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The management of secondary lower limb lymphoedema in cancer patients: A systematic review

Elaine YL Leung[1], Seema A Tirlapur[1] and Catherine Meads[2]

Abstract

Background: Lower limb lymphoedema is a recognised complication of cancer commonly encountered in palliative care, associated with reduced mobility and poor quality of life.

Aim: To evaluate the available evidence for the treatment of secondary lower limb lymphoedema in patients with malignancies.

Design: A systematic review of the literature.

Data sources: The MEDLINE, Embase, LILACS, Science Citation Index, Cochrane Databases and conference proceedings for published data from date of inception to July 2014 were searched. Relevant unpublished studies via relevant databases, Internet searches and hand-searches of the bibliographies of relevant papers were performed.

Results: From 1617 citations, 32 papers were selected for full-text assessment. Two randomised trials and five observational studies were identified. The two randomised controlled trials evaluated graded compression stockings and Coumarin capsules, respectively. The five observational studies evaluated lymphovenous microsurgical shunts, pneumatic compression devices, compression bandages alone, manual lymphatic drainage with compression and a herbal remedy combining Coumarin, Ginkgo and Melitoto (with or without manual lymphatic drainage), respectively. The extracted studies showed substantial heterogeneity. Hence, a meta-analysis was inappropriate and not performed.

Conclusion: Few studies have evaluated the clinical effectiveness and potential side effects of treatments for lower limb lymphoedema. Moreover, symptoms and quality-of-life assessments were inconsistently reported. All included studies report lower limb volume reduction after treatment, which includes complex decongestion therapy, graded compression stockings and lymphovenous microsurgical shunts. Adequately powered randomised controlled trials of these interventions are recommended. Effort should be made to establish standardised outcomes, to minimise bias and to improve reporting quality in future trials of treatment for lower limb lymphoedema.

Keywords

Lower extremities, lymphoedema, neoplasm, systematic review

What is already known about the topic?

- Lower limb lymphoedema (LLL) is a recognised complication of cancer and a common symptom encountered in palliative care worldwide, associated with reduced mobility and poor quality of life.
- The prevalence of LLL and its best treatment in patients with cancer are unclear.
- The efficacy of the existing treatments is unclear.

What this paper adds?

- All included studies in the systematic review evaluated conservative treatments, including pneumatic compression devices, manual lymphatic drainage (MLD), compression bandages and herbal remedy combining Coumarin, Ginkgo and Melitoto (with or without MLD) achieved short-term reduction of limb volume.

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- Surgical management of LLL (lymphovenous microsurgical shunts) can be an effective treatment with long-term improvements reported.
- These studies were heterogeneous and with moderate to high risks of bias.

Implications for practice, theory or policy

- Improving methodological quality of future studies requires minimising the risks of bias, standardising measured outcomes and improving reporting quality.
- Adequately powered randomised trials of complex decongestion therapy, graded compression stockings and microvascular lymphovenous shunts evaluating risks, benefits and cost-effectiveness are recommended.

Background

Lower limb lymphoedema (LLL) is a recognised complication of cancers and its treatment.[1–4] LLL presents as chronic unilateral or bilateral swelling of the lower limbs, which may be accompanied with pain, tissue fibrosis and associated skin changes (e.g. skin thickening and hyperpigmentation). It is associated with reduced mobility, psychosexual dysfunction and poor quality of life (QoL).[4–6] It was estimated that the majority (70%–80%) of all significant lymphoedema referred to specialist units are cancer-related.[7,8] Moreover, more than one-third (36%) have lymphoedema on admission to a specialist palliative care unit,[9] but only a few get referred to specialist lymphoedema services.[10] Although the commonest cause of LLL in developing countries is filarial infection,[11] more than half of the new cancer cases reported worldwide were diagnosed in low- and middle-income countries (LMIC).[12] Patients diagnosed with cancers in LMIC often have limited access to surgery and medical and radiological management of cancer.[13] Palliative care, including the management of LLL, is therefore an important part of comprehensive cancer care that should be incorporated early in a patient's journey.[14]

The risk of LLL in cancer patients and its best management strategy are unknown.[1,3] Moreover, previous reports suggested that clinicians had often shown inadequate knowledge and lack of interest in the evidence-based management of lymphoedema,[15] particularly lymphoedema secondary to non-breast malignancies.[16–19] Standardised assessments of LLL exist (e.g. the International Society of Lymphology lymphoedema staging system[10]) and are routinely used by specialist management units of lymphoedema.[10] Clinical progress can be monitored by standardised pro forma including both symptomatic progress and limb circumference measurements.[10]

Physical therapies promoting lymph drainage are commonly used to treat lymphoedema, with varying success.[10] However, the majority of interventional studies were performed on patients with upper limb lymphoedema secondary to breast cancer.[17–19]

None of the previous systematic reviews have specifically evaluated the evidence available for the treatment of patients with non-infective secondary LLL.[16–19] This study systematically reviewed the current evidence for the treatment of patients with LLL secondary to malignancies and their treatment.

Methods

This systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[20]

Identifications of studies

We searched the MEDLINE, Embase, LILACS, Science Citation Index, Cochrane Central Register of Controlled Trials (CENTRAL) and International Society of Lymphology and the Australian Lymphoedema Association congress proceedings from inception to 5 July 2014 to identify relevant citations. We looked for relevant unpublished studies and those reported in the grey literature in databases such as Systems for Information in Grey Literature (SIGLE). We looked for systematic reviews in the area to find any primary studies they might have included. The search term combination captured the concept 'secondary lower limb lymphoedema' and 'therapy' incorporating Medical Subject Headings (MeSH), free text and word variants (Appendix 2, available online). Language restrictions were not applied.

Inclusion and exclusion criteria

Included were all randomised controlled studies with any number of participants, as well as comparative observational studies (cohort and case-control) with more than 50 participants with secondary LLL. Only studies that have included patients with malignancies or patients who had undergone treatment for their malignancies were included. Excluded were studies of lymphatic flow, biochemical markers, mixed cohorts with no description of the particular effects of treatment on LLL and those exclusively on infective LLL and/or non-malignant (e.g. orthopaedic) conditions.

Study selection

The electronic searches were scrutinised and full manuscripts of all citations likely to meet the predefined selection criteria were selected. Independent reviewers (E.Y.L.L. and S.A.T.) examined these manuscripts and made the final decisions regarding inclusion or exclusion. In cases of duplicate publications, we selected the most recent and complete versions.

Data extraction and assessment of the risks of bias

Two independent reviewers (E.Y.L.L. and S.A.T.) extracted data using pre-designed and piloted data extraction forms. The risks of bias of each study were assessed by different methods according to study design. Randomised controlled trials (RCTs) were assessed by Jadad's Score,[21] and observational studies were assessed by Newcastle–Ottawa Scale (NOS).[22,23]

Results

Paper selection

From 1617 citations, 32 were deemed to be relevant for full-text assessment (Appendix 1, available online). Two randomised trials and five observational studies were identified after full-text assessment (Figure 1). One eligible Italian-language study was identified and translated by a native Italian speaker. Two studies exclusively included patients who had undergone gynaecological operations[24,25] or Classic Kaposi-sarcoma.[26] Other studies included patients with mixed aetiologies,[27–30] that is, participants with malignant and non-malignant conditions. Unfortunately, only pooled results were available for these studies (Table 1). None of the studies explicitly stated the stages of malignancies of their participants. No LLL studies retrieved exclusively recruited participants within a palliative care population.

Summary of results

In total, 778 participants with LLL were included in seven studies (two focused on patients with gynaecological malignancy, one on classic Kaposi lymphoma and four included LLL patients with different aetiologies). The two randomised trials evaluated graded compression stockings (GCSs; $n=10$)[24] compared to conservative management without GCSs ($n=8$) and Coumarin capsules ($n=10$) compared to placebo ($n=11$).[27] The five observational studies evaluated pneumatic compression devices (PCDs)[28] ($n=196$), lymphovenous microsurgical shunts (LMS)[29] ($n=260$), manual lymphatic drainage (MLD) with compression ($n=65$),[26] compression bandages alone ($n=50$)[25] and a herbal remedy combining Coumarin, Ginkgo and Melitoto (with or without MLD) ($n=133$).[30] The summaries of all eligible studies are described in Table 1.

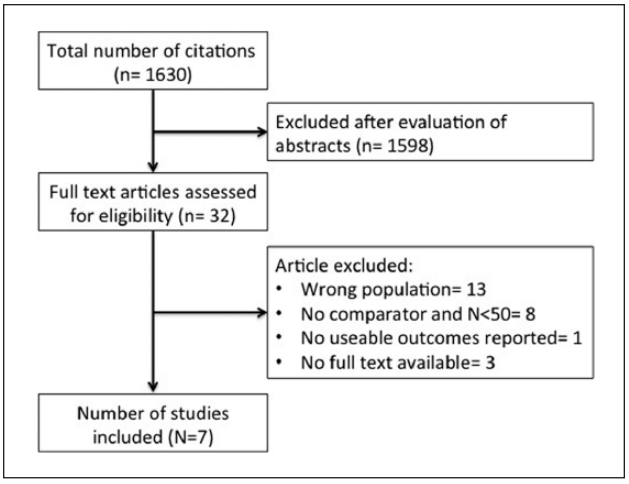

Figure 1. PRISMA flow chart.

Different methods were used to evaluate lymphoedema, and only one study evaluated the impact of observer variability (Table 1).

Assessment of the risks of bias

The included studies showed substantial clinical heterogeneity (Table 1). Hence, a meta-analysis was inappropriate and not performed. In addition, the included studies also showed significant risks of bias. We have summarised the risk of bias assessments of these studies in Figure 2, and a detailed breakdown was described in Appendix 3, available online.

Effects of the treatments

Different volumetric outcomes were used (Table 1). All included studies reported favourable outcomes of the management evaluated. GCS was reported to reduce excess volume by 6.9%[26] and mean lower limb volumes by 350 mL.[24] PCD achieved a mean lower limb volume reduction of 8% or 1150 mL, although the range of response was wide.[28] Complex decongestion therapy reduced the mean percentage excess volume by 20%.[25] Herbal remedies including Coumarin were also reported to reduce limb circumference by 7.8%–17.6%[30] and by 1.39% per month.[27] Microsurgical lymphovenous shunts consistently reduced the mean circumferences ratio of oedematous versus normal limb by 20%–30%.[29] None of the included studies reported confidence intervals of their results.

Patient-reported outcomes and side effects of treatments

Four studies reported QoL assessments,[24,25,27,28] using different instruments and surveys. Only two used validated

Table 1. Summaries of all included studies.

Paper	Design; participants	Methods used to measure lymphoedema	Treatment; duration	Treatment (*n*); Control (*n*);	Volumetric outcome and follow-up
Brambilla et al.[26]	Case-control; Classic Kaposi-sarcoma	• Circumferences were measured from the base of the great toe to the knee at 1.5-cm intervals • Mean lower limb volumes were estimated as if limbs were truncated cones	Custom-made stockings; 15 months	50; 15	*Mean percentage excess volume difference* Treatment group: 30/50 showed reduced excess volume 6.9%; 20/50 showed increased volume of 6.7% Control group: all had increased limb volume of 5.82% Median follow-up: 65 weeks Lost to follow-up: 2 (no further details provided)
Casley-Smith et al.[27]	RCT; mixed aetiologies[a]	• Each limb was measured twice at each follow-up by means of a water-displacement tank • Limb circumferences were measured at up to eight points at 10-cm intervals	5,6-benzo-[alpha]-pyrone (Coumarin); 12 months	10; 11 (participants with LLL)	*Monthly percentage volume difference* Results: volume reduced by 1.39% per month (SE 0.22; 95% CI 0.93–1.85, $p < 0.001$) Last follow-up: 6 months Lost to follow-up: 6 (unclear allocated group)
Kim and Park[25]	Cohort; gynae-oncology post-treatment (unilateral LLL)	• Circumferences were measured at six locations: mid-foot ankle, calf, knee and two along the thigh • Circumferences were average and the mean percentage excess volume calculated • Unaffected limb used as normal control	Complex decongestion therapy; 2–4 weeks (intensive), plus maintenance	65; 0	*Mean percentage excess volume difference* ($p < 0.05$) Baseline: 55.93 (compared to normal limb) At follow-up: 31.56 Last follow-up: 1 month Lost to follow-up: 8
Muluk et al.[28]	Cohort; mixed aetiologies[a]	• Circumferences were measured from the ankle to the groin at 10 cm increments • Mean lower limb volumes were estimated as if limbs were truncated cones	Pneumatic compression devices; median of 55 days	196; 0	*Mean lower limb volumes (LLV)* Mean reduction: 8% or 1150 mL (−1241 to +3084; $p < 0.0001$) Median follow-up: 60 days Lost to follow-up: 60

Table 1. (Continued)

Paper	Design; participants	Methods used to measure lymphoedema	Treatment; duration	Treatment (*n*); Control (*n*);	Volumetric outcome and follow-up
Olszewski[29]	Cohort; mixed aetiologies[a] (unilateral LLL)	• Circumferences were measured at three locations: dorsum of foot, mid-calf and mid-thigh • Limb volume was not estimated • Unaffected limb used as normal control	Microsurgical lymphovenous shunts; operative procedure	260; 0	*Mean circumferences ratio (CR) of oedematous leg versus normal (CR; $p < 0.05$)* At foot level: CR from 1.3 to 1.1 At mid-calf level: CR from 1.8 to 1.6 At mid-thigh level: CR from 2.0 to 1.7 Median follow-up: 5 years (pooled data at 10–40 years) Lost to follow-up: 64
Sawan et al.[24]	RCT; vulval cancer	• Observer identities recorded • Circumferences were measured from 2 cm above the lateral malleolus to 4 cm below the perineum at 4-cm intervals • Mean lower limb volumes were estimated as if limbs were cylinders	Graded compression stocking (GCSs); 180 days	10; 8	*Mean LLV* Treatment group: +607 mL Control group: +953 mL ($p = 0.010$) Last follow-up: 6 months Lost to follow-up: 3 in control group, 1 in treatment group
Vettorello et al.[30]	Cohort; mixed aetiologies[a]	• Circumferences were measured from the malleoli and feet • Limb volume was not estimated	Coumarin, Ginkgo and Melitoto ± manual lymphatic draining; 8 months	133; 10	*Percentage circumference reduction* Results (3 months): 7.8% at malleoli, 10.3% at feet Results (8 months): 12.3% at malleoli and 17.6% at feet Last follow-up: 8 months Lost to follow-up: 67 (no further details provided)

RCT: randomised controlled trial; LLL: lower limb lymphoedema; SE: standard error; CI: confidence interval.
[a]Studies of mixed aetiologies included participants with malignant and non-malignant conditions.

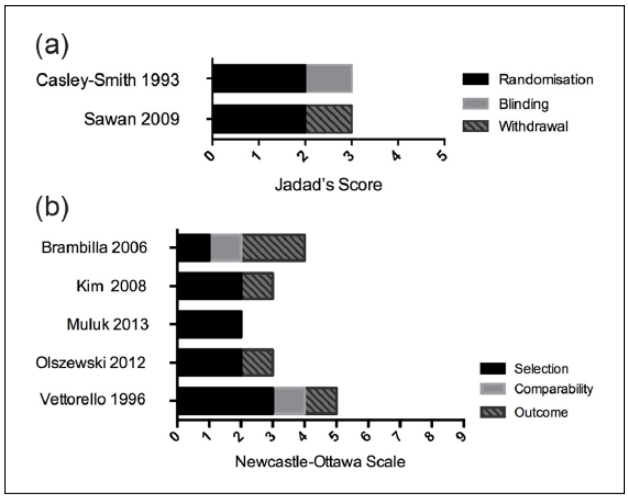

Figure 2. Assessment of the risks of bias: (a) randomised controlled trial assessed by Jadad's Score[21] and (b) observational studies assessed by Newcastle–Ottawa Scale.[22,23]

QoL instruments.[25,27] One of these two studies reported significant improvement of QoL in the treatment group, while the other was a pilot trial with insufficient power to detect any difference in QoL.

All evaluated treatments appeared to be safe, although three studies did not state whether side effects were specifically assessed.[24,26,30] Reported side effects of physical compression treatments include muscle cramps[28] and limb erythema.[28] No side effect was reported from decongestive physical therapy.[25] Herbal remedies containing Coumarin was associated with mild gastrointestinal upset.[27] No surgical complication was reported after LMS.[29]

Discussion

Main findings, strengths and limitations

All included studies reported overall volumetric and symptomatic improvements of LLL after treatment, with minimal side effects. Few studies[24–30] have investigated the effects of different treatments for LLL secondary to malignancies. Although it is not possible to disaggregate information specifically in the end-of-life palliative care populations from the studies, our results highlight the lack of evidence in such population and the potential impact of well-designed research in this area. This systematic review included all randomised controlled studies and observational studies participated by patients with LLL secondary to malignancies. No time and language restrictions were applied to our literature search. A comprehensive list of databases, including grey literature databases, was searched. Moreover, previous systematic reviews only included conservative management of lymphoedema.[17–19] We also included a study on surgical management of LLL in this systematic review.[29]

However, the included studies showed clinical heterogeneity and often included participants with LLL secondary to different aetiologies (Table 1 and Figure 2). In addition, all included studies showed moderate to high risks of bias. As a result of these limitations, it was impossible to accurately estimate the overall effect size of each evaluated treatment for patients with LLL, and whether any one treatment is superior compared to the others.

Different definitions and verification methods of LLL were used to identify participants (Table 1). In addition, various outcome measurements were used to evaluate volumetric changes in these studies (Table 1). In the majority of studies, inter-observer and intra-observer variability of outcome measurements were not taken into account (Table 1). Although five included studies evaluated subjective changes of symptoms,[24,25,27,28,30] only one study[29] specifically evaluated the complications of the treatment.

Recommendations for future studies on the management of LLL

This review suggested that the effectiveness of the treatments for LLL and their side effect profiles are currently unclear. Although our results provided limited evidence to support current clinical decision-making, the included studies[24–30] could guide the planning of future studies.

Patients. A number of included studies recruited participants with LLL secondary to different aetiologies and combining patients with and without malignancies in the same reported cohort. It is unclear whether the aetiologies of lymphoedema have any implications on the response to treatment. For example, in malignancies, lymphoedema can be secondary to both the tumours and their surgical treatment. Studies evaluating the effects of treatment on clinically relevant subgroups will be helpful.

Multiple diagnostic criteria were used to define lymphoedema in the included studies, and often, they were not clearly defined (Table 1). Grading systems for the diagnosis of lymphoedema exist[10] and should be used in future studies.

Interventions and comparison. Although the pharmacological interventions used were well described, studies using other interventions such as GCSs and PCDs provided insufficient methodological details for replication in different populations. In the included case-control studies, information about the control was limited and potential confounding factors could not be satisfactorily evaluated. Sufficient methodological details are needed in future studies.

Outcomes. Only two out of the seven included studies used the same volumetric outcomes (Table 1). Moreover, each study used a different method to measure the limbs, and only one study considered observer variability (Table 1).

The results between these studies were difficult to compare and impossible to combine.

In addition, it is established that immobility leads to morbidities and mortalities through complications such as infection and thromboembolism. Since LLL can lead to reduced mobility, there may be additional adverse effects secondary to LLL that are clinically important. None of the included studies had evaluated these risks. Moreover, the potential side effects of the treatment for LLL have not been evaluated in the existing studies. Finally, long-term outcomes of lymphoedema treatment have rarely been investigated.[17–19]

In 2010, the Core Outcome Measures in Effectiveness Trials (COMET) initiative was launched to develop agreed standardised sets of outcomes to represent the minimum set that should be measured and reported in all randomised trials of a specific condition.[31] We believe core outcomes set should be developed for future trials of LLL. The proposed core outcomes set should not simply focus on volumetric measurements by trained assessors (to reduce inter-observer and intra-observer variability). It should also assess side effects of the evaluated treatment, complications of LLL (including fibrosis and incidence of deep vein thrombosis) and use validated instruments to assess pain and QoL of participants.

Study design. RCT is the most appropriate primary study design to evaluate an intervention.[32] However, only two ongoing clinical trials on the treatment of LLL have been registered – one is investigating a new PCD[33] and the other is evaluating pelvic and lower extremity exercises.[34] Sufficiently powered randomised trials using standardised assessment of LLL and validated outcome measures are needed for improving the treatment of LLL.

Reporting of future studies. It is recognised that RCTs or controlled trials are often not available.[35] Observational studies with comparators are acceptable study designs to evaluate the effects of an intervention. The reporting quality of the observational studies included in this review was poor, which made the assessment of the risks of bias difficult.

Similar to the Consolidated Standards of Reporting Trials (CONSORT) statement[36] for reporting clinical trials, recommendations also exist for the reporting of observational studies. The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) initiative[37] helps support the reporting of observational studies by encouraging comprehensive description of methodology, recognition and reporting of bias and limitations and inclusion of numeric data and unadjusted estimates. We believe the adoption of STROBE can help readers to determine the impact of bias and confounders of studies, as well as allowing appropriate secondary data analysis (e.g. meta-analysis) of similar studies.

Conclusion

Few studies have evaluated the clinical effectiveness and potential side effects of treatments for LLL, a common and disabling symptom in palliative care not only restricted to those who are at the end of life. All studies to date report a reduction of lower limb volume after treatment, but symptom and QoL assessments were inconsistently reported. In this review, complex decongestion therapy, GCSs and LMSs have been shown to produce larger reduction of limb volume. Adequately powered RCTs of these interventions are recommended. Effort should also be made to establish standardised outcomes, to minimise bias and to improve reporting quality in future trials of treatment for LLL.

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E.Y.L.L. contributed to the conception of the research question, acted as the first reviewer and compiled the first draft. C.M. provided initial methodological guidance. S.A.T. contributed as the second reviewer. All authors have contributed to this manuscript and approved the final version.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

Ethics/research governance approvals

This is a systematic review of primary studies. Further ethical approval is not applicable.

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