Technology Assessment

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Diagnosis and Treatment of Secondary Lymphedema

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Diagnosis and Treatment of Secondary Lymphedema

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Executive Summary

Introduction

The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this technology assessment from the Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the McMaster University Evidence-based Practice Center (MU-EPC) (Contract Number: HHSA 290-2007-10060I). The primary goals of the assessment were to examine the performance of diagnostic tests for preclinical or clinically significant secondary lymphedema, as well as to assess conservative, non-pharmacological and non-surgical treatments for secondary lymphedema.

Narrative Review

Lymphedema is a pathological condition of the lymphatic system that results from an accumulation of protein rich fluid in the interstitial space because of congenital or acquired damage to the lymphatic system. Clinically, it presents as edema.[1]

Primary lymphedema occurs in patients who have a congenital abnormality or dysfunction of their lymphatic system.[2,3] Secondary lymphedema is an acquired condition resulting from the disruption or obstruction of the normal lymphatic system. Secondary lymphedema can be caused by disease, trauma, or an iatrogenic process such as surgery or radiation.[2]

Lymphedema is usually staged by observing a patient's physical condition (Table 1).[4] Historically there have been 3 stages of classification but recently Stage 0 (sub-clinical lymphedema) is increasingly recognized as a stage of lymphedema.

Table 1. Stages of Lymphedema

Stage	Description
Stage 0	A latent or sub-clinical condition where swelling is not evident despite impaired lymph transport. Stage 0 may exist months or years before overt edema occurs (Stage I-III).
Stage I	Early accumulation of fluid relatively high in protein content (e.g., in comparison with 'venous' edema) that subsides with limb elevation. Pitting may occur.
Stage II	Limb elevation alone rarely reduces tissue swelling and pitting may or may not occur as tissue fibrosis develops.
Stage III	Lymphostatic elephantiasis. Pitting is absent and trophic skin changes such as acanthosis, fat deposits, and warty overgrowths develop.

In the United States, the most common cause of secondary lymphedema is malignancies and their related treatment (i.e., surgery, radiation).

A sentinel lymph node is any lymph node that receives direct drainage from a tumor site. Sentinel lymph nodes can be biopsied and examined for the presence of micrometastases.[5] Sentinel lymph node biopsy (SLNB) is now part of the standard of care for patients with breast cancer and melanoma. SLNB has been shown to decrease the incidence of lymphedema, although the amount of the reduction is still being studied. A 5 year, prospective trial followed 936 women with breast cancer who underwent SLNB alone or SLNB in combination with axillary lymph node dissection (ALND). The incidence of lymphedema was 5 percent in the SLNB group and 16 percent in the SLNB/ALND group.[6] The Royal Australian College of

Surgeons conducted an international, multicentre, randomized controlled trial (RCT) that examined SLNB versus axillary dissection in women with breast cancer. The study found that women receiving SLNB had less lymphedema, less pain, and less arm dysfunction.[7]

Lymphedema is typically diagnosed by clinical history and physical examination.[2] When imaging tests are required to assist in diagnosis, lymphoscintigraphy is often the test of first choice.[3] When lymphoscintigraphy is not available, magnetic resonance imaging (MRI) and computed tomography (CT) can also be used.[3]

The U.S. Food and Drug Administration (FDA) regulates the marketing and use of medical devices in the United States. The FDA does not specifically mention the use of lymphoscintigraphy, MRI, ultrasound, or CT to diagnose lymphedema.

There are several non-pharmacological and non-surgical treatments for lymphedema, including: compression techniques (e.g., multilayer bandaging techniques, self-adherent wraps, compression garments at prescribed pressure gradients); intermittent pneumatic compression (IPC); decongestive therapy (also known as complex or complete decongestive therapy or complex decongestive therapy [CDT]); manual lymphatic drainage; exercise; laser treatment; ultrasound, and aquatherapy. No single treatment is considered usual care for lymphedema. Treatments are typically administered by physical therapists.

Methods

Literature Review

The following electronic databases were searched by exploding the subject heading 'lymphedema' and also searching it as a textword (lymphedema or lymphoedema):

1. MEDLINE® (1990 – March 20, 2009);
2. EMBASE® (1990 – March 20, 2009);
3. Cochrane Central Register of Controlled Trials® (1990 – March 20, 2009);
4. AMED (1990 – March 20, 2009); and
5. CINAHL (1990 – March 20, 2009).

Further searches were conducted of reference lists of recently published review articles[2,8-10] and bibliographies of abstracted articles.

Inclusion/exclusion criteria. For the diagnostic section, we included articles published in the English language that examined the sensitivity and specificity, or psychometric properties (e.g., reliability, validity, responsiveness) of diagnostic tests for lymphedema. Included articles had to contain an evaluation of the diagnostic test(s) on subjects with secondary lymphedema. For the treatment section, we included articles published in the English language, provided they were RCTs or observational studies with comparison groups (e.g., cohort, case control). We included studies of pediatric and adult patients who received any treatment for secondary lymphedema (except drug therapy or surgery) following any form of illness with the exception of filariasis infection.

Study Selection and Abstraction

A team of trained raters independently applied the inclusion and exclusion criteria to three levels of screening: I – title and abstract first review; II – title and abstract second review; III – full text. Articles that passed full text screening proceeded to full data abstraction.

Two raters independently assessed the quality of the abstracted articles. The quality of diagnostic studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies scale (QUADAS).[11] The quality of treatment studies was assessed using two scales, the modified Jadad scale[12,13] for RCTs and the Newcastle-Ottawa Scale (NOS)[14] for cohort and case control studies. The overall quality of the abstracted articles was rated 'good', 'fair', or 'poor' in accordance with the AHRQ's methods guide.[15]

Results

Diagnosis

Question 1. What is the performance of diagnostic tests for preclinical and/or clinically significant lymphedema?

a) What inclusion criteria (including patient demographics, signs, and symptoms) were used in studies evaluating the performance of diagnostic tests of lymphedema?

Most of the diagnosis studies involved persons with breast cancer. The generally middle-aged nature of study subjects reflected the fact that most studies involved cancer patients, who are typically diagnosed and treated in middle age or later. Other disease-related inclusion criteria were melanoma tumor removal, AIDS and Kaposi's Sarcoma, or lymphedema diagnosis. For comparative purposes, many diagnostic studies also included non-diseased persons, such as clinic staff, healthy patients, or medical students, and surgical residents.

b) Is there any "gold standard" method to formally grade or measure the severity of lymphedema?

Based on the evidence in the abstracted studies, there does not appear to be a gold standard to formally grade or measure the severity of lymphedema.

c) What comparators were used in the studies of diagnostic tests? Was the test compared to a "gold standard", bedside exam, radiologic investigation, or other means?

Although rarely identified as gold standards, the frequency of use of different measures of limb volume or circumference would suggest that these measures are the de facto gold standards for diagnosing secondary lymphedema.

d) What is the sensitivity and specificity of tests used to diagnose lymphedema?

In the seven studies that contained examinations of the sensitivity and specificity of diagnostic tests for secondary lymphedema, sensitivities ranged from 5 to 100 percent (most were at least 40 or 50 percent or above) and specificities ranged from 71 to 100 percent.

e) What are the psychometric properties (reliability, validity, responsiveness) of these diagnostic methods?

Reliability. There is consistent evidence to indicate that lymphedema can be reliably measured using circumferential measures or volume displacement (although volume displacement calculated using Sitzia's method tended to produce the lowest intraclass correlation coefficients, which are measures of reliability). There is too little evidence to draw conclusions

about the reliability of other tests such as tonometry, ultrasound, lymphoscintigraphy, or bioimpedance.

Validity. Based on consistently high correlation coefficients, there is strong evidence that limb volume and circumference are interchangeable among one another.

Responsiveness. Only two of the studies included in this report evaluated the responsiveness to change of diagnostic tests for secondary lymphedema. The dearth of evidence on this topic prohibits one from drawing firm conclusions about responsiveness.

f) How frequently and for how long should patients be measured for the development of lymphedema or its sub-clinical precursor? Does this vary with the diagnostic test method?

There is no evidence to answer these key questions as none of the included diagnostic studies were intended to address either question.

g) Does the diagnostic test method influence the choice of lymphedema treatment or patient outcome? What outcomes were measured in studies of diagnostic tests of lymphedema?

There is no evidence in the 31 diagnostic testing studies to answer either of these questions.

Treatment

Question 2. What were the patient selection criteria in the studies (inclusion and exclusion criteria)? Did they differ by treatment modality?

The major selection criterion in 25 of the 28 treatment studies was that persons had to have lymphedema secondary to breast cancer. Some studies contained specification that participants had to be in remission, have no relapse, or have no metastases. Various studies defined lymphedema as 'mild' or 'chronic'; other definitions included categorization of lymphedema by excess volume in the affected limb, degree of swelling and excess volume, or degree of swelling alone. There was no evidence to suggest that patient selection criteria differed by treatment modality.

Question 3. What were the criteria used to initiate treatment for lymphedema? When was treatment initiated compared to the time of onset of the lymphedema? What were the criteria used to stop therapy? Did these criteria vary with treatment modality?

In all 28 treatment studies abstracted for this report, diagnosis of lymphedema was the only specific criteria used to initiate treatment. Therefore, no evidence exists to provide a clear answer to this key question.

Only five studies reported specific criteria to stop treatment. This number is too small to assess whether stopping criteria varied with treatment modality.

Question 4. Who provided the treatments in the studies? What information was provided on their professional training or certification in lymphedema care?

The authors of 15 of the 28 treatment studies did not detail who provided the lymphedema treatment. In the other 13 studies, the primary providers were physical therapists.

Question 5a. Was one type of pneumatic compression device and sleeve (e.g., non-segmented compression device, sequential segmented compression, or segmented

compression with calibrated gradient pressure) more effective in reducing lymphedema than another for any type of lymphedema along the continuum, or patient characteristic (e.g., demographics, comorbidities)?

There was a lack of evidence from which to determine whether one type of IPC device and sleeve were more effective than others across the continuum.

None of the abstracted studies broke down treatment results by patient characteristics. Therefore, no evidence exists to assess whether one type of IPC device and sleeve were more effective in reducing lymphedema based on specific sets of patient characteristics.

Question 5b. Did the studies of IPC for lymphedema in patients with comorbidities such as wounds, arterial and/or venous insufficiency, diabetes, congestive heart failure, infection, etc., report the need to modify their treatment protocols? Did it affect treatment outcome?

There were no reports in the abstracted studies of the need to modify treatment protocols on account of comorbidity.

Question 5c. Did the timing of IPC application and/or the sequence of use of the various IPC device types (either alone or in combination with other therapies) influence outcomes either positively or negatively?

Evidence to address whether the timing of the IPC application might have influenced the study outcomes was inconclusive. For sequence of use, the evidence was inconclusive as well.

Question 6. What protocols for single modality treatments resulted in the best outcomes of lymphedema therapy? Consider parameters such as usage schedules and characteristics of treatment such as intensity, duration, frequency and setting (self-administered at home versus professionally administered applied in a medical clinic), and, if applicable, pumping times/cycles and pressures.

There were too few studies from which to ascertain whether certain treatment protocols would lead to better outcomes.

Question 7: Were there any treatments, combinations of treatment methods, or sequence of treatments shown to be more effective or ineffective for any type of lymphedema along the continuum, or patient characteristics (e.g., demographics or comorbidities)? Of particular interest: Is there evidence that the use of compression sleeves or low stretch bandaging is effective in maintaining reductions in lymphedema achieved through the use of other modalities (e.g., IPC, manual lymphatic drainage, exercise)?

There is no evidence to answer either part of this question. In no group of studies were the populations defined or the results reported in such a degree of detail that it was possible to identify groups of patients for whom these treatments are more, or less, effective. No studies were designed to examine the role of sleeve or bandaging in maintaining the benefits of initial treatment.

Question 8: What comparators were used in the studies? Are these comparators consistent with usual care for lymphedema?

Many treatments have been suggested to provide benefit for patients with lymphedema. Despite this, no single treatment has emerged as a gold standard in clinical trials. Due to this, there appears to be no agreement on a standard comparator for RCTs.

Question 9: What outcomes were measured in studies of lymphedema therapy? How effective were these treatment methods in reducing lymphedema?

Multiple outcomes were used in these reports (e.g., changes in limb volume or circumference, subjective symptoms [e.g., pain], range of joint motion, intra- and extra-cellular fluid levels through bioimpedance). Objective measurements, usually relating to volume, were the most frequently reported outcomes.

Question 10: Did any studies show that the time of treatment initiation (single modality or combination therapy) relative to symptom onset, any other lymphedema characteristics, or any patient characteristics influenced or predicted treatment outcome?

As few studies were sufficiently powered to detect a difference in the primary outcome (often defined as a reduction in lymphedema swelling over time), most trials were limited in their ability to detect differences in patient subgroups which were predictive for response. Few, if any, trials randomized patients with a stratification scheme or performed adjusted analyses to allow for detection of predictive factors.

Question 11: What was the length of followup in studies of lymphedema therapy? How long were the benefits of treatment maintained?

Considering the chronicity of lymphedema, very few trials performed long term followup in their study populations. Treatment benefits were shown to persist for up to 12 weeks in some studies with short term followup periods. Only seven of 28 studies reported outcomes at 6 months or more, with benefits shown to last for up to one year in some cases, provided there was use of maintenance therapy (i.e., elastic sleeve).

Question 12: What harms have been reported associated with the various treatments for lymphedema? Do any patient characteristics (e.g., demographics, comorbidities) or etiology of lymphedema increase the risk of these harms?

The majority of withdrawals and adverse events were related to treatment scheduling or disease recurrence, neither of which would be the direct result of therapy. Adverse events likely related to study therapy were all rare and were not shown to have a major clinical impact in any of the reviewed studies. No studies reported on factors which may increase the risk of harms associated with treatment.

Discussion

Most of the diagnostic accuracy and treatment studies were conducted in persons with a history of breast cancer. The heterogeneity of the evidence in these studies was too substantial to enable one to draw conclusions about the type of diagnostic test that would be most appropriate for diagnosing secondary lymphedema. The heterogeneity was also substantial enough to prevent one from ascertaining the optimal therapy (or set of therapies) for treating secondary lymphedema.

Based on the evidence, limb and volume circumference are the de facto ‘gold standard’ tests to diagnose secondary lymphedema. However, the evidence does not suggest a standard threshold or cut-off point to indicate the presence or absence of lymphedema. Similarly, there is no consistent means of actually measuring volume or circumference. Although validity assessment suggests good interchangeability between different measures of limb volume or

circumference, there was no evidence to suggest an adequate diagnostic testing protocol. The evidence from the studies failed to provide an indication of the most suitable frequency of testing or the time spans within which testing should be done. Additionally, there was no evidence to suggest whether the type of diagnostic test would have an affect on the choice of treatment or on patient outcomes.

Regarding treatment for secondary lymphedema, there was no evidence concerning the optimal criteria to initiate or stop treatment. While the studies suggested that most treatments did reduce the size of the lymphatic limb, there was too much heterogeneity in terms of treatments, inclusion and exclusion criteria, and treatment protocols to suggest the optimality of one type of treatment over another. Despite the multiplicity of inclusion and exclusion criteria, the studies did not contain reports of treatment benefits in any subgroup of patients.

The methodological quality of the abstracted studies was generally 'fair'. The authors of some studies omitted the reporting of fundamental elements of their research. There were reliability articles that did not contain mention of the intervals between administrations of the tests of interest, the validity studies omitted an indication of whether index test results were interpreted without knowledge of reference test results, and the majority of RCTs did not include comments on whether outcome assessors were blinded. Quality did not appear to play a major role in the interpretation of the answers to the key questions.

Conclusion

Although a great deal of research into the diagnosis and treatment of secondary lymphedema has already been undertaken, there is no evidence to suggest an optimal diagnostic testing protocol, an optimal frequency or duration of treatment, the most efficacious treatment combinations (including the use of maintenance therapy), the length of time for which persons should be tested or treated for lymphedema, and whether certain tests or treatments may benefit some types of patients more than others. The field of research into secondary lymphedema is ripe for advancement and the contents of this report may serve as a springboard to guide future scientific endeavors in this domain.

Technology Assessment

Chapter 1. Introduction

Scope and Purposes of the Technology Assessment

The Centers for Medicare and Medicaid Services (CMS) requested a technology assessment on the diagnosis and treatment (conservative, non-pharmacological) of secondary lymphedema. The purpose of the technology assessment was to provide CMS with evidence-based data to use in the consideration of coverage for these diagnostic and treatment approaches. CMS developed the key research questions listed below.

Diagnosis

1. What is the performance of diagnostic tests for preclinical and/or clinically significant lymphedema? Consider:
    a. What inclusion criteria (including patient demographics, signs, and symptoms) were used in studies evaluating the performance of diagnostic tests of lymphedema?
    b. Is there any "gold standard" method to formally grade or measure the severity of lymphedema?
    c. What comparators were used in the studies of diagnostic tests? Was the test compared to a "gold standard", bedside exam, radiologic investigation, or other means?
    d. What is the sensitivity and specificity of tests used to diagnose lymphedema?
    e. What are the psychometric properties (reliability, validity, responsiveness) of these diagnostic methods?
    f. How frequently and for how long should patients be measured for the development of lymphedema or its sub-clinical precursor? Does this vary with the diagnostic test method?
    g. Does the diagnostic test method influence the choice of lymphedema treatment or patient outcome? What outcomes were measured in studies of diagnostic tests of lymphedema?

Treatment

For the non-pharmacologic/non-surgical methods of treatment of all stages of lymphedema:

2. What were the patient selection criteria in the studies (inclusion and exclusion criteria)? Did they differ by treatment modality?
3. What were the criteria used to initiate treatment for lymphedema? When was treatment initiated compared to the time of onset of the lymphedema? What were the criteria used to stop therapy? Did these criteria vary with treatment modality?
4. Who provided the treatments in the studies? What information was provided on their professional training or certification in lymphedema care?
5. For Intermittent Pneumatic Compression (IPC)
    a. Was one type of pneumatic compression device and sleeve (e.g., non-segmented compression device, sequential segmented compression, or segmented

compression with calibrated gradient pressure) more effective in reducing lymphedema than another for any type of lymphedema along the continuum, or patient characteristic (e.g., demographics, comorbidities)?

b. Did the studies of IPC for lymphedema in patients with comorbidities such as wounds, arterial and/or venous insufficiency, diabetes, congestive heart failure, infection, etc., report the need to modify their treatment protocols? Did it affect treatment outcome?
c. Did the timing of IPC application and/or the sequence of use of the various IPC device types (either alone or in combination with other therapies) influence outcomes either positively or negatively?

6. What protocols for single modality treatments resulted in the best outcomes of lymphedema therapy? Consider parameters such as usage schedules and characteristics of treatment such as intensity, duration, frequency and setting (self administered at home vs. professionally applied in a medical clinic), and if applicable pumping times/cycles and pressures.
7. Were there any treatments, combinations of treatment methods, or sequence of treatments shown to be more effective or ineffective for any type of lymphedema along the continuum, or patient characteristics (e.g., demographics, comorbidities)? Of particular interest: Is there evidence that the use of compression sleeves or low stretch bandaging is effective in maintaining reductions in lymphedema achieved through the use of other modalities (e.g., IPC, manual lymphatic drainage, exercise)?
8. What comparators were used in the studies? Are these comparators consistent with usual care for lymphedema?
9. What outcomes were measured in studies of lymphedema therapy? How effective were these treatment methods in reducing lymphedema?
10. Did any studies show that the time of treatment initiation (single modality or combination therapy) relative to symptom onset, any other lymphedema characteristics, or any patient characteristics influenced or predicted treatment outcome?
11. What was the length of followup in studies of lymphedema therapy? How long were the benefits of treatment maintained?
12. What harms have been reported associated with the various treatments for lymphedema? Do any patient characteristics (e.g., demographics, comorbidities) or etiology of lymphedema increase the risk of these harms?

Background

The circulatory system of the human body is comprised of two closed systems which interact: the arterial-venous system and the lymphatic system. The lymphatic system is a network of vessels (lymphatics) which transport lymph. Lymph is a clear fluid that contains cells and proteins and originates as interstitial fluid (fluid that occupies space between cells). The lymphatic system drains lymph into the venous blood.[16]

Lymphedema is a pathological condition of the lymphatic system. The normal lymphatic system has three major functions, namely to transport lymph from the periphery of the body to the large veins of the chest and neck, to maintain homeostasis, and to regulate immunity.[17] Lymph flow occurs from peripheral lymphatics to the lymph nodes (distal to proximal). Peripheral lymphatics are dead ended and they originate in the distal-most tissues of the skin,

muscles, visceral organs, lung, and intestine. Major lymph node-bearing areas include the neck, chest, abdomen and, importantly for the following discussion, the axilla and groin.

Lymphedema is swelling (edema) that results from an accumulation of protein rich fluid in the interstitial space because of congenital or acquired damage to the lymphatic system.

Primary Versus Secondary Lymphedema

Primary lymphedema occurs in patients who have a congenital abnormality or dysfunction of their lymphatic system. There are different types of primary lymphedema: congenital occurring before 2 years of age; lymphedema praecox, which typically occurs at puberty; and lymphedema tarda, which has an onset after 35 years of age.[2,3]

Secondary lymphedema is an acquired condition resulting from the disruption or obstruction of the normal lymphatic system. Secondary lymphedema can be caused by disease, trauma, or an iatrogenic process such as surgery or radiation.[2]

Staging of Lymphedema

In the United States and globally, lymphedema is currently staged by observing a patient's physical condition (Table 1).[4] Historically, there were three stages of lymphedema; recently Stage 0 (sub-clinical lymphedema) has been increasingly recognized. The 2003 Consensus Document of the International Society of Lymphology (ISL) states that "…a more detailed and inclusive classification system needs to be formulated in accordance with an understanding of the pathogenic mechanisms of lymphedema (p. 3)".[4] At present, a more inclusive classification system has not been developed and thus lymphedema is often staged as shown in Table 1.[4,18]

Table 1. Stages of Lymphedema

Stage	Description
Stage 0	A latent or sub-clinical condition where swelling is not evident despite impaired lymph transport. Stage 0 may exist months or years before overt edema occurs (Stage I-III).
Stage I	Early accumulation of fluid relatively high in protein content (e.g., in comparison with 'venous' edema) that subsides with limb elevation. Pitting may occur.
Stage II	Limb elevation alone rarely reduces tissue swelling and pitting may or may not occur as tissue fibrosis develops.
Stage III	Lymphostatic elephantiasis. Pitting is absent and trophic skin changes such as acanthosis, fat deposits, and warty overgrowths develop.

According to the ISL, within each stage, it is often possible to assess severity based on limb volume increases from baseline.[4]

Pathophysiology of the Causes of Lymphedema

Primary lymphedema. Primary lymphedema results from improper lymphatic development that is not attributed to injury, trauma, illness or disease. The damaged lymphatics cannot propel lymph in adequate quantities and fluid accumulates in the interstitial or lymphatic spaces.[18]

Secondary lymphedema. The exact pathophysiology of secondary lymphedema depends on its etiology. Globally, the most prevalent cause of secondary lymphedema is from infection with the nematode *Wusheria Bancrofti*, which leads to lymphatic filariasis. The filarial larvae enter the human host when a mosquito bites and then grow into adult worms that damage the lymphatic system, leading to a disruption of lymphatic flow. It has been estimated that more than

14 million people worldwide suffer from lymphedema and elephantiasis of the leg caused by lymphatic filariasis.[19] Filariasis is not endemic to the United States (U.S.) and thus incident cases of lymphatic filariasis are rare and occurrences can usually be traced back to a visit to an endemic country.

In the U.S., the most common cause of secondary lymphedema is malignancies and their related treatment (i.e., surgery, radiation). If a malignancy or tumor is present in the lymphatic system, it can act as a physical block to lymph flow, thereby leading to lymphedema. When lymph nodes are removed during the treatment of cancer, scarring and adhesions may develop that decrease or block lymph flow. Radiation therapy over the lymph nodes can cause further damage and scarring, which may impair lymph flow and lead to lymphedema.

Less common causes of secondary lymphedema include trauma, chronic venous insufficiency, non-filariasis infection, and obesity. Trauma can destroy lymphatic structures contained in the skin, resulting in impaired lymph flow (e.g., severe burns).[3] In chronic venous insufficiency, there is usually longstanding damage to the veins and their valves. Valve failure results in a continual backflow of blood in the veins, which increases pressure on the veins and damages the delicate surrounding lymphatic structures. When the lymphatic structures are damaged, lymphedema ensues.[3] Infection in the lymphatics from a variety of sources, including venipuncture, can cause lymphedema. For this reason, patients recovering from cancer treatment must be vigilant about skin care and the prevention of infection.[2]

Obesity has also been shown to impede the flow of lymph, leading to the accumulation of protein-rich fluid in the subcutaneous tissue.[1]

The Incidence of Secondary Lymphedema in Both the Upper and Lower Extremities in the United States

The incidence of secondary lymphedema for all diagnostic categories is generally poorly documented. There is great variability in the incidence rates, which results from the variety of measurement techniques and definitions used in studies that evaluate the rates of lymphedema, as well as a general lack of literature on the incidence of secondary lymphedema.[2]

Filariasis. The incidence of filariasis in the U.S. is essentially zero percent as filariasis is not endemic to the U.S. The rare cases that are recorded can be traced back to travel and exposure in an endemic country.[20]

Upper extremity lymphedema. Breast cancer accounts for the majority of upper extremity secondary lymphedema in the U.S.[2] Rates of lymphedema after mastectomy have been reported between 24 to 49 percent.[2] A 5 year, population based, prospective study of female U.S citizens with incident breast cancer documented a 42 percent cumulative incidence of lymphedema following treatment for breast cancer.[21] Axillary node clearance and radiation therapy to the axilla have been shown to increase the incidence of lymphedema after breast cancer treatment, especially when radiation therapy is used adjunctively.[2,19] Conversely, sentinel node biopsies have been shown to decrease the incidence of secondary lymphedema.[2,6]

Lower extremity lymphedema. The incidence of lower extremity lymphedema is even less well documented than upper extremity lymphedema. Lymph node dissection for malignant melanoma has been shown to have an incidence risk of lymphedema as high as 80 percent, though other studies suggest an incidence between 6 to 29 percent.[19] Treatment for cervical, endometrial, and vulvar malignancies has an incident rate of lymphedema between 5 and 49 percent, with a higher incidence when radiation therapy is used.[19] In prostate cancer, the

incidence of lymphedema has been observed at 3 to 8 percent, with the use of radiation therapy augmenting the incidence by three to fourfold.[19]

Incident data for secondary lymphedema associated with trauma, chronic venous insufficiency, non-filarial infection, and obesity is lacking.

How Might the Adoption of Sentinel Lymph Node Biopsies Influence the Incidence of Secondary Lymphedema?

A sentinel lymph node is any lymph node that receives direct drainage from a tumor site. Sentinel nodes can be identified by lymphatic mapping, which is done through injection of radiocolloid or blue dye. The sentinel lymph node can then be biopsied and examined for the presence of micrometastases.[5] In the event that the sentinel lymph node biopsy (SLNB) is negative, complete lymph node dissection may be avoided in certain types of cancers. SLNB is now part of the standard of care for patients with breast cancer and melanoma as it provides accurate tumor staging, equivalent cancer related outcomes and less morbidity, including a decreased incidence of lymphedema, compared to full regional lymph node removal. At present, SLNB is being studied for use in patients with gynecologic, genitourinary, and gastrointestinal tumors. Cervical cancer is still very difficult to treat with SLNB alone as multiple studies have recorded unacceptable levels of false negative results.[5]

Though SLNB has been shown to decrease the incidence of lymphedema, the amount of reduction is still being studied. A 5 year, prospective trial followed 936 women with breast cancer who underwent SLNB alone or SLNB in combination with axillary lymph node dissection (ALND). The incidence of lymphedema was 5 percent in the SLNB group and 16 percent in the SLNB/ALND group.[6] The Royal Australian College of Surgeons conducted an international, multicentre, randomized controlled trial that examined SLNB versus axillary dissection in women with breast cancer. The study found that women receiving SLNB had less lymphedema, less pain, and less arm dysfunction.[7]

Available Methods to Diagnose Lymphedema

The diagnosis of lymphedema can usually be accomplished through clinical history and physical examination.[2] It is essential to rule out other causes of edema such as deep vein thrombosis (DVT), heart failure, tumor or infection. It is also important to determine if the lymphedema is primary or secondary in nature. If there is doubt to the nature of the lymphedema (primary versus secondary or recurrence of a tumor) or its existence (e.g lymphedema versus venous insufficiency), lymphoscintigraphy can be performed. This test images the lymphatic system and is a form of isotope lymphography and is also known as lymphangioscintigraphy. Isotope lymphography is different from its predecessor, contrast lymphography (lymphangiography). Contrast lymphography involves the injection of radio-opaque lipiodol directly into a peripheral lymph vessel and an x-ray is used to monitor the movement of lipiodol in the lymph system.[3] Contrast lymphography is rarely used today as it requires surgery and has been associated with complications such as wound infection and damage to the lymphatic vessels.[22] On the other hand, lymphoscintigraphy (isotope lymphography) involves the injection of a radioisotope labelled colloid into the interdigital region of the affected limb. A gamma camera is then used to track the flow of colloid as it moves towards the proximal lymph nodes. Lymphoscintigraphy is superior to contrast lymphography as it allows the practitioner to measure

lymph flow and carries less risk of complications.[22] Though lymphoscintigraphy is often recommended as the test of first choice for the detection of lymph flow abnormalities,[3] the test lacks universal standards of application.[23,24] Thus further research is warranted to refine the standards of application. When lymphoscintigraphy is not available or desired, magnetic resonance imaging (MRI) and computed tomography (CT) can be used. Both MRI and CT image lymphedema as a subcutaneous honeycomb pattern, though MRI is seen as superior to CT because it also detects excess fluid.[3] Ultrasound can also be used for evaluation of lymphedema and has been used to correlate subcutaneous tissue thickness with lymphedema and fibrosis progression.[25]

During physical examination for lymphedema of the extremities, various methods of limb volume measurement may be employed to determine if a volume increase is present in the affected limb. These methods include limb circumference measurement, water displacement (volumetry), and perometry. Volume measurements are compared with the unaffected limb and lymphedema is often defined as a 2cm or greater difference in girth, a 200ml or greater difference in volume or a 10% or greater difference in limb volume.[26] Tonometry and tissue dielectric constant may also be used to assess whether lymphedema is present in the limb.

Limb circumference measurement is used to calculate limb volume. A flexible non elastic measuring tape is employed to measure limb circumference at various anatomical landmarks or at given distances from the fingertips or toes.[26-28] Limb volume is then calculated using the frustrum sign method (volume of a truncated cone) or the disk model method (summed truncated cones).[29] The volume of a truncated cone is calculated by taking the circumference of the limb at two different points and using the distance between the two points to calculate volume. The disk model method divides the arm into 10 disks, each with a height of 5cm. The volume of each disk is then calculated and all 10 volumes summed.[29] On the upper limb, the typical points of measurement are at the hand, wrist and above and below the lateral epicondyle. The advantages to limb circumference measurement is that it is fairly easy to perform in a clinical setting, has a low cost and has good reliability.[29,30] A drawback to limb circumference is the inability to accurately measure the volume of the hand due to its irregular shape.[31]

Volumetry is used to calculate limb volume by having subjects submerge their swollen limb in a cylinder filled with a known amount of water. The amount of water that is displaced by the limb is equal to its volume. To measure the amount of displaced water, one can weigh the water or measure the volume. Water displacement is a reliable method of measuring limb volume[29,30] though its use is not very practical in a clinical setting because of water spillage and space considerations.

Perometry, also known as infrared optoelectric volumetry, uses infra red light to measure the volume of a limb. The limb is placed in a solid frame and the perometer scans the limb taking volume measurements at multiple segments. Limb volume is then calculated by summing the volumes of elliptical segments using a special computer program.[27,29] Perometry for the upper limb using Volometer® (Bosl Medizintechnik, Aschen Germany) was shown to have excellent intrarater and interrater reliability (ICC=0.997).[29] Though shown to be reliable, perometry is expensive which may limit its clinical application.

Tonometry measures tissue resistance and attempts to determine the extent of tissue fibrosis. Tonometry is unique in that it tracks tissue resistance instead of volume, offering a different outcome for lymphedema measurement. The original tonometer was developed at Flinders Biomedical Engineering in Australia. It consists of a 200g mass, plunger, reference plate and measurement dials. When the tonometer is placed perpendicular to the skin, the 200g mass

gently pushes the plunger into the skin and the depth that the plunger descends is recorded.[30,32] The disadvanatage to tonometry is that it only has fair to good reliability. In a study by Chen et al[30] intrarater reliability was found to be excellent for forearm and hand tonometry (0.88 and 0.77), but only fair to good (0.66) for fingers. Interrater reliability for all three sites was fair to good (ICC=0.69-0.71).

The tissue dielectric constant is an electrical parameter that can be used to measure the water content in tissue. It is calculated by applying an ultra high frequency electromagnetic (EM) wave to the skin through a probe and measuring how much energy is absorbed and reflected. When the EM wave penetrates tissues below the skin, the wave interacts with water molecules. Water molecules absorb EM energy and thus if there is a greater quantity of water in a given tissue, there will be less reflection of the EM wave. The amount of EM energy reflected is used to calculate the dielectric constant which is directly proportional to tissue water content. Thus it has been proposed that the measurement of tissue dielectric constant can be used to record increases in tissue water content as seen in lymphedematous tissue.[33] At present, the psychometric properties of tissue dielectric constant has not been evaluated in detail.

It is very difficult to detect subclinical lymphedema (Stage 0) with current diagnostic methods. Bioimpedance has been proposed as a method of diagnosing Stage 0 lymphedema. Bioelectrical impedance analysis measures the body's response to an electrical current. A low level current is applied through the body and the impedance (or resistance) to flow is measured. Current flows along the path of least resistance through the body and thus follows tissues with the highest water content, thereby allowing for edema to be measured.[34] Cornish et al.[35] reported that they used multifrequency bioimpedance to diagnose the early onset of lymphedema in 20 patients up to 10 months before lymphedema was clinically confirmed. Further research is needed to examine the psychometric properties of bioimpedance.

In addition to the above techniques for diagnosing and measuring lymphedema, a questionnaire called the Lymphedema and Breast Cancer Questionnaire (LBCQ) has been developed to screen for lymphedema. The LBCQ requires respondents to indicate whether each of 19 symptoms (e.g., heaviness, swelling, numbness) has occurred currently (now or in the past month) or in the past year. Respondents answer 'yes' or 'no' to the current and past year questions for each symptom. Scores for total current symptoms and total symptoms in the past year are calculated, with a resulting maximum score of 38 (1 point for each 'yes' response).[36] The authors of the LBCQ report that it has demonstrated face and content validity and that internal consistency was r=.785 for all 19 items and test-retest reliability was r=.98 when evaluated on 35 healthy women.[36]

What is the FDA Status of any Devices Used to Diagnose Lymphedema?

The U.S Food and Drug Administration (FDA) regulates the marketing and use of medical devices in the United States.

The following is the FDA status of certain devices used in lymphedema diagnosis.

Lymphoscintigraphy. The FDA does not appear to have reviewed lymphoscintigraphy for the diagnosis for lymphedema.

MRI. MRI is 510k cleared by the FDA for medical imaging purposes. There are no specific details about its use in lymphedema diagnosis.[37]

CT. CT scan is 510k cleared for medical use, though highly regulated by the FDA due to radiation risk. The FDA does not specifically mention the use of CT for the diagnosis of lymphedema.

Ultrasound. Ultrasound, which is sometimes used to help with the diagnosis of lymphedema, has been 510k cleared by the FDA for medical imaging. There is no specific mention of the use of ultrasound in the diagnosis of lymphedema.[38]

Bioimpedance devices. Certain bioelectrical impedance devices have 510k clearance from the FDA. Impedimed Imp SFB7 Body Composition Analyzer has been cleared by the FDA as has the Impedimed L-Dex U400 BIS extracellular fluid analysis. The L-Dex U400 BIS has been cleared specifically for lymphedema use.[39,40]

Perometry. No evidence has been found for whether perometry is considered a device or if it has been cleared, either in general or specifically for lymphedema.

Tonometry. A search of the devices product classification database yielded no results for whether tonometry is considered a device or if it has been cleared, either in general or specifically for lymphedema.

Tissue dielectric constant. A search of the devices product classification database yielded no results for whether tonometry is considered a device or if it has been cleared, either in general or specifically for lymphedema.

Non-pharmacologic/Non-surgical Methods of Treatment for Lymphedema

Compression tchniques (including multilayer bandaging techniques, self-adherent wraps, and compression garments at prescribed pressure gradients). Compression techniques consist of bandaging and compression garments. Both act to restore hydrostatic pressure in the limb and improve lymph flow.[41] Bandaging is performed with low stretch bandages designed to maintain a constant pressure at rest and an increased pressure with exercise, thus assisting the muscle pump effect. High stretch bandages are not recommended because their application pressure may be difficult to control at rest, thereby increasing the potential for impaired circulation. During exercise, there may be decreases in the pressure exerted by high stretch bandages, which could obstruct lymph flow.[41,42]

Compression garments are fitted to the individual patient and constructed with the intent of exerting a prescribed pressure on the limb. They can be of use to patients who are unable to self wrap with bandages.

Intermittent pneumatic compression. Intermittent pneumatic compression (IPC) is used in the treatment of lymphedema, as well as arterial disease, DVT, and chronic venous insufficiency.[43]

IPC devices consist of pneumatic cuffs connected to a pump that, when applied to human limbs, mimics the muscle pump effect that naturally occurs when muscles contract around the peripheral lymphatics.[43] It is thought that compression may empty terminal lymphatics, thereby allowing drainage of fluid from the interstitium and possibly facilitate fluid flow from the interstitium to the lymphatics. It is still not known if IPC assists protein clearance from tissue.[43]

With IPC, a pumping action on the limb is created by an air-filled bladder that fills and exerts pressure on the limb. Most pumps are electrically driven and the timing of the IPC application

varies significantly between devices. Cycle time can be as short as 2 seconds or as long as 2 minutes. Typically, devices made for lymphedema contract for a longer period of time because lymph flow is slow and a longer compression time is required to move lymphedema out of the limb.[43]

The pressure applied from an IPC device is usually between 35 and 180mmHg, though it can be as high as 300mmHg. Compression can be applied in a uniform manner using a single chamber cuff or in a sequential manner when a multicompartment cuff is used. IPC may be combined with compression stockings between sessions to help prevent a gradual re-occurrence of edema.[43]

Currently there is no non-invasive method for measuring sudden changes in lymph flow, thus making it difficult to ascertain if a given cuff has actually improved lymph flow or reduced edema. This limitation inhibits the study of the efficacy of IPC devices. The inability to measure lymphatic flow and to objectively assess lymphedema reduction has also prevented the establishment of standard or ideal compression sequences and pressures.[43]

Decongestive therapy. Decongestive therapy, more commonly known as Complex (or Complete) Decongestive Therapy (CDT), is conducted with the intent of decreasing fluid in the lymphedematous limb, preventing infection, and improving the integrity of tissues. CDT is comprised of multiple therapies and is administered in two phases. The first phase is the intensive phase and includes manual lymphatic drainage (MLD), compression of the limb with low stretch bandages, skin care, and moderate exercise while wearing bandages. Ideally, phase 1 is administered one or two times a day, every day for 4 to 6 weeks. Phase two is the maintenance, self management phase. Given that lymphedema is a chronic condition, this latter phase lasts indefinitely. Phase 2 is similar to phase 1, but there is less use of MLD and there is an increased use of compression garments instead of bandaging, which allows patients to self-treat as bandages are hard if not impossible for patients to apply on their own. Exercise and skin care continue from phase 1.[4,41] Some practitioners also incorporate IPC into their CDT regime.

CDT has been observed to have a significant effect on edema reduction and is recognized internationally as a successful treatment for lymphedema.[4,41]

Manual Lymphatic Drainage. Traditional deep tissue massage is not used for lymphedema because it can damage the delicate lymphatic system.[4,44,45] Instead, MLD is administered using light strokes on the limb, working proximally to distally. The goal of MLD is to direct lymph flow away from blocked lymphatics and toward open lymphatics. The light pressure exerted on the tissues is thought to increase lymph flow without crushing the lymphatics.[41,44,45]

Exercise. Exercise is used regularly to treat lymphedema. Historically there was a concern that exercise might exacerbate lymphedema. This concern has subsequently been shown to be unfounded.[46] Exercise helps increase lymph flow via the contraction of muscles around the lymphatics, which helps propel lymph proximally.[42] Exercise also burns calories, which helps in the maintenance of a healthy body weight. Obesity has been shown to be a risk factor for lymphedema and thus weight control is an important part of lymphedema treatment.[1]

Exercise is usually prescribed in conjunction with MLD and bandaging as a part of CDT. Exercise is done at moderate intensity while wearing low stretch bandages or a compression sleeve. Aerobic, resistance, and flexibility exercises are incorporated into the program. Deep breathing exercises are often used as inspiration decreases intrathoracic pressure, thereby promoting the return of lymph to the central veins.[1]

Low level laser. Low level laser therapy (LLLT) has been reported to have a beneficial effect in the treatment of lymphedema.[32] LLLT employs low intensity wave lengths between

650-1000nm in a scanning or spot laser form.[9] It has been suggested that the mechanism of action of LLLT encourages formation of lymphatic vessels (lymphangiogenesis), promotes lymph flow and stimulates the immune system.[9,32] LLLT has also been shown to break down scar tissue.[47]

Ultrasound. Ultrasound (US) has been used for the treatment for lymphedema. It is thought that US promotes lymph flow by way of wave propagation at the cellular level, which modifies cell metabolism and microcirculation.[48] At present there is very little literature examining the use of US for lymphedema management.

Aquatherapy. Aquatherapy, which consists of slow water based exercises, has been tried as a therapy for lymphedema.[49] The physiological rationale for the use of aquatherapy is based on the concepts of hydrostatic pressure, water temperature, and water viscosity. Hydrostatic pressure increases with the depth of water and lymphadematous limbs are thought to benefit from this pressure gradient through the direction of interstitial fluid toward the trunk.[49] Aquatherapy is performed in warm water to prevent capillary vasodilation and decreased flow that can occur at lower temperatures. Water viscosity provides resistance to movement, which is believed to assist lymph flow via the muscle pump effect and promotes muscle strengthening. At present there is very little literature examining the use or efficacy of aquatherapy for lymphedema management.

What Method(s) of Treatment is Considered Usual Care for Lymphedema Management?

No single treatment is considered usual care for lymphedema. At present CDT, which is a combination of therapies, is suggested as the main method of conservative care for lymphedema.[2,4,41] CDT includes MLD, application of compression low stretch bandages, exercise, and skin care. IPC devices are sometimes used to supplement CDT.[4,41]

Who are the Health Care Professionals That Administer These Treatments? Are any Training or Certification Standards Required?

Typically, physical therapists administer lymphedema treatments, though massage therapists, nurses, and physicians may also perform certain kinds of lymphedema treatment. Health care professionals do not require any specific training prior to administering lymphedema treatment other than a valid license to practice their profession. This being said, many practitioners seek out additional specialized training in lymphedema management. The Dr. Vodder School (Austria) offers certification in lymphedema management as does the Foeldi Clinic (Germany), the Casley-Smith School (Australia), and the Le Duc School (Belgium). At all of these schools, practitioners learn MLD techniques and how to incorporate MLD into CDT treatment.[50-52] At the Le Duc School, students also incorporate IPC into treatment.[53]

Chapter 2. Methods

Literature Search Strategy

We conducted a comprehensive search of the literature to capture all relevant, published studies on the topic of diagnosis and treatment of secondary lymphedema. The following electronic databases were searched:

1. MEDLINE® (1990 – March 20, 2009);
2. EMBASE® (1990 – March 20, 2009);
3. Cochrane Central Register of Controlled Trials® (1990 – March 20, 2009);
4. AMED (1990 – March 20, 2009); and
5. CINAHL (1990 – March 20, 2009).

In all of the databases, the term 'lymphedema' was exploded and all subheadings were included in the search. We also searched the titles of all database citations using the keyword 'lymphedema'. Appendix A contains a detailed description of the database search strategies.

To supplement the database search, we examined the reference lists of several recently published review articles[2,8-10] and searched the bibliographies of included articles.

Inclusion/exclusion criteria. There were different sets of inclusion and exclusion criteria for the diagnostic and treatment sections of the report. For the diagnostic section, we included studies published in the English language that examined the sensitivity and specificity, or psychometric properties (e.g., reliability, validity, responsiveness), of diagnostic tests for lymphedema. Included studies had to evaluate the diagnostic test(s) on subjects with secondary lymphedema. Studies that were exploratory in nature or did not use secondary lymphedema subjects were excluded. We also excluded case series, case reports, narrative and systematic reviews, editorials, comments, letters, opinion pieces, abstracts, conference proceedings, and animal experiments.

For the treatment section of the report, we included studies published in the English language, provided they were randomized controlled trials (RCTs) or observational studies with comparison groups (e.g., cohort, case control). We excluded case series, case reports, narrative and systematic reviews, editorials, comments, letters, opinion pieces, abstracts, conference proceedings, and animal experiments. We included studies of pediatric and adult patients who received treatment for secondary lymphedema following any form of illness with the exception of filariasis infection. We also included studies with all forms of treatment for secondary lymphedema except surgery and drug therapy.

Study Selection and Reporting

A team of trained raters applied the inclusion and exclusion criteria to the citations that were retrieved in the literature search. Guidelines and standardized forms were developed to govern the screening process. The forms were created and stored online using Systematic Review Software (SRS) v4.0 (Mobius Analytics Inc., Ottawa, Ontario, Canada). The screening process was divided into three levels. For the first two levels, two independent raters evaluated the titles and abstracts of citations that were obtained from the literature search. Citations that satisfied the inclusion criteria were advanced to the next level. Citations were also advanced if there was insufficient information to determine whether the inclusion criteria were satisfied. The complete,

published manuscript was retrieved for all citations that passed through title and abstract screening. Once retrieved, the complete manuscript was screened to determine if the inclusion criteria were met (level three – full text – screening). At this stage, the raters assigned the studies to the key question or questions to which they applied.

At every stage of screening, agreement was required from both raters for a study to be promoted to the next level. Discrepancies were resolved by consensus. If consensus could not be reached, then a neutral third party reviewed the study in question and made a final decision.

Studies that passed the full text screening phase proceeded to full data abstraction. The following information was abstracted from each diagnosis article: type of diagnostic test, study design, sample size, inclusion and exclusion criteria, sensitivity/specificity, psychometric properties of test, and outcomes. The following information was abstracted from each treatment article: type of treatment, study design, sample size, inclusion and exclusion criteria, criteria used to start and stop therapy, time of treatment initiation, time of lymphedema onset, provider of treatment, comparators in study, parameters of treatment, outcomes, length of followup, and reporting of harms.

The authors of this report reviewed the abstracted data to confirm the accuracy of the work.

Quality Assessment of Included Studies

Following data abstraction, two raters independently assessed the quality of the included studies. Discrepancies were resolved by consensus or third-party review. The quality of diagnostic studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) scale.[11] The QUADAS scale contains 14 questions that examine potential sources of bias in diagnostic studies. Response options are 'yes', 'no', or 'unclear'. The general domains covered by the questions include representativeness of subjects, clear selection criteria, and appropriateness of the reference standard test. Unlike many quality instruments, the QUADAS does not award points for answers that signify 'good quality', nor is there a summary score.

The quality of treatment studies was assessed using two scales, the modified Jadad scale for RCTs and the Newcastle-Ottawa Scale (NOS) for cohort and case control studies. The modified Jadad scale[12,13] contains six questions covering the following domains: randomization, double blinding, tracking of withdrawals and adverse effects, use of statistics, and inclusion and exclusion criteria. One point is awarded for each 'yes' response; zero points for 'no' responses. Additional points may be added or deducted if the randomization scheme and blinding are appropriate or inappropriate. The maximum score is eight points.

The NOS consists of two subscales, one for cohort and the other for case control studies.[14] Both subscales measure the same three broad domains: selection of study groups, comparability of study groups, and means of ascertaining exposure or outcome. The NOS contains a 'star system' to score studies (maximum score is nine stars). Studies are rated using a checklist and stars are awarded for responses that signify the highest possible quality on each checklist item. The QUADAS, Jadad, and NOS instruments are shown in Appendix B.

The overall quality of the abstracted articles was rated 'good', 'fair', or 'poor' in accordance with the recommendations outlined in the Agency for Healthcare Research and Quality's methods guide.[15] Quality cut-off scores were not used to exclude articles. Article quality was discussed in the responses to the key questions when the authors judged that quality had an impact on the evidence.

Answering the Key Questions

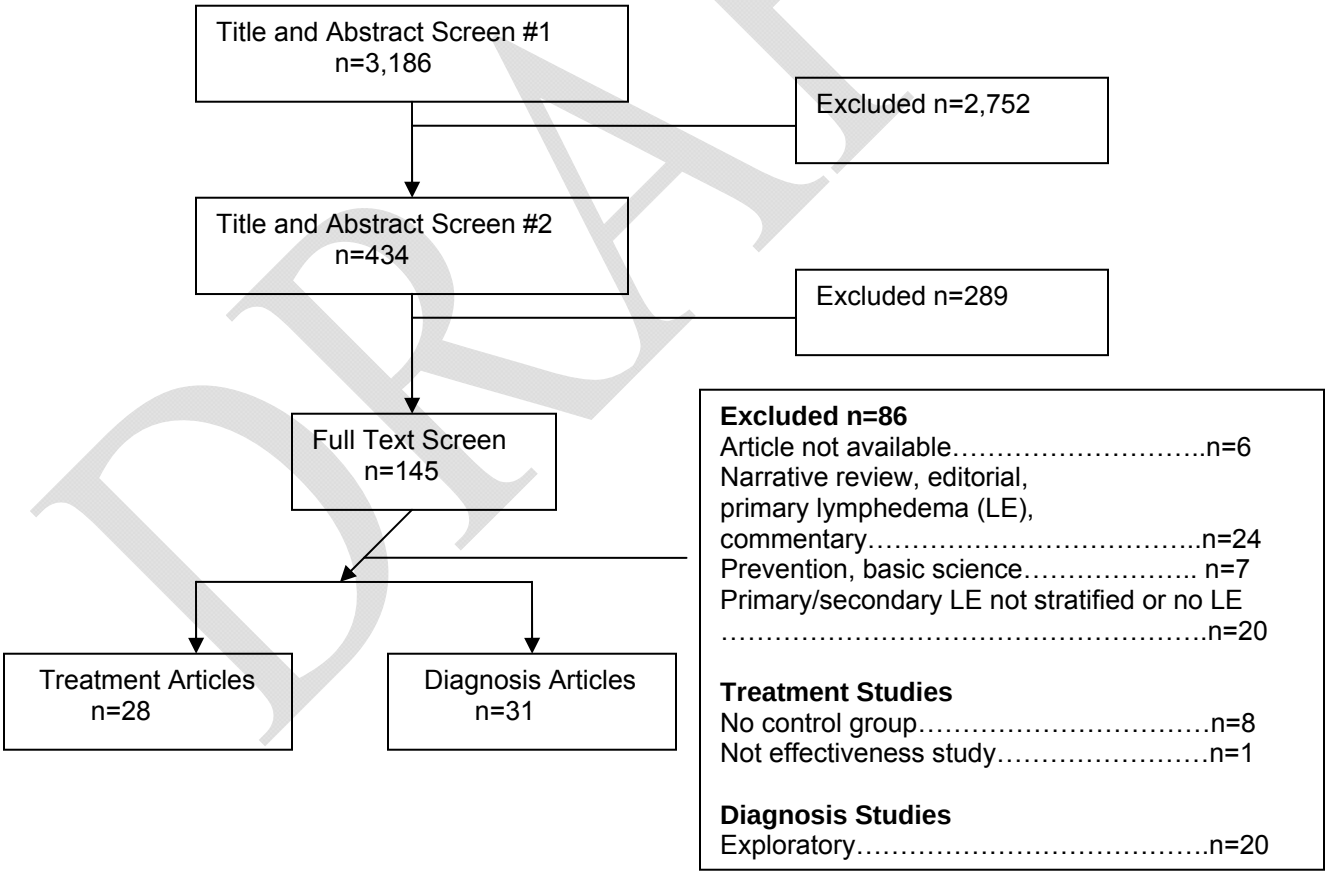
The research team used a qualitative, descriptive approach to answer the key questions. This approach included summarizing the abstracted data in tables and using these summaries to address the key questions. The research team did not believe a meta analysis was feasible because the included studies contained far too much clinical and methodological heterogeneity.

Chapter 3. Results

Literature Review and Screening

The literature search yielded 3,186 unique citations. In total, 2,752 citations (86%) were excluded from further review following the initial level of title and abstract screening. Of the 434 citations promoted to the second level of title and abstract screening, 289 (67%) were excluded and 145 proceeded to full text screening. Of the 145, six[54-59] (4%) could not be retrieved despite extensive searches of library holdings from multiple universities, inter-library loan requests, and contacts with authors. This left 139 articles, of which 59 (42%) passed full text screening and proceeded to data abstraction and quality assessment. Of the 59 included articles, 28 were related to the treatment of lymphedema and 31 were related to the diagnosis of lymphedema. Figure 1 depicts the flow of studies through the screening process. As well, the figure shows the reasons for study exclusion. The remainder of this chapter contains sections describing the evidence for the key questions 1 to 12 and a quality assessment of the studies.

Figure 1. Flow diagram showing the numbers of articles processed at each level

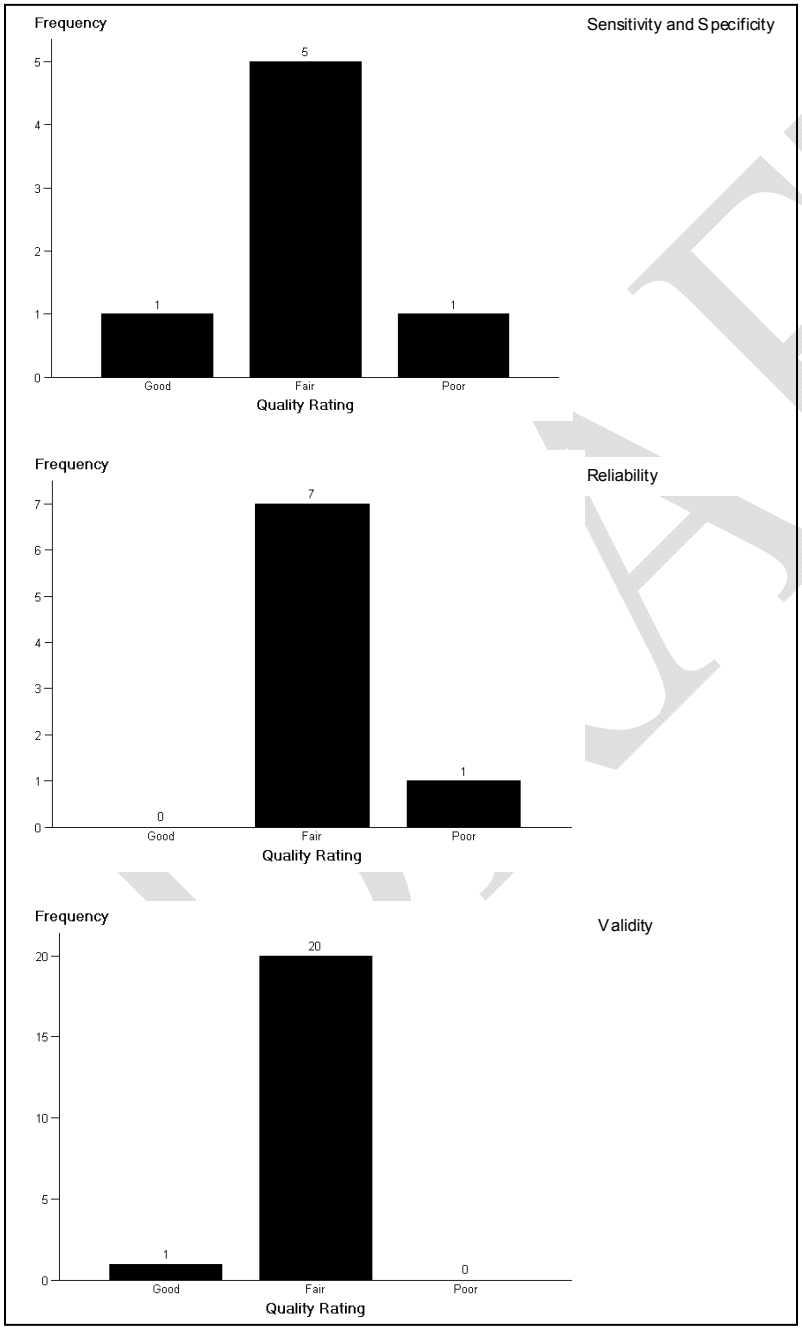


Quality Assessment

Diagnosis

The overall quality assessment for the diagnostic studies was 'fair'. Figure 2 shows the distribution of quality rankings for the 31 studies included in the diagnosis section.

Figure 2. Distribution of quality rankings for diagnostic studies



Frequency=number of studies

The primary quality issue with the diagnostic studies was a lack of clarity in reporting the details of patient withdrawals, intermediate results, and selection and training of raters. The possibility exists that patient withdrawals were minimal or non-existent in most of these studies given the limited number of assessments (usually one or two conducted on the same day) and purpose of the assessments (to examine the utility of diagnostic tests rather than to administer a treatment). The reporting of intermediate results may in fact be irrelevant to most diagnostic studies because the intent is to compare the results of different tests, rather than to follow a cohort of persons over time. Given the intent of diagnostic accuracy studies, the authors may not have thought it necessary to use limited journal space to describe the selection and training of raters. Thus, many of the 'fair' studies may have been rated as such due to reporting or relevancy issues rather than due to fundamental flaws in the research. Certainly, one limitation of quality assessment is that reviewers essentially examine the quality of what was reported in the published article rather than what was actually done in the study.[60]

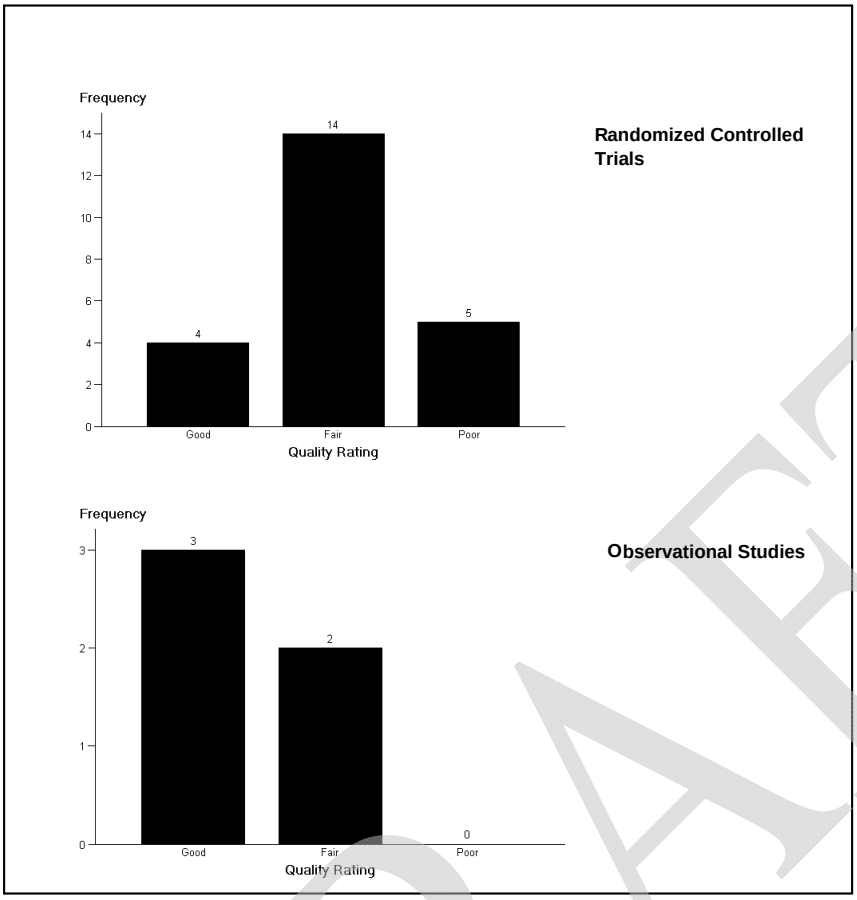
More problematic in terms of quality was the fact that three of eight reliability studies[27,61,62] did not contain reports of whether appropriate intervals were used between administrations of the tests of interest. While this may be a reporting rather than quality issue, a fundamental aspect of any reliability study is to ensure that repeated administrations of the test occur in a timeframe where the underlying condition of interest has not changed, (e.g., the severity of a person's lymphedema remains constant). It will not be possible to assess test-retest or interrater reliability if the underlying condition changes between administrations of the diagnostic test. Authors of reliability studies should comment on the timeframe of their test administrations. Also, none of the 21 validity studies reported whether the results of the index test were interpreted without knowledge of the results of the reference standard. To prevent the results of the first test from biasing the interpretation of results from the second test, different persons should assess the test results in a blinded fashion. Authors of validity studies should report whether the test results were interpreted in a blinded fashion.

Tables 2 to 4 contain a summary of the quality assessment of the diagnostic accuracy studies.

Treatment

Of the 28 studies that looked at treatments for secondary lymphedema, 23 were randomized controlled trials (RCTs)[32,46,63-83] and five were observational (cohort) studies.[48,84-87] The majority of the RCTs were of 'fair' quality and there was a roughly even split between 'good' and 'fair' quality observational studies (Figure 3).

Figure 3. Distribution of quality rankings for treatment studies



Frequency=number of studies

The major quality issues with the RCTs were an inadequate description of the randomization process in about half of the studies, no report of double-blinding in almost all of the studies, and no reporting of methods to assess adverse effects in the studies that contained reports of harms. Lack of reporting of the randomization process is common in many RCTs, although a simple sentence (e.g., "Patients were randomized using a computer-generated sequence of numbers") should suffice to inform readers of the likely integrity of the process. Less acceptable methods of randomization, such as distribution of envelopes containing group assignments or coin tosses, are more susceptible to manipulation or not always truly random. To adequately assess the methodological quality of RCTs, authors should report the randomization process. Blinding may have been impossible in many of the studies due to the nature of the treatments. For example, it would be difficult to blind study participants or the persons administering treatment in an RCT where manual lymphatic drainage (MLD) alone is being compared to MLD plus intermittent pneumatic compression (IPC). However, other methods could be used to correct for the inability to blind. For example, persons assessing outcomes in the study groups could be different from the study investigators and persons who deliver treatment. These assessors could be blinded to participants' treatment regimen. Most of the studies did not mention whether outcome assessors were blinded, so there is no way to ascertain whether knowledge of treatment may have biased any results. Regarding adverse effects, the few RCTs that included reports of harms did not specify how these conditions were defined or measured. Thus, there is no way to determine

whether the ascertainment of adverse effects may have been biased in the abstracted clinical trials.

Turning to the observational studies, the major quality issue was a lack of addressing the comparability of the exposed and unexposed groups in the design or analysis of the studies. In the absence of randomization, control of confounding in observational studies requires techniques such as matching, stratification, or use of multivariable regression analysis. Three of the five studies[84,85,87] did not contain reports of whether methods were used to control for confounding. The authors of the other two studies[48,86] indicated that the exposed and unexposed groups were matched on severity of lymphedema.

Tables 5 and 6 contain a summary of the quality assessment of the treatment studies.

Diagnosis Studies

Question 1. What is the performance of diagnostic tests for preclinical and/or clinically significant lymphedema?

a) What inclusion criteria (including patient demographics, signs, and symptoms) were used in studies evaluating the performance of diagnostic tests of lymphedema?

Of the 31 diagnosis studies contained in the review, 27 included persons who had breast cancer (Table 7).[26,27,29,30,35,36,61,62,88-106] Other disease-related inclusion criteria were melanoma tumor removal,[107] AIDS and Kaposi's Sarcoma,[108] or lymphedema diagnosis.[92,95,96,99,109,110] Miscellaneous criteria included subjects who had a traumatic accident[96] or who lived within a certain radius of the study site.[35,88,97] For comparative purposes, many diagnostic studies also included non-diseased persons such as clinic staff,[27] healthy patients,[95,98] or medical students and surgical residents.[100] Most studies had liberal age requirements (e.g., 18 years or more,[26,89,92,98] less than 75 years[88,97]) and wide ranges of ages of included persons (e.g., 35 to 67 years[90]). Mean and median ages of included persons tended to lie above 50 years.[29,61,62,91,93,94,99,100,109] Time since diagnosis or treatment of the primary condition (e.g., cancer) was an inclusion criterion in three studies.[61,88,107] Timeframes in these studies were variable: six months or less,[88] more than six months,[107] and at least 12 months.[61] Three studies excluded persons with concomitant skin disease.[30,101,102]

b) Is there any "gold standard" method to formally grade or measure the severity of lymphedema?

Only three articles pertaining to diagnostic testing for lymphedema included a measure of severity (Table 7). In a study comparing self reported lymphedema (i.e., patient questionnaire about whether limbs are a different size and whether the differences are noticeable) to physical therapists' measures of arm circumference, the severity of lymphedema was assessed by comparing the circumferential differences between the affected and unaffected arms.[91] Differences of ≤2 cm signified mild lymphedema, >2 or <5 cm indicated moderate lymphedema, and ≥5 cm or more suggested severe lymphedema. This severity scale was developed by the two physical therapists who were involved in the study. The authors did not provide any details about the validity of this classification. The authors also compared self report on the questionnaire to a 'rule-based' assessment of circumferential differences: ≤1 cm meant no lymphedema, >1 cm and ≤2 cm indicated mild lymphedema, >2 cm and <5 cm signified moderate lymphedema, and ≥5

cm meant severe lymphedema. The authors do not cite the source of the rule-based severity classification, nor do they indicate whether the classification has been used elsewhere.

The authors of a study comparing the reliability of lymphoscintigraphy versus a vaguely-defined clinical assessment used a 5-point ordinal scale to grade the severity of lymphedema: 0=healthy; 1=latent; 2=reversible; 3=spontaneously irreversible; 4=elephantiasis.[62] Lymphoscintigrapic and clinical assessors were supposed to use the data from their assessments to classify patients on the scale, but the authors did not provide the scoring rules for making this classification. The authors wrote that their scale was similar to existing recommendations,[111] but they did not explain these similarities nor did they explain points of departure from these similarities.

In another study of lymphoscintigraphy, the authors developed an 8-point scoring system for persons with post-mastectomy lymphedema. The system was based on imaging results and ranged from 0 (normal lymphatic drainage) to 8 (severe lymphatic impairment).[103] The authors report that the system was developed "empirically" (p. 1172), but they do not provide details on its development, nor do they provide a precise set of scoring rules.

c) What comparators were used in the studies of diagnostic tests? Was the test compared to a "gold standard", bedside exam, radiologic investigation, or other means?

The vast majority of diagnostic testing studies in the report included changes in limb volume or circumference as a comparator (Table 8). This included five studies of sensitivity and specificity,[35,88,89,97,107] six reliability studies,[27,29,30,90-92] 15 validity studies,[26,27,36,91-96,98,99,102,103,109,110] and two responsiveness studies.[27,30] Other types of test were used sparingly; vaguely defined or undefined clinical examinations in two studies,[62,108] ^{99m}Tc-hexakis-2-methoxy isobutyl isonitrate scan (MIBI scan) in one study,[108] lymphoscintigraphy in one study,[62] and tissue dielectric constant in two studies.[100,104] The remaining tests (e.g., bioimpedance[93,98,109]) tended to be more narrow in scope, as opposed to general tests such as magnetic resonance imaging (MRI) or computed tomography (CT) scans that are used in many areas of medicine.

The comparator in one study was an author-developed, 4-item questionnaire about truncal swelling.[106] The degree of swelling was scored from 0 to 8, with higher scores indicating more swelling. The authors do not report how they developed this questionnaire, nor whether they tested its psychometric properties prior to use in the study.

The thrust of most of the studies was to compare one or more tests to a measure of limb volume or circumference, thereby suggesting that the gold standard would actually be limb volume or circumference (although these measures were rarely identified as gold standards by study authors). In some cases, volume or circumference measures were compared against one another (e.g., Chen et al.,[30] Karges et al.,[96] Latchford et al.[105]).

d) What is the sensitivity and specificity of tests used to diagnose lymphedema?

The authors of seven studies[35,88,89,91,97,107,108] examined the sensitivity and specificity of tests to diagnose lymphedema (Table 9). Five studies included tests that involved changes in volume or circumference.[35,88,89,97,107] The authors of one study diagnosed lymphedema using a difference in arm circumference of 5 cm between the treated and untreated arms.[97] A second test in the same study was self report, which consisted of a 'yes or no' question about whether subjects experienced swelling since the diagnosis of breast cancer. The test of interest in this study was

bioimpedance. Sensitivity and specificity were 42 percent and 88 percent for arm circumference and 61 percent and 59 percent for self report, compared to bioimpedance.

Another study contained measures of whole limb volume perometry and arm circumference on persons diagnosed with lymphedema following melanoma.[107] Perometry changes of at least 15 percent and circumference changes of at least 7 percent signified lymphedema. The test of interest was patient self-assessment of whether lymphedema was moderate or severe. Sensitivity and specificity were 56 percent and 95 percent for perometry and 50 percent and 100 percent for arm circumference, compared to self-assessment. The authors of another study, conducted with persons suffering from lymphedema following breast cancer, compared an abbreviated number of circumferential measurements to a more extensive number of measurements.[89] For the abbreviated regimen, two measurements were taken, one above and one below the elbow. The comparator test involved measurements taken across the palm of the hand, at the wrist, at 10 cm intervals proximal to the wrist, and at the elbow. Sensitivity and specificity were 37 percent and 92 percent for the abbreviated measurement regimen when a 10 percent change in circumference versus the preoperative state was defined as lymphedema. When the threshold change was lowered to 5 percent, sensitivity was 80 percent and specificity was 71 percent.[89]

Persons with breast cancer were included in a study where the tests of interest involved differences in the sum of arm circumference between the treated and untreated arms.[88] Circumferential differences to diagnose lymphedema were established at ≥5 cm and ≥10 cm. A self report test was also evaluated in the study. Self report contained one question asking patients if they experienced swelling after the diagnosis of lymphedema (response: yes or no). The test of interest was multifrequency bioimpedance. For differences of ≥5 cm versus bioimpedance, sensitivity was 35 percent and specificity was 89 percent; for differences of ≥10 cm versus bioimpedance, sensitivity was 5 percent and specificity was 100 percent; for self-report compared to bioimpedance, sensitivity was 65 percent and specificity was 77 percent.

Bioimpedance was again used diagnostically in a study of 102 persons with breast cancer.[35] Bioimpedeance measures were taken prior to surgery, 1 month post-surgery, and then at two-month intervals until 24 months following surgery. Clinical diagnosis of secondary lymphedema was established through measures of limb volume. The sensitivity of bioimpedance compared to limb volume was 100 percent and the specificity was 98 percent.

A self report served as the test of interest in a study involving persons with breast cancer.[91] This self report contained two questions asking patients whether they noticed if and to what extent their limbs were a different size. The comparator was assessment by a physiotherapist, which was either rule-based (i.e., measured changes in circumferential measurement) or clinical observation. Sensitivity comparisons to the rule-based and clinical assessments ranged from 93 to 96 percent; specificity comparisons ranged from 69 to 75 percent.

In the last of the seven studies, which was composed of persons with AIDS-related Kaposi's Sarcoma, the tests of interest were a ^{99m}Tc-hexakis-2-methoxy isobutyl isonitrate scan (scintigraphy) and an undefined clinical examination.[108] Forty persons were included in the study and 18 were diagnosed with lymphedema using the scan and 12 were diagnosed using the clinical examination.

e) What is the performance of diagnostic tests for preclinical and/or clinically significant lymphedema? Consider – what are the psychometric properties (reliability, validity, responsiveness) of these diagnostic methods?

Reliability. Eight studies examined the reliability of different diagnostic tests for lymphedema (Table 8).[27,29,30,61,90-92,106] Six of the eight studies involved diagnoses using circumferential measurement or volume displacement.[27,29,30,90-92] In general, both test-retest and interrater reliability of circumferential measurement and volume displacement were extremely high, with intraclass correlation coefficients (ICCs) ranging from 0.91 to 0.99.[29,30,90,92] In one study, a single rater had an uncharacteristically low test-retest ICC of 0.62 for indirect volume determination using Sitzia's method (a formulaic method of calculating volume displacement using circumference, with circumference measures of the arm being taken at 8 cm intervals).[92] In fact, it was the use of Sitzia's method that produced the lowest ICCs in any of the seven volume or circumference studies (i.e., all ICCs below 0.91 resulted from tests involving Sitzia's method).

The authors of a study on circumferential measures and water displacement assessed interrater reliability using the intrasubject correlation, which is based on analysis of variance and multilevel modeling.[27] Like the ICCs, the intrasubject correlations were quite high (i.e., 0.94 to 0.99).

In one study, two physiotherapists developed a scale to measure the severity of lymphedema (see Question 1b).[91] The physiotherapists had high interrater agreement with one another; they agreed on ratings for 20 of 25 persons, with a weighted kappa of 0.80.

Tissue resistance measured with a tonometer was evaluated in two studies. ICCs for test-retest and interrater reliability ranged from 0.69 to 0.88[30] The between-subject reproducibility of tonometry, measured by dividing the standard deviation of all patient values by the mean of all patient values (to calculate the covariance), was good because the covariance was low (0.002 to 0.0086).[61] Bioimpedance also had good reliability, which was indicated by a low covariance (0.0129 to 0.0325).[61]

One study contained an assessment of truncal swelling due to secondary lymphedema.[106] On two consecutive days, the authors took truncal skinfold measurements using calipers from five study participants. Test-retest reliability was excellent (correlation coefficient of 0.99).

Validity. Twenty-one studies contained examinations of the validity of various tests to diagnose secondary lymphedema (Table 9). Eighteen studies involved lymphedema of the arm,[26,27,36,62,91-96,98-105] one of the legs,[109] and one of the truncal area.[106] One study included persons with leg or arm lymphedema.[110]

All except five of the validity studies included a test of limb volume or circumference. Of the five exceptions, two studies were undertaken to assess lymphedema using measurements of tissue dielectric constant.[100,104] The correlation between a single measure of tissue dielectric constant and the mean of three measures was greater than or equal to 0.98 in both studies. Another study without limb volume or circumference was a comparison of lymphoscintigraphy and clinical assessment (see Question 1b) to stage lymphedema on a five-point scale.[62] The weighted kappa of 0.77 indicated excellent agreement on staging between these methods. A 4-item questionnaire on truncal swelling was compared to caliper-based skinfold measures of truncal swelling in a study of 12 persons.[106] The questionnaire was developed by the authors and there was no report of whether it was validated prior to use in the study. The correlation between caliper measures of 'creep' (i.e., skin deformations over time) and the questionnaire score (score range is 0 to 8, with higher scores indicating more swelling) was 0.75. The final validity study without a measure of limb volume or circumference compared the torsional rigidity of normal versus lymphedema-affected skin in a group of persons with secondary lymphedema.[101] The authors found that the power to rotate normal skin exceeded the power to rotate diseased skin by

46.3 percent, although the difference was not statistically significant at the 5 percent level (p=0.13).

One validity study examined two different ways of measuring volume.[110] Leg and arm volumes were assessed by tape measure or perometer. Correlation coefficients between measures were 0.98 for legs and 0.96 for arms.

Six studies measured water displacement and made comparisons with limb circumference. In one of these studies, limb circumference was measured using frustrum calculation and tape measure.[96] In frustrum calculation, the limb is viewed as a geometric shape (usually a cone) and specialized formulae are used to measure circumference. In three other studies, limb circumference was calculated using tape measure alone[27,94] or an unexplained method.[95] Correlation coefficients ranged from 0.88 to 0.99. In the fifth study, inverse water volumetry was compared to limb circumference expressed as a ratio between the affected and unaffected limbs and the ICCs ranged from 0.89 to 0.91.[99] In the sixth study, water displacement was compared to Sitzia's method (a specific formula for frustrum calculation[112]) of measuring arm circumference (at 4 or 8 cm intervals) and ICCs ranged from 0.71 to 0.87.[92] Comparison of arm circumference measures at 4 cm with measures at 8 cm yielded ICCs of 0.80 for one rater and 0.92 for a second rater.

The focus of one study was entirely on different interval measures of arm circumference.[105] Intervals of 10 cm were compared to intervals of 3.81 cm (1.5 inches) and the correlation between measures was calculated to be 0.94 or greater.

One study was undertaken to compare two types of physiotherapists' assessments of arm circumference (see Question 1b) to a self report questionnaire.[91] The self report questionnaire asked respondents to indicate whether their affected and unaffected limbs were a different size and whether the differences were noticeable. Weighted kappas ranged from 0.70 to 0.84, primarily depending on the type of assessment. The lowest kappas were estimated when the rule-based assessment of arm circumference was compared to the questionnaire (kappas of 0.70 and 0.76).

Three studies involved bioimpedance and a group of other tests: perometer, tape measure, and the LBCQ[36] in one study,[98] perometer alone,[109] or tape measure alone.[93] In two studies,[98,109] correlation coefficients between all tests ranged from 0.61 to 0.99 with a low of 0.61 between bioimpedance and perometer.[109] Statistically significant correlations between symptoms on the LBCQ and other tests were limited to two domains, namely swelling and firmness/tightness (correlation coefficients between 0.61 and 0.76).[98] The third study involving bioimpedance contained an undefined measure of 'bias', expressed as a percentage, to examine agreement with tape measure.[93] The authors stated that lower bias indicated better agreement. Bias scores decreased from 31 to 15 percent between days 1 to 26 of followup.

Three symptoms on the LBCQ were found to be predictive of a ≥2 cm difference in arm circumference.[36] Odds ratios (95 percent confidence intervals) for each domain were 8.0 (1.2 to 54.7) for heaviness, 96.9 (9.9 to 951.6) for swelling, and 9.9 (1.8 to 53.9) for numbness. The large odds ratio for swelling reflects the fact that all except one subject with swelling also had a ≥2 cm difference in arm circumference.

Ultrasound was used to measure skin thickness in one study with arm circumference as the comparator test.[102] Ultrasound measures of average skin thickness were strongly correlated with arm circumference (r=0.95) and duration of edema (r=0.68). Average subcutis thickness was also strongly correlated with arm circumference (r=0.84) and duration of edema (r=0.67).

In another imaging study, lymphoscintigraphy was compared to arm volume.[103] The outcome of therapy, which was a combination of MLD, compression bandages, and exercise, was moderately correlated with pre-therapeutic axillary radioactivity level (r=0.50). The authors also reported that the lymphoscintigraphy score on the 8-point scoring system (see Question 1b) was positively correlated with the magnitude of excess arm volume, duration of lymphedema prior to receipt of therapy, and elapsed time since surgery for breast cancer. However, no correlation coefficients were provided for these comparisons.

One other study assessed validity without the benefit of using correlation coefficients or ICCs.[26] Four different diagnostic tests were used to estimate the incidence of lymphedema after 6 or 12 months of followup in persons diagnosed with breast cancer.[26] The four tests were 200mL difference in limb volume, 10 percent change in limb volume, 2 cm change in limb volume, or reports of limb swelling or heaviness (currently or in the past year) on the LBCQ. Incidence of lymphedema estimated with the 200 mL test was 24 percent after 6 months and 42 percent after 12 months. Incidence estimated with the 10 percent change test was 8 percent after 6 months and 21 percent after 12 months. Incidence estimated with the 2 cm change test was 46 percent after 6 months and 70 percent after 12 months. Incidence estimated with reports of limb swelling or heaviness was 19 percent after 6 months and 40 percent after 12 months.

Responsiveness. Only two studies contained examinations of responsiveness to change (Table 9).[27,30] In the first study, responsiveness was defined as the smallest difference that could be detectable by the use of water displacement, limb circumference measurement, or tissue resistance.[30] Differences were 75 mL for water displacement, 0.46 to 1.02 cm for limb circumference measurement, and 0.32 to 1.01 mm for tissue resistance. In the second study, a standard error of the mean of less than or equal to 150 mL was found to be measurement error in an investigation of limb circumference measurement and water displacement.[27] Both studies recruited persons with breast cancer, although one study also included an undefined control group.[27]

f) How frequently and for how long should patients be measured for the development of lymphedema or its sub-clinical precursor? Does this vary with the diagnostic test method?

Nine of the 31 diagnostic studies included in this report involved a single assessment of patients (Table 7).[29,30,61,88,94,95,98,107,108] The authors of one of these studies reported that two of 40 patients received a repeat ^{99m}Tc-hexakis-2-methoxy isobutyl isonitrate scan,[108] but no reason was given for performing the second test. None of the authors provided a rationale for limiting their assessments to a single point in time.

The remaining 22 studies involved two or more assessments. In three studies, there were repeat assessments without a clear rationale to explain why. One of these studies contained two assessments (pre-treatment and again after eight to 10 treatments);[110] another contained three assessments per year for up to 3 years;[89] a third contained five assessments spaced at 3 month intervals between 6 and 18 months post-surgery.[97]

Six of the 22 studies contained multiple assessments to permit the study of test-retest or interrater reliability.[27,90-92,96,99] These repeat assessments were typically performed two or three times, either on the same day or 1 week apart. In studies with three assessments, a single rater did two assessments to permit examination of test-retest reliability and a second rater did one assessment to permit investigation of interrater reliability.

In six studies, two assessments were conducted to assess the validity of various tests: lymphoscintigraphy versus clinical examination,[62] lymphoscintigraphy versus arm volume,[103]

torsional rigidity on swollen and non-swollen arms,[101] ultrasound versus arm circumference,[102] LBCQ versus arm circumference,[36] and 10 cm versus 3.81 cm (1.5 inches) measures of arm volume.[105]

One study, on truncal lymphedema, contained two sets of two assessments to examine the test-retest reliability of skinfold caliper measurements and the validity of caliper measurements versus a 4-item questionnaire about truncal swelling.[106]

More than two assessments were done in five of the 22 studies: four assessments to compare a single measure of tissue dielectric constant with the mean of three measures of tissue dielectric constant;[100,104] five quarterly assessments to examine the calculation of incidence of lymphedema over time using each of four methods (i.e., 200mL difference in limb volume, 10 percent change in limb volume, 2 cm change in limb volume, or self reported limb swelling or heaviness);[26] five assessments (baseline, once weekly for 3 weeks, and 1 month post-baseline) to study the correlation of bioimpedance and perometry over time;[109] and a maximum of 14 assessments to examine the diagnostic capability of bioimpedance.[35]

In the last of the 22 studies, measures of limb circumference and bioimpedance were taken daily for 4 weeks as part of the treatment protocol for a larger study being done to investigate a self-management program for lymphedema.[93]

In the 22 studies with multiple assessments, all except five studies[62,100,101,104,106] included either limb volume or limb circumference as a diagnostic test. None of the 22 studies contained recommendations for the length of time that patients should be measured for the development of lymphedema, nor was there any evidence of variance based on type of test.

g) Does the diagnostic test method influence the choice of lymphedema treatment or patient outcome? What outcomes were measured in studies of diagnostic tests of lymphedema?

None of the 31 diagnostic studies reported whether a specific test influenced the choice of treatment or an outcome. In fact, the authors of only four studies mentioned the lymphedema treatment that was being given to patients. Treatments included complex decongestive therapy (CDT),[110] a program to elevate and passively exercise the legs,[109] self-management following an intensive, 4 week phase of compression therapy, massage, and compression bandaging, and[93] a combination therapy of MLD, compression bandaging, and exercise.[103] In three studies, the ongoing evaluation of these three treatments provided an opportunity to investigate diagnostic tests.[93,109,110] The tests did not drive the choice of treatment nor outcome. In the fourth study, patients diagnosed with lymphedema during followup received combination therapy, but the published report did not contain information on the extent to which the therapy may have been selected with the diagnostic test (lymphoscintigraphy) in mind.[103] None of the 31 studies reported on patient outcomes because they were concerned with the diagnosis of lymphedema, rather than the resolution of the condition.

Treatment Studies

Question 2. What were the patient selection criteria in the studies (inclusion and exclusion criteria)? Did they differ by treatment modality?

The primary inclusion criterion in the 28 studies abstracted for the report was lymphedema secondary to breast cancer (Table 10). Twenty-five studies featured this inclusion criterion.[32,46,48,63-65,67-84,87] Focusing only on the RCTs with a Jadad score between 4 and 8 (fair or

good methodological quality), 18 trials included women with secondary lymphedema due to breast cancer. Seven of the 18 RCTs with a Jadad score between 4 and 8 contained specification that participants must be in remission, have no relapse, or have no metastases.[68,70-72,75-77] Eleven of these 18 RCTs contained definitions of lymphedema as 'mild'[70,75] or 'chronic';[71] other definitions included categorization of lymphedema by excess volume in the affected limb,[68,73,74,76] degree of swelling and excess volume,[32,75] or degree of swelling alone.[78,81] Five of the trials with a Jadad score above 3 excluded participants with comorbidities that would affect swelling or the ability to receive treatment,[68,69,71,72,78] five excluded persons who received treatment within the 6 month period prior to baseline (treatment for lymphedema,[69,70,75,83] treatment for something unspecified[72]), and four had a minimum elapsed time requirement between treatment and study enrolment (time since radiation,[68,80] time since surgery,[75] time since 'treatment'[46]). Four trials with Jadad scores between 4 and 8 had age requirements for inclusion[32,46,80,82] and four others had a minimum arm circumference requirement for inclusion.[72,77,79,83] There were 21 other inclusion and exclusion criteria in the 18 RCTs with Jadad scores between 4 and 8 (Table 11); however, none of these criteria appeared in more than three trials and most did not appear in more than one RCT.

There were five RCTs with Jaded scores between 1 and 3 (poor methodological quality).[63-67] The inclusion criteria in these trials did not differ substantially from the trials with Jadad scores between 4 and 8. Four of the five RCTs were conducted in breast cancer survivors. The lone exception was a trial conducted in persons who had been surgically treated for 'hindfoot'.[66]

In the five observational studies included in the review, three were conducted in breast cancer survivors,[48,84,87] with the fourth in persons suffering from Kaposi's Sarcoma[86] and the fifth in persons with various cancers.[85] The observational studies generally had fewer inclusion and exclusion criteria than the RCTs (one observational study excepted[87]), but these criteria did not appreciably differ from the criteria used in the RCTs.

The inclusion and exclusion criteria were spread across the 28 studies. There was no grouping of similar criteria attached to any specific treatment modality.

Question 3. What were the criteria used to initiate treatment for lymphedema? When was treatment initiated compared to the time of onset of the lymphedema? What were the criteria used to stop therapy? Did these criteria vary with treatment modality?

In the 18 RCTs with Jadad scores between 4 and 8, the criterion used to initiate treatment was a diagnosis of secondary lymphedema. Details are shown in Table 11. This basic condition was specified as an inclusion criterion in all of the trials. In seven of these 18 RCTs, the authors specified general timeframes for recruitment compared to the time of onset of lymphedema: at least 3 months[64,78] or greater than 3 months,[74] a median of 9 to 10.5 months,[69] less than 1 year,[72] less than or equal to 2 years,[79] or 0 to 5 years.[73] Nine studies contained reports of the time of recruitment following surgical or chemotherapy treatment for cancer: 3 to 6 weeks,[81] at least 3 months,[68] at least 4 months,[75] at least 6 months,[46,70] at least 12 months,[76,77] between 1 month and 1 year,[71] or at least 4 years.[80] In three RCTs, there was no report of when treatment was initiated compared to time of onset of lymphedema or treatment for cancer.[32,82,83]

Only five studies contained criteria to stop therapy. Four of these studies were RCTs that scored in the 4 to 8 range on the Jadad scale. Two RCTs specified stoppage in the event of adverse effects.[46,72] Other stopping rules included a change of 25 percent change or more in the circumference of the lymphedema-affected arm versus the contralateral arm[70] or completion of the therapeutic regimen.[76] A single observational study contained criteria to stop therapy.

Patients were not included in the second phase of treatment if there was less than a 10 percent volume difference between their abnormal and normal arm.[87]

The RCTs with Jadad scores between 0 and 3, as well as the five observational studies, did not exhibit characteristics that were vastly different from what was described above for the 18 RCTs with Jadad scores greater than 3. The exceptions were two RCTs in the Jadad 0 to 3 range that reported 'extreme' recruitment times of 2 days after surgery[66] or 5 years after surgery.[65]

Question 4. Who provided the treatments in the studies? What information was provided on their professional training or certification in lymphedema care?

Twelve out of the 18 RCTs with a Jadad score between 4 and 8 reported the profession of the person who provided the lymphedema treatment. Some trials contained more than one type of professional.[46,73,76,77,83] The authors of eight trials reported that a physiotherapist provided treatment.[46,69,73-75,79,80,83] For four of these RCTs, the trial publication indicated that the physiotherapists had been trained in the Vodder technique for the provision of MLD.[69,74,75,83] In two other RCTs, the authors wrote that the person who delivered the treatment was trained in the Vodder technique, but they did not mention whether the person was a physiotherapist.[68,71] Other professionals included dietitians,[76,77] "lymphedema practitioner",[77] physiotherapist's assistant,[83] nurse,[76,82] and an exercise physiologist.[46] Two RCTs contained reports of patients self-administering treatment[73,74] and seven RCTs did not report the type of professional who administered lymphedema treatment.[32,68,70-72,78,81] In the two trials involving nurses, one nurse was described as holding a 2 year diploma in the management of chronic edema[82] and the other nurse was described as being 'trained in lymphedema' management.[76] The dietitian in one study was described as "certified".[76]

Four of the RCTs with Jadad scores between 0 and 3 did not describe the professional providing lymphedema treatment. The lone exception indicated that the professional was a physiotherapist trained in MLD.[66] Three of the five observational studies also did not contain reports of the type of professional. The authors of the other two observational studies described the professional as a 'certified therapist'[85] or a physiotherapist trained in the Vodder technique.[87] Details are described in Table 11.

Question 5a. Was one type of pneumatic compression device and sleeve (e.g., non-segmented compression device, sequential segmented compression, or segmented compression with calibrated gradient pressure) more effective in reducing lymphedema than another for any type of lymphedema along the continuum, or patient characteristic (e.g., demographics, comorbidities)?

There were 10 abstracted studies that focused on treatment for lymphedema using an IPC device (Table 12). Six studies were RCTs with Jadad scores between 4 and 8,[68-73] two studies were trials with Jadad scores between 0 and 3,[63,64] and two studies were observational.[48,84] There were seven different types of IPC devices used in these studies: Sequential Circulator 2004, a four-chamber pneumatic sleeve and gradient sequential pneumatic pump operated at 40 to 50 mmHg for 30 minutes per day over 10 days[68] or 60 minutes per day over 30 days;[71] Flexitouch, a home use device consisting of a programmable, pneumatic controller unit, garments capable of fitting an arm or leg, and 26 to 32 independent chambers that inflate and deflate sequentially, used for 1 hour daily over 14 days;[73] Lympha-Press, a pump employing nine compression cells, was operated at 40 to 60 mmHG for 2 hours per day over 2 weeks[69] or at 90 to 120 mmHg twice daily for 20 to 30 minutes over an unspecified followup period;[84] IPC devices described only as

ICH8 electrodes and sleeve (eight electrodes with an impulse frequency of 4.5 KHz), applied in two cycles of 2 weeks, divided by a five-week break (each cycle consisted of 10, 30 minute sessions);[70] a sequential external pneumatic compression sleeve with twelve overlapping compression chambers (60 to 65 mbars) applied for 60 minutes daily over 10 days;[63] a Jobst Extremity Pump used for 6 hours daily for 5 days at 4 month intervals over 1 year;[48] or Flowtron intermittent compression at 80mmHg applied for 20 minutes daily for a minimum of 4 weeks.[84] The specific IPC device was not named in two trials,[64,72] although the authors of both RCTs described the degree of treatment (i.e., two cycles, with each cycle being five 2 hour sessions at 60mmHg separated by 5 weeks;[72] 20 sessions over 4 weeks, with each session consisting of 2 hours of intermittent pressure at 60mmHg[64]). The authors of one[64] of these two studies named the device manufacturer, but not the device itself.

IPC was statistically significantly better than comparator treatments (usually MLD or compression garments alone) in four studies,[63,68,71,73] worse in one study (comparator was laser treatment),[64] and no different in five studies.[48,69,70,72,84] The typical measure of efficacy was a change in arm volume or circumference.

None of the studies contained breakdowns of treatment efficacy by patient characteristics.

Question 5b. Did the studies of IPC for lymphedema in patients with comorbidities such as wounds, arterial and/or venous insufficiency, diabetes, congestive heart failure, infection, etc., report the need to modify their treatment protocols? Did it affect treatment outcome?

The need to modify protocols was not discussed by the authors of nine of the 10 studies that included IPC therapy[48,63,64,68-73] (see Table 12). The authors of one observational study wrote that lower levels of pressure were permitted in some patients treated with compression stockings, but they did not report the number of patients affected by the reductions, the mean decrease in pressure, nor how the reductions may have affected the comparisons with IPC.[84] The authors indicated that the potential for pressure decreases was offered to participants as a means of increasing compliance, thereby suggesting a protocol modification. However, there was no discussion of whether the compliance issue was related to comorbidity.

Question 5c. Did the timing of IPC application and/or the sequence of use of the various IPC device types (either alone or in combination with other therapies) influence outcomes either positively or negatively?

Six of the 10 studies involving IPC contained reports of the timing of the treatment.[64,68,69,71-73] IPC applied within 1 year of onset of lymphedema was not statistically significantly different from skin care and prophylaxis (cleaning wounds, gloves during gardening, avoidance of weight gain and venipuncture, prolonged sun exposure and carrying heavy weights),[72] but it was better as a supplement to MLD and compression garment when applied an average of 60 mths (3-480 mths) after lymphedema onset[71] (see Table 12). In two studies, IPC was applied within 5 years following lymphedema onset, showing better results versus massage as an adjunct to compression garment and showing no difference versus MLD.[69,73] One study had IPC applied at least 12 weeks following cancer treatment and results were better when IPC was added to MLD and compression bandaging versus MLD and bandaging alone.[68]When IPC was applied to patients who had arm lymphedema for at least 3 months, it performed statistically significantly worse than laser.[64] Four studies did not report the precise timing of IPC application, with IPC performing statistically significantly better than massage (followed by elastic bandage).[63] IPC demonstrated no difference versus ultrasound,[48] no difference when added to an elastic sleeve

versus the sleeve alone,[70] and no difference when added to compression stockings versus the stockings alone.[84]

Two RCTs were crossover designs and in neither instance did the sequence of treatment affect the results, whether for IPC versus massage as adjuncts for compression garment[73] or IPC added to MLD and compression garment versus MLD and compression garment alone.[71] When IPC was evaluated as part of combination therapy (MLD, massage, or compression garment prior, concurrently, or afterward), it was better than the comparator in two instances[63,68] and no different in four instances.[48,69,70,84] When IPC was not part of combination therapy, it was worse than the comparator (laser) in one case[64] and no different from skin care and prophylaxis in another case.

Question 6. What protocols for single modality treatments resulted in the best outcomes of lymphedema therapy? Consider parameters such as usage schedules and characteristics of treatment such as intensity, duration, frequency and setting (self-administered at home versus professionally administered applied in a medical clinic), and if applicable pumping times/cycles and pressures.

There were eight studies that contained comparisons of single modality treatments: two involved dietary interventions,[76,77] two involved laser,[32,78] two concerned IPC,[64,72] (one of which was a comparison with laser[64]) one concerned exercise,[46] and the other involved custom-made elastic stockings.[86] Six were RCTs with Jadad scores between 4 and 8, one was an RCT with a Jadad score between 0 and 3,[64] and one was an observational study.[86] See Table 12 for a summary of results.

The two dietary trials were conducted by the same group of researchers. In the first trial, patients were randomized to receive individual dietary advice for weight reduction or a booklet on healthy eating.[76] This RCT consisted of 21 patients and followup was for 12 weeks. At week 12, excess arm volume was lower in the group receiving dietary advice (p=0.003). In the second diet trial (n=51), three groups were followed for a period of 24 weeks.[77] Interventions were dietary advice on weight reduction, diet to reduce fat intake to 20 percent of total energy intake, and a control group told to continue with their habitual diet. Percent excess arm volume decreased in all three groups over the course of followup, but there were no statistically significant differences between groups.

Two laser studies used identical protocols for delivery of laser treatment.[32,78] Three treatment sessions were scheduled per week for a period of 3 weeks. Afterward, there was an 8 week interval before the laser was re-administered using the same 3 week schedule. A total of 1.5 Joules/cm^2 were delivered during each treatment session. Comparators were sham laser treatment using the same schedule[78] or sham treatment during the first 3 week period and actual laser treatment during the second 3 week period.[32] Followup periods (and sample size) were 22 weeks (n=8)[78] or 30 weeks (n=53).[32] In the study with an entirely sham group,[78] decreases in limb circumference were observed in both groups over the course of the trial, but the differences between groups were not statistically significant. In the trial with a partial sham group, the percentage of patients with statistically significant decreases in limb volume of at least 200 mL was higher in the group that received laser therapy at both treatment sessions.

One RCT (n=47) compared laser to IPC over 12 weeks of followup.[64] Laser was delivered in three sessions per week for 4 weeks with a total of 1.5 Joules/cm^2 per session; IPC was given in five sessions per week for 4 weeks at 60mmHg per session. The change in arm circumference

between affected and unaffected limbs was greater for laser than IPC over 12 weeks of followup (p=0.02), but there were no differences on pain or grip strength measures.

A single RCT compared IPC to providing patients with guidelines on skin care for the affected limb.[72] IPC was delivered in two cycles lasting 2 weeks each, with a 5 week separation between the cycles. Each cycle consisted of five sessions per week at 60mmHg. Eighty patients were followed over 9 weeks, and no differences were shown in arm circumference between the groups.

The exercise trial lasted 12 weeks and involved 32 persons.[46] Randomization was to a group that received 20 supervised, aerobic or resistance exercise sessions or to a group that was instructed to continue with habitual activities. No differences in reduction of lymphedema were found between the groups.

An observational study examined the use of below-knee, custom-made stockings versus no treatment for lymphedema in a study of 65 persons that lasted for a mean of 5 to 6 months.[86] Differences in limb volume were highly significant between the groups and favored the stockings.

Question 7: Were there any treatments, combinations of treatment methods, or sequence of treatments shown to be more effective or ineffective for any type of lymphedema along the continuum, or patient characteristics (e.g., demographics, comorbidities)? Of particular interest: Is there evidence that the use of compression sleeves or low stretch bandaging is effective in maintaining reductions in lymphedema achieved through the use of other modalities (e.g., IPC, manual lymphatic drainage, exercise)?

There were 22 articles that addressed this question. Pneumatic compression was used as a study treatment in eight randomized trials. Six of those trials received a Jadad score of 4-8.[68-73] Two trials received a lower score.[63,64] Of the eight trials, it was shown superior to some form of massage-based treatment in three.[63,68,73] In one, it was considered to be inferior to laser with respect to reductions in arm circumference.[64] In the remaining four trials, it was found equivalent to manual lymphatic drainage with or without bandaging,[69,71] elastic sleeve,[70] and skin care.[72]

The addition of massage to more conservative treatments such as bandaging,[79,83] simpler forms of massage,[74,82] elastic sleeve,[75] or physiotherapy alone,[66] was tested in six trials. All but one of these studies achieved a Jadad score of 4-8.[66] These studies typically included skin care and exercise as treatment in both groups. In all cases but one, study subjects had arm lymphedema following treatment for breast cancer. In a single trial, massage was tested in patients following hindfoot (ankle) surgery.[66]

In those studies of arm lymphedema in breast cancer patients, only one suggested that massage provides improvements in arm volume reduction over more conservative therapy (56% vs. 36%).[79] In the single study examining patients following ankle surgery, a benefit of massage was also reported.[66]

One study noted a significant improvement in volume loss when dietary changes occurred with sleeve use versus sleeve alone,[76] while another using dietary changes alone, with neither group using sleeves, did not.[77] Less commonly studied treatments including exercise did not provide any additional benefit.[46,67]

Despite differences occasionally being reported in volume estimates, trials did not typically find differences in outcomes that would more likely effect patient quality of life such as shoulder range of motion,[32,69,78] and quality of life scores.[67,73]

Regarding maintenance of volume reduction following initial treatment, only one study specifically addressed this issue.[71] The authors found that patients who continued with IPC in addition to CDT after initial therapy for volume reduction had a significant further reduction of 90 ml ($p<0.05$) by study end, whereas patients receiving CDT alone did not. While the CDT group regained another 33 ml, it is not reported to what degree those patients maintained their initial volume loss. Unfortunately the authors did not report between group statistical comparisons, leaving readers unsure of the value of additional pneumatic compression for maintenance.

Indirect support for the value of continued therapy for the maintenance of lymphedema volume reduction comes from the observation that four remaining studies which reported long-term reductions in lymphedema volume of at least 24 weeks were those which reported the use of maintenance therapy. In all four studies, therapy was elastic sleeve.[48,65,70,75] No studies demonstrated long term volume reduction without the use of maintenance therapy. None of these studies were designed to examine the role of sleeve or bandaging in maintaining benefits of the initial treatment. No trials were identified which compared sleeve or bandage to no treatment in the volume reduction phase of a study.

Question 8: What comparators were used in the studies? Are these comparators consistent with usual care for lymphedema?

In four non-randomized studies which included a comparator group, all four used different treatments as their comparator. These comparator treatments were pneumatic compression, bandaging, elastic compression garment or no active treatment.[48,84,86,87]

Several RCTs did not identify well which of the treatments was considered experimental and which was considered control. For purposes of this report, it was assumed that the more conservative therapy was the comparator.

There appeared to be little difference between the comparators chosen for higher or lower quality RCTs. The most common comparator use in eight randomized trials was a group of strategies loosely defined as either "usual care", sham treatment or no treatment.[32,46,67,72,76-78,81] The most commonly reported active therapies used as a comparator were some form of decongestive therapy,[65,68,71] or elastic sleeve.[70,75] Less commonly used study comparators were self-massage,[73] bandaging alone,[79,83] or two slightly different therapies both reported as "simple lymphatic drainage".[74,82] Comparators used in single trials included IPC,[64] manual lymphatic drainage alone (without bandaging),[80] and physiotherapy.[66] In two randomized trials involving sequential pneumatic compression, one with MLD,[69] and one with decongestive therapy,[63] it was difficult to interpret which of the two treatments was intended as experimental and which was the control.

Question 9: What outcomes were measured in studies of lymphedema therapy? How effective were these treatment methods in reducing lymphedema?

A multiplicity of outcomes was used to detect benefit in the trials. The vast majority included some form of measurement related to volume of the affected area, although a few simply recorded changes in limb circumferences without reporting volumes.[63,64,70,72,78,81] Other outcomes included subjective symptoms such as pain, heaviness or tension,[64,65,69,78,80,81,87] range of motion in joints (usually shoulder),[32,68,69,75,78,80] grip strength,[64,69] measurements of intra- and extra-cellular fluid levels through bioimpedance,[32,46] skin-fold thickness,[76,77] and skin tonicity using

tonometry.[32,68,71] Finally, several studies attempted to correlate results of lymphedema treatment with changes in quality of life.[67,73]

The five observational studies examined a mixed group of patients and treatments. One study reported on the use of ultrasound and pneumatic pressure therapy in breast cancer patients. For reasons that are not clear only 96 of 150 study patients contributed data to the final analysis. The authors found that both groups experienced a reduction in arm circumference over baseline values but that there was no difference between the two treatment groups.[48] Another study of breast cancer patients included some patients with active disease. The reduction in lymphedema volume was 22 percent regardless of disease status but p values were not reported.[85] A further study of patients with active malignancy included patients with Kaposi's sarcoma. There was a significant improvement in patients wearing a daily compression stocking versus those who did not ($p<0.001$) but the size of the benefit was not reported.[86] A study of compression bandaging with or without MLD reported a significant percent reduction in lymphedema ($p=0.04$) but this significance became borderline when reported as absolute volume ($p=0.07$). Both groups experienced a significant reduction in heaviness and tension but only the group receiving MLD experienced less pain ($p<0.03$). No comparisons were made between groups for these outcomes.[87] A further observational study compared sleeve to IPC. The authors found no significant differences in volume reduction between groups and no point estimates were given.[84]

Of six higher quality trials involving pneumatic compression-based therapies, only two showed benefit over the comparator group, in this case, some form of decongestive therapy. In one, initial volume loss as measured by water displacement was greater in the group receiving pneumatic compression (45%) than in controls (26%).[68] In the same report, these authors also tested the same treatments for maintenance of volume reduction. While their report suggested a superiority for pneumatic compression, they did not perform a statistical comparison between groups.[71] Another report comparing pneumatic compression to self-massage in a randomized crossover study showed that patients lost 208 ml of fluid in the involved arm after 2 weeks of treatment with pneumatic compression, but gained 52 ml after self-massage ($p=0.003$).[73]

Three additional studies failed to show superiority of pneumatic compression over more conservative measures such as lymphatic massage,[69] skin care,[72] or elastic sleeve.[70]

Of 11 trials of non-pneumatic compression treatments, differences between groups by the end of the study were reported in three.[32,79,81] Six studies used some form of massage-based therapy as the study treatment. Of these, only one suggested additional benefit in the massage group.[79] In this study, all patients received compression bandaging with the experimental group randomized to receive lymphatic massage three times per week for 4 weeks. Following treatment, there was a greater volume loss in the group receiving massage (56%) compared to those who did not (36%, $p<0.05$). Both groups increased shoulder mobility, with no difference between groups.

Other studies of arm massage generally found significant volume loss in both study groups but no difference between groups, using bandaging alone,[83] elastic sleeve,[75] or a less intensive version of massage as comparators.[74,82] In these studies, the more intensive treatment trended towards improved benefit with lacking statistical significance, in one case being very close with an additional benefit of 39 ml ($p=0.0053$).[74]

Three studies of laser-based treatment were reported. Superiority of laser over exercise,[81] and sham laser were reported.[32] A third study using sham laser as control suggested a difference at some time points but not at study end. No statistical comparisons were given.[78]

Results on the use of diet were conflicting. One study showed no improvement with either a low fat or low caloric diet,[77] while another showed a dramatic improvement in volume loss (349 ml vs. 11 ml), when dietary advice was given in addition to elastic sleeve.[77] Neither of these studies reported a significant difference in skin fold thickness between groups.

Therapy with a Deep Oscillation machine in addition to MLD was found to provide initial benefit to women who experienced swelling of the breast following surgery but this was not apparent at study end. Shoulder mobility was improved in the control group. This was the only study of breast, as opposed to arm, lymphedema in women with breast cancer.[80]

Lower quality trials were more likely to suggest benefit in the study group. Two involving pneumatic compression reported significantly more reduction in arm circumferences when compared to MLD,[63] but less than seen following laser.[64] A study of bone marrow stromal cell (BMSC) transplantation versus decongestive therapy reported greater reductions in excess arm volumes with transplant (81% vs. 55%; $p<0.001$) by study end. Both groups experienced a reduction in pain. The hypothesis for the transplant study was that BMSCs would promote the regeneration and reconstitution of lymphatic vessels.[65] A study of adding exercise as a method of reducing arm volumes did not suggest any improvement.[67] A further study examined the use of manual drainage in addition to physiotherapy in patients who had recently undergone ankle surgery.[66] The authors reported improved lymphedema volume loss with the addition of MLD (6.4%) over physiotherapy alone (0.1%; $p=0.01$).

Question 10: Did any studies show that the time of treatment initiation (single modality or combination therapy) relative to symptom onset, any other lymphedema characteristics, or any patient characteristics influenced or predicted treatment outcome?

A minority of reports (7/28) commented on factors predictive for response to therapy.[72,73,75,79,83,85,86] With only two exceptions,[85,86] studies reporting on predictive factors were RCTs. No RCTs with a low quality score commented on predictive factors.

Pretreatment lymphedema volume was the most commonly reported factor, with contradictory findings. One study of massage and bandaging suggested a greater percentage response in those patients with mild, as opposed to moderate, cases.[83] Another similar study, however, suggested opposite results but did not provide any supporting statistics.[79] A third study suggested that pretreatment volumes were "predictive of treatment response" but did not report the direction of this association.[73] A fourth study examining pneumatic compression reported no influence of lymphedema severity on response.[113] One study also reported a non-significant trend toward better responses in those patients who had been diagnosed with lymphedema for less than 1 year.[83] Another reported no such difference with respect to duration.[113]

One study of MLD suggested that compliance with the use of elastic compression sleeves predicts for a better treatment response.[75]

Two non-randomized studies reported predictive factors on very specific patient populations in which active disease was allowed in the study groups. One report found no difference in the response to decongestive therapy, regardless of the presence or absence of active disease.[85] A further study found that those patients with leg lymphedema from Kaposi's sarcoma had a similar response to elastic stockings, regardless of chemotherapy use.[86]

Across all studies, several factors were not found to predict treatment response, including a history of prior radiation, prior chemo therapy, type of previous surgery, a history of prior infection, age, body mass index (BMI), and gender.

Question 11: What was the length of followup in studies of lymphedema therapy? How long were the benefits of treatment maintained?

Followup periods varied considerably between studies, with little correlation between followup length and study type, intervention or quality. Many studies ended immediately after treatment, with three studies following patient response for up to 1 year.[48,64,86] The shortest of the studies measured patients immediately after a 10 day course of pneumatic compression.[63] One higher quality RCT suggested that the authors would be reporting followup data in a further report; however, that report was published 4 years ago and an update does not appear to be forthcoming.[79]

Of those studies which suggested an initial benefit to therapy and reported followup beyond treatment, some showed a loss of benefit by the end of the study period. One observational study of elastic sleeve or IPC found that both groups had returned to baseline levels 4 to 12 weeks from cessation of treatment. This occurred despite the use of either sleeve or IPC for maintenance.[84] One report suggested a superior response to laser compared with sham treatment at 3 weeks following the last laser treatment. This benefit was lost by 7 weeks. No therapy was used beyond the initial study treatment.[78]

The majority of studies showing durable benefit also provided patients with some form of maintenance therapy.[48,64,65,68,70,71,75,80,86] The majority of those studies used elastic sleeves as maintenance therapy with exceptions being a choice of either massage and sleeve or IPC,[71] exercises,[64] and MLD.[80] Of those studies using elastic sleeves following initial therapy, one was an observational study of ultrasound or mechanical pressure therapy in which both groups showed prolonged benefit up to 52 weeks.[48] Another followed patients with active Kaposi's sarcoma for over 1 year, using an elastic stocking.[86] Only two RCTs showed benefit for up to 1 year with the use of a sleeve. One study compared MLD to sleeve alone at the initiation of treatment, with both groups showing prolonged benefit.[75] The other compared bone marrow stem cell transplant with CDT.[65] In this study, both groups showed continuing benefit at 1 year but more so in the group receiving transplant. One further trial with sleeve as maintenance therapy showed benefit for up to 6 months following comparison with electronically-stimulated lymphatic drainage.[70] A further study of decongestive lymphatic therapy with or without IPC showed continued benefit with maintenance sleeve in both groups at 40 days, with more benefit in the group receiving IPC.[68]

Only two studies showed benefit beyond the initial treatment phase without the use of maintenance treatment. In one study of IPC versus elastic sleeve, the last assessment was only 1 week following active treatment.[73] In the other study, comparing laser versus sham laser, there was lasting benefit in those patients who had received 2 cycles (each cycle being 9 sessions over 3 weeks) of laser, but not those who only underwent one cycle.[32] This benefit was seen 12 weeks following the last treatment.

Question 12: What harms have been reported associated with the various treatments for lymphedema? Do any patient characteristics (e.g., demographics, comorbidities) or etiology of lymphedema increase the risk of these harms?

The value of any intervention can only be determined when benefit is balanced against potential harm. Unfortunately, few of the identified studies reported adverse events. Harms were not reported in any of the five observational studies or the five lower quality RCTs.

Over all, reporting of adverse events was rare. Only 15 of 28 trials reported on harms. Higher quality studies were more likely to report harms. Thirteen of the 18 RCTs with a Jadad score of

4-8 reported on adverse events.[32,46,68,71-73,76-79,81-83] Two of five lower scoring trials reported adverse events.[64,66] In those trials which commented on adverse events, the total number of patients was 535. The majority of patient withdrawals in those studies were due to reasons such as scheduling, failing to show for visits, personal reasons or refusal of therapy. Overall, 36/535 patients (6.7%) were reported as not receiving therapy as intended.[76,77 32,64,66,72,78,82,83] Unfortunately, it was not possible to discern whether refusal of therapy was due to adverse events in these situations.

Other adverse events more specifically addressed were much rarer. Because the majority of trials addressed lymphedema in patients with cancer, more specifically breast cancer, the most common finding reported was recurrence of malignant disease. Overall, 11 patients (2%) were found to have recurrent disease during or shortly after the study period.[32,46,72,76,77,79] Adverse events which may have been specific to therapy were less common, occurring in less than 1 percent of patients, such as infection, "skin reaction"/ dermatitis,[32,83] arm thrombosis,[32,77,114] headache with elevated blood pressure,[68] and arm pain.[83]

Table 2. Quality of sensitivity and specificity studies using QUADAS

	Hayes[97] 2008 Australia	Spillane[107] 2008 Australia	Peer[108] 2007 Canada	Hayes[88] 2005 Australia	Bland[89] 2003 U.S.	Norman[91] 2001 U.S.	Cornish[35] 2001 Australia
1. Was the spectrum of patients representative of the patients who will receive the test in practice?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Were selection criteria clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Is the reference standard likely to correctly classify the target condition?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the tests?	Unclear	Yes	Unclear	Yes	Unclear	Unclear	Unclear
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	No	Yes	Yes	Yes	Yes	Yes	Yes
6. Did patients receive the same reference standard independent of the index test results?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was the execution of the index test described in sufficient detail to permit replication of the test?	No	Yes	Yes	Yes	Yes	Yes	Yes
9. Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
11. Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
13. Were uninterpretable/ intermediate test results reported?	No	No	Yes	Yes	Unclear	Unclear	No
14. Were withdrawals from the study explained?	No	No	No	No	Yes	No	Yes
Quality Rating	Poor	Fair	Fair	Good	Fair	Fair	Fair

Table 3. Quality assessment of reliability studies with modified QUADAS

Study	Were study patients representative of the patients who will receive the test(s) in practice?	Were selection criteria for patients clearly described?	Were correct statistical measures used?	Was execution of test and comparator described in sufficient detail to permit replication in another study?	Were withdrawls from the study explained?	Were intermediate results/incomplete data reported?	Did assessors have adequate professional training to perform test/measurement?	How were raters selected?	Was interval between test-retest appropriate?	Did independent ratings take place within a time frame that would ensure the condition did not change?	Qualityr rating
Chen[30] 2008 Taiwan	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	Yes	Yes	Fair
Deltombe[29] 2007 Belgium	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Fair
Megens[90] 2001 Canada	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	Yes	Yes	Fair
Meijer[92] 2004 Netherlands	Yes	Yes	Yes	Yes	No	No	Unclear	Unclear	Yes	Yes	Fair
Mosley[61] 2008 Australia	Yes	Yes	No	Yes	No	No	Yes	Unclear	Unclear	Unclear	Poor
Norman[91] 2001 U.S.	Yes	Yes	Yes	Yes	No	Unclear	Yes	Yes	Unclear	Unclear	Fair
Roberts[106] 1995 U.K.	Yes	No	Yes	Yes	No	No	Unclear	Unclear	Yes	Yes	Fair
Taylor[27] 2006 Australia	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Unclear	Unclear	Fair

Table 4. Quality assessment of validity studies using modified QUADAS

Study	Were study patients representative of the patients who will receive the test(s) in practice?	Were selection criteria for patients clearly described?	Were the index test and comparator described in sufficient detail to permit replication in another study?	Were withdrawals from the study explained?	Were intermediate results/incomplete data reported?	Did assessors have adequate professional training to perform test/measurement?	Is the comparator test likely to correctly classify the condition?	Were the correct statistical tests used to measure validity?	Was the time period between the application of the index test and the comparator test short enough to ensure the condition did Not change between tests?	Did all patients who received the index test also receive the comparator test?	Were the index and comparator tests performed independently of one another?	Were the results of the index test interpreted without knowledge of the comparator test?	Quality rating (G/F/P)
Armer[26] 2005 U.S.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No	Fair
Armer[36] 2003 U.S.	Yes	Yes	No	No	No	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear	Fair
Cornish[93] 1996 Netherlands	Yes	Yes	Yes	No	No	Unclear	Yes	Unclear	Yes	Yes	Yes	No	Fair
Damstra[99] 2006 Netherlands	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
Gebousky[62] 2008 Czech Republic	Yes	Yes	Yes	No	No	Yes	Unclear	Unclear	Unclear	Yes	Unclear	No	Fair
Halaska[95] 2006 Czech Republic	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Karges[96] 2003 U.S.	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	No	Fair

Table 4. Quality assessment of validity studies using modified QUADAS (continued)

Study	Were study patients representative of the patients who will receive the test(s) in practice?	Were selection criteria for patients clearly described?	Were the index test and comparator described in sufficient detail to permit replication in another study?	Were withdrawals from the study explained?	Were intermediate results/incomplete data reported?	Did assessors have adequate professional training to perform test/measurement?	Is the comparator test likely to correctly classify the condition?	Were the correct statistical tests used to measure validity?	Was the time period between the application of the index test and the comparator test short enough to ensure the condition did Not change between tests?	Did all patients who received the index test also receive the comparator test?	Were the index and comparator tests performed independently of one another?	Were the results of the index test interpreted without knowledge of the comparator test?	Quality rating (G/F/P)
Latchford[105] 1997 Australia	Yes	No	Yes	No	No	Yes	Yes	Yes	Unclear	Yes	Yes	No	Fair
Mayrovitz[110] 2000 U.S.	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Unclear	Yes	Yes	No	Fair
Mayrovitz[100] 2008 U.S.	Yes	Yes	Yes	No	No	Unclear	Yes	Unclear	Yes	Yes	No	No	Fair
Mayrovitz[104] 2009 U.S.	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	No	Unclear	Fair
Meijer[92] 2004 Netherlands	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Yes	No	Fair
Mellor[102] 2004 U.K.	Yes	Yes	Yes	No	No	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear	Fair
Mirnajafi[101] 2004 Australia	Yes	Yes	Yes	Yes	No	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Fair

Moseley[109] 2002 Australia	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Yes	No	Fair
Norman[65] 2001 U.S.	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Fair
Ridner[98] 2007 U.S.	Yes	Yes	Yes	No	No	Yes	Yes	Unclear	Yes	Yes	Yes	No	Fair
Roberts[106] 1995 U.K.	Yes	No	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Szuba[103] 2002 U.S.	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Taylor[27] 2006 Australia	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Unclear	Yes	Yes	No	Fair
Tewari[94] 2008 Australia	Yes	Yes	Yes	Yes	No	Unclear	Yes	Yes	Unclear	Yes	Yes	No	Fair

Table 5. Quality assessment of RCT's with Jadad Scale

Study	Jadad Score	Quality Rating
Radakovk[63] 1993 Yugoslavia	1	Poor
Hou[65] 2008 China	3	Poor
Kessler[66] 2003 Switzerland	3	Poor
McKenzie[67] 2003 U.S.	3	Poor
Kozanoglu[64] 2000 Turkey	3	Poor
Williams[74] 2002 U.K.	4	Fair
Szuba[68] 2002 U.S.	4	Fair
Andersen[75] 2009 U.K.	4	Fair
Johansson[69] 1998 Sweden	4	Fair
Bertelli[70] 1991 Italy	4	Fair
Szuba[71] 2002 U.K.	4	Fair
Shaw[76] 2000 U.K.	5	Fair

Table 5. Quality assessment of RCT's with Jadad Scale (continued)

Study	Jadad Score	Quality Rating
Shaw[77] 2007 U.K.	5	Fair
KavianI[78] 2007 Iran	5	Fair
Didem[79] 2005 Turkey	5	Fair
Dini[72] 1998 Italy	5	Fair
Jahr[80] 2008 Germany	5	Fair
Maiya[81] 2008 Singapore	5	Fair
Sitzia[82] 2002 U.K.	5	Fair
McNeely[83] 2004 Canada	6	Good
Hayes[46] 2000 Australia	6	Good
Wilburn[73] 2006 U.S.	7	Good
Carati[32] 2003 Australia	8	Good

Table 6. Quality assessment of observational studies using Newcastle-Ottawa Scale (NOS)

Study	Type of Study	NOS Star Rating	Quality Assessment
Johansson[87] 1999 Sweden	Cohort	6	Fair
Berlin[84] 1999 Sweden	Cohort	6	Fair
Pinell[85] 2007 U.S.	Cohort	7	Good
Brambilla[86] 2006 Italy	Cohort	8	Good
Balzarini[48] 1993 Italy	Cohort	8	Good

Table 7. Basic data diagnostic studies

Author	Study Type (Reliability, Validity, Sensitivity/ Specificity)	Sample Size	Question # 1a Inclusion/ Exclusion Criteria	Question # 1b Measure of Severity of LE	Question # 1f Frequency of Assessment for LE	Question #1g Outcomes
Armer[26] 2005 U.S.	Validity	n=221	Persons diagnosed with BCa, scheduled for Rx, no prior history of LE or BCa, >18 years of age in the Midwest	NR	5 quarterly assessments to track incidence of LE	NR
Armer[36] 2003 U.S.	Validity	n=80	40 women with LE, 40 healthy control, no history of breast Ca or LE	NR	2 assessments to measure validity	NR
Bland[89] 2003 U.S.	Sensitivity and Specificity	n=32 with LE n-58 without LE	Newly diagnosed resectable BCa. Age: ≥18 years, male or female, average age 53.7 years, all female, half of patients had radiation therapy Eligible patients were scheduled for mastectomy or lumpectomy, with lymph node sampling, dissection, or sentinel node biopsy, or breast conservation therapy followed by radiation therapy Previous axillary surgery or radiation, planned mastectomy without axillary surgery or radiation therapy, inability to provide consent, or no plans to followup after surgery	NR	3 assessments per year for up to three years	NR

Abbreviations: AIDS-KS=Acquired Immune Deficiency Syndrome-Karposi's Sarcoma, BCa=Breast Cancer, BIS=Bioimpedance Spectroscopy, Dx=diagnosis HV=healthy volunteer, LE=Lymphedema, MFBIA=Multifrequency Bioelectrical Impedance, NR=Not Reported, Pts=Patients, RT=Radiotherapy, Rx=Treatment, SD=Standard Deviation

Table 7. Basic data diagnostic studies (continued)

Author	Study Type (reliability, validity, Sensitivity/ Specificity)	Sample Size	Question # 1a Inclusion/ Exclusion Criteria	Question # 1b Measure of Severity of LE	Question # 1f Frequency of Assessment for LE	Question #1g Outcomes
Chen[30] 2008 Taiwan	Reliability	Total n=31 Trial 1: Water displacement and circumference n=14 Trial 2: Tonometry n=17	Pts who developed LE after breast carcinoma surgery Those with skin problems or wounds around measurement areas	NR	Single assessment	NR
Cornish[35] 2001 Australia	Sensitivity and Specificity	n=102 LE patients n=60 healthy control	102 pts with BCa from 25 to 82 years old, living within 50km of Brisbane 60 female volunteers	NR	Maximum of 14 assessments to examine Dx capability of BIS	NR
Cornish[93] 1996 Netherlands	Validity	LE patients n=20 Control n=20	Pts with ≥Grade II unilateral LE of upper limb after surgery and/or radiotherapy for BCa. Mean age 60 yrs (32-78) Controls volunteers from clinic and staff	NR	Daily measurements for four weeks as part of treatment protocol	NR
Damstra[99] 2006 Netherlands	Validity	n=25	Females suffering from LE age range 47-82 years (mean ± SD: 61.7±9.5); complete and partial mastectomy following BCa surgery axillary node dissection No signs of metastasis	NR	Multiple assessments to permit study of test-retest or interrater reliability	NR

Deltombe[29] 2007 Belgium	Reliability	n=30 LE patients	Women with chronic arm LE secondary to unilateral BCa Rx Dx was clinically evident LE All had axillary lymph node dissection, 27 total mastectomy, 3 partial mastectomy, 8 chemotherapy, 29 radiation. Age range 46 - 79 years (mean 63.9 ± 9 years)	NR	Single assessment	NR
Gebousky[62] 2009 Czech Republic	Validity	n=88 women	Women with suspicion of unilateral secondary LE of upper limbs due to BCa Rx, aged 39-84 years (60.2±10.4)	5-point ordinal scale to grade severity	2 assessments to measure validity	NR
Halaska[95] 2006 Czech Republic	Validity	Total n=101 Group A n=60 (circumference & MFBIA): subgroups A1 n=7 (circumference & MFBIA 1-100kHz & water displacement), A2 n=20 (& MFBIA 200kHZ) Group B n=5 (circumference & MFBIA); Group C n=36 (circumference & MFBIA)	Group A: healthy women as control, mean age 40.20 years (22-75yrs) Group B: pronounced LE, mean age 63.3 years (55-78 yrs) Group C: undergoing BCa surgery, mean age 60.0 years (37-76yrs)	NR	Single assessment	NR

Hayes[88] 2005 Australia	Sensitivity and Specificity	Total n=294 clinical component n=218 data complete n=176	Women diagnosed unilateral BCa ≤6 months Age: ≤75 years, residing within 100km of Brisbane	NR	Single assessment	NR
Hayes[97] 2008 Australia	Sensitivity and Specificity	n=287	Women with unilateral breast cancer (BCa) with or without LE after Rx age: <75 years, (aged 54±10 years on average) residing within 100km of Brisbane	NR	5 assessments at 3 mo intervals 6 to 18 mo post surgery	NR
Karges[96] 2003 U.S.	Validity	n=14	Dx of upper-extremity LE and receiving intervention, 12 postmastectomy LE and 1 LE from traumatic accident Selected in a consecutive manner. Sample of convenience	NR	Multiple assessments to permit study of test-retest or interrater reliability	NR
Latchford[105] 1997 Australia	Validity	n=15	15 consecutive patients with Grade 1, unilateral post-mastectomy LE, with mean age of 60 years	NR	2 assessments to measure validity	NR
Mayrovitz[100] 2008 U.S.	Validity	n=10	Ten women (mean 71 +/- SD 14.1) with unilateral LE subsequent to BCa surgery or radiation Rx	NR	4 assessments	NR
Mayrovitz[104] 2009 U.S.	Validity	n=30	10 women with unilateral arm LE subsequent to BCa surgery or RT 20 women with no history of LE	NR	4 assessments to compare single vs. 3 measures of tissue dielectric constant	NR

Mayrovitz[110] 2000 U.S.	Validity	Total pts n=62 legs n=142 arms n=42	Patients referred to an outpatient wound healing and LE center	NR	2 assessments pre and post treatment	NR
Megens[90] 2001 Canada	Reliability	n=25	Women at risk for LE who had undergone axillary lymph node dissection surgery for BCa age range 35-67 years	NR	Multiple assessments to permit study of test-retest or interrater reliability	NR
Meijer[92] 2004 Netherlands	Reliability and Validity	n=18 right upper extremity n=12 left upper extremity	BCa Rx-related LE of upper extremity Age: ≥18 years (mean 56.4 ± 11.6 SD) Co-morbidity, recent operations on the upper extremity, inability to elevate the upper extremity 90 degrees in the shoulder girdle, inability to extend the elbow	NR	Multiple assessments to permit study of test-retest or interrater reliability	NR
Mellor[102] 2004 U.K.	Validity	n=10	Ten women (mean 59 +/- SD 9) with LE subsequent to unilateral BCa surgery or radiation Rx Skin disease or skin trauma	NR	2 assessments to measure validity	NR
Mirnajafi[101] 2004 Australia	Validity	n=17	Seventeen women with unilateral arm LE secondary to axillary clearance and RT Skin comorbidities	NR	2 assessments to measure validity	NR

Moseley[61] 2002 Australia	Reliability	n=12 healthy volunteers n=12 LE patients	Women who had breast conserving surgery for BCa (± radiotherapy ± chemotherapy) ≥12 months ago and who were in remission. Aged 48-82 years (mean 61.6 ± 9.7 years); time since surgery range 2 - 20 years (mean 8.7 ± 4.7 years)	NR	Single assessment	NR
Mosely[109] 2002 Australia	Validity	n=33 n=28 women n=5 men	Secondary LE (28 women, 5 men) aged 39-88 years (mean 59 ± 13 years) with a Dx of LE of lower extremities	NR	5 assessments to study correlation of BIS and perometry over time	NR
Norman[91] 2001 U.S.	Sensitivity and Specificity and reliability	Total n=43 measured independently by 2 physical therapists for interobserver agreement n=25	LE following Rx for BCa. 41 unilateral, 2 bilateral mean age 54.1 years; all female; all women had LE diagnosed by their therapists	Comparing circumferential differences between affected and unaffected arms	Multiple assessments to permit study of test-retest or interrater reliability	NR
Peer[108] 2007 Canada	Sensitivity and Specificity	n=40	21 men and 19 women, mean age 36.68 years, range 20 - 71 years) with AIDS-KS; Dx confirmed by titer and biopsy Children, pregnant/lactating women, patients undergoing Rx	NR	Single assessment	NR

Ridner[98] 2007 U.S.	Validity	Study completers n=31 Data included n=25 Healthy volunteers (HV) n=14 LE patients n=11	HV group: ≥18 years with no self reported LE or BCa LE group: ≥18 years with BCa Rx LE in one arm only no swelling or primary LE before BCa Rx, no medical contraindications; no pregnant women; no metal implants or pacemakers that would interfere with impedance measurements	NR	Single assessment	NR
Roberts[106] 1995 U.K.	Validity and Reliability	n=15	14 subjects with LE 1 healthy subject	NR	Two sets of 2 assessments to measure test-retest reliability and validity	NR
Spillane[107] 2008 Australia	Sensitivity and Specificity	n=66	Inguinal or ilio-inguinal dissection for melanoma >6 months previous 31 male, 35 female Age: median 44.2 years (range, 20 - 95 years) 9 received radiotherapy	NR	Single assessment	NR
Szuba[103] 2002 U.S.	Validity	n=19	19 consecutive prospectively identified patients with post-mastectomy LE (average age 67+/- 10.1 years) Exclusion: recurrent or active malignancy	8-point scoring system	2 assessments to measure validity	NR

Taylor[27] 2006 Australia	Reliability and Validity	BCa and LE n=22, BCa no LE n=19, control n=25	BCa patients and from healthy controls. All women	NR	Multiple assessments to permit study of test-retest or interrater reliability	NR
Tewari[94] 2008 Australia	Validity	Total n=87 arms measured n=174	Women from a breast clinic with sentinel node biopsy with axillary clearance for BCa, mean age 58.6 years (range 17-81 years)	NR	Single assessment	NR

Table 8. Psychometric properties of diagnostic studies

Author	Test(s)	Sample Size	Reliability	Validity	Responsiveness
Armer[26] 2005 U.S.	Circumferential measurements, infrared laser perometry LE and Breast Cancer Questionnaire (LBCQ)	n=221	NR	Tests (Incidence of lymphedema 6 months/12 months) 200mL difference in limb volume (24%/42%) 10% change in limb volume (8%/21%) 2 cm change in limb volume (46%/70%) LBCQ (19%/40%)	NR
Armer[36] 2003 U.S.	Lymphedema Breast Cancer Questionnaire (LBCQ) vs. arm circumference measurements	n=40 LE group n=40 Control group	NR	LBCQ be predictive of ≥2cm difference in arm circumference	NR
Bland[89] 2003 U.S.	Index Test: Circumferential measurements Reference Test: 10% change or more in volume. 1 cm change in circumference at any site	n=90	NR	NR	NR
Chen[30] 2008 Taiwan	Water displacement Circumference measurement Tonometry	Total n=31 Trial 1: Water displacement and circumference n=14 Trial 2: Tonometry n=17	ICCs for test-retest and interrater reliability ranged from 0.69 to 0.88	NR	Defined as smallest difference detectable 75 ml for water displacement 0.46 to 1.02cm for limb circumference measurement 0.32 to 1.01mm for tissue resistance

Abbreviations: BCa=Breast Cancer, BIS=Bioimpedance Spectroscopy, BMI=Body Mass Index, ICC=intraclass correlation, IWV=Inverse water Volumetry, LBCQ=Lymphedema Breast Cancer Questionnaire, LE=Lymphedema; MFBIA=Multiple Frequency Bioelectrical Impedance Analysis, NR=Not Reported (indicates that no information on this item was contained in the published study), SOAC=Sum of Arm Circumference, TDC=Tissue Di-electric constant

Table 8. Psychometric properties of diagnostic studies (continued)

Author	Test(s)	Sample Size	Reliability	Validity	Responsiveness
Cornish[35] 2001 Australia	Index Test: MFBIA Reference Test: Limb circumference	n=102 LE patients n=60 healthy control	NR	NR	NR
Cornish[93] 1996 Netherlands	Bioimpedance daily measurements vs.circumferential measurements taken daily throughout 4 weeks of lymphedema treatment	n=20 LE Patients n=20 Control	NR	Bias scores decreased from 31% to 15% between 1 and 26 days of followup. Lower bias scores indicate better agreement	NR
Damstra[99] 2006 Netherlands	Inverse water volumetry vs. circumferential measurements (Herpertz method)	n=25	NR	ICCs ranged from 0.89 to 0.91	NR
Deltombe[29] 2007 Belgium	Circumferential measurements using frustum sign method and the disk model method, water displacement, and optoelectronic volumetry	n=30 LE patients	ICC for interrater reliability: Frustrum sign 0.937 Disk method 0.990 Water 0.987 Opto-Electronic 0.997 ICC for intrarater reliability: Frustrum sign 0.958 Disk method 0.989 Water 0.991 Opto-Electronic 0.997	NR	NR

Gebousky[62] 2009 Czech Republic	Index Test: Lymphoscintigraphy Reference Test: Clinical examinations	n=88 Number of limbs n=176	NR	Model predicts expert's conclusions on lymphedema in 95% of the cases	NR
Halaska[95] 2006 Prague	Multifrequency bioelectrical impedance, circumferential measurements, subgroup with water displacement	Total n=101 Group A n=60 (circumference & MFBIA):subgroups A1 n=7 (circumference & MFBIA 1-100kHz & water displacement), A2 n=20 (& MFBIA 200kHZ) Group B n=5 (circumference & MFBIA); Group C n=36 (circumference & MFBIA)	NR	Correlation between circumferential measurements and water displacement was 0.94	NR
Hayes[88] 2005 Australia	Index Test: Multifrequency bioelectrical impedance Reference Test: Sum of arm circumference and self report	Total n=294 Clinical component n=218 Data complete n=176	NR	NR	NR
Hayes[97] 2008 Australia	Index Test: Bioimpedance spectroscopy Reference Test: Comparator: Sum of arm circumference and self report	n=287	NR	NR	NR

Karges[96] 2003 U.S.	Volumetric measurements taken with a volumeter minus fingers (UE-F) circumferential measures taken with a tape measure, calculated volume formula using truncated cone formula	n=14	NR	Correlation coefficient for volumetric measurements and tape measure was 0.98	NR
Latchford[105] 1997 Australia	Arm circumference measurements every 10 cm vs. arm circumference measurements every 4 cm	n=15	NR	Correlations between interval measures of 10cm and 3.81 cm was 0.94	NR
Mayrovitz[100] 2008 U.S.	Tissue Di-electric constant	n=10	NR	Correlations were 0.99 for the nonedematous arm, and 0.98 for the edematous arm	NR
Mayrovitz[104] 2009 U.S.	One Tissue Di-electric constant measurement vs. average Tissue Di-electric constant measurements	n=10 LE group n=20 Control group	NR	Correlation between single TDC measurement and average TDC measurements were: Edematous arm: 0.98 Non-edematous arm: 0.99	NR
Mayrovitz[110] 2000 U.S.	Circumference measurements: Manual (Gulick tape measure) vs. automated (optoelectric system [Pero-System, Perometer Model 350S})	Total pts n=62 legs n=142 arms n=42	NR	Correlation coefficients between measures were 0.98 for legs and 0.96 for arms	NR

Megens[90] 2001 Canada	Circumference and volume measurements	n=25	ICCs for interrater and test-retest reliability: Circumferential data 0.99 Volumetric data 0.99	NR	NR
Meijer[92] 2004 Netherlands	Indirect volume determination (Sitzia's method) vs water displacement	n=30	Intrarater reliability for water displacement ranged from 0.95 to 0.98 Intrarater reliability for Sitzia's method ranged from .90 to .99 with one low ICC of .62	Comparing Sitzia's method to water displacement: ICCs ranged from 0.71 to 0.87 Comparison of arm circumference measures at 4 cm with measures at 8 cm ICCs of 0.80 for one rater and 0.92 for a second rater	NR
Mellor[102] 2004 U.K.	Dermascan ultrasound	n=10	NR	Ultrasound strongly correlated with arm circumference, r=0.95	NR
Mirnajafi[101] 2004 Australia	Torsional rigidity of skin	n=17	NR	Power to rotate normal skin exceeded power to rotate diseased skin by 46.3%. Not significant (p=0.13)	NR

Moseley[61] 2002 Australia	Bioimpedance vs. Tonometry	n=12 healthy volunteers n=12 LE patients	Covariance for bioimpedance ranged from 0.002 to 0.0086 Covariance for tonometry ranged from 0.0129 to 0.0325	NR	NR
Moseley[109] 2002 Australia	Perometry and bioimpedance	n=33	NR	Correlation coefficient between perometry and bioimpedance was 0.61	NR
Norman[91] 2001 U.S.	Index Test: Self report questionnaire Reference Test: arm circumference	Total n=43 Measured independently by 2 physical therapists for interobserver agreement n=25	Interobserver agreement high, weighted kappa of 0.80	Weighted kappas ranged from 0.70 to 0.84	NR
Peer[108] 2007 Canada	Index Test: ^{99m}Tc-MIBI Whole Body Scan Reference Test: Clinical assessment	n=40	NR	NR	NR
Ridner[98] 2007 U.S.	Circumference measurements, infrared laser perometry, bioelectrical impedance (BIS) and lymphedema and breast cancer questionnaire (LBCQ)	Study completers n=31 Data included n=25 Healthy volunteers (HV) n=14 LE n=11	NR	Correlations among instruments ranged from 0.71 to 0.99 Significant correlation LBCQ and tests for swelling (0.61-0.76) and tightness (0.61-0.68)	NR
Roberts[106] 1995 U.K.	Modified Harpenden Skinfold Calipers Arm volume measurements	n=14 LE patients n=1 Healthy subject	Coefficient of standard variation of 5%	Correlation between caliper measures and questionnaire scores was 0.75	NR

Spillane[107] 2008 Australia	Index Test: Infrared optoelectronic perometer technique Reference Test: circumference measurements, brief questionnaire	n=66	NR	NR	NR
Szuba[103] 2002 U.S.	Quantitative radionuclide lymphoscintigraphy	n=19	NR	Correlation of outcome of therapy with pre-therapeutic axillary radioactivity level r=0.5	NR
Taylor[27] 2006 Australia	Circumferential measurements vs. water displacement	Total n=66 n=22 BCa w/o lymphedema n=19 BCa with lymphedema, n=25 control group	Interrater reliability for circumferential measurements ranged from 0.97 to 0.99 Interrater reliability for water displacement measurements ranged from 0.94 to 0.99	Correlations between methods was 0.98	Standard error of mean ≤150mL
Tewari[94] 2008 Australia	Circumferential measurements	n=87 total n=174 arms measured	NR	Pearson's correlation between circumferential and volumetric measurements was 0.92 for narrow tape and 0.88 for wide tape	NR

Table 9. Sensitivity and specificity studies

Author	Study Design	Sample Size	Inclusion/Exclusion Criteria	Index Test	Reference Test	Sensitivity/Specificity
Bland[89] 2003 U.S.	Sensitivity/Specificity	n=90	≥18 years, male or female eligible. New diagnosed resectable BCa. Scheduled for mastectomy or lumpectomy, with lymph node sampling, dissection, or sentinel node biopsy, or breast conservation therapy followed by radiation therapy. Participants average age was 53.7 years, all female, half of patients had RT	Percent change in circumferential measurements above and below the elbow	10% change or more in volume. 1 cm change in circumference at any site	Sensitivity 37% and Specificity 92% for a 10% change in circumference above and below elbow Sensitivity 80% and Specificity 71% for a 5% change in circumference above and below elbow
Cornish[35] 2001 Australia	Sensitivity/Specificity	n=102 n=60 control	Dx BCa, living within 50 km of Brisbane pathological confirmation of tumor malignancy Axillary dissection	Bioimpedance (BI)	Limb volume	Sensitivity BI vs. limb Volume=100% Specificity BI=98%
Hayes[88] 2005 Australia	Sensitivity/Specificity	Total n=294 Clinical component n=218 Data complete n=176	Dx with unilateral BCa ≤6months, aged ≤75 years, residing within 100km of Brisbane	MFBIA	SOAC Self report	Difference in SOAC>5cm: Sensitivity 35%, Specificity 89%. Difference in SOAC >10cm: Sensitivity 5%, Specificity 100%; Self report Sensitivity 65%, Sensitivity 77%
Hayes[97] 2008 Australia	Sensitivity/Specificity	n=287	Women with unilateral BCa <75 years, (avg 54±10 years) residing within 100km of Brisbane; with or without LE after Rx	BIS	SOAC Self report	Sensitivity 42% SOAC vs. BIS, Specificity 88% Sensitivity 61% Self report vs. BIS, Specificity 59%

Abbreviations: AIDS-KS=Acquired Immune Deficiency Syndrome-Karposi's Sarcoma, BCa=Breast Cancer, BI=Bioimpedance, BIS=Bioimpedance Spectroscopy, Dx=Diagnosis LE=Lymphedema, MFBIA=Multifrequency Bioelectrical Impedance, Rx=treatment, SOAC=Sum of Arm Circumference

Table 9. Sensitivity and specificity studies (continued)

Author	Study Design	Sample Size	Inclusion/Exclusion Criteria	Index Test	Reference Test	Sensitivity/Specificity
Norman[91] 2001 U.S.	Sensitivity/Specificity, reliability and validity	Total n=43 measured independently by 2 physical therapists for interobserver agreement n=25	LE following Rx for BCa; 41 unilateral, 2 bilateral; mean age 54.1 years; all female; all women had LE diagnosed by their therapists	Self report questionnaire	Clinical assessment (limb circumference measurement)	Questionnaire sensitivity 93 to 96% and Specificity 69 to 75% for the Dx of LE
Peer[108] 2007 Canada	Sensitivity/Specificity	n=40	21 men and 19 women, mean age 36.68 (20-71) years with AIDS-KS; Dx confirmed by titer and biopsy	^{99m}Tc-MIBI Whole Body Scan	Clinical assessment	18/40 subjects diagnosed with LE using ^{99m}Tc-MIBI 12/40 subjects diagnosed with LE using clinical examination
Spillane[107] 2008 Australia	Sensitivity/Specificity	n=66	Patients who had previously undergone an inguinal or ilio-inguinal dissection for melanoma >6 months previous, 31 male, 35 female, median age 44.2 (20-95) years range (20-95 years), 9 received RT	Infrared optoelectronic perometer technique	Arm circumference Self assessment questionnaire	Sensitivity 56% and Specificity 95% for perometry vs. self assessment Sensitivity 50% and Specificity 100% for perometry vs. arm circumference

Table 10. Treatment basic study data

Study	Study Design	Type of Treatment	Sample Size	Cause of Lymphedema	Definition of Lymphedema	Co-morbidities	Other inclusion/Exclusion Criteria
RCT'							
Andersen[75] 2000 Denmark	Prospective Randomized Study	MLD as adjunct therapy	Intervention: n=20 Control: n=22	≥4 months post surgery LE secondary to BCa treatment	1+ LE symptoms volume ≥ 200ml between arms and/or ≥ 2cm circumference difference	NR	Exclusion: - bilateral BCa - treatment for LE during previous 3 mos - BCa recurrence - severe LE arm volume difference >30%
Bertelli[70] 1991 Italy	RCT	Electronically stimulated lymphatic drainage (ESLD)	n=37 ESLD n=37 Control	LE secondary to unilateral radical, modified mastectomy or quadrantectomy with axillary node dissection	Mild LE (delta value >10cm and <20 cm)	NR	Inclusion: - no evidence of distant metastases or local relapse - no Rx in last 6 mos - no signs of lymphangitis Exclusion: - wearing a cardiac stimulator - currently receiving CT or RT
Carati[32] 2003 Australia	RCT crossover plus within group comparison of one cycle vs. two cycle	LLLT one cycle vs. LLLT two cycles	n=37 n=27	LE secondary to BCa treatment	>200ml difference between arms or ≥2 cm difference in arm circumference	NR	Inclusion: - female Exclusion: - presence of comobidities - significant change to the arm in past 3 months - inability to abduct arm for measurement - presence of primary LE of lower limbs

Abbreviations: BCa=Breast Cancer, BMI=Body Mass Index, BMSC=Bone Marrow Stromal Cell Transplantation, Ca=Cancer CB=Low stretch compression bandaging, CDP=Complex Decongestive Physiotherapy, CDT=Complex Decongestive Physiotherapy, CT=chemotherapy, DLT=Decongestive Lymphatic Therapy, ESLD=Electronically Stimulated Lymphatic Drainage, IPC=intermittent pneumatic compression, ISL=International Society of Lymphology, LE=Lymphedema, LLLT=Low-level Laser Treatment, MLD=Manual Lymph Drainage, mo=Month, NR=Not Reported, PC=Pneumatic Compression, pts=patients, RT=Radiation Therapy, RCT=Randomized Control Trial, RT=radiotherapy, Rx=Treatment, SEPC=Sequential External Pneumatic Compression, SLD=Simple Lymphatic Drainage, SP=Standard Physiotherapy, SPC=Sequential Pneumatic Compression, UE=Upper extremity, UST=Ultrasound therapy

Table 10. Treatment basic study data (continued)

Study	Study Design	Type of Treatment	Sample Size	Cause of Lymphedema	Definition of Lymphedema	Co-morbidities	Other Inclusion / Exclusion Criteria
Didem[79] 2005 Turkey	RCT	Complex Decongestive Physiotherapy vs. Standard Physiotherapy	n=27 CDP n=26 SP	LE following BCa surgery and/or RT/CT	Arm circumference difference of 2-5 cm	NR	Inclusion: - LE ≥1 year Exclusion: - obvious psychiatric Illness - severe pain in axillary region - severe cardiac disease - uncontrolled hypertension - malignancy
Dini[72] 1998 Italy	RCT	IPC	n=40 IPC n=40 Control	LE following BCa surgery and/or RT/CT	Arm circumference difference of 2-5 cm from unaffected arm	NR	Inclusion: - LE ≥1 year - no lymphangitis - no evidence of local or distant relapse - no other serious or psychiatric illness that would preclude treatment or follow-up Exclusion: - prior specific therapy for LE - bilateral breast surgery - bilateral axillary node dissection

Hayes[46] 2009 Australia	RCT	Mixed exercise program (aerobic and resistance)	n=16 Exercise n=16 Control	LE secondary to BCa treatment	Upper limb LE diagnosed by a health professional	NR	Inclusion: - women <76 years with completed Rx for unilateral BCa ≥ 6 months prior - able to travel to clinic for exercise for 12 weeks
Hou[65] 2008 China	RCT	Bone Marrow Stromal Cell Transplantation or Complex Decongestive Therapy	n=15 BMSC n=35 CDT	Lymphedema secondary to breast cancer	NR	NR	Exclusion: - radiotherapy
Jahr[80] 2008 Germany	RCT	Deep Oscillation® (DO) plus MLD	n=11 DO + MLD n=10 MLD	LE secondary to BCa treatment	NR	NR	Inclusion: - age 18-80 years, updated documentation of aftercare - pt living near study center - ≥6 weeks since RT Exclusion: - Deep Oscillation® Rx in 3 months preceding study - acute inflammation - acute thrombosis - heart disease - electronic implant - pregnancy subject - sensitivity to electric fields

Johansson[69] 1998 Sweden	RCT	MLD vs. sequential pneumatic compression	n=14 MLD n=14 SPC	Unilateral LE after BCa surgery with axillary nodal dissection	>10% difference in LE affected arm vs. unaffected arm	NR	Exclusion: - previous contralateral breast disease - intercurrent disease affecting the swollen arm - difficulty participating for reasons such as dementia - treatment within the last 6 mos (except for wearing compression sleeve) - resolution of LE during initial use compression sleeve by all participants
Kaviani [78] 2006 Iran	RCT	LLLT	n=4 LLLT n=4 Control	LE secondary to BCa treatment	≥2 cm swelling in affected arm	NR	Inclusion: - no contraindications to laser therapy Exclusion: - metastatic disease
Kessler[66] 2003 Switzerland	RCT	Standard physiotherapy plus manual lymphatic drainage	n=11 SP and MLD n=12 SP	LE following hindfoot surgery	Clinically diagnosed post-operative swelling	NR	- Age: 18-75 yrs - good physical condition - no contraindications for lymph drainage

Kozanoglu[64] 2009 Turkey	RCT	Pneumatic compression vs. low level laser therapy	n=25 PC n=25 LLLT	Modified radical mastectomy with complete axillary dissection and radiotherapy	LE defined as difference of more than 2 cm at 3/7 points		Inclusion: - history of arm LE for at least 3 months Exclusion: - metastases - ongoing RT - cellulitis - venous thrombosis - inflammatory disease - history of severe trauma - photosensitivity - medications that affect electrolyte balance - limitation in UE joints - physical therapy other than skin care - home exercises for LE in past 6 months
Maiya[81] 2008 India	RCT	LLLT and exercise	n=10 LLLT + exercise n=10 control (compression + exercise)	LE secondary to BCa treatment	circumference of UE 2 cm at any 2 points compared to normal limb	NR	Inclusion: - mastectomy for BCa - completion of RT Exclusion: - primary LE - infection of the limb
McKenzie[67] 2003 Canada	RCT	Exercise (resistance training plus arm ergometer)	n=7 Exercise n=7 Control	LE secondary to BCa	LE >2 cm and <8 cm at 1 measurement point	NR	Exclusion: - stage III LE - bilateral disease - medication that effects swelling

McNeely[83] 2004 Canada	RCT	MLD with CB vs. CB alone	n=22 intervention n=20 control	LE secondary to BCa	≥150 ml difference between arms	NR	Inclusion: - ≥ 4 months since wearing compression sleeve - ≥6 months since active Rx for LE Exclusion: - local Ca recurrence - distant metastases - undergoing RT or CT - infection in LE limb - evidence of contraindications to Rx - uncontrolled hypertension - heart disease - renal insufficiency - venous thrombosis
Radakovic[63] 1998 Yugoslavia	RCT	Manual drainage vs. sequential external pneumatic compression	n=18 manual drainage n=18 SEPC	Women with amputated breast and axillary gland	NR	NR	Inclusion: - women with no sign of metastatic changes - patients referred after RT
Shaw [76] 2007 U.K.	RCT	Weight reduction program along with conventional treatment with compression hosiery	n=21 intervention n=11 control n=10	Arm LE following surgery for BCa	Affected arm volume ≥15% larger than unaffected	May or may not have been receiving hormone treatment	Inclusion: - remission from Ca - BMI ≥25 kg/m²
Shaw [77] 2007 U.K.	RCT	Diet intervention plus multilayer bandaging then compression hosiery or hosiery alone	n=19 weight reduction n=17 low fat diet n=15 control	Arm LE secondary to BCa treatment	≥20% greater volume than unaffected arm	NR	Inclusion: - Ca remission

Sitzia[82] 2002 U.K.	RCT	MLD vs. SLD	n=15 MLD n=13 SLD	LE secondary to BCa	Moderate or severe edema (≥20%)	NR	Inclusion: - 18+ yrs - no active disease - no previous Rx except support hosiery
Szuba[68] 2002 U.S	Study 1 Randomized prospective study	IPC as adjunct therapy to decongestive lymphatic therapy	Study 1 n=12 IPC and DLT n=11 DLT	Study 1 unilateral BCa related LE	≥20% increase in volume compared to unaffected arm	NR	Inclusion: - ≥12 wks post Rx Exclusion: - active infection - Ca recurrence - concomitant venous occlusion
Szubz[71] 2002 U.S.	Study 2: Randomized controlled crossover study	IPC as adjunct therapy to daily maintenance (compression garment, self administered manual lymphatic massage)	Study 2: n=13 maintenance n=12 maintenance + IPC	Study 2 unilateral BCa related chronic LE	NR	NR	Inclusion - completed intensive DLT ≥1 mo and < 1 yr previously Exclusion: - active infection - Ca recurrence - concomitant venous occlusion - bilateral LE of upper extremity
Wilburn[73] 2006 U.S.	RCT crossover trial with 30 day washout period	IPC Maintenance Therapy Flexitouch™ vs. standard care (self-administered message plus elastic compression garment	n=5 Flexitouch n=5 control	Unilateral, BCa associated LE	≥10% volume increase over normal arm	NR	Exclusion: - bilateral LE of upper extremity - active Ca - active infection - clinical evidence of venous obstruction or active thrombophlebitis - pulmonary edema - congestive heart failure - history of pulmonary embolism - contraindications to the Rx used in study

Williams[74] 2002 U.K.	Randomized Controlled Crossover	MLD and SLD	Group A: n=15 Group B: n=16	LE secondary to BCa	>10% excess volume measured two times	NR	Inclusion: - >3 months, >1 yr post Ca Rx Exclusion: - active Ca - odema-influencing drugs
Observational Studies							
Balzarini[48] 1993 Italy	Cohort	Ultrasound Therapy	n=50 treatment n=100 control	LE Secondary to BCa	% difference between arms Mild ≤6.5% Moderate 6.5 to 13% Severe ≥13%	NR	Inclusion: - chronic arm LE Exclusion: - patients who underwent regional RT
Berlin[84] 1999 Sweden	Cohort	Compression with sleeves vs. intermittent compression with Flowtron vs. intermittent compression Lympha-Press + compression sleeves	Total: n=46 Group 1: n=28 Group 2: n=8 Group 3: n=19 *actual total is 55	LE secondary to BCa surgery	≥100ml difference between arms	NR	
Brambilla[86] 2006 Italy	Cohort	Elastic compression stockings	n=50 Elastic stockings n=15 Control	Classic Kaposi's sarcoma-associated LE	Grade II LE according to ISL	NR	Inclusion: - LE limited to below the knee

Johansson[87] 1999 Sweden	Cohort	CB vs CB + MLD	n=18 CB group n=20 CB+MLD	Unilateral arm LE after BCa surgery with axillary nodal dissection	≥10% difference in volume between abnormal and normal arm	NR	Exclusion: - contralateral breast disease - intercurrent disease affecting the swollen arm - difficulty participating for reasons such as dementia - Rx within the last 6 mos (except for wearing compression sleeve)
Pinell[85] 2007 U.S.	Cohort	Manipulative therapy plus bandaging	n=16 LE patients with associated chest wall/axillary or pelvic/inguinal tumors n=56 LE patients without mass	Cancer survivors with LE previously treated with surgery, RT or both	≥2 cm difference in girth between patient's limbs	NR	Inclusion: - referred to 2 Atlanta area clinics

Table 11. Key questions treatment

Study	Question # 3 Time of Lymphedema Onset Time of Rx initiation Criteria used to Start/stop therapy	Question # 4 Provider of Treatment and Qualifications	Question # 7 Treatment Parameters	Question #8 Comparators in Study Consistent With Usual Care	Question #9 Patient Outcomes Results	Question #11 Length of Study Length of Followup	Question #12 Did any Harms (adverse events) Occur From Rx?
RCT's							
Andersen[75] 2000 Denmark	LE onset: After surgery Time Rx start: ≥ 4 months from BCa Rx Criteria to start Rx: Unilateral LE of arm after early treatment of breast cancer Criteria to stop Rx: NR	"an experienced and certified lymphotherapist according to the Vodder school of practice"	Intervention Group: standard care + MLD and training in self-massage. Standard care=custom-made sleeve and glove garment providing 32-40 mmHg compression; educational information and recommendations; instruction in physical exercises; education in skin care. MLD=8 1hr session over 2 wk period Control Group: Standard care as described above (control group was allowed to crossover to treatment group after 3 mths)	Comparator was standard care Usual care	Change in volume of affected arm patient-reported symptoms related to LE No significant difference in arm volume or patient-reported symptoms between the 2 groups	Length of study: 2 weeks Length of followup: 12 months	NR

Abbreviations: AROM=Active Range of Motion; BCa=Breast Cancer; BMI=Body Mass Index; BMSC=Bone Marrow Stomal Cell Transplantation; CB=Low stretch compression bandaging; CDP=Complex Decongestive Physiotherapy; CDT=Complex Decongestive Therapy; DLT=Decongestive Lymphatic Therapy DO®=Deep Oscillation; ESLD=Electronically Stimulated Lymphatic Drainage; HRQOL=health related quality of life; KS=Karposi's Sarcoma; LC=Limb Circumference; LE=Lymphedema; LLLT=Low-level Laser Therapy; LS=Lymphedema Specialist Nurse; MLD=Manual Lymph Drainage; MPT=mechanical pressure therapy; NR=Not Reported; NS=No Significance; PC=Pneumatic Compression; PCEV=Percentage Change in Excess limb Volume; PML=Post Mastectomy Lymphedema; PT=physical therapist; pts=patients; RT=Radiation Therapy; QoL=Quality of Life; RCT=Randomized Control Trial; ROM=Range of Motion; Rx=Treatment; SEPC=Sequential External Pneumatic Compression; SF-36=short form 36; SLD=Simple Lymphatic Drainage; SP=Standard Physiotherapy; SPC=Sequential Pneumatic Compression; UST=Ultrasound therapy; VAS=visual analogue scale; wk=week; wks=weeks

Table 11. Key questions treatment (continued)

Study	Question # 3 Time of Lymphedema Onset Time of Rx Initiation Criteria Used To Start/stop Therapy	Question # 4 Provider of Treatment and Qualifications	Question # 7 Treatment Parameters	Question #8 Comparators in Study Consistent With Usual Care	Question #9 Patient Outcomes Results	Question #11 Length of Study Length of Followup	Question #12 Did any Harms (adverse events) Occur From Rx?
Bertelli[70] 1991 Italy	LE onset: NR Time Rx start: ≥6 months after BCa Rx Criteria to start Rx: diagnosis of secondary LE Criteria to stop Rx: change of ≥25% in circumference of LE affected arm vs contralateral arm	NR	Intervention group: wearing standard elastic sleeve 6 hrs/day for 6 mos + ESD applied in 2 cycles of 2 wks each divided by 5 wk interval Each cycle=10 x 30 min sessions Control group: wearing standard elastic sleeve for 6 hrs/day for 6 mos	Wearing standard (not customized) elastic sleeve Consistent with usual care	Mean variation in limb measurements in 2 groups Clinically significant reduction of LE (≥ 25% compared to the initial values) No significant difference between the 2 groups <50% achieved a clinically significant reduction (48.4% controls and 41.4% intervention)	Length of study: 6 months Length of followup: NR	NR

Carati[32] 2003 Australia	LE onset: NR Time Rx start: NR Criteria to start Rx: Diagnosis of Post Mastectomy LE Criteria to stop Rx: NR	NR	Intervention Group: LLLT 1 Block (9 sessions, 17 minutes each, 3x/ week x 3 weeks), 8 weeks rest followed by a repeat block of laser Control Group: Sham First Block (9 sessions, 3x week x 3 weeks), 8 weeks rest followed by a block of LLLT	LLLT vs sham laser treatment Not consistent with usual care	Groups matched at baseline 2 LLLT sessions: 31% of pts had reduction in 2-3 mos time (>200 mls); 1 LLLT session and sham session showed NS Measured by perometry, bioimpedance, tonometry and goniometer	Length of study: 24 months Length of followup: 3 months	NR

Didem [79] 2005 Turkey	LE onset: LE onset >1 year after surgery Time Rx start: Rx started average of 3 years after surgery Criteria to start Rx: Diagnosis of LE (mild to moderate) Criteria to stop Rx: NR	Physiotherapist	Therapy sessions: 3x/wk x 4 wks Intervention group: CDP (MLD, compression, exercise & skin care) Control group: PT (bandage, elevation, exercises) Both groups: trained for home program of compression bandage, exercise, self message, skin care, and walking	Complex decongestive therapy vs. physiotherapy Consistent with usual care	Circumference volume Range of motion (goniometry) and shoulder function CDP decrease >PT ($p<0.05$). No significant difference between groups ROM	Length of study: 4 weeks Length of followup 3,6,12,&24 months to be reported later	NR

Dini[72] 1998 Italy	LE onset: Onset of LE less than one year before start of study Time Rx start: 1>yr after LE Criteria to start Rx: LE defined as >10cm difference between upper extremities Circumference recorded at 7 points LE was mild to moderate Criteria to stop Rx: occurrence of adverse event	NR	IPC: 2 cycles of 2 weeks, separated by a five week interval. Each cycle consisted of five x 2 hour sessions / week at a constant pressure. No other concomitant physical treatment	Guidelines about skin care and prophylaxis for edematous limb Not consistent with usual care	Limb circumference at 7 points Within group significant difference Between group not significantly different	Length of study: N 9 weeks Length of followup: none	Withdrawals but no adverse events/harms
Hayes[46] 2009 Australia	LE onset: NR Time Rx start:≥ 6 months after BCa Rx Criteria to start Rx: Finished BCa treatment 6 months prior and have LE Criteria to stop Rx: Occurrence of adverse event	Exercise physiologist Physiotherapist No details provided about qualifications	12 weeks of moderate intensity, aerobic and resistance exercise (supervised) 20-45 min per session (progressed) 3-4x/week (progressed)	NR	Bioimpedance Perometry No significant change between groups	Length of study: 12 weeks Length of followup: 3 months	One person had significant increase in swelling throughout study. Diagnosed with recurrent cancer 6 months after end of study

Hou[65] 2008 China	LE onset: NR Time Rx start: 5 years after surgery Criteria to start Rx: Diagnosis of secondary LE Criteria to stop Rx: NR	Provider qualifications not stated	Intervention group: BMSC one time operation followed by custom garment Control group: CDT (MLD, compression therapy, remedial exercises and deep breathing) details not reported	Stromal cell transplant vs. decongestive therapy BMSC not usual care	Volume (disk model), pain (self report scale) Both groups reduction in volume and pain; BMSC group had better long-term results	Length of study: NR Length of followup: 52 weeks	NR
Jahr [80] 2008 Germany	LE onset: NR Time Rx start: Rx started ~4 years and 1 month after surgery Criteria to start Rx: Diagnosis of secondary LE Criteria to stop Rx: NR	Physiotherapist	Intervention group: 2-3 x/ wk x 4 wks combined therapy + 8 weeks of MLD Control group: 1-2 sessions of 30-45 min/ week of MLD	Deep Oscillation ® + MLD vs. MLD Consistent with usual care	Pain (VAS) Swelling Pain: DO+MLD decrease of 4.0 to 2.0 VAS MLD no change Swelling: DO+MLD >decrease MLD. No significant difference between groups	Length of study: 4 weeks Length of followup: 8 weeks	NR

Johansson[69] 1998 Sweden	LE onset: Median of 9-10.5 months Time Rx start: Median of 9-10.5 months Criteria to start Rx: Unilateral arm lymphedema Criteria to stop Rx: NR	MLD provided by physiotherapist trained in Vodder technique	Both groups wore a compression sleeve for 2 wks then the MLD group had MLD treatments (Vodder technique) lasting 45 min/day 5 day/wk for 2 wks SPC group were treated with Lympha-Press pump for 2 hrs/day, 5 days/wk for 2 wks	MLD vs SPC Consistent with usual care	Arm volume body weight passive mobility isometric muscle strength subjective assessment MLD or SPC when applied in conjunction with a compression sleeve resulted in a notable reduction of lymphedema but no significant difference between the two treatment regimes	Length of study: 2.5 years Length of followup: NR	NR
Kaviani [78] 2006 Iran	LE onset: 3 mths Time Rx start: Lymphedema ≥3 mos Criteria to start Rx: Diagnosis of unilateral arm lymphedema Criteria to stop Rx: NR	NR	Intervention group**:** LLLT: 5 points 3x/ wk x 3 wks; 8 wk interval, then repeat same protocol x 3 weeks Control group: Sham irradiation Assessments at weeks 3, 9, 12, 18, and 22	LLLT vs. Sham therapy	Reduction in limb circumference Pain reduction ROM and Heaviness Reduction in limb circumference: Laser >control except for week 22 Pain reduction: laser >control ROM and heaviness: NS	Length of study: 22 weeks Length of followup: None	NR

Kessler[66] 2003 Switzerland	LE onset: NR Time Rx start: 2nd post surgery day Criteria to start Rx: Clinically diagnosed post-operative swelling Criteria to stop Rx: NR	Physical therapist with specific training provided physiotherapy (PT) and MLD Nurse applied new bandage after each measurement session	Intervention group: Daily PT exercises (50 without resistance and 25 with slight resistance) along with 30 minute MLD while in hospital Control group: Daily PT exercises same as intervention group	PT exercises alone or with manual lymphatic drainage Consistent with usual care	% change in leg, foot volume (water displacement) Significant volume reduction intervention vs. control (6.4% vs. 0.1%, p=0.011)	Length of study: NR Length of followup: NR	NR
Kozanoglu[64] 2009 Turkey	LE onset: History of arm LE >3 mo Time Rx start: LE >3 mo Criteria to start Rx: LE defined as difference of ≥2cm at least 3/7 points Criteria to stop Rx: NR	Physician performed assessments No details of who performed treatment No other details provided	IPC: 2 hrs at 60 mmHg x 20 sessions over 4 wks Laser: 20 min/3x wk x 4 wks (2800Hz, 1.5J/cm2) with a Ga-As 904nm laser device (Electronica Pagani IR27/4) 12 sessions total Both groups daily limb exercises, hygiene and skin care	Pnematic compression and laser therapy Could be seen as usual care	Limb circumference Visual Analogue Scale Grip strength Significant difference LC and VAS from pretreatment to 12 month followup	Length of study: 4 weeks Length of followup: 12 months	Withdrawals but not mention of adverse events

Maiya[81] 2008 India	LE onset: NR Time Rx start: 3-6 weeks following mastectomy Criteria to start Rx: Lymphedema defined by 2 cm difference at 2 or more points on upper extremity Criteria to stop Rx: NR	NR	LLLT: (He-Ne Laser-632.8nm and Diode Laser 850nm) at different points in axillary region. 2.4J/cm2 of laser energy per point was given for total of 34 min/day for 10 days After laser, patients performed exercise program for upper extremity (no details given) Control Group: Upper extremity exercises and compression garments for 10 days (no other details provided) Both groups advised to continue their regular daily activity	Upper extremity exercise + compression garments Consistent with usual care	Pain Limb Circumference at 4 points Significant difference mean pain score between groups Significant difference mean circumference at 10cm and 15cm LE between groups	Length of study: 10 days Length of followup: NR	"All patients completed the 10 days of treatment without any adverse reactions"

McKenzie[67] 2003 Canada	LE onset: NR Time Rx start: >6 months post treatment for cancer Criteria to start Rx: Diagnosis of LE (arm difference between 2 cm and 8 cm) Criteria to stop Rx: NR	NR	8 week progressive exercise program of stretching, resistance training 3x wk and after 2 weeks upper body aerobic exercise using are cycle ergometer added	No specific exercise instruction Consistent with usual care	Arm circumference arm volume and QoL No change in circumference or volume, change in quality of life not statistically significant	Length of study: 8 weeks Length of followup: none	NR
McNeely[83] 2004 Canada	LE onset: NR Time Rx start: NR Criteria to start Rx: Diagnosis unilateral LE, mild, moderate or severe, both early and chronic Criteria to stop Rx: NR	MLD provided by Physical Therapist trained in the Vodder method Bbandaging by physical therapist assistant	Intervention Group: 45 minutes of daily MLD 5 days/week x 4 weeks + bandaging each day Control Group: short stretch bandaging 5 days/week x 4 weeks Both groups educated on proper arm and skin care	Vodder MLD + short stretch bandaging vs. short stretch bandaging alone Consistent with usual care	Volume (volumetry) Circumference Significant reduction in both groups; but between groups: NS largest reduction in MLD/CB group with early, mild LE	Length of study: 4 weeks Length of followup: None	1 pt withdrew due to skin reaction, 1pt due to discomfort of bandages

Radakovic [63] 1998 Yugoslavia	LE onset: NR Time Rx start: after radiotherapy (RT) Criteria to start Rx: BCa mastectomy patients Criteria to stop Rx: NR	NR	Intervention group: SEPC 60 min x 10 consecutive days, followed by elastic bandages Control group: 30 min of MLD x 10 days + elastic bandages	MLD vs pneumatic compression Consistent with usual care	Change in arm volume (limb circumference) SEPC 2.24 cm (range 0.6 - 8.4 cm) MLD 0.95 cm (range 0.1 - 3.9 cm). SEPC 2.3X greater than MLD	Length of study: 10 days Length of followup: none	NR
Shaw [76] 2007 U.K.	LE onset: NR Time Rx start: Rx onset ≥12 months after chemo or RT Criteria to start Rx: Diagnosis of arm LE Criteria to stop Rx: Completion of regimen	Dietary intervention provided by Registered Dietition Conventional therapy provided by trained LE nurses	Intervention Group: Individualized dietary advice given on weight reduction diet; dietary compliance assessed at Week 4 and Week 8 visits Control Group: Healthy eating booklet with no specific dietary intervention	Dietary intervention Not consistent with usual care	Changes in arm volume (manual measurements) Significant change in lymphedema arm (7% ± 6%) vs. normal arm (3% ± 6%) in dietary group	Length of study: 12 weeks Length of followup: NR	NR

Shaw [77] 2007 U.K.	LE onset: NR Time Rx start: ≥12 months after Rx for cancer Criteria to start Rx: Diagnosis of secondary LE Criteria to stop Rx: NR	Registered dietitian Arm measurements taken by LE practitioners	Intervention group: Group 1: Weight reduction (reduced energy intake) Group 2: Low fat diet (no reduction in energy intake) Control group: No dietary change	2 dietary interventions vs. no diet intervention Not consistent with usual care	Change in arm volume (Perometer) circumference (measured manually) Significant reduction body weight, BMI and skinfold thickness. NS change arm volume. Significant correlation weight loss and decreased arm volume	Length of study: 24 weeks Length of followup: none	NR
Sitzia [82] 2002 U.K.	LE onset: NR Time Rx start: NR Criteria to start Rx: Secondary arm LE after BCa surgery Criteria to stop Rx: NR	Lymphedema specialist Nurse (LS) MLD training (2 year diploma) in specialist management of chronic edema	Intervention Group: MLD: 40 - 80 minutes 5 x week x 2 weeks Control Group: SLD: 20 minutes 5x week x2 weeks	MLD vs SLD Consistent with usual care	% Change in excess limb volume (PCEV) MLD: 33.8%, SLD: 22.0% (mean difference 11.8%)	Length of study: 2 weeks Length of followup: NR	NR

Szuba[71] 2002 U.S.	Study 2: LE onset: NR Time Rx start: between 1 month and 1 yr post intensive decongestive lymphatic therapy (DLT) Criteria to start Rx: diagnosis of secondary LE Criteria to stop Rx: NR	MLD performed according to Vodder School technique (no details on Rx providers)	Study 2 (2 month-groups switched treatment after 1 month): Group 1: daily self-administered MLD and use of Class II compression garment Group 2: same + 1 hr daily IPC (40-50 mm Hg)	Study 2: DLT alone (regular care)	Study 2: Arm volume, skin elasticity (tissue tonometry) Joint range of motion (goniometry) IPC was effective as adjunct therapy; there was no impact on skin elasticity or joint ROM	Length of study: 2 months Length of followup: 6 months	Study 2: No adverse responses

Szuba[68] 2002 U.S.	Study 1: LE onset: NR Time Rx start: ≥3 months from BCa Rx Criteria to start Rx: Diagnosis of secondary LE Criteria to stop Rx: NR	MLD performed according to Vodder School technique (no details on Rx providers)	Study 1 (10 days): Intervention group-daily MLD followed by IPC (30 min at 40-50 mm Hg) then compression bandaging Control group-daily MLD followed by compression bandaging After completion of intervention both groups were fitted with Class II compression garment and instructed in self-applied MLD to be done daily at home	Study 1: DLT alone Consistent with usual care	Study 1: Arm volume, skin elasticity (tissue tonometry) Joint range of motion (using goniometry) IPC was effective as adjunct therapy; there was no impact on skin elasticity or joint ROM	Length of study: 10 days Length of followup: 30 days	Study 1: One participant reported repetitive headache and modest increase in blood pressure during IPC therapy

Wilburn [73] 2006 U.S.	LE onset: 34 ± 34 months Time Rx start: 0-5 months after LE onset Criteria to start Rx: Lymphedema of the upper extremity after surgical and/or radiotherapy Criteria to stop Rx: NR	Initial decongestive therapy: physiotherapist self-massage and Flexitouch therapy training: Not reported Flexitouch therapy and/or daily massage: patients self-administered	Intervention group: Use of Flexitouch machine for 1 hour daily Control group: Self-message for 1 hr daily, then oucompression garment Each treatment phase lasted 14 days at home with one week washout period between treatments	Self-message and compression garment Consistent with usual care	Limb volume measurements Flexitouch™ mean -208 ± 157 ml; Control: +52 ± 106 ml p=0.007 HRQOL with SF-36: NS	Length of study: 42 days Length of followup: NR	NR

Williams[74] 2002 U.K.	LE onset: LE >3 mths Time Rx start: LE >3 mths Criteria to start Rx: Diagnosis of secondary LE Criteria to stop Rx: NR	Therapists qualified in Vodder method of MLD SLD performed by participants (self) after training	Group A: 3 wks (5x wk) daily 45 min MLD treatment followed by 6 wks no treatment followed by 3 wks daily 20 min SLD treatment Group B: 3 wks daily 20 min SLD treatment followed by 6 wks no treatment followed by 3 wks (5x wk) daily 45 min MLD treatment	Both groups same treatment but in reverse order; SLD was comparator treatment Usual Care	Limb volume, caliper creep, dermal thickness, QoL, altered symptoms/ sensations MLD reduced volume and dermal thickness, improved some measures of QoL and some symptoms sensations	Length of study: 12 weeks Length of followup: NR	NR

Observational Studies							
Balzarini[48] 1993 Italy	LE onset: Intervention group- 3-52 months Control group- 5-57 months Time Rx start: NR Criteria to start Rx: Diagnosis of secondary LE Criteria to stop Rx: NR	NR	Intervention: 2 UST cycles at 4 month intervals--one cycle=10-30 min sessions Control: MPT, 1 cycle (6 hrs/day for 5 consecutive days) at 4 mo intervals for 1 year *subsets of each group were also given an elastic sleeve to wear	Mechanical pressure therapy (MPT) Usual care	Arm volume Skin firmness The UST group had greater softening of the arm, better relief of pain, greater scapulo-humeral motion	Length of study: 12 months Length of followup: NR	NR

Berlin[84] 1999 Sweden	LE onset: NR Time Rx start: NR Criteria to start Rx: Diagnosis of secondary LE Criteria to stop Rx: NR	NR	Group 1: Arm compression stockings only for minimum of 4 wks Compression used varied between 25 and 50 mmHg Group 2: Intermittent compression with Flowtron used at least 20 min/day minimum 4 wks Group 3: Pneumatic compression with Lympha Press--pressure 90-120 mmHg for 20-30 min 2x/day 5 day/wk Patients also received compression stockings	1)compression with sleeves 2) intermittent compression with Flowtron 3) intermittent compression Lympha-Press + compression sleeves Not consistent with usual care	Group 1: Arm compression stockings only for minimum of 4 wks. Compression used varied between 25 and 50 mmHg Group 2: Intermittent compression with Flowtron used at least 20 min/day minimum 4wk Group 3: Pneumatic compression with Lympha Press-pressure 90-120 mmHg for 20-30 min 2x/day 5 day/wk Patients also received compression stockings	Length of study: 5 years Length of followup: NR	NR

Brambilla[86] 2006 Italy	LE onset: NR Time Rx start: NR Criteria to start Rx: Grade II lymphedema Criteria to stop Rx: NR	NR	Intervention Group: Compression stocking from morning until bedtime, stockings were replaced every 6 months Control Group: No treatment physical exams	No treatment Not consistent with usual care	Change in limb volume Intervention Group: 30/50 reduction 6.9% ± 5.1 20/50 increase: 6.7% ± 6.2 Control group: 15/15 increase 5.82% ± 2.16	Length of study: Intervention group: Mean 66 weeks Control group: Mean 64 weeks Length of followup: NR	NR
Johansson[87] 1999 Sweden	LE onset: NR Time Rx start:NR Criteria to start Rx: Diagnosis of secondary unilateral LE Criteria to stop Rx: Therapy stopped with resolution of arm swelling	Physiotherapist trained in bandaging and in the Vodder MLD technique	Part 1: Both groups received 2 weeks of CB (bandage changed every 2nd day) Part 2: During the 3rd week both groups continued CB but one group also received MLD 45 min/day x 5 days	CB alone vs CB + MLD Consistent with usual care	Arm volume body weight subjective assessment CB+MLD group had significant difference % volume reduction	Length of study: 19 days Length of followup: NR	NR

Pinell[85] 2007 U.S.	LE onset: NR Time Rx start: NR Criteria to start Rx: Secondary LE with or without axillary or inguinal disease Criteria to stop Rx: NR	Certified therapist	Intervention group: Skin and nail care, mulitlayer compression bandages worn at all times and decongestive exercise, MLD 60 - 90 minute/day. Modified MLD technique for patients with axillary or inguinal disease at time of therapy Control group: Same as intervention group without modification	Manipulative therapy (MLD) plus compression bandages Consistent with usual care	Interval measurements of girth along affected limb and computation of volume	Length of study: 39 months Length of followup: NR	NR

Table 12. IPC treatment

Study	Question # 5 a Type of IPC Device	Question # 5 a Pumping Time/Cycles and Pressures	Question # 5 b Co-morbidities of Patients	Question # 5 b Modification of Protocol for Co-morbidities	Question # 5 c Timing of IPC Application
RCT's					
Bertelli[70] 1991 Italy	Electronically Stimulated Lymphatic Drainage (ICH8 Linfomed Fisioline)	Pump Time: 10x 30 min sessions Cycle: 2 cycles of 2 weeks separated by 5 weeks Pressure: 4.5khz frequency sequential stimulation of 8 electrodes	NR	NR	NR
Dini[72] 1998 Italy	NR	Pump Time: 2 hrs x 5 days/week Cycle: 2 cycles of 2 weeks separated by 5 weeks Pressure: 60 mmHg (constant pressure)	NR	NR	1 year of LE onset
Johansson[69] 1998 Sweden	Lympha-Press Type: 9 Compression Cells	Pump Time: 2 hrs/day Cycle: 5 day/week x 2 weeks Pressure: 40-60 mmHg	NR	NR	LE duration 6.5 months (2.3-68.3)
Kozanoglu[64] 2009 Turkey	IPC device (MJS Healthcare Ltd. U.K.)	Pump Time: 2 hours IPC Cycle: 20 sessions x 4 weeks Pressure: 60 mmHg (intermittent pressure)	NR	NR	Arm LE at least 3 months
Radakovic[63] 1998 Yugoslavia	Sleeve with 12 overlapping compression chambers	Pump Time: 60 min/day Cycle: 1/day x 10 days Pressure: 60 - 65 mbar (gradually activated over 7 min)	NR	NR	NR

Abbreviations: BMI=Body Mass Index, Ca=Cancer ESD=Electronically Stimulated Lymphatic Drainage, Hrs=Hours, IPC=Intermittent Pneumatic Compression, LE=Lymphedema, min=minutes, NR=Not Reported, RCT=Randomized Control Trials, yrs=years

Table 12. IPC treatment (continued)

Study	Question # 5 a Type of IPC Device	Question # 5 a Pumping Time/Cycles and Pressures	Question # 5 b Co-morbidities of Patients	Question # 5 b Modification of Protocol for co-Morbidities	Question # 5 c Timing of IPC Application
RCT's					
Szuba[71] 2002 U.S.	Sequential Circulator 2004: (BioCompression Systems Inc)	Pump Time: 60 min/day Cycle: 1 month Pressure: 40-50 mmHg (4 chamber, sequential)	NR	NR	Average duration LE 5 yrs Average time since surgery 9 yrs
Szuba[68] 2002 U.S.	Sequential Circulator 2004: (BioCompression Systems Inc)	Pump Time: 30 min/day Cycle: Daily: 10 days Pressure: 40-50 mmHg (4 chamber, sequential)	NR	NR	Average duration LE 4 yrs
Wilburn [73] 2006 U.S.	Flexitouch™ Type: Lightweight portable device for home use consisting of up to 32 separate chambers	Pump Time: 1 hour/day Cycle: 1/day x 14 days Pressure:1-3 seconds of mild pressure	NR	NR	LE onset 34±34 months (1-99 months)
Observational Studies					
Balzarini[48] 1993 Italy	Jobst Extremity Pump	Pump Time: 6 hrs/day for 5 consecutive days Cycle: 1 cycle every 4 months over 1 yr Pressure: 30-40 mmHg (uniform pneumatic sleeve)	NR	NR	NR

Berlin[84] 1999 Sweden	1) Flowtron 2) Lympha Press	Pump Time: Flowtron: 20 min/day Lympha Press: 20-30 min/day Cycle: Flowtron: 1x/day x4 weeks Lympha Press: 2x/day x unspecified weeks Pressure: Flowtron: 80 mmHg, inflate/deflate x 2 min Lympha Press: 90-120 mmHg, build 20 sec, hold 6 sec, release 4 sec	NR	Lower levels of pressure were permitted in some patients treated with compression stockings	NR

Chapter 4. Discussion

Diagnosis

Question 1. What is the performance of diagnostic tests for preclinical and/or clinically significant lymphedema?

a) What inclusion criteria (including patient demographics, signs, and symptoms) were used in studies evaluating the performance of diagnostic tests of lymphedema?

Most of the diagnosis studies involved persons with breast cancer. Caution must be used when applying the results of diagnosis studies done in one patient population to another population as the specific characteristics of a test might not be easily transferrable. For example, a test developed for assessing lymphedema in persons with breast cancer may contain built-in nuances from this disease population, thereby rendering it non-transferrable to other populations. All diagnostic tests should be validated in the population of interest before widespread use in that population.

The age range of persons in the 31 studies was wide enough to encompass younger, non-diseased persons who were used as comparators in some of the diagnostic testing publications. The generally middle-aged nature of study subjects reflected the fact that most studies involved cancer patients, who are typically diagnosed and treated in middle age or later.

b) Is there any "gold standard" method to formally grade or measure the severity of lymphedema?

Only three of the studies in the diagnostic testing portion of this report contained methods to grade the severity of lymphedema.[62,91,103] The methods were either non-validated,[91] vaguely defined,[62] or both.[103] None of the methods was described as a gold standard.

The remaining diagnostic studies were conducted with the intent of evaluating tests that would differentiate persons with and without lymphedema. There was no attempt to stage the severity of lymphedema in any of these studies.

Based on the evidence from the abstracted studies, there does not appear to be a gold standard for grading the severity of lymphedema.

c) What comparators were used in the studies of diagnostic tests? Was the test compared to a "gold standard", bedside exam, radiologic investigation, or other means?

Although rarely identified as gold standards, the frequency of use of different measures of limb volume or circumference would suggest that these measures are the de facto gold standards for diagnosing secondary lymphedema. Furthermore, the consistent reliability and validity of these measures (see Question 1e) indicates that they are well suited for use as gold standards. It should be recognized that among lymphedema researchers, some will accept a gold standard such as limb volume assessed through water displacement, but there is no evidence to suggest a definitive gold standard.[92] However, based on the extent of use, as well as the consistent evidence for reliability and validity, it is recommended that limb volume or circumference be considered the gold standard for diagnosing secondary lymphedema.

Interestingly, in the narrative review (see Chapter 1), the medical textbook literature suggests that imaging tests such as ultrasound and lymphoscintigraphy should be used as gold standards to

diagnose lymphedema. However, few of the abstracted studies included ultrasound or lymphoscintigraphy; studies that included these imaging tests did not consider them to be gold standards. Rather, these tests were evaluated as index tests (the tests under investigation).

d) What is the sensitivity and specificity of tests used to diagnose lymphedema?

In the seven studies that contained examinations of the sensitivity and specificity of diagnostic tests for secondary lymphedema, sensitivities ranged from 5 to 100 percent and specificities ranged from 71 to 100 percent. However, it was not possible to rank order the tests in terms of performance because there were too few studies from which to permit generalization, persons with three different underlying conditions were the subject of the studies (breast cancer, melanoma, Kaposi's Sarcoma), a mix of different tests were used (changes in circumference with different cut points, self reports, imaging), and four different reference standards were also used. The authors of one study did not clearly specify a reference standard. Researchers must use a common reference standard as a first step to providing a clearer picture of the sensitivity and specificity of tests in persons with secondary lymphedema.

e) What are the psychometric properties (reliability, validity, responsiveness) of these diagnostic methods?

Reliability. There is consistent evidence to indicate that lymphedema can be reliably measured using circumferential measures or volume displacement. It should be noted that these studies were conducted in breast cancer patients with secondary lymphedema primarily in the upper extremities. One study pertained to the trunk of the body.[106] The excellent reliability of these measures might not be transferable to situations where lymphedema occurs in other parts of the body, or to cases where lymphedema occurs secondarily to other diseases besides breast cancer.

There is too little evidence to draw conclusions about the reliability of other tests such as tonometry, ultrasound, lymphoscintigraphy, or bioimpedance.

Validity. Sixteen of the 21 validity studies involved some use of volume displacement or limb circumference as a diagnostic test for secondary lymphedema. Based on consistently high correlation coefficients, there is strong evidence that displacement and circumference are interchangeable amongst one another in terms of results. This interchangeability applies despite the various means of measuring displacement or circumference.

Tests involving bioimpedance show good validity when compared to tape measured circumference or perometry, although the correlation coefficients were not as high as the coefficients in the displacement-circumference comparisons. Self reported symptoms on the Lymphedema and Breast Cancer Questionnaire (LBCQ) also show good validity in comparison to bioimpedance, perometer, and tape measure, although the evidence is limited to a single study and correlation coefficients were also lower than the ones calculated for the displacement-circumference comparisons.[98]

The validity of ultrasound and lymphoscinitgraphy was evaluated in three studies. There is little evidence for the validity of these tests owing to the limited number of studies, small sample sizes, a questionable reference standard in one study,[62] and questionable means of scoring lymphoscinitgraphy in two studies.[62,103]

Given the limited extent to which the LBCQ has been examined as a diagnostic tool for secondary lymphedema, and the lower correlation coefficients found in the bioimpedance studies, the evidence suggests that volume displacement or limb circumference are the most valid

means of diagnosing secondary lymphedema. Most of the validity studies included breast cancer patients, so the conclusions about validity may not be wholly transferrable to other disease groups. Further work must be done to establish the diagnostic validity of these tests in populations other than persons with breast cancer.

Responsiveness. There is a dearth of evidence on the responsiveness to change of diagnostic tests for secondary lymphedema. Only two of the studies included in this report[27,30] evaluated responsiveness to change; both were conducted in the breast cancer population. Researchers in the field should certainly be cognizant of the results of these studies if they choose water displacement, limb circumference, or tissue resistance as a means of testing for lymphedema in their own research projects. However, more work needs to be done to establish the property of responsiveness in common diagnostic tests for lymphedema. Until such work is completed, one cannot draw any conclusions about responsiveness to change in this area.

f) How frequently and for how long should patients be measured for the development of lymphedema or its sub-clinical precursor? Does this vary with the diagnostic test method?

There is no evidence to answer either key question as none of the included diagnostic studies addressed either question. These studies were undertaken to examine the sensitivity, specificity, or psychometric properties of various tests in comparison to one another, so persons who were included in these studies typically had a diagnosis of lymphedema. Non-lymphedema control groups were included in some instances to provide comparisons, but not to ascertain measurement times for development of lymphedema. One study did specifically compare the incidence of lymphedema over time using four tests and five assessments,[26] but the sole rationale for conducting five assessments at quarterly intervals was that the assessments could be performed at the same time as regularly scheduled followup appointments with oncologists. The suitability of five quarterly assessments was not under study. Another study conducted followup a maximum of 14 times per participant, but the rationale for this number was not provided by the authors.[35]

The studies that did provide a rationale for multiple assessments were designed to examine test-retest and interrater reliability, or validity, so multiple assessments were necessary. None of these studies were designed to investigate the frequency or length of time necessary for persons to be measured for the development of lymphedema. Consequently, there was no pattern of frequency or length associated with any specific test.

For question 1f to be answered, a group of persons without lymphedema at baseline would have to be followed up for a set amount of time. During this time, different tests at regular intervals could be employed to assess whether lymphedema develops. The testing intervals could be varied (within or between tests) on different subgroups of patients to get a clearer picture of the issues at hand.

g) Does the diagnostic test method influence the choice of lymphedema treatment or patient outcome? What outcomes were measured in studies of diagnostic tests of lymphedema?

There is no evidence in the 31 diagnostic testing studies to answer either of these questions. Only four studies contained mention of the type of treatment offered to patients, and the point of these studies was not to examine treatment itself, but to study diagnostic test properties. Outcomes of treatment were not reported in three of the studies.[93,109,110] In the fourth study,

outcomes were reported, but the authors made no attempt to link outcomes to the choice of diagnostic test.[103]

Treatment

Question 2. What were the patient selection criteria in the studies (inclusion and exclusion criteria)? Did they differ by treatment modality?

There were 28 different inclusion and exclusion criteria spread across the 28 studies. There was no grouping of criteria attached to any specific treatment modality. Consequently, there is no evidence to suggest that patient selection criteria differed by treatment modality.

Question 3. What were the criteria used to initiate treatment for lymphedema? When was treatment initiated compared to the time of onset of the lymphedema? What were the criteria used to stop therapy? Did these criteria vary with treatment modality?

In all 28 treatment studies abstracted for this report, a diagnosis of lymphedema was the only specific criteria used to initiate treatment. Only seven studies reported the approximate time of recruitment following onset of lymphedema. All except one of these studies began recruitment within 1 year of onset, but there was a wide range of recruiting times within this 1 year period. It should be noted that these are recruitment times following onset of lymphedema, not the times to initiation of treatment. Although it is likely that lymphedema treatment was initiated soon after recruitment, the time frame between recruitment and initiation was not reported in any article. Therefore, no evidence exists to provide a clear answer to the question about time of treatment initiation.

Only five studies reported specific criteria to stop treatment.[46,70,72,76,87] This number is too small to assess whether stopping criteria varied with treatment modality in the 28 studies that were abstracted for this report.

Question 4. Who provided the treatments in the studies? What information was provided on their professional training or certification in lymphedema care?

The authors of 15 of the 28 treatment studies did not detail who provided the lymphedema treatment. Except in the case of patient self-massage, the provision of lymphedema treatment requires a trained professional such as a physiotherapist or a technician familiar with the operation of an IPC device. To enhance reporting, as well as to facilitate judgments about the generalizability of published studies, authors of future studies in the domain of lymphedema treatment should report on the professional status and qualifications of the persons delivering lymphedema therapy.

Question 5a. Was one type of pneumatic compression device and sleeve (e.g., non-segmented compression device, sequential segmented compression, or segmented compression with calibrated gradient pressure) more effective in reducing lymphedema than another for any type of lymphedema along the continuum, or patient characteristic (e.g., demographics, comorbidities)?

Ten studies evaluated IPC treatment.[48,63,64,68-73,84] There was no evidence from which to determine whether one type of IPC device and sleeve were more effective than others across the continuum. The lack of evidence was partly a result of the fact that there were simply too few studies from which to conduct meaningful comparisons. Of the studies that were abstracted for

the report, comparison was further inhibited by the degree of heterogeniety between articles: seven different types of IPC were investigated against six different types of comparator. Comparators included MLD,[68,69,71] compression bandage or sleeve,[68-71,73] massage,[63,73] skin care and prophylaxis,[72] laser,[64] or ultrasound.[48] In two studies, the authors did not clearly describe the IPC device.[64,72]

The lack of evidence was further driven by the fact that IPC was delivered in conjunction with other treatments in five studies. IPC was given at the same time as study participants received MLD and compression bandages[68] or compression garments or stockings.[73,84] IPC was given after 2 weeks of treatment with a compression sleeve[69] or it was followed by the application of elastic bandages.[63] These differing regimens made it difficult to tease out the effects of IPC alone when conducting indirect comparisons across studies.

The same IPC devices were used in two sets of studies. The Sequential Circulator 2004 demonstrated statistically significant reductions versus MLD and compression garments in two studies,[68,71] but the treatment regimens involving IPC differed across the studies in terms of length of daily IPC application and number of applications. Also, one study used IPC to treat persons with an initial diagnosis of lymphedema[68] and the other used IPC as maintenance treatment.[71] These characteristics worked against the extent to which the performance of the Sequential Circulator IPC could be indirectly compared across these two studies.

Lympha-Press was another IPC system used in two studies.[69,84] Indirect cross comparisons between these two studies were also difficult because of differences in treatment regimen (Lympha-Press following 2 weeks with a compression sleeve[69] or Lympha-Press concomitantly with compression stockings[84]). There were also differences in comparators (MLD,[69] compression stockings or Flowtron IPC[84]).

None of the abstracted studies broke down treatment results by patients characteristics. Therefore, no evidence was found to assess whether one type of IPC device and sleeve were more effective in reducing lymphedema based on specific sets of patient characteristics.

Question 5b. Did the studies of IPC for lymphedema in patients with comorbidities such as wounds, arterial and/or venous insufficiency, diabetes, congestive heart failure, infection, etc., report the need to modify their treatment protocols? Did it affect treatment outcome?

There were no reports in the abstracted studies of the need to modify treatment protocols on account of comorbidity. It would appear that most comorbidities with a potential effect on treatment outcome were addressed at the design stage of the studies, through the specification of exclusion criteria (e.g., exclude persons with congestive heart failure or any other contraindication to treatment[73]). In some cases, participants were removed from a study during followup due to the development of an adverse effect such as lymphangitis.[70] Neither the use of exclusion criteria nor removal because of adverse effects suggests a protocol modification. There was no evidence in the abstracted studies to address whether protocol modifications would affect treatment outcome.

Question 5c. Did the timing of IPC application and/or the sequence of use of the various IPC device types (either alone or in combination with other therapies) influence outcomes either positively or negatively?

There is no evidence to address whether the timing of the IPC application might have influenced the study outcomes. Five of the studies did not contain reports on timing.[48,63,64,70,84] In the other five studies, the treatment regimens were too heterogeneous to allow for the isolation of

any potential effect of timing. For sequence of use, the conclusion is the same: the mix of different treatments does not permit the isolation of the effect of sequence. Hence, there is no evidence for sequence as well. Additionally, there are simply too few studies from which to establish definitive patterns about timing or sequence.

Question 6. What protocols for single modality treatments resulted in the best outcomes of lymphedema therapy? Consider parameters such as usage schedules and characteristics of treatment such as intensity, duration, frequency and setting (self-administered at home versus professionally administered applied in a medical clinic), and if applicable pumping times/cycles and pressures.

There were only eight studies that examined single modality treatments for lymphedema. This reflects the fact that most lymphedema treatment is delivered as some form of combination therapy. Most of the studies adopted unrealistic comparators to maintain the 'single modality' distinction. For example, it is unlikely that persons with secondary lymphedema would be treated in standard clinical practice with only a booklet on healthy eating[76] or instructions to continue with usual activities,[46,77] or no treatment whatsoever.[86] By the same token, the use of sham laser[32,78] is questionable because there is no actual treatment given to patients. Ideally, the comparator should be the standard, medically-accepted treatment for lymphedema in the locality where researchers are conducting the study.

Notwithstanding the above, there was no evidence from which to ascertain whether certain treatment protocols would lead to better outcomes. Certainly this was the case for exercise[46] and elastic stockings,[86] where one study of each treatment negated any ability to compare protocols. For the other treatments (diet, laser, IPC), two studies in each diet,[76,77] IPC,[64,72] or three studies (laser[32,64,78]) were included in the review. These numbers were also not sufficient to study the effect of protocol differences on outcomes. In fact, the protocols for diet, IPC, and laser were similar across the studies, so there was even less of an evidentiary basis for assessing whether protocols make a difference.

To address the effect of protocol on outcome, a series of studies with nearly identical samples, lengths of followup, comparator therapies, and outcomes would need to be constructed, with the only difference being the protocol used to deliver the treatment of interest. In the diet, laser, and IPC studies, there was little standardization in most of these areas (with the exception of the definition of outcome). Additionally, epidemiologic and statistical issues such as bias and power would have to be addressed in the design and analysis of the studies to increase the confidence in results. In one RCT, placebo patients were allowed to cross over to the active treatment group and analyses were conducted with these 'crossovers' included in both groups. Also, all of the studies had fewer than 100 participants. From a methodological perspective, there is simply too much noise from which to tease out the signal of a protocol effect on outcome.

Question 7: Were there any treatments, combinations of treatment methods, or sequence of treatments shown to be more effective or ineffective for any type of lymphedema along the continuum, or patient characteristics (e.g., demographics, comorbidities)? Of particular interest: Is there evidence that the use of compression sleeves or low stretch bandaging is effective in maintaining reductions in lymphedema achieved through the use of other modalities (e.g., IPC, manual lymphatic drainage, exercise)?

As studies used multiple outcomes in a variety of patient types, comparisons of treatments to identify those which are more or less effective are problematic. In no group of studies were the

populations defined or the results reported to such a degree of detail that it is possible to identify groups of patients for whom these treatments are more, or less, effective.

It was noted that RCTs of higher Jadad scores were less likely to demonstrate differences between study groups (7/18) than their lower quality counterparts (4/5), suggesting a quality-related bias in the literature.

A further potential reason for the lack of benefit seen in many studies is the issue of sample size. While some authors reported attempts at sample size calculations,[72,73,75,77,83,115] very few provided any indication of estimates of benefit or variance in the study groups or study power and as a whole, did not report on sample size calculations. One group of authors did report on sample size calculations and reported less eligible patients than initially anticipated.[76] The majority of studies enrolled 50 patients or less, suggesting that authors were expecting a large difference in benefit between study groups. As there was little detail in the majority of studies, it is unclear if statistical significance was not achieved due to overestimation of benefit or underestimation of variance within the groups.

Studies were even less likely to show a treatment benefit to patients regarding arm function and quality of life. Several potential reasons may explain this. Firstly, variance of these measures within studied populations may be such that statistical detection of change may be unlikely with limited study numbers. Additionally, in those studies which did result in reduced lymphedema volume, these reductions may not have been sufficient to have resulted in a quality of life change. Finally, patient satisfaction outcomes may not be well correlated to arm volume. Perhaps other non-measured items are at play such as stiffness or pain.

Bandaging and elastic sleeves are commonly prescribed treatments, likely because of their low cost and relative availability. No studies compared these treatments to more conservative measures making it difficult to comment on their benefit, relative to other therapies. Low quality evidence of modest benefit is provided from pre-post measurements of some studies,[75,79,83,87] but should be interpreted with caution as there is no evidence to suggest that such reductions would not have happened in the absence of any care. Further low quality evidence for a benefit from elastic sleeves comes from the observation that patients using sleeves in studies with long term followup were more likely to retain initial benefit compared to patients from studies that did not. This issue was further addressed in Chapter 3. Again, this should be interpreted with caution, as no included studies were intended to specifically address this observation.

Question 8: What comparators were used in the studies? Are these comparators consistent with usual care for lymphedema?

Many treatments have been suggested to provide benefit for patients with lymphedema. Despite this, no single treatment has emerged as a gold standard in clinical trials thus there appears to be no standard comparator for RCTs. Elastic sleeve was used in 4/28 trials and was most common comparator against the study treatment.[70,75,76,84] Compression bandaging was used in 3 trials.[79,83,87] These two were likely chosen as the most common two comparators due to their low cost and relative availability and not because of evidence of benefit.

Question 9: What outcomes were measured in studies of lymphedema therapy? How effective were these treatment methods in reducing lymphedema?

Multiple outcomes were used in these reports. Objective measurements, usually relating to volume were most reported.

Many studies reported that treatment brought about a reduction in lymphedema volume. However, relative benefit is difficult to appreciate in that despite studies including comparator groups, some provided pre- and post-treatment assessments of each group but did not provide between group comparisons.[71,85] Other studies provided p values for comparisons but did not report point estimates in differences of benefit[70,72,84,86] leaving clinicians to question the clinical benefit of treatment. Even in those studies that did report point estimates of benefit, the specific outcome reported varied such that comparisons are not valid. For instance, arm measurements may have resulted in reporting of circumferences differences,[63] percent volume loss,[82] absolute volume loss,[69] or proportion of patients achieving a pre-specified degree of benefit.[70]

Of note, randomized trials of higher quality displayed a trend of being less likely to show differences in benefit at study end between study groups (6/18) than their counterparts of lower quality (4/5).

Question 10: Did any studies show that the time of treatment initiation (single modality or combination therapy) relative to symptom onset, any other lymphedema characteristics, or any patient characteristics influenced or predicted treatment outcome?

Since few studies were sufficiently powered to detect a difference in the primary outcome, most trials were did not have power to detect differences in patient subgroups which were predictive for response. Few trials randomized patients with a stratification scheme or performed adjusted analyses to allow for detection of predictive factors.

Question 11: What was the length of followup in studies of lymphedema therapy? How long were the benefits of treatment maintained?

Considering the chronicity of lymphedema, very few trials performed long term followup in their study population. Only seven of 28 trials reported outcomes at 6 months or beyond.[48,64,65,70,71,75,86] One study reported outcomes at week 30 of the study, but this was only 12 weeks from the last treatment.[32] There was no consistent evidence on the length to which treatment benefits could be maintained.

Question 12: What harms have been reported associated with the various treatments for lymphedema? Do any patient characteristics (e.g., demographics, comorbidities) or etiology of lymphedema increase the risk of these harms?

Due to the nature of these reports, it was not always possible to delineate which patients were in which treatment group, preventing readers from drawing conclusions about the relative harms of various treatments. The majority of withdrawals and adverse events were related to treatment scheduling or disease recurrence, neither of which would be the direct result of therapy. Adverse events likely related to study therapy were all rare. As with other outcomes, harms were less likely to be reported in lower quality studies.

Even if all adverse events were in the treatment groups, their infrequency would be unlikely to result in statistical significance if formally tested. No studies reported on factors which may increase the risk of harms associated with treatment. There was no evidence in the abstracted studies to answer this question.

Conclusions

Most of the diagnostic accuracy and treatment studies were conducted in persons with a history of breast cancer. This is important to note because the sensitivity and specificity, and psychometric properties, of the diagnostic tests for secondary lymphedema could differ in non-breast cancer patient populations. This suggests that the diagnostic tests should be evaluated in non-breast cancer populations prior to the tests' use in these populations. The need for evaluation in these populations certainly applies to measures of limb volume or circumference, despite the fact that these tests were shown to have very good properties in the breast cancer population. The same caution must be issued for treatments of secondary lymphedema. Most treatments were evaluated in the breast cancer population, so there is no assurance that their efficacy is transferable to other populations. Evaluation of treatment efficacy in other populations is necessary.

Based on the evidence, limb and volume circumference are the de facto 'gold standard' tests from which to assess the presence of secondary lymphedema. However, these tests do not have a standard threshold or cut-off point to indicate the presence or absence of lymphedema. Similarly, there is no consistent means of actually measuring volume or circumference. Although validity assessment suggests good interchangeability between different measures of limb volume or circumference, the heterogeneity of the evidence was too substantial to enable the drawing of conclusions about the type of measure that would be most appropriate for diagnosing secondary lymphedema. In addition, the different methods of measuring volume or circumference detract from comparisons of sensitivity and specificity. These comparisons are best done by selecting a set measurement method and then varying the cut-off points to estimate the optimal cut-off point using a receiver operating characteristic (ROC) curve.[116] None of the diagnostic testing studies employed an ROC curve, perhaps due to the lack of agreement on a gold standard means of diagnosing lymphedema.

There was no evidence to suggest an adequate diagnostic testing protocol. The studies failed to provide an indication of suitable frequencies of testing or time spans within which testing should be done. Additionally, there was no information to suggest whether the type of diagnostic test would have an affect on the choice of treatment or on patient outcomes.

Regarding treatment for secondary lymphedema, there was no evidence concerning the optimal criteria to initiate or stop treatment. While the studies suggested that most treatments did reduce the size of the lymphatic limb, there was too much heterogeneity in terms of treatments, inclusion and exclusion criteria, and treatment protocols to suggest the optimality of one type of treatment over another. Despite the multiplicity of inclusion and exclusion criteria, the studies did not contain reports of treatment benefits in any subgroup of patients.

Adverse effects were only reported in a small number of studies. The adverse effects that were reported were generally rare and mild, and unlikely to be a major clinical issue.

The methodological quality of the abstracted studies was generally regarded as 'fair'. Many of the quality issues were possibly related to a lack of adequate reporting rather than to methodological shortcomings in the conduct of the research. However, the authors of some studies omitted the reporting of fundamental elements of their research. There were reliability articles that did not contain mention of the intervals between administrations of the tests of interest, none of the validity studies indicated whether index test results were interpreted without knowledge of reference test results, and the majority of RCTs did not include comment on whether outcome assessors were blinded. While reporting oversight may be one reason for these

omissions, the fundamental nature of the omitted elements suggests a certain degree of caution should be exercised when interpreting study results. This is reflective of one possible default attitude toward quality, namely to assume inadequate quality unless the study authors present evidence to the contrary.[60]

Although the quality of the abstracted articles suggests the need for a guarded approach to interpreting results, quality did not appear to play a major role the answers to the key questions. The articles were far too heterogeneous in terms of test, treatment, and outcome to ascertain whether studies of a certain quality tended to group around any particular test, treatment, or outcome. Indeed, most of the studies were of 'fair' quality anyway, which suggests that quality is not a major factor in the response or interpretation of the key questions.

In looking at the abstracted articles as a whole, it can be concluded that there is no evidence in the literature to suggest an optimal diagnostic testing protocol, an optimal frequency or duration of treatment, the most efficacious treatment combinations (including the use of maintenance therapy), and the length of time for which persons should be tested or treated for lymphedema.

Recommendations for Future Research

Diagnostic Testing. Prior to the initiation of further research into diagnostic testing, clinicians and researchers in the field of secondary lymphedema need to agree on a uniform, gold standard, diagnostic test. Existing work suggests that limb volume or circumference has already emerged as the de facto gold standard, but a set means of measuring volume or circumference should be adopted by the clinical and research communities. Ideally, this set means should be accessible by clinical and research centers globally to promote uniformity. If the strong validity of different measures of volume or circumference in persons with breast cancer is emblematic of the situation in other patient populations, then simple, basic, readily usable, and currently existing methods should be preferred to expensive devices that might not provide an improvement in diagnostic accuracy. In other words, a simple tape measure need not be replaced by an expensive machine if the concurrent validity between methods is good and the machine does not improve upon the number of patients who can be assessed within a clinically relevant timeframe.

Once the gold standard test has been adopted, work must proceed to establish a meaningful cut-off point that will be uniformly regarded as the threshold to distinguish a person with secondary lymphedema from a person without secondary lymphedema. Comparison of different cut-off points using ROC curves is recommended to achieve this objective.

Over time, new and better tests may be developed and this will necessitate a comparison against the gold standard. A comparative study should recruit patients immediately after a medical event (e.g., tumor resection) that is known to cause secondary lymphedema. Patients would then be assessed at regular intervals using the gold standard test and the new test. It may not be possible to blind patients to the type of test they receive, but different assessors should be employed to independently assess each patient on the different tests within a time frame that is short enough to control for changes in patients' lymphedema status over time. The tests results could be used to calculate test-retest and interrater reliability, as well as validity and sensitivity and specificity. The cut-off points for the new test could also be varied to create ROC curves.

Treatment. Different treatment regimens should be compared in RCTs. Treatment protocols should be clearly described and randomization should be conducted via computer-generated

algorithms. RCTs must be adequately powered to detect a clearly defined primary outcome. As a multiplicity of outcomes has been reported, making cross study comparisons and any future meta-analyses difficult, commonly agreed upon outcomes should be encouraged. If the authors believe a priori that important subgroup effects are possible, then the study should be powered to detect effects in these subgroups as well. Experimental and comparator treatments must be clearly labeled and the comparator should be a standard treatment regimen for secondary lymphedema. Although sham treatments (e.g., laser) may satisfy the minimum regulatory requirements for showing efficacy, the real-world clinical utility of a novel treatment would best be demonstrated against an existing, standard treatment. Sham treatment may be an option if the experimental treatment is intended to be an adjunct to standard therapy (e.g., laser given in addition to MLD and compression bandaging, with one group getting real laser treatment, the other getting sham laser, and both receiving MLD and compression bandaging). Maintenance therapies, where used, should be clearly described by study authors. Blinding of study participants, clinicians, and the healthcare professionals who administer treatment may not be possible due to the nature of the therapies, but at a minimum the outcome assessors should be blinded to treatment.

Most of the studies abstracted for this report involved lymphedema to the upper extremities. Lower limb lymphedema was not well represented in the studies, despite its high incidence from cancer treatment.[19] More RCTs should be conducted in patients with secondary lymphedema in the lower limbs.

Although a great deal of research into the diagnosis and treatment of secondary lymphedema has already been undertaken, there is no evidence to suggest the optimal diagnostic test or treatment. Similarly, there is no evidence to suggest whether certain tests or treatments may benefit some types of patients more than others. The field of research into secondary lymphedema is ripe for advancement and the contents of this report may serve as a springboard to guide future scientific endeavors in this domain.

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