REVIEW

Breast Cancer–Related Lymphedema

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Every year in the United States, breast cancer is diagnosed in more than 200,000 women. Because of the prevalence of breast cancer, treatment-related sequelae are of importance to many survivors of the disease. One such sequela is upper extremity lymphedema, which occurs when fluid accumulates in the interstitial space and causes enlargement and usually a feeling of heaviness in the limb. Axillary surgery contributes considerably to the incidence of lymphedema, with the incidence and severity of swelling related to the number of lymph nodes removed. Lymphedema after standard axillary lymph node dissection can occur in up to approximately 50% of patients. However, the risk of lymphedema is decreased substantially with newer sentinel lymph node sampling procedures. Adjuvant radiotherapy to the breast or lymph nodes increases the risk of lymphedema, which has been reported in 9% to 40% of these patients. Management of lymphedema requires a multidisciplinary approach to minimize the effect on the patient's quality of life. This review presents an overview of the pathophysiology, diagnosis, prevention, and treatment of breast cancer–related lymphedema.

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ALND = axillary lymph node dissection; SLN = sentinel lymph node

Breast cancer is the most commonly diagnosed cancer in women and accounts for approximately 15% of all cancer deaths in women in the United States. In 2005, an estimated 211,000 women will receive a diagnosis of breast cancer, and an estimated 40,000 will die of the disease.[1,2] Breast cancer treatment includes surgery, radiotherapy, chemotherapy, and hormonal therapy. Although these treatments have improved patient outcomes, they have been associated with substantial adverse effects.

Lymphedema, a sequela of breast cancer and breast cancer therapy, changes functional abilities and may affect a patient's psychosocial adjustment and overall quality of life. This review presents an overview of the pathophysiology, diagnosis, prevention, and treatment of breast cancer–related lymphedema.

ANATOMY OF THE LYMPHATIC SYSTEM AND PATHOPHYSIOLOGY OF LYMPHEDEMA

The lymphatic system is composed of superficial and deep lymphatic vessels that collect lymph from the skin, subcutaneous tissue, muscle, bone, and other structures. Lymph fluid consists of water, protein, cellular debris, toxins, and other macromolecules. The lymphatic system is designed to drain this fluid and return it to the intravascular circulation. Lymph fluid enters the interstitium, which increases oncotic pressure, thereby drawing water into the interstitium. When this drainage is compromised, fluid collects in the interstitial space, resulting in swelling. Lymphedema is the accumulation of lymph fluid in the interstitial space and may be secondary to infection, trauma, or congenital abnormalities. Fluid accumulation in the limbs causes enlargement, often with a feeling of heaviness.[3] Chronic inflammation leads to fibrosis of the lymphatics, which compounds the problem.[4]

Lymphedema is classified as primary or secondary. Primary lymphedema is the rare result of a developmental abnormality of the lymphatic system manifesting either an early or late clinical presentation. These hereditary lymphedemas include congenital lymphedema, lymphedema praecox, and lymphedema tarda.[5]

Secondary, or acquired, lymphedema is the most common lymphedema worldwide, with a total incidence of more than 100 million cases.[6] Most of these cases are due to an infectious process such as filariasis. Other risk factors for acquired lymphedema include obesity, inflammation, trauma, and malignancy. Breast cancer–associated lymphedema can result from tumor compression or lymphatic vessel obstruction but is caused more commonly by breast cancer therapy such as surgery and radiotherapy.[7]

BREAST CANCER AND LYMPHEDEMA

Sentinel lymph node (SLN) mapping studies have confirmed the presence of 3 interconnecting lymphatic systems in the breast[8,9]—the dermal, subcutaneous, and parenchymal lymphatics, which travel along the routes of the breast's blood supply to the regional lymphatics. The primary drainage is to the axilla, with only a small proportion of the lymph draining to extra-axillary sites (internal mammary, infraclavicular, and supraclavicular lymph nodes). Metastatic spread to the axilla occurs in approximately

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30% of patients with breast cancer and is the strongest prognostic factor in breast cancer.[10]

Lymph node status is the most powerful predictor of survival in patients with breast cancer.[11] The most recent Surveillance, Epidemiology, and End Results Program data showed a 29% incidence of regional lymph node metastases at the time of breast cancer diagnosis.[12] Although lymph node status is important for prognosis, it also provides information to determine the necessity and methods of further treatment such as chemotherapy, hormonal therapy, or radiotherapy. Surgical removal of the lymph nodes may improve locoregional control by decreasing the risk of axillary nodal failure.

Surgical evaluation of the axilla has been accomplished traditionally by axillary lymph node dissection (ALND) in which level I and level II lymph nodes were removed. This procedure can be associated with substantial morbidities, such as pain, numbness, decreased range of motion of the shoulder, injury to the axillary vein, seroma formation, infection, and lymphedema.[13] To help minimize the adverse effects of these potential morbidities, newer surgical techniques such as lymphatic mapping and sentinel lymphadenectomy are being performed increasingly.

Lymphatic mapping with SLN biopsy is performed to stage the axilla, as is done in standard axillary dissections. The procedure involves the identification and removal of the first lymph node(s), called the SLN(s), to receive lymphatic drainage from the breast parenchyma and tumor. This procedure, first used in patients with melanoma, is accepted for the evaluation of clinically occult lymph node metastasis (staging the axilla) in stage I and stage II breast cancer. If performed by an experienced surgeon, the false-negative rate for SLN biopsies is 12% or less.[14,15]

With ALND, many studies have shown a correlation between the number of lymph nodes removed and the severity of the lymphedema.[16-20] These series have reported various rates of lymphedema for axillary sampling, partial lymphadenectomy, and total axillary lymphadenectomy. The reported incidence of lymphedema after standard axillary dissection can be as high as 56%.[19,21,22]

Current literature suggests that lymphatic mapping with SLN biopsy accurately stages the axilla and decreases the morbidity associated with ALND.[18,23,24] In retrospective series comparing both techniques, the risk of lymphedema associated with SLN biopsy is less than that with ALND.[18,23-30] Lymphedema is decreased with SLN biopsy because fewer lymph nodes are removed and because no further axillary dissection is needed if the SLN findings are negative on pathologic analysis. A recent randomized trial of 298 patients with early-stage breast cancer assigned patients to undergo ALND or SLN biopsy followed by ALND if node results were positive. The findings of this study showed a significant decrease of 70% in the overall odds of lymphedema in patients undergoing SLN biopsy compared with those who underwent ALND (P=.004).[31]

Lymphedema can be exacerbated by adjuvant radiotherapy. Patients with breast cancer typically receive adjuvant radiotherapy after breast-conservation surgery or mastectomy if there is a high chance of local or regional recurrence. Patients receiving radiotherapy can have breast or arm edema. When treatments are directed to the regional nodes, the risk of lymphedema is increased.[20,32] Several studies have examined the incidence of lymphedema when axillary radiation is given after axillary dissection vs radiation to an undissected axilla. The risk of lymphedema is higher in women treated with axillary dissection and adjuvant radiation to the axilla, with edema reported in 9% to 40% of patients.[19] Patients receiving radiotherapy to the axilla without ALND have a much lower risk of lymphedema.[33-35] Furthermore, the risk of lymphedema in patients who undergo breast surgery only, without axillary surgery or axillary radiation, is approximately 0%.[35] The pathophysiology of radiation-induced lymphedema has not been established entirely but is believed to be related to fibrosis affecting the lymph nodes and causing constriction of lymphatic channels.[35]

Reports conflict regarding predisposing factors for the development of lymphedema after breast cancer treatment. Most of these reports have specifically examined patient age, weight, infection, preexisting cardiovascular conditions, and the surgical technique used.[36,37] Although published evidence shows a positive association with weight gain, number of nodes removed, tumor size, and surgical technique, several other investigators have not validated these findings.[25,38]

Although the reported incidence of lymphedema varies with the clinical definition and methods of assessment, the incidence of lymphedema has been shown to increase each year after initial breast cancer treatment.[38,39]

SYMPTOMS AND DIAGNOSIS OF LYMPHEDEMA

Patients with breast cancer and lymphedema may report symptoms such as a sensation of arm fullness and mild discomfort, which are seen in the early stages of the condition. Joint immobility, pain, and skin changes are noted frequently in the later stages of lymphedema. Patients also may be predisposed to infections involving the affected extremity.

Diagnosis of lymphedema requires a detailed medical history and physical examination. Changes may include pitting of tissues, increased thickness of skin folds, and enlargement of the affected limb. Patients who have undergone breast cancer surgery can be taught to check for early

TABLE 1. **Staging of Lymphedema**

Stage	Description	Characteristics
I	Reversible lymphedema	Swelling reduced with elevation of the swollen extremity Pitting
II	Spontaneously irreversible lymphedema	Increased fibrous tissue with progressive skin hardening Frequent infections No pitting No reduction in swelling with elevation of the extremity
III	Lymphostatic elephantiasis	Progressive fibrosclerosis Skin changes (large hanging skin folds, papillomas) Association with Stewart-Treves syndrome

signs of lymphedema by examining the arm and looking for changes in blood vessels and bony or tendon landmarks.

Physical examination techniques include sequential circumferential measurements of the arm, water displacement volumetry, and tissue tonometry.[40] Circumferential arm measurement is used most frequently, although water displacement volumetry has been shown to be more accurate.[36] Other quantitative measures involve radiological imaging studies such as computed tomography, magnetic resonance imaging, ultrasonography, lymphoscintigraphy, and lymphangiography. Both computed tomography and magnetic resonance imaging show a distinctive honeycomb pattern within the lymphatic system that helps differentiate lymphedema from other potential cancer-related causes of edema such as deep venous thrombosis.[41]

Lymphangiography was used extensively in the past as an imaging technique but is associated with inflammation, scarring, and atrophy that can affect the remaining lymphatic vessels; therefore, lymphoscintigraphy, which has not been associated with these problems, has become the gold standard. Lymphoscintigraphy uses a radiopharmaceutical such as technetium Tc 99m–filtered sulfur colloid to help determine functional and morphologic changes of the lymphatic system, which provides a qualitative and quantitative assessment of lymphedema. Lymphoscintigraphy has been shown to be the safest and most accepted method of diagnostic testing for lymphedema.[21] It is an effective tool that is most useful for diagnosing edema in patients with no known risk factors. It is also efficacious in distinguishing lymphedema from nonlymphatic causes of edema such as venous edema or lipedema.[42]

The specific advantage of lymphoscintigraphy is that it can identify pathways of lymphatic drainage, dermal backflow, collateral lymph channels, number of lymph nodes, and clearance times of the radiopharmaceutical.[43-45] Also, changes can be seen with lymphoscintigraphy that can aid in assessing the results of therapeutic interventions. The sensitivity of this technique reportedly ranges from 73% to 97% with a specificity of 100%.[46,47] However, results vary among clinical centers because there is no specific protocol for lymphoscintigraphy regarding type of radioactive tracer, site of injection, and use of static or dynamic images.[15]

STAGING OF LYMPHEDEMA

A staging system has been developed for lymphedema (Table 1). Many clinicians have defined clinically significant lymphedema as a difference in circumference of greater than 2 cm between the extremities.[21,36,48,49] However, most clinical trials have used volume-based rating scales to assess edema. Other parameters that have been used to determine the stage of lymphedema include limb circumference, tissue texture, dermal changes, subjective sensations, and tissue responses to gravity or pressure.[50] Subjective reporting based on patient questionnaires also is used, but patients' assessments can be limited by other factors such as weight gain or inherent muscle differences between the extremities. Currently, attempts are under way to develop 1 set of criteria that can be used by all investigators to grade lymphedema in future epidemiological trials.[50]

TREATMENT

The treatment of lymphedema associated with breast cancer can include combined modality approaches, compression therapy, therapeutic exercises, and pharmacotherapy.

Complex Decongestive Physiotherapy

One of the most common forms of treatment consists of a multimodality approach called *complex decongestive physiotherapy*. This therapy involves various techniques such as manual lymphatic drainage, external compression devices, and exercises administered by well-trained therapists. Complex decongestive physiotherapy (also known as *comprehensive decongestive treatment*, *complete decongestive physiotherapy*, and *multimodal physical therapy*) includes 2 phases. In phase I, acute management is in an outpatient clinic setting. On average, it consists of a 4-week program of manual lymphatic drainage, short-stretch compression bandaging, exercise, and proper skin and nail care. Specifically, manual lymphatic drainage uses light massage strokes that first stimulate the functioning lymph vessels in the trunk and contralateral arm and then, working from the proximal to distal aspect, pushes the stagnant fluid from the edematous arm. Manual lymphatic drainage also stimulates the contractility of the lymphatic system to help with protein transport and the breaking up of fibrotic tissue.[51] These techniques usually are performed by physical

therapists who have been well trained specifically in these treatment approaches. The specialized massage techniques require about 45 minutes for each extremity.[52] Several studies have shown a greater than 50% volume reduction of the affected limb in patients who undergo complex decongestive physiotherapy.[21] Phase II, maintenance at home by the patient or family, involves continued proper skin care and exercise, self-massage, and use of a compression sleeve and glove during the day and bandaging at night.

Compression Therapy

Compression therapy includes compression bandages, compression garments, gradient compression devices, or pneumatic compression devices to mobilize the lymph fluid. Compression pumps typically are used daily for 30 minutes to several hours and should be used in addition to other forms of manual treatment. Caution must be used with these pumps because of potential damage to the vasculature. In patients with congestive heart failure, active infection, or deep venous thrombosis, pneumatic compression devices are contraindicated.[53] Recent data, primarily showing the lack of improvement in the edematous extremity,[54] also suggest that pumps are not as efficacious as other treatment methods. Furthermore, proper techniques must be used in applying these devices, which can be arduous for patients who have physical, psychosocial, or emotional difficulties.[52]

Therapeutic Exercises

Therapeutic exercises are a recognized treatment of lymphedema. These include remedial exercises that aid lymph flow through repeated contraction and relaxation of muscles. These exercises should be individualized and should be performed while the edematous arm is bandaged. Ideally, these exercises are initiated by well-trained therapists and then continued at home.

Pharmacotherapy

Pharmacological interventions to treat lymphedema include antibiotics for treatment of infections, benzopyrones, flavonoids, diuretics, hyaluronidase, pantothenic acid, and selenium.[55] Benzopyrones, although not approved by the US Food and Drug Administration, have been used widely in Europe to treat lymphedema. Coumarin is 1 drug in this class that has been used extensively. In a study by Casley-Smith et al,[55] coumarin was given in a randomized, double-blind, placebo-controlled study to determine whether it decreased lymphedema. A total of 31 patients with edema from breast cancer treatment received 400 mg of coumarin (18 patients) or placebo (13 patients) for 6 months. The authors noted a significant decrease in the mean amount of edema fluid in the upper extremities of patients receiving coumarin. However, Loprinzi et al[56] found no significant difference in arm volumes at 6 and 12 months in 140 patients with breast cancer treated with 200 mg of oral coumarin twice daily for 6 months. Diuretics have shown no significant benefit in the treatment of lymphedema.[57] Selenium has been shown to be effective in improving radiation-induced secondary lymphedema.[58] This was confirmed in a small study by Micke et al[59] in which arm circumference decreased in 83% of patients (10 of 12) after administration of selenium. No toxicities were observed with selenium use in this setting, although nausea, vomiting, diarrhea, and tachycardia are documented adverse effects.[60] Further validation of the efficacy and tolerability of selenium in this setting should be performed in a larger trial setting.

SUMMARY

Lymphedema is a chronic and debilitating disease that can arise from breast cancer treatment. It generally is underreported and undertreated. The effects of lymphedema on a patient's quality of life are substantial and can be devastating. Further education and better clinical trials are needed to address the importance of early recognition and treatment of lymphedema after breast cancer.

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