team mit Erfahrung in mikrochirurgischen Techniken [19]. Die Verwendung geeigneter Bildgebungswerkzeuge zur Dokumentation der Wirksamkeit ist zudem erforderlich. Wird eine LVA im frühen Krankheitsverlauf der Lymphödeme durchgeführt – bevor Schäden an der lymphatischen Wand und eine beeinträchtigte lymphatische Kontraktilität aufgetreten sind – wird ein größerer und länger anhaltender Nutzen vermutet [15].

LVA wird unter dem Mikroskop mit supermikrochirurgischen Instrumenten durchgeführt

Das Verfahren wird unter einem Mikroskop mit maximaler Vergrößerung durchgeführt. Aus diesem Grund sind speziell konstruierte supermikrochirurgische Instrumente sowie Nahtmaterial mit der Größe von 11,0 und 12,0 erforderlich. Um gesunde und funktionierende Lymphgefäße darzustellen und die Durchgängigkeit der Anastomose zu bestätigen, kann zusätzlich zur LVA die Verwendung der Indocyaningrün (ICG) Fluoreszenz Lymphangiographie als neuer technologischer Fortschritt im Zusammenhang mit dem Verfahren der LVA angewendet werden [20]. Die Durchgängigkeit der Anastomosen kann zusätzlich während einer Nachuntersuchung mit Lymphszintigraphie oder ICG-Lymphographie bestätigt werden [16, 20, 21].

weiterer technischer Fortschritt ist Anwendung von ICG Lymphographie

Wissenschaftliche Fragestellung

Forschungsfrage

Sind lymphovenöse Anastomosen im Vergleich zu konservativen oder anderen chirurgischen Behandlungen (z. B. Lymphknotentransfer/-transplantation) bei PatientInnen mit Lymphödem Stadium I, II und III im Hinblick auf Schmerzen, Funktionalität, Lebensqualität, Rezidiven und Komplikationen wirksamer und sicherer?

Methoden

systematische Literatursuche

Die Beantwortung der Forschungsfrage bezüglich Wirksamkeit und Sicherheit erfolgte anhand einer systematischen Literatursuche in folgenden Datenbanken:

- ✿ Medline via Ovid
- ✿ Embase
- ✿ The Cochrane Library
- ✿ CRD (DARE, NHS-EED, HTA).

Studienauswahl, Datenextraktion und Bewertung durch 2 AutorInnen

Zusätzlich wurde eine Handsuche durchgeführt. Die Studienauswahl, Datenextraktion sowie die Bewertung der methodischen Qualität der Studien erfolgte unabhängig durch zwei AutorInnen. Insgesamt wurden 629 Zitate identifiziert wovon fünf Publikationen (eine nicht-randomisierte kontrollierte Studie und vier prospektive einarmige Studien) für eine Datensynthese eingeschlossen wurden.

14 systematische Reviews & HTAs aufgrund methodischer Unterschiede ausgeschlossen

Darüber hinaus wurden in der systematischen Literatursuche 14 systematische Übersichtsarbeiten und Health Technology Assessments zu LVA bei Lymphödem gefunden, die aufgrund methodischer Unterschiede (z. B. andere Studienziele, Einschluss retrospektiver Studien) von der Analyse ausgeschlossen wurden.

Suche nach laufenden Studien

Zusätzlich wurde eine Suche in drei klinischen Studienregistern (ClinicalTrials.gov, WHO-ICTRP, EU Clinical Trials) durchgeführt, um laufende und unveröffentlichte Studien zu identifizieren. Die Suche resultierte in 15 Treffern, wovon elf Studien als potentiell relevant eingeschätzt wurden.

Die Daten, die für die Entscheidung herangezogenen Endpunkte, wurden aus den einzelnen Studien extrahiert und zusammengefasst und nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) bewertet.

Studienbewertung nach GRADE

Klinische Wirksamkeit

Zur Bewertung der Wirksamkeit wurden die folgenden entscheidenden Endpunkte für eine Empfehlung herangezogen:

entscheidende Endpunkte für Wirksamkeit ...

- ✿ Lebensqualität (QoL)
 - ✿ Schmerzen
 - ✿ Funktionalität
- ✿ Rezidive.

Sicherheit

Zur Bewertung der Sicherheit wurden die folgenden entscheidenden Endpunkte für eine Empfehlung herangezogen:

... und Sicherheit

- ✿ Komplikationen
 - ✿ unerwünschte Ereignisse (verfahrensbezogen)
 - ✿ unerwünschte Ereignisse (nicht-verfahrensbezogen).

Ergebnisse

Verfügbare Evidenz

Insgesamt konnte eine nicht-randomisierte kontrollierte Studie (NRCT) und vier prospektive einarmige Studien identifiziert werden, die den Einschlusskriterien des vorliegenden Berichts entsprachen. Für prospektive einarmige Studien wurde ein Cut-Off von zehn oder mehr PatientInnen als Einschlusskriterium festgelegt.

1 nicht-randomisierte kontrollierte Studie und 4 prospektive einarmige Studien

Ausgewertet wurden Daten zur Wirksamkeit und Sicherheit von insgesamt 56 bzw. 217 PatientInnen.

Klinische Wirksamkeit

Zur Beurteilung der Wirksamkeit der LVA für die Behandlung von Lymphödemem konnte nur eine nicht-randomisierte kontrollierte Studie (NRCT) mit insgesamt 43 PatientInnen im Vergleich zu 13 PatientInnen mit vaskularisiertem supraklavikulärem Lymphknotentransfer (VSLNT) identifiziert werden.

nur 1 nicht-randomisierte kontrollierte Studie

Zu den kritischen Endpunkten Schmerz, Funktionalität und Rezidiven wurde keine Evidenz gefunden.

keine Evidenz zu kritischen Endpunkten

Die einzige NRCT bewertete den wichtigen Endpunkt der Veränderungen des postoperativen Volumens. Der Vergleich wurde zwischen der LVA- und der VSLNT-Gruppe unter Verwendung des Lower-Extremity-Lymphödem-Index (LEL) durchgeführt. Die mittleren Volumenveränderungen gegenüber den präoperativen Volumina waren in der VSLNT-Gruppe statistisch signifikant [22].

wichtiger Endpunkt „Veränderungen des postoperativen Volumens“ in VSLNT-Gruppe statistisch signifikant

kritischer Endpunkt unerwünschte Ereignisse:	Sicherheit
in NRCT keine unerwünschten Ereignisse mit LVA; mit VSLNT 3 von 13 PatientInnen (23,1 %)	Für die Beurteilung der Sicherheit von LVA (43 PatientInnen) und VSLNT (13 PatientInnen) konnte die identifizierte NRCT ebenfalls herangezogen werden. Darüber hinaus wurden die Sicherheitsendpunkte in vier prospektiven einarmigen Studien (161 PatientInnen) berichtet.
in prospektiven Studien: 2 von insgesamt 161 PatientInnen (1,2 %)	In der NRCT Studie wurden in der LVA-Gruppe keine unerwünschten Ereignisse und in der VSLNT-Gruppe bei drei von insgesamt 13 PatientInnen (23,1 %), die das Follow-Up durchliefen, unerwünschte Ereignisse mit statistischer Signifikanz zugunsten der LVA berichtet.
häufigstes unerwünschtes Ereignis: LVA: Hautirritationen nach Kontrastmittel-injektion (n=2); VSLNT: Kongestion der Haut (n=3);	Für die Sicherheitsanalyse können auch verfahrensbezogene Komplikationen von prospektiven einarmigen Studien in Betracht gezogen werden, da diese direkt dem Eingriff zuzurechnenden Effekte ohne Kontrollgruppe analysiert werden können. In den prospektiven einarmigen Studien traten bei zwei von insgesamt 161 PatientInnen (1,2 %), die das Follow-Up durchliefen, verfahrensbezogene unerwünschte Ereignisse auf. Die am häufigsten berichteten unerwünschten Ereignisse waren Kongestion der Haut in drei PatientInnen (23,1 %) nach der Behandlung mit VSLNT [22] und Hautreizungen an der Stelle der Kontrastmittelinjektion in zwei Patienten (10 %) nach der Behandlung mit LVA [21].
3 laufende RCTs	Keine der Studien berichtete über nicht-verfahrensbezogene unerwünschte Ereignisse.
8 weitere laufende Studien (4 NRCTs und 4 einarmige Studien)	Laufende Studien
Verfahren in Österreich derzeit nicht erstattet	Aktuell sind drei laufende RCTs registriert, die möglicherweise einen Effekt der LVA mit einer höheren Evidenzqualität zeigen könnten: zwei RCTs evaluieren LVA im Vergleich zur komplexen physikalischen Entstauungstherapie (NCT02790021 & JPRN-UMIN000025137) und eine laufende Pilotstudie, die die Wirksamkeit der Roboter-assistierte LVA mit der konventionellen LVA evaluiert (NTR6465).
Stärke der Evidenz für klinische Wirksamkeit und Sicherheit sehr gering	Darüber hinaus konnten acht weitere laufende Studien identifiziert werden: vier NRCTs und vier nicht-randomisierte einarmige Studien.
moderates bis hohes Biasrisiko	Kostenerstattung
	In Österreich werden die Kosten der LVA zur Behandlung von Lymphödemen derzeit nicht erstattet.
	Diskussion
	Das Ziel des vorliegenden Berichts war es, die klinische Wirksamkeit und Sicherheit der LVA im Vergleich zu der Vergleichsgruppe (z. B. VLNT) für die Behandlung von Lymphödemen zu bewerten. Insgesamt kann die Stärke der Evidenz für die klinische Wirksamkeit und Sicherheit als „sehr gering“ eingestuft werden, aufgrund von hohem Bias-Risiko in der NRCT, eingeschlossenen Beobachtungsstudien, mangelhafte Ergebnisberichte und geringen Anzahl an PatientInnen.
	Das Biasrisiko wurde als moderat bis hoch eingestuft, da keine Randomisierung oder Verblindung durchgeführt wurde, sowie aufgrund unzureichender Berichterstattung über kritische Ergebnisse (z. B. QoL), unklarem Berichten von Störvariablen und die konsekutive Rekrutierung von PatientInnen.

In Anbetracht der Ergebnisse der eingeschlossenen Studien zeigen sich unterschiedliche Ergebnisse nach einer LVA. Darüber hinaus variiert die Qualität dieser Studien. Wesentlicher Kritikpunkt der meisten identifizierten prospektiven einarmigen Studien ist die geringe Anzahl eingeschlossener PatientInnen. Zur Identifikation von seltenen unerwünschten Ereignissen könnte die kleine Fallzahl unzureichend sein. Ein weiterer essentieller Kritikpunkt sind die relativ kurzen Nachbeobachtungszeiträume in den einzelnen Studien. Lediglich eine Studie hatte einen Nachbeobachtungszeitraum von mehr als 12 Monaten [20]. Daher fehlen zuverlässige Daten über die längerfristigen Sicherheits- und Wirksamkeitsergebnisse. Ein weiterer Kritikpunkt dieses Berichts besteht darin, dass die eingeschlossenen Studien hinsichtlich der Studien des Lymphödems, der Lokalisation des Lymphödems (obere oder untere Extremität) unterschiedlich waren und die Ergebnisse der primären und sekundären Lymphödeme nicht getrennt berichtet wurden, was zu Abweichungen der Wirksamkeit und Sicherheit der Ergebnisse führen kann.

Nichtsdestotrotz scheint eine LVA für die Behandlung von primärem und sekundärem Lymphödem sicher zu sein. Jedoch konnte keine Evidenz aus kontrollierten Studien für entscheidende Endpunkte identifiziert werden, die die LVA mit einem Komparator vergleicht. PatientInnenrelevante Endpunkte wie QoL wurden nur in den prospektiven einarmigen Studien beschrieben und inkonsistent berichtet (z. B. unterschiedliche Messskalen). Da die eingeschlossenen Studien eine schlechte Evidenzqualität und ein hohes Verzerrungspotenzial aufweisen, ist es nicht möglich, eine verlässliche Aussage zur klinischen Wirksamkeit der LVA zu ziehen.

Zukünftige RCTs und/oder prospektive NRCTs müssen durchgeführt werden, um den optimalen Algorithmus zur Behandlung des Lymphödems zu finden und um die genaue PatientInnengruppe zu bestimmen, die am meisten von dem Verfahren profitieren würde. Darüber hinaus sollten diese Studien durchgeführt werden, um die Ergebnisse, insbesondere im Hinblick auf QoL, zu bestätigen und weitere Kenntnisse in diesem Bereich zu erlangen.

Empfehlung

Auf der Grundlage der verfügbaren Evidenz können keine Schlussfolgerungen gezogen werden, ob das bewertete Verfahren der LVA mindestens gleich wirksam und sicherer ist wie die Vergleichsbehandlung mit VLNT. Aufgrund der methodischen Mängel der vorliegenden Evidenz (lediglich ein wichtiges Ergebnis, aber nicht entscheidend für die Empfehlung, wurde in dem einzigen NRCT berichtet), können keine Rückschlüsse auf die Wirksamkeit des Verfahrens gezogen werden. Qualitativ hochwertige Studien sind aufgrund konsistenter positiver Befunde, die auf Beobachtungsdaten in Bezug auf die Volumenreduktion der Extremitäten basieren, erforderlich. Hinsichtlich der Sicherheitsergebnisse wurden nur verfahrensbedingte Komplikationen auf der Grundlage von Daten aus einem NRCT und vier prospektiven einarmigen Studien berichtet, die auf ein relativ sicheres LVA-Profil hindeuten. Neue Studienergebnisse, die auf einem qualitativ hochwertigen RCT basieren, könnten die Effektschätzung erheblich beeinflussen.

Eine Re-Evaluierung wird nach 2021 empfohlen, wenn die potenziell relevanten laufenden Studien abgeschlossen sind und lediglich wenn patientInnenrelevante Endpunkte zur Ableitung einer Empfehlung einbezogen werden. Ansonsten können nach wie vor keine Aussagen zu patientInnenrelevanten Endpunkten getroffen werden.

Studien zeigen unterschiedliche Ergebnisse und Qualität ist niedrig

LVA könnte sicheres Verfahren sein, aber niedrige Evidenzqualität → verlässliche Aussage zur klinischen Wirksamkeit nicht möglich

weitere hochwertige Studien notwendig, um Ergebnisse zu bestätigen (z. B. QoL) und jene PatientInnen zu erreichen, die am meisten von dem Verfahren profitieren

Evidenz unzureichend → LVA derzeit nicht empfohlen

Re-Evaluierung nach 2021 empfohlen, wenn derzeit laufende Studien patientInnenrelevante Endpunkte beinhalten

1 Scope

1.1 PICO question

Is lymphovenous anastomosis in comparison to conservative or other surgical treatments (e.g., lymph node transfer/transplantation) in patients with lymphoedema stage I, II and III more effective and safer concerning pain, functionality, quality of life (QoL), recurrence or complications?

PIKO-Frage

1.2 Inclusion criteria

Inclusion criteria for relevant studies are summarized in Table 1-1.

**Einschlusskriterien
für relevante Studien**

Table 1-1: Inclusion criteria

Population	<p>Patients with primary or secondary lymphoedema stage I, II and III in whom a conservative treatment (e.g., CDT) is ineffective or does not lead to a substantial improvement of the lymphoedema.</p> <p>Lymphoedema is a swelling (oedema) that results from an accumulation of protein-rich fluid in the interstitial space because of congenital or acquired damage to the lymphatic system (lymph vessels or lymph nodes).</p> <p>ICD-10 codes:</p> <p>I89.0- Lymphoedema, not elsewhere classified I89.8 Other specified noninfective disorders of lymphatic vessels and lymph nodes I89.9 Noninfective disorder of lymphatic vessels and lymph nodes, unspecified I97.2- Postmastectomy lymphoedema syndrome</p> <p>MeSH-terms: Lymphoedema (Breast Cancer Lymphoedema, Non-Filarial Lymphoedema)</p>
Intervention	<p>Lymphovenous/lymphaticovenous/lymphaticovenular anastomosis (LVA) Lymphovenous/lymphaticovenous/lymphaticovenular bypass</p> <p>The procedure is a microsurgical/supermicrosurgical technique, where a surgical union or shunt between ducts, tubes, or vessels is made. It may be end-to-end, end-to-side, side-to-end, or side-to-side.</p> <p>MeSH term: Anastomosis, Surgical; No MeSH terms for lymphovenous/lymphaticovenous available.</p>
Control	<p>Conservative or other surgical treatments (vascularized lymph node transfer/transplantation [VLNT]).</p>
Outcomes	
Efficacy	<p>Clinical endpoints:</p> <ul style="list-style-type: none"> ✦ Quality of Life <ul style="list-style-type: none"> ✦ Functionality (retain or restore function, range of joint motion) ✦ Pain (alleviate pain & discomfort) ✦ Recurrence <p>Surrogate endpoints:</p> <ul style="list-style-type: none"> ✦ Limb volume reduction (limb circumference, intra-/extracellular fluids)
Safety	<ul style="list-style-type: none"> ✦ Complications (e.g., infection, lymphorrhea) ✦ Adverse events, procedure-related (e.g., infection, additional procedure, re-exploration) ✦ Adverse events, procedure unrelated

Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective case-series ($n \geq 10$ patients)

2 Methods

2.1 Research questions

Description of the technology	
Element ID	Research question
B0001	What is lymphovenous anastomosis?
B0002	What is the claimed benefit of lymphovenous anastomosis in relation to the comparators?
B0003	What is the phase of development and implementation of lymphovenous anastomosis?
B0004	Who administers lymphovenous anastomosis and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use lymphovenous anastomosis and the comparator(s)?
B0009	What supplies are needed to use lymphovenous anastomosis and the comparator(s)?
A0020	For which indications has lymphovenous anastomosis received marketing authorisation or CE marking?
A0021	What is the reimbursement status of lymphovenous anastomosis?

Health problem and Current Use	
Element ID	Research question
A0001	For which health conditions, and for what purposes is lymphovenous anastomosis used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are lymphovenous anastomosis utilised?

Clinical Effectiveness	
Element ID	Research question
D0005	How does lymphovenous anastomosis affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does lymphovenous anastomosis affect progression (or recurrence) of the disease or health condition?
D0011	What is the effect of lymphovenous anastomosis on patients' body functions?
D0016	How does the use of lymphovenous anastomosis affect activities of daily living?
D0012	What is the effect of lymphovenous anastomosis on generic health-related quality of life?
D0013	What is the effect of lymphovenous anastomosis on disease-specific quality of life?
D0017	Was the use of lymphovenous anastomosis worthwhile?
D0001	What is the expected beneficial effect of lymphovenous anastomosis on mortality?
D0003	What is the effect of lymphovenous anastomosis on the mortality due to causes other than the target disease?

Safety	
Element ID	Research question
C0008	How safe is lymphovenous anastomosis in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying lymphovenous anastomosis?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of lymphovenous anastomosis?
C0007	Are lymphovenous anastomosis and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of lymphovenous anastomosis and the comparator?

2.2 Sources

Description of the technology

**Quellen:
systematische Suche,
Handsuche sowie
Informationen des
einreichenden
Krankenhauses**

- ✦ Handsearch in the POP, AdHopHTA, and CRD databases for Health Technology Assessments, and in Google
- ✦ Background publications identified in database search: see Section 2.3
- ✦ Questionnaire completed by the submitting hospitals

Health problem and Current Use

- ✦ Handsearch in the UpToDate database, POP, AdHopHTA, and CRD databases for Health Technology Assessments and in Google
- ✦ Background publications identified in database search: see Section 2.3
- ✦ Questionnaire completed by the submitting hospitals
- ✦ Handsearch for management guidelines in the National Guideline Clearinghouse and in the database of the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF)

2.3 Systematic literature search

The systematic literature search was conducted on the 14th of December 2017 in the following databases:

- ✧ Medline via Ovid (including PubMed)
- ✧ Embase
- ✧ The Cochrane Library
- ✧ CRD (DARE, NHS-EED, HTA)

The systematic search was not limited to years, but it was limited to articles published in English or German and to only prospective or randomized controlled trials. After deduplication, overall 628 citations were included. The specific search strategy employed can be found in the Appendix (Chapter “Literature search strategies”).

The submitting hospital sent 7 publications of which 0 new citations were identified.

By hand-search, one additional article was found, resulting in overall 629 hits.

A total of 14 systematic reviews and health technology assessments (HTAs) on lymphovenous anastomosis (LVA) could be identified through the systematic literature search. However, due to methodological differences (e.g., other study purposes, inclusion of retrospective studies) of the reviews, we decided to exclude the systematic reviews and HTAs from our analysis. Nonetheless, we searched through the reviews to see if they identified studies that we did not find via our systematic literature search. Most of these provided relevant background information for this report but no additional studies were identified.

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 09.01.2018 resulting in 15 hits. Of those 15 hits, 11 were identified as potentially relevant trials and included in the Appendix (see Chapter “List of ongoing trials”). The other four ongoing trials were excluded because of other study aims or different scopes of application of LVA.

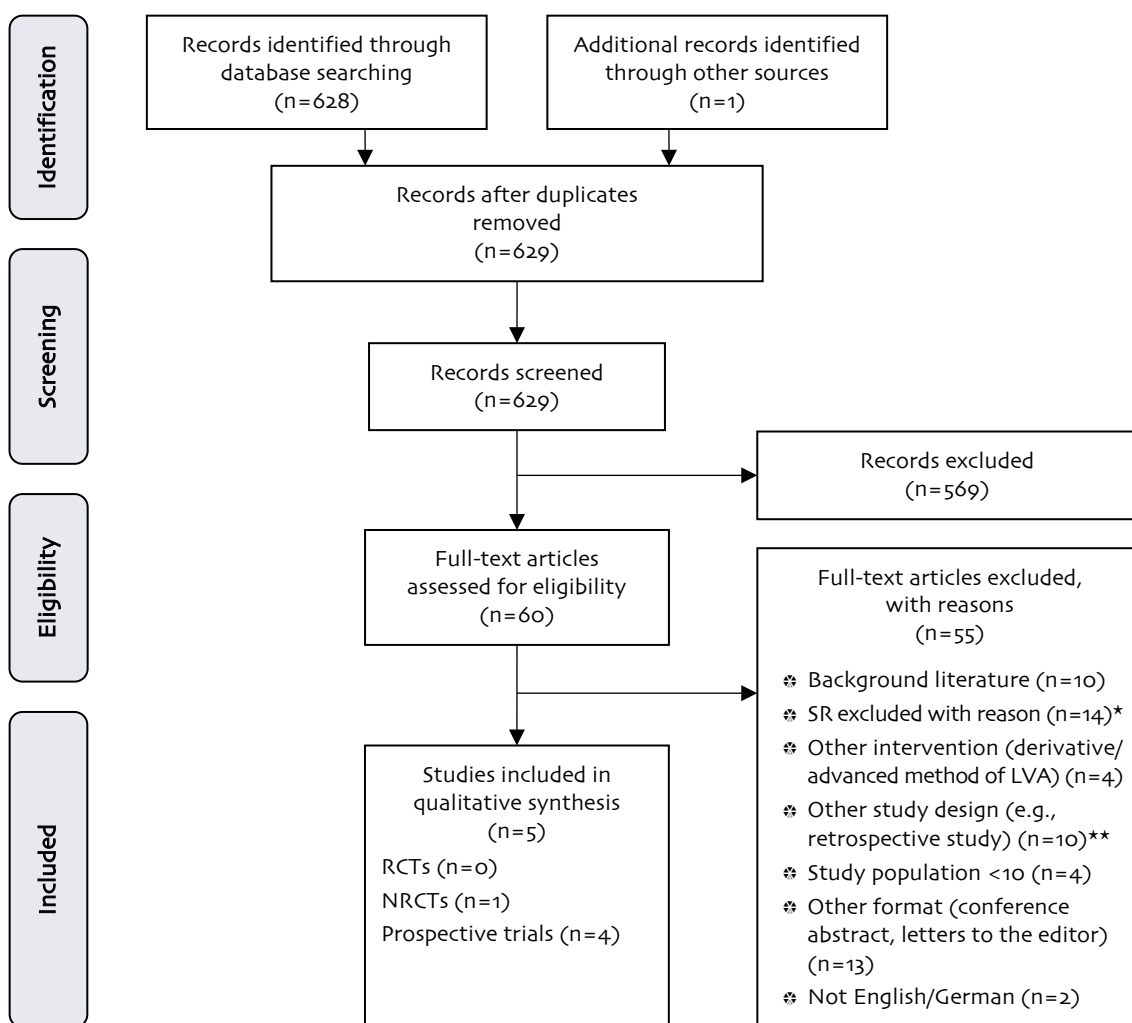
**systematische
Literatursuche in vier
Datenbanken**

**insgesamt 629
Publikationen
identifiziert**

**Suche nach
laufenden Studien**

2.4 Flow chart of study selection

Literatúrauswahl Overall 629 hits were identified. The references were screened by two independent researchers (KR, MS) and in case of disagreement, a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.



* Systematic reviews were excluded if they had other aims, included retrospective studies, compared surgical methods without patient outcomes, or were written in another language.

** 1 publication presented sub-analytical results of another already included observational study. Therefore, only the overall data of the primary study are presented in the outcomes.

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

The data retrieved from the selected studies (see Chapter 2.4) were systematically extracted into a data-extraction-table (see Appendix Table A-1 and Table A-2). No further data processing (e.g., indirect comparison) was applied. The studies were systematically assessed for quality and risk of bias (RoB) by two independent researchers (KR, MS) using the risk of bias assessment tool for non-randomized controlled studies (RoBANS) [26] and the IHE Risk of Bias checklist for case series [27] presented in the Appendix (see Table A-3 and Table A-4).

**Datenextraktion
und Bewertung
des Bias-Risikos laut
RoBANS & IHE Checkliste**

2.6 Synthesis

Based on the data-extraction-table (see Appendix Table A-1 and Table A-2), data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [28]. The research questions were answered in plain text format with reference to GRADE evidence tables that are included in the Appendix, results were summarized in Table 7-1.

**Evidenzsynthese
mittels GRADE**

3 Description and technical characteristics of technology

Features of the technology and comparators

Boo01 – What is lymphovenous anastomosis?

LVA is the focus of this report and aims to anastomose distal subdermal lymphatic vessels and adjacent venules with the diameter of less than 0.8 mm (it is difficult to find larger lymphatic vessels because most are 0.8 mm or under in diameter) [13, 14]. Early stage lymphoedema normally may not affect distal subdermal lymphatic vessels, so those are more readily available for a surgical procedure than deeper lymphatic vessels [8, 13]. Further, blood pressure is lower in subdermal venules than in deeper, larger veins. It is very important that the pressure in the lymphatic vessel is higher than in the recipient venule to allow the lymphatic fluid to enter the venous bloodstream through the LVA procedure. Therefore, utilizing small venules as recipient vessels might lower the risk of obstruction of the LVA due to the backflow of the vein [8, 13]. Hence, a smaller amount of venous backflow in subdermal vessels can be reported and may probably result in an ongoing improvement of lymphoedema [13].

The aim of LVA is to restore lymphatic circulation and bypass obstructions and destructions in lymphatics by constructing an alternative lymph drainage pathway [12]. Therefore, a connection of functioning lymphatic vessels and similarly sized subdermal venules is made to allow unidirectional flow of lymphatic fluid directly into the venous system, meaning that the lymph does not need to pass the damaged lymphatic area to return to the circulation [5, 15, 16]. In addition, with the intention to achieve a more permanent improvement of lymphoedema, subdermal venules should be used because the pressure is lower than that in the deep, larger veins resulting in less venous backflow [24, 25].

LVA can be performed in four basic ways: end-to-end (E-E; distal or proximal portion of a lymphatic vessel is anastomosed to the proximal portion of a venule), side-to-side (S-S; the side wall of a lymphatic vessel is anastomosed to the side wall of a venule), end-to-side (E-S; distal or proximal portion of a lymphatic vessel is anastomosed to the side wall of a venule), and side-to-end (S-E; proximal portion of a venule is anastomosed to the side wall of a lymphatic vessel) (Figure 3-1) [17, 18]. These formations allow the establishment of unidirectional lymph flow from the distal limb of the lymphatic collector.

Additionally, to the basic four types of LVAs, there are several other (advanced) methods described in the literature – like the π -shaped LVA or the “octopus”-LVA. The difference to the basic LVA methods is merely the additional anastomosis of the lymphatic vessel to the venule [25, 29].

LVA ist supermikrochirurgische Methode, die distale subdermale Lymphgefäße und benachbarte Venolen mit einem Durchmesser von < 0,8 mm anastomosiert

**Blutdruck ist niedriger in subdermalen Gefäßen
→ venöser Rückfluss in Gefäße geringer**

Ziel der LVA ist die Wiederherstellung des lymphatischen Kreislaufs und die Umgehung von Hindernissen in Lymphgefäßen, indem ein alternativer Lymphdrainageweg konstruiert wird

LVA kann end-zu-end, seit-zu-seit, seit-zu-end und end-zu-seit, wobei end-zu-end die einfachste Methode zu sein scheint

darüber hinaus gibt es noch weitere andere/ weiterentwickelte LVA Arten (z. B. π -shaped LVA)

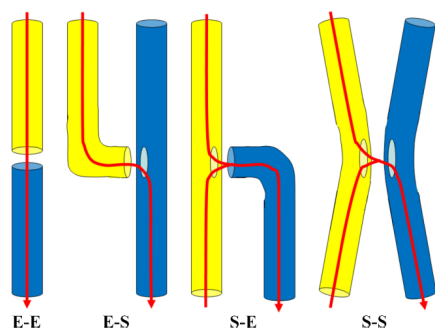


Figure 3-1:
Basic four types of LVA (Source: [17])

LVA ist weniger invasiv, scheint bessere ästhetische Ergebnisse zu erzielen, weniger Komplikationen, kürzere Krankenhausaufenthalte und Behandlungsdauer, sowie geringere Notwendigkeit einer nachfolgenden Kompressionstherapie

Boo02 – What is the claimed benefit of lymphovenous anastomosis in relation to the comparators?

Supermicrosurgical techniques such as LVA aim to redirect the lymphatic fluid into venous circulation and to restore lymphatic drainage. They are a minimally invasive method to reconstruct the lymphatic pathway, and require less use of compression therapy postoperatively. Furthermore, LVA can potentially provide a more permanent solution to chronic lymphoedema [2, 16, 30].

According to the information provided by the submitting hospital and the literature, LVA in lymphoedema may lead to a significant improvement in functionality, prevention of the progressive fibrosis of the tissue, and lesser susceptibility to infections (erysipelas, phlegmon, necrotizing fasciitis). Therefore, it may lead to reduction in the complication rate, shortened length of hospital stay, and shorter treatment duration (no further treatment with conservative treatment or compression therapy [use of compression garments] is necessary). For the reasons above, an increased quality of life (QoL) and functionality may be recorded [1, 5].

Since its development, the procedure has gained popularity because of its minimal invasiveness, better aesthetic outcome, and lower costs in comparison to physical medicine (e.g., lower [personnel] expenditures) [2, 31].

Boo03 – What is the phase of development and implementation of lymphovenous anastomosis?

Verfahren seit 90er Jahre in Anwendung

Supermicrosurgical techniques such as LVA are used with satisfactory results since the first description of the technique for lymphoedema in the late '90s by Koshima [21, 32].

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

Boo04 – Who administers lymphovenous anastomosis and in what context and level of care are they provided?

Boo08 – What kind of special premises are needed to use lymphovenous anastomosis?

Boo09 – What supplies are needed to use lymphovenous anastomosis?

Lymphgefäße haben meist einen Durchmesser von >0,1 bis 0,6 mm → supermikrochirurgische Techniken sind notwendig

According to the information received by the submitting hospital, LVA is a supermicrosurgical procedure in which an outflow-obstructed lymphatic vessel with a diameter of >0.1 and under 0.8 mm is microsurgically attached to a superficial small vein. As most lymphatics range from 0.1 to 0.6 mm in diameter, supermicrosurgical techniques are required [33]. On that basis, the lymph can be removed via the venule and the swelling of the affected area decreases.

The procedure is technically demanding, time-consuming, and requires a specialized team with experience in microsurgical techniques [19]. Thus, LVA is performed in institutions with trained personnel in both (super-)microsurgery and lymphology and with appropriate infrastructure. The utilization of appropriate imaging tools to document efficacy is necessary. If performed early in the course of lymphoedema before damage to the lymphatic wall and impaired lymphatic contractility have occurred, it is suggested that there is a greater and longer lasting benefit [15].

In general, microsurgical procedures are performed in local or general anaesthesia. In children, they need to be performed with special caution [21, 34]. The procedure is performed under microscope with maximum magnification and therefore, specifically designed supermicrosurgical instruments as well as suture material with the size of 11.0 and 12.0 are required.

Further, to map healthy and functioning lymphatic vessels and to approve the patency of the anastomosis, one recent technological advance in LVA procedures is the use of indocyanine green (ICG) fluorescence lymphangiography [20]. After ICG dye is injected and has been absorbed by the lymphatic vessels, fluorescence lymphangiography identifies the near-infrared light emitted by ICG dye and so illustrates the path of the lymphatic vessels and enables surgeons to locate and make incisions precisely over functioning lymphatics. Ongoing anastomosis patency can be confirmed during follow-up with lymphoscintigraphy or ICG lymphography. This additional ICG procedure, more precise microscopes, and optimal patient selection make the LVA procedure less invasive, may reduce operating time substantially, and improve the outcome of LVA procedures [16, 20, 21].

Regulatory & reimbursement status

A0020 – For which indications has lymphovenous anastomosis received marketing authorisation or CE marking?

Since lymphovenous anastomosis is a procedure, no marketing authorisation or CE marking can be assigned.

A0021 – What is the reimbursement status of lymphovenous anastomosis?

Currently, lymphovenous anastomosis for lymphoedema is not included in the Austrian DRG-system (Leistungsorientierte Krankenanstaltenfinanzierung/LKF). Therefore, the procedure itself is not reimbursed by the Austrian health care system.

Verfahren erfordert spezialisiertes Team mit Erfahrung in mikrochirurgischen Techniken und Lymphologie sowie entsprechende Infrastruktur

LVA wird unter lokaler oder allgemeiner Anästhesie und unter dem Mikroskop mit supermikrochirurgischen Instrumenten sowie Nahtmaterial durchgeführt

weiterer technischer Fortschritt ist Anwendung von ICG Lymphographie

keine CE-Zertifizierung, da LVA ein Verfahren ist

Verfahren wird in Österreich derzeit nicht erstattet

4 Health Problem and Current Use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is lymphovenous anastomosis used?

According to the guideline of the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF) “S2k guideline for the diagnosis and therapy of lymphoedema” (S2k Leitlinie – Diagnostik und Therapie der Lymphödeme)¹, LVA can be used as a surgical treatment option for primary and secondary lymphoedemas, if no additional venous outflow obstruction is present [1]. According to the submitting hospital, LVA is used for patients with peripheral primary or secondary lymphoedema of all entities and in whom a conservative treatment has failed. Further, the pump function of the lymphatic vessels has to be maintained as a mandatory requirement for the transaction of LVA.

Appropriate patients for lymphatic reconstruction like LVA are less frequently found among patients with primary lymphoedema, due to variations in lymphatics and lymph nodes. In this situation, it could be possible that the majority of primary lymphoedema patients have a clinical manifestation of a developmental defect. Further, difficulties with LVAs occur if primary lymphoedema involves the lymphatic vessel (e.g., aplasia, hypoplasia) [19].

Patients with secondary lymphoedema often have a surgically correctable lesion along the major lymphatics; hence, immediate and long-term results may often be better in these patients. LVA seems to be a good option to restore normal lymphatic function in secondary lymphoedema due to cancer surgery and/or radiation therapy. In this condition, the lymph nodes have a selective damage and the distal lymph-collecting vessels remain intact [19].

Furthermore, LVA seems to be more effective in early stages of lymphoedema because functional lymphatics remain and minimal fibroadipose deposition occurs [19, 35].

Supermicrosurgical LVA is usually performed under general or local anaesthesia with minimal invasion, thus it is possible for high-risk patients (e.g., elderly patients and those with cardiopulmonary diseases or terminal cancer) to undergo the procedure [3, 36].

Indications for performing surgical treatment options are, besides others, intractable pain, insufficient lymphoedema reduction, recurrent episodes of lymphangitis, decreasing limb function, patient dissatisfaction with conservative methods, the patients’ wish to proceed to surgery, and quality of life and psychosocial burden [16].

Surgical methods, such as LVA, should not be carried out if a malignant lymphoedema² and an internal/anaesthesiological contraindication are present [1].

LVA kann als eine chirurgische Behandlungsoption bei primären und sekundären Lymphödem eingesetzt werden, wenn keine zusätzliche venöse Abflussbehinderung vorliegt (AWMF S2k-Leitlinie)

geeignete PatientInnen sind weniger häufig von primären Lymphödem betroffen, da häufig entwicklungsbedingter Defekt vorliegt

bei sekundärem Lymphödem liegt häufig eine chirurgisch korrigierbare Läsion entlang der Hauptlymphgefäße vor

für HochrisikopatientInnen geeignet, da minimal-invasiv

Indikationen für LVA: anhaltende Schmerzen, unzureichende Lymphödemreduktion, etc.

LVA nicht indiziert bei malignem Lymphödem und interner/ anesthesiologischer Kontraindikation

¹ Diagnostic guideline; S2k = guideline based on formal consensus finding.

² Florid, malignant diseases causing lymphoedema, lead to a progressive deterioration of lymphatic transport. Such an increasing reduction in lymphatic transport would counteract any operational measures aimed at increasing this transport performance.

Fokus: peripheres primäres oder sekundäres Lymphödem

A0002 – What is the disease or health condition in the scope of this assessment?

In the scope of this assessment, peripheral lymphoedema is the condition of interest. Lymphoedema is a chronic disease and requires treatment [1].

Overall, lymphoedema can be congenital or acquired, so-called:

- ✿ primary lymphoedema, caused by a congenital abnormality or malfunction in the lymphatic system, and
- ✿ secondary lymphoedema, acquired condition caused by defects to the lymphatic system, usually due to cancer treatment, infection, trauma, etc. [2-4].

Lymphoedema can occur at any age – in childhood, primary forms are more common [1]. Secondary lymphoedema is more frequent than primary lymphoedema [16].

bedeutender Risikofaktor: maligne Erkrankungen und deren Behandlungen

A0003 – What are the known risk factors for lymphoedema?

The leading cause of lymphoedema in developed countries is mostly the consequence of malignancies and its treatments. Especially breast cancer therapies in the forms of radiotherapy and lymph node dissection are seen as the classic precursor of secondary lymphoedema [10, 16, 23].

Axillary lymph node dissection, radiation therapy to the axillary region, post-operative seroma in the axillary region, and obesity are seen as further major risk factors for developing lymphoedemas [8].

anfängliche proteinreiche Flüssigkeit im interstitiellen Raum → Entzündung des Gewebes → Verschlechterung der Lymphfunktion führt weiters zu Fettablagerung, Schmerzen und schränkt tägliche Aktivitäten ein
chronische und schwächende Erkrankung verursacht durch beeinträchtigtes Lymphsystem
ohne angemessene Behandlung führen Lymphödeme zu Schmerzen, Infektionen, Funktionseinschränkungen, verminderter Lebensqualität etc.

A0004 – What is the natural course of lymphoedema?

For patients who suffer from lymphoedema, the onset of the disease is variable [23]. A lymphoedema arises from a composition of protein-rich fluid in the interstitial space with initial symptoms of soft, pitting oedema in the affected extremity. This can cause inflammation of tissues and a stimulation of fibrosis. The worsening of the lymphatic function further results in adipose deposition in the subcutaneous tissues. All these factors influence the lymphoedema which leads to a worsening of symptoms and progresses to a thick, fibrotic, fatty, oedematous, and painful extremity that debilitates patients' daily activities [23].

There is no cure for lymphoedema [2, 5, 6]. It is a chronic, progressive, and debilitating condition caused by an affected lymphatic system. Without appropriate management, lymphoedema may worsen causing pain and comprise body image disturbances, infections, restrictions in range of motion (functional impairment/restricted mobility), swelling, cellulitis, and a decrease in patients' QoL with functional, aesthetic, and psychic repercussions (e.g., ability to work, feeling of tightness, heavy feeling, narrowness of clothing, shoes and jewellery, and skin alterations). It may also lead to irreversible changes like fibrosis or the excess of adipose tissue. These patient-reported symptoms can occur individually or in combination [1, 7-11].

Early lymphoedema management (diagnosis and treatment) is the main challenge for treatment since the progress of chronic lymphoedema will generate interstitial fibrosis and worsening of the lymphatic ducts and nodes [10].

Effects of the disease or health condition on the individual and society

Aoo05 – What is the burden of disease for patients with lymphoedema?

Patients with lymphoedema are at high risk to suffer from recurrent cellulitis, limitation of function, deformity or disfigurement, pain, and diminished QoL including emotional and psychosocial distress [2, 13].

Furthermore, recurrent infections may be caused by progressive enlargement and lymphatic stasis and have been shown to significantly reduce the quality of life (QoL) of patients (e.g., pain and functionality). Lymphoedema constitutes a major health problem because of its high prevalence, the associated work incapacity for affected patients, and the increase of health care costs [5, 31].

PatientInnen mit Lymphödem leiden häufig an Zellulitis, Funktionseinschränkung, Deformität, Schmerzen und verminderte Lebensqualität (QoL)

Aoo06 – What are the consequences of lymphoedema for the society?

It is assumed that on the basis of the fact that lymphoedemas will probably occur more often in the future due to cancer treatments, and due to the aging population, the incidence of lymphoedema will presumably increase over time [16, 37]. In Austria, 39,906 newly diagnosed cancer patients were recorded in 2015. Of those, 4,854 men were affected by prostate cancer and 5,390 women by breast cancer, which are the leading cancers in men and women, respectively, and also the major risk factors for the incidence of extremity lymphoedema [38].

Krebs und dessen Therapien als wesentliche Risikofaktoren für Lymphödeme
zunehmende Häufigkeit aufgrund alternder Bevölkerung

Current clinical management of the disease or health condition

Aoo24 – How are lymphoedemas currently diagnosed according to published guidelines and in practice?

No Austrian guidelines for the diagnosis (and treatment) of lymphoedema were identified. Though, the Austrian Lymph-Liga refers in its description of lymphoedemas to the guideline of the AWMF for “S2k guideline for the diagnosis and therapy of lymphoedema” (S2k Leitlinie – Diagnostik und Therapie der Lymphödeme) [1].

According to this guideline, the pillars of the baseline diagnostics of lymphoedemas are patient history, inspection, and palpation and should be performed in this order. The patient history include specific lymphatic anamnesis of oedemas. The baseline diagnostics should allow a clinical assessment for aetiology, patient-reported outcome, stage, and location of lymphoedema. If the baseline diagnostics cannot provide a clear diagnosis, further diagnostic procedures should be performed for clarification. Advanced diagnostics are used to verify oedema and/or to detect or rule out a morphological or functional disorder of the lymphatic system as the cause of oedema, as well as to plan surgery and therapy monitoring. To proof the diagnosis of a lymphoedema, different methods depending on the stage are possible (e.g., baseline diagnostics, indirect lymphangiography, ICG lymphography, computed tomography, lymphoscintigraphy, etc.) [1].

eine deutsche Leitlinie zu Diagnostik und Therapie der Lymphödeme (AWMF)

Basisdiagnostik der Lymphödeme umfasst Anamnese, Inspektion und Palpation

zur weiteren Abklärung und Sicherung der Diagnose sollten weitere diagnostische Verfahren angestrebt werden

The basis for early diagnosis and follow-up are, in addition to risk stratification, pre- and post-interventional measurement methods such as volume and/or circumference measurement [1].

Staging of lymphoedema

am häufigsten verwendete Stadieneinteilung für Lymphödeme: ISL und Campisi

Lymphoedema is usually staged by monitoring the physical condition of the patients [4]. The most common staging systems used for lymphoedema are the International Society of Lymphology (ISL) and the Campisi staging systems [39] (see Table 4-1). Further staging systems are, for example, the Koshima Staging System of Lymphoedema and the M.D. Anderson Lymphoedema Classification based on ICG Lymphangiography [20].

Table 4-1: ISL and Campisi staging of lymphoedema

ISL stage and description		Campisi stage and description	
stage o (latency stage, subclinical stage)	<ul style="list-style-type: none"> ✳ non-clinical apparent lymphoedema, but partly pathological lymphoscintigram; ✳ swelling is not yet evident; ✳ subtle alterations in tissue fluid/composition and changes in subjective symptoms; 	stage I, a	a. "Latent" lymphoedema, without clinical evidence of oedema, but with impaired lymph transport capacity (provable by lymphoscintigraphy) and with initial immuno-histochemical alterations of lymph nodes, lymph vessels and extracellular matrix.
stage I (spontaneously reversible)	<ul style="list-style-type: none"> ✳ oedema of soft texture; ✳ elevating of affected parts reduces the swelling; ✳ early accumulation of fluid relatively high in protein count which subsides with limb elevation; 	stage I, b	b. "Initial" lymphoedema, totally or partially decreasing by rest and draining position, with worsening impairment of lymph transport capacity and of immuno-histochemical alterations of lymph collectors, nodes, and extracellular matrix.
stage II (not spontaneously reversible)	<ul style="list-style-type: none"> ✳ oedema with secondary tissue alterations; ✳ elevating of affected parts does not or rarely eliminates the swelling; ✳ pitting is manifest; 	stage II	a. "Increasing" lymphoedema, with vanishing lymph transport capacity, relapsing lymphangitic attacks, fibroindurative skin changes, and developing disability.
			b. "Column shaped" limb fibrolymphoedema, with lymphostatic skin changes, suppressed lymph transport capacity and worsening disability.
stage III	<ul style="list-style-type: none"> ✳ distorting hard swelling, partly lobar form with typical skin alterations; ✳ encompasses lymphostatic elephantiasis (pitting can be absent and trophic skin changes have developed). 	stage III	a. Properly called "elephantiasis", with scleroindurative pachydermitis, papillomatous lymphostatic verrucosis, no lymph transport capacity and life-threatening disability.
			b. "Extreme elephantiasis" with total disability.

Sources: [1, 15, 39]

A0025 – How are lymphoedemas currently managed according to published guidelines and in practice?

Behandlung der Lymphödeme umfasst konservative und chirurgische Verfahren derzeitiger Behandlungsstandard sind konservative Therapien

The treatment of peripheral lymphoedema is divided into conservative (non-surgical) and surgical [15]. Conservative treatment of primary and secondary lymphoedema comprises of compression techniques (including multilayer bandaging techniques, self-adherent wraps, and compression garments at prescribed pressure gradients), intermittent pneumatic compression, complex decongestive therapy (CDT), manual lymphatic drainage, exercise, low-level laser, ultrasound, and aquatherapy [4].

Currently, standard of care for the treatment of early lymphoedema are conservative therapy options. Conservative therapies aim to control symptoms by minimising fluid build-up, hence they are not curative, but delay the progression [2, 7, 8, 15, 35]. According to the submitting hospital, conservative therapy has failed in controlling the progression of lymphoedema when, despite exhausting all measures of the CDT, there is no improvement or even worsening of the symptoms [19]. If peripheral lymphoedema is refractory to conservative therapies, surgical methods (e.g., LVA) are becoming a treatment option [17].

According to the AWMF guideline for “S2k guideline for the diagnosis and therapy of lymphoedema” (S2k Leitlinie – Diagnostik und Therapie der Lymphödeme), surgical treatment should be considered if a patient has a burden or an increase in secondary tissue changes despite guideline conservative therapy and adherence to therapy. When deciding on an operative method, the reconstruction of the interrupted lymphatic system or a deviating procedure should be considered a priority [1].

Surgical approaches are classified as *reductive* (e.g., liposuction, skin/subcutaneous excision) or *physiological* (e.g., lymphovenous anastomosis [LVA], vascularized lymph node transfer/transplantation [VLNT]) [5, 36]. Surgical approaches also include supermicrosurgical procedures. These supermicrosurgical procedures comprise of *derivative methods* (e.g., LVA) and *reconstructive methods* (sophisticated techniques which involve the use of a lymphatic collector [LLA] or an interposition vein segment [LVLA] to restore lymphatic continuity in lymphoedema conditions) [15]. A stage-related and individually customised treatment modality has to be considered [1].

According to the guideline of the AWMF “S2k guideline for the diagnosis and therapy of lymphoedema” (S2k Leitlinie – Diagnostik und Therapie der Lymphödeme), surgical treatment should only be offered to adult patients with phase I and II lymphoedema after a guideline-compliant ambulatory and/or inpatient CDT for the period of at least six months [1]. In selected patients, a combination of LVA and VLNT procedures may be considered effective [40].

If the treatment of lymphoedema is in an advanced stage, the aim of the treatment is to return the lymphoedema to a lower lymphoedema stage [1].

Target population

A0007 – What is the target population in this assessment?

The target population in this assessment are patients with primary and secondary lymphoedema stage I and II in whom a conservative treatment (e.g., CDT) is ineffective or does not lead to a substantial improvement of the lymphoedema after the recommended conservative treatment period.

bei Versagen von konservativen Therapien (z. B. keine Verbesserung oder Verschlechterung der Symptome) sollten chirurgische Verfahren in Betracht gezogen werden

chirurgische Verfahren bestehen wiederum aus derivativen (e.g., LVA) und rekonstruktiven Methoden

laut AWMF S2k-Leitlinie sollten chirurgische Verfahren nur Erwachsenen und erst nach leitliniengerechter physikalischer Entstauungstherapie für min. 6 Monate angeboten werden

PatientInnen mit Lymphödem Stadium I & II und ineffektiver konservativer Therapie bzw. ohne wesentlicher Verbesserung

A0023 – How many people belong to the target population?

geschätzte Inzidenz des primären Lymphödems bei Geburt: 1:6,000, Prävalenz für >20-Jährige bei 1:87,000 (geschätzt)

spezifische Daten für sekundäres Lymphödem schwer zu bestimmen → geschätzte Inzidenz 0.13-2 % (lt. AWMF)

internationale Studien berichten eine Inzidenz von 10-50 %, abhängig von Krebsart und Behandlung

2008 in Österreich 6 Operationen aufgrund von Lymphödem

According to the guideline of the AWMF for “S2k guideline for the diagnosis and therapy of lymphoedema” (S2k Leitlinie – Diagnostik und Therapie der Lymphödeme), the incidence of primary lymphoedema at birth is (estimated) about 1: 6,000, with a prevalence of about 1: 87,000 among <20 year old patients. Exact data on the occurrence of secondary lymphoedema are difficult to determine. In industrialized countries, the incidence of secondary lymphoedema is estimated to be around 0.13-2%. Women are significantly more often affected (by primary lymphoedema) than men (male: female=1: 4.5 to 1: 6.1). The number of people affected increases with age. According to the AWMF guideline, the incidence of lymphoedema 12-24 months after breast carcinoma after axillary lymph node removal is 19.9%; after sentinel node biopsy 5.6%. For gynaecological tumours, a lymphoedema incidence of approximately 20% is indicated after lymph node removal [1].

International studies report an incidence of lymphoedema that ranges from 10% to 50%, depending on the treatment procedure and cancer type. Lymphoedema after breast cancer treatment is the most common form with a variation of 24-49% following mastectomies and 4-28% following breast-conserving therapy [8, 11].

According to the “Yearbook of Health Statistics 2008” (Jahrbuch der Gesundheitsstatistik 2008) of *Statistik Austria*, there were 6 surgeries of patients with lymphoedema/elephantiasis recorded in 2008 [41]³. In 2016, *Statistik Austria* recorded 9,908 hospital stays due to operations on lymph nodes or lymphatics [42].⁴

Specific data for Austria on the actual number of patients affected by lymphoedema could not be identified.

A0011 – How much is lymphovenous anastomosis in lymphoedema utilised?

Frequenz von LVA von einreichender Institution auf ~30/Jahr, für Gesamtösterreich auf ~100/Jahr geschätzt

According to the information provided by the submitting hospital, the annual frequency in this hospital (number of beds= ~270) is estimated to be 30 LVA procedures in lymphoedemas. The total estimations provided regarding the annual frequency in Austria is 100 LVA procedures.

³ No current data available.

⁴ However, the number of hospital stays is not reported for indications separately.

5 Clinical effectiveness

5.1 Outcomes

LVA in lymphoedema is primarily used to reduce limb volume or circumference reduction, hence reducing pain and cellulitis with the aim to improve patients' QoL and functionality. LVA is not used for a curative treatment, hence the procedure does not influence patients' survival. Therefore, this outcome was not listed as crucial or important for the recommendation.

The following outcomes were defined as *crucial* to derive a recommendation:

- ✧ Quality of life (QoL)
 - ✧ Pain
 - ✧ Functionality
- ✧ Recurrence.

Further outcomes were defined as *important, but not crucial* to derive a recommendation:

- ✧ Limb volume or circumference reduction

entscheidungsrelevante Endpunkte für die Wirksamkeit:

- ✧ Lebensqualität
 - ✧ Schmerzen
 - ✧ Funktionalität
- ✧ Wiederauftreten

wichtige Endpunkte: Reduktion des Extremitätenvolumens oder -umfangs

5.2 Included study

To assess the clinical effectiveness of LVA in patients with lymphoedema, we only identified one non-randomized controlled study (NRCT) [22] with 43 patients treated with LVA and 13 patients treated with vascularized supraclavicular lymph node transfer (VSLNT) for the lower extremities, respectively.

Study characteristics

The NRCT was conducted in Japan in a university hospital and a cancer centre [22]. The procedure was either performed side-to-end or end-to-end, and the operation time in lower extremity lymphoedema was reported in this study with a mean of 213 minutes. The diameter of lymphatic vessels in which LVAs were performed was not described in this study.

The NRCT only included patients with advanced primary or secondary lower extremity lymphoedema, hence only patients with severe/advanced stages of lymphoedema, but had unclear reporting of lymphoedema staging classification [22]. In this NRCT, patients with early-stage lymphoedema were excluded.

Patient characteristics

The mean age of patients ranged from 54.1 years in the LVA group to 63.7 years in the VSLNT group. The mean age was significantly lower in the LVA group. The female study participants were overrepresented in both groups ranging from 93.0 to 100%, respectively.

The mean follow-up ranged from 15.1 months (VSLNT) to 18.3 months (LVA). No losses to follow-up were reported in the NRCT.

1 kontrollierte Studie mit 43 (LVA) vs. 13 (VSLNT) PatientInnen

untere Extremitäten, seit-zu-end oder end-zu-end, Operationszeit durchschnittlich 213 min

nur PatientInnen mit fortgeschrittenem primären oder sekundären Lymphödem

mittleres bis höheres Alter, überwiegend weibliche PatientInnen, Beobachtungszeitraum durchschnittlich bis zu 15.1 (VSLNT) vs. 18.3 Monate (LVA)

**betreute
Kompressionstherapie
min. 3 Monate vor
Eingriff, nach dem
Eingriff eigenständige
einfache Lymphdrainage
und elastische Bandagen
bis zum Ende der
Beobachtungszeit**

The underlying disease of secondary lymphoedema was assumingly cancer (lymph node dissection) and phlegmon in 52 patients, while no underlying disease was reported for four patients of the LVA group (probably primary lymphoedema). The mean duration of persistent lymphoedema was not reported.

All patients received supervised compression therapy for at least three months before surgery and ICG lymphography as pre-interventional procedures. Simple self-lymph drainage directly after discharge was used together with the occasional elastic garments until the final follow-up. No additional interventions were performed.

Study characteristics and results of the included study are displayed in Table A-1 and in the evidence profile in Table A-6.

5.3 Results

Morbidity

Do005 – How does lymphovenous anastomosis affect symptoms and findings (severity, frequency) of lymphoedema?

**keine Evidenz für
kritische Outcomes
Schmerz und
Funktionalität
Veränderungen
des postoperativen
Volumens wurde mittels
LEL Index erhoben
statistisch signifikante
Verbesserung der
durchschnittlichen
Volumensveränderung
in VSLNT Gruppe
keine Evidenz**

No evidence was found on the two crucial outcomes pain and functionality.

In the NRCT, changes in the postoperative volume were compared using the Lower Extremity Lymphoedema index (LEL). This index was calculated from the circumferences of 5 points on the limb (the superior edge of the patella, 10 cm above and below the patella, the lateral malleolus, and the dorsum of the foot) and the body mass index, which aimed to yield an accurate quantitative assessment of the severity of lymphoedema [22].

The mean changes of volume compared with preoperative volumes were in the LVA group 21.2 (± 2.0) and in the VSLNT group 26.5 (± 4.4) with statistical significance in favor of the VSLNT group.

Do006 – How does lymphovenous anastomosis affect progression (or recurrence) of lymphoedema?

No evidence was found on the crucial outcome remission.

Function

Do011 – What is the effect of lymphovenous anastomosis on patients' body functions?

keine Evidenz

No evidence was found to answer the research question.

Do016 – How does the use of lymphovenous anastomosis affect activities of daily living?

keine Evidenz

No evidence was found to answer the research question.

Health-related quality of life

D0012 – What is the effect of lymphovenous anastomosis on generic health-related quality of life?

No evidence was found on the crucial outcome QoL.

keine Evidenz

D0013 – What is the effect of lymphovenous anastomosis on disease-specific quality of life?

No evidence was found to answer the research question.

keine Evidenz

Patient satisfaction

D0017 – Was the use of lymphovenous anastomosis worthwhile?

No evidence was found to answer the research question.

keine Evidenz

Mortality

D0001 – What is the expected beneficial effect of lymphovenous anastomosis on mortality?

No evidence was found to answer the research question

keine Evidenz

D0003 – What is the effect of lymphovenous anastomosis on the mortality due to causes other than the target disease?

No evidence was found to answer the research question.

keine Evidenz

6 Safety

6.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

- ✧ Complications
 - ✧ Adverse events, procedure-related (e.g., infection, additional procedure, re-exploration)
 - ✧ Adverse events, procedure-unrelated (e.g., infection, lymphorrhea)

In accordance with the European Commission guidelines for medical devices⁵ on serious adverse event reporting, the following definition was applied:

Procedure-related adverse events are complications that are associated with the surgical intervention. Possible procedure-related complications are events associated with anaesthesia, infections, damages to nerves or blood vessels, bleeding, or the occurrence of blood clots (e.g. thrombosis).

**entscheidungsrelevanter
Endpunkt für die
Sicherheit:
unerwünschte
Ereignisse**

6.2 Included Studies

The study inclusion criteria for assessing safety differed from the ones for assessing clinical effectiveness. In addition to NRCTs, prospective studies without a control group (interventional single-arm studies, case series, and registry studies), but with patient numbers of greater than or equal 10 patients, were considered for the assessment of safety.

In order to assess safety-related outcomes of LVA in patients with lymphoedema, we identified only one comparative study [22] with 43 patients treated with LVA and 13 patients with VSLNT. Patient and study characteristics are displayed in Chapter 5.2.

Four prospective interventional single-arm, single-centre studies also met our inclusion criteria [3, 10, 20, 21] with a total of 161 patients⁶, for the assessment of safety of LVA. In those studies, LVA was performed in the upper extremities in 150 patients and in lower extremities in 11 patients.

Study characteristics

The four prospective interventional single-arm studies were conducted in the US [20], Netherlands [3, 21], and France [10]. One study was supported by the Kyte Research and Education Fund and the National Institutes of Health through M.D. Anderson's Cancer Center Support Grant [20]. Three studies did not report on funding [3, 10, 21].

**1 kontrollierte Studie
mit 43 (LVA) vs.
13 (VSLNT) PatientInnen
(siehe 5.2)**

**4 prospektive einarmige
Studien mit 161
PatientInnen; obere
Extremitäten in 150 und
untere Extremitäten in
11 PatientInnen**

**Studien in US,
Niederlanden
und Frankreich
durchgeführt; eine
Studie mit Förderung**

⁵ http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_3_en.pdf

⁶ It is important to note that in the study of Chang 2013 [20] 100 patients are included, but the outcome data is only reported on 37 patients and the baseline data is reported on an unknown number of patients. We decided to report outcomes of this study, but consequently, data may be imprecise.

end-zu-end oder end-zu-seit, Operationszeit durchschnittl. 60-240 min

The procedure was either performed end-to-end or end-to-side [20], end-to-side [3] or end-to-end [10]. One study did not report on the procedure modality of the performed LVA's [21].

Universitätskrankenhaus, Krebs-Zentrum und Tageschirurgie, Durchmesser der Lymphgefäße für LVA umfasste durchschnittlich 0.2 bis 1.0 mm

All of the studies were conducted in university hospitals or cancer centres, except for one that was conducted in a day surgery setting [10]. Mean operation time of upper extremity lymphoedema ranged from 60 to 240 minutes across studies. The operation time in lower extremity lymphoedema was not reported in one study [20]. The diameter of lymphatic vessels in which LVAs were performed was described in two studies with a mean of ≤ 0.3 mm [3] and 0.2-1.0 mm [20]. The other three studies did not report on this procedure characteristic [10, 21, 22].

Einschlusskriterien teilweise unterschiedlich: Lymphödem mind. 12 Monate, keine Reaktion auf bisherige Therapien, Lymphödem aufgrund von Brustkrebs, Frauen, >18 Jahre

Inclusion criteria differed slightly between the included prospective interventional single-arm studies. One study included all patients with secondary extremity lymphoedema [20]. No other inclusion criteria were set for this study. One study included only female patients over 18 years of age [10]. Across studies, patients were eligible for inclusion if they had lymphoedema for more than 12 months, absence of skin infections, no response to physiotherapy or complex decongestive therapy for a minimum of three months, and lymphoedema secondary to breast cancer [3, 10, 21].

All of the studies included patients with moderate and severe lymphoedema stages. The staging of lymphoedema was reported with ISL [21] or Campisi staging [3]; the other studies had unclear reporting of lymphoedema staging or did not report this characteristics.

Exclusion criteria were only reported in one study: one prospective interventional single-arm study excluded patients if they were not treated with previous physiotherapy for lymphoedema or if they refused to sign the informed consent [10].

For detailed information see Appendix (Table A-1 and Table A-2).

Patient characteristics

mittleres bis höheres Alter, nur weibliche Patientinnen, Beobachtungszeitraum durchschnittlich von 7.8 bis 30.4 Monaten, durchschnittlich 3.5 bis 6.6 Jahre persistentes Lymphödem

The mean age of patients ranged from 54 to 64 years across trials. The female study participants were overrepresented in all (100%), but one study. This study did not report on the gender of included patients [20].

The mean follow-up of the studies ranged from 7.8 [21] to 30.4 months [20]. One study reported no losses to follow-up [3], while two other studies had unclear reporting of loss to follow-up [10, 21], and one study did not report loss to follow-up [20].

The mean duration of persistent lymphoedema was 3.5 to 6.6 years across studies. One study did not report on the mean duration of lymphoedema in their patient group [10].

zugrundeliegende Erkrankung bei 150 Patientinnen Brustkrebs

The underlying diseases causing lymphoedema were breast cancer in 150 patients [3, 10, 20, 21], sarcoma in three patients, melanoma in two patients, and gynaecologic cancer in six patients [20], respectively. Skin infection was additionally reported with breast cancer in five patients in one study [21].

ICG Lymphographie, standardisierte konservative Therapie für 3 Monate vor Eingriff und perioperative Gabe von Antibiotika

Pre-interventional procedures comprised of ICG lymphography in two studies [20, 21], and standardized conservative treatment for three months and perioperative usage of antibiotics in another study [3]. The fourth study did not report on pre-interventional procedures [10].

Compression bandages and elevation of affected limb were performed as post-interventional procedures in two studies [3, 20]. Further procedures were removal of the sleeve and lymphatic drainage physiotherapy beginning two weeks post-surgery [10], prophylactic intravenous antibiotics and compression garments four weeks post-surgery [20], and elastic stockings during follow-up [3]. One study did not report on post-interventional procedures [21].

Additional interventions were only reported in one study: VLNT was performed due to no improvement of lymphoedema after an LVA in one patient [20].

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2 and in the evidence profile in Table A-6.

nach dem Eingriff:
Kompressionsbandagen,
Lymphdrainage,
prophylaktische Gabe
von Antibiotika und
elastische
(Kompressions-)
Bandagen während
Beobachtungszeit

6.3 Results

Patient safety

C0008 – How safe is lymphovenous anastomosis in comparison to the comparator(s)?

Only one NRCT could be identified and reported procedure-related adverse events [22]. In the LVA group of this study, no adverse events were reported compared to the VSLNT group, where adverse events were reported in three patients who completed the follow-up, out of 13 patients (23.1%), with statistical significance in favor of LVA.

Procedure-related complications of prospective interventional single-arm studies can also be considered for the analysis of safety because the effects directly attributable to the procedure can be analyzed without a control group. In these studies, adverse events occurred in two patients who completed the follow-up, out of 161 included patients across these studies (1.2%).

Adverse events, procedure related

The most frequent adverse events reported were congestion to the skin paddle in three patients (23.1%) after the treatment with VSLNT [22], and skin irritation at the site of contrast injection in two patients (10%) after the treatment with LVA [21].

Two studies did not report any procedure related adverse events for the treatment with LVA [10, 20].

One study did not report on procedure-related adverse events for LVA [3].

Adverse events, procedure unrelated

None of the studies reported on procedure unrelated adverse events.

C0002 – Are the harms related to dosage or frequency of applying lymphovenous anastomosis?

No evidence was found to answer the research question.

Endpunkt unerwünschte
Ereignisse:
in kontrollierter Studie
keine unerwünschten
Ereignisse mit LVA;
mit VSLNT 3 von 13
PatientInnen (23,1 %);
in prospektiven Studien:
2 von insgesamt
161 PatientInnen (1,2 %)

häufigstes
unerwünschtes Ereignis:
LVA:
Hautirritationen nach
Kontrastmittelinjektion
(n=2);
VSLNT: Kongestion
der Haut (n=3);
2 Studien berichteten
keine und 1 Studie
berichtete nicht von
unerwünschten
Ereignissen

keine Evidenz

Co004 – How does the frequency or severity of harms change over time or in different settings?

keine Evidenz No evidence was found to answer the research question.

Co005 – What are the susceptible patient groups that are more likely to be harmed through the use of lymphovenous anastomosis?

keine Evidenz No evidence was found to answer the research question.

Co007 – Are lymphovenous anastomosis and comparator(s) associated with user-dependent harms?

keine Evidenz No evidence was found to answer the research question.

Investments and tools required

Bo010 – What kind of data/records and/or registry is needed to monitor the use of lymphovenous anastomosis and the comparator?

keine Evidenz No evidence was found to answer the research question.

7 Quality of evidence

RoB for individual studies was assessed with the IHE checklist for case series [27] and with the RoBANS risk of bias assessment tool for non-randomized controlled studies [26] and is presented in Table A-3 and Table A-4 in the Appendix.

The NRCT was graded with a *moderate to high* RoB, although the tool is not intended to produce an overall rating. The reasons for downgrading were no randomization, unclear reporting of confounding variables, no blinding of outcome assessors, and no reporting on critical outcomes (e.g., QoL, pain). Regarding the four case series, two were assessed with a *moderate* RoB and two with a *high* RoB, due to unclear reporting of study design and study characteristics, no reporting on staging of lymphoedema, insufficient reporting on QoL, discrepancy in patient numbers for loss to follow-up, and unclear reporting on competing interests and sources of support.

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [28] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [28].

GRADE uses four categories to rank the strength of evidence:

- ✦ **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- ✦ **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- ✦ **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- ✦ **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-6.

Overall, the strength of evidence for the effectiveness and safety of LVA is very low.

RoB bewertet mit
RoBANS und
IHE Checkliste

moderater bis
hoher RoB in den
eingeschlossenen
Studien

Qualität der Evidenz
nach GRADE

GRADE Tabelle
nächste Seite

Gesamtstärke der
Evidenz für klinische
Wirksamkeit und
Sicherheitsendpunkte
sehr niedrig

Table 7-1: Summary of findings table of LVA

Outcomes	Anticipated absolute effects [†] (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with VSLNT	Risk with LVA				
Mean changes of volume compared with preoperative volume measurements follow up: mean 15.1-18.3 months	Improvement value of LEL index: LVA: 21.2 (+-2.0) vs. VSLNT: 26.5 (+-4.4), s.s.		-	56 (1 observational study)	⊕○○○ VERY LOW ^{a,b}	Data of 1 non-randomized controlled study (Akita 2015)
Quality of life – not reported	-	-	-	-	-	This outcome was not reported.
Recurrence (worsening of lymphoedema) – not reported	-	-	-	-	-	This outcome was not reported.
Procedure-related adverse events follow up: mean 7.8-30.4	231 per 1.000	0 per 1.000 (0 to 0)	not estimable	207 (4 observational studies)	⊕○○○ VERY LOW ^{c,d}	Data of 1 non-randomized controlled study (Akita 2015) and 3 prospective interventional single-arm studies (Chang 2013, Cornelissen 2017, Poumellec 2017).
Procedure-unrelated adverse events – not reported	-	-	-	-	-	This outcome was not reported.

Abbreviation: s.s. statistical significant

^a High risk of selection, detection and reporting biases.

^b Small sample size, small number of events.

^c No control group in three studies [10, 20, 21].

^d Insufficient outcome reporting: Chang [20] reported on 100 patients, but outcome data is only reported for 37 patients.

8 Discussion

Lymphoedema is a chronic and not curable disease and is often accompanied with patient morbidity [5]. Lymphoedema is considered to be one of the main complications of cancer treatments, especially breast cancer treatments. It has a decisive impact on the quality of life of its patients and on their ability to work and participation in social activities. Consequently, the improvement of patients' quality of life is the main goal of lymphoedema treatments [21].

With the advancement of microsurgical techniques, LVA is gaining popularity and is used as a surgical treatment for extremity lymphoedema regardless of the fact its clinical profile is not supported by high-quality data. The purpose of LVA is to relieve lymphatic obstruction and restore normal lymphatic function [8, 19, 22]. As reported in the included literature, LVA seems to be successful in controlling the progression of early stages of lymphoedema [19]. Although it is still a not fully established concept – for example, there is no evidence to suggest an optimal diagnosis and ideal duration or frequency of treatment, and no evidence to assess the severity or quality of lymphoedema which actually correlates with clinical findings. A further difficulty is the understanding of the optimal patient selection for LVA procedures as well as the optimal number of LVAs performed on the patient [4, 20]. Yet with imaging modalities such as ICG lymphography the identification of suitable lymphatic vessels for LVA procedures improved dramatically, and hence, the right patient population can be discerned by ICG lymphography [7, 43]. According to the literature, there seem to be two factors that determine the effectiveness of LVA: the identification of viable lymphatic vessels and the extent of tissue fibrosis related to lymphoedema [24].

Interpretation of the findings

The aim of this report was to assess the clinical effectiveness and safety of LVA compared to the comparator (e.g., VLNT) for the treatment of lymphoedema. A total of 629 articles were identified in the systematic literature search. Among them 14 systematic reviews and HTAs on LVA were found, but excluded for analysis: four of these were systematic literature reviews [2, 5, 31, 44], one was written in French [11], five were excluded because of different aims (e.g., prevention, diagnosis) [4, 9, 16, 45, 46], one systematic review was excluded because of inclusion of animal studies [43], and three were found potentially relevant, but included also retrospective studies [7, 47, 48]. Despite the fact that retrospective studies were included, the evidence converges with our findings.

Our systematic search was not limited to a specific time period, but to specific study designs – only RCTs, NRCTs, and prospective (controlled) studies were included in order to assess outcomes on clinical effectiveness and safety. Despite the fact that LVA has been clinically used for decades, we identified only one NRCT for assessing the clinical effectiveness and safety of LVA and four additional single-arm studies for assessing safety. A total of 217 patients were enrolled in the included studies (204 treated with LVA and 13 with VSLNT).

LVA als effektives chirurgisches Verfahren zur Behandlung von Lymphödemen der Extremitäten angesehen

ABER: es gibt keine allgemein gestützte Beurteilung der Schwere von Lymphödemen, die mit klinischen Befunden korrelieren sowie Schwierigkeit der optimalen Patientenauswahl für LVA-Verfahren

Ziel: Beurteilung der klinischen Wirksamkeit und Sicherheit der LVA

14 systematische Übersichtsarbeiten identifiziert, aber aufgrund methodologischer Unterschiede ausgeschlossen

1 kontrollierte prospektive Studie und 4 prospektive einarmige Studien eingeschlossen (insgesamt 217 PatientInnen mit LVA und 13 mit VSLNT)

<p>Unterschiede in post-interventionellen Behandlungen wie Kompressionstherapie → widersprüchlich ob wirksam oder nicht (möglicherweise Confounder)</p>	<p>Across all studies, LVA was performed slightly different (side-to-end, end-to-end or end-to-side; primary and/or secondary lymphoedema) and the number of performed anastomoses differed also across the studies. One important finding is that four of the included studies performed different post-interventional procedures, such as compression bandages in two studies [3, 20] or lymphatic drainage in two other studies [10, 22]. The fifth study did not report on this baseline characteristic, but stated the importance of discontinuation of compressive stockings after surgery [21]. Hence, it is currently unknown, due to conflicting evidence, if peri-interventional procedures such as compression therapy directly post-surgery may either harm or benefit the effectiveness of LVA. Further, it might also be a confounder of the post-procedural lymphoedema evaluation.</p>
<p>trotz kontrollierter Studie keine robuste Evidenz für klinische Wirksamkeit → lediglich ein Outcome berichtet („mittlere Volumenänderung im Vergleich zu präoperativen Volumina“)</p>	<p>Details on the applicability of the body of evidence can be found in the Appendix (see Applicability table).</p> <p>Effectiveness data from observational studies</p> <p>To proof the clinical effectiveness of LVA procedures, the evidence from RCTs is necessary. The lack of RCTs restricted our analysis to NRCTs as the best available evidence. We could only identify one NRCT to assess the efficacy of LVA due to the lack of trials with a comparative treatment arm. This NRCT provided only one outcome on the clinical effectiveness of LVA. Eligible patients of this study had primary or secondary advanced lower extremity lymphoedema. No other inclusion criteria were reported. Because of the absence of other NRCT (with regard to upper extremities and different [early] stages of lymphoedema), the determination of the best time point at which to perform the LVA procedure is difficult to state.</p>
<p>signifikante Verbesserung des Lymphödemvolumens in VSLNT Gruppe</p>	<p>The only reported outcome in the NRCT was the mean change of volume compared with preoperative volumes (difference), however, this outcome was deemed important but not crucial to derive a recommendation as it is considered a surrogate parameter. The improvement in the LVA group was 21.2 and in the VSLNT group 26.5, with statistical significance in the VSLNT group. The difference in volume change can be explained by different numbers of patients in the groups (LVA, n=43, vs. VSLNT, n=13) and potentially different underlying lymphoedema (primary vs. secondary).</p>
<p>aus Ergebnisse der prospektiven Studien können keine Rückschlüsse gezogen werden</p>	<p>Due to the limited number of NRCTs (n=1), we extracted also data from prospective interventional single-arm studies (n=4). However, no conclusions on the clinical effectiveness on LVA can be made on the basis of these studies. Nonetheless, the data from the prospective interventional single-arm studies show a possible effect concerning crucial and important outcomes (QoL, recurrence, and limb volume or circumference reduction).</p>
<p>Verbesserung des Lymphödemvolumens der oberen Extremitäten</p> <p>nicht signifikantes Ergebnis in 1 Studie (keine Kompressionstherapie nach LVA)</p>	<p>Mean volume or circumference reduction was reported in three case series. The mean volume difference ranged from 33.5% in [3] to 42% in [20] one year postoperatively. Another study reported on lymphoedema improvement postoperatively, and a mean overall improvement of 24.7% [10]. One prospective interventional single-arm study reported of a non-significant mean change of volume postoperatively of 12.9% for upper extremity lymphoedema [21]. This study was the only case series that had controversial reporting on post-interventional treatments such as compression therapy. No reporting on volume or circumference reduction was done for lower extremity lymphoedema across studies.</p>

In the observational studies, the QoL was assessed by various tools. The individual tools and scores for QoL measurements are further explained in the evidence tables (see Appendix Table A-2) where applicable. One study reported improvement in QoL one year postoperatively in eight patients out of 20 (40%) [21]. Another study only reported on unsatisfactory improvement of QoL one year postoperatively, but improvement of functionality (however, the number of patients included for this outcome was unclear) [10]. QoL was insufficiently reported in two prospective interventional single-arm studies [3, 20], and one study had unclear reporting on the questionnaire [10].

The outcome on recurrence was only reported in one prospective interventional single-arm study, where four patients (19.7%) stated worsening of lymphoedema or recurrence [10].

Nonetheless, all the data is reported from prospective interventional single-arm studies and hence, did not involve control groups and are very prone to bias.

Safety data from observational studies

In terms of safety, four of the five included studies (one NRCT and three prospective interventional single-arm studies) reported on procedure-related adverse events. Only two patients out of the overall 204 patients across studies treated with LVA reported procedure-related adverse events [21], whereas three patients out of 13 in the VSLNT group reported adverse events [22]. One prospective interventional single-arm study did not report on adverse events [3]. Hence, procedure-related adverse events for LVA seem to be rare and may only be determined in studies with larger patient samples.

Quality of Evidence

Overall, the quality of evidence was very low due to high risk of bias in the NRCT, the observational study design, insufficient outcome reporting of one study, and small sample sizes (see Table 7-1). Further, the included patient group in the NRCT was not representative of the range of LVA patients because only patients with advanced primary and secondary lymphoedema of the lower extremities were included [22].

The overall risk of bias was considered moderate to high because no randomization or blinding was performed, and because of insufficient reporting on critical outcomes (e.g. QoL), unclear reporting of confounding variables, and patients' consecutive recruitment (see Appendix Table A-3 and Table A-4).

The included studies in this report demonstrate mixed results following the LVA procedures and the quality of these studies varies. A major concern of most of the identified prospective interventional single-arm studies is the low number of included patients. For instance, one study included only 10 patients [3]. In order to identify rare procedure related adverse events, low patient numbers are insufficient. Moreover, only one study had a longer follow-up period of 12 months [20]. Therefore, reliable data of long-term safety and efficacy outcomes are missing.

The NRCT [22] was conducted in two centres and the other four prospective interventional single-arm studies in only one centre. One of these studies included 100 patients, but outcome data is only reported on 37 patients and baseline data on an unknown number of patients [20]. This may distort the effect of LVA.

1 Studie: Verbesserung der QoL (n=8)

1 Studie: unbefriedigende Verbesserung der QoL, Verbesserung der Funktionalität

Rezidive nur in 1 Studie berichtet: 4 PatientInnen betroffen

Daten basierend auf prospektiven einarmigen Studien

eingeschlossene Studien zeigen, dass LVA eine sichere Intervention für PatientInnen mit primären oder sekundären Lymphödem darstellen könnte

Stärke der Evidenz für klinische Wirksamkeit und Sicherheit sehr gering: hohes Biasrisiko, relativ kleine Fallzahlen etc.

moderates bis hohes Biasrisiko

Studien zeigen unterschiedliche Ergebnisse und Qualität ist niedrig

unklare Anzahl an eingeschlossenen PatientInnen in 1 Studie

**prospektives
Studiendesign fraglich
in 1 Studie**

Consecutive patient recruitment and the prospective study design were unclear in one study [10], but the study was still included⁷. Another study was included at first, but excluded after data extraction because of retrospective analysis of patient data [8].

**unterschiedliche LVA
Methoden und post-
interventionelle
Therapien könnten
Einfluss auf Ergebnisse
der Studien haben**

The utilised LVA methods (end-to-side, end-to-end or side-to-end) and post-interventional therapies differed slightly between the included studies. For instance, in several studies, patients were treated with compression bandages following LVA and in other studies not. It is possible that these treatment modalities have had an impact on the recorded outcomes (such as circumference reduction or QoL).

**3 laufende
randomisierte
kontrollierte Studien**

We identified 3 ongoing studies, which might show effects of LVA with a higher quality of evidence: one ongoing randomized controlled trial evaluates the improving quality of survivorship for breast cancer-related lymphoedema by lymphaticovenous anastomosis compared to complex decongestive therapy with the primary outcome of relative arm volume of the affected arm compared to the unaffected arm (estimated completion date May 2019) (NCT-02790021).

One ongoing randomized controlled trial evaluates lymphatic venous anastomosis for secondary lymphoedema in comparison with complex decongestive physiotherapy with the primary outcome of change in the incidence of cellulitis (estimated completion date December 2020) (JPRN-UMIN000025137).

Another ongoing study is a pilot study on robot-assisted microsurgical lymphatico-venular anastomosis evaluating the efficacy of robot-assisted LVA in comparison to conventional LVA (estimated completion date February 2019) (NTR6465).

**8 weitere laufende
Studien (4 kontrollierte
nicht-randomisierte und
4 einarmige Studien)**

Furthermore, we identified 8 ongoing parallel non-randomized (n=4) and single-arm non-randomized studies (n=4). Of those, 5 ongoing studies may be connected and may represent sub-analytical results. Further information on the eight ongoing observational studies is presented in the Appendix (see List of ongoing trials).

**keine der laufenden
Studien inkludiert
patientInnenrelevante
Outcomes**

None of the ongoing trials includes patient-relevant outcomes to assess efficacy. Thus, while the study quality might be better due to the comparative designs, the crucial outcomes to derive a positive recommendation for LVA are probably missing.

**mögliche Limitationen:
keine RCT's verfügbar,
deshalb auch
prospektive Studien
eingeschlossen;
größtenteils
einarmige Studien
→ Bias-Risiko hoch**

Limitations

First of all, no RCT's were found in our literature search. Therefore, we decided to include prospective interventional single-arm studies for assessing the safety of LVA. We only considered prospective case-series with a patient cut-off of at least 10 patients treated for lymphoedema. Presumably, there were some prospective studies with less than 10 patients that were not included. Furthermore, there were numerous retrospective studies that were not included. Since we included also prospective interventional single-arm studies, the possibility of systematic errors due to confounding and bias is high.

⁷ A request to the author was made on this behalf but to date no response was received.

An additional limitation is that patient-relevant outcomes are missing in the included studies. Further, some of the studies rely on subjective reported outcomes. For example, QoL data are based on subjective VAS scores and may be confounded.

keine Outcomes relevant für PatientInnen

Another limitation of this review is that the studies included varied in terms of stages of lymphoedema, localisation of lymphoedema (upper or lower extremity), and outcomes were not reported separately on primary and secondary lymphoedema, this may lead to a variation in efficacy and safety of the results.

Studien basieren teilweise auf subjektiven Angaben

Further, there are several studies which describe the use of LVA as preventive procedure after cancer therapies. Hence, LVA may be a role in prevention of lymphoedema [49-51]. As it was not the scope of the assessment, we did not include those studies in this report, therefore, we cannot conclude if LVA is effective and safe as a prevention treatment for secondary lymphoedema.

unterschiedliche Lymphödem-Schweregrade in Studien

Conclusion

LVA seems to be safe for the treatment of primary and secondary lymphoedema. Nevertheless, no controlled evidence for crucial outcomes could be identified evaluating LVA and a comparator. Patient-relevant outcomes, such as QoL (pain and functionality) were only described in uncontrolled studies and inconsistently reported (e.g., different measurement scales). Because the included studies showed poor quality of evidence and high risk of bias, it is not possible to draw a reliable conclusion on the clinical effectiveness of LVA.

LVA könnte sicheres Verfahren sein, aber niedrige Evidenzqualität → verlässliche Aussage nicht möglich

Further, there were various methods of LVA performed in the studies, data on upper extremity lymphoedema was reported more frequently, and the estimation of ongoing post-interventional treatments (e.g., compression treatment etc.) is scarce and presented a large variety. Future RCTs and/or prospective NRCTs need to be performed to find the optimal lymphoedema management algorithm and to help determine the exact patient group that would benefit most from the procedure. In addition, these studies need to be conducted to confirm the outcomes, especially on QoL, and to further knowledge of this field.

weitere hochwertige Studien notwendig, um Ergebnisse zu bestätigen (z. B. QoL) und jene PatientInnen zu erreichen, die am meisten von der Intervention profitieren

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Empfehlungsschema

Table 9-1: Evidence based recommendations

	The inclusion in the catalogue of benefits is recommended .
	The inclusion in the catalogue of benefits is recommended with restrictions .
X	The inclusion in the catalogue of benefits is currently not recommended .
	The inclusion in the catalogue of benefits is not recommended .

Reasoning:

On the basis of the available evidence, we cannot conclude if the assessed procedure LVA is at least equally effective and safer as the comparator VLNT or conservative treatment. Due to the methodological shortcomings of the available evidence (because only one important outcome, but not decisive for the recommendation, was reported in the only comparative study), no conclusions are made about the effectiveness of the procedure. There is a need for high-quality studies due to consistent positive findings based on observational evidence with respect to limb volume reduction. Concerning safety outcomes, only procedure-related complications were reported based upon data from one NRCT and four prospective interventional single-arm studies. These suggest a relatively safe profile of LVA. New study results based on a high-quality RCT will potentially influence the effect estimate considerably.

The re-evaluation is recommended after 2021, if the potentially relevant ongoing studies are completed and only if patient-relevant outcomes are included to derive a recommendation (see Appendix List of ongoing trials). Otherwise, still no conclusions can be drawn on patient-relevant outcomes.

Evidenz unzureichend
→ LVA derzeit nicht empfohlen

Re-Evaluierung nach 2021 empfohlen, wenn derzeit laufende Studien patientInnenrelevante Outcomes beinhalten

10 References

- [1] Gesellschaft Deutschsprachiger Lymphologen (GDL). S2k Leitlinie – Diagnostik und Therapie der Lymphödeme. AWMF Reg.-Nr. 058-001. 2017 [cited 22.12.2017]; Available from: http://www.awmf.org/uploads/tx_szleitlinien/058-001_S2k_Diagnostik_und_Therapie_der_Lymphoedeme_2017-05.pdf.
- [2] Sharkey AR, King SW, Ramsden AJ, Furniss D. Do surgical interventions for limb lymphoedema reduce cellulitis attack frequency? *Microsurgery*. 2017;37(4):348-53.
- [3] 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*. 2009;113(2):199-206.
- [4] Oremus M, Walker K, Dayes I, Raina P. Diagnosis and Treatment of Secondary Lymphedema – Technology Assessment Report. Agency for Healthcare Research and Quality; 2010 [cited 06.02.2018]; Available from: <https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id66aTA.pdf>.
- [5] Carl HM, Walia G, Bello R, Clarke-Pearson E, Hassanein AH, Cho B, Pedreira R, Sacks JM. Systematic Review of the Surgical Treatment of Extremity Lymphedema. *J Reconstr Microsurg*. 2017;33(6):412-25.
- [6] Ingianni G. [Microsurgical lympho-venous anastomosis in the treatment of secondary lymphoedema of the upper extremity]. *Handchir Mikrochir Plast Chir*. 2003;35(4):216-20. Mikrochirurgische lympho-venose Anastomose beim sekundären Lymphodem der oberen Extremität.
- [7] Scaglioni MF, Fontein DBY, Arvanitakis M, Giovanoli P. Systematic review of lymphovenous anastomosis (LVA) for the treatment of lymphedema. *Microsurgery*. 2017;37(8):947-53.
- [8] Winters H, Tielemans HJP, Hameeteman M, Paulus VAA, Beurskens CH, Slater NJ, Ulrich DJO. The efficacy of lymphaticovenular anastomosis in breast cancer-related lymphedema. *Breast Cancer Res Treat*. 2017;165(2):321-7.
- [9] Leung EYL, Tirilapur SA, Meads C. The management of secondary lower limb lymphoedema in cancer patients: a systematic review. *Palliat Med*. 2015;29(2):112-9.
- [10] Poumellec M-A, Foissac R, Cegarra-Escolano M, Barranger E, Ihrai T. Surgical treatment of secondary lymphedema of the upper limb by stepped microsurgical lymphaticovenous anastomoses. *Breast Cancer Res Treat*. 2017;162(2):219-24.
- [11] Witty MF, Larouche K. [Treatment of cancer-related secondary lymphedema]. Montreal: L'institut National d'excellence en Sante et en Services Sociaux; 2011.
- [12] National Institute for Health and Care Excellence (NICE). Liposuction for chronic lymphoedema. 2017 [cited 16.02.2018]; Available from: <https://www.nice.org.uk/guidance/ipg588>.
- [13] Mehrara B. Surgical treatment of primary and secondary lymphedema. In: Berman RS, Butler CE, Collins KA, editors. *UpToDate*. Waltham, MA. (cited 17.01.2018): *UpToDate*; 2017.
- [14] Chiu TW. Management of secondary lymphoedema. *Hong Kong Medical Journal*. 2014;20(6):519-28.
- [15] The diagnosis and treatment of peripheral lymphedema: 2016 consensus document of the International Society of Lymphology. *Lymphology*. 2016;49(4):170-84.
- [16] Markkula Silja P, Leung N, Allen Victoria B, Furniss D. Surgical interventions for the prevention or treatment of lymphoedema after breast cancer treatment. *Cochrane Database of Systematic Reviews* [Internet]. 2014 [cited 25.01.2018]; (12). Available from: <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011433/abstract>.
- [17] Yamamoto T, Yoshimatsu H, Narushima M, Yamamoto N, Shim TWH, Seki Y, Kikuchi K, Karibe J, Azuma S, Koshima I. Sequential anastomosis for lymphatic supermicrosurgery: multiple lymphaticovenular anastomoses on 1 venule. *Ann Plast Surg*. 2014;73(1):46-9.

- [18] Visconti G, Hayashi A, Salgarello M, Narushima M, Koshima I, Yamamoto T. Supermicrosurgical T-shaped lymphaticovenular anastomosis for the treatment of peripheral lymphedema: Bypassing lymph fluid maximizing lymphatic collector continuity. *Microsurgery*. 2016;36(8):714-5.
- [19] Lee BB, Laredo J, Neville R. Current status of lymphatic reconstructive surgery for chronic lymphedema: It is still an uphill battle! *International Journal of Angiology*. 2011;20(2):73-9.
- [20] Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. *Plast Reconstr Surg*. 2013;132(5):1305-14.
- [21] Cornelissen AJM, Kool M, Lopez Penha TR, Keuter XHA, Piatkowski AA, Heuts E, van der Hulst RRWJ, Qiu SS. Lymphatico-venous anastomosis as treatment for breast cancer-related lymphedema: a prospective study on quality of life. *Breast Cancer Res Treat*. 2017;163(2):281-6.
- [22] Akita S, Mitsukawa N, Kuriyama M, Kubota Y, Hasegawa M, Tokumoto H, Ishigaki T, Togawa T, Kuyama J, Satoh K. Comparison of vascularized supraclavicular lymph node transfer and lymphaticovenular anastomosis for advanced stage lower extremity lymphedema. *Ann Plast Surg*. 2015;74(5):573-9.
- [23] Allen RJ, Jr., Cheng M-H. Lymphedema surgery: Patient selection and an overview of surgical techniques. *J Surg Oncol*. 2016;113(8):923-31.
- [24] Chang DW. Lymphaticovenular bypass for lymphedema management in breast cancer patients: a prospective study. *Plast Reconstr Surg*. 2010;126(3):752-8.
- [25] Ayestaray B, Bekara F. pi-shaped lymphaticovenular anastomosis: the venous flow sparing technique for the treatment of peripheral lymphedema. *J Reconstr Microsurg*. 2014;30(8):551-60.
- [26] Kim SY, Park JE, Lee YJ, Seo H-J, Sheen S-S, Hahn S, Jang B-H, Son H-J. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *Journal of Clinical Epidemiology*. 2013;66(4):408-14.
- [27] Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014; [cited 26.01.2018]; Available from: <http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about>.
- [28] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*. 2011;64:383-94.
- [29] Chen WF, Yamamoto T, Fisher M, Liao J, Carr J. The "Octopus" Lymphaticovenular Anastomosis: Evolving Beyond the Standard Supermicrosurgical Technique. *J Reconstr Microsurg*. 2015;31(6):450-7.
- [30] Kung TA, Champaneria MC, Maki JH, Neligan PC. Current Concepts in the Surgical Management of Lymphedema. *Plast Reconstr Surg*. 2017;139(4):1003e-13e.
- [31] Hadamitzky C, Pabst R, Gordon K, Vogt PM. Surgical procedures in lymphedema management. *Journal of Vascular Surgery: Venous and Lymphatic Disorders*. 2014;2(4):461-8.
- [32] Koshima I, Inagawa K, Urushibara K, Moriguchi T. Supermicrosurgical lymphaticovenular anastomosis for the treatment of lymphedema in the upper extremities. *J Reconstr Microsurg*. 2000;16(6):437-42.
- [33] Granzow JW, Soderberg JM, Kaji AH, Dauphine C. Review of current surgical treatments for lymphedema. *Ann Surg Oncol*. 2014;21(4):1195-201.
- [34] Chan VSH, Narushima M, Hara H, Yamamoto T, Mihara M, Iida T, Koshima I. Local anesthesia for lymphaticovenular anastomosis. *Ann Plast Surg*. 2014;72(2):180-3.
- [35] McLaughlin SA, DeSnyder SM, Klimberg S, Alatrisme M, Boccardo F, Smith ML, Staley AC, Thiruchelvam PTR, Hutchison NA, Mendez J, MacNeill F, Vicini F, Rockson SG, Feldman SM. Considerations for Clinicians in the Diagnosis, Prevention, and Treatment of Breast Cancer-Related Lymphedema, Recommendations from an Expert Panel: Part 2: Preventive and Therapeutic Options. *Ann Surg Oncol*. 2017;24(10):2827-35.
- [36] Mihara M, Hara H, Tange S, Zhou HP, Kawahara M, Shimizu Y, Murai N. Multisite Lymphaticovenular Bypass Using Supermicrosurgery Technique for Lymphedema Management in Lower Lymphedema Cases. *Plast Reconstr Surg*. 2016;138(1):262-72.

- [37] Statistik Austria. Prognose der Krebsinzidenz und Krebsmortalität. 2018 [cited 14.02.2018]; Available from: http://statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/prognose_krebsinzidenz_krebsmortalitaet/index.html.
- [38] Statistik Austria. Krebs im Überblick. 2018 [cited 14.02.2018]; Available from: http://statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/krebs_im_ueberblick/index.html.
- [39] Campisi C, Campisi C, Accogli S, Campisi C, Boccardo F. Lymphedema staging and surgical indications in geriatric age. *BMC Geriatrics*. 2010;10(Suppl 1):(A50).
- [40] Garza R, 3rd, Skoracki R, Hock K, Povoski SP. A comprehensive overview on the surgical management of secondary lymphedema of the upper and lower extremities related to prior oncologic therapies. *BMC Cancer*. 2017;17(1):468.
- [41] Statistik Austria. Jahrbuch der Gesundheitsstatistik. 2008 [cited 22.01.2018]; Available from: http://statistik.at/web_de/nomenu/suchergebnisse/index.html?searchQuery=Jahrbuch%20der%20Gesundheitsstatistik%20&no=1&n1=1&n2=1&n3=1&n4=1&n5=1&n7=1&n8=1&n9=1&n6=11.
- [42] Statistik Austria. Medizinische Einzelleistungen. 2017 [cited 22.01.2017]; Available from: http://statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/stationaere_aufenthalte/medizinische_leistungen/index.html.
- [43] Tourani SS, Taylor GI, Ashton MW. Long-Term Patency of Lymphovenous Anastomoses: A Systematic Review. *Plast Reconstr Surg*. 2016;138(2):492-8.
- [44] Abbas S, Seitz M. Systematic review and meta-analysis of the used surgical techniques to reduce leg lymphedema following radical inguinal nodes dissection. *Surgical Oncology*. 2011;20(2):88-96.
- [45] Winters H, Tielemans HJP, Sprangers PN, Ulrich DJO. Peri-operative care for patients undergoing lymphaticovenular anastomosis: A systematic review. *J Plast Reconstr Aesthet Surg*. 2017;70(2):178-88.
- [46] Jorgensen MG, Toyserkani NM, Sorensen JA. The effect of prophylactic lymphovenous anastomosis and shunts for preventing cancer-related lymphedema: a systematic review and meta-analysis. *Microsurgery* [Internet]. 2017 Mar 28; 28:[28 p.]. [cited 26.02.2018]; Available from: <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=medp&AN=28370317>.
- [47] CADTH. Lymphatic-Venous anastomosis for lymphedema: clinical and cost-effectiveness. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2013.
- [48] 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(4):905-13.
- [49] Szolnoky G, Dobozy A, Kemeny L. Towards an effective management of chronic lymphedema. *Clin Dermatol*. 2014;32(5):685-91.
- [50] Boccardo F, Valenzano M, Costantini S, Casabona F, Morotti M, Sala P, De Cian F, Molinari L, Spinaci S, Dessalvi S, Campisi CC, Villa G, Campisi C. LYMPHA Technique to Prevent Secondary Lower Limb Lymphedema. *Ann Surg Oncol*. 2016;23(11):3558-63.
- [51] Gomberawalla A, Vandenberghe J, Borden B, Rohde C, Ascherman J, Taback B, Chen M, Feldman S. Lymphatic microsurgical preventive healing approach (LYMPHA) for the primary prevention of lymphedema. *Cancer Research*. 2017;77(4).
- [52] Gartlehner G. Internes Manual. Abläufe und Methoden. Teil 2 (2. Aufl.). Wien 2009 [cited 06.02.2018]; Available from: <http://eprints.hta.lbg.ac.at/713/>.
- [53] EUnetHTA Joint Action 2. Internal validity of non-randomised studies (NRS) on interventions. 2015 [cited 05.02.2018]; Available from: http://www.eunetha.eu/wp-content/uploads/2018/01/Internal-validity-of-non-randomised-studies-NRS-on-interventions_Guideline_Final-Jul-2015.pdf.

Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: LVA: Results from one non-randomized controlled study

Author, year	Akita, 2015 [22]
Country	Japan
Sponsor	-
Intervention	LVA (side-to-end or end-to-end) Lower extremity
Comparator	VSLNT
Study design	Two-centre NRCT
Setting (e.g. outpatient, university hospital etc.)	University Hospital & Cancer Center
Number of pts	LVA: 43 VSLNT: 13
Inclusion criteria	Patients with advanced primary or secondary lower extremity lymphoedema
Exclusion criteria	Early stage lymphoedema
Mean age of patients, yrs (range)	LVA: 54.1 (\pm 14.8) ⁸ , s.s. VSLNT: 63.7 (\pm 7.0)
Sex, female vs. male (% female)	LVA: 40 vs. 3 (93.0) VSLNT: 13 vs. 0 (100)
Mean lymphoedema duration, yrs (range)	NR
Underlying disease	(assumably) cancer (lymph node dissection) & phlegmon in 39 pts (LVA) and in 13 pts (VSLNT)
Assessment of severity of lymphoedema	ICG lymphography
Stage of lymphoedema (e.g.; ISL/Campisi)	Early-stage lymphoedema in 63 limbs ⁹ Advanced stage lymphoedema in 64 limbs
Follow-up (months)	LVA: 18.3 (\pm 8.8) VSLNT: 15.1 (\pm 1.9)
Loss to follow-up, n (%)	-
Pre-interventional procedure (n)	Supervised compression therapy (for min. 3 mo before surgery)
Post-interventional procedure (n)	Simple self-lymph drainage after discharge; Elastic garments occasionally until the final follow-up
Additional interventions	-
Diameter of lymphatic vessel, mm	NR
Mean operation time, min	LVA: 213 (\pm 68), s.s. VSLNT: 414 (\pm 65)
Mean BMI, kg/m ²	LVA: 24.8 (\pm 5.8) VSLNT: 23.0 (\pm 2.8)
Mean number of LVAs performed	NR
Mean preoperative volume differential compared with unaffected limb, %	NR

⁸ Presumably it is the mean age of patients.

⁹ Unclear reporting of lymphoedema staging.

Author, year	Akita, 2015 [22]
Outcomes	
Efficacy	
Mean volume or circumference reduction, %	NR
Mean changes of volume compared with preoperative volumes, difference % (SD)	<i>Improvement value of Lower Extremity Lymphoedema index (LEL)¹⁰</i> LVA: 21.2 (± 2.0) vs. VSLNT: 26.5 (± 4.4), s.s.
Quality of life (QoL), %	NR
Recurrence (worsening of lymphoedema), n (%)	NR
Safety	
Overall complications, n (%)	0 vs. 3
Procedure-related adverse events, n (%)	<i>LVA group: 0</i> <i>VSLNT group: congestion to the skin paddle, 3 (23.1*)</i> s.s.
Procedure-unrelated adverse events, n (%)	NR

* own calculations

Abbreviations: ICG = Indocyanine green; ISL = International Society of Lymphology; NR = not reported; n.s. not significant; LEL = lower extremity lymphoedema; pts = patients; s.s. = statistical significant; VLNT = vascularized lymph node transfer; VSLNT = vascularized supraclavicular lymph node transfer;

¹⁰ *LEL index:* Changes in the postoperative volume were compared using the LEL index, which was calculated from the circumferences of 5 points on the limb (the superior edge of the patella, 10 cm above and below the patella, the lateral malleolus, and the dorsum of the foot) and the body mass index, which yielded an accurate quantitative assessment of the severity of lymphoedema [22].

Table A-2: LVA: Results from prospective interventional single-arm studies

Author, year	Chang, 2013 [20]	Cornelissen, 2017 [21]	Damstra, 2009 [3]	Poumellec, 2017 [10]
Country	USA	Netherlands	Netherlands	France
Sponsor	Kyte Research and Education Fund; National Institutes of Health through M. D. Anderson's Cancer Center Support Grant CA016672;	NR	NR	NR
Intervention	LVA (lymphovenous bypass) (end-to-end or end-to-side) 89 upper extremities & 11 lower extremities	LVA (NR) Upper extremity	LVA (end-to-side) Upper extremity	LVA (end-to-end) Upper extremity
Comparator	-	-	-	-
Study design	Single-centre prospective interventional single-arm study	Single-centre prospective interventional single-arm study	Single-centre prospective interventional single-arm study	Single-centre prospective interventional single-arm study ¹¹
Setting (e.g. outpatient, university hospital etc.)	University Hospital Cancer Center	University Medical Centre	Hospital (Lymphoedema Department)	Day Surgery Setting (Breast Cancer Surgery Center)
Number of pts	100 ¹²	20	10	31
Inclusion criteria	<ul style="list-style-type: none"> ✱ Patients with secondary extremity lymphoedema 	<ul style="list-style-type: none"> ✱ Absence of skin infections and complex decongestive therapy for at least 3 months; ✱ Evidenced upper limb lymphoedema secondary to breast cancer in stage 1 or 2A according to the ISL classification; ✱ Patent lymphatic ducts seen by ICG lymphangiography; 	<ul style="list-style-type: none"> ✱ No volume reduction after 3 months of complex decongestive treatment including manual lymph drainage, compression therapy, and physiotherapy, with persistent complaints such as heaviness, pain, shoulder function impairment, and recurrent attacks of erysipelas; ✱ Proven scintigraphic signs of obstruction by absence of liver uptake and highly pathological transport index; ✱ Persistent volume excess of more than 800cc measured by inverse water volumetry; ✱ No recurrent malignancy; ✱ Good patient compliance and willingness to wear therapeutic elastic stockings; ✱ Operability; 	<ul style="list-style-type: none"> ✱ Female patient; ✱ Age >18 years; ✱ Lymphoedema evolving for at least 12 months and not responding to physiotherapy; ✱ History of axillary dissection surgery for breast cancer treatment; ✱ Lymphoedema with at least 2-cm augmentation of the circumference of the dissected limb compared with the healthy limb;

¹¹ Unclear study design. A request to the author was made on this behalf but to date no response was received.

¹² Outcome data is only reported on 37 patients; baseline data reported on an unknown number of patients (lacking table with baseline characteristics).

Author, year	Chang, 2013 [20]	Cornelissen, 2017 [21]	Damstra, 2009 [3]	Poumellec, 2017 [10]
Exclusion criteria	NR	NR	NR	✱ No previous physiotherapy for lymphoedema; ✱ Refusal to sign informed consent;
Mean age of patients, yrs (range)	54.0	55.9 (range, 51.9-59.9)	58.7 (range, 46-68)	64 (range, 38-65)
Sex, female vs. male (% female)	NR	20 vs. 0 (100)	10 vs. 0 (100)	31 vs. 0 (100)
Mean lymphoedema duration, yrs (range)	Upper extremity: 3.5 (range, 1-10) ¹² Lower extremity: 6.6 (range, 1-25)	6 (range, 2-30)	5.3 (range, 3-14)	NR
Underlying disease	Upper extremity lymphoedema: breast cancer (n=89); Lower leg extremity lymphoedema: sarcoma (n=3), melanoma (n=2), gynecologic cancer (n=6)	Breast cancer Skin infection in 5 pts. (25%)	Breast cancer	Breast cancer
Assessment of severity of lymphoedema	ICG lymphangiographic findings	NR	NR	NR
Stage of lymphoedema (e.g.; ISL/Campisi)	Unclear ⁹	ISL Stage 1: n=1 Stage 2A: n=19	<i>Campisi staging</i> Stage III (n=10)	NR
Follow-up (months)	Upper extremity: 30.4 (range, 3-84) Lower extremity: 18.2 (range, 1-36)	7.8 (range, 6.3-9.3)	12	Mean 12.8 ¹⁴
Loss to follow-up, n (%)	NR	Unclear ¹³	-	unclear
Pre-interventional procedure (n)	ICG lymphography (n=65);	ICG lymphangiography	Standardized conservative treatment for 3 months; Perioperative usage of antibiotics;	NR
Post-interventional procedure (n)	Compression bandages and elevation of affected limb; Prophylactic intravenous antibiotics; 4 weeks after surgery: use of compression garments	NR	Compression bandages and elevation of affected limb at night; Elastic stockings during follow-up	Removal of the sleeve and lymphatic drainage physiotherapy beginning two weeks post surgery
Additional interventions	VLNT due to no improvement after LVA (n=1)	NR	NR	NR
Diameter of lymphatic vessel, mm	Upper extremity: 0.2-1.0 Lower extremity: NR	NR	≤ 0.3	NR

¹³ Unclear reporting of losses to follow-up.

Author, year	Chang, 2013 [20]	Cornelissen, 2017 [21]	Damstra, 2009 [3]	Poumellec, 2017 [10]
Mean operation time, min	Upper extremity: 240 (range, 3-5 hrs) Lower extremity: NR	92 (range, 84-100)	60	120 ¹⁴
Mean BMI, kg/m ²	Upper extremity: 30 (range, 20-51) Lower extremity: 31 (range, 22-42)	25.1 (range, 21-33)	NR	25.3 (± 6.4) ¹⁴
Mean number of LVAs performed	Unclear ¹⁵	1.5	unclear ¹⁶	NR
Mean preoperative volume differential compared with unaffected limb, %	Upper extremity: 32 (range, 1-112) Lower extremity: 37.6 (range, 7-85)	NR	35.2 (range, 20-50)	NR
Outcomes				
Efficacy				
Mean volume or circumference reduction, %	Overall ¹⁷ : 3 mo postoperatively: 33 6 mo postoperatively: 36 12 mo postoperatively: 42 Lymphoedema stage I or II (upper extremity, 30 pts): 3 mo postoperatively: 58 6 mo postoperatively: 52 12 mo postoperatively: 61 Lymphoedema stage III or IV (upper extremity, 30 pts): 3 mo postoperatively: 12 6 mo postoperatively: 16 12 mo postoperatively: 17	NR	Mean volume difference: 12 mo postoperatively: 33.5 (range, 18-49) Hertz circumferential measurement: improvement of 4.8% 1 year postoperatively	Overall lymphoedema decrease postoperatively ¹⁸ : Stage II: 29.5% Stage III: 13.1% Stage IV: 0% Mean overall decrease: 24.7%
Mean changes of volume compared with preoperative volumes, difference % (SD)	Upper extremity ¹⁹ : 3 mo postoperatively: -9.6 (9.1), s.s. 6 mo postoperatively: -8.5 (11.2), s.s. 12 mo postoperatively: -7.7 (8.2), s.s. Lower extremity: NR	Upper Extremity Lymphoedema index (UEL-index): Preoperatively: 14.92 (±8.01) Postoperatively: 12.99 (±7.47), n.s.	Hertz method at 0-12 months 1.7*	NR

¹⁴ Different numbers in text compared to baseline data table.

¹⁵ It is reported to be 5.6 (in pts with ICG lymphography), but patient group is unclear.

¹⁶ It is reported that at least 3-4 anastomoses are performed, but only 11 LVA procedures in 10 patients.

¹⁷ Unclear number of total patients. Insufficient data on lower extremity lymphoedema.

¹⁸ Data extracted from the discussion section.

¹⁹ Unclear number of total patients.

Author, year	Chang, 2013 [20]	Cornelissen, 2017 [21]	Damstra, 2009 [3]	Poumellec, 2017 [10]
Quality of life (QoL), %	Insufficient reporting	<p>Mean VAS Scores according to the Lymph-ICF questionnaire (Dutch version)²⁰</p> <p><i>Overall</i> Preoperatively: 44 (n=20) 3 mo postoperatively: 31 (n=8), s.s. 6 mo postoperatively: 30 (n=8), s.s. 12 mo postoperatively: 14 (n=8), s.s.</p> <p><i>Physical Function Domain</i> Preoperatively: 48 (n=20) 3 mo postoperatively: 26 (n=8), s.s. 6 mo postoperatively: 46 (n=8) 12 mo postoperatively: 13 (n=8), s.s.</p> <p><i>Mental Function Domain</i> Preoperatively: 42 (n=20) 3 mo postoperatively: 22 (n=8), s.s. 6 mo postoperatively: 15 (n=8), s.s. 12 mo postoperatively: 11 (n=8), s.s.</p> <p><i>Household Activities Domain</i> Preoperatively: 52 (n=20) 3 mo postoperatively: 42 (n=8) 6 mo postoperatively: 33 (n=8), s.s. 12 mo postoperatively: 28 (n=8), s.s.</p> <p><i>Mobility Activities Domain</i> Preoperatively: 41 (n=20) 3 mo postoperatively: 36 (n=8) 6 mo postoperatively: 33 (n=8) 12 mo postoperatively: 11 (n=8), s.s.</p> <p><i>Life and Social Activities Domain</i> Preoperatively: 41 (n=20) 3 mo postoperatively: 39 (n=8) 6 mo postoperatively: 28 (n=8), s.s. 12 mo postoperatively: 11 (n=8), s.s.</p>	<i>SF 36 questionnaire²¹</i>	<p><i>QoL evaluation questionnaire²²:</i> 1 yr postoperatively: <4 (unsatisfactory) <i>Functionality:</i> 55% score of >7 (significant functional improvement) 29% scores 4-7 (moderate functional improvement)</p>
Recurrence (worsening of lymphoedema), n (%)	-	NR	NR	4 (19.7)

²⁰ Lymphoedema international classification of functioning (Lymph-ICF) questionnaire (Dutch version): This questionnaire comprises five domains. The values range from 1 to 100; a lower score on the questionnaire indicates a better quality of life. The Lymph-ICF questionnaire gives a score on five different domains, which may provide a wider coverage of all the aspects related to lymphoedema. This questionnaire can determine changes over time and may provide useful and detailed information for long-term follow-up. Furthermore, the used questionnaire is the only lymphoedema-related questionnaire that uses a VAS score answering model, which is more sensitive to subtle changes [21].

²¹ Unclear reporting on the questionnaire: 0-6 months postoperatively: slight subjective improvement in 5 patients who felt less disabled.

²² Unclear reporting on the questionnaire.

Author, year	Chang, 2013 [20]	Cornelissen, 2017 [21]	Damstra, 2009 [3]	Poumellec, 2017 [10]
Safety	-	2 (10)		
Overall complications, n (%)	-	Skin irritation at the site of contrast injection, 2 (10)	NR	-
Procedure-related adverse events, n (%)	NR	NR	NR	-
Procedure-unrelated adverse events, n (%)			NR	NR

* own calculations

Abbreviations: ICG = Indocyanine green; ISL = International Society of Lymphology; NR = not reported; n.s. = not significant; LEL = lower extremity lymphoedema; pts = patients; s.s. = statistical significant; VLNT = vascularized lymph node transfer;

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [52] and in the Guidelines of EUnetHTA [53].

Table A-3: RoBANS risk of bias assessment tool for non-randomized controlled studies, see [26]

Study reference/ID	Selection of participants	Confounding variables	Intervention (exposure) measurement	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Overall Risk of Bias
Akita, 2015 [22]	High ²³	Unclear ²⁴	Low	High ²⁵	High ²⁶	High ²⁷	Moderate to High ²⁸

²³ No randomization.

²⁴ Unclear reporting of confounding variables.

²⁵ No blinding of outcome assessors.

²⁶ Only reporting on one important, but not crucial outcome.

²⁷ Critical outcomes (e.g., QoL, pain) not reported.

²⁸ Not intended to produce an overall rating.

Table A-4: Risk of bias – study level (case series), IHE checklist, see [27]

Study reference/ID	Chang, 2013 [20]	Cornelissen, 2017 [21]	Damstra, 2009 [3]	Poumellec, 2017 [10]
Study objective				
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes
Study design				
2. Was the study conducted prospectively?	Yes	Yes	Yes	Unclear ²⁹
3. Were the cases collected in more than one centre?	No	No	No	No
4. Were patients recruited consecutively?	Yes	Yes	Unclear ²⁹	Unclear ²⁹
Study population				
5. Were the characteristics of the patients included in the study described?	Partial ³⁰	Yes	Yes	Partial ¹⁹
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Partial ³¹	Partial ³¹	Partial ³¹	Yes
7. Did patients enter the study at a similar point in the disease?	Unclear ³²	Yes	Yes	Unclear ³²
Intervention and co-intervention				
8. Was the intervention of interest clearly described?	Yes	Partial	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes	Yes
Outcome measures				
10. Were relevant outcome measures established a priori?	No	Yes	Yes	Partial ³³
11. Were outcome assessors blinded to the intervention that patients received?	Unclear ³⁴	Unclear ³⁴	Unclear ³⁴	Unclear ³⁴
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Partial ³⁵	Yes	Yes	Partial ³⁵
13. Were the relevant outcome measures made before and after the intervention?	Unclear ³⁶	Yes	Yes	No

²⁹ Not explicitly stated in the study.

³⁰ See extraction tables in the Appendix for reporting on baseline characteristics.

³¹ No exclusion criteria were stated.

³² No reporting on staging of lymphoedema.

³³ Not all outcome measures were stated a priori.

³⁴ No information on blinding was available.

³⁵ Insufficient reporting on QoL.

³⁶ Volume measurements were made pre- and postoperatively, but the other outcomes were only reported postoperatively.

Study reference/ID	Chang, 2013 [20]	Cornelissen, 2017 [21]	Damstra, 2009 [3]	Poumellec, 2017 [10]
Statistical Analysis				
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Unclear	Unclear
Results and Conclusions				
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes
16. Were losses to follow-up reported?	No	Unclear ³⁷	Yes	Unclear ³⁷
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Partial	Partial	Partial	No
18. Were the adverse events reported?	Yes	Yes	No	Yes
19. Were the conclusions of the study supported by results?	No	No	No	No
Competing interests and sources of support				
20. Were both competing interests and sources of support for the study reported?	Unclear ³⁸	Unclear ³⁸	No	Unclear ³⁸
Overall Risk of Bias	High	Moderate	Moderate	High

³⁷ Discrepancy between text and tables/figures in patient numbers for loss to follow-up.

³⁸ Either reporting on conflict of interest or funding, not both.

Table A-5: Evidence profile: efficacy and safety of LVA surgical treatment in lymphoedema

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LVA	VSLNT	Relative (95% CI)	Absolute (95% CI)		
Mean changes of volume compared with preoperative volume measurements (follow up: mean 15.1-18.3 months)												
1	observational studies (before-after study)	very serious ^a	NA (only 1 trial)	not serious	very serious ^b	none	Improvement value of LEL index: LVA: 21.2 (±2.0) vs. VSLNT: 26.5 (±4.4), s.s.		⊕○○○ VERY LOW		IMPORTANT	
Quality of life – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Recurrence (worsening of lymphoedema) – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Procedure-related adverse events (follow up: mean 7.8-30.4)												
4	observational studies (before-after studies)	very serious ^c	not serious	not serious	not serious	publication bias strongly suspected ^d	2/194 (1.0 %)	3/13 (23.1 %)	not estimable	not estimable	⊕○○○ VERY LOW	CRITICAL
Procedure-unrelated adverse events – not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

Abbreviation: s.s. = statistical significant

comments:

^a High risk of selection, detection and reporting biases.

^b Small sample size, small number of events.

^c No control group.

^d Chang reported on 100 patients, but outcome data is only reported for 37.

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

Applicability table

Table A-6: Summary table characterizing the applicability of a body of studies

Domain	Description of applicability of evidence
Population	All studies included mostly female patients with lymphoedema (primary or secondary to cancer treatment). Two studies only included patients with advanced lymphoedema, which is likely to have influenced the effects of the procedure. The studies included a total of 204 patients with LVA treatment and 13 patients with VSLNT treatment. The mean age of included patients was consistent across studies and ranged from 54.0-64.0 years. The inclusion criteria and the population in the studies seem to be in accordance with the intended patient population for the procedure.
Intervention	<p>Patients in the included studies were treated with LVA in primary or secondary lymphoedema of the upper and/or lower extremities. The procedure was performed either side-to-end, end-to-end or end-to-side. The diameter of lymphatic vessel was described in two studies for upper extremities and ranged from 0.2 to 1.0 mm. Three studies did not report on the diameter of lymphatic vessels on which the LVAs were performed.</p> <p>In most of the studies, pre-interventional (e.g. standardized conservative methods, compression therapy) as well as post-interventional (e.g. compression bandages, lymphatic drainage) treatments were performed. It is unclear if variations in the performed methods of LVA or the additional performed treatments (pre- and post-interventional) are likely to have a meaningful impact on patient outcomes.</p>
Comparators	One study was comparing LVA and VSLNT. The VSLNT procedure may represent an alternative to the LVA procedure, but may be more effective in advanced stages of lymphoedema, as this study showed. To date, we found no published RCTs in which LVA is compared to conservative or other surgical treatments, such as VLNT/VSLNT.
Outcomes	<p>None of the crucial outcomes for clinical effectiveness were reported in the only included NRCT. Only one important outcome, mean changes of volume, was reported in this study. The time period for this outcome was not reported in the study. The outcome of clinical effectiveness showed a potential benefit of the treatment with VSLNT in comparison to LVA for patients suffering from advanced lymphoedema.</p> <p>The most frequently reported critical outcome for safety was procedure-related adverse events across studies. One prospective interventional single-arm study did not report this outcome. For the safety assessment only, two patients (2/204) reported adverse events of LVA during the procedure (skin irritation after contrast injection).</p> <p>However, the presented data in the included studies is limited, especially due to small sample sizes in some of the studies, unclear reporting of patient numbers in one study (which may lead to imprecise data), and no reporting of critical outcomes for efficacy data in the controlled study.</p>
Setting	<p>The procedure was performed under local or general anaesthesia. One study was a non-randomized controlled two-centre study carried out in Japan. The other four studies were single-centre prospective interventional single-arm studies conducted in the US (1) and Europe (3). The studies carried out in Europe were based in the Netherlands (2) and France (1).</p> <p>The studies were published between 2009 and 2017. The procedure was performed in university hospitals and/or cancer centres across four studies. In one study, LVA was performed in a day surgery setting because of its minimal invasiveness and short recovery time.</p> <p>The settings of the studies reflect the clinical settings in which the technology is intended to be used in an appropriate way. No applicability issues are expected from the geographical setting.</p>

List of ongoing trials

Table A-7: List of ongoing randomised controlled trials of LVA

Source	Identifier/Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
ClinicalTrials.gov	NCT02790021 Improving Quality of Survivorship for Breast Cancer-related Lymphoedema by Lymphaticovenous Anastomosis: A Randomized Controlled Trial	Woman >18 years old; treated for early stage breast cancer and underwent an SLNB, ALND or axillary radiotherapy; early stage lymphoedema of the arm (stage 1 or 2a on ISL classification); excess limb volume $\geq 10\%$ (relative volume of the unaffected arm compared to the affected arm); previously had three months conservative therapy (standard of care); primary breast cancer; Unilateral disease/treatment;	Lymphatic-ovenous anastomosis (LVA)	Complex decongestive therapy	Relative arm volume of the affected compared to the unaffected arm	May 2019	Maastricht University Medical Center
WHO-ICTRP	JPRN-UMIN000025137 Lymphatic Venous Anastomosis for Secondary lymphoedema	Male and Female; patients who received lymphatic surgery/reconstructive surgery; patients diagnosed with secondary lower extremity lymphoedema by lymphoscintigraphy; patients judged to have the ability to answer interrogation; patients who obtained document consent by the patients themselves freely with sufficient understanding after receiving sufficient explanation for participation in this study; in cases where the patient is a minor; in addition to the patient caregiver sufficient understanding, document consent is obtained;	Lymphatic venous anastomosis	Complex decongestive physiotherapy	Change in the number of times of cellulitis. (Cellulitis is defined as having inflammatory findings such as redness and heat sensation on the affected limbs and having a fever of 38.5 degrees or more.)	December 2020	Saiseikai Kawaguchi General Hospital
WHO-ICTRP	NTR6465 Pilot study on robot-assisted microsurgical lymphatico-venular anastomosis Pilot study on robot-assisted microsurgical lymphatico-venular anastomosis	Female gender; age 18 years or older; treated for primary early stage breast cancer; early stage lymphoedema of the arm (stage 1 or 2 on ISL classification); ELV $\geq 10\%$; suffering unilateral disease and treatment;	Robot-assisted LVA	Conventional LVA	Efficiency of LVA is measured assessing the quality of the completed lymphovenular anastomosis	February 2019	Maastricht University Medical Center (MUMC+); Microsure

Table A-8: List of ongoing trials of LVA (parallel non-randomized and single-arm non-randomized studies)

Source	Identifier/ Trial name	Study type	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
ClinicalTrials.gov	NCT02020837 A Pilot Study Assessing the Effect of Lymphaticovenous Micro-Anastomosis in the Treatment of Postmastectomy Lymphoedema	Single-arm non-randomized	18-70 years of age; stage II-IV unilateral lymphoedema	Lymphaticovenous Micro-Anastomosis	-	Changes relative to baseline in the volume of the affected limb at 3 and 6 months from surgery	September 2019	University of Arkansas
WHO-ICTRP	JPRN-UMIN000017768 Study of the effectiveness of early lymphatic venous anastomosis	Single-arm non-randomized	Male and Female; ≤90 years-old; secondary lymphoedema patients	LVA	-	Circumference of the leg (LEL index); the presence or absence of cellulitis	NR	The University of Tokyo Hospital
WHO-ICTRP	JPRN-UMIN000022689 Examination of the lymphoedema improvement with the surgical combination therapy for secondary limbs lymphoedema	Parallel non-randomized	≤30 years old, male and female, patients with secondary lymphoedema, and expect surgical cure; persons who are available for LVA conducts LVA by ICG lymphangiography; persons with LVA treatment resistance receive LNT or VLNT+LVA; years-old	Vasculized lymph node transfer(VLNT)	Vasculized lymph node transfer, Lymphaticovenuler anastomosis (LVA) vs. Lymphaticovenuler anastomosis	Limbs circumference, ICG fluorescent lymphography, SF36	NR	Cancer Institute Hospital
WHO-ICTRP	JPRN-UMIN000019140³⁹ Prospective study on the effectiveness assessment of Indocyanine Green Lymphography and Lymphatic Surgery for lymphoedema and lymphatic disease.	Parallel non-randomized	Male and female; all subjects included in this study are lymphoedema and lymphatic disease patients undergoing surgical treatment at our department who have been fully informed of all clinical tests, questionnaires, surgical treatments, and the purpose and analysis of this study and have all consented in writing. No age restriction and exclusion criteria were set.	Indocyanine green (ICG) lymphography and Lymphatic venous anastomosis (Modified Campisi's LVA for subclinical and early-stage lymphoedema)	ICG lymphography and lymph node transfer & ICG lymphography and liposuction	Pre and postoperative course, limb circumference, tissue stiffness; echogram, CT, MRI, lymphoscintigraphy, indocyanine green lymphography, and lymphoangiography observations; blood; histopathological analysis; clinical; health-related QOL analysis using Short Form (SF)-36 Health Survey; patient weight; general physical and image observations	March 2018	Saiseikai Kawaguchi General Hospital

³⁹ These studies may be connected and may represent sub-analytical results.

Source	Identifier/ Trial name	Study type	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
WHO-ICTRP	JPRN-UMIN000027759 ³⁹ Prospective study on the effectiveness assessment of Indocyanine Green Lymphography and Lymphatic Surgery for lymphoedema and lymphatic disease.	Single-arm non-randomized	Male and female; all subjects included in this study are lymphoedema and lymphatic disease patients undergoing surgical treatment at our department who have been fully informed of all clinical tests, questionnaires, surgical treatments, and the purpose and analysis of this study and have all consented in writing. No age restriction and exclusion criteria were set.	Indocyanine green (ICG) lymphography and ultrasound for the patency rate of Lymphatic venous anastomosis(LVA)	-	Pre and postoperative course, limb circumference, tissue stiffness; echogram, CT, MRI, lymphoscintigraphy, indocyanine green lymphography, and lymphoangiography observations; blood; histopathological analysis; clinical; health-related QOL analysis using Short Form (SF)-36 Health Survey; patient weight; general physical and image observations; patency rate of lymphatic venous anastomosis.	NR	Saiseikai Kawaguchi General Hospital
WHO-ICTRP	JPRN-UMIN000014748 ³⁹ Prospective study on the effectiveness assessment of Indocyanine Green Lymphography and Lymphatic Surgery for lymphoedema and lymphatic disease.	Parallel non-randomized	Male and female; all subjects included in this study are lymphoedema and lymphatic disease patients undergoing surgical treatment at our department who have been fully informed of all clinical tests, questionnaires, surgical treatments, and the purpose and analysis of this study and have all consented in writing. No age restriction and exclusion criteria were set.	Indocyanine green (ICG) lymphography and Lymphatic venous anastomosis (LVA)	ICG lymphography and lymph node transfer & ICG lymphography and liposuction	Pre and postoperative course, limb circumference, tissue stiffness; echogram, CT, MRI, lymphoscintigraphy, indocyanine green lymphography, and lymphoangiography observations; blood; histopathological analysis; clinical; health-related QOL analysis using Short Form (SF)-36 Health Survey; patient weight; general physical and image observations.	NR	Saiseikai Kawaguchi General Hospital
WHO-ICTRP	JPRN-UMIN000021762 ³⁹ Prospective study on the effectiveness assessment of Indocyanine Green Lymphography and Lymphatic Surgery for lymphoedema and lymphatic disease.	Parallel non-randomized	Male and female; >20 years old; All subjects included in this study are lymphoedema and lymphatic disease patients undergoing treatment at our department team (including collaboration with other hospital team) who have been fully informed consented. No age restriction and exclusion criteria were set.	Indocyanine green (ICG) lymphography and Lymphatic venous anastomosis (LVA)	ICG lymphography and drug treatment & ICG lymphography and radiological treatment	Pre and postoperative course, limb circumference, tissue stiffness; echogram, CT, MRI, lymphoscintigraphy, indocyanine green lymphography, and lymphoangiography observations; blood; histopathological analysis; clinical; health-related QOL analysis using Short Form (SF)-36 Health Survey; patient weight; general physical and image observations; analysis of chylous and volume of chylous thoracs and ascites.	December 2020	Saiseikai Kawaguchi General Hospital

Source	Identifier/ Trial name	Study type	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
WHO-ICTRP	JPRN-UMIN00025891 ³⁹ Prospective study on the effectiveness assessment of Indocyanine Green Lymphography and Lymphatic Surgery for lymphoedema and lymphatic disease.	Single-arm non-randomized	Male and female; Saitamaken Saiseikai Kawaguchi General Hospital patients who received lymphatic surgery/ reconstructive surgery; patients diagnosed with secondary lower extremity lymphoedema by lymphoscintigraphy; patients judged to have the ability to answer interrogation; patients who obtained document consent by the patients themselves freely with sufficient understanding after receiving sufficient explanation for participation in this study; in cases where the patient is a minor, in addition to the patient caregiver sufficient understanding, document consent is obtained.	Indocyanine green (ICG) lymphography and Lymphatic venous anastomosis (LVA)	-	Pre and postoperative course, limb circumference, tissue stiffness; echogram, CT, MRI, lymphoscintigraphy, indocyanine green lymphography, and lymphoangiography observations; blood; histopathological analysis; clinical; health-related QOL analysis using Short Form (SF)-36 Health Survey; patient weight; general physical and image observations.	NR	Saiseikai Kawaguchi General Hospital

Literature search strategies

Search strategy for Cochrane

Search Name: Lymphatovenous anastomosis for lymphoedema	
Search Date: 14/12/2017	
ID	Search
#1	MeSH descriptor: [Lymphoedema] explode all trees
#2	lymphoedema* (Word variations have been searched)
#3	lymphoedema* (Word variations have been searched)
#4	lymph-edema* (Word variations have been searched)
#5	lymph-oedema* (Word variations have been searched)
#6	lymph* near (edema* or oedema*) (Word variations have been searched)
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	MeSH descriptor: [Anastomosis, Surgical] explode all trees
#9	(lymphoven* or lymphaticoven* or lymphatic vein*) near (anastomos* or bypass* or shunt* or surg* or micro*surg*) (Word variations have been searched)
#10	LVA:ti,ab,kw (Word variations have been searched)
#11	#8 or #9 or #10
#12	#7 and #11
Total: 12 Hits	

Search strategy for CRD (DARE, NHS-EED, HTA)

#### Lymphovenous anastomosis for lymphoedema	
Search Date: 14/12/2017	
1	MeSH DESCRIPTOR Lymphoedema EXPLODE ALL TREES
2	(Lymphoedema*)
3	(Lymphoedema*)
4	(lymph* NEAR (edema* OR oedema*))
5	#1 OR #2 OR #3 OR #4
6	MeSH DESCRIPTOR Anastomosis, Surgical EXPLODE ALL TREES
7	((lymphoven* OR lymphaticoven* OR lymphatic vein*) NEAR (anastomos* OR bypass* OR shunt* OR surg* OR micro*surg*))
8	(LVA)
9	#6 OR #7 OR #8
10	#5 AND #9
Total: 4 Hits	

Search strategy for Embase

No.	Query results	Results	Date
#9	#4 AND #8	531	14 Dec 2017
#8	#5 OR #6 OR #7	1,804	14 Dec 2017
#7	lva:ti,ab	1,184	14 Dec 2017
#6	((lymphoven* OR lymphaticoven* OR 'lymphatic vein*') NEAR/5 (anastomos* OR bypass* OR shunt* OR surger* OR surgic* OR micro*surg*)):ti,ab	446	14 Dec 2017
#5	'lymphovenous anastomosis'/exp	468	14 Dec 2017
#4	#1 OR #2 OR #3	21,937	14 Dec 2017
#3	(lymph* NEAR/5 (edema* OR oedema*)):ti,ab	2,798	14 Dec 2017
#2	lymph*edema*:ti,ab	11,777	14 Dec 2017
#1	'lymphoedema'/exp	18,558	14 Dec 2017

Search strategy for Medline via Ovid

Database: Ovid MEDLINE(R) <1946 to December Week 1 2017>, Ovid MEDLINE(R) Epub Ahead of Print <December 13, 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 13, 2017>, Ovid MEDLINE(R) Daily Update <December 13, 2017>	
Search Date: 14.12.2017	
Search Strategy:	
1	exp Lymphoedema/ (11581)
2	lymph?edema*.mp. (11925)
3	(lymph* adj5 (edema* or oedema*)).mp. (2108)
4	1 or 2 or 3 (15993)
5	exp Anastomosis, Surgical/ (89367)
6	((lymphoven* or lymphaticoven* or lymphatic vein*) adj5 (anastomos* or bypass* or shunt* or surger* or surgic* or micro?surg*)).mp. (410)
7	LVA.ti,ab. (924)
8	5 or 6 or 7 (90457)
9	4 and 8 (432)
10	remove duplicates from 9 (407)



Ludwig Boltzmann Institut
Health Technology Assessment