REVIEW

Arm Edema in Breast Cancer Patients

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The improvement in the life expectancy of women with breast cancer raises important questions about how to improve the quality of life for women sustaining complications of breast cancer treatment. In particular, attention to common problems, such as arm edema, is of critical importance. We reviewed published breast cancer guidelines and literature identified via MEDLINE® searches in an effort to summarize the research literature pertinent to management of breast cancer-related arm edema, including incidence, prevalence, and timing; risk factors; morbidity; prevention; diagnosis; and efficacy of nonpharmacologic and pharmacologic interventions. We found that arm edema is a common complication of breast cancer therapy that can result in substantial functional impairment and psychological morbidity. The risk of arm edema increases when axillary dissection and axillary radiation therapy are used. Recommendations for preventive measures, such as avoidance of trauma, are available, but these measures have not been well studied. Nonpharmacologic treatments, such as massage and exercise, have been shown to be effective therapies for lymphedema, but the effect of pharmacologic interventions remains uncertain. Comparing results across studies is complicated by the fact that the definitions of interventions and measures of outcomes and risk stratification vary substantially among studies. As arm edema becomes more prevalent with the increasing survival of breast cancer patients, further research is needed to evaluate the efficacy of preventive strategies and therapeutic interventions. [J Natl Cancer Inst 2001;93:96–111]

In recent years, breast cancer mortality rates have declined *(1),* reflecting advances in early detection as well as more widespread application of effective adjuvant therapies. Many women diagnosed with breast cancer today can expect survival that is similar to age-matched women without breast cancer as a result of advances in early detection and effective adjuvant therapies. This is particularly the case for the increasing proportion of newly diagnosed women who have stage 0 or very favorable stage 1 breast cancer (e.g., tumors that are <1 cm in size) *(2).* Consequently, effective prevention and management of treatment sequelae that can impair function or detract from quality of life have taken on increasing importance.

Arm edema after breast cancer surgery and radiation therapy is one of these sequelae *(1,3–7).* Arm edema in the breast cancer patient is caused by interruption of the axillary lymphatic system by surgery or radiation therapy, which results in the accumulation of fluid in subcutaneous tissue in the arm, with decreased distensibility of tissue around the joints and increased weight of the extremity *(3).* Chronic inflammatory changes result in both subcutaneous and lymph vessel fibrosis *(8).*

Patients with arm edema secondary to breast cancer therapy can experience a substantial degree of functional impairment and psychological morbidity and diminished quality of life. Functional impairment can result from decreased range of motion in the affected upper extremity joints and decreased healing capacity of the affected tissue, with resultant increased risk of infection *(3),* as well as from pain *(9).* Anxiety, depression, and emotional distress are more common in patients with lymphedema than in those without *(5,10,11).* Psychological distress and pain in these patients adversely affect their quality of life *(12).*

The purpose of this review is to summarize the research literature pertinent to the management of arm edema in women with breast cancer. We systematically examined the literature to assess what is and is not known about the efficacy of interventions for arm edema in women with breast cancer. We focus on the incidence, prevalence, and timing of arm edema following breast cancer treatment, risk factors, morbidity, prevention, diagnosis/evaluation, and nonpharmacologic and pharmacologic interventions.

METHODS

To establish the evidence base for care of breast cancer patients with arm edema, we reviewed existing guidelines and literature. Published guidelines for breast cancer care primarily address treatment aspects, rather than long-term care for morbid conditions secondary to treatment. Of 17 published guidelines *(13–29)* for breast cancer care, only two *(14,20)* addressed care of patients with treatment-related lymphedema.

A total of 10 MEDLINE® literature search strategies were used. Three initial literature search strategies for articles on breast cancer-related arm morbidity covered 1993–1999 and resulted in 127 entries associated with 96 unique articles. The three search strategies were as follows: 1) (subject: mastectomy) *AND* (subject: activities of daily living *OR* lymphedema *OR* arm) *OR* (keyword: arm) (50 entries); 2) (subject: breast neoplasms, radiotherapy *OR* radiotherapy, adjuvant) *AND* (subject: activities of daily living *OR* lymphedema *OR* arm) *OR* (keyword: arm) (11 entries); and 3) (subject: breast neoplasms) *AND* (subject: activities of daily living *OR* lymphedema *OR* arm) *AND* (keyword: function or functional) (66 entries).

Seven subsequent search strategies for articles on lymphedema covered 1985–1999 and resulted in 381 entries associated with 311 unique articles. The strategies were as follows: 1) (subject: breast neoplasms) *AND* (keyword: lymphedema treatment) (20 entries); 2) (keyword: post-mastectomy lymphedema *OR*

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See "Notes" following "References."

post-mastectomy arm) (49 entries); 3) (title word: post-mastectomy lymphedema) (22 entries); 4) (subject: lymphedema) *AND* (keyword: prevention) (21 entries); 5) (subject: breast neoplasms) *AND* (keyword: lymphedema therapy) (68 entries); 6) (subject: lymphedema) *AND* (keyword: treatment) (19 entries); and 7) (subject: lymphedema, therapy) (182 entries).

In addition, we examined key references from the articles generated by the literature search.

RESULTS

Incidence/Prevalence/Timing

The reported incidence of arm edema after breast cancer therapy varies widely across treatments. Table 1 summarizes reports of 10 studies of lymphedema incidence following a variety of surgical procedures and adjuvant therapies. Of note is the broad range of incidence based on the definition of lymphedema used, the type of breast cancer therapy provided, and the time since treatment. In addition, Kissin et al. *(30)* reported that lymphedema (measured by limb volume) was present in 25% of the members of a cohort of 200 patients after a variety of surgical treatments for breast cancer overall and in 38% of patients receiving axillary node dissection plus radiation therapy. Across treatments and times since treatment, approximately one in four women develops arm edema after treatment of breast cancer. In our review, the overall incidence of reported arm edema was 26%, with a range from 0% with partial or total mastectomy and sentinel node biopsy *(31)* to 56% 2 years after surgery (modified radical mastectomy or breast-conserving surgery with axillary radiation therapy) and axillary dissection *(32).* Citing an incidence rate of 20% *(30,33–36),* Petrek and Lerner *(37)* note that lymphedema following breast cancer therapy currently affects some 400 000 women in the United States.

The prevalence of lymphedema increases over time. In a longitudinal study of 93 patients after breast cancer surgery, Tasmuth et al. *(4)* found the prevalence of arm edema to increase from 22% at 1 month after surgery to 36% at 1 year. In a survey of 1151 women treated for breast cancer, Mortimer et al. *(38)* reported that the prevalence of arm edema increases over time after radiation therapy, from 23% at 0–2 years after treatment to 45% at 15 years or more since treatment. A smaller increase in the prevalence of arm edema over time was apparent for the group treated with surgery alone, in which prevalence increased from 20% at 0–2 years after treatment to 30% at 15 years or more since treatment *(38).*

The timing of onset of lymphedema following breast cancer treatment varies. Guedes Neto *(39)* found that 73% of 142 patients with arm edema had developed the edema within 1 year of treatment for breast cancer. In a cohort of 282 patients treated with breast-conserving surgery and radiation therapy, Werner et al. *(34)* found that the mean time from treatment to development of lymphedema was 14 months (range, 2–92 months) and that 97% of patients who developed arm edema did so within 4 years of treatment. Dennis *(40)* reported on only nine patients but observed a large variability in the time between surgery and onset of lymphedema (i.e., between 2 months and 3 years).

An observational study of 231 untreated patients evaluated in a lymphedema clinic *(41)* suggests that the severity of arm edema is associated with duration of symptoms. Untreated patients had a mean duration of 2.1 years for less severe edema and a mean duration of 5.6 years for more severe edema with fibrosis.

No large population-based studies of the incidence of lymphedema have yet been carried out with the use of standardized procedures for diagnosis, measurement, and follow-up time *(37,42).* Accordingly, physicians may have difficulty providing patients with precise estimates of the probability for arm edema.

Risk Factors

Patients who receive axillary node dissection and/or axillary radiation therapy for breast cancer are at particular risk for the development of lymphedema as well as other arm morbidities, such as pain, paresthesias, weakness, and impaired shoulder function. In a cohort study of 223 patients treated for nonrecurrent breast cancer with surgery and axillary dissection, Maunsell et al. *(5)* found an incidence of arm morbidity at 3 months as follows: swelling, 25%; pain, 56%; numbness, 62%; weakness, 26%; limitation in range of motion, 33%; and stiffness, 42%.

In one series of 278 patients receiving total axillary lymphadenectomy, radiation therapy to the breast and to the breast and axillary nodes increased arm edema over mastectomy alone by 4%–15% and 30%, respectively *(43).* However, Liljegren and Holmberg *(44),* in a randomized controlled trial of the use of postoperative radiotherapy in 381 patients with sector resection and axillary dissection, found that radiation therapy to the breast alone did not adversely affect arm symptoms during the first 3 postoperative years. In another cohort of 136 breast cancer patients *(45),* those treated with axillary radiation had a higher incidence of arm edema (58%) than those treated with parasternal/supraclavicular radiation therapy (17%) or no radiation therapy (21%). Borup Christensen and Lundgren *(46),* in a study of 100 patients who had undergone partial or total mastectomy, found that arm edema was associated with degree of axillary surgery (30% of 47 patients with axillary dissection developed arm edema versus none of the 48 patients with axillary sampling) and with the use of axillary radiation therapy (23% of 52 patients with axillary radiation therapy developed arm edema versus 5% of 43 patients without radiation therapy). Studying a series of 57 women treated with mastectomy and partial axillary dissection, Ryttov et al. *(35)* found that the relative risk of arm edema in patients treated with axillary radiation was 6.9 (95% confidence interval [CI] = 1.5 to 32.5) times that of patients who did not receive axillary radiation therapy. However, Gerber et al. *(32)* reported no significant difference in the extent of arm edema among 237 patients randomly assigned to receive either modified radical mastectomy or local excision, axillary dissection, and radiation therapy. Across a number of studies *(38,45,47–50),* lymphedema has been reported to occur in approximately 41% (range, 21%–51%) of patients who undergo axillary radiation therapy in addition to surgery as opposed to approximately 17% (range, 6%–39%) of patients treated with surgery but no axillary radiation therapy.

The degree of arm edema is also associated with the extent of axillary surgery. In a study of 381 patients with stage 1 breast cancer, Liljegren and Holmberg *(44)* found that only age and number of lymph nodes excised predicted number of arm problems (edema or subjective arm symptoms) in a multivariate model: The relative risk of arm problems was 0.93 per year of increasing age (95% CI = 0.91 to 0.97) and 1.11 per lymph node excision (95% CI = 1.05 to 1.18). Similarly, Kiel and Rademacker *(51)* found that the actuarial probability of edema was predicted by age, number of lymph nodes dissected, and

Table 1. Incidence of lymphedema following breast cancer therapy: description of 10 studies

	Study (reference No.)			
	Schrenk et al. *(31)*	Liljegren et al. *(44)*	Kiel and Rademacker *(51)*	Keramopoulos et al. *(48)*
Year	2000	1997	1996	1993
Country	Austria	Sweden	United States	Greece
Clinical setting	Department of Surgery	Department of Surgery	Radiation Oncology	Breast Division, Department of Obstetrics and Gynecology
Type of study	Prospective cohort	Prospective randomized trial	Prospective cohort	Prospective cohort
Statistical analysis method	Fisher's exact test, χ^2	Logistic regression	Kaplan–Meier	Multiple regression
Total study No.	70	381	183	104
Type of breast surgery	Quadrantectomy or mastectomy	Sector resection	Breast-conserving surgery	Segmental resection or modified radical mastectomy
Type of axillary surgery (% of patients)	Sentinel node biopsy (50%) or axillary dissection (50%)	Axillary dissection (100%)	Axillary dissection (82%)	Not reported
Axillary radiation therapy, % of patients	0%	0%	Not reported	70%
Breast radiation therapy, % of patients	70%	Randomly assigned 184 patients	100%	Not reported
Lymphedema measurement method	Self-reported arm symptoms*	Calculated arm volume† Subjective arm symptoms‡	Measured arm circumference§	Measured arm circumference‖
Lymphedema definition	Subjective self-report of arm swelling as none, mild, moderate, or severe	>100-mL difference in arm volume	>1-cm increase in circumference compared with the measurement at the previous examination	Upper limb measurement difference of >2 cm between arms
Overall incidence of lymphedema in subgroups	With sentinel node biopsy: any edema, 0% With axillary dissection "Mild" edema, 40% "Moderate" edema, 14%	3–12 mo, 2.4% 13–36 mo, 11.2%	Any edema, 35% Grade 2–4 edema, 17.5%	17%

	Study (reference No.)		
	Gerber et al. *(32)*	Segerström et al. *(57)*	Senofsky et al. *(49)*
Year	1992	1991	1991
Country	United States	Sweden	United States
Clinical setting	Rehabilitation Medicine	Surgery	Surgical Oncology
Type of study	Prospective randomized trial	Prospective cohort	Prospective cohort
Statistical analysis method	Wilcoxon rank	χ^2, linear regression	χ^2, Kaplan–Meier
Total study No.	237	136	278
Type of breast surgery	Breast-conserving surgery or modified radical mastectomy	Modified radical mastectomy	Segmental or total mastectomy
Type of axillary surgery (% of patients)	Axillary dissection (100%)	Axillary dissection (100%)	Total axillary lymphadenectomy (100%)
Axillary radiation therapy, % of patients	50% (chosen at random)	42%	10.3%
Breast radiation therapy, % of patients	Not reported	Not applicable	23%
Lymphedema measurement method	Measured arm circumference¶	Volume measurement by water displacement#	Clinical evaluation of edema as grades I–IV**
Lymphedema definition	Upper limb measurement of difference of ≥2 cm between arms	≥150-mL difference in arm volume	Grade I = minimal to mild; grade II = requires a compression stocking for control; grade III = requires use of lymphedema pump and stocking; grade IV = poorly controlled lymphedema
Overall incidence of lymphedema in subgroups	At 1 y, 39% At 2 y, 56%	43%	9.4%

(Table continues)

Table 1 (continued). Incidence of lymphedema following breast cancer therapy: description of 10 studies

	Study (reference No.)		
	Werner et al. *(34)*	Lin et al. *(33)*	Paci et al. *(112)*
Year	1991	1993	1996
Country	United States	United States	Italy
Clinical setting	Radiation Oncology	Surgery	Tumor registry
Type of study	Prospective cohort	Retrospective cohort	Retrospective cohort
Statistical analysis method	Cox proportional hazard	Descriptive	Descriptive
Total study No.	282	283	238
Type of breast surgery	Breast-conserving surgery	Radical mastectomy, modified radical mastectomy, lumpectomy	Mastectomy, lumpectomy, quadrantectomy
Type of axillary surgery (% of patients)	Axillary dissection (100%)	Axillary dissection (100%)	Not reported
Axillary radiation therapy, % of patients	23%	6%	Not reported
Breast radiation therapy, % of patients	100%	17%	Not reported
Lymphedema measurement method	Measured arm circumference††	Measured arm circumference‡‡	Measured arm circumference§§
Lymphedema definition	⩾2.5-cm difference between the affected arm and the unaffected arm	⩾2-cm difference between the affected arm and the unaffected arm	Sum of the differences between affected and unaffected arms: "light" edema = <4 cm; "moderate" edema = 4–8 cm; "heavy" edema = ⩾8 cm
Overall incidence of lymphedema in subgroups	19.5%	⩾2 cm, 16% ⩾3 cm, 6% ⩾4 cm, 2%	Early‖‖ edema, 16.4%; late¶¶ light edema, 8.7%; late moderate edema, 13.7%; late heavy edema, 7.9%

*None = no arm swelling, tightness, or heaviness; mild = periods of arm swelling but no constant increase in greatest diameter and clothes fit the same; moderate = constant arm swelling and heaviness, clothes do not fit the same, physical discomfort but no decrease in functional activity; severe = constant arm heaviness, disability, decreased functional activity, huge arm swelling.

†Lymphedema defined as a greater than 100-mL difference in arm volume between operated and nonoperated side.

‡Pain, numbness, impaired shoulder mobility, weakness.

§Measured 15 cm above and 10 cm below the olecranon. Lymphedema was defined as present if either measurement was greater than 1 cm more than the measurement at the previous examination. Edema was graded as follows: grade 1, difference from previous measurement of greater than 1 cm in the affected arm if on the nondominant side (i.e., right or left handedness) or greater than 1.5 cm in the affected arm if on the dominant side; grade 2, difference of 2 cm or more between arms; grade 3, symptomatic edema necessitating treatment; grade 4, edema causing loss of arm function.

‖Measured 15 cm above and 10 cm below the lateral epicondyle.

¶Measured at ulnar styloid, olecranon, and 35 cm proximal to the ulnar styloid.

≠Lymphedema defined as 150 mL or greater difference in arm volume between operated and nonoperated side.

**Clinical evaluation: grade 1 = minimal to mild edema, requiring no intervention or only elevation on one or two pillows at night; grade II = required an external compression stocking for satisfactory control; grade III = required use of lymphedema pump and stocking for control; grade IV = poorly controlled lymphedema or edema complicated by lymphangitis.

††Measured 13 cm above and 10 cm below the olecranon.

‡‡Measured 10 cm above and 10 cm below the olecranon.

§§"Early" lymphedema not defined; "late" lymphedema defined as 5 years after surgery. Amount of edema defined as sum of differences between affected and unaffected arm measured at 6 points: "light" edema 4 cm or lower, "moderate" = 4–8 cm, "heavy" = 8 cm or higher.

‖‖Early sequelae not defined.

¶¶Late sequelae assessed at 5 years.

number of positive lymph nodes dissected in a cohort of 183 patients treated with breast-conserving surgery and breast radiation therapy. Yeoh et al. *(52),* in a study of 187 patients after surgery and radiation therapy, found that the degree of arm dysfunction (arm edema and limitation of shoulder mobility) was predicted by the extent of axillary surgery. The 30-month actuarial rate of arm edema ranged from 25% for patients without axillary surgery, to 50% for patients with axillary sampling, to 84% for patients with axillary dissection. In a cohort of 223 patients after surgery for nonrecurrent breast cancer, Maunsell et al. *(5)* found that, regardless of the type of mastectomy, women who had undergone axillary dissection had significantly more self-reported arm problems (24%–64%) than women who had not undergone axillary dissection (0%–33%). In a recent prospective study comparing morbidity following sentinel node biopsy versus that following axillary node dissection in 70 patients, Schrenk et al. *(31)* reported no significant difference in arm circumference in the sentinel node biopsy group but a significant ($P = .0001$) increase in arm dimension in the axillary dissection group.

The combination of axillary radiation therapy and axillary surgery substantially increases the risk of arm edema. In a randomized controlled trial of 100 patients treated either with axillary dissection or with axillary sampling with or without radiation therapy, Borup Christensen and Lundgren *(46)* found that the incidence of arm edema was significantly higher in the group with axillary dissection and axillary radiation therapy (44%) than in the group with axillary dissection alone (10%) or

in the groups with axillary sampling, with or without radiation therapy (0%) (intergroup difference $P = .001$). Kissin et al. *(30)* reported that the incidence of lymphedema in a cohort of 200 patients after breast cancer surgery was 8.3% for women additionally treated with axillary radiotherapy alone, 9.1% for women treated with axillary sampling and radiation therapy, 7.4% for women treated with axillary dissection alone, and 38.3% for women treated with axillary dissection and axillary radiation therapy. These findings have important implications in the context of arm edema risk, given the resurgence of interest in postmastectomy axillary radiation therapy because of recent findings of improved survival, especially for patients with more than three positive axillary nodes *(53)*.

Morbidity

Lymphedema can cause limitation in range of motion and pain, weakness, or stiffness in the affected extremity *(5,54)*. In a case–control study, Tobin et al. *(55)* found that 46% of 50 patients with lymphedema reported some degree of functional impairment, as measured by the Karnofsky performance scale *(56)*, whereas 50 control patients without lymphedema reported no such impairment. In a cohort study of 93 patients treated with mastectomy, axillary clearance, and radiation therapy, Segerström et al. *(57)* found that, of the 40 patients (43%) with arm edema, 36 (90%) reported functional impairment (shoulder, arm, or hand symptoms). In another study *(58)*, decreased arm function (swelling, pain, limited movement in the arm or shoulder, or loss of feeling) interfered with daily activities by self-report for 33% of 76 patients in a cross-sectional study of breast cancer patients treated with breast-conserving surgery.

Lymphedema also results in psychological morbidity, as documented in a wide range of studies. Case examples and descriptive studies have identified several common psychological problems related to lymphedema, including anxiety, depression, sexual dysfunction, social avoidance, and exacerbation of existing psychiatric illness *(11)*. In a qualitative study *(59)*, 10 lymphedema patients reported distress arising from limited physician knowledge of their condition, limited treatment options, anxieties regarding social and personal relationships and body image, and changes in work habits and lifestyles. At one site, 10% of patients in rehabilitation for breast cancer-related lymphedema were referred for psychiatric evaluation *(11)*.

A number of cohort studies have evaluated aspects of psychological distress secondary to lymphedema. A recent study of 101 breast surgery patients *(12)* used the SF-36 (a generic health status instrument) to measure overall quality of life and showed that patients with lymphedema had significantly lower scores in the domain of mental health. In a study of 223 patients treated surgically for nonrecurrent breast cancer, Maunsell et al. *(5)* found the adjusted odds ratios (ORs) for psychological distress, as measured by the Psychiatric Symptom Index *(60,61)*, to be proportional to the number of arm problems (defined as swelling, weakness, limited range of motion, stiffness, pain, or numbness) reported at 3 and 18 months, respectively. As compared with patients with no arm problems, the OR for experiencing psychological distress at 3 months after treatment was 1.2 for patients with one or two problems, 2.3 for patients with three or four problems, and 3.1 for patients with five or six problems ($P = .002$; no CIs reported); at 18 months after treatment, the OR was 1.9 for patients with one or two problems, 4.4 for patients with three or four problems, and 6.0 for patients with five or six problems ($P = .0002$) *(5)*. Passik et al. *(62)*, in a study of 69 women being treated for breast cancer treatment-related lymphedema, found that 25% of lymphedema patients experienced pain and that lymphedema was associated with distress, decreased functioning, and decreased sexual desire. Although patients with arm edema had high levels of psychological distress and of sexual and social dysfunction as measured by the Brief Symptom Inventory *(63)*, no linear relationship between severity of edema and levels of distress was identified *(62)*. In a group of 76 patients who had been treated for early-stage breast cancer with wide excision and axillary dissection, the presence of arm edema had a stronger association with psychological functioning and perceptions of body image in younger patients ($\leqslant$60 years old) and for patients treated more than 5 years earlier than in older patients and those treated less than 5 years earlier *(58)*.

Psychological dysfunction secondary to lymphedema has also been described in case–control studies. Tobin et al. *(55)* conducted a series of case–control studies with 100 subjects to identify the degree of psychological dysfunction experienced by patients with lymphedema. Patients with lymphedema had significantly more anxiety and depression based on the Clinical Interview Scale, a semistructured standard mental state examination *(64)*; they also experienced poorer adjustment to their illness, as measured by the Psychosocial Adjustment to Illness Scale *(65)*, in the areas of vocational, domestic, and social environments as well as sexual relationships and psychological distress *(55)*. This impaired psychosocial adjustment was not consistently related to the amount of edema; in fact, it persisted after a significant reduction in edema following 6 months of individualized lymphedema treatment in the majority of patients (81%) *(55)*.

Prevention

The literature on prevention of lymphedema focuses primarily on specific surgical techniques to reduce damage to the axillary lymphatic system. No randomized controlled trials or cohort studies were identified that addressed interventions designed specifically to prevent lymphedema after treatment with surgery or radiation therapy. Although a number of recommendations for preventing lymphedema can be found in review articles and in the nursing literature, no evidence base exists that demonstrates the efficacy of one mode of prevention over another or even the efficacy of preventive measures versus no preventive measures.

One important category of prevention relates to the known association between axillary node dissection and the incidence of arm edema. The introduction of the sentinel node biopsy as a way to identify women who truly need axillary node dissection may translate into a smaller number of women undergoing axillary node dissection *(66)*. However, a substantial number of women will still have to undergo axillary node dissection. Some of these women will also undergo radiation therapy and so be at high risk for arm edema *(3,67)*. Thus, other strategies to prevent or minimize arm edema must be developed.

Four categories of prevention interventions are repeatedly mentioned across the breast cancer literature: 1) avoidance of trauma/injury, 2) prevention of infection, 3) avoidance of arm constriction, and 4) use and exercise of the limb. Strategies for implementing these measures include using protective gloves for household work and gardening *(68–72)*; avoiding venipuncture,

blood pressure measurement, and injections in the affected arm *(37,68–73);* preventing infection with timely first aid *(37,70,71,73);* immediately identifying and treating any sign of infection *(37,68–71,73);* avoiding heat and excessive sun exposure *(37,68–71,73);* avoiding constricting clothing on the affected extremity *(37,70–73);* using the affected limb in moderation *(71,72);* not carrying heavy objects *(69–73);* and avoiding repetitive motion *(37,68–73).* However, no scientific evidence exists to show that any of these strategies is more effective than any other or even that preventive measures have any effect. Moreover, teaching patients about these strategies is a challenge because breast surgery is commonly done in the outpatient setting or with very short hospital stays. The opportunity to provide education in the hospital postoperatively has, therefore, been reduced.

Diagnosis/Evaluation

Lymphedema is primarily diagnosed clinically by medical history and physical examination *(8,74).* Sequential circumferential measurement of the affected extremity is a simple and inexpensive method to evaluate the extent of arm edema. Arm volume can be estimated by taking several circumferential measurements at standard distances. In fact, estimated volumetric measurements are now commonly used as a way to quantify arm edema *(75).* Circumferential measurement has been shown be to highly correlated ($r = .93–.98$) with the results of the more exact water displacement method *(76).* Differences of greater than 2 cm between the affected and normal arms are considered to be clinically significant *(77).*

Newer methods of definitive diagnosis and measurement have been developed, including the use of bioelectrical impedance *(78,79)* to quantify the amount of fluid accumulation and of lymphoscintigraphy, which allows visualization of the lymphatic system. Lymphoscintigraphy is minimally invasive and has become a major tool in the diagnostic evaluation of edema *(3,38,80,81).* These diagnostic measures may also be supplemented by computed tomography or magnetic resonance imaging *(81,82).* The literature only infrequently reports the use of the newer diagnostic methods in research or clinical practice.

Standardization of measurement methods would allow a clearer understanding of incidence, prevalence, and relative risk in subgroups of patients and more meaningful comparisons of the efficacy of preventive and therapeutic measures. Sitzia et al. *(75),* in a review of outcome indicators in lymphedema, noted the lack of consistency and rigor in measurement methods. They recommended a multidimensional approach to outcomes measurement in lymphedema, to take account of the fact that neither physical examination by a doctor at one point in time nor patient self-report of arm edema severity as a single measure reliably quantifies arm edema severity.

The literature does not systematically address how or when physicians or nurses should query breast cancer patients about the presence or absence of arm edema. The literature also does not address the systematic education of patients by physicians or nurses so that they are told of the need to inform their health-care providers if they develop new or worsening arm swelling.

Nonpharmacologic Treatment Interventions

Common nonpharmacologic treatment interventions for lymphedema include elevation, massage and exercise, application of external pressure with compression garments or compression pumps, and complex physical therapy *(83).* Less common therapies for lymphedema include surgical procedures and electrically stimulated lymphatic drainage.

Articles addressing the nonpharmacologic treatment of breast cancer treatment-related arm edema were gleaned from literature searches and from references within these articles. Table 2 gives the study description, patient characteristics, treatment type, and study results for 15 studies conducted since 1989 (17 publications) that have systematically evaluated a nonpharmacologic intervention for patients with breast cancer-related arm edema and reported outcomes. The studies were conducted in referral centers in six countries: six lymphedema clinics, five rehabilitation or physical therapy services, two oncology clinics, and two surgery clinics. Three study designs involved a randomized controlled trial (with 80, 74, and 25 patients), and the remaining were cohort studies that evaluated patients before and after an intervention. The mean age of the patients ranged from 50 years to 71 years.

A history of the use of axillary dissection was reported in six studies, and a history of the use of radiation therapy was reported in six studies; five studies reported both. Time since primary breast cancer therapy was noted in only two studies, and lymphedema duration was noted in seven studies. Lymphedema severity was noted in nine studies, although the system used for evaluating severity varied: a formal grading system (in three studies), differences in circumferential measurement between normal and affected arms (in three studies), volumetric measurement (in one study), and a qualitative comment regarding severity (in two studies).

Therapies are often used in combination, as can be seen in the studies cited. Therapies used include the following: elevation, massage and exercise with and without compression sleeve, standard elastic sleeve, standard elastic sleeve with and without electrically stimulated lymphatic drainage, uniform pneumatic compression, sequential compression using hydrostatic pressure of mercury, complex physical therapy, complex physical therapy and sequential pneumatic compression, liposuction followed by custom compression garment, and surgical excision and lymphatico-venous shunt.

Elevation alone is not an effective treatment of breast cancer treatment-related arm edema *(84),* although elevation may be used as an adjunct to other therapies *(83,85).*

Massage and exercise are most often prescribed as part of a multidisciplinary treatment program *(83,85,86).* A specific form of massage known as manual lymphatic drainage is designed to mobilize edema fluid from distal to proximal areas and from areas of stasis to healthy lymphatics *(87–89).*

Standard elastic compression garments (elastic sleeve or elastic bandage) have been shown to be effective in the treatment of breast cancer treatment-related lymphedema *(90–92).* In one study *(90),* simple elastic compression treatment for lymphedema resulted in a substantial reduction in arm edema in 34% of patients at 2 months and in 39% of patients at 6 months, and it was equally successful in patients older than age 65 years as in those 65 years old or younger.

Compression therapy may also be provided with the use of compression pumps. These pumps are typically pneumatic and provide intermittent uniform or sequential compression to the affected extremity. The treatment schedule is usually daily or 5 days per week, but it varies in length (90 minutes to 6 hours) and

Table 2. Nonpharmacologic treatment of lymphedema after breast cancer therapy: 15 studies

	Study (reference No.)		
	Swedborg et al. *(84)*	Hornsby *(92)*	Bertelli et al. *(90)*
Study description			
Year	1993	1995	1992
Country	Sweden	England	Italy
Clinical setting	Rehabilitation service	Lymphedema clinic	Rehabilitation service of cancer institute
Type of study	Cohort pretherapy/post-therapy	Randomized control trial	Cohort pretherapy/post-therapy
Statistical analysis method	Paired Student's *t* test	Descriptive	Multiple regression
Total study No.	33	25	120*
Patients with upper extremity edema, No.	33	25	120
Patients with edema secondary to breast cancer treatment, No.	33	25	120
Measurement method	Arm volume by water displacement	Arm volume by water displacement	Difference in circumference of affected limb in comparison with normal limb
Patient characteristics			
Mean age (range or ±standard deviation)	71 y (range, 43–87 y)	Not reported	Median age 65 y (range, 45–88 y)
Type of surgery	Modified radical mastectomy	Not reported	Complete or partial mastectomy
Axillary dissection, % of patients	100%	Not reported	100%
Radiation therapy, % of patients	73%	Not reported	50%
Time since primary breast cancer therapy, y	Not reported	Not reported	Not reported
Lymphedema duration, mean y ±standard deviation	2.7	Not reported	Not reported
Lymphedema severity	Affected arm volume at least 10% greater than nonaffected arm	Not reported	At least 10-cm difference between normal and affected arms
Treatment			
Treatment type	Elevation	Massage and exercise with and without compression sleeve	Standard elastic sleeve alone or in combination with pneumatic compression or electrically stimulated lymphatic drainage
Treatment frequency	Single treatment	Massage and exercise frequency not reported; compression sleeve worn continuously	Continuous
Total No. of treatments	1	Not applicable	Not applicable
Treatment duration	5 h	Not applicable	6 mo
No. of courses of treatment‡	1	1	1
Follow-up time(s) after completion of therapy	Immediately after treatment	4 wk	2 mo (during therapy) 6 mo (completion of therapy)
Results			
Improvement in edema	Reduction in arm volume 5 h after treatment: Affected arm, 3.1 ± 0.07% Non-affected arm, 3.3 ± 0.03% (Not significant)	Percent of patients with reduction in edema: Experimental group, 86% Control group, 36% (Significance not reported)	Difference in circumference of affected arm compared with normal arm: Baseline, 19.7 cm 2 mo, 16.8 cm ($P \leqslant .001$) 6 mo, 17.2 cm ($P \leqslant .001$)

(Table continues)

Table 2 (continued). Nonpharmacologic treatment of lymphedema after breast cancer therapy: 15 studies

	Study (reference No.)		
	Bertelli et al. *(91)*	Dini et al. *(94)*	Palmer et al. *(114)*
Study description			
Year	1991	1998	1991
Country	Italy	Italy	United States
Clinical setting	Rehabilitation service of cancer institute	Cancer institute	Physical therapy department
Type of study	Randomized control trial	Randomized control trial analyzed by intent to treat	Cohort pretherapy/post-therapy
Statistical analysis method	Wilcoxon, Mann–Whitney rank sum, chi-square	Comparison of means	Descriptive
Total study No.	74	80	12
Patients with upper extremity edema, No.	74	80	8
Patients with edema secondary to breast cancer treatment, No.	74	80	Not reported
Measurement method	Difference in circumference of affected limb in comparison with normal limb	Difference in circumference of affected limb in comparison with normal limb	Cross-sectional area by circumferential measurements; computed tomography scan
Patient characteristics			
Mean age (range or ±standard deviation)	Median 64 y (range, 45–78 y)	Not reported	Not reported
Type of surgery	Mastectomy or quadrantectomy	Mastectomy or lumpectomy	Not reported
Axillary dissection, % of patients	100%	100%	Not reported
Radiation therapy, % of patients	Not reported	44%	Not reported
Time since primary breast cancer therapy, y	Not reported	Not reported	Not reported
Lymphedema duration, mean y ±standard deviation	Not reported	<1 y	"Years"
Lymphedema severity	At least 10-cm difference between normal and affected arms	At least 10-cm difference between normal and affected arms	Not reported
Treatment			
Treatment type	Standard elastic sleeve with and without electrically stimulated lymphatic drainage	Uniform pneumatic compression†	Sequential compression using hydrostatic pressure of mercury
Treatment frequency	Weeks 1 and 2: therapy 5 days/wk Weeks 3–7: no therapy Weeks 9 and 10: therapy 5 days/wk	Weeks 1 and 2: therapy 5 days/wk Weeks 3–7: no therapy Weeks 9 and 10: therapy 5 days/wk	Weekly or semiweekly
Total No. of treatments	20	20	4–8
Treatment duration	9 wk (including 5 wk with no therapy)	9 wk (including 5 wk with no therapy)	1 mo
No. of courses of treatment‡	1	1	1
Follow-up time(s) after completion of therapy	2 mo and 6 mo	Immediately after treatment	1 mo
Results			
Improvement in edema	Percent of patients with responses to therapy: Responses§ Stabilization‖ 2 mo: 17% 31% 6 mo: 23% 25% (Difference between groups, not significant)	Difference in circumference of affected arm compared with normal arm: Treatment group, 14.2 cm Control group, 14.1 cm (Not significant)	Percentage ± standard deviation decrease in lymphedema: Wrist, 14 ± 16 Mid-forearm, 6 ± 9 Mid-arm, 3 ± 7 (Significance not reported)

(Table continues)

Table 2 (continued). Nonpharmacologic treatment of lymphedema after breast cancer therapy: 15 studies

	Study (reference No.)		
	Morgan et al. *(101);* Casley-Smith and Casley-Smith *(102)*	Boris et al. *(103)*	Daane et al. *(104)*
Study description			
Year	1992	1994	1998
Country	Australia	United States	United States
Clinical setting	Lymphedema clinic	Lymphedema clinic	Rehabilitation service
Type of study	Cohort pretherapy/post-therapy	Cohort pretherapy/post-therapy	Cohort pretherapy/post-therapy
Statistical analysis method	Paired Student's *t* test	Paired Student's *t* test	Descriptive
Total study No.	78	38	20
Patients with upper extremity edema, No.	78	16	20
Patients with edema secondary to breast cancer treatment, No.	78	16	20
Measurement method	Volume estimation by circumferential measurement	Volume estimation by circumferential measurement	Calculated difference in mean arm circumference
Patient characteristics			
Mean age (range or ±standard deviation)	Mean age 55 y (±11 y)	Mean age 53 y	Mean age 57 y
Type of surgery	Mastectomy or lumpectomy	Not reported	Mastectomy
Axillary dissection, % of patients	Not reported	Not reported	Not reported
Radiation therapy, % of patients	90%	Not reported	Not reported
Time since primary breast cancer therapy, y	Not reported	Not reported	Not reported
Lymphedema duration, mean y ±standard deviation	Grade 1,¶ 0.84 ± 0.97 Grade 2, 4.41 ± 4.03	5.7 y	Not reported
Lymphedema severity	Grade 1, 22% Grade 2, 78%	Grade 1, 19% Grade 2, 81%	Characterized as signifcant arm edema, but not defined
Treatment			
Treatment type	Complex physical therapy#	Complex physical therapy	Complex physical therapy
Treatment frequency	5 days/wk	4 h/day	Not reported
Total No. of treatments	20	Not reported	Mean of 15.3 visits
Treatment duration	4 wk	Over a 30-day period	Over a period of 3–4 wk
No. of courses of treatment‡	1 or 2	1	1
Follow-up time(s) after completion of therapy	End of first course, end of second course, and at 1 y	Immediately after treatment	6 mo
Results			
Improvement in edema	Volume reduction:	Volume reduction:	Circumference reduction:
	Grade 1 edema: End of 1st course, 103% ($P \leqslant .001$) End of 2nd course, 31% ($P \leqslant .05$) End of 1st y, 34% ($P \leqslant .001$)	After treatment,†† 73% ($P \leqslant .001$)	Mean reduction, 73% 40%–60% reduction, 20% 60%–80% reduction, 50% >80% reduction, 30%
	Grade 2 edema: End of 1st course, 60% ($P \leqslant .001$) End of 2nd course, 59% ($P \leqslant .001$) End of 1st y, 10% ($P \leqslant .001$)		(Significance not reported)

(Table continues)

Table 2 (continued). Nonpharmacologic treatment of lymphedema after breast cancer therapy: 15 studies

	Study (reference No.)		
	Ko et al. *(105)*	Foldi et al. *(87)*	Boris et al. *(106)*
Study description			
Year	1998	1989	1997
Country	United States	Switzerland	United States
Clinical setting	Lymphedema clinic	Lymphedema clinic	Lymphedema clinic
Type of study	Cohort pretherapy/post-therapy	Cohort pretherapy/post-therapy	Cohort pretherapy/post-therapy
Statistical analysis method	Comparison of means	Descriptive	Repeated measures analysis of covariance
Total study No.	299	399	119
Patients with upper extremity edema, No.	149	399	56
Patients with edema secondary to breast cancer treatment, No.	133	399	Not reported
Measurement method	Volume estimation by circumferential measurement	% volume reduction of lymphedematous arm	Volume estimation by circumferential measurement
Patient characteristics			
Mean age (range or ±standard deviation)	Mean age 60 y (±12 y)	Not reported	Median age 50 y‡‡
Type of surgery	Mastectomy or lumpectomy	Mastectomy	Not reported
Axillary dissection, % of patients	69%	Not reported	Not reported
Radiation therapy, % of patients	62%	Not reported	Not reported
Time since primary breast cancer therapy, y	Not reported	Not reported	Not reported
Lymphedema duration, mean y ±standard deviation	Not reported	Not reported	3.4 ± 1.1
Lymphedema severity	Not reported	Not reported	Grade 1, 21%; grade 2, 79%
Treatment			
Treatment type	Complex physical therapy	Complex physical therapy	Complex physical therapy
Treatment frequency	Daily	Not reported	2–4 h/day
Total No. of treatments	Not reported	Not reported	Not reported
Treatment duration	4–25 days**	Not reported	Over a 30-day period
No. of courses of treatment‡	1	Not reported	1
Follow-up time(s) after completion of therapy	Immediately after treatment, at 6 mo and at 12 mo	Immediately after treatment and at 3 y	Immediately after treatment Every 3 mo for 36 mo
Results			
Improvement in edema	Volume reduction (compared with pretreatment): After treatment, 59% ± 8.3% (i.e., ±standard deviation) ($P \leq .05$) 6 mo, 57% ± 14.3% ($P \leq .05$) 12 mo, 53% ± 16.9% ($P \leq .05$)	Volume reduction: After treatment No change 5% 1%–24% reduction 8% 25%–49% reduction 31% ≥50% reduction 56% 3 y Results not maintained 10% Results maintained or insignificant increase 89% (Significance not reported)	Volume reduction: After treatment 63% 18 mo 97% 36 mo 64% (Significance not reported) Effect of compliance:§§ Noncompliant 43% 25% compliant 53% 50% compliant 60% 75% compliant 58% 100% compliant 79% ($P \leq .001$) (Significance reported only for 100% compliance)

(Table continues)

Table 2 (continued). Nonpharmacologic treatment of lymphedema after breast cancer therapy: 15 studies

	Study (reference No.)		
	Bunce et al. *(97)*; Mirolo et al. *(95)*	Brorson and Svensson *(107)*	Filippetti et al. *(108)*
Study description			
Year	1994, 1995	1997	1994
Country	Australia	Sweden	Italy
Clinical setting	Oncology clinic	Plastic surgery service	Department of Surgery
Type of study	Cohort pretherapy/post-therapy	Cohort pretherapy/post-therapy	Cohort pretherapy/post-therapy
Statistical analysis method	Regression/analysis of variance	Student's *t* test	Descriptive
Total study No.	25	28	36
Patients with upper extremity edema, No.	25	28	36
Patients with edema secondary to breast cancer treatment, No.	25	28	36
Measurement method	Volume estimation by circumferential measurement	Arm volume by water displacement	Lymphoscintigraphy and ultrasound
Patient characteristics			
Mean age (range or ±standard deviation)	Mean age 58 y (±10 y; range, 39–81 y)	Mean age 63 y (range, 46–81 y)	Not reported
Type of surgery	Not reported	Mastectomy	Mastectomy
Axillary dissection, % of patients	Not reported	100%	Not reported
Radiation therapy, % of patients	Not reported	100%	Not reported
Time since primary breast cancer therapy, y	8.3 (± 8.9 standard deviation); range, 0.6–37.6	8; range, 1–24	Not reported
Lymphedema duration, mean y ±standard deviation	Not reported	7; range, 1–23	Not reported
Lymphedema severity	"Moderate to severe" *(95)* lymphedema	Not reported	Not reported
Treatment			
Treatment type	Complex physical therapy and sequential pneumatic compression	Liposuction followed by custom compression garment	Surgical excision and lymphatico-venous shunt
Treatment frequency	5 days/wk	Single surgical intervention Continuous compression garment	One surgical procedure
Total No. of treatments	20	Not applicable	Not applicable
Treatment duration	4 wk	Not applicable	Not applicable
No. of courses of treatment‡	1	1	1
Follow-up time(s) after completion of therapy	Immediately after treatment 1, 6, 12 mo	2 wk and 1, 3, 6, and 12 mo	6 mo and 18 mo
Results			
Improvement in edema	Percent of excess volume in affected arm: Pretreatment 35% After treatment:‖‖ Immediately 19.6% 1 mo 19.6% 6 mo 17.2% 12 mo 20.4% (Reported as significant with no *P* value given)	Mean edema volume: Preoperative, 1845 mL 12 mo, 30 mL ($P \leqslant .001$)	Surgical results, % of patients: 6 mo / 18 mo Good¶¶ 19% / 18% Fair## 55% / 41% Poor*** 26% / 41% (Significance not reported)

*120 patients treated in two prospective phase II studies *(90,91)*.

†Pneumatic therapy treatment included hygiene education; control group received hygiene education only.

‡Course of therapy is a definitive course of treatment, usually time limited.

§Decrease in amount of difference between affected and normal arm was greater than 25%.

‖Increase or decrease in amount of difference between affected and normal arm was less than 25%.

¶International Society for Lymphology Grading: grade 1 = little fibrosis, pits readily, and substantial reduction with simple elevation; grade 2 = much fibrosis, does not pit, and little reduction with elevation.

#Also known as complex decongestive therapy, complex lymphedema therapy, multimodal physical therapy, complex decongestive physiotherapy, and complete decongestive physiotherapy.

**Followed by phase II maintenance therapy carried out at home: compression garment, nighttime bandaging, and exercises.

††After treatment indicates immediately following the course of treatment.

‡‡Median age of group with upper extremity edema.

§§Compliance defined as the percentage of time the patient wore a compression garment and adhered to special physical therapy exercises. Edema reduction measured "during follow-up."

‖‖No *P* values given for immediate, 1, and 6 months after treatment data; 12-month result reported as "significant"—no *P* value given.

¶¶Reduction in limb volume more than 50%, disappearance of subjective symptoms, and episodes of lymphangitis.

##Reduction in limb volume less than 50%, improvement of subjective symptoms, and disappearance of episodes of lymphangitis.

***No reduction in limb volume, no symptomatic improvement, and persistent episodes of lymphangitis.

duration (2–3 days to 4 weeks), depending on the practitioner *(93–96).*

Pneumatic compression, with and without physical therapy, has been shown to decrease lymphedema *(97,98).* In one study *(95),* an intensive 4-week multimodal treatment program—consisting of massage, sequential pneumatic compression, and compression bandaging, along with patient education in self-management skills of bandaging, massage, and exercise—for patients with lymphedema secondary to breast cancer treatment decreased the degree of lymphedema and the need for physical assistance and increased the perceived comfort and strength of the extremity and quality of life. Although intermittent pneumatic compression is often used, a number of issues about its use remain to be resolved, including the optimum amount of pressure, the most efficacious treatment schedule, and whether maintenance therapy is needed after the initial reduction of edema *(83).* In addition, a consensus statement *(99)* recommends that the use of compression pumps be avoided in the absence of a multidisciplinary treatment program for lymphedema.

Complex physical therapy (also known as complex decongestive therapy, complex lymphedema therapy, multimodal physical therapy, complex decongestive physiotherapy, and complete decongestive physiotherapy), which consists of skin care, manual lymphedema treatment, exercises, and compression wrapping, followed by a maintenance program and psychosocial rehabilitation, has been recommended as a primary treatment by consensus panels *(74,83,100)* and is an effective therapy for lymphedema unresponsive to standard elastic compression therapy *(87,101–106).* Complex physical therapy resulted in some volume reduction of the affected extremity in 95% of 399 patients (≥50% reduction in 56% of patients, 25%–49% reduction in 31%, and 1%–24% reduction in 8%), 54% of whom maintained the therapeutic result at 3 years *(87).*

Surgical interventions, although rarely used, include liposuction, superficial lymphangiectomy, fasciotomy, and microsurgical lymphatico-venous anastomoses *(107,108).*

Many authorities, including two consensus panels *(21,99),* advocate the use of a multidisciplinary treatment program for lymphedema management. For example, Brennan and Miller *(83)* advocate a treatment plan that includes addressing infection, limitations in range of motion, impairment in activities of daily living, and psychological issues in addition to providing therapies aimed at reducing the amount of edema.

The literature seems to be clear on the efficacy of nonpharmacologic treatment. While the exact measure of outcomes of nonpharmacologic treatment for edema varies from study to study, most studies have used some variation on the percentage of reduction in limb volume or circumference and show fairly dramatic improvement with reductions of 15%–75% in volume or circumference. Although not all of the studies differentiated grades of edema, every indication is that both more and less severe cases showed improvements.

The largest number of studies described the efficacy of complex physical therapy, although all were cohort studies that evaluated patients before and after therapy. The three randomized control trials each evaluated a different mode of therapy and studied fewer than 100 patients. There is clearly a need for large randomized control trials to determine the relative efficacy of interventions (both individually and in combination), the optimal timing for the institution of various treatment modalities, and the effect of treatment on disease progression *(99).*

Pharmacologic Treatment

Drug therapy is used primarily as an adjunct to other lymphedema therapy *(83,99).* Benzopyrones, flavonoids, antibiotics, and diuretics have been used in the treatment of lymphedema *(3,100).* Table 3 shows the results from the three randomized controlled trials evaluating pharmacologic treatment of lymphedema following breast cancer therapy. Using a crossover design to study 31 lymphedema patients, Casley-Smith et al. *(109)* reported that 6 months of coumarin treatment results in a reduction of 20% in excess volume of the affected limb ($P<.001$). However, in another crossover randomized controlled study to evaluate the efficacy of 6 months of coumarin treatment in 138 patients *(110),* no measurable difference was observed in arm volume. Moreover, this study found that 6% of patients on coumarin versus 0% on placebo had reversible increases (i.e., >2.5 times the upper limit of normal) of serum aminotransferase ($P = .006$). The authors note that, during the time of this clinical trial, coumarin was removed from the market in at least two countries following patient deaths. Benzopyrones are not currently available for use in the United States *(99).*

A study of the flavonoid drug, Daflon, revealed a trend toward a reduction in limb volume after a 6-month course of treatment, but the effect was not statistically significant. Diuretics have little, if any, benefit, and there is no evidence to support their use in the treatment of lymphedema *(83,102).* Antibiotics should be used aggressively for the treatment of cellulitis and lymphangitis. While antibiotic prophylaxis is appropriate for use in the treatment of recurrent cellulitis, there are no data suggesting that its routine use is of benefit *(3,100).* Thus, the role of pharmacologic interventions in the treatment of arm edema remains unclear.

Discussion

The increased use of screening mammography has been associated with a substantial decrease in the size of primary breast cancers at diagnosis. As a result, fewer women diagnosed with primary breast cancer have axillary node involvement. In turn, more women with breast cancer diagnoses are living with the expectation that their cancer will not be the reason for their death. They concentrate on minimizing the side effects of treatment and improving health-related quality of life for the decades that remain in their lives *(67).* Although arm edema is rarely life-threatening, the problem has substantial prevalence. It is often painful, limits function, and increases the risk of infection. Moreover, it is associated with psychological morbidity.

Risk factors for the development of arm edema following breast cancer therapy relate primarily to the degree of interruption of the axillary lymph system by surgery or radiation therapy. There is a need for better understanding of the prevalence and morbidity of arm edema in population-based studies that are stratified by type of surgical intervention. Particular attention should be paid to the incidence of arm edema following sentinel node biopsy as compared with that following more traditional axillary node dissection. The ongoing randomized trials of sentinel node biopsy (e.g., National Surgical Adjuvant Breast and Bowel Project B-32) *(111),* which include prospective evaluation of arm edema, arm mobility, and self-reported symptoms should provide prospective data on the incidence, prevalence, and natural history of this problem with different treatments.

Table 3. Pharmacologic treatment of lymphedema following breast cancer therapy: three studies

	Study (reference No.)		
	Casley-Smith et al. *(109)*	Pecking et al. *(115)*	Loprinzi et al. *(110)*
Study description			
Year	1993	1997	1999
Country	Australia	France	United States
Clinical setting	Research Center	Nuclear Medicine Service	Not reported
Type of study	Randomized control trial crossover	Randomized control trial	Stratified* randomized control trial crossover
Statistical analysis method	Student's *t* test; linear regression	Student's *t* test, chi-square, analysis of variance with repeated measures	Student's *t* test; Wilcoxon rank sum
Total study No.	52	94	138
Patients with upper extremity edema, No.	31	94	138
Patients with edema secondary to breast cancer treatment, No.	31	94	138
Measurement method	Difference in circumference of affected limb in comparison with normal limb, arm volume by water displacement; symptom report,† tonometry, skin temperature	Lymphoscintigraphy, volume estimation by circumferential measurement, discomfort, and heaviness scales‡	Volume estimation by circumferential measurement, symptom report,§ perceived benefit‖
Patient characteristics		Treatment group / Placebo	
Mean age (±standard deviation)	63 y ± 3 y	61.5 y ± 10.8 y / 57.3 y ± 9.8 y	<60 y = 68 (49%); ⩾60 y = 70 (51%)
Type of surgery	Mastectomy	Not reported / Not reported	Mastectomy = 114 (83%); lumpectomy with radiation = 24 (17%)
Axillary dissection, % of patients	Not reported	Not reported / Not reported	Not reported
Radiation therapy, % of patients	Not reported	82.4% / 90.6%	54%
Time since primary breast cancer therapy	Not reported	Mean . . . 34 mo / 35 mo	<2 y = 19 (14%) 2–4 y = 42 (30%) >4 y = 77 (56%)
Lymphedema duration	Mean 8 y ± 1.6 y	Mean . . . 47 mo / 31 mo	1–2 y = 43 (31%) >2 y = 95 (69%)
Lymphedema severity	"Moderately severe to severe grade 2"	"Mild to severe"	Rated by patient and physician as "sufficiently severe to warrant treatment"
Treatment			
Treatment type	5,6-benzo-[α]-pyrone (coumarin), 400 mg	Daflon, 1000 mg	Coumarin, 200 mg
Treatment frequency	Daily	Daily	Twice daily
No. of treatments	Not applicable	Not applicable	Not applicable
Treatment duration	6 mo in each treatment arm	6 mo	6 mo in each treatment arm
No. of courses of treatment¶	1	1	1
Follow-up time(s) after completion of therapy	Immediately after treatment	Immediately after treatment	Immediately after treatment
Improvement in edema	Coumarin / Placebo Change in circumference, cm: −0.56 (*P*<.001) / +0.25 Change in limb volume, (L): −3.3 (*P*<.001) / +1.2 Arm symptoms (% better/% worse) Bursting pain: 72/7 / 12/46 Tightness: 75/16 / 17/37 Tension: 59/16 / 11/31 Heaviness: 66/17 / 20/39 Hardness: 70/5 / 20/37 Loss of mobility: 65/14 / 9/26 General well-being: 67/12 / 22/22 (all other symptoms not significant between treatment groups)	For n = 24 patients with more severe edema: Daflon / Placebo Lymphatic migration speed, cm/min: 0.84 / 0.14 (*P* = .005) Colloid half-life, min: 10.3 / 0.53 (*P* = .034) Colloid clearance, μL/min: 2.18 / 0.11 (*P* = .054) Limb volume#: −7% / +8% (Not significant) Discomfort: (Not significant) Heaviness: (Not significant) (For n = 70 patients with less severe edema, all comparisons were not significant)	Coumarin / Placebo Change in limb volume, mL: 53 / 39 Arm symptoms, mean grade: 1.1** / 1.0** Perceived benefit Did not help: 63% / 71% Helped a little: 27% / 19% Helped a moderate amount: 6% / 8% Helped a large amount: 4% / 2%

*Stratified by age, therapy for breast cancer, history of cellulitis in the involved arm, duration of lymphedema, time since surgery or radiation therapy, and tamoxifen therapy.

†Symptoms reported as better, the same, or worse: bursting pain, burning pain, cramps, paresthesias, feeling of tightness in limb, feeling of tension in limb, feeling of swelling in limb, feeling of heaviness in limb, feeling of hardness in limb, loss of mobility of limb, raised temperature of limb, secondary acute inflammation, dryness of skin, warts, and general well-being.

‡Discomfort assessed by visual analog scale; heaviness assessed by 4-point Likert scale (absent, inconstant, constant, and invalid).

§Arm symptoms assessed by subjects were swelling, pressure, tightness, heaviness, and loss of mobility. Symptoms were graded as 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

‖Perceived benefit rated as: No, did not help; Yes, helped a little; Yes, helped a moderate amount; or Yes, helped a large amount.

¶Course of therapy is a definitive course of treatment, usually time limited.

#Approximation based on graph, volume change not quantified.

**Approximation based on graph, mean grade not qualified.

The appropriate degree of health-care provider surveillance and the interaction of surveillance with patient education in the early recognition of symptoms are poorly understood. Among the many unanswered questions are the following: Is there value to early diagnosis in providers regularly examining patients' arms for edema or querying patients about subjective arm symptoms, or can diagnosis be left to evaluation following patient-initiated report of symptoms? How often do patients with arm edema need to be evaluated by providers in the absence of a change of symptoms?

There has also been virtually no systematic research in the area of preventive strategies for arm lymphedema. The relative efficacy of different preventive measures has not been evaluated, nor has it even been shown that preventive strategies are of any benefit. Randomized controlled trials or cohort studies are clearly needed that evaluate the efficacy of preventive measures versus no preventive measures, the efficacy of preventive interventions specifically designed to prevent lymphedema after the initial surgery or radiation treatment, and the efficacy of one mode of prevention over another.

Arm edema has become one of the most feared long-term complications of breast cancer treatment. Although all aspects of care for arm edema of women with breast cancer have not been fully addressed in the literature, certain aspects of treatment have been well evaluated. Moreover, the literature supports interventions aimed at early diagnosis and nonpharmacologic interventions. These efforts toward the treatment of morbidities should be implemented as soon as possible after treatment, when they are more likely to be effective.

A number of questions about treatment efficacy remain that warrant further investigation. For example, to what extent do improvements in physical and psychosocial functions follow improvements in arm edema associated with treatment? In addition, the data that are available on the efficacy of treatments, individually or in combination, need to be refined for specific patient subsets, such as those with recent versus long-standing edema, those with mild versus severe edema, and those with edema refractory to treatment. Other questions include the following: What is the duration of the resolution or improvement in arm edema associated with each of the interventions? What is the most effective means of long-term control of lymphedema after initial treatment? Are there safe and effective pharmacologic interventions for the treatment of lymphedema?

Studies to evaluate the use of interventions known to be efficacious, and obstacles to their use, could be very important for women with breast cancer treatment-related arm edema and for health-care providers responsible for designing managed care and other treatment protocols for women with breast cancer. As survival continues to improve for these patients, quality-of-life issues take on increasing importance. There is a critical need for simpler, more effective interventions to prevent and treat arm edema in women with breast cancer. In the meantime, the literature summarized here can provide guidance to clinicians and patients on what is and is not known about the management of arm edema after breast cancer treatment.

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