

Primary Prevention of Cancer-Related Lymphedema Using Preventive Lymphatic Surgery: Systematic Review and Meta-analysis

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Indian J Plast Surg 2022;55:18–25.

Abstract

Background Several studies have proven prophylactic lymphovenous anastomosis (LVA) performed after lymphadenectomy can potentially reduce the risk of cancer-related lymphedema (CRL) without compromising the oncological treatment. We present a systematic review of the current evidence on the primary prevention of CRL using preventive lymphatic surgery (PLS).

Patients and Methods A comprehensive search across PubMed, Cochrane-EBMR, Web of Science, Ovid Medline (R) and in-process, SCOPUS, and ScienceDirect was performed through December 2020. A meta-analysis with a random-effect method was accomplished.

Results Twenty-four studies including 1547 patients fulfilled the inclusion criteria. Overall, 830 prophylactic LVA procedures were performed after oncological treatment, of which 61 developed lymphedema.

The pooled cumulative rate of upper extremity lymphedema after axillary lymph node dissection (ALND) and PLS was 5.15% (95% CI, 2.9%–7.5%; $p < 0.01$). The pooled cumulative rate of lower extremity lymphedema after oncological surgical treatment and PLS was 6.66% (95% CI < 1 –13.4%, p -value = 0.5). Pooled analysis showed that PLS reduced the incidence of upper and lower limb lymphedema after lymph node dissection by 18.7 per 100 patients treated (risk difference [RD] – 18.7%, 95% CI – 29.5% to – 7.9%; $p < 0.001$) and by 30.3 per 100 patients treated (RD – 30.3%, 95% CI – 46.5% to – 14%; $p < 0.001$), respectively, versus no prophylactic lymphatic reconstruction.

Conclusions Low-quality studies and a high risk of bias halt the formulating of strong recommendations in favor of PLS, despite preliminary reports theoretically indicating that the inclusion of PLS may significantly decrease the incidence of CRL.

Keywords

- ▶ “lymphedema” (mesh)
- ▶ “lymphatic vessels” (mesh)
- ▶ “primary prevention” (mesh)
- ▶ “microsurgery” (mesh)
- ▶ “lymph node excision” (mesh)

published online
February 25, 2022

DOI <https://doi.org/10.1055/s-0041-1740085>.
ISSN 0970-0358.

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Introduction

Lymphedema occurs when there is lymphatic fluid accumulation and stasis. This triggers an inflammatory response in the interstitial compartment, ultimately causing adipose tissue proliferation and fibrous tissue deposition with mild-to-severe permanent edema of an affected body part and serious functional impairment.¹⁻⁵ Additionally, the resulting edema can be further complicated by wound healing problems and infections, resulting in induration and disfigurement.¹⁻⁵ Once lymphedema becomes clinically evident, its response to treatment is modest and tends to worsen, causing further destruction of the remaining functional lymphatic channels and irreversible fibrotic changes.^{1-3,5,6}

With the inclusion of microsurgery, most efforts have been directed to the early secondary prevention of lymphedema or even tertiary prevention with excisional procedures in the setting of secondary lymphedema,⁷⁻¹¹ which is more prevalent in industrialized countries following tumoral staging, lymph node dissection, and adjuvant radiotherapy for locoregional control of neoplastic disease.^{12,13} Since the introduction of the concept of lymphatic microsurgical preventing healing approach (LYMPHA),¹⁴ the use of prophylactic lymphovenous anastomosis (LVA) after lymph node dissection (LND) has been implemented by several surgeons in recent reports in an attempt to reduce the risk of lymphedema without compromising the oncological treatment.^{15,16} However, there are few studies quantitatively synthesizing the magnitude of this intervention for both upper and lower extremity. Herein, we present a systematic review and meta-analysis of the current evidence on the primary prevention of cancer-related lymphedema (CRL) utilizing preventive lymphatic surgery (PLS).

Patients and Methods

Literature Search

A comprehensive systematic review and meta-analysis of the literature was performed based on the guidance of the Cochrane Handbook for Systematic Reviews of Interventions.^{17,18} The medical indices PubMed MEDLINE, Cochrane-EBMR, Web of Science, Ovid Medline(R), SCOPUS, and ScienceDirect were queried from database inception through December 2020. The following terms were searched in different combinations: ("Lymphedema" [Mesh]) OR ("Lymphedema/prevention and control" [Mesh]) OR ("Non-Filarial Lymphedema/prevention and control" [Mesh]) OR ("Non-Filarial Lymphedema" [Mesh]) AND ("Lymphedema/surgery" [Mesh]) OR (LVA) OR (Lymphovenous AND anastomosis) OR (Lymphaticovenous AND anastomosis) OR (lymph AND node AND transplant) OR (Lymph AND node AND transfer) AND (Prophylactic) OR (Prophylaxis) OR (Immediate) OR (Preventive) OR (Prevent) OR (Prevention). See ► **Supplementary Table S1** (online only), which displays the search strategy. A manual search of references was executed to find additional relevant studies.

Selection Criteria

Randomized and nonrandomized trials, observational cohort studies, case-control studies, and case series written in English were included. We included (i) single-arm studies reporting outcomes of microsurgical interventions directed toward the primary prevention of CRL, and (ii) double-arm studies encompassing a control group (no microsurgical intervention to prevent CRL) and an experimental group receiving microsurgical interventions for the primary prevention of CRL. Primary prevention was defined as therapeutic interventions directed to prevent a disease from occurring; thus, the target population comprehended subjects with no clinical or paraclinical evidence of lymphedema.^{19,20} Studies solely addressing lymphatic mapping were excluded. Studies including interventions directed to secondary or tertiary lymphedema prevention, and single case reports, were also excluded.

Data Extraction and Quality Assessment

After duplicates were omitted, citations were screened based on title and abstract by two independent reviewers (J.M.E and V.P.B). Afterward, the reviewers performed a full-text assessment using the inclusion and exclusion criteria. Discrepancies were solved by the senior author (P.C.). Data extraction was performed by two independent reviewers. The number of patients, type of malignancies, LND, number of nodes removed, diagnostic modality, number of veins and lymphatic vessels anastomosed, type of LVAs, other reconstructive procedures, complications, and follow-up were extracted. The Oxford Centre for Evidence-Based Medicine (OCEBM) was used to provide critical appraisal of the level of evidence.²¹ The risk of bias within studies was assessed employing the Cochrane Collaboration tool.^{22,23}

Statistical Analysis

Our primary outcome was to assess the rate of upper and lower extremity CRL after PLS, and to determine the risk difference (RD) of CRL following LND and PLS in comparison to no prophylactic lymphatic reconstruction. Therefore, for meta-analysis, an event was defined as a patient with a diagnosis of CRL.²⁴ Jamovi 1.2.27.0 (Jamovi, Sydney, Australia) was used for statistical analysis.²⁵⁻²⁷ The pooled rate of postoperative CRL after PLS was estimated as the proportion of events over the total number of patients evaluated in the last follow-up. Due to the methodological heterogeneity within and between studies, a random-effect model meta-analysis of prevalence using the Hartung-Knapp-Sidik-Jonkman model was conducted on studies with a single intervention cohort. The effects size of study-specific incidence was expressed by proportions 95% confidence intervals (CI) and the overall pooled estimate with 95% binomial CI.²⁸

In studies with both an experimental and a control group, a random-effect model meta-analysis for dichotomous outcomes using the Hartung-Knapp-Sidik-Jonkman method was accomplished to calculate the RD of developing lymphedema implementing PLS after LND.²⁸⁻³⁰ The RD was the calculated difference between the observed risks (proportions

of individuals with the outcome of interest) in two cohorts (experimental vs. control).^{28–30}

Heterogeneity was evaluated with the Q statistic p values and I^2 statistic.²² Substantial heterogeneity was considered if I^2 was greater than 50%.³¹ Statistical significance was considered at p -value < 0.05 .³¹ Publication bias was assessed qualitatively using a funnel plot graph and quantitatively with an Egger's regression test.³² We estimated the number of unpublished null studies (which fail to show a reduction in the incidence of CRL using PLS) required to eliminate the significance from our findings employing the Rosenthal's fail-safe N method.

A sensitivity analysis was conducted to assess the influence of certain features in the magnitude and precision of the overall prevalence of CRL following PLS. The following characteristics were excluded: < 10 participants and preliminary reports.

Results

Study Characteristic

Our search yielded 678 citations, from which 159 duplicates were removed. Records were screened based on title and abstract, and 425 references were eliminated. Full-text assessment was performed on 94 collated reports, and 75 did not meet the inclusion criteria. A manual search of the references of included studies yielded five additional articles for review. Twenty-four studies fulfilled the inclusion criteria (**Fig. 1**).^{5,14,33–54} An overview of each study is summarized in **Supplementary Table S2** (available online only). Ten and six single-arm studies reporting outcomes of PLS for upper (**Supplementary Table S3**; available online only) and lower (**Supplementary Table S4**; available online only) extremity CRL were included, respectively. Seven and three double-arm studies reporting outcomes of PLS for upper (**Supplementary Table S5**; available online only) and lower extremity (**Supplementary Table S6**; available online only) CRL were included, respectively.

Eighteen studies were observational studies, two were randomized control studies, one was a case series, and three were abstracts or conference presentations (**Supplementary Table S2**; available online only). The OCEBM level of evidence for the articles was as follows: eight articles had a level of evidence 3b and sixteen a level of 4.

Patient Characteristics

The qualitative analysis included 1547 patients (**Supplementary Table S2**; available online only). The age of patients undergoing oncologic surgical treatment ranged from 18 to 87 years, and the follow-up period ranged from 6 to 156 months. Overall, 1247 patients (80.6%) underwent axillary lymph node dissection (ALND), 1178 (75.6%) for breast cancer and 69 (4.4%) for melanoma. Three-hundred patients (19.4%) underwent ilioinguinal, para-aortic, inguinofemoral lymph node dissection, and/or wide tissue excision of the inguinal region; the oncologic indications were highly heterogeneous (**Supplementary Table S2**; available online only).

Overall, 830 prophylactic LVA procedures were performed after oncologic surgical treatment, of which 61 resulted in CRL during the follow-up period. Double-arm studies included 681 controls, of which 188 developed lymphedema during the follow-up period (**Supplementary Tables S3–S6**; available online only).

Different lymphedema diagnostic modalities were reported. Five studies used a combination of methods while nineteen used a single diagnostic modality. Eight used volumetry, eight used circumferential measures, seven defined lymphedema clinically, four used lymphoscintigraphy, and four used bioimpedance spectroscopy (**Supplementary Table S2**; available online only).

Six studies implemented the supermicrosurgery technique in which LVAs were performed in an end-to-end or end-to-side fashion when lymphatics and veins had a good size match. Twenty studies reported the use of sleeve LVAs when a substantial size mismatch occurred between the recipient vein and the available lymphatics. One study reported the use of S-LYMPHA technique (**Supplementary Tables S3–S6**; available online only).

Complications were not ubiquitously reported. However, the most common complications were soft-tissue infections in 38 patients, lymphocele in seven patients, skin necrosis in five patients, venous backflow in one patient, transient arm swelling in two patients, and an infected seroma in one patient.

Primary Prevention of CRL in Single Cohort Studies

The pooled cumulative rate of upper extremity lymphedema after ALND and PLS was 5.15% (95% CI 2.9%–7.5%, $p < 0.001$) (**Supplementary Fig. S1**; available online only). No significant heterogeneity was present across studies ($I^2 = 4.6\%$, $p = 0.9$).

The pooled cumulative rate of lower extremity lymphedema after oncological surgical treatment (ilioinguinal, para-aortic, inguinofemoral lymph node dissection, or wide tissue excision) and PLS was 6.66% (95% CI $< 1\%$ –13.4%, $p = 0.05$) (**Supplementary Fig. S2**; available online only). Considerable heterogeneity was present across studies ($I^2 = 61.1\%$, $p = 0.17$).

When excluding studies with a sample size less than 10 and preliminary reports, the pooled rate of CRL was 5% (95% CI 2.5%–7.6%, $p < 0.001$) and 6.9% (95% CI $< 0.1\%$ –14.8%, $p = 0.08$) for upper and lower extremity, respectively.

Primary Prevention of CRL in double-arm Studies

The measure of effect used to compare the risk of developing CRL among double-arm studies was RD. The pooled analysis showed that PLS reduced the rate of upper limb lymphedema after ALND by 18.7 per 100 patients treated (RD – 18.7%, 95% CI – 29.5% to – 7.9%; $p < 0.001$; 10 studies, grade = low) (**Supplementary Fig. S3**; available online only). Heterogeneity was substantial with significant clinical relevance ($I^2 = 70.7\%$, $p = 0.04$). Pooled analysis showed that PLS reduced the rate of lower limb lymphedema after ilioinguinal lymph node dissection by 30.3 per 100 patients treated (RD – 30.3%, 95% CI – 46.5% to – 14%; $p < 0.001$; 3 studies, grade = low).

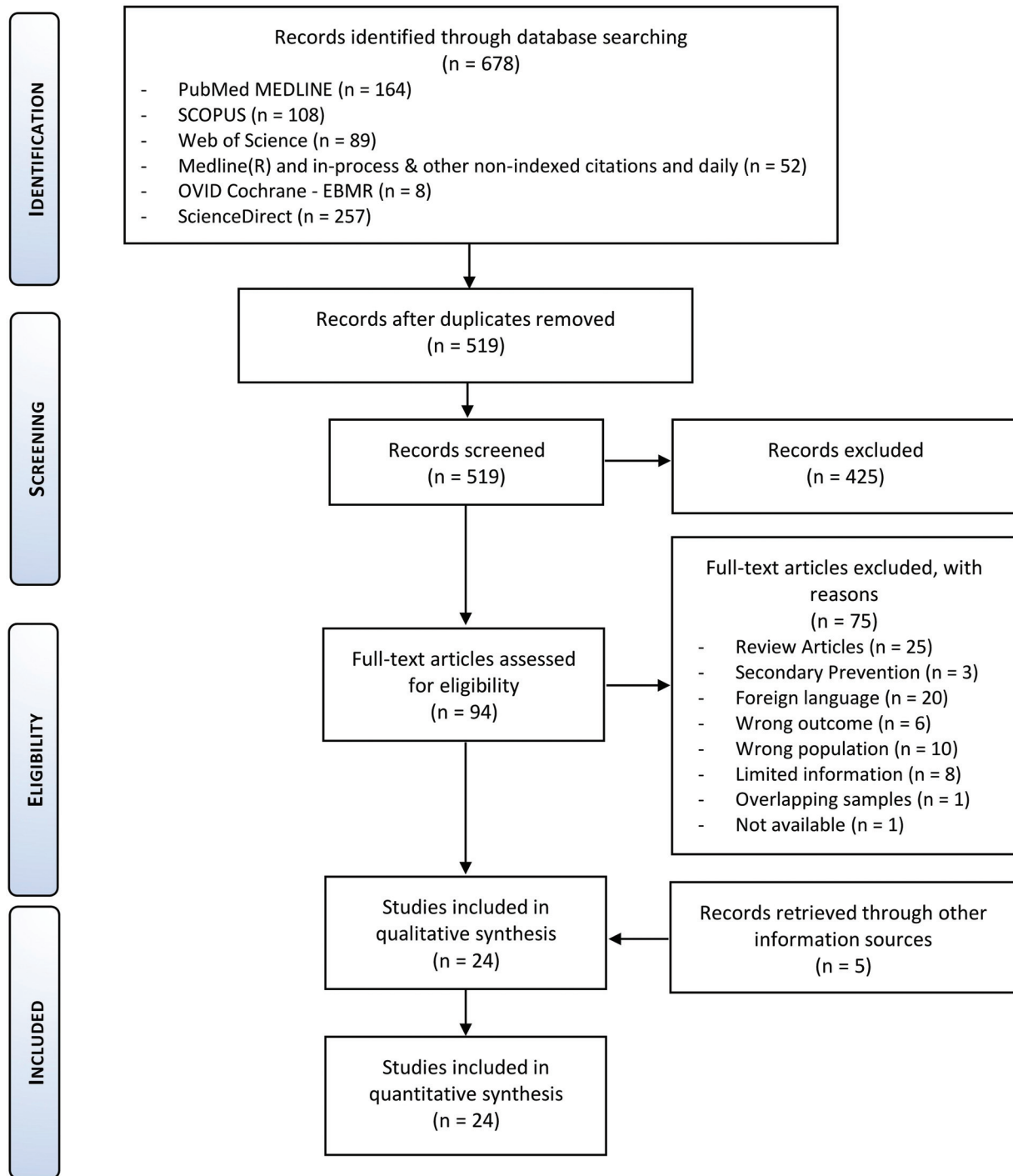


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

(► **Supplementary Fig. S4**; available online only). No significant heterogeneity was present across studies ($I^2 = 37.32\%$, $p = 0.29$)

Publications Bias

The funnel plot of the different meta-analyses showed asymmetry (► **Supplementary Fig. S5**; available online only). Quantitatively, meta-analysis for single-arm studies using PLS for the primary prevention of upper extremity (Egger's test p -value 0.519) and lower extremity lymphedema (Egger's test p -value 0.184) did not display significant

bias. Similarly, the meta-analyses of dichotomous outcomes for double-arm studies of upper extremity (Egger's test p -value 0.445) and lower extremity lymphedema (Egger's test p -value 0.831) using PLS did not exhibit significant bias. We estimated that 119 and 22 unpublished null studies would be required to disregard the significance of the conclusions from the meta-analyses of dichotomous outcomes for upper and lower extremity, respectively.

Included articles did not report the method used to generate the allocation sequence, conceal the allocation sequence, or blind study participants and personnel. Due

	Sequence Generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Orefice et al. 1988	-	-	-	?	?	-
Takeishi et al. 2006	-	-	-	+	?	?
Boccardo et al. 2009	-	-	-	+	?	?
Casabona et al. 2009	-	-	-	+	?	-
Boccardo et al. 2011	?	-	-	+	?	?
Boccardo et al. 2013	-	-	-	+	?	-
Morotti et al. 2013	-	-	-	+	?	?
Boccardo et al. 2014	-	-	-	+	?	?
Campsis et al. 2014	?	?	?	?	?	-
Feldman et al. 2015	-	-	-	+	?	-
Boccardo et al. 2016	-	-	-	+	?	-
Agrawal et al. 2018	-	-	-	+	?	?
Hahamoff et al. 2018	-	-	-	+	?	?
Ozmen et al. 2018	-	-	-	+	?	-
Cakmakoglu et al., 2019	-	-	-	+	?	-
Johnson et al. 2019	-	-	-	+	-	-
Nacchiero et al. 2019	-	-	-	+	?	?
Schwarz et al. 2019	-	-	-	+	-	?
Cook et al. 2020	-	-	-	+	?	-
Levy et al. 2020	?	?	?	?	-	?
Scaglioni et al. 2020	-	-	-	+	?	?
Shaffer et al. 2020	-	-	-	+	-	?
Somashekhar et al. 2020	?	?	?	?	-	?
Ezawa et al. 2021	-	-	-	+	?	-

Fig. 2 Risk of bias analysis of included studies. (Red [-]: high risk of bias; yellow (?): unclear risk of bias; green (+): low risk of bias).

to its investigational nature, the experimental groups in some studies had a lower sample size in comparison to control groups; however, the completeness of outcome data did not seem to be compromised. All articles were highly biased, and the protocols of the included studies were not documented on international registries (► Fig. 2).

Discussion

Ninety-nine percent of secondary nonfilarial lymphedema results from the treatment of malignancies.^{55,56} Therefore, strategies directed to treat CRL beyond the secondary or tertiary prevention are currently considered indispensable.⁴⁴ Since Boccardo et al published their study LYMPHA, in which breast CRL (BCRL) was prevented in a cohort of 18 patients who underwent prophylactic LVAs after ALND,⁴⁹ further studies have been published portraying promising

results using preventive LVA to preclude secondary lymphedema.^{5,51,53,54}

A recent meta-analysis reported that the pooled incidence of lymphedema after ALND was 14.1%, and 33.4% when ALND was associated with regional lymph node radiation (RLNR).⁵⁷ In our meta-analysis, 22.39% of patients in the control group developed lymphedema after ALND, which lies within previously reported data, suggesting an acceptable external validity to overall patient population despite the undetermined risk of selecting outcome reporting. In fact, the incidence of BCRL 5 years postoperatively has been documented to be from 3% to 42.2% depending on several factors such as the diagnostic methods and the adjuvant oncologic treatment.⁵⁸

With this precedent, several techniques like axillary reverse mapping (ARM) have demonstrated to improve the primary prevention of BCRL.^{44,59} For instance, the incidence of upper extremity lymphedema was approximately 1 to 2% when patients underwent sentinel lymph node biopsy (SLNB) in association with ARM and 2 to 6% when ALND was performed in conjunction with ARM.^{44,59-61} Therefore, further reduction of the risk of lymphedema may be achieved with the implementation of prophylactic LVAs, as we found in the present meta-analysis that PLS significantly reduced the risk of CRL after ALND in comparison to no intervention (RD – 30.3%, 95% CI – 46.5% to – 14%).

Since first introduced by Orefice and colleagues in 1988,⁴³ lower extremity PLS has become more popular. Hyngstrom et al reported that after superficial inguofemoral LND for the locoregional control of melanoma, lymphedema at a 12-month follow up period occurred in 61.5% of patients.⁶² Similarly, in a recent meta-analysis, the pooled incidence of lower limb lymphedema in women who specifically underwent inguofemoral lymph node dissection for the treatment of vulva cancer was estimated at 32.1% (95% CI 20.2–44.0).⁶³ Remarkably, our findings indicated that PLS reduced the risk of lymphedema after ilioinguinal LND in comparison to no prophylactic intervention (risk difference – 30.3%, 95% CI – 46.5% to – 14%), with a pooled cumulative incidence for lower extremity lymphedema of 6.66% (95% CI < 1%–13.4%).

Despite overcoming the limitation previously reported in different reviews by segregating the outcomes for upper and lower limb CRL,¹⁶ several other limitations were found in our meta-analysis. For instance, the different levels and regions of LND, types of LVA (E-E or telescoping), past radiation therapy, diagnostic modalities, and the different follow-up periods provided a very heterogenous sample, affecting the overall methodology and increasing the risk of bias toward better outcomes, especially in cases where selective outcome reporting was uncertain. Remarkably, the diagnostic assessment of lymphedema was severely heterogeneous with less reliable tools (e.g., volumetry, clinical examination, and circumferential measures) being implemented in the majority of studies, which increased the risk of bias in the setting of unblinded protocols. Indeed, only 16.6% of the studies used reliable methods with an appropriate sensitivity and specificity like lymphoscintigraphy.^{64,65}

Overall, only 33.3% of included studies reported outcomes with an average follow-up of 2 years or more. This may affect in great part the prevalence of lymphedema, as a minimum follow-up of 3 years after starting oncologic treatment should be contemplated to satisfactorily identify patients suffering with CRL in subclinical and early stages as well as any aftermath related to the recurrence of neoplastic diseases.^{56,66,67}

Complications associated with PLS in the form of prophylactic LVA are in the majority Clavien–Dindo classification I and II.^{68,69} This includes surgical site infection, lymphocele, skin necrosis, and transient swelling, which may be attributed in great part to the concurrent oncologic excision and lymphadenectomy performed in the same surgical time of the LVA. PLS by means of LVA may add 15 to 45 minutes to the surgical time if performed orthotopically or 46 to 120 minute if performed heterotopically.¹⁶ Nonetheless, further studies are required to unveil the effects of additional operative time for LVA and the morbidity associated with the overall procedure.

In a recent economic analysis of PLS among breast cancer patients receiving mastectomy with ALND, an estimated \$7,646.65 cost saving per patient was calculated in patients undergoing prophylactic LVA. This sum represented 42% of the total cost per patient in whom no prophylactic intervention was performed.⁷⁰ Likewise, in a cost-utility analysis presented by Johnson et al, immediate lymphatic reconstruction after ALND was more cost-effective in comparison to ALND alone, with an incremental cost-utility ratio of \$1587.73 per quality-adjusted life year.⁷¹ Similarly, in patients undergoing RLNR, the incorporation of immediate lymphatic reconstruction provided an incremental cost-utility ratio of \$699.84 per quality-adjusted life year.⁷¹ No reported cost-effective analysis was found in literature regarding PLS on the lower extremity; however, from a cost minimization perspective, the inclusion of LVA for the prevention of CRL seems promising. In this setting, although PLS is not a therapeutic approach that can be graded with a strong recommendation given the low confidence in the effect estimates.⁷² PLS has shown to significantly decrease the incidence of lymphedema and decrease the economic burden of this disease with a low associated morbidity despite the high risk of bias of published reports.⁷³

To our knowledge, there are no published cases reporting the transfer of vascularized lymph node flaps, used solely for the primary prevention of CRL. This, due to the risk for complications and the invasive nature of these procedures, make them less appealing from a preventive standpoint. In this review, Scaglioni et al presented a series of seven patients undergoing margin-free surgical resection for sarcomatous tumors along the groin and/or adductors compartment. Following resection, patients underwent reconstruction with a superficial circumflex iliac artery perforator (SCIP) flap with lymphatic preservation and at least one LVA at the level of the knee. Lymphoscintigraphy was performed at 6 months postoperatively showing no signs of lymphedema.⁴⁷

Similarly, Gentileschi et al reported a cohort of patients undergoing bilateral groin dissection in which a pedicled SCIP flap with lymphatic preservation was used in one side,

while the contralateral side was closed customarily.⁷⁴ Postoperatively, the limbs treated with the SCIP flap showed no pathological swelling while the control limbs displayed a significantly increased postoperative volume and moderate-to-severe signs of lymphedema. Certainly, flaps with lymphatic preservation seem to be a feasible alternative for the primary prevention of CRL. However, the surgeon must accomplish a thorough patient selection process and a benefit-risk analysis if a chimeric flap with lymphatic preservation or lymph node transfer is intended to prevent lymphedema given the associated morbidity of these procedures.

Limitations

The included studies were mostly of low quality which caused a significant heterogeneity in type of cancer, lymphadenectomy technique, location of LND, rate of adjuvant radiotherapy, and lymphedema diagnostic modality. Given that PLS is presently attaining responsiveness, there is a potential risk of publication bias, as studies may be discontinued or not published if unsuccessful results ensue.⁷⁵ A prospective protocol was established and accepted by all the reviewers; however, it was not registered.

Conclusions

Given the safety profile, effectiveness, and feasibility of LVA, preliminary reports theoretically favor the inclusion of PLS for primary prevention of CRL. Nonetheless, low-quality studies with great heterogeneity, high risk of bias within studies, short follow-up periods, and variability among diagnostic modalities hinder the formulation of strong recommendations in favor of this intervention. High-quality studies are necessary to determine evidence-based recommendations regarding the use of preventive lymphatic surgery.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding

None of the authors received any funds or has any financial interests to disclose for the research, authorship, and publication of this article.

Conflict of Interest

None declared.

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