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The treatment of lymphedema related to breast cancer: a systematic review and evidence summary

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Abstract *Goals of work:* To provide an evidence summary report on the question: What are the treatment options for women with lymphedema following treatment for breast cancer? *Methods:* Cancer Care Ontario's Supportive Care Guidelines Group (SCGG) employed systematic review methodology to produce an evidence summary on this topic. Evidence-based opinions were formulated to guide clinical decision making, and a formal external review process was conducted to validate the relevance of these opinions for Ontario practitioners. *Results:* The systematic review search strategy identified ten randomized controlled trials which form the basis of this evidence summary report. Four key opinions offered by the SCGG are outlined below. Responses from the practitioner feedback process supported the validity of these opinions in Ontario. (1) There is some evidence to suggest that compression therapy and manual lymphatic drainage may improve established lymphedema, but further studies are needed. Compression garments should be worn from morning to night and be removed at bedtime. Patients should be advised

that lymphedema is a lifelong condition and that compression garments must be worn on a daily basis. Patients can expect stabilization and/or modest improvement of edema with the use of the garment in the prescribed fashion. (2) There is no current evidence to support the use of medical therapies, including diuretics. (3) Additional efforts to define relevant clinical outcomes for the assessment of patients with lymphedema would be valuable. (4) These opinions are appropriate for patients with more than mild lymphedema, where the signs and symptoms are considered significant from the patients' perspective.

Keywords Lymphedema · Breast neoplasms · Systematic review · Evidence summary · Lymphedema management

Introduction

Lymphedema is a major source of morbidity for people living with cancer, either as a direct result of the tumor or

as a side effect of treatment. Quality of life, in both a physical and emotional sense, can be dramatically affected.

Breast cancer patients are particularly prone to lymphedema. In Ontario, it was estimated that there would be 8000 new cases of breast cancer in 2003. The exact incidence of lymphedema has been difficult to establish given the variability in how lymphedema is defined, the degree to which it is clinically relevant, the extent of surgery or radiotherapy, and potential reporting bias [12, 18, 19, 21]. Estimates of lymphedema incidence among breast cancer patients include 10% from surgery alone, increasing to 20–30% when the treatment includes radiation therapy [12, 18, 19, 21]. Sentinel lymph node biopsy is associated with a lower risk of morbidity including lymphedema [4, 10, 16, 29]. While the use of this technique could reduce the likelihood of developing lymphedema, the effectiveness in providing prognostic information over more traditional lymph node dissection procedures remains to be defined. In addition, lymphedema remains a problem for those patients who have high-risk disease where axillary lymph node dissection and/or irradiation are deemed necessary.

In Ontario, between 800 and 2400 women diagnosed with breast cancer in 2003 can expect to develop lymphedema at some point during their life. The risk of developing lymphedema following the management of breast cancer is related to the type of treatment received, such as axillary lymph node dissection (versus the use of sentinel lymph node biopsy) and nodal irradiation. While the majority of women with breast cancer-related lymphedema will have mild swelling that may never require treatment, a significant subset of patients will have clinically significant lymphedema that would benefit from and warrant consideration for active intervention. Information and resources for treatment are limited and may be difficult to access. Problems associated with lymphedema are economic as well as cosmetic—public and private health insurance plans usually cover only a limited proportion of the costs associated with ongoing management.

Given the diversity of treatments for this condition, the Supportive Care Guidelines Group (SCGG), part of Cancer Care Ontario's (CCO) Program in Evidence-based Care (PEBC), performed a systematic overview and developed an evidence summary to address the following question: What are the treatment options for women with lymphedema following treatment for breast cancer?

The original intention was to develop a clinical practice guideline with recommendations to address this question, through the process of updating the evidence and recommendations previously published in the Canadian national guideline on this topic produced by the Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer [11]. However, the PEBC distinguishes between clinical practice guidelines and evidence summaries, based on the level of evidence available. Guideline documents are produced for topic areas where sufficient high quality evidence exists

to make clinical recommendations. Evidence summaries are produced for topic areas where, although the evidence is insufficient to make recommendations, that evidence can be synthesized, gaps and limitations presented, and opinions offered for clinical practice. An explicit decision is made by each PEBC guidelines group to select the appropriate format for the presentation of the evidence. Within this framework, the relative lack of sufficient high-quality evidence on the current topic precluded definitive recommendations on which to base a practice guideline. This report presents the resulting evidence summary and interpretation of the evidence that clinicians may use as an aid to providing evidence-based care for lymphedema.

Methods

Evidence summary development

This evidence summary was developed by CCO's PEBC, using the methods of the Practice Guidelines Development Cycle [5]. A detailed description of the methods used for the systematic review and evidence summary development is available at <http://www.cancercare.on.ca/pdf/pebc13-1f.pdf>.

Literature search strategy

The SCGG used the evidence presented in the national guideline on the same topic produced by the Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer [11]. The national guideline was based on a systematic review of the English-language literature found in MEDLINE (1966 to April 2000) and CANCERLIT (1985 to April 2000) and references cited in reviews and textbooks. The SCGG conducted a search for new evidence for the period from May 2000 through March 2002 in MEDLINE, CANCERLIT, HealthStar, CINAHL, PREMEDLINE, and the Cochrane Library. The search used the exploded subject headings 'breast neoplasms', 'lymphedema' and 'clinical trials', the text words 'breast', 'mammary', 'carcinoma', 'cancer', 'neoplasm', 'lymphedema' and 'lymphoedema', and the publication type 'clinical trial'. Reference lists in papers found by the update search and relevant databases were also searched to identify new and ongoing trials. Evidence was selected and reviewed by two members of the SCGG.

Inclusion and exclusion criteria

Studies were eligible for inclusion in the evidence summary if they (1) were randomized trials or systematic reviews of randomized trials of treatments for lymphedema related to treatment for breast cancer and (2) measured the effect of therapy for lymphedema on arm volume, symptom control, quality of life, or cosmetic results. Due to resource limitations, reports published in languages other than English were excluded.

Outcomes of interest

The primary outcome of interest was the proportion of patients with a reduction in lymphedema. Secondary outcomes included the difference in arm volume between the patient's treated and control

Table 1 Interventions evaluated in randomized controlled trials of therapy for lymphedema related to breast cancer (for details on interventions, see Table 3)

	Refer- ence	Placebo control	No- treatment control	Exercise + self-massage therapy	Elastic sleeve/com- pression garment	Manual lymph drainage	Pneumatic compres- sion pump	Electrically stimulated lymphatic drainage	Medical therapy
Treatment	13			+	+				
	1				+	+			
	8		+				+		
	17					+	+		
	3				+			+	
	7	+							+
	26	+							+
	27	+							+
	20	+							+
Prevention	27		+		+	+			

arm, the reduction in symptoms associated with lymphedema, quality of life, and adverse effects of treatment.

Synthesizing the evidence

The randomized studies were categorized by the interventions being evaluated. A detailed discussion of each study and the outcomes of interest are presented below. Pooling the available data was not felt to be appropriate for several reasons. Not only did physical and medical therapies need to be considered separately, but also no two physical therapy trials compared the same or similar types of therapy. Furthermore, there was significant variation in outcome assessment methods across the studies.

External review of the evidence summary report

External review of the evidence summary report was obtained through a mailed survey from a sample of Ontario oncologists, nurses, and physiotherapists. Survey items addressed the quality of the evidence summary report, the interpretation of the available evidence, and whether there is a need to develop a practice guideline when sufficient evidence is available. Written comments were invited. The SCGG reviewed the results of the survey and revised the evidence summary report in response to the external reviewers' comments. CCO's Practice Guidelines Coordinating Committee (PGCC) gave final approval to the evidence summary.

Main results

Evidence summary

Literature search results

The Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer published a national guideline to provide an evidence-based approach to the management of lymphedema in women who have been treated for breast cancer in Canada [11]. Five systematic reviews identified [6, 9, 15, 22, 24] by the SCGG included fewer trials than did the national guideline [11]. Results for the two Cochrane systematic review protocols found are not yet available [2, 14]. However, ten ran-

domized controlled trials (RCT) met the eligibility criteria and form the basis of this evidence summary [1, 3, 7, 8, 13, 17, 20, 25, 26, 27]. Seven of these trials were included in the national guideline [1, 3, 7, 8, 17, 20, 27], and three were identified by update searches [13, 25, 26]. Several other groups have produced clinical practice guidelines on lymphedema [23, 30]¹, but these were not based on systematic reviews of the evidence. Trial characteristics are described below and are summarized in Tables 1 and 2; results are presented in Table 3.

Study interventions

The interventions evaluated in the randomized trials included compression bandaging, compression garments, manual lymphatic drainage (MLD), comprehensive lymphedema management programs/complex physical therapy/complex decongestive therapy (CDT)/complete decongestive therapy, pneumatic compression pumps, electrically stimulated lymphatic drainage, and medical therapies (Table 1; intervention descriptions in Table 4).

Six randomized trials evaluated physical therapies [1, 3, 8, 13, 17, 25] and four assessed medical therapies [7, 20, 26, 27]. One study employed physical therapy as a preventive therapy between surgery and the commencement of radiotherapy [25], while the remaining nine studies used therapy for symptomatic lymphedema. The studies were generally small and underpowered, with sample sizes ranging from 25 to 104 patients.

Of the physical therapy trials, two incorporated a no-intervention control arm [8, 25], and four employed active controls [1, 3, 13, 17] comparing two different forms of

¹ Two additional clinical practice guidelines, one by the New Zealand Guidelines Group (NZGG) on surgical management of breast cancer, and one by the National Breast Cancer Centre in Australia on management of early breast cancer surgery, were identified online at the time of our search but are no longer electronically accessible.

Table 2 Characteristics of randomized trials of therapy for lymphedema

	Reference	Experimental treatment	n	Control treatment	n	Duration of therapy (weeks)	First outcome assessment	Subsequent outcome assessments	Definition of lymphedema	Duration of lymphedema
Physical therapy as treatment	13	Elastic compression sleeve worn day and night + exercise and self-massage	14	Exercise and self-massage	11	4–28	4 weeks	8–28 weeks	Not reported	Not reported
	1	Manual lymphatic drainage eight times over 2 weeks + daily self-massage + standard therapy	20	Standard therapy: compression garment, education, exercises	22	2	4 weeks	3–12 months	Difference in volume between arms ≥ 200 ml or in circumference ≥ 2 cm (at one point); difference in volume $< 30\%$	14.5 months (median)
	8	Intermittent pneumatic compression (constant pressure of 60 mmHg) five times per week for 2 weeks, repeated after 5-week break	40	No treatment	40	9	9 weeks	None	Difference in circumference between arms > 10 cm (totaled over seven points)	6.5 months (mean)
	17	Sequential pneumatic compression (40–60 mmHg) five times per week for 2 weeks + compression sleeve	12	Manual lymphatic drainage five times per week for 2 weeks + compression sleeve	12	2	2 weeks	None	Difference in volume between arms $> 10\%$	10 months (median)
	3	Electrically stimulated lymphatic drainage, two 2-week cycles with 5-week break between + elastic sleeve	34	Elastic sleeve	34	9	2 months	6 months	Difference in circumference between arms > 10 and < 20 cm (summed over seven points)	Not reported
Medical therapy as treatment	7 (cross over)	Coumarin (5,6-benzo- $[\alpha]$ -pyrone) (400 mg once a day for 6 months)	18	Placebo	13	24	6 months	None	“Moderately severe to severe grade 2”	8 years (mean)
	27 (cross-over)	O-(β -hydroxyethyl)-rutosides (1000 mg three times a day for 6 months)	13	Placebo	13	24	1 month	2–6 months	Grade III by International Society for Lymphology criteria, “not spontaneously reversible by ... elevation, compression, etc.”	6.6 years (mean)
	20 (cross over)	Coumarin (5,6-benzo- $[\alpha]$ -pyrone) (200 mg twice a day for 6 months)	67	Placebo	71	24	2 months	4–6 months	“Not immediately reversible by elevation or compression of the arm”	1–2 years: 31%; > 2 years: 69% (median)
	26	Daflon (500 mg twice a day for 6 months)	51	Placebo	53	24	6 months	None	“Mild to severe”	3.2 years (median)
Physical therapy as prophylaxis	25	Active arm 1: lymphatic drainage day 1 beginning of RT, time not stated; Active arm 2: compression adhesive bandages day 1 beginning of RT, time not stated	^a	No treatment	^a	Day after surgery to start of RT	Day 5 after surgery	Prior to RT, then 6 months and 5 years after RT	Not reported	None

^a 50 patients randomized, 10 excluded

physical therapy. None of these trials used blinded outcome assessments. All four medical therapy studies were placebo-controlled and employed a crossover design with no washout period [7, 20, 26, 27].

Patient characteristics

All studies included patients with established arm lymphedema, with the exception of one prophylactic study in women undergoing mastectomy and lymph node dissection [25]. Two studies included patients with leg edema but the results of these studies were presented

Table 3 Results of randomized trials of therapy for lymphedema

Reference	Intervention	Response rate ^a n (%)	Mean reduction in arm volume from baseline	Improvement of symptoms
13	Compression sleeve + exercise/ massage	12 (86%)	Not reported	Not reported
1	Exercise + self-massage MLD + self massage + standard therapy	4 (36%); <i>P</i> =0.042 ^b Not reported	48% (95% CI 32–65%) ^c 60% (95% CI 43–78%) ^c ; <i>P</i> =NS	No significant difference between groups
8	Standard therapy: compression garment, education, exercise Intermittent pneumatic compres- sion	10 (25%)	1.9±3.7 cm	Not reported
17	No treatment Sequential pneumatic compres- sion	8 (20%) Not reported	0.5±3.3 cm; <i>P</i> =NS 28 ml	No significant difference between groups
3	Manual lymphatic drainage Electrically stimulated lymphatic drainage	13 (38%)	75 ml; <i>P</i> =0.11 “About 17% in both groups”	Not reported
7	Elastic sleeve 5,6-Benzo- α -pyrone	10 (29%) Not reported	35±0.42% ^c 41±0.43% ^{c,d} ; <i>P</i> <0.001	48 3; <i>P</i> <0.001
27	Placebo <i>O</i> - α -Hydroxyethyl-rutosides	Not reported	Not reported, <i>P</i> <0.01 in favor of drug	28
20	Placebo Coumarin	Not reported	Increased by 58 ml	12; <i>P</i> <0.05 No significant difference be- tween groups
26	Placebo Daflon Placebo	Not reported	Increased by 21 ml; <i>P</i> =0.8 “No significant differences”	Discomfort score: 4.7 (SD 1.9) Discomfort score: 4.8 (SD 2.1); <i>P</i> =NS
25 (pro- phylaxis)	Manual lymphatic drainage Compression–adhesive bandages No treatment	Lymphedema in 30% Lymphedema in 55% Lymphedema in 45%	Not reported	Not reported

^a Response rate; patients with reduction in swelling; Hornsby [13] defined response rate as any reduction in arm volume; Dini [8] and Bertelli [3] defined response rate as a reduction in volume (delta) of at least 25%

^b Reviewer’s calculation; Fisher’s exact test (one-tailed)

^c Reduction in difference between normal and affected arm

^d Mean percent of normal calculated by volume of edematous arm/volume of normal arm

separately for patients with lymphedema related to breast cancer [7, 27]. Definitions of lymphedema varied, and the reports of two studies did not provide a definition [13, 26]. The duration of established lymphedema prior to entering the study differed between the physical and medical therapy trials, with the median or mean duration of lymphedema for the physical therapy studies ranging from 6.5 to 14.5 months and 3.2 to 8 years for the medical therapy trials.

Outcome assessment

The methods by which outcomes are measured can have a direct impact on the reliability and validity of the resulting outcome. In the included studies, lymphedema and its response to therapy were determined in a variety of ways. In four trials, arm volume was measured using the water-

tank submersion method [7, 13, 17, 27]. In six studies arm volume was estimated by taking limb circumference measurements at a number of sites (between five and eight) [1, 3, 8, 20, 25, 26]. The amount of edema was determined by calculating the difference in volume between the edematous and the normal arm. Outcomes were expressed as either an absolute difference in size between the affected and the contralateral arm [8, 17, 20] or as the relative change in the amount of edema (reported as a percentage of baseline) [1, 3, 7, 26, 27]. Table 3 provides definitions of response rates.

The proportion of patients developing lymphedema was used as an outcome measure in the prophylactic study by Pecking et al. [25]. Lymphedema was defined as an increase in arm circumference of 2 cm or more, but the measurement location was not stated [25].

The reports of six studies included symptoms associated with lymphedema (swelling, discomfort, cramping,

Table 4 Interventions assessed in randomized trials

Intervention	Description
Compression bandaging	This is usually the first therapy used to reduce edema. Multilayered “short-stretch” bandages are used in the reduction phase of treatment. These bandages provide low compression at rest and enhance the effect of muscular activity on the clearance of lymphatic fluid from the limb.
Compression garments	A compression sleeve may be used to reduce edema in mild cases or to maintain the reduction achieved by compression bandaging or other volume-reducing techniques described below. It is custom fitted to apply external pressure in the range of 20–60 mmHg. These garments typically cover the arm from wrist to mid-humerus and may be prescribed with an attached gauntlet or separate glove. They are usually removed overnight.
Manual lymphatic drainage	Gentle massage of the skin surface performed by a specially trained massage therapist. The massage typically starts at the trunk, bordering the edematous area, and slowly moves more distally, ending with the hand and fingers. The aim is to stimulate and direct lymphatic flow from areas of stasis to functioning lymphatics. It is the only treatment that moves fluid out of the upper arm and shoulder where it accumulates above the compression bandage or sleeve.
Comprehensive lymphedema management programs; complex physical therapy; complex decongestive therapy (CDT); complete decongestive therapy	These therapies include all of the above-mentioned treatments in an intensive regimen that includes patient education, meticulous skin hygiene, manual lymph drainage, bandaging, exercises, and compression garments. Patients are typically seen daily for approximately 6 weeks and then fitted with a compression garment.
Pneumatic compression pump	Pneumatic devices are used to administer pressure on the involved arm, using either a single chamber or multichamber sleeve. The pump is set to deliver a prescribed amount of intermittent pressure. The multichamber sleeve is able to deliver the pressure in a sequential fashion. Pumps are available through some physiotherapists, or patients can buy or rent them from a home health supply company. The pump is used for several hours a day and the patient must apply compression in the form of bandaging or a sleeve following a pump-down session. A course of treatment lasts from a few days to 4 weeks. The amount of compression used must be prescribed by a physician.
Electrically stimulated lymphatic drainage	A less commonly used intervention involves a sequence of electrical impulses delivered through electrodes placed over lymphatic stations or motor points between the supraclavicular region and the wrist.
Medical therapies	Treatment with oral drugs, such as benzopyrones, that have the potential to stimulate proteolysis by tissue macrophages have been evaluated in clinical trials.

heaviness, pain, tightness, aching, paresthesia, inflammation, dryness, impaired function, and decreased mobility), and some included general well-being [1, 7, 17, 20, 26, 27]. Scales included better/same/worse [1, 7, 27], none/mild/moderate/severe [20], and visual analogue scales [17, 26]. The effect of therapy on quality of life was not evaluated in any of the trials. Adverse effects of therapy were discussed in none of the reports of physical therapy trials, but were discussed in the reports of two of the four medical therapy trials [20, 26], but with no grading classification.

Summary of trial results

In only one trial [25] was the use of a compression garment/elastic sleeve compared with no treatment. There was no significant difference in the rates of edema between the two groups (55% with compression garments versus 45% for no treatment). Time to development of edema was similar in the two groups (16.6 months for compression garment versus 17.3 months for no treatment).

Hornsby [13] compared the use of a compression garment plus self-massage with self-massage alone in women referred to a lymphedema clinic. Patients in the

experimental treatment group were fitted with elastic compression sleeves to be worn day and night. A physiotherapist taught both experimental and control patients exercises and self-massage. Although treatment and follow-up was intended to last 12 months, 32% of the participants dropped out after the 4-week assessment. By 16 weeks, the entire control group and half the experimental group had left the trial. During the first 4 weeks of treatment, 12 of 14 women in the experimental group and 4 of 11 in the control group showed a reduction in swelling as measured by the amount of fluid displaced from an immersion tank (odds ratio for reduction in swelling, 6.4; 95% confidence interval, 0.8 to 55.2; reviewer's calculation).

In the only trial in which the prophylactic effects of MLD were compared with no treatment, Pecking et al. [25] found that fewer patients developed lymphedema with MLD (30% versus 45% for no treatment), but the difference was not statistically significant. The time to development of lymphedema was 25.3 months versus 17.3 months ($P=0.02$), favoring MLD. In no study was MLD evaluated as a single modality versus no intervention for the treatment of established lymphedema.

Pecking et al. [25] also compared MLD with the use of compression garments for the prevention of lymphedema. Fewer patients developed lymphedema with MLD (30%

versus 55% for no treatment), but the difference was not statistically significant.

Anderson et al. [1] compared standard therapy (compression garment + education + exercise) with complex physical therapy (MLD + self massage + standard therapy) in women with lymphedema following breast cancer treatment. Custom-made sleeves and gloves were used providing 32–40 mmHg of compression. The daily duration of use was not specified. MLD was performed over a 1-h period eight times over 2 weeks. Lymphedema was measured at 1 and 3 months from baseline. There was a reduction in edema in both groups over a 3-month period but no significant difference between treatments (a 60% reduction in the difference between arms from baseline for control versus 48% for MLD). There were no significant differences in symptom improvement between the groups. The protocol allowed members of the control group to cross over to MLD after 3 months in the trial. From this point on, all participants were followed for a further 9 months. Of 22 control patients, 10 elected to receive MLD plus standard therapy after the 3-month assessment.

Dini et al. [8] randomized women with postmastectomy lymphedema to either intermittent pneumatic compression or no treatment. Constant pressure of 60 mmHg was applied throughout a 2-h treatment session and repeated five times per week for two consecutive weeks, which constituted one cycle of treatment. After a 5-week gap, the cycle was repeated. Thus, the total intervention time was 9 weeks, during which no concomitant physical therapy was allowed. The average difference between arms (delta) after 9 weeks was 14.1 cm for the control group and 14.2 cm for the pneumatic compression group. When the post-treatment delta was adjusted for baseline value, the difference between groups was not significant ($P=0.084$). Of the control patients and patients in the treatment group, 20% and 25%, respectively, experienced reductions in lymphedema of 25% or more ($P=0.59$).

Johansson et al. [17] compared pneumatic compression with MLD. The administration of pressure to the involved arm was quite different from that used by Dini et al. [8] and involved a sequential approach in which nine compression cells applied 40–60 mmHg pressure in a 2-hour treatment session. Treatment was administered 5 days per week for 2 weeks. Patients wore a compression sleeve for 2 weeks before randomization and were instructed to wear the sleeve during the day for the duration of the trial. Although no significant differences were detected between groups, lymphedema was reduced by 49 ml (7%) during the 2-week prerandomization phase when compression sleeves were worn. Further reductions of 75 ml in the MLD group and 28 ml in the pneumatic compression group ($P=0.11$) were achieved during 2 weeks of treatment.

Bertelli et al. [3] compared electrically stimulated lymphatic drainage plus the use of a compression garment

with a compression garment used alone. Patients in both groups wore a standard (not custom-made) elastic sleeve for 6 h per day. Electrically stimulated lymphatic drainage (ESD) was used as induction therapy in the experimental group. Eight electrodes were placed between the supraclavicular region and the wrist over lymphatic stations or motor points. A sequence of electrical impulses at 4.5 kHz was administered over 30 minutes. No other treatment for lymphedema was permitted during the 9-week duration of the trial. The mean absolute differences (delta) between the edematous and normal arm at 2 months were 12.6 cm and 12.1 cm, respectively, for the treatment and control groups. At 6 months from baseline (i.e., 4 months after the end of treatment), the mean delta values were 12.4 and 11.6, respectively. Response rates at 2 months were 38.3% with ESD and 29.4% without. None of the differences between groups were statistically significant.

Three different medical therapies were tested in four placebo-controlled RCTs. Benzopyrones, compounds with the potential to stimulate proteolysis by tissue macrophages, were evaluated in three trials. Casley-Smith et al. [7] and Loprinzi et al. [20] used 5,6-benzo- α -pyrone (coumarin); Piller et al. used *O*- β -hydroxyethyl-rutosides [27]. In two of these trials, patients with leg edema were included in addition to patients with arm lymphedema from breast cancer, but the data on response to treatment were presented separately for the two patient groups [7, 27]. Pecking et al. studied Daflon, a purified micronized flavonoidic fraction with a potential mechanism of action that improves venous tone, capillary permeability and resistance, and lymphagogue activity [26]. These drugs were taken orally for 6 months.

The participants in the medical therapy RCTs tended to have lymphedema of greater severity and longer duration than those in the physical therapy trials described above. In two of the three benzopyrone trials statistically significant reductions in arm volume and improvements in symptoms were detected in favor of the active drug compared with the placebo (Table 3) [7, 27]. No significant difference between coumarin and placebo [20] was detected. Although no serious adverse effects were reported for the first two trials [7, 27], 9 of 140 women treated with coumarin for 6 months had evidence of hepatotoxicity (serum aminotransferase concentrations 2.5 times the upper limit of normal), compared with none during placebo treatment ($P<0.006$) [20]. There was no significant difference in arm volume or discomfort score between Daflon and placebo [26].

Synthesizing the evidence

Among the RCTs evaluating physical therapies, the only positive finding was an incremental benefit when an elastic sleeve was added to self-massage therapy [13].

Table 5 Practitioner feedback survey results for oncologists

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear	125 (97%)	2 (2%)	1 (1%)
There is a need for an evidence summary on this topic	105 (82%)	20 (16%)	3 (2%)
The literature search is relevant and complete in this evidence summary	115 (91%)	11 (9%)	1 (1%)
I agree with the methodology used to summarize the evidence	121 (95%)	5 (4%)	1 (1%)
I agree with the overall interpretation of the evidence in the evidence summary	122 (95%)	5 (4%)	1 (1%)
The Opinions of the Disease Site Group section of this evidence summary is useful	105 (84%)	16 (13%)	3 (2%)
An evidence summary of this type will be useful for clinical decision making	86 (68%)	33 (26%)	6 (5%)
At present, there is insufficient evidence to develop a practice guideline on this topic	97 (77%)	16 (13%)	13 (10%)
There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available	107 (86%)	13 (10%)	2 (2%)
Do you believe that the evidence supports the use of compression therapies in your own practice?	Very likely or likely 74 (59%)	Unsure 31 (25%)	Not at all likely or unlikely 21 (17%)

Pneumatic compression, compared to no intervention, was not associated with a significant improvement [8]. However, the direction of the observed response rates and changes in arm volume favored pneumatic compression. None of the other more-aggressive approaches showed a benefit when compared with less-aggressive controls.

In terms of medical therapies, there was contradictory evidence about the role of coumarin in lymphedema management. In two trials very similar study designs were used but opposite conclusions were arrived at [7, 20]. This difference may be explained by the fact that ongoing physical therapy appeared to be expected in one trial [20], while in the other [7] the use of physical therapy was excluded. The role of *O*- β -rutosides is promising but requires further study [27]. The data do not suggest that Daflon has clinically significant activity in the treatment of lymphedema [26].

None of the trials showed significant adverse effects related to the test interventions, but this should not be interpreted as evidence supporting the use of therapies with no proven value. The psychological, economic, and time implications cannot be ignored. There were no trials meeting the eligibility criteria designed to address the role of common clinical recommendations such as the use of diuretics, general skin care, or non-medical therapies (i.e., magnetic therapy or infrared garments). Therefore, recommendations on their use cannot be made.

Prevention of lymphedema was addressed in only one trial, in which compression bandages were compared to lymphatic drainage. The choice of radiotherapy and surgical techniques (e.g., sentinel lymph node biopsy) may have a more prominent role in reducing lymphedema than interventions designed to manage established lymphedema.

External review of the evidence summary report

A draft report of the evidence summary was reviewed and feedback was obtained through a mailed survey of 287 practitioners in Ontario (107 medical oncologists, 45 radiation oncologists, and 135 surgical oncologists) and 52 non-physician health-care professionals (22 nurses, 19 physiotherapists, and 11 professionals with interest in lymphedema management).

Results of practitioner feedback mailing to oncologists

Out of 287 surveys sent to oncologists, 158 responses were received (55% response rate). Key practitioner feedback survey results for the 125 oncologists that indicated that the report was relevant to their clinical practice are summarized in Table 5.

Results of practitioner feedback mailing to health-care professionals

Out of 52 surveys sent to non-physician health-care professionals, 33 responses were received (63% response rate). Key survey results for the 28 respondents of this group for whom the report was relevant are summarized in Table 6.

Summary of written comments (oncologists)

Written comments were provided by 48 oncologists (38%). Several commented that the evidence summary confirmed that lymphedema is a difficult problem to deal

Table 6 Practitioner feedback survey results for non-physician health-care professionals

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear	27 (96%)	1 (4%)	0
There is a need for an evidence summary on this topic	26 (93%)	2 (7%)	0
The literature search is relevant and complete in this evidence summary	13 (54%)	7 (29%)	4 (17%)
I agree with the methodology used to summarize the evidence	21 (78%)	6 (22%)	0
I agree with the overall interpretation of the evidence in the evidence summary	21 (78%)	3 (11%)	3 (11%)
The Opinions of the Disease Site Group section of this evidence summary is useful	22 (92%)	0	2 (8%)
An evidence summary of this type will be useful for clinical decision making	23 (82%)	2 (7%)	3 (11%)
At present, there is insufficient evidence to develop a practice guideline on this topic	23 (82%)	3 (11%)	2 (7%)
There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available	28 (100%)	0	0
Do you believe that the evidence supports the use of compression therapies in your own practice?	Strongly agree or agree 20 (71%)	Neither agree nor disagree 8 (29%)	Disagree or disagree strongly 0

with effectively and that there is insufficient evidence available at this time for a practice guideline.

In terms of the scope of the evidence summary, several practitioners suggested including opinions on the use of diuretics, general skin care, vacuum-assisted closure, microvascular surgery, and non-medical therapies such as magnetic therapy and infrared garments. A statement that such recommendations cannot be made due to insufficient evidence was added to the document. Suggestions were also made to include the methods of measuring lymphedema and outcome assessment. The SCGG found this to be beyond the scope of the evidence summary but agreed that standardization of these parameters is strongly encouraged in future studies. Two practitioners suggested including literature related to prevention; however, this was also beyond the focus of the report. A comment on the risk factors for lymphedema, such as axillary node dissection and nodal irradiation, was added. Several practitioners commented that compression therapy has an important role in the management of lymphedema and that they will continue to use this technique. The remaining comments were of an editorial nature, and the SCGG modified the final report accordingly.

Summary of written comments (health-care professionals)

Written comments were provided by 23 non-physician health-care professionals (82%). There was general agreement that more evidence is needed to support recommendations and that the benefits of current therapies are unproven. Three respondents stressed the need for practical advice concerning skin care, exercise, and maintenance of a healthy body weight. One respondent questioned whether evidence on sentinel node biopsy and the inci-

dence of lymphedema exists. Comments in response to these requests were added to the final document. Seven respondents noted that the limitation to English-language articles was too restrictive. The PEBC typically limits searches to English-language articles. However, in response to the comments, non-English articles will be included in the next update of this evidence summary. Three respondents felt that the issue of quality of life needed to be addressed. Quality of life was included as one of the outcomes of interest; however, no data were available from the included studies.

Four respondents expressed concern that the first statement in the Opinions section might lead physicians to tell patients that nothing can be done. They suggested that other methods of supportive care such as education and general skin care advice be included in this section. Several respondents agreed that more and better-designed trials are required to evaluate all types of compression, including compression pumps, bandaging, and garments, as well as the effectiveness of complete decongestive therapy and MLD and other types of massage. The need to educate medical professionals to recognize and treat lymphedema, as well as the prophylactic education of patients, was also noted. One respondent suggested establishing a database in Ontario to track the incidence of lymphedema in cancer patients. Two respondents stressed the need for consistency in defining and measuring lymphedema and also clinically relevant outcome measures. The authors agreed with the comments made and hoped that the evidence summary would provide the impetus for further research in this area.

Practice Guidelines Coordinating Committee approval process

After data and comments from the external review process were incorporated, the evidence summary report was circulated to 13 members of the PGCC of CCO. All 8 of the 13 members who returned ballots approved of the evidence summary.

Conclusions

The feedback from nurses, physiotherapists, and oncologists from the external review process confirmed the need for an evidence summary on this topic. The lack of sufficient high-quality evidence precludes definitive recommendations. Instead, the SCGG elected to present the evidence through an evidence summary and offers the following opinions based on the evidence reviewed:

- There is some evidence to suggest that compression therapy and MLD may improve established lymphedema, but further studies are needed.
- There is no current evidence to support the use of medical therapies, including diuretics.
- Additional efforts to define relevant clinical outcomes for the assessment of patients with lymphedema would be valuable.
- The SCGG endorses the recommendations from the Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. The use of compression garments is consistent with what is commonly practiced clinically.
- The opinions are appropriate for patients with more than mild lymphedema, where the signs and symptoms are considered significant from the patients' perspective.
- There is insufficient evidence to support an evidence-based recommendation on which to base a practice guideline for the treatment of lymphedema.
- Compression garments should be worn from morning to night and be removed at bedtime. Patients should be informed that lymphedema is a lifelong condition and that compression garments must be worn on a daily basis. Patients can expect stabilization and/or modest improvement of edema with the use of the garment in the prescribed fashion.

Responses from the practitioner feedback process supported the validity of these opinions for Ontario practice.

Future research

Further studies are required to address the role of physical therapies, alone or in combination with other treatment modalities. Fundamental to the interpretation of the evidence are two key methodological issues that require definition to facilitate future research.

1. What is the current standard therapy? Reaching consensus among clinicians and researchers as to what constitutes the 'standard' clinical approach for established lymphedema would be useful. It should be kept in mind that the effects of complex physical therapy and pneumatic compression will not be sustained unless they are complemented with compression bandaging or sleeves.
2. Which outcomes are clinically relevant? Consensus on the important outcomes and how to define them in clinical trials is important. These could include parameters such as the proportion of patients with response, symptom scores, adverse effects, and compliance.

From a measurement perspective, arm volume should be calculated. This method is clinically feasible and gives a better picture of the absolute volume of lymphedema than do circumference measurements [28]. Five-point measurement in both the affected and control limb, as well as hand measurement including several fingers, has been advocated. Definitions for the classification of lymphedema such as mild (<250 ml), marked (250–500 ml) or severe (>500 ml) have been recommended. Validation of these definitions against symptom profiles and patient perceptions could be useful.

From a clinical perspective, the measurement of morbidity related to lymphedema, using tools such as lymphedema-specific quality of life, symptom-measurement instruments, and functional assessments, would provide a more comprehensive assessment. Studies based on these outcomes are more likely to influence clinical practice.

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References

1. Anderson L, Hojris I, Erlandsen M, et al (2000) Treatment of breast-cancer-related lymphedema with or without manual lymphatic drainage: a randomized study. *Acta Oncol* 39:399–405
2. Badger C, Seers K, Preston N, et al (2002) Physical therapies for reducing and controlling lymphoedema of the limbs (Protocol for a Cochrane Review). In: *The Cochrane Library*, issue 2. Update Software, Oxford
3. Bertelli G, Venturini M, Forno G, et al (1991) Conservative treatment of post-mastectomy lymphedema: a controlled, randomized trial. *Ann Oncol* 2:575–578
4. Blanchard DK, Donohue JH, Reynolds C, et al (2003) Relapse and morbidity in patients undergoing sentinel lymph node biopsy alone or with axillary dissection for breast cancer. *Arch Surg* 138:482–487
5. Browman GP, Levine MN, Mohide EA, et al (1995) The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 13:502–512
6. Browning C (1997) The management of lymphoedema. In: Redman S, Pillar C, Turner J, Boyle F (eds) *Lymphoedema: prevalence, risk factors and management: a review of research*. NHMRC National Breast Cancer Centre, Sydney
7. Casley-Smith JR, Morgan RG, Piller NB (1993) Treatment of lymphedema of the arms and legs with 5,6-benzopyrone. *N Engl J Med* 329:1158–1163
8. Dini D, Del Mastro L, Gozz A, et al (1998) The role of pneumatic compression in the treatment of postmastectomy lymphedema. A randomized phase III study. *Ann Oncol* 9:187–191
9. Erickson VS, Pearson ML, Ganz PA, et al (2001) Arm edema in breast cancer patients. *J Natl Cancer Inst* 93:96–111
10. Golshan M, Martin WJ, Dowlatshahi K (2003) Sentinel lymph node biopsy lowers the rate of lymphedema when compared with standard axillary lymph node dissection. *Am Surg* 69:209–211
11. Harris SR, Hugi MR, Olivotto IA, et al, for the Steering Committee for Clinical Practice Guidelines for the Care and Treatment of Breast Cancer (2001) Clinical practice guidelines for the care and treatment of breast cancer: 11. Lymphedema. *CMAJ* 164:191–199
12. Hoe AL, Iven D, Royle GT, et al (1992) Incidence of arm swelling following axillary clearance for breast cancer. *Br J Surg* 79:261–262
13. Hornsby R (1995) The use of compression to treat lymphoedema. *Prof Nurs* 11:127–128
14. Howell D, Ezzo J, Tuppo K, et al (2002) Complete decongestive therapy for lymphedema following breast cancer treatment (Protocol for a Cochrane Review). In: *The Cochrane Library*, issue 2. Update Software, Oxford
15. Jacobson JS, Workman SB, Kronenberg F (2000) Research on complementary/alternative medicine for patients with breast cancer: a review of the biomedical literature. *J Clin Oncol* 18:668–683
16. Jani AB, Basu A, Heimann R, et al (2003) Sentinel lymph node versus axillary lymph node dissection for early-stage breast carcinoma: a comparison using a utility-adjusted number needed to treat analysis. *Cancer* 97:359–366
17. Johansson K, Lie E, Ekdahl C, et al (1998) A randomized study comparing manual lymph drainage with sequential pneumatic compression for treatment of postoperative arm lymphedema. *Lymphology* 31:56–64
18. Kissin MW, Querci della Roveret G, Easton D, et al (1986) Risk of lymphoedema following the treatment of breast cancer. *Br J Surg* 73:680–684
19. Logan V (1995) Incidence and prevalence of lymphedema: a literature review. *J Clin Nurs* 4:213–219
20. Loprinzi CL, Kugler JW, Sloan JA, et al (1999) Lack of effect of coumarin in women with lymphedema after treatment for breast cancer. *N Engl J Med* 340:346–350
21. Markowski J, Wilcox J, Helm P (1981) Lymphedema incidence after specific postmastectomy therapy. *Arch Phys Med Rehabil* 62:449–452
22. Megens A, Harris SR (1998) Physical therapist management of lymphedema following treatment for breast cancer: a critical review of its effectiveness. *Phys Ther* 78:1302–1311
23. Oncology Nursing Society (1998) *Manual for radiation oncology nursing practice and education*. Oncology Nursing Press, Pittsburgh, PA (summary at http://www.ons.org/xp6/ONS/Library.xml/ONS_Publications.xml/Book_Excerpts.xml/ManualRadiationOncology/FrontPage.xml)
24. Pain SJ, Purushotham AD (2000) Lymphoedema following surgery for breast cancer. *Br J Surg* 87:1128–1141
25. Pecking A, Lasry S, Boudinet A, et al (1988) Post surgical physiotherapeutic treatment: interest in secondary upper limb lymphedemas prevention. *Prog Lymphology* 11:562–564
26. Pecking AP, Fevrier B, Wargon C, et al (1997) Efficacy of Daflon 500 mg in the treatment of lymphedema (secondary to conventional therapy of breast cancer). *Angiology* 48:93–98
27. Piller NB, Morgan RG, Casley-Smith JR (1988) A double-blind, cross-over trial of O-(beta-hydroxyethyl)-rutosides (benzopyrones) in the treatment of the arms and legs. *Br J Plast Surg* 41:20–27
28. Ramos SM, O'Donnell LS, Knight G (1999) Edema volume, not timing, is the key to success in lymphedema treatment. *Am J Surg* 178:311–315
29. Schijven MP, Vingerhoets AJ, Rutten HJ, et al (2003) Comparison of morbidity between axillary lymph node dissection and sentinel node biopsy. *Eur J Surg Oncol* 29:341–350
30. Scottish Intercollegiate Guidelines Network (1998) *Breast cancer in women* (publication no. 29). <http://www.show.scot.nhs.uk/sign/guidelines/fulltext/29/index.html>