



Lymphedema: From diagnosis to treatment

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ABSTRACT

Lymphedema is a chronic and progressive disorder resulting from impaired lymphatic system function. In developed countries, upper extremity lymphedema is mainly the consequence of breast cancer surgery in which axillary lymph node dissection and radiation alter upper extremity lymphatic flow.

Diagnosis of lymphedema is made clinically. Nevertheless, there are numerous diagnostic tools available for disease staging. Recently, a new technology namely magnetic resonance lymphangiography has emerged in the medical field to assist in both diagnosis and management.

There are non-surgical and surgical treatment options available. Non-surgical methods are always the first-line treatment; however, surgical options can be explored in appropriate patients. Recent studies focus on the prevention of lymphedema using surgical techniques utilizing axillary reverse mapping to delineate arm lymphatics from axillary lymphatics.

Finding the most suitable technique for each type of lymphedema with variable stages is one of the most complicated decisions for practitioners. More studies are needed to reveal the exact biology of lymphedema to ensure complete understanding of the disease and improve outcomes.

Keywords: Diagnosis, lymphedema, treatment

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INTRODUCTION

Lymphedema (LE) is the accumulation of protein-rich fluid in tissues. The impaired function of lymph vessels interrupts the drainage of lymphatic system that is a part of the circulatory system just like the arterial and venous structures. Lymph vessels remove excess fluid from tissues and transport it back to the circulation. In addition, the maturation of immune cells takes place in the lymphatic system; thus, it constitutes one of the most critical defense mechanisms throughout the body. Lymph capillaries are located in the dermis, woven like a cobweb, then drain to lymphatic vessels in the subcutaneous plane and ultimately to the deeper system and the thoracic duct.

Lymphedema can either be primary or secondary. Regardless of the etiology, it is clinically characterized with chronic swelling, localized pain, atrophic skin changes and secondary infections (1). However, the main devastating aspect of LE is the appearance of the affected limb that causes psychological morbidity. Primary LE is related to developmental abnormalities of the lymphatic system whereas secondary LE is attributed to the impairment of lymphatic vessels due to an acquired condition such as trauma, tumor, surgery or infection (Table 1). In developing countries, secondary LE is mainly due to infections-infestations influencing lymphatic channels. On the other hand, in developed countries, secondary LE occurs most commonly after surgical removal of lymph nodes for cancer treatment (2). Breast cancer is the most common cancer among women in the world and Breast Cancer Related Lymphedema (BCRL) occurs more often than any other type of LE (3). This review will focus on BCRL.

Incidence

Breast Cancer Related Lymphedema is detected in 7-77% of patients who undergo axillary lymph node dissection (ALND) due to transection of lymph vessels as depicted in selected studies (4). Sentinel lymph node biopsy (SLNB) significantly reduces this risk to 3-7% (5, 6). This incidence is based on multiple factors such as extent of disease, treatment modality (i.e. radiotherapy), and duration of follow-up (6, 7). In addition to these, a study revealed that patients with occupations that require extra upper extremity activity had the worst stage and grade LE clinically (3). In another study, factors associated with the development of BCRL included occupation, infection, and increased BMI. Immediate reconstruction of the breast was not found as a risk factor for BCRL (8). A recent study reported a risk assessment tool using these BCRL predictors (RATE-L), which included significant predictors such as post-mastectomy radiation, age above 65 years, and axillary dissection (9).

Table 1. The etiology of lymphedema	
Primary	Secondary
Congenital	Trauma
Milroy disease	Tumor
Lymphedema praecox	Surgery
Lymphedema tarda	Infection-infestation
	Post-venous thrombosis

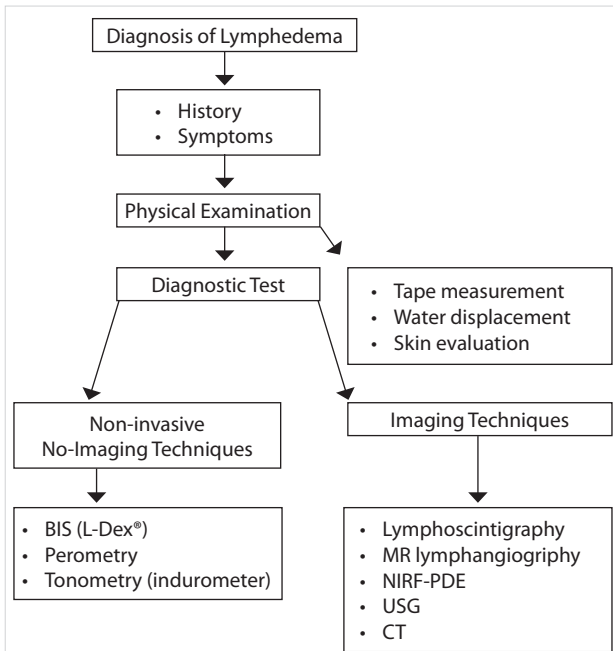


Figure 1. A scheme for the available options in the diagnosis of lymphedema

BIS: bioimpedence spectroscopy; MRI: magnetic resonance imaging; NIRF: near infra-red fluorescence imaging; PDE: photo dynamic eye (PDE; Hamamatsu Photonics K.K., Hamamatsu, Japan); USG: ultrasonography; CT: computed tomography



Figure 2. Near Infra-Red Fluorescence imaging (NIRF) for preoperative-intraoperative planning

DIAGNOSIS

Although there is no unique sign or criteria for defining LE, the diagnosis is usually made clinically by thorough evaluation and physical examination (2, 3, 10). Family history is important in the diagnosis of primary LE. The main symptoms are

chronic swelling, progressive atrophic skin changes, and recurrent infections. It is important to identify whether the swelling is transient or persistent. In one study, it was reported that one-third of initial swelling attacks were transient (10). Since effective treatment of LE can be established in early stages, accurate and timely diagnosis is crucial (11). History of trauma or surgery must be addressed clearly. Physical examination consists of volume and shape discrepancies, and skin changes among the extremities. Figure 1 outlines the alternatives in the diagnosis of LE.

Circumferential (>2 cm) and/or volume (>200 mL) differences between the affected and non-affected extremity can be performed to confirm the diagnosis (2). Volume can be measured by tape, water displacement or perometry (Perometer; Perosystems, Wuppertal, Germany) (12). Tape measurements require formula calculations; therefore, it is recommended that the measurements should be performed by the same person at defined intervals (12). It is mainly preferred on head and neck lymphedema follow-ups. Water displacement is an accurate method that is the gold-standard for volume assessment, especially on extremities (12); however, it is not used in daily practice because it doesn't delineate the affected area. If there is an open wound, it is not feasible to use this technique. Perometry is a computer-based study that calculates the volume of the affected limb via infra-red optical electronic scanner and can demonstrate small changes, but is expensive (2).

Non-invasive measurements (tonometry, bioimpedence spectroscopy) and imaging techniques (lymphoscintigraphy, ultrasonography, computed tomography, and magnetic resonance imaging) may aid in the detection of LE. The principal mechanism of a tissue tonometer is to evaluate tissue resistance by applying compression. Skin pliability and fibrosis can be measured with a tonometer. It gives a good idea about how changes occur during LE treatment. Tissue dielectric constant and tonometry can measure skin texture and resistance (12-14). Ultrasonography, computed tomography and magnetic resonance imaging can show the presence of extra fluid within tissues (12).

Bioimpedence spectroscopy (BIS) is a new diagnostic tool to diagnose LE. It is a technique that assesses the extracellular fluid compartment before visible changes have settled (15). BIS mainly focuses on changes in electrical conductance of extracellular fluid. Since it depends on water content of the study area, advanced and fibrotic edema detected in late-stage LE may not be diagnosed properly by BIS (12). In other words, BIS is reliable in early-stage BCRL. A prospective observational study demonstrated the impact of L-Dex® (L-Dex; Impedimed, Brisbane, Australia) measurements in identification of subclinical BCRL and its use in routine clinical practice (16). L-Dex® is the score representing extracellular fluid ratio of the affected limb to the unaffected limb, and is sensitive in predicting the onset of LE up to 10 months prior to clinical diagnosis (15).

Lymphoscintigraphy is a nuclear medicine study and demonstrates slow or absent lymph flow usually in later stages of LE (12). Technetium 99m sulfur colloid is injected intradermally and the transit time to lymph node basins can be measured; however, subdermal lymphatics cannot be assessed. A new technique for imaging lymph vessels is Near Infra-Red Fluorescence

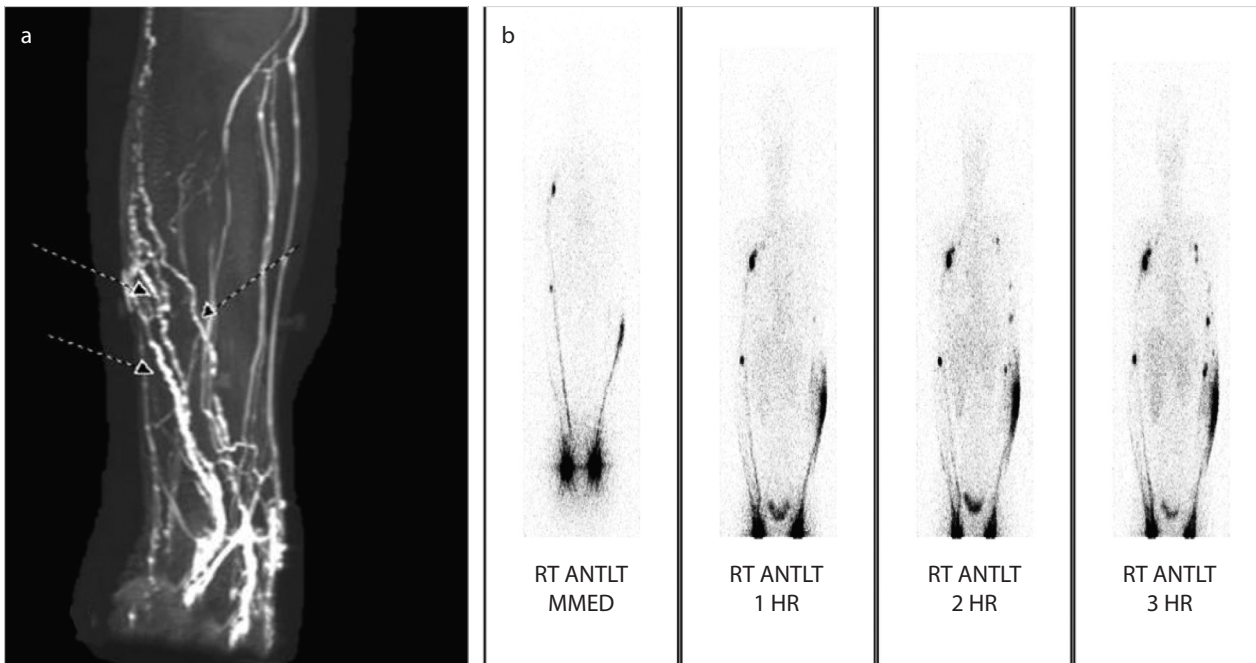


Figure 3. a, b. (a) Magnetic resonance lymphangiography. Three irregular tubular structures extending from the dorsal aspect of the wrist to the lateral/dorsal aspect of the right forearm are compatible with enlarged lymphatics. These vessels are subcutaneous and measure up to 3-4 mm in caliber. In the lateral and ventral aspect of the mid-portion of the forearm (in proximity to the expected location of two lymphovenular anastomosis), there seems to be communication between these lymphatics and small venules, branches of the basilic and ventral branches of the cephalic vein. There is minimal dermal backflow in the lateral aspect of the mid-portion of the right forearm. (b) Lymphoscintigraphy. Abnormally delayed lymphatic transit and dermal backflow are identified in the left forearm

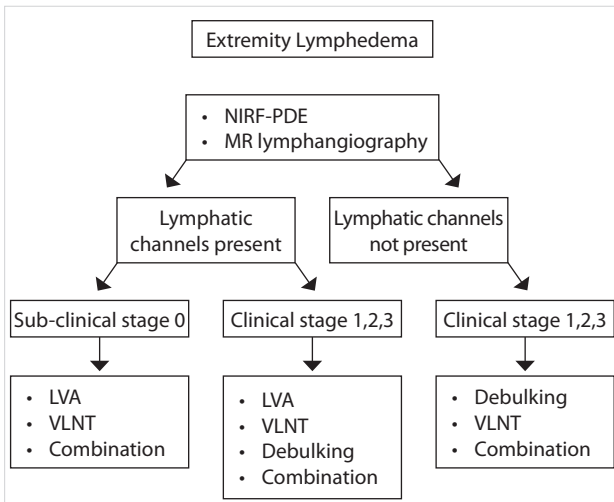


Figure 4. An algorithm for the treatment of lymphedema according to magnetic resonance lymphangiography
LVA: lymphaticovenular bypass; VLNT: vascularized lymph node transfer

rescence Imaging (NIRF) by using indocyanine green. This dynamic test allows visualization of superficial lymphatic flow and functioning lymphatic vessels; thus, finds abnormalities at early stages. It can be used to stage the severity of disease and for preoperative-intraoperative planning (17, 18) (Figure 2). Lymphography is another entity where radio-opaque material is directly injected into peripheral lymph vessels. This technique is rarely done due to the risk of damaging lymph vessels.

Magnetic resonance lymphangiography is a new entity that involves the injection of Gadolinium into the hand or foot to

Table 2. Staging of lymphedema adapted from The International Society of Lymphology

Stage	Description	Characteristics
0	Latent	Some damage to lymphatics; No visible edema yet
1	Spontaneously reversible, acute phase	Pitting edema; reversible with elevation of the arm. Usually, upon waking in the morning, the limb(s) or affected area is normal or almost normal size
2	Spontaneously irreversible, chronic phase	Spongy consistency and is "non-pitting," Fibrosis found in Stage 2 lymphedema marks the beginning of the hardening of the limbs and increasing size
3	Elephantiasis; irreversible, end-stage	Irreversible and usually the limb(s) is/are very large. The tissue is hard (fibrotic) and unresponsive; consider debulking surgery at this stage

clarify the course of lymphatics. Gadolinium can also get into the venous system making the interpretation of lymphatic channels difficult (19). Magnetic resonance venogram and ferumoxytol (Feraheme; Advanced Magnetics, Cambridge, MA, USA) are used to help to differentiate lymphatics from veins (19, 20). With the advent of magnetic resonance lymphangiography, the severity of LE can be delineated while the anatomy of the lymphatic channels and the status of the soft tissues can also be depicted (20) (Figure 3). We suggested an algorithm for the management of patients with LE, by using Magnetic resonance lymphangiography and LE stage in this review (Figure 4).

Non-surgical treatments	Surgical treatments
Complete decongestive therapy	Reductive techniques
Manual lymph drainage	Direct excision
Compression therapy	Liposuction
Exercise	Physiological techniques
Skin care	Lymphatico-lymphatic by-pass
Compression garments	Lymphatico-venous by-pass
Advanced pneumatic compression therapy	Lymph node transfer
Laser therapy	

The International Society of Lymphology classified LE into 4 stages to overcome multiple classification schemes and obtain a consensus (3) (Table 2). In addition, Campisi et al. (21) proposed a staging system consisting of 3 stages, especially for elders.

TREATMENT

The management of LE consists of accurate diagnosis, successful classification and patient education. Unfortunately, there is no absolute cure for LE. On the other hand, effective treatment is available. Two main modalities include non-surgical and surgical options (Table 3). The mainstays of non-surgical LE treatment modalities are complete decongestive therapy (CDT), compression therapy, advanced pneumatic compression pumps and exercise. These treatments are effective mainly in early-stage LE (2). There is a global trend for surgical intervention and surgical techniques including physiological and reductive methods.

Non-Surgical Treatments

Patient education is both crucial and mandatory (22). Self-care and risk-reductive practices, self-lymph drainage, skin care, proper alignment of bandages and garments, good nutrition, exercise and weight control are the basics prior to LE treatment (12).

Complete Decongestive Therapy

Complete Decongestive Therapy (CDT) is considered the gold-standard treatment method in the management of LE and includes two phases: reductive (phase 1) and maintenance (phase 2) (23). CDT is a good option in decreasing LE volume and includes manual lymph drainage, compression therapy, physical exercise, skin care as self-management, followed by wearing compression garments (23, 24). Although it is safe and effective in most patients, it is expensive, time-consuming and needs certified therapists. In addition, patient compliance to long-term CDT is challenging. Nevertheless, CDT can be individualized with modifications until the lymphedematous volume reduction has been maximized.

Manual lymph drainage (MLD): MLD is a hands-on technique and differs from standard massage by orienting the lymphedematous fluid to proper functioning lymphatics (24).

Compression Therapy: Compression therapy includes effective gradient compression with tubular bandaging on the af-

ected limb (25). Short-stretch bandages provide low “resting pressure” when the patient is at rest and “working pressure” which allows muscle contractions to direct interstitial fluid flow (23, 25). These bandages also reduce fibrosis in the skin (25). Compression garments are different from compression bandages and are preferred in long-term treatment.

Exercise: Specific exercise is beneficial for LE patients (12). It is recommended that compression bandages or garments should be worn during activity (12). Patients with LE or people at-risk for LE are encouraged to exercise. A meta-analysis showed that active exercising reduces edema volume in BCRL (26). A recent pilot study demonstrated that yoga has beneficial effects on an individuals’ posture and strength (27).

Skin Care: Establishing proper hygiene is important for patients with LE. Low pH moisturizers are recommended to overcome skin cracking and drying, in order to prevent entrance of microorganisms (12).

Compression Garments: Initial control of LE can be achieved with the use of compression bandages. Long term control is obtained with compression garments (12). The type of the garment depends on the body part. Patients should have several garments to alternate and ensure the proper pressure and hygienic control. Accurate fitted garments are essential. Some patients require additional coverage night-or-day to control or reduce LE (12).

Advanced New Generation Pneumatic Compression Therapy

Advanced Pneumatic Compression (APC) therapy can be used as an adjunct to CDT either in early or late phases (12, 28). It mimics the pump effect of muscular contraction on lymphatic system (2). Ranging between 35 and 180 mm-Hg, pump pressures are adjusted to mostly 20-60 mm-Hg (2, 12). The pressure must be individualized in order to prevent skin damage during application. APC therapy was found beneficial in reducing LE, whereas compression sleeves prevented additional swelling without influencing volume reduction (2).

Laser Therapy

A number of randomized trials have reported that Low-Level Laser Therapy (LLLT) improved measurable physical parameters as well as subjective pain scores (29). LLLT increases lymphatic drainage by stimulating the formation of new lymph vessels, by improving lymphatic motricity, and by preventing formation of fibrotic tissue (30). Usually, LLLT is used in combination with CDT. Most studies did not report any adverse events to participants, although one study stated development of cellulitis in LLLT patients as an adverse event (31). Its causal relationship to LLLT was unknown.

SURGICAL TREATMENTS

Reductive Techniques

Direct excision: These techniques include removal of lymphedematous tissue. Previously described methods such as the Charles procedure include complete removal of all subcutaneous tissue and skin grafting (32). This method, although effective at volume reduction, can be quite disfiguring. It also can require blood transfusions and lengthy wound healing. Another technique used in the past involved buried dermal flaps



Figure 5. Lymphovenous anastomosis. Please note supermicrosurgery is used to establish such an anastomosis

with variable success (33). Direct excision techniques may involve full-thickness skin grafting (FTSG) or vacuum-assisted closure therapy (2). In extreme cases, these techniques allow for improvement in quality of life.

Liposuction: Surgical debulking of the affected extremity using liposuction has been shown to be very effective at reducing the volume to near normal (34). This technique has been used in both congenital and acquired LE. It has also been used in cases of lipedema. It has been reported that liposuction technique provides long standing reduction in extremity size as compared to the normal side (35). This technique requires patient compliance with compression therapy to prevent regression. Patients considering this technique should undergo pre-operative conservative management with no pitting edema (34). It has been shown to be effective both in the upper and lower extremity, although it is more effective in the upper extremity. It is known that adipose tissue functions as a crucial organ and a cytokine-activated cell in LE (36). The removal of adipose tissue using liposuction does not affect the already decreased lymph transport system in LE (34). Moreover, a significant improvement was detected in skin blood flow and quality of life after liposuction (37, 38). Its complications include infection, skin necrosis and recurrence.

PHYSIOLOGIC TECHNIQUES

Lymphatic venous anastomosis, lymphatico-lymphatic bypass, and lymph node transfer can be listed as physiologic methods. Many of these methods use recent developments in technology to assist in identifying lymphatic channels and lymph nodes (2, 39).

Lymphatic Venous Anastomosis (LVA) or Bypass

LVA was first described in an animal model with several human studies to follow (40, 35). This technique involves the creation of connections between the lymphatic system and the venous system in the distal or proximal extremity. Superficial or deep lymphatics are anastomosed with neighboring veins. Fluorescence is used to help identify the lymphatic system and an operating microscope is used to assist in microsurgery (41). Single

or multiple LVA's have been reported by different authors using differing surgical sites (39, 42-44). Supermicrosurgery (anastomosis less than 0.8 mm vessels) is used in this technique, in which lymphatic vessels and adjacent venules are anastomosed, mostly in an end-to-end fashion (39, 43) (Figure 5). Variations on the configuration of anastomosis type were described in several studies with variable success rates (45, 46). Studies have reported improvement in patients both subjectively and objectively. In general, LVA's have been shown to be a safe technique for the management of LE (39, 43).

Vascularized Lymph Node Transfer: Vascularized lymph node transfer was first introduced in animal models (47). It has recently been applied to humans with gaining popularity. There are different options for lymph node transfer, namely the location of the donor and the recipient sites. Options for lymph node harvest include the lateral thoracic region, groin, submental region, supraclavicular region and intraabdominal lymph nodes (44, 48, 49). Each donor site has its particular anatomic advantages and disadvantages, and contains varying number of lymph nodes ranging from 1-10. The lymph nodes can be harvested together with a portion of the skin if necessary. These operations require microsurgical skills to perform an arterial and venous anastomosis to provide blood supply to the transferred tissue. The results of lymph node transfer are quite promising and have been shown to provide both objective and subjective improvements (35).

One consideration for lymph node transfer is the concern for possible LE at the donor site (50). Reverse lymph node mapping, originally described as a technique to refine axillary dissection, can be used to minimize lymph node harvest related morbidity (51). It allows differential identification of nodes which drain the neighboring extremity in addition to the ones that are included in the tissue to be removed. Reverse lymph node mapping involves the use of the photodynamic eye, Technetium and ICG dye. Using this technique, the surgeon can be reassured that no lymph nodes are removed that drain the extremity (51). Clinically, the benefit of lymph node transfer is to restore immunologic function to the extremity and improve fluid drainage. However, the action mechanism of lymph node transfers is poorly understood. The transferred nodes have been shown to be active in a number of studies. One proposed mechanism suggests that the new lymph nodes act as "pumps" which filter the surrounding fluid (52). The best site for lymph node implantation is currently unknown. In some cases, the nodes have been placed distally whereas in others they were implanted proximally (52). Well-designed controlled prospective studies are needed to clarify if the suggested functional surgical methods are beneficial in the long-term.

A variety of lymph node transfers includes a tissue portion to be transferred with lymph nodes. Such examples include transferring the lower abdominal tissue in case of total breast anatomical reconstruction (TBAR) and latissimus dorsi flaps with lymph nodes. In such cases, both the breast and the lymph nodes are reconstructed (44, 50, 53). Other types of flaps such as those harvested intraabdominally carry lymphatic tissue from the omentum (49). These can be harvested either by open surgery or laparoscopically.

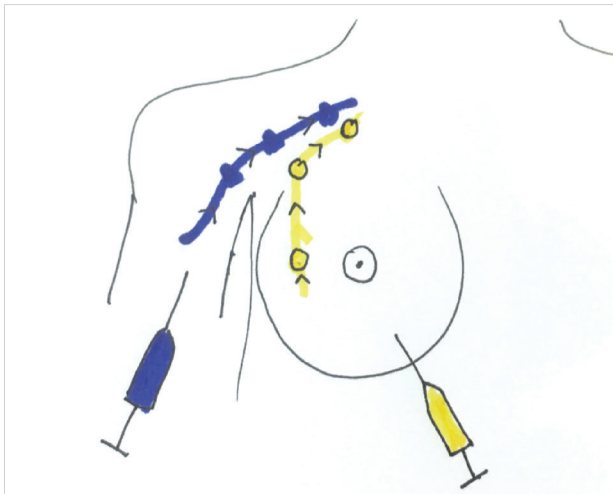


Figure 6. The mapping of axillary lymphatics. A radioisotope is injected into the breast, whereas blue-dye is administered subcutaneously to the upper arm. The lymphatic flow of the breast and arm is separately revealed

Intraoperative Considerations

The nodal status defines one of the most important prognostic factors in breast cancer. However, although necessary, axillary dissection may compromise the lymphatic system thus contributing to the development of LE.

Recently, the lymphatic drainage of the arm and breast tissue were studied and it was found that preserving arm lymphatics during SLNB and/or ALND via a new concept called axillary reverse mapping (ARM) may reduce the risk of BCRL (4, 54, 55). ARM is based on the hypothesis that drainage of arm lymphatics differs from that of breast lymphatics (4, 54). However, it was shown that lymphatic interconnections exist in the axilla between arm and breast lymphatics (56). The technique of mapping the arm and breast lymphatics is comprised of radioisotope injection to the breast and blue dye injection to the upper arm (Figure 6). The lymphatic pathways and interconnections are determined. When a crossover is identified, blue nodes should be removed (55). ARM reduced BCRL when compared with conventional breast cancer surgeries, nevertheless, randomized controlled studies are needed (55).

CONCLUSION

Breast Cancer Related Lymphedema is a devastating disease affecting millions of women. Its treatment is aimed at curing the disease and reducing recurrence rate. However, treatment methods create both physical and psychological morbidity to the patients. BCRL influences daily activities and affects patient self-esteem in various ways. Modern surgical and non-surgical techniques offer numerous methods for the patients to overcome BCRL. In the future, we hope to ensure 100% success in the control or elimination of BCRL. Until then, the exact biology, pathogenesis of lymphatic system diseases and the treatment options require further research to be able to understand this devastating disease.

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or Processing - O.K., C.D.L.A., K.T., A.T.; Analysis and/or Interpretation - O.K., C.D.L.A., K.T., A.T.; Literature Search - O.K., C.D.L.A., K.T., A.T.; Writing Manuscript - O.K., C.D.L.A., K.T., A.T.; Critical Reviews - O.K., C.D.L.A., K.T., A.T.

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