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Prevention and Management of Arm Lymphedema in the Patient With Breast Cancer

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Arm lymphedema, the accumulation of protein-rich fluid in the interstitial spaces of the ipsilateral arm, develops in 10%–35% of patients who undergo axillary dissection and/or nodal radiation therapy for breast cancer.^{1–13} This progressive and often debilitating condition is without a known cure.¹⁴ Studies of patients treated for breast cancer have demonstrated a progressive decline in quality of life for those with lymphedema and other chronic arm symptoms resulting from axillary dissection.^{8–10} In rare cases, long-term lymphedema is associated with the development of rapidly fatal lymphangiosarcoma or Stewart-Treves syndrome.¹⁵

Breast cancer is the most common form of cancer in women in the United States; the National Cancer Institute estimates that over 2.3 million women with a history of breast cancer were alive in 2002.¹⁶ Lymphedema related to breast cancer treatment is a significant health issue; fortunately, there is increasing interest in understanding, preventing, and treating this serious condition.

Anatomy and Physiology of Lymphatics

The lymphatic system uses filtration to collect lymph and large molecules that reach the interstitial space from the intravascular space. The fluid consists of proteins, lipids, water, and products from cellular breakdown. The lymph in the interstitial space increases oncotic pressure and draws water into the lymphatic spaces; the lymphatic vessels usually do not contain a basement membrane, allowing large molecules to enter that can-

Abstract Arm lymphedema develops in 10%–35% of patients who undergo axillary dissection and/or nodal radiation therapy for breast cancer. Lymphedema that occurs in the first 18 months after surgery or radiation is described as acute lymphedema, and can be managed with conservative measures such as elevation of the arm and mild compression. Chronic lymphedema, the more serious form, has a progressive and generally irreversible course. Risk factors associated with the development of lymphedema include greater extent of axillary surgery; more positive axillary nodes; a postoperative axillary hematoma, seroma, or infection; and use of nodal radiation. The most common method of lymphedema measurement is the circumference 10 cm above and below the olecranon process, although most clinicians do not take measurements in the preoperative setting for comparison. Treatment strategies include elevation, complete decongestive physiotherapy, pneumatic pumps, and, after failure of all other methods, surgery. Lymphangiosarcoma is a rare and late complication of longstanding extremity lymphedema. The advent of sentinel lymph node biopsy as an alternative to axillary dissection should decrease the rate of lymphedema. The increasing number of breast cancer survivors and the high prevalence of the disease will continue to make lymphedema a significant consequence of breast cancer treatment.

not be absorbed readily by venous return. Lymph then travels through multiple lymphatic channels and nodes and returns to the venous system via the thoracic duct. In the healthy individual, the entry of fluid and other materials into the interstitial space is balanced by outflow of lymphatic fluid from the limb, thus maintaining standard limb volume.

PATHOPHYSIOLOGY

In the disease state, lymphatic drainage is compromised by interruption or obstruction of the lymphatic system that leads to accumulation of fluid in the limb. Compromise of lymphatic drainage may result from removal of the lymph nodes or obstruction of the lymphatic channels by tumor, scar tissue, or infection. In this state of functional overload, the accumulation of macromolecules

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Figure 1 Postmastectomy Patient With Chronic Lymphedema in the Right Arm

produces edema, and the resulting inflammatory reaction leads to fibrosis. The persistent swelling may predispose the patient to recurrent bouts of infection, inflammatory reaction, and fibrosis, propagating a vicious cycle of lymphedema.

ACUTE VERSUS CHRONIC LYMPHEDEMA

Lymphedema that occurs in the first 18 months after surgery or radiation therapy is described as acute lymphedema. This early onset lymphedema usually results from reversible obstruction of lymphatic outflow by the swelling of surrounding tissues due to surgical dissection or early radiation effects. Such early edema may be precipitated by episodes of repetitive arm use or by infection, both of which increase vascular inflow and/or increase vessel permeability. As the transient swelling from these events decreases, lymphatic channels reopen and the edema resolves. Conservative measures, such as elevation of the arm and mild compression, usually settle acute lymphedema.

Chronic lymphedema (Figure 1) is insidious and has a progressive and generally irreversible course. This more serious form of lymphedema is thought to result from fibrosis and obstruction of lymphatic outflow channels. Fibrosis may be caused by scarring at the surgical bed from the removal of lymph nodes, patient immobility, tumor progression, or radiation damage. This lymphatic obstruction leads to the accumulation of fluid and pitting edema. With prolonged lymphatic obstruction, the skin thickens, and there is transition to non-pitting edema.

The literature on axillary dissection suggests that approximately 75% of persistent lymphedema will develop within 3 years of surgery.¹⁷

Risk Factors

Several factors predict a higher risk for development of lymphedema. These aspects include a greater extent of axillary surgery; more positive axillary nodes; a postoperative axillary hematoma, seroma, or infection; and use of nodal

radiation. Patient risk factors include obesity and poor shoulder mobility.

EXTENT OF AXILLARY SURGERY

The pathologic status of the axillary lymph nodes remains the most important prognostic factor in patients with breast cancer. Metastatic tumor deposits in the axillary nodes indicate a poorer prognosis and often prompt a recommendation for more aggressive systemic and local therapies. Surgical staging of the axilla is a routine component of breast cancer treatment for the majority of the more than 200,000 patients diagnosed with invasive breast cancer in the United States each year.¹⁸

Historic rates of lymphedema after radical mastectomy, in which the levels I, II, and III axillary lymph nodes are removed, range from 30%–60%.^{19,20} As surgical therapy for breast cancer has evolved, the removal of the level III nodes (those medial to the pectoralis minor muscle) was shown to provide no added survival benefit; after 1970 (approximately), the standard dissection included levels I and II axillary nodes only. Two large international studies^{21,22} found that the rate of lymphedema has fallen drastically to between 6%–30% as a result of limiting surgery to levels I and II. In the largest study of lymphedema to date ($n = 5,868$), Schunemann et al²³ showed that patients treated with radical mastectomy, modified radical mastectomy, and breast conservation demonstrated reduction in lymphedema rates from 44% to 29% to 10.1%, respectively, with progressively less invasive surgical procedures.

As discussed in the section on lymphedema prevention, it is expected that even greater reductions in the rate of lymphedema will be achieved through the use of sentinel node biopsy as an alternative to axillary dissection in eligible patients.

LYMPH NODE TUMOR BURDEN

The number of lymph nodes involved with the tumor also affects lymphedema rates. Advanced stage at presentation with enlarged lymph nodes is a subsequent risk factor for develop-

ing lymphedema.^{4,23} These patients also tend to receive more extensive axillary surgery and radiation therapy, which complicates any analysis of the factors contributing to lymphedema.

REGIONAL NODAL RADIATION AND LYMPHEDEMA

In certain cases, regional nodal radiation therapy is recommended after either breast-conserving therapy or mastectomy. Radiation therapy to the axillary and supraclavicular nodes is recommended in clinical situations that predict a high risk of nodal recurrence. Nodal radiation therapy is used for most large or locally advanced primary tumors (T3 and T4), cases with multiple positive axillary nodes, and cases with extranodal axillary tumor deposits.

The treated nodal areas may include the axillae and/or supraclavicular nodal basins. Nodal radiation may be delivered as “high tangents”: that is, either by the elevation of the standard breast tangent fields to include the low axillae or by the addition of fields that cover the axillary and supraclavicular nodes. The dose of radiation to the nodal areas is generally 5,000 cGy.

After a modified radical mastectomy, the addition of nodal radiation therapy to axillary dissection showed an increase in lymphedema of 6%–8% when compared with a population who received surgery alone.^{24,25} The addition of nodal radiation therapy to lumpectomy and axillary dissection also increased the risk of lymphedema.⁵ Even standard breast tangent radiation therapy after lumpectomy and axillary dissection can increase arm edema rates by 3%–10%. This increase is probably related to irradiation of the lower axillary nodes that often occurs with standard breast tangent radiation therapy.²⁶

Axillary irradiation may cause lymphedema by inducing fibrosis of axillary tissue surrounding the lymphatics, even though the lymphatics themselves tend to be radiation-resistant.^{2,27} In contrast, the lymph nodes are radiation-sensitive, with post-irradiation findings of lymphocyte depletion and fibrosis in the areas of preexisting tumor. These data suggest that lymphedema is caused by soft-tissue fibrosis, and they support the hypothesis that lymphedema may be triggered by events such as postoperative hematomas, seromas, and infections that cause tissue inflammation and subsequent fibrosis.

Diagnosis

The differential diagnosis of new ipsilateral arm edema in a patient with a history of breast cancer includes recurrent tumor and deep venous thrombosis as well as lymphedema; evaluation should first look for tumor recurrence and clot, with appropriate treatment if they are discovered. Lymphedema secondary to nonmalignant lymphatic obstruction, the most common etiology of arm swelling in a breast cancer patient, is a diagnosis of exclusion.

Debate exists about the most appropriate methods for screening and monitoring lymphedema. Outside of a research setting, evaluation of lymphedema is usually initiated by patient complaints of arm heaviness and fullness, often accompanied by visible asymmetry. The edema may involve the en-

tire arm or be limited to the hand, forearm, or upper arm.

Information obtained from the patient should include the type of surgery, any postoperative complications, radiation history, tumor stage and pathology, and timing of the onset of symptoms. A variety of methods have been used to measure lymphedema and monitor response to treatment, including measurements of arm circumference, volumetric measurements using water displacement, photography, skin and soft-tissue tonometry, lymphoscintigraphy, laser perometry, and lymphangiography.

MEASUREMENT

The most common method of lymphedema measurement is of the circumference 10 cm above and below the olecranon process.²⁸ Optimal sequential measurements would be made preoperatively and at fixed intervals after surgery. An increase > 2 cm in circumference relative to preoperative baseline is diagnostic of lymphedema—unfortunately, most clinicians do not take measurements in the preoperative setting. If preoperative measurements are not available, a second test is an arm comparison. Most individuals do not have a > 2 cm difference in arm circumference between the dominant and non-dominant limbs. A difference > 2 cm between the two arms has also been used to diagnose lymphedema.

A highly accurate technique is water displacement, which measures the volume of water displaced by a submerged arm. This test is cumbersome and not often used outside of the research setting. Skin tonometry, which uses a tension-measuring device, has not been standardized. Lymphoscintigraphy has been used to detect functional changes of the lymphatic system and also quantitates lymphedema.^{3,29} Lymphedema may also be assessed using a perometer, an optoelectric device that projects a series of light beams every 3 mm along the length of a limb and performs a reproducible volumetric measurement of limb volume.^{30,31} Each institution should develop its own standard of testing for lymphedema and strive to achieve a reliable and reproducible method of measurement.

LYMPHANGIOSARCOMA

A rare and late complication of longstanding extremity lymphedema is the development of lymphangiosarcoma. Initially described in association with post-mastectomy arm edema by Stewart and Treves in 1948, the incidence is less than 0.09%.^{32,33} The median time to development is 10 years. Multiple satellite lesions and metastasis are common early in the presentation of this disease. Long-term survival is rare.

Management

The simplest method of treatment includes elevation of the extremity above the level of the heart, especially at night. Unfortunately, compliance with these recommendations is difficult; patients should also be fitted with an elastic sleeve (Figure 2) and/or glove for maintenance after the initial reduction in swelling. It is critical to find a therapist who is experienced in measurements and the different classes of garments in relation



Figure 2 Lymphedema Arm Sleeve

to pressure. Use of the garments for 6 consecutive hours per day has been shown to offer the most benefit.²⁶ This approach may be appropriate for mild, early-onset lymphedema but often proves inadequate for more severe or chronic lymphedema.

In recent years, there has been increased interest in complex or complete decongestive physiotherapy (CDP), also known as complex physical therapy. This approach involves the use of skin care, gentle massage, and manual lymphatic drainage, with application of multilayer bandaging followed by a compression garment. Several methods of CDP have been described that include two stages of therapy,^{34,35} which require specially trained physical therapists for its administration. The first phase involves one or two treatments a day for a period of up to 4 weeks. Treatment includes skin and nail care, manual lymphatic drainage, low-stretch multilayer bandaging, and subsequent physical therapy. Manual lymphatic drainage is thought to stimulate lymph vessels to contract and move fluid toward functional lymph node basins. The multilayer bandaging is performed immediately after manual lymph drainage and the arm is wrapped from the fingertips to the axilla with maximal distal pressure. The bandaged extremity is then guided through range-of-motion and joint-functioning exercises. The second phase of CDP includes fitting the patient with specially measured garments with 30–50 mm Hg of compression. Therapists emphasize the use of low-stretch, multilayer

bandages at night and continued skin and nail care.

Pneumatic pumps have been used extensively in the past. Older models include a single-chamber non-segmented device, which may cause back flow that can exacerbate distal swelling. Fortunately, newer models have multiple chambers and provide sequential compression.^{36–38} Pneumatic pumps offer gradient delivery of pressure that differs by 10 mm Hg between chambers. This therapy requires supervision by experienced personnel and a minimum of 1 hour per session with the patient reclined.

Pharmacologic approaches have not been successful in the management of lymphedema. Diuretics mobilize fluid only temporarily, as the oncotic pressure of increased protein left in the interstitial space will quickly drive replacement of the lost fluid. Benzopyrones, which work by decreasing lymphedema through the stimulation of proteolysis, have also been studied with conflicting results. One study³⁹ showed a mild improvement, and the second⁴⁰ demonstrated no improvement over placebo but did show a worrisome increase in liver toxicity. Vitamin E and pentoxifylline have also proved ineffective.⁴¹

A significant limitation of all techniques to manage lymphedema is that their results may not correlate well with patient symptoms. Some patients will have increased arm size measurements without symptoms, and others will have marked subjective symptoms despite only minimally increased objective arm size. Some investigators have suggested that patient symptoms are the most relevant criteria for the diagnosis of lymphedema and that treatment strategies should have reduction of subjective symptoms as their primary goal.^{42–44}

SURGERY

Surgical management of lymphedema is mainly of historic interest, but may be considered after failure of all conservative measures. Surgical approaches have included physiologic and reductive approaches. The physiologic approach entails microsurgical attempts to create lymphatic-to-venous shunts or lymphatic venous anastomoses to increase lymphatic outflow. They are highly complicated surgical procedures, which include multiple fasciotomies to improve drainage through muscle and the deep lymphatics.^{45,46}

The reductive approaches include removal of excess subcutaneous fat and placement of a dermal flap within the muscle to encourage lymphatic anastomosis of the superficial-to-deep channels. A second approach includes skin and subcutaneous tissue removal and coverage of the extremity with split-thickness skin graft. Both of these approaches have yielded poor results with high morbidity.⁴⁷

Prevention

Although a number of factors may contribute to the risk of lymphedema after breast cancer treatment, the precise causes of lymphedema remain poorly understood. However, it is clear that the extent of axillary surgery is the major contributing factor, as limitation of axillary dissection to levels I and II significantly decreased lymphedema rates compared with dissec-

tion of levels I, II, and III.^{21–23}

More recently, the use of sentinel node biopsy has been shown to reduce rates of lymphedema even further. Early results of the use of sentinel node biopsy for axillary staging suggest that lymphedema rates may be < 5%.^{48–50} Randomized prospective trials have confirmed that the sentinel node biopsy approach is effective, with low axillary failure rates.^{51,52} Across major studies, the mean number of lymph nodes harvested with the sentinel node procedure is 2, in contrast with a mean of 15 nodes removed with a level I or II axillary dissection. Range-of-motion limitations, paresthesias, postoperative pain, and other complications have also decreased dramatically with the advent of sentinel lymph node biopsy.^{51,53,54}

Surgical approaches should also strive to prevent development of a postoperative hematoma, seroma, or wound infection, all of which are thought to increase scarring in the axilla and add to the risk of lymphedema. Early range-of-motion exercises and surgery help increase lymphatic drainage and may help prevent and reduce lymphedema rates.^{55–57}

Clinicians routinely suggest a number of other restrictions to patients after axillary dissection or radiation therapy to reduce the risk of lymphedema, although none of these techniques has been rigorously evaluated. They include avoiding injections, blood draws, and blood pressure monitoring, as well as constrictive clothing or jewelry on the affected arm. Because some episodes of lymphedema seem to be triggered

by infection of the arm or by repetitive or heavy arm exercise, patients are instructed to avoid skin breaks, observe meticulous nail care, and avoid heavy or repetitive arm activities. Some patients are cautioned to wear a compression garment during airplane travel. The efficacy of all of these precautions is unproven.

Many patients who develop lymphedema in the first 18 months after surgery will experience complete or near complete resolution of symptoms with treatment. Patients in whom lymphedema is detected and treated soon after its initial appearance have a higher rate of recovery and fewer long-term sequelae. Patients should be instructed to report any signs of new lymphedema immediately, and early signs of infection should be treated with antibiotics, limb elevation, and compression immediately. It is important to recognize that complete clearance of cellulitis in a lymphedematous arm will often require a prolonged course of antibiotic therapy. Recurrent episodes of infection are not uncommon.

Conclusion

The increasing number of breast cancer survivors and the high prevalence of the disease will continue to make lymphedema a significant consequence of breast cancer treatment. Effective care requires a multimodal approach, and more research directed toward improving prevention and management of this side effect is necessary.

Peer viewpoints on this article by Dr. Sheila H. Ridner and Dr. Ian S. Dayes appear on page 389 and page 392.

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