A PRACTICE GUIDELINE FOR THE MANAGEMENT OF LYMPHOEDEMA

The Japan Lymphoedema Study Group

Management and treatment options for lymphoedema in Japan have traditionally varied between different healthcare institutions. The authors of this article have developed guidelines to standardise treatment of lymphoedema patients, based on scientific evidence. Consensus methods based on the Delphi technique were used when formulating the guidelines. A literature search was conducted and a clinical guideline for lymphoedema, including 11 specific recommendations for clinicians, was constructed. In future, the clinical efficacy of this guideline should be tested in a clinical setting.

Key words

Lymphoedema
Evidence-based medicine
Clinical questions
Delphi method

In Japan, medical reimbursement for compression therapy (garments and bandages) and for prophylactic self-care such as massage in patients at risk of postoperative limb lymphoedema has been accepted by the Ministry of Health, Welfare and Labour since April 2008.

Currently, there are no universally accepted criteria in Japan for the management and treatment of patients with lymphoedema. It is hoped that the guideline outlined in this article will help to inform clinical practice.

The first edition of this guideline was produced in June 2006 by a research group funded by the 12th Japanese Society of Breast Cancer Group Research (Kitamura Research Group) and was entitled *Multi-institutional survey of Lymphoedema and Producing a Clinical Guideline Based on Scientific Evidence*. The process of producing the guideline was governed by the *Handbook of Making Clinical Guidelines (Minds)* (Fukui, 2007).

Method

Evidence-based medicine dictates that several steps should be taken to obtain, analyse, assess and make the most effective use of information.

As a result of the multi-institutional survey, the authors recognised that Japanese surgeons had little interest in lymphoedema. Thus, an evidence-based guideline was developed to raise awareness of the management and treatment of lymphoedema among medical staff.

Step 1: The clinical question

Members of the Japanese Association of Lymphedema (JAL) agreed on eleven areas seen to be important for the treatment of lymphoedema, namely:

- Aetiology
- Risk
- Diagnosis
- Lymph drainage
- Compression garments
- Compression bandaging
- Intermittent pneumatic compression (IPC)
- Exercise
- Surgery
- Supportive care
- Prophylaxis.

Finally, the authors proposed 11 clinical questions (*Table 1*) and adapted them to patients, exposure, comparison and outcome form, the so-called PECO form. The Patient Intervention Comparator and Outcome (PICO) or Case Assay Predicate and Outcome (CAPO) strategies are tools to help with forming questions.

Step 2: Literature search

PubMed and secondary references were used for literature searches. A literature search was performed on clinical questions 1–3 (*Table 1*) using key words related to the diagnosis of lymphoedema. Key words depended on each category, for example, lymphoedema and compression garments, or garments or compression were used for the

Kaoru Kitamura is President, Nagumo Clinic Fukuoka, Fukuoka; Satoru Iwase is Vice Director and Yujiro Kuroda is Accessory Professor at the Department of Palliative Medicine, University of Tokyo Hospital; Takuhiro Yamaguchi is Accessory Professor at the Department of Clinical Trial Data Management, Graduate School of Medicine, University of Tokyo; Daigo Yamamoto is Assistant Professor, Department of Surgery, Kansai Medical University Hirakata Hospital; Hiroki Odagiri is Associate Professor, Department of Gasroenterological Surgery, Hirosaki University Graduate School of Medicine, Hirosaki; Yoshifumi Komoike is Director at the Department of Breast & Endocrinological Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases; Taku Iwamoto is a Chief Doctor at Department of Plastic and Reconstructive Surgery Services, Tomei-Atsugi Hospital; Yoshihiro Ogawa is Director at the Limbs Tokushima Clinic, Tokushima; Hiroshi Yagata is Assistant Head Physician at the Department of Breast Surgical Oncology, St. Luke's International Hospital, Tokyo; Hiroaki Kubota is Marketing Supervisor-General, Senior Manager at Department of Clinical, Regulatory Affairs & Quality Control, Collagen K.K.; Seiichi Teramoto is Chief Physician at the Department of Breast Surgery, Kyushu Central Hospital, Fukuoka

Table 1

The 11 clinical questions

- Are better outcomes achieved when compression therapy is included in the care plan for the treatment of lymphoedema?
- Is there a better outcome when manual lymph drainage (MLD) is performed?
- Is there a better outcome with compression therapy using multilayer lymphoedema bandaging?
- Is there a better outcome when obesity is evaluated in patients with lymphoedema?
- Could post-node dissection cellulitis be a risk factor of onset or aggravation of lymphoedema?
- Is there a better outcome when intermittent pneumatic compression (IPC) therapy is performed?
- Is there a better outcome when exercise is involved in the treatment of lymphoedema?
- Is there a better outcome when psychological interventions are used?
- Is there a better outcome when drug therapy is used?
- Is there a better outcome when surgery is undertaken?
- Is there a better outcome when treatment modalities apart from complete decongestive therapy (compression garments, compression bandaging, MLD, exercise and skin care) are included in the care plan, than when complete decongestive therapy is performed alone?

clinical question 1. PubMed was used to search UK medical papers that had been published between 1980 and 2007. The authors used the Cochrane Library, Up-to-Date and Clinical Evidence to source secondary material.

Inclusion criteria were:
- Original articles on diagnosis and treatment for patients with lymphoedema, clinical trials, meta-analysis, randomised controlled trials
- Articles whose primary end-points were quality of life (QoL), physical pain, psychological pain, influence on daily life, prognosis, or survey.

Exclusion criteria were:
- Articles on paediatric patients
- Articles on drug therapy, prophylaxis or surgery
- Articles where the primary end-points were non-clinical parameters, such as cytokines, nutrition or immunology
- Articles on patients in the terminal stage (i.e. whose life expectancy was six months or less)
- Short reports on full-length papers.

Step 3: Evidence level of literature

Each article's level of evidence was evaluated according to the standards in the *Handbook of guidelines ver. 4.3* (www.cebm.net/levels-of-evidence.asp#level), i.e:
- Systematic review/meta-analysis of randomised comparison study
- One or more randomised comparison study
- Non-randomised comparison study, including prospective studies
- Analysed aetiological study (cohort study)
- Analysed aetiological study (case controlled study/cross-sectional study)
- Descriptive study (case report, case series, qualitative study, etc)
- Expert opinion not based on patient data, studying a physiological parameter not related to clinical outcomes.

Step 4: Recommendation grade

The evidence level of references was based on the recommended grades (www.cebm.net/levels-of-evidence.asp#level):
- A — definitive evidence of effectiveness and clinical agreement; this treatment is strongly recommended according to patient requests
- B — sufficient evidence of effectiveness for clinical agreement; this treatment is recommended according to patient requests
- C — insufficient evidence to develop clinical agreement; treatment recommended based on patient requests and clinical results
- D — there is no evidence of usefulness or clinical agreement. Treatment requires both patient request and clinical need
- E — evidence of adverse effect or morbidity; treatment should **not** be performed.

Step 5: Inspection of adequacy

- Five non-group members (three doctors, one nurse and one statistician, who had not been involved in the guideline) evaluated the clinical questions with a checklist that incorporated the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument, checklist by Shaneyfelt et al, and the Conference on Guideline Standardization (COGS). Each each result was sent back to the authors.

Step 6: Renewal of guideline

The Japanese Association of Lymphedema has the role of re-evaluating the latest articles to update the domestic guideline in Japanese every two years.

Results

Specific recommendations

Clinical question 1

Are better outcomes achieved when compression therapy is included in the care plan for the treatment of lymphoedema? (recommendation grade: C)?

Compression garments (sleeves, gloves and stockings) can help to reduce swelling. The patient's physical and psychosocial needs should be considered when choosing compression garments.

Compression garments should be changed every 4–6 months and patients should be given instruction on their use to prevent disease worsening or infection.

Badger et al (2000) studied the significance of compression therapy in a prospective randomised trial of multilayer lymphoedema bandaging and compression garments in patients with upper and lower limb lymphoedema. Ninety female patients with ipsilateral lymphoedema of the limb, and volume gains exceeding 20% on the intact side were randomly divided into two groups. One group was treated with multilayer lymphoedema bandaging for 18 days, followed by the application of compression garments for up to 24 weeks; the other group were only treated with compression garments for 24 weeks.

The compression garments were customised to each patient's needs. Each patient was instructed to wear the compression garments during the day, from morning to night, and to change sleeves every 3–4 months and stockings every six months. Volume changes were measured at day one, day 19, week seven, week 12, and week 24 in both groups.

The median improvement rate at 24 weeks in the multilayer lymphoedema bandaging plus garment group was 31%, compared to 15.8% in the garment-only group (95% confidence interval (CI), p=0.001) (Badger et al, 2000).

Hornsby (1995) carried out a randomised study on the efficacy of sleeves. Twenty-five patients were randomly divided into two groups following instructions on exercise, simple lymph drainage and skin care. The effects of treatment were evaluated by upper limb volume and a four-weekly questionnaire on subjective symptoms and pain control (Hornsby, 1995). Circumferential diameters of the upper limb were measured at 15cm above and below the elbow joint, and limb volume was also measured. Twelve out of 14 patients in the intervention group, and four out of 11 patients in the control group, showed a decrease in lymphoedema in the first four weeks.

Bertelli et al (1991) considered the usefulness of electrically-stimulated lymphatic drainage (ESD) in a prospective study. Seventy-four patients were randomly divided into two groups and treated with either a sleeve alone, or a sleeve plus ESD for six months (Bertelli et al, 1991). The entire average diameter was initially 14.8 ± 0.3cm, but decreased to 12.3 ± 0.5cm at two months and to 12.0 ± 0.6cm at six months ($p<0.0001$). There was no significant difference between the two groups.

Bertelli et al (1992) also checked the efficacy of sleeves in 120 patients who had undergone surgery for breast cancer. There was an overall improvement of lymphoedema in 14% of patients, and 25% in patients without body weight gain.

Compression garments are useful for treating lymphoedema, and their efficacy can be further improved when combined with additional physical therapies.

Clinical question 2

Is there a better outcome when manual lymph drainage (MLD) is performed? (recommendation grade: C)?

There are two kinds of lymph drainage, manual lymph drainage (MLD) and simple lymph drainage (SLD) — these are mainly self-care measures. Manual lymph drainage increases the activity of injured and/or obstructed lymphatic tracts, and drains the remaining tissue fluid through a lymphatic bypass.

Clinicians agree that MLD is useful, but there is no scientific evidence to support its benefit. Manual lymph drainage is also termed lymphatic massage or manual hand drainage, but the authors have referred to both as MLD in this article. Simple lymph drainage is an interventional method that allows disease management at home. Patients with lymphoedema should learn SLD and be instructed by expert practitioners to achieve the best outcomes.

Williams et al (2002) compared the outcome of MLD with SLD in terms of improvement of QoL and symptoms in patients with post-mastectomy lymphoedema. Thirty-one patients with post-mastectomy lymphoedema were randomly divided into two groups. In group A, MLD was performed for three weeks, followed by a six-week no-treatment period, then a three-week period of simple lymph drainage. In group B, simple lymph drainage was performed for three weeks, followed by a six-week no-treatment period, then three weeks of MLD. Manual lymph drainage was performed for 45 minutes per session on Monday through to Friday (total 15 episodes). Simple lymph drainage was taught for 20 minutes every day by a trained therapists. There was no statistical significance in the background of the groups. Manual lymph drainage dramatically improved excessive volume of the upper limb ($p=0.013$), the skin thickness of the lesion ($p=0.03$), and QoL in terms of depressive feeling ($p=0.006$), dyspnoea ($p=0.04$), insomnia ($p=0.03$), and pain and dullness. Simple lymph drainage did not improve these factors in this study (Williams et al, 2002).

Anderson et al (2000) examined whether MLD improved standard therapy, including compression garments, exercise, and skin care for treatment of post-mastectomy upper limb lymphoedema. Forty-two patients were randomly divided into two groups — patients in the MLD group underwent eight sessions of MLD plus standard therapy for two weeks; patients in the control group received only standard therapy. The average volume of limbs was 346ml (range 78–1,297ml) before treatment, and the volume was measured at one, three, six, nine and 12 months. Volume loss was 45% in the MLD group at three months following treatment, and 60% in the control group. There was, however, no significant difference in the volume or QoL score ($p=0.66$) (Andersen et al, 2000).

McNeely et al (2004) assessed whether MLD improved the effect of compression therapy in patients with post-mastectomy lymphoedema. Forty-five patients with ipsilateral upper limb lymphoedema were divided into two groups — one where patients were given MLD plus compression therapy; the other, compression alone. All patients received standard education, including skin care, and each treatment was performed for four weeks before measurement of limb

volume. At four weeks post treatment, improvement of lymphoedema was significantly higher in the MLD group compared to the compression-only group ($p<0.001$); volume decrease (%) was 46.1% in the MLD group and 38.6% in the control group (McNeely et al, 2004).

Johansson et al (1998) performed a randomised trial to compare the effect of MLD with sequential pneumatic compression. Twenty-eight patients with post-axillary dissection lymphoedema were divided into a MLD group or a sequential pneumatic compression group after wearing a compression sleeve for two weeks. Manual lymph drainage was performed for 45 minutes, five days per week for up to two weeks, and sequential pneumatic compression was performed at 40–60mmHg for two hours during the same period. In those wearing a compression sleeve for two weeks, a volume loss of 49ml (7%, $p=0.01$) was seen, compared to a volume loss of 75ml (15%) in the MLD group. The use of MLD also improved uncomfortable tension symptoms ($p=0.01$) and feelings of 'heaviness' ($p=0.008$). Visual analogue scale (VAS) assessment of upper limb function, pain, and sensitivity correlated with volume loss of the limb and feelings of heaviness and tension (Johansson et al, 1998).

Manual lymph drainage is usually included in complete decongestive therapy and mild lymphoedema can be improved by 2–3 weeks' treatment by specialists. Leduc et al (1998) treated 220 patients with post-mastectomy lymphoedema with a combination of MLD, multilayer lymphoedema bandaging and IPC 10 times over two weeks, and examined the decrease of both circumferential diameter and oedema volume. Changes were most evident during the initial week (first five treatments) and plateaued during the second week, with little improvement during the last week (up to 10 treatments) (Leduc et al, 1998).

Szuba et al (2000) performed a prospective randomised study to evaluate the efficacy of complete decongestive therapy composed of MLD, compression bandaging, and exercise in patients with lymphoedema. Manual lymph drainage was initially performed for 0.5–1 hour, then simple lymph drainage was performed after the third treatment day. After MLD, compression therapy was performed using bandages. Patients with mild lymphoedema received up to five daily treatments, and other patients with intermediate to severe lymphoedema received the same treatment for 10–15 days. Volume decreased by 44% ± 62% in the upper limbs, and 42% ± 40% in the lower limbs in the short course group. The final volume decrease was 38% ± 56% in the upper limbs, and 41% ± 27% in the lower limbs at 38 days ± 52 days from the end of treatment (Szuba et al, 2000).

Combined physical therapy with MLD is effective, but MLD provides no benefit above standard treatment.

Clinical question 3

Is there a better outcome with compression therapy using multilayer lymphoedema bandaging? (recommendation grade: C)?

Multilayer lymphoedema bandaging is used for the immediate improvement of lymphoedema, skin condition and fibrosis, as an initial treatment in patients with severe lymphoedema.

Badger et al (2000) compared the effectiveness of multilayer lymphoedema bandaging and sleeves as an initial treatment of lymphoedema. Ninety patients who had ipsilateral lymphoedema (excessive volume of 20% or more) in upper or lower extremities were treated with either multilayer lymphoedema bandaging for 18 days followed by wearing sleeves or stockings for 24 weeks, or compression garments alone for 24 weeks. Two or more layers of bandaging were applied to patients with leg lymphoedema. Exercise, skin care, and simple lymph drainage were taught to all patients in both groups.

Multilayer lymphoedema bandaging demonstrated a two-fold improvement in diameters compared with sleeves alone, with average decrease rates at 24 weeks of 31% in the multilayer lymphoedema bandage group and 15.8% in the control group ($p=0.001$) (Badger et al, 2000).

McNeely et al (2004) performed a prospective randomised study in 50 patients to compare the effectiveness of multilayer lymphoedema bandaging ± MLD in terms of volume reduction in upper limb lymphoedema. Patients were treated for four weeks and the end-point was the reduction of lymphoedema, evaluated by limb volume and limb diameter. Reduction rate of limb volume was compression alone (38.6%) versus compression plus MLD (46.1%), respectively ($p<0.001$) (McNeely et al, 2004).

Johansson et al (1999) compared the effect of compression bandaging alone, or with MLD in 38 patients with arm lymphoedema. All of the patients received compression bandaging for two weeks, after which they were randomly divided into two groups — compression bandaging or MLD — for an additional week. Limb volume reduced by 188ml (26%, $p<0.001$) after two weeks of bandaging. Further volume loss was 20ml in the group treated by multilayer lymphoedema bandaging alone, and 47ml in the group treated with multilayer lymphoedema bandaging plus MLD after another week of treatment ($p=0.07$). However, the reduction rates were 4% ($p<0.001$) and 11% ($p=0.04$), respectively.

Multilayer lymphoedema bandaging has not been studied in isolation. Vignes et al (2007) examined the usefulness of complete decongestive therapy, including multilayer lymphoedema bandaging, in a prospective randomised trial of 537 patients. Patients received MLD for 30 minutes followed by low pressure multilayer lymphoedema bandaging and instructions in exercise and skin care. The average limb volume before intervention was 1,054 ± 633ml, reducing to 647 ± 351ml ($p<0.0001$). Multilayer lymphoedema bandaging reduced the risk of lymphoedema exacerbation by 50% (1.55; 95% CI: 1.3–1.76; $p<0.0001$) (Vignes et al, 2007).

Didem et al (2005) examined the efficacy of complete decongestive therapy with or without MLD plus multilayer lymphoedema bandaging for 53 lymphoedema patients with postoperative ipsilateral breast cancer. The control group consisted of 26 patients treated with general complete decongestive therapy (compression

bandaging, arm raising, exercise and skin care). The remaining 27 patients received additional MLD, multilayer lymphoedema bandaging and complete decongestive therapy for four weeks and experienced a greater effect. The mean reduction rates were 55.7% and 36%, respectively ($p<0.05$) (Didem et al, 2005). Consequently, complete decongestive therapy, MLD, multilayer lymphoedema bandaging, compression garments, exercise and skin care are generally recommended, although the relative contribution of each modality is not established.

Clinical question 4

Is there a better outcome when obesity is evaluated in patients with lymphoedema? (recommendation grade: C)?

Obesity is a risk factor for lymphoedema in postoperative breast cancer patients, and evaluation is useful for lymphoedema treatment. The significance of maintaining normal weight during lymphoedema treatment is unclear. Patients who are obese should reduce their body mass index (BMI) to 25 or less, especially those with a BMI of 30 or more.

Werner et al (1991) evaluated risk factors for onset and severity of upper limb lymphoedema. The study featured 282 patients who were diagnosed as having stage I/II breast cancer, treated with mastectomy and irradiation between 1980 and 1989. Researchers measured the circumferential diameters of the patients' bilateral upper limbs every 3–12 months. Lymphoedema was diagnosed when diameter laterality was more than 2.5cm on the treated side. The median period of follow-up was 37 months, the incidence of onset 19.5% (55 patients), and the mean time to onset 14 months. Multivariate analysis was performed by categorising all factors into three groups, treatment-, disease- and patient-related factors, to examine the predictive indicators for lymphoedema. BMI strongly correlated with the incidence and severity of lymphoedema (Werner et al, 1991).

Goffman et al (2004) performed a follow-up of 230 patients who underwent irradiation following breast cancer surgery to examine the risk factors of lymphoedema. The median follow-up was 27 months, and the incidence of lymphoedema in the upper limb was 7.6% (n=18) and in the chest 9.6% (n=23). Higher BMI was a predictive factor for chest lymphoedema by student t-test and multivariate analysis ($p=0.043$ and $p=0.0038$, respectively) (Goffman et al, 2004).

Petrek et al (2001) performed a questionnaire survey on 923 patients who had undergone breast cancer surgery and were followed up for 20 years. 263 patients who had not suffered any recurrence of breast cancer were asked the incidence of lymphoedema and any environmental factors. Lymphoedema had occurred in 128 patients (49%) and 33 (13%) had experienced severe lymphoedema of more than 5cm in the upper limb. The majority of patients (77%) experienced lymphoedema onset within three years, increasing 1% per year.

Postoperative infection or injury and body weight gain significantly correlated with lymphoedema incidence. Patients who were obese at initial diagnosis had a higher risk of lymphoedema, however, post-treatment weight gain was a stronger predictive factor of lymphoedema ($p=0.02$). Most (70%) patients with intermediate or severe lymphoedema gained their body weight after a diagnosis of lymphoedema, and 22 out of 33 patients were categorised as having severe lymphoedema (Petrek et al, 2001).

In UK lymphoedema guidelines, skin care, exercise and weight control are important in managing lymphoedema (Harris et al, 2001). In post-mastectomy patients, increased BMI can decrease patients' QoL (Beaulac et al, 2002).

Shaw et al (2007) studied whether dietary therapy for weight loss was effective for the treatment of lymphoedema in patients who had undergone mastectomy. Twenty-one patients were randomly divided into two groups — one received nutritional instruction for weight control; members of the other group were simply provided with a dietary booklet. Improvement of lymphoedema was seen in the nutritional instruction group with calorie control at 12 weeks ($p=0.003$). At 12 weeks, BMI and body weight were also significantly decreased in the group who had been given advice on nutrition ($p=0.02$ and $p=0.016$, respectively) (Shaw et al, 2007).

Overall, it appears that obesity is a risk factor for lymphoedema following breast cancer surgery, and weight control is useful in treating it. Obesity should be evaluated following mastectomy in patients with breast cancer.

Clinical question 5

Could post-node dissection cellulitis be a risk factor of onset or aggravation of lymphoedema (recommendation grade: B)?

Cellulitis can occur some time after lymph node dissection for cancer treatment due to degeneration of the lymphatic tract and venous circulation following surgery and irradiation.

In one study, cellulitis occurred in 50 out of 580 post-surgical breast cancer patients (8.3%) (Indelicato et al, 2006), while lymphoedema, obesity, ecchymosis, haematoma, and seroma were all extracted as risk factors for cellulitis by multivariate analysis in another study of 37 patients (Brewer et al, 2000).

Mertz et al (1998) reported that nine patients with partial mastectomy had 13 episodes of cellulitis, which were seen in eight episodes (61.5%) at three months postoperatively and two patients developed recurrent cellulitis (four times in one patient and twice in the other, respectively) within a six-month period.

Simon and Cody (1992) reported that cellulitis was seen in the treated side of upper limbs in 15 (5.5%) of 273 patients with post-breast cancer surgery at 42 months follow-up. Erythema, and oedema occurred approximately 12 months or later postoperatively.

In a study by Staren et al (1996), ten patients (5%) in whom breast cellulitis developed three or more months after surgery were compared with 174 patients who did not develop cellulitis. The cellulitis resolved in five patients with one recurrence, and the others persisted for four months or more. The five patients with persistent cellulitis underwent biopsies, and recurrent cancer was found in one patient.

Using multivariate analysis, Dupuy et al (1999) performed a case-control study to evaluate the risk factors of cellulitis in lower limbs, and identified destruction of the skin barrier, lymphoedema, venous dysfunction, oedema of the legs, and obesity as independent factors.

Ko et al (1998) performed a prospective study of 229 post-mastectomy patients who received complete decongestive therapy, including MLD, multilayer lymphoedema bandaging, exercise and skin care as maintenance therapy, and found that the incidence of cellulitis reduced from 1.1 times to 0.65 times per patient annually (Ko et al, 1998).

Using both mono-variant and multi-variant analysis, Vignes et al (2007) demonstrated a statistical correlation between lymphoedema and a history of cellulitis in 807 patients with secondary lymphoedema in the upper limb.

Soran et al (2006) reported a significantly higher incidence of infection in patients with severe lymphoedema than those with no or mild lymphoedema in a case control study.

Many studies thus indicate the correlation between lymphoedema and cellulitis.

Clinical question 6

Is there a better outcome when intermittent pneumatic compression therapy (IPC) is performed? (recommendation grade: D)?

Currently, there is no evidence that IPC decreases the circumferential diameter of limbs with lymphoedema. Pneumatic compression therapy is used for both primary and secondary lymphoedema and employs an inflatable bag that holds the involved limbs. Compression is usually set at 30–40mmHg for 30–120 minutes per session and can be provided by single-cell or multi-cell bags, which are divided into 3, 5, and 10 cells. Cell pressure is exerted equally on the limbs through each bag.

There have been several case control studies on IPC. Szuba et al (2002) performed a prospective randomised study on the efficiency of IPC in patients who had undergone post-breast cancer treatment. In the initial treatment, 23 patients with ipsilateral lymphoedema in the upper limb were divided into two groups. Patients in group 1 were treated with pneumatic compression therapy for 30 minutes each day for 10 days between sessions of MLD and multilayer lymphoedema bandaging. Patients in group 2 were treated with MLD and multilayer lymphoedema bandaging without IPC.

Arm size decreased by 4.3% in group 1, and 26% in group 2 at the end of each treatment ($p<0.05$) (Szuba et al, 2002).

For maintenance treatment, 27 patients with chronic, stable lymphoedema following breast cancer received either simple lymph drainage plus multilayer lymphoedema bandaging, or IPC alone for one hour. Treatment regimens were changed after one month and new treatments continued for two months, with follow-up performed at six months. No differences were seen between the groups based on treatment order (Szuba et al, 2002).

Johansson et al (1999) performed a randomised test of manual lymph drainage and sequential pneumatic compression in lymphoedema treatment. Twenty-eight patients with ipsilateral breast cancer were treated with either MLD or sequential pneumatic compression for two weeks following a fortnight of compression therapy using a sleeve. Manual lymph drainage and sequential pneumatic compression each decreased arm volume, but not significantly. Manual lymph drainage improved subjective evaluation of sensation of tension or arm heaviness, but the groups were not actually different (Johansson et al, 1999).

Another study found that sequential pneumatic compression did not improve outcomes *versus* no treatment in a randomised study of 80 patients with postoperative lymphoedema. A decrease in diameter was seen in both groups, 1.9 ± 3.7cm in the sequential pneumatic compression group and 0.5 ± 3.7cm in the no treatment group (Dini et al, 1998).

Bergan et al (1998) performed a randomised trial using one, three or 10-cell compression pumps. The average reduction in limb volume was +0.4% in the single-cell (50 mmHg) group, +7.3% in the three-cell (50 mmHg each) group, and -32.6% in the 10-cell (30–80 mmHg each) group ($p<0.001$) (Bergan et al, 1998).

Overall, the efficacy of sequential pneumatic compression is unclear and the technique does not have a standardised use, optimal pressure or treatment regimen, or support programme after initial treatment. Further research is required.

Clinical question 7

Is there a better outcome when exercise is involved in the treatment of lymphoedema? (recommendation grade: D)?

Exercise therapy generally includes repeated physical action without interruption for the maintenance and improvement of health, physical strength, and athletic ability. However, lymphoedema could restrict joint activity and reduce physical ability, both of which would induce further lymphatic congestion.

Exercise is an important factor for protecting against malignant circulation in conservative therapy for lymphoedema. Here, the authors have defined exercise therapy in patients with lymphoedema to maintain limb function and activity as follows:

- Passive exercise assisted by physical trainers or caregivers is acceptable for patients with palsied limbs
- Exercise includes limb elevation, walking, swimming, cycling or mild aerobics, etc
- Stretching is recommended for preventing joint contractures
- Exercise therapy should be combined with garments and/or bandages.

However, evidence for the efficacy of exercise is unclear, and adverse effects such as onset of lymphoedema can occur.

The *Best Practice for the Management of Lymphoedema* (Lymphoedema Framework, 2006) defined exercise therapy as rehabilitation used to decrease lymphoedema, but no study has

demonstrated that exercise could actually have this effect. Therefore, the authors of this article define improvement as increased upper extremity joint movement.

Ahmed et al (2006) examined the effect of upper and lower body exercise instruction in 45 patients with breast cancer. In this study, participants met twice-weekly with a certified fitness instructor to receive weight training for the first three months. The participants then continued exercising, with access to the fitness trainers, for a further three months. Bi-weekly intervention was instituted for six months, with the affected limb circumference being measured before and after intervention, and clinical findings and self-reporting were also evaluated. No patient showed significant improvement (≥2.0cm after a six-month exercise intervention), or improved clinical findings or symptoms after intervention (Ahmed et al, 2006).

Johansson et al (2005) studied the influence of exercise and wearing sleeves during exercise in 31 patients with upper limb lymphoedema. Exercise using a dumbbell was performed twice on the first and fourth day — a sleeve was worn during one session. Upper limb volume significantly increased immediately after exercise in both groups ($p<0.01$), then decreased 24 hours after exercise ($p<0.05$). These patients had mild to intermediate lymphoedema and the results might not apply to patients with severe lymphoedema (Johansson et al, 2005).

Moseley et al (2005) studied the effectiveness of exercise (upper limb exercise and deep breathing) in 38 postoperative lymphoedema patients with breast cancer. Upper limb exercise combined with deep breathing was performed 25 times for 10 minutes. Limb volume was reduced by 5.8% (mean 52ml, $p=0.004$) 10 minutes after exercise and 5.3% (mean 50ml, $p=0.006$) 30 minutes after exercise. However, limb volume gradually returned to baseline 60 minutes later. Volume loss was 46ml (4.3%, $p=0.04$) 24 hours later and 33ml (3.5%, $p=0.03$) seven days later (Moseley et al, 2005).

McKenzie and Kalda (2003) examined the usefulness of exercise in 14 postoperative lymphoedema patients with breast cancer. Exercise (resistance training and aerobic exercise) was performed for eight weeks and did not alter the circumferential diameter or volume, although it did improve QoL scores (psychological function, general condition and vitality) (McKenzie and Kalda, 2003).

Harris and Niesen-Vertommen (2000) evaluated upper body exercise in 20 patients following lymph node dissection. Diameter was measured pre-exercise, and at the beginning and end of exercise, but no patients showed significant change between pre- and post exercise data (Harris and Niesen-Vertommen, 2000).

Courneya et al (2005) performed a randomised trial of loading test or aerobic exercise in 242 patients with breast cancer (mean 17 weeks of chemotherapy), and found that exercise improved self-respect, aerobic fitness, body fat percentage, muscle power and chemotherapy completion rate, and did not exacerbate lymphoedema.

Several studies demonstrated that exercise does not exacerbate lymphoedema, but none showed a significant improvement in lymphoedema. Consequently, there is no consensus even on the indirect effectiveness of exercise. Furthermore, data on the optimal regimen or application are lacking (Harris and Niesen-Vertommen, 2000).

Clinical question 8

Is there a better outcome when psychological interventions are used? (recommendation grade: D)?

Maunsell et al (1993) evaluated operative influence and psychological stress in 223 patients with postoperative breast cancer. Eighty-two per cent of the patients had more than one problem at three months after surgery (oedema 24%; dizziness 26%; position limit 32%; stiffness 40%; pain 55%; and numbness 58%). The odds ratio of psychological stress at three months after surgery correlated with the number of problems in the affected limb. Patients who had undergone partial/total mastectomy with axillary dissections had more problems in the affected arm than those with no dissection (Maunsell et al, 1993).

Tobin et al (1993) compared the degree of psychological stress in 50 patients with lymphoedema using a psychological interview. Patients with lymphoedema had more difficulties with anxiety, depression, employment, family, society and sex life, than those in a control group.

Sitzia and Sobrido (1997) examined the influence of lymphoedema treatment on health-related QoL (HRQoL) in 34 lymphoedema patients using the Nottingham Health Profile (NHP), Part 1. The entire score significantly decreased at four weeks after treatment ($z=3.1$, $p<0.01$), with an improvement in HRQoL. However, only physical mobility was improved ($z=3.1$, $p<0.01$), and there was no correlation of limb volume to NHP score except in skin condition and pain ($r=0.53$, $p<0.01$).

Mirolo et al (1995) performed intensive treatment (MLD, multilayer lymphoedema bandaging and simple lymph drainage, IPC and exercise) for four weeks in 25 postoperative patients with intermediate to severe lymphoedema. The effectiveness of treatment was evaluated by measuring diameter, volume and QoL using the Functional Living Index-Cancer (FLIC) and Wesley Clinic Lymphoedema Scale (WCLS). Limb volume and diameter were significantly reduced to 40% at one month after treatment, and later reduced to 50%. FLIC scores improved from 86% pre-treatment to 91% 12 months post treatment. WCLS scores decreased from 78.5% at pre-treatment to 66.7% just after treatment, but then increased at six and 12 months after treatment (Mirolo et al, 1995).

Beaulac et al (2002) performed a retrospective cohort study on QoL for 151 patients with and without lymphoedema after breast cancer treatment. Patients with early breast cancer were evaluated by upper limb volume and QoL score, physical phase,

activity phase, psychological phase, social phase, and confidence related to breast cancer treatment using the Functional Assessment of Cancer Therapy (FACT-B). Limb volume reduction (>200 cm^3) was seen in 42 patients (27.8%). QoL score significantly declined in the lymphoedema group compared to the non-lymphoedema group for the entire FACT-B (109.1 ± 2.9 vs 122.7 ± 1.4, p<0.001) and physical phase, activity phase, psychological phase, and in confidence related to breast cancer treatment (Beaulac et al, 2002).

In summary, there has not been enough research to demonstrate the usefulness of psychological interventions in patients with lymphoedema.

Clinical question 9

Is there a better outcome when drug therapy is used? (recommendation grade: E)?

There is no evidence for the effectiveness of drug therapy for the treatment of lymphoedema, but adverse effects have been reported. Clinical studies on the efficacy of coumarin, flavones, flavone derivatives and a benzopyrone analogue for treatment of lymphoedema have been reported. Coumarin causes liver dysfunction, and its use as either a supplement or a drug has been prohibited in several countries, such as the USA, UK and Japan.

Coumarin and analogous drugs have been found to reduce lymphoedema. Burgos et al (1999) performed a double-blind study of 77 postoperative patients with breast cancer from six institutes. Patients were divided into group A (coumarin plus troxerutin 90mg), or group B (coumarin plus troxerutin 135mg), and changes in limb volume were compared 12 months later. Lymphoedema decreased by 17.9% in group A and 13.2% in group B, and the entire clinical score improved, with no statistical significance between the groups (Burgos et al, 1999).

Casley-Smith et al (1993a) performed a double-blind study of 216 patients with lower limb lymphoedema in India. There were four interventions:

- Group 1: placebo plus placebo
- Group 2: benzo-alpha-pyrone plus placebo
- Group 3: diethylcarbamazine plus placebo
- Group 4: diethylcarbamazine plus benzo-alpha-pyrone.

Benzo-alpha-pyrone gradually but significantly reduced lymphoedema at two-year follow-up (group 1) (p<0.0001). Diethylcarbamazine reduced the incidence of lymphoedema, pain, fungal infection, and lymphangitis when it was combined with benzo-alpha-pyrone (group 4) (Casley-Smith et al, 1993a).

Benzo-alpha-pyrone significantly decreased lymphoedema with all grades (p=0.001), and the effect lasted after follow-up (p=0.026) (Casley-Smith et al, 1993c).

Casley-Smith et al (1993b) reported a randomised double blind study of 104 patients with lymphoedema in China who were treated with coumarin (400 mg per day) or placebo, with limb volume assessed every three months. Treatments were crossed over at six months. Coumarin decreased limb volume by 46% in the upper limb, and by 25% in the lower limb (Casley-Smith et al, 1993b). Due to the short-term administration, no liver toxicity was observed.

Loprinzi et al (1999) performed a double-blind study of 140 postoperative patients with breast cancer treated with either coumarin or placebo for six months, followed by crossover for six more months. Limb volume increased by 21ml during placebo treatment, but by 58ml in the coumarin group at six months after crossover (p=0.80). Limb volume improved by 15% in the coumarin group and by 10% in the placebo group at six months after cross-over. Coumarin did not improve lymphoedema and showed a high incidence of hepatotoxicity (6% vs <1% previously reported) (Loprinzi et al, 1999).

Chang et al (1996) performed a six-month randomised study of coumarin *versus* placebo in 60 patients with lymphoedema. After each administration, compression therapy was performed for a further six months. Limb volume decreased by 20% and diameter and tonometry data both improved in the coumarin group. However, at the end of the study, there was a better treatment effect in the placebo group (p=0.03) than the coumarin group (p=0.8 to 0.002) (Chang et al, 1996).

Cluzan et al (1996) performed a crossover study of *Ruscus* plus hesperidin methyl chalcone (CYCLO 3 FORT) and a placebo in 57 patients with breast cancer. Twice-weekly MLD was performed on all patients and at three months after treatment CYCLO 3 FORT had improved lymphoedema symptoms by 12.9% more than the placebo (p=0.009) (Cluzan et al, 1996).

Jamal and Casley-Smith (1989) performed a comparative study of Benzo-alpha-pyrone and diethylcarbamazine in 169 patients with lymphoedema. Extremity volume significantly decreased from 40% to 25% at two years in the benzopyrone group, with no improvement seen in the diethylcarbamazine group (Jamal and Casley-Smith, 1989).

Pecking et al (1997) performed a randomised double-blind study of flavonoid fractions (Dios; Daflon 500mg) and placebo in 104 postoperative patients with breast cancer. There was no treatment effect in the first six months, but lymphoscintigraphy significantly improved in the Dios group in 24 patients with severe lymphoedema (Pecking et al, 1997).

Piller et al (1988) performed a randomised double-blind trial of hydroxyethyl plus benzo-alpha-pyrone *versus* placebo in 26 post-mastectomy patients with lymphoedema and 14 patients with lower limb lymphoedema. The treatments were switched at six months and limb volume, diameter, tonometry and skin temperature were evaluated in each group. Hydroxyethyl plus benzo-alpha-pyrone improved volume, diameter and skin temperature (volume: p<0.05 to 0.01; diameter: p<0.01 to 0.001; skin temperature: p<0.05 to 0.01), as well as mobility of

upper limb, pain, and heaviness (Piller et al, 1988).

Coumarin has not been reported to be effective in the treatment of lymphoedema, and has been banned from medical use in the US because of adverse effects.

Clinical question 10

Is there a better outcome when surgery is undertaken? (recommendation grade: D)?

There is no robust evidence for the efficacy of surgery for lymphoedema and its use should be carefully considered.

Surgical treatment for improving function and cosmesis in limb lymphoedema can be divided into three categories:

- Surgical reduction
- Procedures that bypass lymphatic obstructions
- Liposuction.

The aim of surgical reduction is to improve symptoms due to severe lymphoedema by removing fibrotic skin and tissue. Surgery involves subcutaneous tissue and excess skin resection and skin suturing. Problems include long hospitalisation, delayed wound healing, visible incision size, hypersensitivity, residue of local lymphoedema and cosmesis.

Various surgical procedures, such as lymphatic duct anastomosis, lymphatic duct transplantation and auto-venous transplantation can create a new lymphatic tract.

Campisi and Boccardo (2002) performed long-term follow-ups in 95 of 133 patients with obstructive lower limb lymphoedema after lymphatic tract anastomosis. The improvement ratio was favourable in patients with stage II–III lymphoedema. Lymphangitis onset became less frequent. The average incidence was preoperatively once per 0–1 year, while it was only once per 3–4 years postoperatively. Limb volume loss was seen immediately after surgery, and it lasted for 1–5 years.

Campisi and Boccardo (2002) performed microsurgery in 843 patients with limb lymphoedema (upper, 231 patients; lower, 612 patients), and surgical results were evaluated by limb volume and lymphoscintigraphy (Campisi et al, 2006). Postoperative volume loss of more than 75% was seen in 616 patients (73%), more than 50% in 202 patients (24%), and 25% or less in 25 patients (3%).

Microsurgery using lymphatic tract grafts or lymph node transplantation has been effective in some patients. Weiss et al (2003) transplanted a lymphatic tract in eight patients with lower limb lymphoedema and found that lymphatic function significantly improved postoperatively in all eight patients ($p<0.01$). Weiss et al (2003) described that lymphoscintigraphy is useful as a minimally invasive procedure to compare the flow between pre- and postoperative anastomosed lymphatic ducts.

Becker et al (2006) analysed the long-term results of microsurgery for patients with post-mastectomy lymphoedema. Ten patients were judged as cured, 12 patients as improved, with lymphoedema persisting in two patients even after microsurgery (Becker et al, 2006).

Liposuction removes excess fatty tissue and is sometimes used in patients who have both primary and secondary chronic lymphoedema following conservative management or microsurgery. Liposuction has been used for long-term survivors of breast cancer. Brorson et al (2006) compared 35 patients with upper limb lymphoedema who were treated with either controlled compression therapy (CCT) alone, or controlled compression therapy plus liposuction. The aim was to assess limb volume and QoL (Brorson et al, 2006). There was twice as much limb volume reduction with liposuction than CCT alone. Functional scores also improved more with liposuction.

Surgical trials have generally been small and limited. Microsurgery has consensus as a standard treatment but requires but requires more standardisation as a procedure.

Clinical question 11

Is there a better outcome when treatment modalities apart from complete decongestive therapy (compression garments, compression bandaging, MLD, exercise and skin care) are included in the care plan, than when complete decongestive therapy is performed alone? (recommendation grade: D)?

There is neither sufficient evidence to demonstrate the usefulness of treatment modalities other than complete decongestive therapy, nor has a clinical consensus been established. Treatment modalities such as cold therapy, subcutaneous neuro-electric stimulation therapy, pulse magnetic field (hyperthermia or vibration massage), hyperthermia, ultrasonic wave, and alternative therapy are reviewed below.

Hyper-oxygen therapy improves the ischaemic conditions of bone or injured soft tissue after irradiation for early breast cancer, however, the effectiveness on lymphoedema has not been evaluated. Gothard et al (2004) examined the treatment effect of hyper-oxygen in 21 postoperative lymphoedema patients with ipsilateral breast cancer. Limb volume was measured by perimeter and a reduction of 20% or more was regarded as effective. Average volume loss was 7.68% (95% CI), and three patients were considered responsive.

Hyper-oxygen therapy used in patients with chest lymphoedema produced angiogenesis after 20 treatments and the endpoints included changes in upper extremity volume, platelet counts, plasma levels of vascular endothelial growth factor (VEGF), and lymph angiogenic-associated VEGF-C (Teas et al, 2004).

Teas et al (2004) performed a pilot study with a similar protocol for 10 postoperative lymphoedema patients with breast cancer. Upper limb volume was evaluated initially within one week of hyper-oxygen therapy, then three days post-treatment, and finally one month after the final treatment. Volume laterality, based on bilateral circumferential diameters of upper limbs, ranged from 287–1,946ml. Symptoms such as numbness and

stiffness of the affected arm were improved by treatment in nine patients.

Carati et al (2003) performed a prospective randomised study to examine the effect of low-level laser therapy (LLT) for patients with post-mastectomy lymphoedema. Twenty-eight patients were in the placebo group, with 33 in the treatment group. Treatment was delivered in blocks of nine sessions (active laser or placebo), in which one block comprised treatment three times per week for three weeks. Participants in the placebo group received one block of 'sham' therapy (where the laser had been disabled with no apparent change in its function), which was followed by an eight-week rest period and then one block of LLLT. The active group received two blocks of LLLT, separated by an eight-week rest period. Two laser treatments improved limb volume, extracellular fluid, and tissue stiffness by 33% on the postoperative axilla of post-mastectomy patients (Carati et al, 2003).

Breathing exercises can activate central lymphatic ducts and promote peripheral lymphatic flow. Moseley et al (2005) examined the effectiveness of a combination of deep breathing and mild upper limb exercise in patients with breast cancer and postoperative lymphoedema. One minute of exercise and one minute of rest were repeated five times for one cycle (a cycle being 10 minutes of standardised arm exercise and deep breathing). Patients performed five cycles (total 25 times). Limb volume decreased by 52ml of the median (5.8%, p=0.004) immediately after 10 minutes of exercise, which was maintained at a decrease of 50ml (5.3%, p=0.006) 30 minutes after exercise. Limb values gradually returned to baseline at 60 minutes after exercise. Patients were directed not to do any further exercise, and limb volume decreased by 46ml (4.3%, p=0.04) at 24 hours, and by 33ml (3.5%, p=0.03) one week after exercise.

Exercise combined with deep breathing has a high tolerability and no critical adverse effects, but efficacy is unclear (Moseley et al, 2005).

To conclude, treatment modalities other than complete decongestive therapy currently have no evidence of clinical usefulness in lymphoedema.

Evaluation by external appraisers

External appraisers, selected from specialists in lymphoedema management with no connection to the development of this review, were expected to evaluate objectively whether each clinical question had an adequate conclusion (recommendation grade) based on the evidence. The external appraisal team consisted of one lymphoedema specialist, two professional nurses, one biostatistician, and one patient.

The appraisal was performed using AGREE (Appraisal of Guidelines for Research and Evaluation) (Kopp and Lelgemann, 2005), the appraisal tool developed by Shaneyfelt et al (2006) and COGS (Shiffman et al, 2003) appraisal method.

Appraisal using AGREE

AGREE consists of 23 key themes organised into six domains:

- Scope and purpose
- Stakeholder involvement
- Rigour of development
- Clarity and presentation
- Applicability
- Editorial independence.

Twenty-three items were categorised into these six domains and rated on a four-point scale ranging from 4 ('strongly agree'), to 1 ('strongly disagree' or 'no information available').

The mean scores for each domain were:

- Rigour of development: 3.17
- Scope and purpose: 3.13
- Stakeholder involvement: 2.68
- Clarity and presentation: 2.65
- Editorial independence: 2.33
- Applicability: 2.13.

The scores for the categories of 'scope and purpose' and 'rigour of development' were considered good, however, those for 'stakeholder involvement', 'clarity and presentation', 'applicability', and 'editorial independence', indicated that there was room for improvement.

In addition, for 'subject independence' and 'editorial independence', the evaluation of the non-medical external appraisers was slightly high compared to those with a medical background However, on the whole, consistent results were obtained.

The items with a high appraisal were: item 1: 'The overall aim of the guideline is specifically documented'; item 8: 'Statistical methods were used to gather the evidence'; item 9: 'The standards for including evidence are clearly documented'; item 10: 'The methods to formulate the recommendations are clearly documented', and so on.

On the other hand, the items with a low appraisal were: item 23: 'The conflict of interest from the guideline development group is documented'; item 7: 'The guideline represents the views of its intended users' and so on.

In item 7, the prerequisites of the questions had not been established due to comments such as 'there is no appraisal because I did not understand the meaning of the question'. Moreover, the medical and non-medical personnel gave different assessments for item 2: 'The clinical concerns addressed in the guidelines are specifically documented'; item 3: 'The target patient population for the guideline is specifically documented'; item 13: 'An external review was performed prior to the favourable appraisal of the guideline'; and item 22: 'The guideline is independent from the source of funding for the editorial.'

In the overall evaluation, to the question: 'Do you recommend the use of this guideline in clinical settings?', 40% of the appraisers responded 'it is very useful' and the rest 'it is useful'.

Appraisal using the Shaneyfelt et al (2006) method

The Shaneyfelt et al (2006) method of appraisal is made up of 25 items to which all the responses are either 'yes' or 'no'. The response of 100% of appraisers was 'yes' to nine items, such as item 7: 'The main usable options for diagnosis, treatment and prevention are covered.' On the other hand, there was a very low response rate for items 18: 'The benefits

and risks are documented quantitatively'; 19: 'The effect on the cost of diagnosis is documented'; and 20: 'The cost is presented quantitatively.'

Appraisal using COGS

The COGS appraisal is made up of 18 items and, as in the Shaneyfelt et al (2006) method, the responses are either 'yes' or 'no'. The response of 100% of appraisers to four items, including item 2: 'Focus (the main patients/diseases, interventions/services/techniques addressed in the guideline are documented. Almost all preventive, diagnostic, and medical interventions considered during the development are presented)' was 'yes'.

On the other hand, 20% of appraisers responded 'yes' to item 11: 'Pre-release review (the procedure on how the guideline developers examined and tested the guideline is documented)' and item 12: 'Update plan (declaration on whether or not an update is planned).'

Conclusion

With all the appraisal methods, a high score was obtained for the development of the guidelines and the rigour of the development. However, a low appraisal was obtained for stakeholder involvement and conflict of interest from the guideline development group. These results had been predicted, however, the issue is how to interpret them. Moreover, the number of appraisers was limited to five and even an adequate investigation of the comparison of the specialists and non-specialists was impossible.

In the future, it is important that physicians, nurses, allied healthcare professionals or patients provide an opinion on the use of this guideline in actual clinical settings. In addition, the type of appraisal method that would be appropriate to use needs to be investigated further.

A multifaceted appraisal of this guideline was achieved with the combination of three types of external appraisals, including AGREE. The mean score of the overall appraisal using AGREE was 2.68, greatly exceeding the overall percentage of appraisers that responded 'yes' to all the items of Shaneyfelt and COGS combined. This suggests that although some problems remain, the appraisal of this guideline was generally high. JL

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