

Article

Lymphedema in Breast Cancer

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SUBMISSION TRACK

Received: Januari 20, 2021
Final Revision: June 09, 2021
Available Online: June 28, 2021

KEYWORDS

Breast, Lymphatic flow

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A B S T R A C T

Forearm edema in breast cancer is caused by disruption of the axillary lymphatic system by surgery or radiotherapy, which causes fluid accumulation in the subcutaneous tissue of the arm, with decreased distensibility of the tissues around the joints and increased weight of the extremities. Risk factors with strong clinical evidence include extensive surgery (eg, axillary lymph node dissection, more dissection of lymph nodes, mastectomy) and being overweight or obese. A BMI greater than or equal to 30 kg / m² is an independent risk factor for lymphedema associated with breast cancer. Subclinical edema and cellulitis in the literature have also been cited as risk factors for lymphedema associated with breast cancer. The mechanism underlying lymphedema is dysfunction in the lymphatic transport system. of interstitial pressure. Lymphatic fluid, known as lymph, is drained by blind-ended lymphatic capillaries. It is then filtered through the lymph nodes and eventually re-enters the circulatory system, through the thoracic duct, where peripheral venous blood enters the right atrium of the heart. Under normal conditions, the same amount is transported to the interstitial as is transported from the interstitial, a balance that is disturbed in lymphedema due to reduced lymph transport capacity, leading to fluid accumulation and swelling. Options include bioelectrical impedance analysis (BIA), band measurement, perometry, and water displacement. Lymphoscintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI) can also be used to describe lymphatic dysfunction. Management of lymphedema associated with breast cancer conservatively with controlled and operative compression therapy with resection, microsurgery, tissue transfer and liposuction

Lymphedema and Breast Cancer

Edema of the arm is a sequela after breast cancer surgery and radiation therapy.¹ Arm edema in breast cancer is caused by disruption of the axillary lymphatic system by surgery or radiotherapy, which causes fluid accumulation in the subcutaneous tissue in the arm, with decreased distensibility of the tissue around the joints and increased weight limb.¹

Epidemiology

In a meta-analysis study the overall estimated incidence of chronic arm edema after breast cancer was found to be 21.4%, indicating that Breast cancer-related lymphedema (BCRL) is a widespread problem that affects 1 in 5 patients after breast cancer treatment.²

Risk Factors

Breast cancer-related lymphedema (BCRL) has been recognized as a sequel to surgery and adjuvant therapy for the treatment of breast cancer.⁽²⁸⁾ Patients who undergo breast-conservation surgery for breast cancer are, in theory, at a higher risk of developing BCRL because of surgical incisions and tissue dissection with the potential for impaired chest lymphatic drainage.

Risk factors for which there is strong clinical evidence are extensive surgery (eg axillary lymph node dissection, more dissection of lymph nodes, mastectomy) and being overweight or obese.²

Boughey et al. assess clinical and surgical factors associated with development of breast cancer-related lymphedema (BCRL). They found that the risk of developing BCRL was primarily related to the performance of each axillary surgery but not to the extent of axillary surgery or the number of lymph nodes removed. Other factors associated with BCRL are increased body mass index, incision location, and previous surgical excisional biopsy.³

Risk factors related to treatment

The main risk factors related to treatment for Breast cancer-related lymphedema (BCRL) is an axillary lymph node dissection (ALND) and regional lymph node radiation (RLNR). In addition, there is evidence of lack of breast reconstruction as another risk factor associated with treatment.^{4,5,6} In contrast, there is disagreement in the literature about the risks posed by taxane-based chemotherapy.

Type of axillary surgery

The type of surgery determines the individual risk of developing lymphedema. Both axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SNLB) give patients a long-term risk of developing lymphedema due to the removal of one of the axilla cells, in ALND cases, or a few lymph nodes sentinel clearness in SNLB cases.^{7,8,9,10,11,12,13} However, a new meta-analysis study of BCRL incidence in patients with unilateral breast cancer has estimated that patients with ALND have a four times higher incidence of lymphedema than with those who received SNLB.² Thus, SNLB is an effective option for axillary staging while minimizing the risk of lymphedema in patients with clinically node negative breast cancer,¹⁴ including contralateral SNLB in patients undergoing prophylactic mastectomy equivalent to therapeutic mastectomy.

RLNR

Radiotherapy to regional lymph nodes, or RLNR, has been shown to be a significant risk factor for the development of lymphedema.^{7,14,14,16,17,18} Warren and colleagues demonstrated that RLNR, either supraclavicular with or without a posterior axillary boost, significantly increases the risk of lymphedema compared with breast / chest wall radiotherapy

alone.¹⁷ A new meta-analysis by Shaitelman and colleagues calculated the pooled incidence for patients undergoing breast / chest wall radiation alone of 7.4% (95% CI: 5.1-10.0), but incidence collected for various RLNR combinations varied from 10.8% to 15.5%. Thus, patients undergoing RLNR, even without ALND, should be considered a high-risk group for developing lymphedema, and all patients undergoing ALND and / or The RLNR should be screened prospectively.

Lack of breast reconstruction

The effect of reconstruction on BCRL risk is an area of interest in the literature study. A prospective cohort study by Miller and colleagues investigated immediate implant reconstruction and autologous implant reconstruction compared to mastectomy without reconstruction.¹⁷ They found that immediate reconstruction significantly reduced the risk of lymphedema. In fact, in a retrospective study by Card and colleagues found that patients who did not undergo reconstruction were more likely to develop BCRL than patients who underwent reconstruction.¹⁹ In contrast to this study, Basta and colleagues did not find the presence or absence of reconstruction as a significant factor influencing lymphedema risk., but this retrospective study and the lack of objective measurement-based diagnostic criteria limit the scope of these findings

Adjuvant and neo-adjuvant chemotherapy

While ALND and RLNR are identified risk factors for BCRL and lack of reconstruction may also increase the risk of BCRL, there is less conclusive evidence that chemotherapy is a risk factor. Several studies point to adjuvant chemotherapy as a potential risk factor for BCRL,^{15,25,26,34,35,36} whereas other studies have not.^{16,24} On the contrary, Swaroop and colleagues did not find taxane-based chemotherapy to be a risk factor for BCRL. However, they found docetaxel treatment, but not paclitaxel treatment, to be a risk factor for mild swelling compared without chemotherapy and non-taxane-based chemotherapy.²⁴ Thus, clear taxanes, particularly docetaxel, cause edema, as there is no clear consensus in the literature on chemotherapy. taxane-based as a risk factor for BCRL.

The effect of neoadjuvant chemotherapy on the risk of BCRL is unclear. Neoadjuvant chemotherapy is used in the treatment of breast cancer to reduce the size of the primary tumor and affected lymph nodes, possibly reducing the extent of the operation. It has been suggested that neoadjuvant chemotherapy could, in theory, reduce the incidence of BCRL by reducing the number of positive lymph nodes.^{28,29}

Risk factors associated with non-therapy

BMI

A high BMI at diagnosis of breast cancer is well recognized as a risk factor for developing BCRL.^{5,9,10,17,21} In a prospective cohort study, Jammallo and colleagues found a BMI greater than or equal to 30 kg / m² was an independent risk factor. for BCRL.³⁰ Something similar was found in the study of Ridner and colleagues using perometry in which they found that patients with a BMI of 30 kg / m² or more had a 3.6 times higher risk of developing lymphedema.³¹

Subclinical Edema

Subclinical edema has been shown to be a risk factor for BCRL.^{12,17,32} Specht and colleagues first studied the association between subclinical edema and progression to lymphedema - defined as a relative volume change of > 10% - to assess at what level the edema needs intervention. They prospectively examined 1,173 patients treated for breast cancer by perometry, and they found a small increase in arm volume ($\geq 3\%$ but $< 5\%$) as well as an increase in arm volume ($\geq 3\%$ but $< 10\%$) within 3 months of surgery. increases the risk

of BCRL. After the third postoperative month, only a greater increase in arm volume ($\geq 5\%$ but $< 10\%$) was correlated with an increase in the incidence of BCRL.³²

Cellulitis

Cellulitis is a risk factor for BCRL which is well known in the literature. In their recent large prospective cohort study, Ferguson and colleagues demonstrated that cellulitis infection significantly increased the risk of BCRL ($P < 0.001$). They also demonstrated that ipsilateral 'risk events', such as blood draws and injections, were not correlated with cellulitis infection, and they further suggested that this routine medical procedure may not expose the axilla to a substantial risk of infection when performed in a sterile environment.⁹ However, patients already undergoing treatment for breast cancer should be aware of the risk of infection after surgery. More research is needed to fully delineate the link between cellulitis and BCRL to help reduce the risk of both.

Pathophysiology

The mechanism underlying lymphedema is dysfunction in the lymphatic transport system. The three primary functions of the lymphatic system are to maintain fluid balance, function as a nutritional supplement, and aid in the defense of the host against disease.^{33,34} The lymphatic system maintains fluid balance by removing excess fluid from capillaries that accumulates in the interstitial to maintain a stable state of interstitial pressure. Lymphatic fluid, known as lymph, is drained by blind-ended lymphatic capillaries. It is then filtered through the lymph nodes and eventually re-enters the circulatory system, through the thoracic duct, where peripheral venous blood enters the right atrium of the heart.³⁵ Under normal conditions, the same amount is transported to the interstitial as is transported from the interstitial, a balance that is disturbed in lymphedema due to reduced lymph transport capacity, leading to fluid accumulation and swelling. Disruption of this system in turn causes a decrease in oxygen pressure resulting in reactive tissue fibrosis and chronic inflammation of the tissue. In addition, the accumulation of protein in the interstitial leads to increased osmotic pressure which pushes fluid into the interstitial causing edema and the clinical manifestations of lymphedema.^{35,36}

Table 1. Determination of Staging and Grading of Lymphedema

Table 1. Staging and grading of lymphedema^[8,66-68]

Stage	International society of lymphology	Campisi <i>et al.</i> ^[67]	Chang <i>et al.</i> ^[68]
0	Latent or subclinical Patients complain of heavy sensation and/or numbness in arm May exist for months to years before overt edema occurs		
1	Early accumulation of protein-rich fluid May have soft, pitting edema: limb elevation leads to complete resolution of swelling No fibrosis	A. No clinical edema despite the presence of lymphatic dysfunction as demonstrated on lymphoscintigraphy B. Mild edema that spontaneously regresses with elevation Limb excess volume: 0%-20%	Many patent lymphatic vessels, with minimal, patchy dermal backflow
2	Limb elevation alone rarely reduces swelling Fibrosis present: reduces ability of skin to indent with pressure	Persistent edema that regresses only partially with elevation Limb excess volume: 21%-40%	Moderate number of patent lymphatic vessels, with segmented dermal backflow
3	Lymphostatic elephantiasis: no pitting edema present Severe fibrosis and hypertrophic skin changes such as hyperkeratosis, fat deposits and warty outgrowths	Persistent, progressive edema; recurrent erysipeloid lymphangitis Limb excess volume: 41%-60%	Few patent lymphatic vessels, with extensive dermal backflow involving the entire arm
4		Fibrotic lymphedema with column limb Limb excess volume: > 60%	No patent lymphatic vessels seen, with severe dermal backflow involving the entire arm and extending to the dorsum of the hand
5		Elephantiasis with severe limb deformation, including scleroinductive pachydermitis and widespread lymphostatic warts Limb excess volume: > 60%	

According to the traditional definition, lymphedema is divided into two types: primary and secondary. Primary lymphedema is often classified according to the age when edema first appeared: congenital lymphedema, (present at birth), precocious lymphedema (present at puberty or until the third decade of life), and lymphedema tarda (usually occurs after age 35).³⁷ Secondary lymphedema is caused by extrinsic disorders, or blockage of the lymphatic system due to trauma. Forms of trauma include axillary surgery, radiation therapy, chemotherapy, or inflammation and scarring of metastases to lymph nodes.

Clinical Appearance

The clinical presentation of lymphedema is secondary to the inflammatory response to chronic accumulation of protein-containing interstitial fluid and adipose tissue. Lymphatic stasis or decreased flow has been shown to contribute to lipogenesis and fat deposition which in turn leads to increased fibrocyte activation and connective tissue growth. There are many grading scales to characterize the clinical development of lymphedema. The International Society of Lymphology has developed a staging system to classify lymphedema based on the clinical appearance of the arm (Table 1).⁴⁰ In each stage, the severity based on the difference in limb volume can be characterized as minimal (<20%), moderate (20% - 40%), or severe (> 40%).⁴¹

Diagnosis

The diagnosis of BCRL is based on consideration of risk factors, associated symptoms, and clinical signs and is usually made during a physical exam. Clinically proven lymphedema will present with varying degrees of pitting edema, which can involve any aspect of the upper limb, which is usually first seen on the fingers. Affected patients may complain of heaviness in the arm and decreased activity of the affected arm. Because BCRL can develop months to years after lymphatics are affected, it is important for patients to be followed up even when there are no symptoms of BCRL. A study of 1,713 women who underwent breast conserving therapy showed that 40% of those with arm edema had mild edema at the time of diagnosis.⁵⁷ When evaluating women being treated for breast cancer other than BCRL, other causes of swelling of the arm, such as other malignancies, deep vein thrombosis of the upper limb, and infection should also be considered. Therefore, if there are indications, it is important to carry out the appropriate tests, to rule out the diagnosis. The literature has demonstrated a variety of noninvasive methods for evaluating limb volume when lymphedema is clinically proven. Options include bioelectrical impedance analysis (BIA), band measurement, perometry, and water displacement.⁵⁸

The methods commonly used to diagnose upper limb edema are circumferential and volumetric measurements using anatomical landmarks.⁵⁹ The circumference of the worn and undisturbed arm is measured sequentially at 4 points: the metacarpophalangeal joint, wrist, 10 cm distal to the lateral epicondyle, and 15 cm proximal to the lateral epicondyle. A difference of 2 cm or more, or if converted to volume, 10% or an increase of 200 mL, at any point compared to the contralateral arm is considered by some experts to be clinically significant.^{60,61} This method requires consideration of patient factors such as baseline differences between limbs, dominant and non-dominant, differences in muscle mass, body habitus, and possible post-treatment changes. The arm size of patients diagnosed with breast cancer has been shown to vary over a wide range.⁶² Volume changes correlate with preoperative arm volume, patient weight, and BMI but relative volume change (RVC) is independent of patient weight. To move towards establishing a standard BCRL classification,

the RVC would be a more precise measure of change in absolute volume.⁶³ Newer methods have emerged to classify BCRLs more accurately. It has been shown that quantification methods that include absolute volume changes for the diagnosis of BCRL are inaccurate and vary from patient to patient.

National Cancer Institute, which has produced standard reports on adverse events in clinical trials classifying lymphedema rates by percentage difference in volume / circumference between arms, based on the Common Terminology Criteria for Adverse Events, v4.0 (CTCAE):⁶⁴

Level 1: 5% -10%;

Level 2: > 10% -30%;

Level 3: > 30% - Limfore and gross anatomical deviation from normal contours may occur. This level interferes with the activities of daily living;

Level 4: Although rarely progression to a malignancy such as lymphangiosarcoma can occur, amputation of the limb may be required. In other classification systems, this level may also be referred to as "endstage" lymphedema.

The CTCAE criteria offer both subjective and objective measures to classify lymphedema accurately, which offers a more standardized assessment of lymphedema.

Radionuclide imaging of the lymphatic system, lymphoscintigraphy may be required although it is not a widely used technique. Lymphoscintigraphy is a relatively noninvasive technique that involves intradermal injection of radiolable colloids distal to the affected limb followed by lymphatic vascular imaging.⁴⁹ This method can describe the anatomy and function of the lymphatics. Common abnormal findings include absent or delayed radiotracer transport and poorly visualized lymphatic collectors and lymph nodes.

The keys to a timely and accurate diagnosis of BCRL require a thorough history and examination, early detection and coordination of a team in care, which can be complemented by a variety of studies and imaging modalities in subclinical BCRL cases.

Governance

Conservative

Initial treatment of clinically proven BCRLs should be conservative (non-operative). The reliability of conservative therapy hinges on the finding that reduction in pitting edema is achieved by compression. This often involves multilayer inelastic lymphedema dressings or controlled compression therapy, in which the size of the compression garment is regularly reduced as swelling is reduced.⁶⁸

Operative Action

In selected patients with long-term complications from BCRL or patients who fail conservative management, surgery may be considered. Surgical options include resection, microsurgery, tissue transfer, and liposuction

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