Interventional procedure overview of lymphovenous anastomosis during axillary or inguinal node dissection for preventing secondary lymphoedema

Contents

Table 1 Abbreviations

Abbreviation	Definition
ALND	Axillary lymph node dissection
BCRL	Breast cancer-related lymphoedema
CI	Confidence interval
DLT	Decongestive lymphatic therapy
ICG	Indocyanine green (dye)
ILND	Inguinal lymph node dissection
ILR	Immediate lymphatic reconstruction
ITT	Intention to treat
LE	Lymphoedema
LVA	Lymphovenous anastomosis
LYMPHA	Lymphatic microsurgical preventing healing approach
OR	Odds ratio
RCT	Randomised controlled trial
S-LYMPHA	Simplified lymphatic microsurgical preventing healing approach
UEL	Upper extremity lymphoedema

Indications and current treatment

LE is the build-up of lymph fluid in a limb, causing swelling of that limb. It is a common complication after treatments for various cancers, and can be chronic and debilitating. The condition can severely damage the skin of, and cause aching in or difficulty moving the affected limb. There can also be recurrent skin infections, needing frequent antibiotic use and sometimes hospitalisation.

There are no curative treatments but there are various treatments to help control the symptoms of LE. They aim to reduce swelling and infection while improving lymphatic flow in the body, and include:

- DLT, which comprises compression garments, manual lymphatic draining, skin care, exercise and massage done with specialist help or alone by the person with LE
- the 2 surgical techniques, liposuction and LVA.

What the procedure involves

This version of LVA is known as LYMPHA (lymphatic microsurgical preventative healing approach). It is done during axillary or inguinal node dissection to reduce the risk of LE developing after surgery. It involves creating a bypass from the transected lymphatics to nearby veins. Before the node dissection, a blue dye is injected to map the lymphatic circulation from the arm or thigh. During the node dissection, the surgical team inserts the cut lymphatic vessels into a small branch of the axillary or saphenous veins with the aim of restoring normal lymph flow.

The standard LYMPHA technique is done by surgeons with microvascular experience, using an operating microscope and, typically, 9-0 to 12-0 sutures. There is also a simplified technique known as S-LYMPHA, which can be done by surgeons without microsurgical training, without an operating microscope and using 7-0 sutures.

Outcome measures

The main outcomes included incidence of LE, successful completion of the preventative LVA procedure and perioperative complications.

Evidence summary

Population and studies description

This interventional procedures overview is based on 1,969 patients from 4 systematic reviews, 1 prospective cohort study and 6 retrospective cohort studies. Of these 1,969 patients, 1,084 patients had the procedure. This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 11 studies as the key evidence in table 2 and table 3, and lists 10 relevant studies in table 5.

Chun (2022) was a review and meta-analyses of 13 international studies of ILR for preventing secondary LE. It included 789 patients, 665 who had upper extremity ILR and 124 who had lower extremity ILR. Five studies were from Italy, 1 from India and 7 from the US. Ten of the studies focused on ALND for breast

cancer in which 98% were women and 3 focused on ILND for malignant melanoma in which 46% were women. The mean age across the studies was 54 years and follow up ranged from 1 month to 42 months. Only 2 of 13 included studies reported control group outcomes and 5 studies were retrospective analyses. The authors highlighted many limitations of the meta-analysis. They recommended additional high-quality studies to better establish evidence-based guidelines for the procedure in different patient cohorts with comorbidities.

Cook (2022) was a review of 5 international retrospective studies on preventative ILR for BCRL. Some of these studies were included in meta-analyses. The mean age of study patients was 54 years and 249 of the 251 were women. Follow up ranged from 6 months to 48 months. The studies were limited by the small sample size, short follow up and a retrospective, non-randomised design.

Jorgensen (2017) was a systematic review of the effect of prophylactic LVA and shunts for preventing cancer-related LE. It included 12 studies in a qualitative analysis, and 4 studies in a quantitative analysis. The qualitative analysis reported outcomes for 284 patients. For 270 of these patients, the LVA procedure was feasible and completed. The studies that make up the review were international. Five focused on breast cancer, 3 on gynaecological cancers, 1 on vulvar cancer, 1 on melanoma, 1 on vulvar cancer and melanoma, and 1 on melanoma, squamous cell cancer and anal cancer. Eight of the studies were single intervention studies and 4 included a control group. But none included allocation concealment or blinding, and only 1 mentioned randomisation. The quantitative analysis included the 4 studies with control groups. These included a total of 82 patients who had prophylactic LVA and 94 patients acting as controls. The ages of study participants was not reported and follow up ranged from 3 months to 69 months. The authors reported that all the studies were highly biased.

Markkula (2019) was a Cochrane review including 3 papers, 2 of which focused on LE prevention and 1 of which focused on LE treatment. The LE prevention studies were both RCTs and done in the same single centre in Italy. In 1, 25 of 49 patients had LVA and, in the other, 23 of 46 patients had LVA. The mean ages in the 2 relevant studies ranged from 54 to 57 years, and follow up was reported at intervals up to 24 months. The authors stated that there was an unclear or high risk of bias in multiple domains in the 2 RCTs.

Weinstein (2022) was a prospective study with 66 of 78 patients having LVA for preventing BCRL. It was done in the US and 100% of participants were women. The mean age was 53 years, and follow up was 8 months.

Ozmen (2019) was a retrospective study of a simplified approach of LYMPHA for preventing BCRL. It was done in the US and included 380 patients, 74 of whom

had the LVA procedure. In all, 99% (377/380) of the patients were women, the mean age was 53 years, and follow up was 15 months.

Herremans (2021) was a retrospective study of a breast surgeon's 5-year experience with LVA for preventing BCRL in the US. It included 132 women, 76 of whom had the intervention alongside ALND and 56 of whom had ALND alone. The mean age was 56 years, and follow up was 40 months.

Ozmen (2022) was a retrospective study in the US of a simplified approach of LYMPHA for preventing BCRL. It evaluated how the procedure affected the chance of having LE. It included 194 patients, of whom 110 had LYMPHA with ALND and 84 had ALND alone. A total of 189 (97%) were women, the mean age was 50 years for the LYMPHA group and 53 years for the non-LYMPHA group, and follow up was 47 months.

Nacchiero (2022) was a retrospective study of the effect of LVA on the secondary development of LE in patients with melanoma. It was done in Italy, and 52 of 172 patients had LVA. The median age was about 54 years, 51% of the patients were men, and follow up was 6 months.

Levy (2022) was a retrospective study in the US of LYMPHA done during ALND. It included 90 women, 45 of whom had LYMPHA alongside ALND and 45 of whom had ALND alone. The mean age in the LYMPHA group was 54 years and in the ALND-alone group was 51 years. Median follow up in the LYMPHA group was 57 months and in the ALND-alone group was 63 months.

Chungsiriwattana (2022) was a retrospective study in Thailand of the effect on LE of LVA during surgery for patients with skin cancer of the lower extremities. Seven of 29 patients had LVA at the groin and 22 had wide resection of the skin cancer and ILND alone. Fifteen (52%) of the patients were women, the median age was 68 years and mean follow up was 38 months.

Table 2 presents study details.

Figure 1 Flow chart of study selection

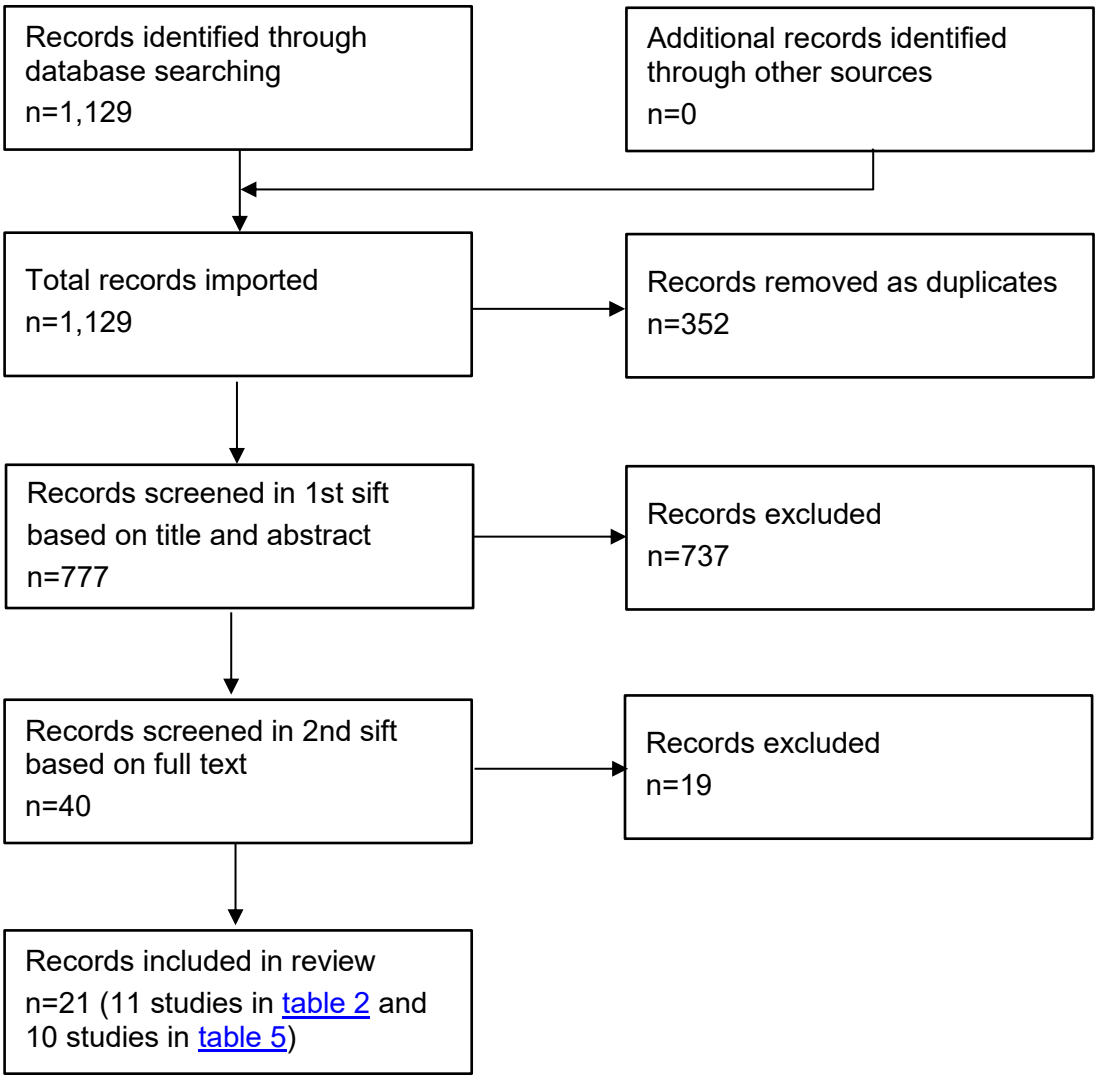

Table 2 Study details

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
1	Chun, 2022 Multiple	N=789 (upper, 99.4% female; lower, 69.4% male)	Mean age between upper/lower = 53.6 to 54.3 years	Systematic review and meta-analysis (13 studies)	ILR done to restore lymphatic drainage at the time or during the index procedure under a single anaesthesia **Exclusions:** Non-ILR interventions	ILR for preventing of upper or lower extremity LE	1 to 42 months
2	Cook, 2022 Multiple	N=251 (2:249)	Mean age = 53.8 years	Systematic review (5 studies)	Observational studies and RCTs	ILR was done concurrently with ALND for breast cancer	6 to 48 months
3	Jorgensen, 2017 Multiple	N=284	NR	Systematic review and meta-analysis (12 studies; 4 studies with control groups included in the meta-analysis)	Patients had lymphadenectomy as part of their cancer treatment Authors reported LE outcome	Prophylactic LVA for preventing (upper or lower) extremity LE	3 to 69 months
4	Markkula, 2019 Italy and Greece	N=95 (across 2 studies for preventing LE);	Mean age between studies = 47.7 to 57 years	Systematic review (3 studies)	RCTs for preventing or treating LE Pre-defined criteria for assessing LE	2/3 studies focused on preventative LVA (1 focused on	Up to 24 months

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
		(having preventative LVA, n=48)			Patients who had treatment for their breast cancer	treatment for LE) for UEL	
5	Weinstein, 2022 US	N=81 (0:81) (having ILR, n=66)	Mean age = 52.6 years	Prospective cohort study	Inclusion criteria mentioned but specifics not reported **Exclusions:** Preoperative ipsilateral LE Death during study period	ILR to prevent UEL	8 months
6	Ozmen, 2019 US	N=380 (3:377) (having LYMPHA, n=74)	Median age = 53 ± 11.61 years	Retrospective cohort study	Patients with breast cancer with axillary involvement having ALND	S-LYMPHA to prevent UEL	15 months
7	Herremans, 2021 US	N=132 (0:132) (having LYMPHA, n=76)	Mean age = 56.4 years	Retrospective cohort study	Patients having ALND for cT1-4N1-3M0 breast cancer	LYMPHA to prevent UEL	Mean = 40 months
8	Ozmen, 2022 US	N=194 (5:189) (having LYMPHA, n=110)	Mean age with LYMPHA = 50 ± 12 years	Retrospective cohort study	Patients with breast cancer and axillary involvement having ALND with or without S-LYMPHA	S-LYMPHA to prevent UEL	Median = 47 ± 37 months

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
			Mean age without LYMPHA = 53 ± 10 years		**Exclusions:** No post-op L-Dex measurements Lost to follow up		
9	Nacchiero, 2022 Italy	N=172 (having LVA, n=52) (26:26) (not having LVA, n=120) (64:56)	Median age = 53.3 to 54.8 years	Retrospective cohort study	Patients affected by melanoma of the trunk who had sentinel lymph node biopsy in the axilla or groin **Exclusions:** Presence of stage 4 melanoma or other carcinoma Compromised lymphatic drainage secondary to prior procedures	LVA to prevent upper or lower extremity LE	6 months
10	Levy, 2022 US	N=90 (0:90) (having LYMPHA, n=45)	Mean age (LYMPHA) = 54.2 ± 11 years Mean age (no LYMPHA) = 51.2 ± 12.7 years	Retrospective cohort study	Women with breast cancer who presented with axillary metastases needing ALND and possibly adjuvant radiotherapy for treatment **Exclusions:** Lympharzurin blue allergy	LYMPHA to prevent UEL	Median 57 to 63 months

Study no.	First author, date country	Patients (male: female)	Age	Study design	Inclusion criteria	Intervention	Follow up
					Pregnancy		
11	Chungsiriwattana, 2022 Thailand	N=29 (14:15) (having LVA, n=7)	Median = 68 years (range 5 to 86)	Retrospective cohort study	Patients with either invasive squamous cell carcinoma or malignant melanoma skin cancer of the lower extremities with a histologically confirmed or clinically positive groin lymph node	LVA to prevent lower extremity LE	Mean = 38 months

Table 3 Study outcomes

First author, date	Efficacy outcomes	Safety outcomes
Jorgensen, 2017	**LE incidence:** From the pooled analysis of 4 studies with a control group, there is a 0.33 (95% CI 0.19 to 0.56) risk ratio of LE development for prophylactic LVA groups compared with the control groups (p<0.001).	**Postoperative complications** 1/12 studies reported postoperative complications. 1 case of lymphorrhoea was reported in a study of 10 LVA procedures for gynaecological cancer.
Markkula, 2019	**LE incidence:** Pooled estimate from 2 RCTs puts the risk ratio for LE development at 0.20 (95% CI 0.06 to 0.63) after LVA compared with standard care (p=0.006).	Not reported
Cook, 2022	**LE incidence:** 5.9% of patients (15/251) developed LE at a median of 10.3 months post lymphatic reconstruction. The weighted proportion of patients who acquired LE after LVA was 6.6% (95% CI 3.9 to 10.3) compared with patients without LVA, 30.5% (95% CI 4.0 to 68.1). **LVA completion:** Lymphatic reconstruction was attempted but not completed in 14.7% of patients (23/156), in 3 studies. Reasons for aborting lymphatic reconstruction included: inability to find afferent lymphatics, lack of adequate vein for LVA, or profound metastatic disease.	Not reported
Chun, 2022	**LE incidence:** The pooled LE incidence for the upper extremity subgroup was 2.7% (95% CI 1.1 to 4.4) after LVA (p=0.469).	**Postoperative complications**

First author, date	Efficacy outcomes	Safety outcomes
	The pooled LE incidence for the lower extremity was 3.6% (95% CI 0.3% to 10.1%) for the 60.6% of patients followed up, on average, to 30 months after LVA (p=0.951). There were no statistically significant outcomes in relative risk of developing LE in the 2 studies that compared ILR intervention with a control group when doing a pairwise comparison.	1/3 studies for melanoma reported a wound infection
Weinstein, 2022	**LE incidence:** 4/66 (6%) patients who had LVA with ALND developed LE. 1/12 (8%) who did not have LVA developed LE. 3/5 patients with LE presented within 5 months of the operation and endorsed a rapid onset of symptoms. Statistically significant difference between LE incidence in LVA group (6%) compared with a retrospective cohort subsequently analysed at the same institution who had ALND with no LVA (44%) (p<0.0001) **LVA completion:** LVA could not be attempted in 12/78 patients. Patients were unable to have LVA after reverse lymphatic mapping because of:; inability to identify afferent lymphatics (4), inadequacy of recipient veins (3), spatial relationship incompatible with anastomosis (1).	**Postoperative complications** No LVA-associated postoperative complications were identified

First author, date	Efficacy outcomes	Safety outcomes
	In 4 patients, lymphatics were identified, appeared intact within the field and were not disrupted for anastomosis.	
Ozmen, 2019	**LE incidence:** LE incidence was statistically significantly lower in the S-LYMPHA group compared with the non-LYMPHA group (OR=0.12, 0.03 to 0.5; p=0.001). LE incidence was 3% (2/74) in the LYMPHA group and 19% (11/87) in the non-LYMPHA group (p=0.022). In ITT analysis, the LYMPHA group experienced a 4% (3/82) LE incidence rate compared with 13% (10/79) in the non-LYMPHA group (p=0.036). LE incidence rates were equivalent (13%) between the group who didn't attempt LYMPHA and the group where LYMPHA was attempted but was unsuccessful (p=0.99). **LVA completion:** S-LYMPHA was completed in 74/82 patients (90%).	Not reported
Herremans, 2021	**LE incidence:** Statistically significantly lower LE incidence in the LYMPHA group of 13.2% (10/76) compared with 28.6% (16/56) in the ALND-alone group (p=0.045). In propensity matched analysis, the LE incidence rate was lower in the LYMPHA group (16.1%, 9/56) compared with the ALND-alone group (28.6%, 16/56) but was not a statistically significant difference (p=0.091).	Not reported

First author, date	Efficacy outcomes	Safety outcomes
Ozmen, 2022	**LE incidence:** The LE incidence rate was statistically significantly lower in the S-LYMPHA group (16%, 18/110) than patients who had ALND alone (32%, 27/84) (p=0.01). The OR of developing LE is 0.4 (0.2 to 0.8) for patients who had S-LYMPHA than if they had had ALND alone (p=0.01). S-LYMPHA led to lower LE rates in univariate and multivariate analyses, and when looking at the outcomes from a single surgeon.	Not reported
Nacchiero, 2022	**LE incidence:** LE incidence was 4.3% (1/23) and 3.5% (1/29) in the LVA Groups 1 and 2 respectively, which was statistically significantly lower (p=0.03 and p=0.01) compared with a rate of LE development of 24.2% (29/120) in the control group. LE incidence was statistically significantly lower in LVA Groups 1 (7.7%, 1/15) and 2 (5.6%, 1/18) compared with the control group (31.9%, 22/69) for procedures at the groin (p=0.05 and p=0.02). LE incidence for procedures at the axilla was 13.7% (7/51) in the control group compared with 0 cases in either LVA group (statistical significance not calculated).	**Overall survival:** No statistically significant difference between groups who had LVA and the control group in overall survival at 3 years. **Disease-free days:** No statistically significant difference between groups who had LVA and the control group for length of disease-free period.
Levy, 2022	**LE incidence:** 31.1% (14/45) of LYMPHA patients developed LE compared with 33.3% (15/45) of the non-LYMPHA group (p>0.99).	Not reported

First author, date	Efficacy outcomes	Safety outcomes
	No statistically significant difference between groups when focusing on obese patients (p=0.31), patients who had radiotherapy (p=0.79), or both combined (p>0.99).	
Chungsiriwattana, 2022	**LE incidence:** 42.9% (3/7) of LVA patients developed LE compared with 54.5% (12/22) in the control group (p=0.682). The LVA group had a longer median time to LE occurrence (70 compared with 17 months).	No statistically significant difference between groups in events/complications. The reported events were cancer-related, not LE-related.

Procedure technique

Surgical technique was described in 9 studies.

A variety of agents including blue dye, ICG and fluorescein were used to visualise the lymphatic circulation. Anastomosis techniques included end-to-end, 'dunking' technique, U stitch and aborised (Chun, 2022; Weinstein, 2022). The simplified approach, or S-LYMPHA, involved using 7-0 nylon sutures without an operating microscope (Ozmen, 2019; Ozmen, 2022) as opposed to more typical approaches to LVA using 9-0, 10-0 or 11-0 sutures (Levy, 2022; Chungsiriwattana, 2022). LE measurement differed across studies. Combinations of bioimpedance, lymphoscintigraphy and other imaging, volumetry and circumferential measurements were used to assess presence of LE.

Efficacy

LE incidence

All 11 studies reported on the frequency or rate of LE incidence. Some studies reported the number of patients for whom LE developed out of a given number of patients while others gave a risk ratio or OR for LE development comparing an LVA intervention group with a control group. Four studies included some form of pooled or matched analysis for LE incidence. A few studies reported control group outcomes, and some were retrospective, potentially skewing effect size and introducing recall or selection bias.

For the meta-analysis by Chun (2022), the pooled estimate of LE incidence after LVA was 2.7% (95% CI 1.1 to 4.4, I^2=0%; 10 studies) for upper extremity indications and 3.6% (95% CI 0.3 to 10.1, I^2=0%; 3 studies) for lower extremity indications. There were no statistically significant outcomes on relative risk of developing LE in the 2 studies that compared ILR intervention with a control group when doing a pairwise comparison.

The retrospective study by Cook (2022) reported a 5.9% LE incidence rate for patients who had LVA across all 5 studies. The pooled estimate for LE incidence for patients who had LVA was 6.6% (95% CI 3.9 to 10.3, I^2=0.0%; 5 studies) compared with 30.5% (95% CI 4.0 to 68.1, I^2=65.8%; 2 studies) for patients who did not have LVA.

The pooled analysis in the systematic review by Jorgensen (2017) estimated a risk ratio of 0.33 (95% CI 0.19 to 0.56) for developing LE after prophylactic LVA compared with no prophylactic LVA (p<0.001). The authors concluded that the results should be viewed with caution because the included studies were of low quality, heterogeneous and at high risk of bias.

Markkula (2019) estimated a risk ratio of 0.2 (95% CI 0.06 to 0.63) for developing LE for patients who had LVA compared with patients who did not (p=0.006) for the pooled analysis of 2 RCTs. The Cochrane reviewers stated that the certainty provided by the 2 included RCTs was low, and concluded that the evidence was not sufficient enough to support widespread adoption of the procedure.

In the retrospective analyses by Ozmen (2019 and 2022), S-LYMPHA was compared with non-S-LYMPHA. They found an OR of LE incidence of 0.12 (95% CI 0.03 to 0.50, p=0.001; Ozmen, 2019) and 0.40 (95% CI 0.2 to 0.8, p=0.01; Ozmen, 2022). Ozmen (2019) observed LE rates of 3% (2 of 74) in the LVA group and 19% (11 of 87) in the control group (p=0.022). The ITT analysis estimated rates of 4% in the LVA group and 13% in the control group (p=0.036). For patients in whom LVA was attempted but not successfully completed, LE incidence was 13%. This was equivalent to that in the group in which LVA was not attempted (p=0.99). Ozmen (2022) reported LE rates of 16% (18 of 110) in patients who had LVA and 32% (27 of 84) in patients who did not (p=0.01).

The matched analysis by Herremans (2021) estimated a lower LE rate of 16.1% after LVA than without LVA (28.6%) but this was not statistically significant (p=0.091).

The reported LE incidence rates ranged from 0% to 42.9% in the LVA groups across the studies. For upper extremity indications, the rate of LE incidence was reported as 0% (Nacchiero, 2022), 2.7% (Chun, 2022), 3.0% to 4.0% (Ozmen, 2019), 5.9% (Cook, 2022), 6.0% (Weinstein, 2022), 13.2% to 16.1% (Herremans, 2021), 16.0% (Ozmen, 2022) and 31.1% (Levy, 2022). For lower extremity indications, the rate of LE incidence was reported as 3.6% (Chun, 2022), 5.6% to 7.7% (Nacchiero, 2022) and 42.9% (Chungsiriwattana, 2022).

Weinstein (2022) reported an LE incidence of 6% (4 of 66) with LVA compared with 8% (1 of 12) in the control group. When compared with a retrospective cohort at the same institution, the LE incidence was estimated as 44% for patients who did not have LVA (p<0.0001).

Herremans (2021) reported LE rates of 13.2% (10 of 76) in patients who had LVA and 28.6% (16 of 56) in the control group (p=0.045).

Nacchiero (2022) reported an LE incidence of 4.3% (1 of 23) in the first LVA group, 3.5% (1 of 29) in the second LVA group and 24.2% (29 of 120) in the control group (p=0.03 and p=0.01 respectively). Results for these intervention groups and the control group were also given by axilla or groin indication. For the groin, 7.7% (1 of 15) and 5.6% (1 of 18) in the LVA groups developed LE compared with 31.9% (22 of 69) in the control group (p=0.05 and p=0.02 respectively). For the axilla, 0% (0 of 8) and 0% (0 of 1) in the LVA groups developed LE compared with 13.7% (7 of 51) in the control group.

In the Jorgensen (2017) meta-analysis, 14.6% (12 of 82) in the LVA groups developed LE and 56.4% (53 of 94) in the control groups developed LE. Based

on this, the authors suggested that the external validity of these studies was low and that the LE rates perhaps do not represent the general patient population, which it stated would usually be in the range of 20% to 40%.

In Levy (2022), the LE incidence in the LVA group was 31.1% (14 of 45) compared with 33.3% (15 of 45) in the control group, and the difference was not statistically significant (p=0.99).

Chungsiriwattana (2022) reported no statistically significant difference between groups (p=0.682). The LE incidence in the LVA group was 42.9% (3 of 7) compared with 54.5% (12 of 22) in the control group.

LVA completion

Three studies reported on the successful completion of preventative LVA.

In some studies, preventative LVA could not be attempted and in others it could be attempted but was not successfully completed. LVA was not attempted or completed in 10.0% (8 of 82; Ozmen, 2019), 14.7% (23 of 156; Cook, 2022; 3 studies) and 15.4% (12 of 78; Weinstein, 2022) of patients.

LVA could not be completed or attempted for the following reasons:

- inability to find afferent lymphatics
- lack of an adequate vein for LVA
- profound metastatic disease
- a spatial relationship that was incompatible with anastomosis.

Safety

Postoperative complications

Five studies reported on complications related to LVA.

One case of lymphorrhoea was reported in a study of 10 LVA procedures for gynaecological cancer (Jorgensen, 2017; 12 studies).

One patient had a wound infection in a study of melanoma with 23 patients (Chun, 2022; 3 studies).

Nacchiero (2022) included an analysis on overall survival and disease-free days, which showed that there was no statistically significant difference in overall survival at 3 years or disease-free days between the LVA and control groups.

Weinstein (2022) reported that no LVA-associated postoperative complications were identified.

Chungsiriwattana (2022) reported that there was no statistically significant difference between LVA and control groups in events or complications. The events that were reported were cancer-related and not associated with LVA or LE.

Six studies did not report complications or safety outcomes.

Anecdotal and theoretical adverse events

Expert advice was sought from consultants nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might possibly occur, even if they had never happened (theoretical).

They listed the following anecdotal adverse events:

- development of LE
- anaphylaxis to blue dye (estimated at 1.8%) or ICG.

No theoretical adverse events were described by experts, but a unique concern was presented in Chungsiriwattana (2022). The authors expressed concerns that the tumour might be spread by reconnecting the lymphatic pathway.

Three professional expert questionnaires for this procedure were submitted. Find full details of what the professional experts said about the procedure in the specialist advice questionnaires for this procedure.

Validity and generalisability

- The 4 systematic reviews synthesised data from multiple countries. Of the 17 studies that were not systematic reviews, 11 studies were done in the US and 3 were done in Italy. None were done in the UK.
- While some of the evidence was from RCTs and prospective studies, the sample sizes were small. The 2 RCTs evaluated by Markkula (2019) included a total of 95 patients and were designated ‘low certainty evidence’.
- Most of the evidence focused on BCRL, so the generalisability of this procedure for preventing lower extremity LE, as well as UEL, has limitations.
- The different ways that the presence of LE was assessed could have influenced the outcomes of individual studies.
- Most selected studies did not mention comorbidities, which may have affected results. This is because certain comorbidities affect LE incidence, for example, chronic venous insufficiency, venous leg ulcers, uterine cancer and prostate cancer.
- The average follow-up time in most studies was relatively short, limiting the evaluation of long-term effectiveness. Ozmen (2019) noted that 25% of LE cases will develop after 3 years and very few studies followed up to 36 months and beyond.
- The use of different diagnostic modalities for LE could have affected the quality of outcomes and risk of bias when comparing studies:

  - For example, Jorgensen (2017) stated that the studies it included diagnosed LE based on either circumference measurements or other volumetric methods. The authors stated that volumetric measurements are prone to bias, especially in the unblinded setting. They concluded that diagnosis should preferably be established as a combination of clinical and imaging evaluation.
  - The control groups in the Jorgensen (2017) meta-analysis found 56% of patients developed LE. Based on this, the authors suggested that the external validity of these studies was low, and the LE rates perhaps do not represent the general patient population, which it stated would usually be in the range of 20% to 40%.
- Levy (2022) and Chungsiriwattana (2022) reported high rates of LE in the LVA groups (although, lower than their respective comparators). Both of these studies had small sample sizes (n=90 and n=29 respectively). Levy (2022) explored potential bias, including overly broad assessment of LE. The authors remained doubtful of the long-term benefit of LVA. Chungsiriwattana (2022) did not recommend prophylactic LVA.
- Few studies report complications specific to the LVA component of this multifaceted surgery. The evidence and professional expert testimony suggests that preventative LVA does not bring additional risk of complications to the cancer-related and lymph node surgeries.
- Sample sizes varied greatly across studies, with some as low as 7 patients in the LVA group or 22 patients overall.
- No concerns around funding disclosures or conflicts of interest were identified across the studies.

Ongoing trials include NCT04328610, NCT03941756, NCT04687956.

Related NICE guidance

Interventional procedures

NICE's interventional procedures guidance on liposuction for chronic lymphoedema (Recommendation: standard arrangements).

Medical technologies

NICE's medtech innovation briefing on L-Dex U400 for lymphoedema after breast cancer treatment

Professional societies

- British Lymphology Society
- Royal College of Surgeons of England
- Royal College of Surgeons of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow
- Association of Breast Surgery
- British Association of Plastic, Reconstructive and Aesthetic Surgeons.

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6. Ozmen T, Lazaro M, Zhou Y et al. (2019) Evaluation of simplified lymphatic microsurgical preventing healing approach (S-Lympha) for the prevention of breast cancer-related clinical lymphedema after axillary lymph node dissection. Annals of surgery, 270(6), 1156-1160
7. Herremans KM, Cribbin MP, Riner AN et al. (2021) Five-Year Breast Surgeon Experience in LYMPHA at Time of ALND for Treatment of Clinical T1–4N1–3M0 Breast Cancer. Annals of surgical oncology, 28(10), 5775-5787
8. Ozmen T, Layton C, Friedman-Eldar O et al. (2022) Evaluation of Simplified Lymphatic Microsurgical Preventing Healing Approach (SLYMPHA) for the prevention of breast cancer-related lymphedema after axillary lymph node dissection using bioimpedance spectroscopy. European Journal of Surgical Oncology, 48(8), 1713-1717
9. Nacchiero E, Maruccia M, Robusto F et al. (2022) Prevention of Secondary Lymphedema after Complete Lymph Node Dissection in Melanoma Patients: The Role of Preventive Multiple Lymphatic–Venous Anastomosis in Observational Era. Medicina, 58(1), 117
10. Levy AS, Murphy AI, Ishtihar S et al. (2020) Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) for the Primary Prevention of Lymphedema: A 4-year Follow-up Matched Cohort Study. Plastic and Reconstructive Surgery, 10-1097
11. Chungsiriwattana W, Kongkunnavat N, Kamnerdnakta S et al. (2023). Immediate inguinal lymphaticovenous anastomosis following lymphadenectomy in skin cancer of lower extremities. Asian Journal of Surgery, 46(1), 299-305

Methods

NICE identified studies and reviews relevant to LVA during ALND or ILND for preventing secondary LE from the medical literature. The following databases were searched between the date they started to 20 February 2023: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search:

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that are not available in the published literature.
- Patients with cancer conditions needing ALND or ILND.
- Intervention or test: (preventative) LVA.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy, or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	21/02/2023	1946 to February 20, 2023
MEDLINE In-Process (Ovid)	21/02/2023	1946 to February 20, 2023
MEDLINE Epubs ahead of print (Ovid)	21/02/2023	1946 to February 20, 2023
EMBASE (Ovid)	22/02/2023	1974 to 2023 February 22
EMBASE Conference (Ovid)	22/02/2023	1974 to 2023 February 22
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	21/02/2023	Issue 2 of 12, February 2023
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	21/02/2023	Issue 2 of 12, February 2023
International HTA database (INAHTA)	22/02/2023	-

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

1 Anastomosis, Surgical/ 34,790
2 Anastomos*.tw. 73,401
3 1 or 2 86,709
4 Lymphedema/su [Surgery] 1,648
5 Lymphed*.tw. 8,138
6 4 or 5 8,670
7 3 and 6 715
8 (MLVA or LVA or LYMPHA).tw. 2,457
9 ((Lymphaticoven* or Lymphoven* or Lymphatic-ven*) adj4 anastomos*).tw. 625
10 Lymph Node Excision/ 37,512
11 (Lymp* node adj4 (excision* or dissect* or ablat* or cut* or remove*)).tw. 21,147
12 ((Axill* or Inguin*) adj4 lymph node adj4 (excision* or dissect* or ablat* or cut* or remove*)).tw. 3,960
13 (ALND or INLD).tw. 1,419

14 Lymphangitis/su [Surgery] 19
15 Lymphangit*.tw. 1,376
16 lymphatic microsurgical preventive healing approach.tw. 9
17 Lymphedema/pc 578
18 or/7-17 52,118
19 *Breast Neoplasms/ 279,369
20 *Penile neoplasm/ 5,089
21 *Vulvar neoplasm/ 7,389
22 *skin neoplasm/ 118,043
23 *Melanoma/ 79,301
24 or/19-23 450,891
25 Lymphedema/ 10,411
26 24 and 25 2,104
27 Breast Cancer Lymphedema/ 384
28 BCRL.tw. 373
29 ((Breast* or penile* or vulva* or skin* or melanom*) adj4 (neoplasm* or cancer* or carcino* or adenocarcino* or tumour* or tumor* or malignan* or lump* or metast*) adj4 lymphed*).tw. 1,135
30 or/26-29 2,579
31 18 and 30 1,000
32 animals/ not Humans/ 5,060,889
33 31 not 32 995
34 limit 33 to english language 893
35 limit 34 to ed=20150101-20230228 449

Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5.

Table 5 additional studies identified

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Boccardo F, Casabona F, DeCian F et al. (2014) Lymphatic microsurgical preventing healing approach (LYMPHA) for primary surgical prevention of breast cancer-related lymphedema: Over 4 years follow-up. Microsurgery, 34(6), 421-424	N=78 (Had LYMPHA, n=74) Follow up = 4 years	4.05% LE incidence after LYMPHA compared with referenced rates of LE after sentinel lymph node biopsy of 6-13%, and axillary dissection alone of 13-65%.	Included in systematic reviews.
Feldman S, Bansil H, Ascherman J et al. (2015) Single institution experience with lymphatic microsurgical preventive healing approach (LYMPHA) for the primary prevention of lymphedema. Annals of surgical oncology, 22, 3296-3301	N=37 Median follow up = 6 months	12.5% LE incidence rate in a high-risk cohort of patients	Included in systematic reviews.
Boccardo F, Valenzano M, Costantini S et al. (2016) LYMPHA technique to prevent secondary lower limb lymphedema. Annals of surgical oncology, 23, 3558-3563	N=27 (n=11 with vulvar cancer, n=16 with melanoma)	6.25% (transient) LE incidence in the melanoma group (n=16) and 9% permanent LE incidence in the vulvar cancer group (n=11).	Included in systematic reviews.
Agrawal J, Mehta S, Goel A et al. (2018)	N=35	5.7% (transient) LE incidence	Other studies included with

Lymphatic Microsurgical Preventing Healing Approach (LYMPHA) for Prevention of Breast Cancer-Related Lymphedema—a Preliminary Report. Indian Journal of Surgical Oncology, 9(3), 369-373			greater sample sizes.
Schwarz GS, Grobmyer SR, Djohan RS et al. (2019) Axillary reverse mapping and lymphaticovenous bypass: Lymphedema prevention through enhanced lymphatic visualization and restoration of flow. Journal of Surgical Oncology, 120(2), 160-167	N=60 (Had LVA, n=58) Median follow up= 11.8 months	3.4% LE incidence	Included in systematic reviews.
Johnson AR, Kimball S, Epstein S et al. (2019) Lymphedema incidence after axillary lymph node dissection: quantifying the impact of radiation and the lymphatic microsurgical preventive healing approach. Annals of Plastic Surgery, 82(4S), S234-S241	N=1,419 (Had LYMPHA, n=48) Median follow up = 25.7 months	Pooled estimate of LE incidence was 2.1% with LYMPHA compared with 14.1% in the control group (p=0.029).	Included in systematic reviews.
Cakmakoglu C, Kwiecien GJ, Schwarz GS et al. (2020) Lymphaticovenous bypass for immediate lymphatic reconstruction in locoregional advanced melanoma patients. Journal of Reconstructive Microsurgery, 36(04), 247-252	N=22 Follow up = up to 12 months	4.5% LE incidence	Other studies included with greater sample sizes.

Johnson AR, Fleishman A, Granoff MD et al. (2021) Evaluating the impact of immediate lymphatic reconstruction for the surgical prevention of lymphedema. Plastic and reconstructive surgery, 147(3), 373e-381e	N=97 (Had ILR, n=32) Median follow up = 11.4 months	12.5% transient and 3.1% permanent LE incidence	Included in systematic reviews.
Cook JA, Sasor SR, Loewenstein SN et al. (2021) Immediate lymphatic reconstruction after axillary lymphadenectomy: a single-institution early experience. Annals of Surgical Oncology, 28, 1381-1387	N=33 Mean follow up = 9 months	9.1% transient and 6.1% permanent LE incidence	Other studies included with greater sample sizes.
Katz LM, Connolly EP, Choi JC (2022) Lymphatic Bypass in Patients Receiving Regional Nodal Radiation. International Journal of Radiation Oncology, Biology, Physics, 114(3), e32	N=54 (Had LYMPHA, n=27)	25.9% LE incidence in both LYMPHA and control groups.	Other studies included with greater sample sizes.