

## Lymphedema: Current Issues in Research and Management

Jeanne A. Petrek, MD; Peter I. Pressman, MD; and Robert A. Smith, PhD

### Abstract

*Lymphedema is a common and troublesome problem that can develop following breast cancer treatment. As with other quality-of-life and nonlethal conditions, it receives less research funding and attention than do many other areas of study.*

*In 1998, an invited workshop sponsored by the American Cancer Society reviewed and evaluated the current state of knowledge about lymphedema. Recommendations and research initiatives proposed by the 60 international participants are presented in the conclusion section of the article, following a summary of current knowledge of the anatomy, physiology, detection, and current treatment of lymphedema.*

*The etiology of lymphedema is multifaceted; all of the factors that contribute to the condition and the nature of their interaction have not yet been identified. To compound the problem, methods of assessing the degree of arm and hand swelling vary and are not agreed upon, and reliable methods of assessing the functional impact of lymphedema have not yet been developed.*

*In the absence of a cure for lymphedema, precautions and prevention are emphasized. Current treatments include elevation, elastic garments, pneumatic compression pumps, and complete decongestive therapy; surgical and medical techniques remain controversial. Elements and details of these treatments are described. (CA Cancer J Clin 2000;50:292-307.)*

### Introduction

Approximately 15% to 20% of breast cancer patients develop lymphedema following breast cancer treatment. This means that of perhaps two million US breast cancer survivors, after lymphadenectomy, approximately 400,000 cope on a daily basis with the disfigurement, discomfort, and disability associated with arm and hand swelling. Lymphedema is among the most dreaded sequelae of breast cancer treatment.

Lymphedema is a common and troublesome problem: The cosmetic deformity can not be disguised with normal clothing; physical discomfort and upper-extremity disability are associated with enlargement and recurrent episodes of cellulitis, and lymphangitis may be expected in this setting.

In addition to these physical symptoms, patients may experience distress caused unintentionally by clinicians whose primary focus is cancer recurrence and who may therefore trivialize lymphedema because of its nonlethal nature. For the patient, however, the appearance of arm swelling may be more distressing than living with a mastectomy, as the latter can be easily hidden while the disfig-

---

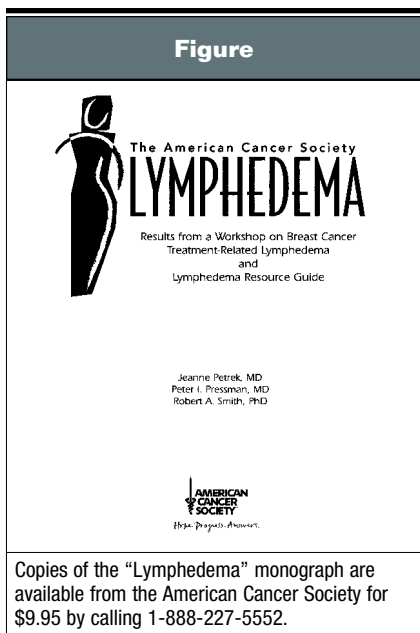
Dr. Petrek is Director, Surgical Program, Evelyn H. Lauder Breast Center, and Attending Surgeon, Breast Service, Department of Surgery at Memorial Sloan-Kettering Cancer Center in New York City, NY.

Dr. Pressman is Clinical Professor of Surgery at Albert Einstein School of Medicine and Beth Israel and Lenox Hill Hospitals, New York City, NY.

Dr. Smith is Director of Cancer Screening with the American Cancer Society, Atlanta, GA.

This article is also available online at [www.ca-journal.org](http://www.ca-journal.org).

## Figure



ured arm/hand is a constant reminder of the breast cancer and a subject of curiosity to others.

### The American Cancer Society Workshop and Invited Conference on Lymphedema

The study of the incidence, etiology, and treatment of lymphedema is hampered by the decades-long course of this complication. Furthermore, lymphedema, along with other quality-of-life and nonlethal conditions, has received less research funding than have many other areas of study. To generate new attention for the problem of breast-cancer-treatment-related lymphedema, the American Cancer Society and the Longaberger Company (Newark, Ohio) sponsored an invited workshop to review and evaluate the current state of knowledge of the condition. The workshop, which took place in February 1998 in New York City, featured 60 in-

ternational experts (including the authors of this article) who made recommendations for basic research, clinical practice, and public and professional education and advocacy. (See "Recommendations and Research Initiatives," page 303).

The workshop carefully reviewed the standard treatment of lymphedema, and faculty from each of the four main treatment schools and clinics discussed their respective techniques of manual lymphatic drainage (MLD). The entire proceedings of the meeting, including recommendations summarized in workshop reports are available as a journal supplement (*Cancer* 1998;83:2775-2890) and as a separate 129-page monograph from the American Cancer Society<sup>1</sup> (Fig.). The publication concludes with a lymphedema resource guide listing information on professional organizations addressing lymphedema, lymphedema support groups, online groups and information sources, suppliers of lymphedema pumps and garments, and schools for complex decongestive therapy, as well as a recommended reading list.

### Anatomy and Physiopathology of Lymphedema

Lymph is normally cleared from tissue spaces through a network of thin-walled lymphatics, which traverse the axillary nodal basin and ultimately empty into the venous system. Lymphedema is the accumulation of protein-rich fluid in soft tissues resulting from overload of these lymphatics (i.e., when lymph volume exceeds transport capabilities). *Primary lymphedema* refers to rare developmental abnormalities in the lymphatics and can present early or late in life. *Secondary lymphedema* is more common and includes among its causes surgery, irradiation, and infection (e.g., filariasis).

In secondary lymphedema, lymph transport is interrupted due to physical disruption or compression of lymphatic channels.<sup>2</sup> Patients with breast cancer de-

velop lymphedema from surgical resection of lymphatic vessels and lymph nodes, from radiation-induced fibrosis around these structures, and from obstruction of lymphatics and lymph nodes by metastatic tumor.

The accumulation of interstitial macromolecules raises tissue oncotic pressure, while the disruption and blockage of lymphatics raise the hydrostatic pressure within the remaining lymphatics. Both contribute to increased tissue edema. Stasis of protein-rich fluid, combined with impaired immune clearance in the extremity devoid of lymph nodes, permit repeated episodes of lymphangitis and cellulitis. Such chronic inflammation leads to further fibrosis and impairment of the affected limb. In this way, lymphedema can begin insidiously at variable periods after axillary treatment and progress from a barely noticeable condition to one involving a severely impaired limb.

### **Presentation and Progression of Lymphedema**

Lymphedema is the result of a functional overload of the lymphatic system in which lymph volume exceeds transport capabilities. The build-up of interstitial macromolecules leads to an increase in oncotic pressure in the tissues, producing more edema. Persistent swelling and the build-up of stagnant protein eventually lead to fibrosis and provide an excellent medium for repeated bouts of cellulitis and lymphangitis. With dilatation of the lymphatics, the valves become incompetent, causing further stasis. The muscle compartments below the deep fascia, however, are spared.

Lymphedema can begin insidiously at variable periods after axillary treatment. The swelling may range in severity from mild and barely noticeable in the early stages, to extreme in later stages, causing a seriously disabling enlargement of the affected limb. A brawny skin appearance develops owing to the fibroscler-

osis of the skin and subcutaneous tissue. With repeated episodes of cellulitis and lymphangitis, the skin becomes indurated, leathery, and hyperkeratotic.

### **Lymphedema Assessment: Physical Measures and Imaging Techniques**

About 50% of patients with documented minimal enlargement (1 to 2 cm) suffer symptoms of "arm heaviness."<sup>3</sup> A mail questionnaire found that half of the patients describing lymphedema had nevertheless not reported this problem to any doctor.<sup>4</sup> The psychosocial aspects of lymphedema, which have been unforgivably ignored in the past, were recently reviewed by Passik and McDonald.<sup>5</sup> Women who experience pain, have lymphedema in the dominant hand, enjoy poor social support, and/or have a passive and avoidant coping style report the highest level of disability.<sup>6</sup>

Three physical measures of lymphedema<sup>7</sup> are available, including circumferential measures at various points (with bony landmarks as references), volumetric measures using limb submersion in fluid, and skin/soft-tissue tonometry in which soft-tissue compression is quantified.

The traditional method for measuring lymphedema is the tape-measured arm circumference 10 cm below or 10 cm above either the olecranon or the lateral epicondyle. While seemingly straightforward, such measurements can vary according to the degree to which the tape itself constricts soft tissue. Furthermore, it is wise to measure at least one location on the lower arm and two locations on the upper arm (instead of relying on a single value), as the shape of the arm can differ before and after swelling.

Measurement of the arm volume by water displacement is more accurate and results in a single value, but the technique is unwieldy and infrequently employed. Skin/soft-tissue tonometry, performed with a tension-measuring device that presses on the skin, is not a standardized

procedure. Other, more sophisticated methods that are still experimental include dichromatic differential absorptiometry,<sup>8</sup> CT scanning,<sup>9</sup> MRI,<sup>10</sup> and optoelectronic scanning.<sup>11</sup>

There is no standard degree of enlargement that constitutes lymphedema. Although a 2-cm difference between arms is the most common definition, such swelling could be severe in a thin arm and unnoticeable in others. In rare cases, natural variation can account for up to a 2-cm greater circumference in the dominant and overused extremity.<sup>12</sup> Thus, both arms must be measured preoperatively for an accurate lymphedema assessment. While physical measures and imaging techniques provide quantitative assessment of arm enlargement, no reliable or standard measure exists to assess the functional impact of lymphedema.

Recently, some investigators have begun to explore noninvasive, and to some extent invasive, imaging techniques to diagnose and help manage lymphedema.<sup>13</sup> Lymphoscintigraphy, for example, has been used in a preliminary way to predict which patients are at increased risk for lymphedema after axillary treatment<sup>14,15</sup> with the hope of emphasizing prevention strategies and the value of frequent follow-up. In the future, lymphoscintigraphy, dichromatic differential absorptiometry,<sup>8</sup> CT scanning,<sup>9</sup> and optoelectronic scanning<sup>11</sup> may all be used to direct management and assess results.

## Lymphedema Incidence

The incidence of lymphedema reported in different studies has varied widely as a result of variations in a number of factors, including the extent of axillary treatment, the interval between axillary treatment and measurement, methods used to define lymphedema, and the completeness of follow-up.

A comprehensive computerized search<sup>16</sup> of the worldwide medical literature on the incidence of lymphedema re-

lated to breast cancer treatment yielded 35 reports since 1970. Data from seven of the reports with the greatest relevance for current patients (dating from 1990; five countries) are presented in Table 1. The reports of Ferrandez et al<sup>17</sup> and Schunemann and Willich<sup>18</sup> have been translated from the French and German, respectively. Unfortunately, the type of breast carcinoma treatment used in the studies that are detailed in Table 1 could not be included because only a few investigators reported this important variable. (The majority of participants in the study by Lin<sup>19</sup> and all patients in those by Werner<sup>20</sup> and Ivens,<sup>21</sup> underwent breast-conservation therapy.) Nevertheless, as they are all recently published reports, these seven studies should be most relevant for current patients.

All reports on the incidence of lymphedema, including the seven studies highlighted in Table 1, are retrospective, and the denominator (i.e., the number of patients at risk for developing lymphedema in a particular population) is imprecise or unknown. The incidence of lymphedema in the seven selected reports varied from 6%<sup>22</sup> to 30%.<sup>23</sup> The report with the lowest incidence of lymphedema also had the shortest follow-up, and the same surgeon, one of its authors, operated on all of the reported patients.<sup>22</sup>

## Lymphedema: Etiologic Factors

### SURGERY

Surgery that includes extensive removal of lymph nodes has been an integral part of breast carcinoma treatment since the end of the last century. In the standard radical mastectomy, virtually all lymphatics were interrupted and removed, along with the adjacent muscles of the chest wall, the breast, and the overlying skin, so that skin grafting was required to close the defect. Operations for breast cancer have become progressively more modest,<sup>24</sup> and almost all studies in the past 20 years<sup>12,21,25-29</sup> report that the inci-

**Table 1**  
**Incidence of Lymphedema Based on Reports Published Since 1990**

| Year | First Author/<br>Journal                                    | Country | Type of<br>Measurement       | Definition                                   | Incidence             | Follow up           | No. of Patients<br>Source<br>Treatment Yrs |
|------|---|---------|------------------------------|--|-----------------------|---------------------|--|
| 1991 | Werner <sup>20</sup><br><i>Radiology</i>                    | US      | Circumference                | ≥ 2.5 cm                                     | 19.5%                 | 37 months*          | 282<br>Clinic F/U<br>1980-1989             |
| 1992 | Ball <sup>22</sup><br><i>Ann R Coll Surg<br/>Engl</i>       | England | Circumference                | > 3 cm                                       | 6%                    | > 12 months         | 50<br>1 surgeon<br>1982-1990               |
| 1992 | Ivens <sup>21</sup><br><i>Br J Cancer</i>                   | England | Patient Report<br>Volumetric | N/A<br>> 200 ml                              | 16%<br>10 %           | 2 yrs*              | 106<br>Clinic F/U<br>1986-1990             |
| 1993 | Lin <sup>19</sup><br><i>J Clin Oncol</i>                    | US      | Circumference                | a) < 3 cm<br>b) 3 cm – 4 cm<br>c) > 4 cm     | 16%<br>6%<br>2%       | 2 yrs*              | 283<br>4 surgeons<br>1988-1990             |
| 1996 | Ferrandez <sup>17</sup><br><i>Bull Cancer</i>               | France  | Circumference                | a) > 3 cm – < 10 cm<br>b) ≥ 10 cm            | 14.3%<br>2.6%         | 14 months*          | 683<br>Clinic F/U<br>1994                  |
| 1996 | Paci <sup>23</sup><br><i>Tumori</i>                         | Italy   | Circumference                | a) ≤ 4 cm<br>b) > 4 cm – < 8 cm<br>c) ≥ 8 cm | 8.7%<br>13.7%<br>7.9% | 5 yrs*              | 238<br>Tumor Registry<br>1985-1986         |
| 1997 | Schunemann <sup>18</sup><br><i>Dtsch Med<br/>Wochenschr</i> | Germany | Circumference                | ≥ 2 cm                                       | 24%                   | 11 yrs <sup>†</sup> | 5,868<br>Clinic F/U<br>1972-1995           |

\* Median time F/U † Total F/U = follow-up  
Copyright 1998 American Cancer Society. Reprinted with permission from *Cancer* 1998;83:2778.

dence rate and the degree of resultant lymphedema correlate with the extent of surgical dissection. As more nodes are excised—such as in sampling (retrieving three to eight lymph nodes) or in standard axillary dissection<sup>26</sup>—the incidence rate of lymphedema increases in an approximately linear fashion. In two large studies,<sup>20,30</sup> however, a relationship between extent of dissection and lymphedema could not be demonstrated, perhaps because rather small differences in extent of dissection were compared.

Today, a level I-II axillary dissection is generally routine and in rare cases, if the lymph nodes are found to be positive, the dissection is extended to include level III. Attempts are now made to modify the scope of the operation to fit the extent of the disease being treated. Aware of the risks of lymphedema, surgeons often carefully attempt to preserve fatty axillary tissue medial, lateral, and superior to the axillary vein, because this tissue may contain important lymphatic trunks, preferring to dissect the tissue below the vein.

#### RADIATION THERAPY

In every study that has evaluated the relationship between lymphedema and extent of surgical dissection, the addition of radiation therapy to the dissected axilla has proved to be a strong predictor of lymphedema.<sup>12,26,28,30</sup> Therefore, if a complete axillary dissection has been carried out—even with findings of positive lymph nodes and extracapsular extension—axillary radiation can often be avoided without high risk of axillary recurrence.

Even when the intent is to irradiate only the breast (such as following lumpectomy), some radiation dosage reaches level I and even level II of the axilla, depending on the radiation-therapy technique used and on the patient's anatomy. Breast radiation-therapy techniques designed specifically to avoid the dissected axilla and the pathophysiology of radiation-related lymphedema were recently

reviewed.<sup>31</sup> For precise radiation technique, it is helpful to mark the surgical boundary with radiopaque clips, thus indicating the extent of the axillary dissection. The radiation therapist can then see the dissected area on the simulation films and avoid it with greater accuracy.

#### SENTINEL LYMPH NODE BIOPSY

Sentinel lymph node biopsy (SLNB) (see Hsueh et al, page 279) should decrease the risk of lymphedema.<sup>32</sup> If only one or two lymph nodes are carefully excised, it stands to reason that edema will probably not occur. The sentinel node operation is not always so limited, however. The sentinel node may, in fact, be located very high at the level of the axillary vein and the lymph trunks. Dissection at that site could theoretically result in lymphedema. The risk of lymphedema has not yet been assessed in the follow-up of patients treated with sentinel lymph node technology. Further, if axillary radiation therapy is added to SLNB, the risk of lymphedema increases. It is important to remember that in international series reporting axillary radiation therapy but no axillary surgery at all, lymphedema incidence ranged from 2% to 5%.<sup>20,21,25,30,31</sup> Therefore, lymphedema incidence will be at least that high if SLNB and axillary radiation therapy are combined. Lymphedema after axillary radiation therapy alone was shown to develop later than that developing after combined axillary surgery and breast radiation therapy.<sup>21</sup>

Beyond these two definite factors—extent of surgical dissection and radiation to the axilla—exists a wide range of possible etiologic factors that have not been evaluated systematically. Some women treated decades ago with radical mastectomies and full radiation therapy, ribs thinly covered with skin grafts, did not develop lymphedema. On the other hand, there are women recently treated with modest tumorectomies, limited axillary dissections, and radiation to the breast who have developed lymphedema.

Research to date has revealed few consistent clues to the etiology of lymphedema. One study,<sup>27</sup> for example, reported older age at diagnosis to be a significant factor; in another,<sup>12</sup> this variable was unrelated to lymphedema incidence; in still others, it was curiously omitted altogether. In one study, a tendency toward lymphedema was seen when the dominant hand was on the side that had been operated on,<sup>21</sup> but another report<sup>12</sup> could not confirm this. Patient weight (height was not recorded) was a significant factor in two studies,<sup>20,29</sup> but obesity, surprisingly, was not evaluated in other studies. One study on surgical technique found a higher incidence of lymphedema with splitting the pectoralis minor muscle,<sup>25</sup> and two studies correlated lymphedema with greater postoperative fluid formation.<sup>33,34</sup> It is surprising that the incidence of lymphedema with bilateral axillary dissection is not any higher than that after unilateral axillary dissection.<sup>16,35</sup>

In sum, etiologic factors for lymphedema have not been well studied because: 1) the course of the condition is prolonged; 2) individual patients lack long-term contact with the original surgeon and/or the radiation therapist who treated them; and, most importantly, 3) lymphedema, along with other quality-of-life issues, is perceived as less worthy of research funding.

### Prevention of Lymphedema

As controlling lymphedema requires daily attention, and as a "cure" for lymphedema has not been established, emphasis must be placed on prevention. Nevertheless, without evidence-based knowledge of etiologic factors, the list of post-treatment arm precautions is based on intuitive reasoning.

It is important to remember that each woman has a congenitally different anatomy, which, like the rest of the vascular system, is probably uniquely prone to degenerative conditions. Such anatom-

ic factors have been studied in a limited fashion with lymphoscintigraphy.<sup>13-15</sup> Individual patient factors, combined with axillary treatment factors, must be the main determinants of preventive strategies, notwithstanding the fact that lymphedema may occur several years after treatment. The study of events or activities in the subsequent years and decades of the patient's life for the purpose of determining which are causative factors and to what degree has not been carried out. In fact, so little is known that it may be the case for some women that precautionary advice is, in fact, counterproductive, as "overprotection" can lead to underuse and muscle atrophy.

### ARM AND HAND PRECAUTIONS

Arm and hand precautions are loosely based on two overarching principles: 1) The production of lymph, which is directly proportional to blood flow, should not be increased; and 2) the blockage to lymph transport should not be increased. Heat, such as that in a sauna, significant infections, and vigorous arm exercise increase blood flow in the arm and thereby increase lymph production. Likewise, tight arm garments or infections with ensuing fibrosis and stenosis of lymphatic vessels may result in obstruction of lymph flow.

To avoid arm swelling and/or infection, the patient should be instructed to:

1. Avoid vaccinations, injections, blood-pressure monitoring, blood drawing, and intravenous administration in the affected arm.
2. Avoid puncturing or injuring the skin in any way. Use meticulous skin and nail/cuticle care. Pay immediate attention to and use standard first-aid care on all small or large injuries. Utilize antibiotics liberally.
3. Avoid constricting sleeves or jewelry and wear a padded bra strap to avoid constriction and pressure.
4. Avoid heat, including sunburns or tanning, hot baths, and saunas.
5. Avoid violent exercise and strenuous



exertion. Consider vigorous aerobic arm exercise only when the arm is supported by compression garments.

There are no data to govern any of these recommendations. The finding that no increase in risk of lymphedema was noted in women who had had *bilateral* axillary dissection compared with those who had had *unilateral* axillary dissection<sup>16,35</sup> calls into question the implication that blood drawing, intravenous administration, blood-pressure monitoring, and injections hasten the development of lymphedema. Data for any of the other arm and hand precautions are even more speculative. On the other hand, breaking the skin barrier, even during medical procedures, could predispose to infection, and blood-pressure monitoring could cause injury.

Lymphoscintigraphic techniques are now being used to study the lymphatics of the upper limb after axillary treatment and may help to provide answers regarding arm and hand precautions.<sup>15</sup> Dynamic as well as static images may be obtained at various levels in the affected arm and under various standardized conditions (during and/or after various periods of rest, during and/or after exercise, etc.).

Such research is desperately needed. All patients are currently instructed in the same arm and hand care precautions; however, these precautions may be too severe for those at low risk, while not aggressive enough for those at the greatest risk. Furthermore, as lymphedema may occur even several decades<sup>36</sup> after axillary treatment, patients are admonished to follow these demanding precautions for the remainder of their lives.

#### LYMPHEDEMA TREATMENTS

Therapeutic nihilism (i.e., no treatment at all) for lymphedema is deplorable, although quite common. All too often, a woman is told that she "should be thankful to be alive" and that she must "learn to live with it." The fact that the average clinician is ill prepared to both detect and

recognize early signs of lymphedema must be remedied, as data suggest that the sooner the treatment is started, the smaller the amount of treatment required to prevent further progression, and the better the ultimate result.

The treatment of established lymphedema varies from doing nothing at all to pursuing a host of aggressive surgical procedures, as was particularly the case in the past. Between these two extremes lie various combinations of conservative treatments, the most important of which are elevation, the use of compression garments, centripetal massage and exercises, the use of pneumatic compression devices, and a program of complete (or complex) decongestive physiotherapy, known as CDP.

#### 1. CDP

CDP has been widely available in Europe for many years. This therapeutic approach takes into account the fact that lymphedema exists in an entire body quadrant, although its effects are most distressing in the arm or hand, and includes skin care, gentle specific massage, known as manual lymphatic drainage or MLD, low-stretch multilayer compression bandaging (followed by a fitted compression garment when edema is reduced), and therapeutic exercises with the garment or bandages in place.

The 1998 American Cancer Society Workshop on Breast Cancer Treatment-Related Lymphedema included a review of the modifications and features of the various CDP programs described by Vodder,<sup>37</sup> Leduc,<sup>38</sup> Foldi,<sup>39</sup> and Casley-Smith.<sup>40</sup> Although the principles followed are the same for each school, the massage techniques vary somewhat in terms of the degree of pressure and motion applied and the timing of strokes. Additionally, the Leduc technique uses low, intermittent pneumatic pressure (<40 mm Hg) pumps, and the Casley-Smith group uses benzopyrone medication.

CDP must be performed by skilled, specially trained therapists. A typical



**Table 2**  
**Complex Decongestive Therapy (CDT)**

**Phase I: Treatment—1 to 4 weeks**

- Meticulous skin and nail care
- Manual lymphatic drainage
- Low-stretch multilayer bandaging
- Physical therapy in bandages

**Phase II: Maintenance**

- Meticulous skin and nail care
- Low-stretch multilayer bandages worn overnight
- Prescribed exercises in bandages [Surgical support garments (30-50mm Hg) for ongoing control]

American program includes four phases. During Phase I (the treatment phase), the patient is given one or two 75- to 90-minute treatments daily over a period of one to four weeks. In Phase II (the maintenance phase), the patient maintains and optimizes the results by applying some of the techniques learned in the treatment phase, as well as by wearing an elastic sleeve during the day, bandaging the affected limb overnight (as described below), and exercising for 15 minutes a day while wearing the bandages. Phase II is continued indefinitely or until the limb no longer swells.

Phase I of CDP treatment consists of four steps:

1. Meticulous skin and nail care, which can optimize the supple normal texture.
2. MLD or manual lymph therapy (MLT), a delicate massage technique that stimulates lymph vessels to contract more frequently, directing and channeling fluid toward adjacent, functioning lymph basins. Manual lymph drainage begins with stimulation of the

lymph vessels and nodes in unaffected and opposite basins (neck, contralateral axilla, ipsilateral groin). Edema fluid and obstructed lymphatics are made to drain toward functioning lymph basins across the midline of the body, down toward the groin, over the top of the shoulder, around the back, etc. Finally, in segmental order, massage of the involved trunk, the shoulder, upper arm, forearm, wrist, and hand.

3. Multilayer low-stretch bandaging is done immediately following manual lymph drainage. Bandages are wrapped from the fingertips to the axilla with maximal pressure distally and less pressure proximally. Many layers of minimally elastic cotton bandages are used, beneath which layers of foam rubber padding are inserted to ensure uniform pressure distribution or to increase pressure in areas that are particularly fibrotic.
4. The bandaged patient is next guided through exercises involving active range of motion with the muscles and joints functioning within the closed space of the bandaging. Isometric exercise is generally avoided.

The steps involved in the maintenance phase of CDP are shown in Table 2. After volume reduction has been accomplished, well-fitted compressive garments continue ongoing control of edema. It is generally not helpful to fit the garment prior to volume reduction. The patient should be re-measured and the garment replaced every three months. The patient and the patient's family will have been trained to continue the maintenance program at home. Follow-up visits to the center usually take place at six-month intervals for measurements and continued instruction about different components of the program.

A recent short-term study of 28 women randomized to either the Vodder technique or to sequential pneumatic compression ("pumping") favored the CDP program.<sup>41</sup> Low-stretch compres-

sion bandaging, as in Phase I, has also been used alone (without MLD) with some good effects.<sup>42</sup> Although this burgeoning technique appears more successful than other modalities in reversing lymphedema, the availability of patient services and treatment centers that can utilize CDP is limited.

Representatives of the four schools have recently reviewed and discussed issues of patient accessibility<sup>43</sup> and professional education for physical therapists.<sup>44</sup> Ongoing training of therapists and physicians is offered at several centers to teach CDP techniques. (The theories and clinical applications of the four schools of manual lymphatic technique are reviewed in the American Cancer Society monograph by their respective faculties.<sup>37-40</sup>)

## 2. Elevation and Elastic Garments

The elements of elevation and some details of the use of elastic garments are presented here.<sup>45</sup> Although elevation may be helpful in reducing swelling from lymphedema through the use of gravity, it is impractical. A patient with lymphedema should be fitted with an elastic sleeve from wrist to axilla if the edema is mild; if the edema is moderate, the fitting should take place *after* the reduction of swelling. A separate, removable gauntlet or hand-piece allows the patient to wash her hands without removing the entire sleeve.

The physician who prescribes the support garment should be aware of the different products that are available and should order a garment in the proper compression class. These classes are:

- I. 20 to 30 mm Hg
- II. 30 to 40 mm Hg
- III. 40 to 50 mm Hg
- IV. 50 to 60 mm Hg

For upper extremity lymphedema, a Class II or III support is generally required.

The person measuring the lymphedematous arm and hand should be trained in fitting such garments and in instructing patients in their proper application. Too often, however, this task is left

to a clerk in a surgical supply store who lacks specific training.

A statistically significant reduction in edema has been reported in women who wore compression garments for six consecutive hours per day.<sup>46</sup> Using these garments during exercise, physical activity, and air travel is recommended.

## 3. Pneumatic Pumps

The older intermittent, single-chamber, nonsegmented compression pumps provide even pressure throughout the treated arm; however, they also allow backflow of the lymphatic fluid, which may cause an increase of fluid in the distal arm. Newer devices have multiple chambers and can provide sequential compression.

The standard sequential system is a multichamber pump that delivers the compression at the same pressure in each garment section from distal to proximal tissues. The gradient sequential system delivers pressures that differ by approximately 10 mm Hg between each chamber, with the higher pressures delivered to the distal chamber. A minimum of one hour per pumping session is required, and lower pressures for longer periods are more effective than higher pressures for shorter periods. The arm should be elevated during pumping. Women with lymphedema should not simply be dispatched to the medical supply house with a prescription and instructions to buy a pump and to begin using it after reading the accompanying instructions.

Individualized, tailored pumping programs are based on empirical knowledge of what will work for each individual patient. Recommendations for the use of a particular pump and program should be based on measurable efficacy and tolerability, as evidenced by serial assessment in that patient. The patient is then instructed about the limitations and use of her pump before she is placed on a home program.

Several controlled studies<sup>47-51</sup> have reported reductions in lymphedema with the use of various devices. Although the

use of machinery for the pumping action on the arm lymphatics is theoretically attractive, pumping has not been as effective clinically as had been hoped.

While CDP is quite successful for lymphedema, constraints created by the need for experienced personnel and by time requirements for treatment limit its availability. It has been hoped that pneumatic compression devices or "pumps" could duplicate the beneficial effects of massage.<sup>45</sup> Such pumps can force protein-rich edema fluid toward the shoulder, an area already congested, but not, however, through the axillary blockage; lymphedema involves the whole quadrant of the ipsilateral trunk, the area that the obstructed axillary channels would normally drain. In particular, pneumatic compression therapy appears less useful in advanced lymphedema because of skin thickening and fibrosis. For recent reviews of the rationale for and controversies about pumps, see Brennan and Miller<sup>45</sup> and Rinehart-Ayres.<sup>52</sup>

#### 4. Surgical Treatment

Operations with intent to cure lymphedema are cited here mainly for historical interest. Numerous surgical procedures have been proposed and attempted in the treatment of chronic lymphedema yet none has been clinically successful.

Surgical approaches can be divided into two categories, physiologic and reductive. Physiologic approaches aim to restore lymphatic flow to the limb either by reconstruction of lymphatic channels or by bridging lymphedematous tissue to areas with normal lymphatics, usually by direct microsurgical anastomosis of several lymphatics to veins. Reductive approaches simply remove excess tissue and edema to reduce the limb to a more functional size. These operations include removal of skin and subcutaneous tissue followed by skin grafting (Charles procedure), or staged subcutaneous excision beneath skin flaps (Sistrunk procedure).

Very recently, short-term success with liposuction has been noted in Sweden by one group,<sup>53-55</sup> although the long-term efficacy of the procedure is not known. The state of knowledge about surgical procedures for lymphedema was recently reviewed by Brennan and Miller.<sup>45</sup>

#### 5. Medications

Diuretics are not effective in high-protein edemas such as lymphedema. Although the diuretics can temporarily mobilize water, the osmotic pressure from the increased protein in the interstitial space causes rapid reaccumulation of edema.

Benzopyrones belong to a group of drugs that include the bioflavonoids and the coumarins. The former occur widely in nature, especially in fruits and vegetables. Benzopyrones improve chronic lymphedema<sup>56-57</sup> by stimulating macrophage activity for increased proteolysis and, thereby, for the removal of stagnant, excess protein in the tissue spaces; this results in decreased oncotic pressure and edema fluid.

Several European and Australian researchers<sup>58-62</sup> have experimented with 5,6-benzo- $\alpha$ -pyrone and reported that it produces a slow reduction of lymphedema. Their centers include these drugs in physical rehabilitation programs. The benzopyrones may cause liver toxicity, and deaths have been reported.

In 1993, in an Australian study, a randomized, double-blind, placebo-controlled, crossover trial of 5,6-benzo- $\alpha$ -pyrone demonstrated its efficacy.<sup>63</sup> Although the effect was mild, it was statistically significant. More recently, however, a larger number of lymphedematous breast cancer patients participated in an American multicenter study of similar study design led by the Mayo Clinic. In this study, the benzopyrone showed no value beyond the placebo effect.<sup>64</sup> Moreover, 6% of the study subjects had worrisome elevation of liver-function tests.

## American Cancer Society Workshop on Breast Cancer Treatment-Related Lymphedema: Recommendations and Research Initiatives

Approximately 60 invited participants were organized into five concurrent workgroups, each of which focused on a dimension of the current challenge of lymphedema, and each of which was charged with issuing recommendations for research, clinical practice, public and professional education, and advocacy. Workgroup reports and recommendations were published as part of the proceedings of the conference and are summarized here.

### Workgroup I: Treatment of the Axilla with Surgery and Radiation—Preoperative and Postoperative Risk Assessment

Lymphedema of the arm is caused by treatment of the axilla with surgery or radiation, and risk of lymphedema is increased when the axilla is treated with both modalities. Recommendations to reduce risk of lymphedema without compromising the fundamental intent of breast cancer treatment included:

1. Avoidance of axillary lymph node dissection for patients with low-risk lesions (i.e., ductal carcinoma *in situ* or certain T1 lesions)
2. Support for continued research on lymphatic mapping and SLNB, and for training and credentialing in these new techniques. Although these new techniques appear to offer great potential to reduce the risk of lymphedema in patients with lower-risk lesions, patients undergoing treatment with SLNB should be informed of the lack of long-term follow-up with these techniques and, ideally, should be enrolled in a prospective study.
3. For patients who must be managed with standard treatment, painstaking care in the technical aspects of surgery itself and radiation planning can reduce the risk of lymphedema.
4. Research is needed on pre- and post-imaging studies (e.g., lymphoscintigraphy) to evaluate the status of the axillary lymph nodes and lymphatic drainage of the arm and breast.
5. Include assessment of symptoms associated with early signs of lymphedema in routine follow-up after breast cancer treatment. *All clinical trials of breast cancer treatment, such as chemotherapy assessment, should include lymphedema assessment as an additional endpoint.*<sup>65</sup>

### Workgroup II: Patient Education—Pre- and Post-treatment

Most breast cancer patients do not appear to be informed about the potential for lymphedema as a consequence of treatment for breast cancer. Pre- and post-treatment education is needed, as early signs of lymphedema may not be recognized, leading to delays in treatment and potentially to irreversible progression. Furthermore, although little is definitely known about activities or trigger events associated with lymphedema onset, patients should be fully informed so that risk-reducing behavior can be adopted. Treatment advances may offer women opportunities for informed decisions about breast cancer treatment based in part on risk of subsequent lymphedema. Informed decision-making must take place when these treatment options exist. Specific recommendations included the following:

1. Verbal and written pretreatment education on the risk of lymphedema should be introduced into discussion of breast cancer treatment options; written material should be culturally sensitive and evidence-based.
2. Post-treatment education should stress the importance of recognizing early signs of lymphedema, include information on hand and arm precautions, and offer practical advice for avoiding situations associated with lymphedema risk. Advice should be offered about what to do if these situations are encountered (i.e., a wound on the affected arm).
3. Patients who develop lymphedema should be evaluated comprehensively by experienced professionals and be fully informed about treatment options, management of acute lymphedema, and self-maintenance of stable but chronic forms of lymphedema.<sup>66</sup>

### Workgroup III: Diagnosis and Management

Although lymphedema is a prevalent disorder, there is a tendency toward “therapeutic neglect” of lymphedema following treatment for breast cancer. Second, while there are different therapeutic approaches to lymphedema, consensus has not been reached on whether one approach is preferable to another, or under what circumstances one approach may be more appropriate than another.

### Lymphedema Workshop -Continued

Chronic lymphedema is best treated by specialists using a multimodal approach of decongestive lymphatic therapy, which includes proper skin care, manual lymphatic therapy, multilayered low-stretch bandages, and exercise. After arm-volume reduction, ongoing control of edema must be maintained through properly fitted compression garments. Another modality that may be used *in addition* to decongestive lymphatic therapy is intermittent compression pumps. The workgroup recommended:

1. All patients treated for breast cancer should be assessed for signs and symptoms of lymphedema at an early interval following completion of healing from breast cancer therapy (within the first 12 weeks). Clinicians should pay attention to physical signs of lymphedema as well as to the patient's subjective awareness of symptoms, as the latter may reveal early signs of an underlying pathology.
2. Research should focus on the development of screening modalities predictive of lymphedema, such as enhanced lymphoscintigraphic techniques used to measure degrees of lymphatic dysfunction.
3. Investigation of the importance of early detection and aggressive intervention for reducing severity and progression of lymphedema should be undertaken.
4. Research to determine the relative efficacy of each component of a comprehensive treatment program, including optimal timing of application.<sup>57</sup>

#### Workgroup IV: Lymphedema Treatment

##### Resource—Professional Education and Availability of Patient Services

Health care providers are not sufficiently informed about lymphedema, may not recognize early symptoms of the condition, and generally are uninformed about treatment options and the availability of treatment in their communities. Because of the pivotal role played by health care professionals in terms of informing and meeting the needs of patients, recommendations relate to the development and cost-effectiveness of both professional education and patient interventions. These included:

1. Development of clinical-practice guidelines focusing on professional education, lymphedema recognition, and intervention strategies in patients treated for breast cancer;

2. Promotion of professional education focused on lymphedema, including grand rounds, continuing medical education, and greater attention to lymphedema in medical textbooks and graduate medical education;
3. Establishment of a multidisciplinary task force to establish certification guidelines for specific treatments and treatment facilities;
4. Expansion of the number of facilities available to treat lymphedema, and development of a resource guide for lymphedema clinical services;
5. Development of cost/economic analysis of the burden and treatment of lymphedema.<sup>58</sup>

#### Workgroup V: Collaboration and Advocacy

Meeting the current and future challenge of lymphedema will be accomplished faster and more efficiently if organizations work together and address a common mission. Collaboration has the potential to reduce duplication, maximize resources, encourage greater innovation, and hasten progress. A common advocacy position among leading and influential organizations can also be more persuasive and more effective in changing policy than uneven and uncoordinated efforts.

The workgroup focused on the need for collaboration and called for the inclusion of representatives from all advocacy positions (including the American Cancer Society, the National Lymphedema Network, the National Alliance of Breast Cancer Organizations, the Susan G. Komen Foundation, Y-ME National Breast Cancer Organization, Arm-in-Arm, and Bosom Buddies) in future initiatives. Collaborative efforts should focus on patient and provider education, standards for informed consent and information, and legislative and patient advocacy. A workgroup should be established to develop a model for insurance coverage of lymphedema treatment services; the provision of coverage was advocated for state-of-the-art treatment by third-party payers. The workgroup stressed the need for effective advocacy for standards of treatment and management of lymphedema, calling for collaboration within the medical and scientific community to establish the evidence upon which future advocacy and collaborative efforts could be built.<sup>69</sup>

## Multidisciplinary Treatment

CERTIFIED THERAPISTS, such as physical and occupational therapists, typically plan rehabilitation interventions, generally in concert with a prescribing physician. Other individuals, including nurses and licensed massage therapists, may employ these techniques as well. Therapists should also identify and address pain, limitations in range of motion, and impaired activities of daily living.

- For mild lymphedema (resolves completely overnight):
  1. Counsel: Use arm/hand precautions; normalize body weight; employ meticulous arm/hand care.
  2. Elevate; employ centripetal self-administered massage.
  3. Use compression garment, particularly during work, exercise, and air travel.
- For moderate and severe lymphedema: (*referral to a rehabilitation center recommended*)
  1. Counsel: Use arm/hand precautions; normalize body weight; employ meticulous arm/hand care.
  2. Elevate; employ centripetal self-administered massage.
  3. Use compression garment.
  4. Employ complete decongestive physiotherapy (CDP) program AND/OR intermittent pneumatic compression devices under guidance of a therapist.

## Conclusion

Lymphedema is an important health problem for many women who have been treated for breast cancer. It is especially dispiriting to women who have been assured that their prognosis is excellent and that reconstruction will allow them to continue their lives with few visible reminders of their disease. For many women, lymphedema is not only a debilitating condition, but also a daily reminder of the health care system's failure to educate them appropriately and to respond effectively to their condition. Many of the recommendations for addressing the challenge of lymphedema are interrelated and are thus dependent on concomitant and synchronous progress in the development of a solid research base, treatment modalities for the reduction of risk of lymphedema, improvements in the clinical response to symptoms of lymphedema, improvements in provider and patient education, and changes in health care policy. In the interim, patients and health care providers must be fully appraised of what we know and what we do not know about breast-cancer-treatment related lymphedema. **CA**

## References

1. American Cancer Society Workshop on Breast Cancer Treatment-Related Lymphedema. New York, New York, USA. February 20-22, 1997. *Cancer*. 1998 Dec 15;83(12 Suppl American):2775-2890.
2. Mortimer PS: The pathophysiology of lymphedema. *Cancer* 1998;83(12 Suppl American):2798-2802.
3. Brennan MJ: Lymphedema following the surgical treatment of breast cancer: A review of pathophysiology and treatment. *J Pain Symptom Manage* 1992;7:110-116.
4. McCaffrey JF: Lymphedema: Its treatment. In Paterson AHG, Lees AW (eds): *Fundamental problems in breast cancer*. Boston, Martinus Nijhoff Publishing, 1987; pp. 259-263.
5. Passik SD, McDonald MV: Psychosocial aspects of upper extremity lymphedema in women treated for breast carcinoma. *Cancer* 1998;83(12 Suppl American):2817-2820.
6. Passik SD, Newman M, Brennan M, Tunkel R: Predictors of psychological distress, sexual dysfunction and physical functioning among women with upper extremity lymphedema related to breast cancer. *Psycho-Oncology* 1995;4:255-263.



7. Gerber LH: A review of measures of lymphedema. *Cancer* 1998;83(12 Suppl American):2803-2804.
8. Bolin FP, Preuss LE, Beninson J: Di-chromatic differential absorptiometry for assessment of lymphedema. *Int J Nucl Med Biol* 1980;7:359-360.
9. Stewart G, Hurst PAE, Thomas ML, Burnand KG: CAT scanning in the management of the lymphedematous limb. *Immunol Haematol Res* 1988;2:241.
10. Duwell S, Hagspiel KD, Zuber J, et al: Swollen lower extremity: Role of MR imaging. *Radiology* 1992;184:227-231.
11. Stanton AW, Northfield JW, Holroyd B, et al: Validation of an optoelectronic limb volumeter (Perometer). *Lymphology* 1997;30:77-97.
12. Kissin MW, Querci della Rovere G, Easton D, Westbury G.: Risk of lymphoedema following the treatment of breast cancer. *Br J Surg* 1986;73:580-584.
13. Bourgeois P, Leduc O, Leduc A: Imaging techniques in the management and prevention of post-therapeutic upper limb edemas. *Cancer* 1998;83(12 Suppl American):2805-2813.
14. Carena M, Baiardi P, Saponaro M, et al: Scintigraphic evaluation of predisposition to post-mastectomy lymphedema, in Lokiec FM, Cluzan RV, Pecking AP et al: (eds): *Progress in Lymphology XIII*. Berlin, Springer-Verlag, 1992; p. 325.
15. Pecking AP, Floiras JL, Rouesse J: Upper limb lymphedema's frequency in patients by conservative therapy in breast cancer. *Lymphology* 1996;29(Suppl):293.
16. Petrek JA, Heelan MC: Incidence of breast carcinoma-related lymphedema. *Cancer* 1998;83(12 Suppl American):2776-2781.
17. Ferrandez JC, Serin D, Bouges S: Frequency of lymphedema of the upper limb after treatment of breast cancer. Risk factors. Apropos of 683 cases. *Bull Cancer* 1996;83:989-995.
18. Schunemann H, Willich N: Lymphedema after breast carcinoma. A study of 5868 cases. *Dtsch Med Wochenschr* 1997;122:536-541.
19. Lin PP, Allison DC, Wainstock J, et al: Impact of axillary lymph node dissection on the therapy of breast cancer patients. *J Clin Oncol* 1993;11:1536-1544.
20. Werner RS, McCormick B, Petrek JA, et al: Arm edema in conservatively managed breast cancer: Obesity is a major predictive factor. *Radiology* 1991;180:177-184.
21. Ivens D, Hoe AL, Podd TJ, et al: Assessment of morbidity from complete axillary dissection. *Br J Cancer* 1992;66:136-138.
22. Ball AB, Waters R, Fish S, Thomas JM: Radical axillary dissection in the staging and treatment of breast cancer. *Ann R Coll Surg Engl* 1992;74(2):126-129.
23. Paci E, Cariddi A, Barchielli A, et al: Long-term sequelae of breast cancer surgery. *Tumori* 1996;82:321-324.
24. Pressman PI: Surgical treatment and lymphedema. *Cancer* 1998;83(12 Suppl American):2782-2787.
25. Pezner RD, Patterson MP, Hill LR, et al: Arm lymphedema in patients treated conservatively for breast cancer: Relationship to patient age and axillary node dissection technique. *Int J Radiat Oncol Biol Phys* 1986;12:2079-2083.
26. Yeoh EK, Denham JW, Davies SA, Spittle MF: Primary breast cancer. Complications of axillary management. *Acta Radiol Oncol* 1986;25:105-108.
27. Delouche G, Bachelot F, Premont M, Kurtz JM: Conservation treatment of early breast cancer: Long term results and complications. *Int J Radiat Oncol Biol Phys* 1987;13:29-34.
28. Aitken RJ, Gaze MN, Rodger A, et al: Arm morbidity within a trial of mastectomy and either nodal sample with selective radiotherapy or axillary clearance. *Br J Surg* 1989;76:568-571.
29. Larson D, Weinstein M, Goldberg I, et al: Edema of the arm as a function of the extent of axillary surgery in patients with stage I-II carcinoma of the breast treated with primary radiotherapy. *Int J Radiat Oncol Biol Phys* 1986;12:1575-1582.
30. Dewar JA, Sarrazin D, Benhamou E, et al: Management of the axilla in conservatively treated breast cancer: 592 patients treated at Institut Gustave-Roussy. *Int J Radiat Oncol Biol Phys* 1987;13:475-481.
31. Meeke AG: Breast radiotherapy and lymphedema. *Cancer* 1998;83(12 Suppl American):2788-2797.
32. Giuliano A, Jones RC, Brennan M, Statman R: Sentinel lymphadenectomy in breast cancer. *J Clin Oncol* 1997;15:2345-2350.
33. Tadych K, Donegan WL: Postmastectomy seromas and wound drainage. *Surg Gynecol Obstet* 1987;165:483-487.
34. West JP, Ellison JB: A study of the causes and prevention of edema of the arm following radical mastectomy. *Surg Gynecol Obstet* 1959;109:359.
35. Mortimer PS, Bates D, Brassington H, et al: The prevalence of arm oedema following treatment for breast cancer. *QJM* 1996;89:377-380.
36. Brennan MJ, Weitz J: Lymphedema 30 years after radical mastectomy. *Am J Phys Med Rehabil* 1992;71:12-14.
37. Kasseroller RG: The Vodder School: The Vodder method. *Cancer* 1998;83(12 Suppl American):2840-2842.
38. Leduc O, Leduc A, Bourgeois P, Belgrado JP: The physical treatment of upper limb edema. *Cancer* 1998;83(12 Suppl American):2835-2839.
39. Foldi E: The treatment of lymphedema. *Cancer* 1998;83(12 Suppl American):2833-2834.
40. Casley-Smith JR, Boris M, Weindorf S, Lasinski B: Treatment for lymphedema of the arm—the Casley-Smith method: A noninvasive method produces continued reduction. *Cancer* 1998;83(12 Suppl American):2843-2860.
41. Johansson K, Lie E, Ekdahl C, Lindfeldt J: A randomized study comparing manual lymph drainage with sequential pneumatic compression for treatment of postoperative arm lymphedema. *Lymphology* 1998;31:56-64.
42. Johansson K, Albertsson M, Ingvar C, Ekdahl C: Effects of compression bandaging with or without manual lymph drainage treatment in patients



- with postoperative arm lymphedema. *Lymphology* 1999;32:103-110.
43. Thiadens SR: Current status of education and treatment resources for lymphedema. *Cancer* 1998;83(12 Suppl American):2864-2868.
  44. Augustine E, Corn M, Danoff J: Lymphedema management training for physical therapy students in the United States. *Cancer* 1998;83(12 Suppl American):2869-2873.
  45. Brennan MJ, Miller LT: Overview of treatment options and review of the current role and use of compression garments, intermittent pumps, and exercise in the management of lymphedema. *Cancer* 1998;83(12 Suppl American):2821-2827.
  46. Bertelli G, Venturini M, Forno G, et al: An analysis of prognostic factors in response to conservative treatment of postmastectomy lymphedema. *Surg Gynecol Obstet* 1992;175:455-460.
  47. Klein MJ, Alexander MA, Wright JM, et al: Treatment of adult lower extremity lymphedema with the Wright Linear pump: Statistical analysis of a clinical trial. *Arch Phys Med Rehabil* 1988;69:202-206.
  48. Kim-Sing C, Basco VE: Postmastectomy lymphedema treated with the Wright linear pump. *Can J Surg* 1987;30:368-370.
  49. Pappas CJ, O'Donnell TF Jr: Long-term results of compression treatment for lymphedema. *J Vasc Surg* 1992;16:555-562.
  50. Richmand DM, O'Donnell TF Jr, Zelikovski A: Sequential pneumatic compression for lymphedema: A controlled trial. *Arch Surg* 1985;120:1116-1119.
  51. Zanolla R, Monzeglio C, Balzarini A, Martino G: Evaluation of the results of three different methods of postmastectomy lymphedema treatment. *J Surg Oncol* 1984;26:210-213.
  52. Rinehart-Ayres ME: Conservative approaches to lymphedema treatment. *Cancer* 1998;83(12 Suppl American):2828-2832.
  53. Brorson H, Svensson H: Complete reduction of lymphoedema of the arm by liposuction after breast cancer. *Scand J Plast Reconstr Surg Hand Surg* 1997;31:137-143.
  54. Brorson H, Svensson H: Liposuction combined with controlled compression therapy reduces arm lymphedema more effectively than controlled compression therapy alone. *Plast Reconstr Surg* 1998;102:1058-1067.
  55. Brorson H, Svensson H, Norrgren K, Thorsson O: Liposuction reduces arm lymphedema without significantly altering the already impaired lymph transport. *Lymphology* 1998;31:156-172.
  56. Piller NB, Clodius L: The role of the mononuclear phagocytic system in lymphoedema and its relationship with histopathological changes in the functioning of the blood-tissue system. *Z Lymphol* 1980;4:35-42.
  57. Casley-Smith JR, Gaffney RM: Excess plasma proteins as a cause of chronic inflammation and lymphedema: Quantitative electron microscopy. *J Pathol* 1981;133:243-272.
  58. Cluzan R, Pecking A: Benzopyrone (Lysedem) double blind cross-over study in patients with secondary upper limb edemas, in Nishi M, Uchino S, Yabuke S (eds): *Progress in lymphology XII, Excerpta Med Int Cong Ser* 887. Amsterdam, Elsevier, 1990, pp. 453-454.
  59. Pecking AP, Fevrier B, Wargon C, Pillion G: Efficacy of Daflon 500 mg in the treatment of lymphedema (secondary to conventional therapy of breast cancer). *Angiology* 1997;48:93-98.
  60. Casley-Smith JR: There are many benzopyrones for lymphedema. *Lymphology* 1997;30:38-39.
  61. Taylor HM, Rose KE, Twycross RG: A double-blind clinical trial of hydroxyethylrutinosides in obstructive arm lymphedema. *Phlebologie* 1993;22 (Suppl 1):190.
  62. Burgos A, Alcaide A, Alcoba C, et al: Comparative study of the clinical efficacy of two different coumarin dosages in the management of arm lymphedema after treatment for breast cancer. *Lymphology* 1999;32:3-10.
  63. Casley-Smith JR, Morgan RG, Piller NB: Treatment of lymphedema of the arms and legs with 5,6-benzo-[alpha]-pyrone. *N Engl J Med* 1993;329:1158-1163.
  64. Loprinzi CL, Kugler JW, Sloan JA, et al: Lack of effect of coumarin in women with lymphedema after treatment for breast cancer. *N Engl J Med* 1999;340:346-350.
  65. Leitch AM, Meek AG, Smith RA, et al: American Cancer Society Lymphedema Workshop. Workgroup I: Treatment of the axilla with surgery and radiation—preoperative and postoperative risk assessment. *Cancer* 1998;83(12 Suppl American):2877-2879.
  66. Runowicz CD, Passik SD, Hann D, et al: American Cancer Society Lymphedema Workshop. Workgroup II: Patient education—pre- and posttreatment. *Cancer* 1998;83(12 Suppl American):2880-2881.
  67. Rockson SG, Miller LT, Senie R, et al: American Cancer Society Lymphedema Workshop. Workgroup III: Diagnosis and management of lymphedema. *Cancer* 1998;83(12 Suppl American):2882-2885.
  68. Walley DR, Augustine E, Saslow D, et al: American Cancer Society Lymphedema Workshop. Workgroup IV: Lymphedema treatment resources—professional education and availability of patient services. *Cancer* 1998;83(12 Suppl American):2886-2887.
  69. Canceira M, Schuch W, Greiner L, et al: American Cancer Society Lymphedema Workshop. Workgroup V: Collaboration and advocacy. *Cancer* 1998;83(Suppl American):2888-2890.