Lymphedema in survivors of breast cancer (Review)

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Abstract. The tremendous improvement of survival in patients with breast cancer can be attributed to several treatment strategies, but these strategies also lead to the occurrence of breast cancer-related lymphedema (BCRL). BRCL is regularly associated with factors such as axillary lymph node dissection and local lymph node radiotherapy and manifests as an increase of >10% in the volume of affected limbs. Being overweight or having obesity (body mass index $\geq$25 kg/m^2), an excessive number of positive lymph nodes (>8) and capsular invasion by a tumor are additional risk factors for lymphedema. It is worth assessing the risk before surgery as this can prevent the occurrence of BCRL at the initial stage of breast cancer management. The clinical utility of many diagnostic tools and lymphedema surveillance allows early stage and even subclinical BCRL to be diagnosed, and allows real-time monitoring of the disease. The early diagnosis of BRCL allows treatment at an early stage, which is beneficial to the reduction of excess limb volume and the improvement of quality of life. At present, the major therapeutic methods of BCRL include complex decongestive therapy, pneumatic compression devices, participating in exercise, microsurgery and liposuction, each of which alleviates lymphedema effectively. No medications for treatment of BRCL have yet been developed. However, the recent findings on the success of molecular therapy in animal models may remedy this deficiency. Furthermore, the volume reduction of swollen limbs without swelling rebound by transplanting autologous stem cells has been successfully reported in some pilot studies, which may provide a new technique for treating BCRL. This review aimed to discuss the pathogenesis, clinical manifestation, risk factors, advantages and disadvantages of diagnostic tools, lymphedema surveillance and the characteristics of traditional and newly emerging BCRL treatments.

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1. Introduction

Survival improvement in breast cancer has been attained using surgical treatment, radiotherapy and targeted therapy, however, patients experience discomfort related to treatment related complications including breast cancer-related lymphedema (BCRL) (1). The first common consequence of trauma, infection, surgery or irradiation injury is BCRL, especially in lymphadenectomy, and this manifests as regionalized damage to the normal vasculature and an increase in limb volume by $\geq$10% (2). BCRL severely affects the quality of life of patients due to lifestyle and occupational alterations, changes in functional status, as well as changes in psychosocial and economic aspects (3-10). Survivors of breast cancer suffer from a perpetual risk of BCRL occurrence, with an average time of 14.4 months after treatment (11,12) and an estimated risk of 14-40% after treatment completion (13). Sentinel node sampling techniques lower the risk estimation to 6-10% (14).

Clinical manifestations of BCRL vary widely and include swelling, pain, discomfort, reduced joint dexterity due to fibrosis and hardening of affected tissues, as well as enhanced infection risk caused by static protein-rich ambience fostering bacteria. According to the National Comprehensive Cancer Network Guidelines for Survivorship, Lymphedema 2018.1 (15), lymphedema can be categorized into 4 stages as presented in Table I. In the earliest stage of BCRL, slight changes occur in the surface architecture of arms or hands of patients accompanied by feelings of limb heaviness, discomfort or both (Fig. 1A and B). The first common site of swelling is the forearm, which is usually soft and the swelling disappears by external compression. Initial swelling may also occur in the axilla, scapular region or breast. In the moderate-to-advanced stage, limb edema is no longer relieved by lifting it or by external pressure; the affected area may become larger and show a peau d'orange appearance (Fig. 2A and B). Clinical symptoms vary according to the severity and course of BCRL.

BCRL is a natural process that ranges from initial swelling to progressive structural malformation, often occurring over a period of several weeks or months (16).

The purpose of the present review is to discuss the pathogenesis, risk factors, prevention, diagnosis and surveillance, as well as the traditional and new therapeutic approaches for BCRL.

2. Pathogenesis

The pathogenesis for lymphedema remains unclear, however, the traditional view of lymphatic obstruction is insufficient to explain the generation of lymphedema. There are three linked newly-presented hypotheses about the pathogenesis of BCRL.

The hypothesis of lymphatic failure. In a normal physiological state, there is a dynamic equilibrium between lymphatic load and transport capacity that makes the lymphatic system effective at absorbing and transporting lymphatic fluid back to the venous system (17). Lymphatic load refers to the volume of lymphatic fluid, which predominately includes interstitial water and protein filtrate. Transport capacity is the maximum lymphatic volume that can be transported by the lymphatics in a given period of time. However, when the transport capacity is inadequate to meet the needs of lymphatic load, lymphatic failure occurs and gives rise to interstitial edema (Fig. 3) (17).

The hemodynamic hypothesis. Total arm blood flow (volume x blood flow/ml) is increased in the swollen arm, but blood flow per unit volume is not elevated, causing the vasodilatation of existing resistance vessels and capillary angiogenesis near existing vessels. Capillary angiogenesis can augment the surface area of the vascular bed size, which, along with total arm blood flow, positively facilitates capillary filtration in the whole limb. When the filtration load exceeds the outflow of liquid from the tissue, edema of the limb is further aggravated, forming a vicious circle (Fig. 3) (18).

The interstitial hypothesis. Since Lymphatic failure leads to a decrease of the interstitial fluid velocity, and subsequent lymphatic regeneration and increased lymphatic vascular endothelial growth factor C (VEGF-C) (19). Lymphatic growth requires the binding of VEGF-C to the VEGF receptor (VEGFR) (20). When blood flow is absent, the increased VEGF-C diffuses to the VEGFR on blood vessels, inducing vascular endothelial growth and increasing the vascular bed size to promote capillary filtration (20). This contributes to an increased interstitial fluid volume and interstitial pressure, and the imbalance of hydrostatic pressure difference between the lymphatics and the interstitium (21). These factors in turn elicit the fluid flow towards those lymphatics, thus curtailing the production of VEGF-C and finally reaching a stable state (Fig. 3) (21). Due to the deterioration of lymphatic failure, the fluid flow rate decreases again, which induces production of VEGF-C and the cycle repeats until a new stable equilibrium is reached.

3. Risk factors

Currently, there is no reliable way of distinguishing patients who are likely to develop lymphedema, but a consensus has been reached on some well-defined risk factors, including axillary lymph node dissection (ALND), which is associated with early-onset disease (22), regional lymph node radiotherapy, which is related to late-onset disease (22), high body mass index (BMI) at the time of breast cancer diagnosis (BMI $\geq$25 kg/m^2) (23), a high number of positive lymph nodes (>8) (24) and capsular invasion of the tumor (24).

In order to reduce the incidence rate and avoid the occurrence of BCRL, a position statement by the National Lymphedema Network has outlined the recommended preventive measures, including the avoidance of flight, trauma, skin infection, extreme temperature, venipuncture (such as blood draws) and limb compression such as blood pressure readings on the affected arm (25). However, two clinical studies demonstrated that injection, flight, blood draws and blood pressure readings were not significantly associated with the increase in arm volume, indicating that they are not risk factors for BCRL (23,26). By contrast, Clark *et al* (27) demonstrated that hospital skin puncture was a high-risk factor for the development of BCRL.

Similarly, it remains controversial whether age and chemotherapy are risk factors for BCRL. Previous reports have suggested that younger survivors are more likely to experience lymphedema (28,29) because they tend to have more aggressive tumors and more intensive therapy, but some studies have indicated that older age is a high-risk factor (30,31). Other studies have shown that age is not associated with BCRL (32,33). It was demonstrated that women treated with chemotherapy, specifically with taxane-based chemotherapy were more likely to develop lymphedema (34,35), but with inconsistent results (36). Extreme temperature and hypertension are risk factors for BCRL that have been confirmed in certain studies (37,38), however, further investigation is required. A study attempted to explore whether race affected the occurrence of BCRL, and it found that black women may have a higher prevalence of BCRL than white women (28 vs. 21%), although the results were not statistically significant (39).

There may be a genetic predisposition for BRCL. Studies have identified several single nucleotide polymorphisms associated with the development of secondary lymphedema within the genes for hepatocyte growth factor, Met protooncogene, gap junction protein γ2, interleukin (IL)-1A, IL-4, IL-6, IL-10, IL-13, VEGF-C, NF-κB, lymphocyte cytosolic protein 2, neutropilin 2, spleen-associated tyrosine kinase, vascular cell adhesion molecule 1, forkhead box C2, VEGFR2, VEGFR3 and RAR-related orphan C (40,41). By identifying patients with breast cancer who harbor these molecular biomarkers, numerous precautionary measures can be taken before surgery to reduce the incidence of BCRL.

4. Prevention

In the initial stage of breast cancer management, especially before surgery, the assessment of risk factors and a selection of appropriate surgical scenarios are available to prevent the occurrence of BCRL (42). The BCRL rate is significantly reduced in patients who receive lumpectomy compared with those who receive total mastectomy or modified radical mastectomy (43). Historically, complete ALND is the standard treatment of axillary intervention for certain patients,

Table I. Stages of lymphedema.

| Stage	Affected area	Limb
0, latent/subclinical	Lymphatic dysfunction without swelling	A feeling of heaviness or fatigue may exist
1, spontaneously reversible	The accumulation of fluid and protein causing swelling; pitting edema may be overt; increased girth, heaviness, and/or stiffness	Swelling that subsides with elevation
2, irreversible	Spongy tissue consistency; less evidence of pitting edema as swelling aggravation; tissue fibrosis and increased fat deposition leads to increased girth and stiffness	Swelling that does not subside with elevation
3, lymphostatic elephantiasis	Severely dry, scaly, thickened skin; increased swelling and girth	Non-pitting edema; fluid leakage and blisters are common
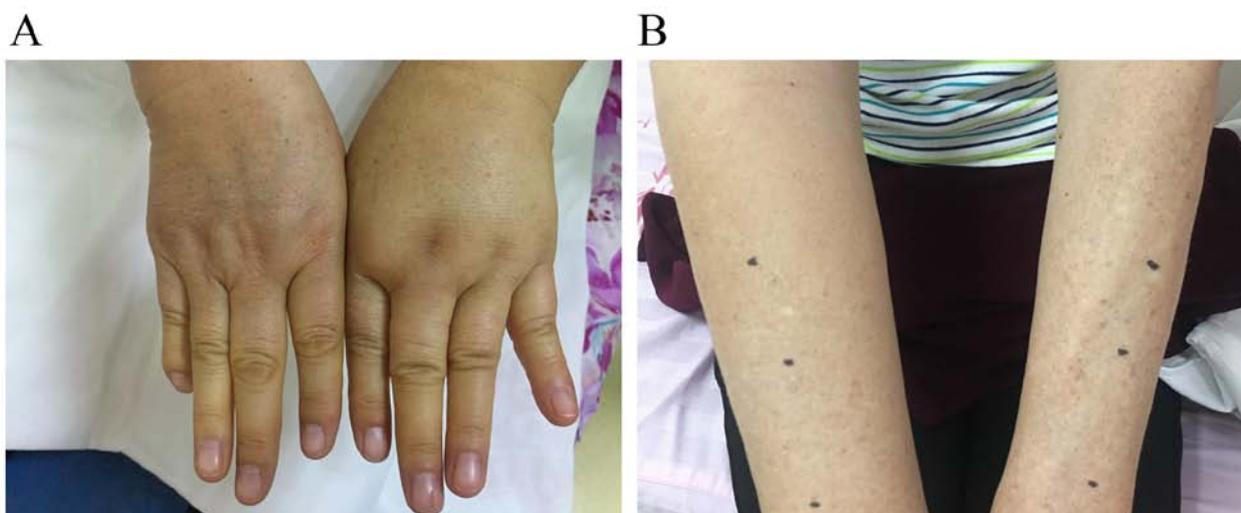
Figure 1. Early stage of breast cancer-related lymphedema. (A) Swollen hand; (B) swollen arm.

including pregnant women, male patients, patients with inflammatory breast tumor or those requiring mastectomy or receiving systemic neo-adjuvant chemotherapy. In recent years, advances have been made in identifying the population of patients who really need ALND. Findings demonstrate that axillary lymph node biopsy (ALNB) is a reliable and safe approach for predicting the status of residual nodes following systematic neo-adjuvant chemotherapy (44-46). Axillary intervention for patients undergoing mastectomy can be downgraded to sentinel lymph node dissection (47), and those who are eligible for lumpectomy can choose a feasible modality of ALNB (48), that does not increase the incidence of lymphedema (49). Axillary radiotherapy may effectively replace complete ALND to control disease relapse and metastasis in patients who have had mastectomy or y lumpectomy (50), and potentially in elderly (>70 years) patients with node-negative luminal breast cancer who have undergone lumpectomy and tamoxifen treatment (51). The long-term recurrence of early-stage breast cancer is associated with biological characteristics instead of anatomical factors; therefore, avoidance of axillary intervention purely for the optimization of prognosis is suggested (52,53).

In 2007, two clinical studies introduced a pioneering technique for mapping lymphatic drainage in the axillary region called axillary reverse mapping (ARM) (54,55). ARM can be used to identify the lymphatic drainage of the upper extremities and the breast by injecting blue dye into the arm during the ALND procedure, resulting in the exclusive removal of lymphatics of the breast and the preservation of lymphatics of the arm to avoid the incidence of lymphedema caused by resection of arm lymphatics. This technique is underpinned by the assumption that the lymphatic drainage of the arm and breast are separate in the axillary region but are anatomically interconnected (56). An increasing body of clinical trials has confirmed a significantly lower incidence rate of BCRL in women undergoing ARM during ALND procedure compared with those receiving ALND alone (57-59). However, it is necessary to consider oncological safety when the arm nodes are conserved, particularly for patients with sentinel lymph node-positivity, as the co-localization of arm nodes and sentinel lymph nodes is as great as 27%, which is a key factor in metastasis (60). Fortunately, the risk of metastasis can be lowered if patients with sentinel lymph node receive neo-adjuvant chemotherapy (61).
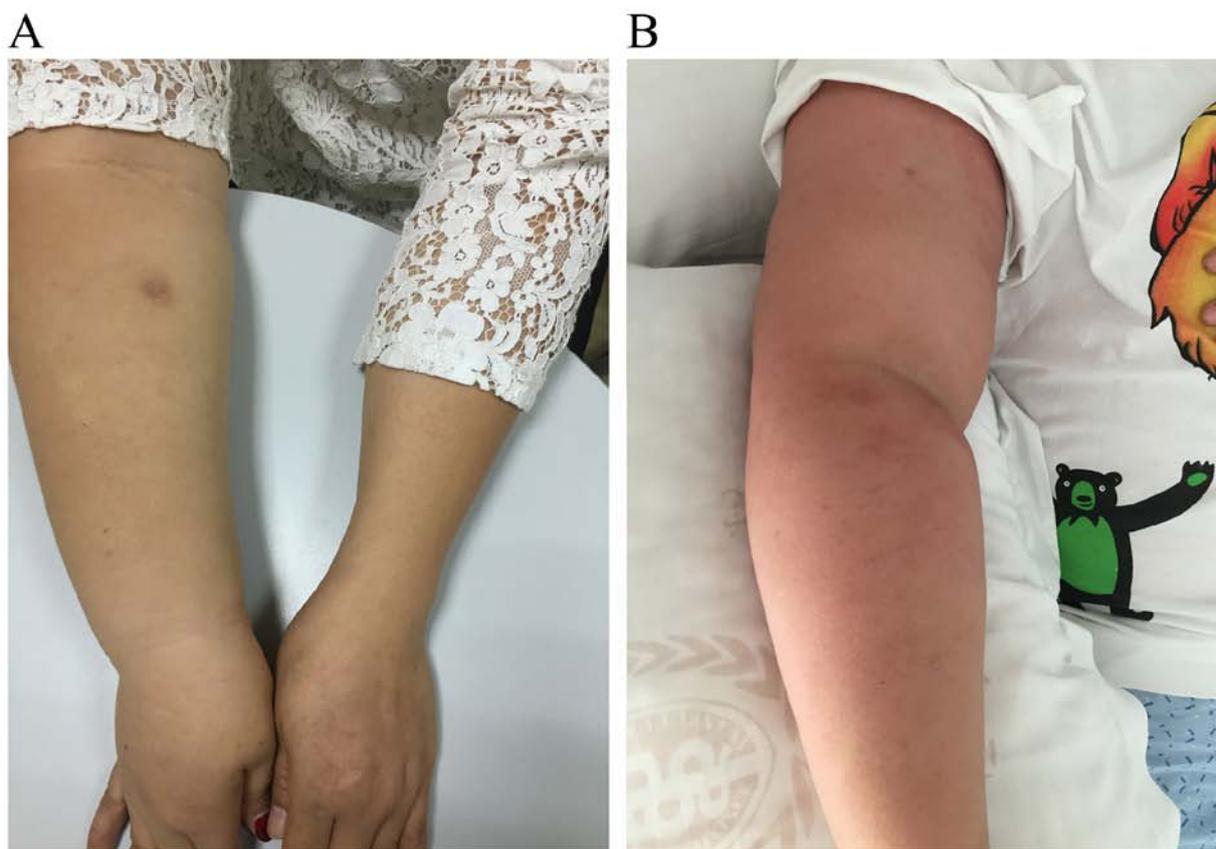
Figure 2. Advanced stage of breast cancer-related lymphedema and peau d'orange appearance of the affected limb. (A) Advanced stage of disease; (B) peau d'orange appearance of the affected limb.
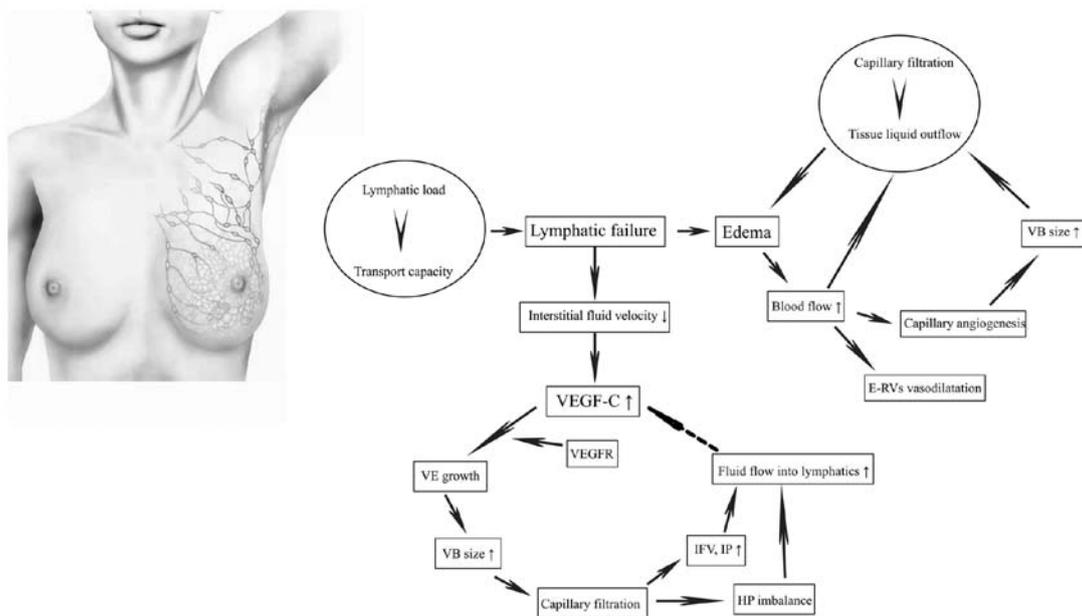

Figure 3. Pathogenesis for lymphedema. Schematic representing the pathogenesis of lymphedema. VEGF-C, vascular endothelial growth factor C; VEGFR, vascular endothelial growth factor receptor; VE, vascular endothelial; VB, vascular bed; IFV, interstitial fluid volume; IP, interstitial pressure; HP imbalance, the imbalance of hydrostatic pressure difference; E-RVs, existing resistance vessels.

5. Diagnosis and surveillance

Accurate diagnosis of BCRL depends on a combination of assessments that include risk evaluation, physical condition and objective examination of patients (1). The common subjective clinical symptoms are pain, swelling, numbness, arm heaviness, stiffness of affected segments and impaired joint activity, but not all patients experience these symptoms (1). Those

considered to be at high-risk should monitor their physical condition by objective examination. An increasing number of techniques and instruments are used for objective examination of lymphedema, including limb measurements, bioimpedance spectroscopy (BIS), dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), computed tomography (CT), color Doppler imaging, lymphoscintigraphy and indocyanine green (ICG) lymphography.

Clinically, BCRL is diagnosed in terms of the degree of distortion of limb measurements. The standard methods for obtaining limb measurements include perometry, limb circumference and water displacement (1). However, results vary widely because they depend on the subjective estimation of operators, and the assessment of volume alone is insufficient (62). Diagnosis tools such as ultrasound and DXA, which allow assessment of arm tissue composition, should be recommended for patients in which the thickness of muscle in the affected arm is less than that in the unaffected arm, and the muscle growth rates differ between the arms (63). In 2018, Engin *et al* (64) used a new volumeter called 'easy volumeter' to measure water displacement with regard to the limb volume in patients with BCRL. The easy volumeter was designed for home use and is more durable, lightweight and easier to clean than a standard volumeter (64). In this study, the measurements from easy volumeters were valid and consistent with those of standard volumeters, suggesting that it was a promising tool to investigate BCRL (64).

In 2000, a modality was added to the diagnosis tools for lymphedema called BIS which measures the volume of extracellular fluid via detecting a physical reaction to an impressed electrical current (65). In comparison to conventional methods, the measurement of BIS is more objective and specific (80-99%) (66-69), with a wide range of sensitivity (30-100%) (66-70), but a higher false-negative rate (36%) (71). Notably, BIS permits identification of lymphedema earlier, when it is in the subclinical stage, and tracks disease progression persistently, making timely intervention of lymphedema a reality (72). Timely intervention dramatically reduces the incidence rate of lymphedema from 36.4 to 4.4% (72).

DXA is effective and credible in quantifying the soft-tissue masses of the upper and lower extremities and the composition of arms, including fat, lean and bone mineral masses (73). Compared with BIS and limb circumference measurements, DXA has similar precision in detecting the percentage differences between the affected and unaffected arms (73). Moreover, DXA has superior repeatability in volume measurement yields compared with the measurements of limb circumference and water displacement, particularly in the affected arm, but not in the unaffected arm (74).

MRI has been used for decades to diagnose lymphedema, especially when it is coupled with edema in fat tissue (1). Compared to lymphoscintigraphy, MRI has a higher specificity in detecting delayed lymphatic drainage (85.7 vs. 66.7%) and greater sensitivity for delineating the architecture of lymphatic vessels (100 vs. 83.3%) (75). In some instances, the excessive water retention in subcutaneous tissue and reasons for lymphatic vessel interruption or obstruction maybe determined by this technique (1). Nevertheless, MRI is expensive and cannot achieve real-time diagnosis (76). Commonly, the detection of lymphedema is not recommended by CT

or ultrasonography (US) due to their low sensitivity, but CT can be used to assess the excessive growth of fibrous tissue during the procedure of lymphedema (77). The low sensitivity of ultrasound can be attributed to several factors, including excessive edema, tissue fibrosis caused by irradiation injury and focal short-section vein occlusion beneath the clavicle or in the deep pelvis (1). Venous obstruction occurs concurrently with chronic lymphedema, with an incidence rate of 4.6%, and may be falsely evaluated by US as a negative result owing to technical difficulties (78). Fortunately, this problem is solved by color Doppler imaging that can be used to visualize vessels with a diameter of only 1-2 mm, thus enabling the detection of the anatomy and function of damaged veins (78).

Provided that the aforementioned approaches cannot affirm the diagnosis, the standard recommendation is to apply radionuclide lymphoscintigraphy, a nuclear medicine imaging technique that allows visualization of lymphatic drainage into the axillary lymph nodes by subcutaneous injection of radiolabeled sulfur colloid into the hand (79). A tardive axillary visualization coupled with dermal lymphangiectasia will occur if there is lymphedema (79). Early-stage lymphoscintigraphy is an effective diagnostic tool; however, it has many disadvantages such as radiation exposure, low resolution, high costs and increased invasiveness (1). Lymphography is a newer, systematic method to evaluate limb edema and lymph circulation without radiation exposure (71). Lymphography has higher specificity and sensitivity, and longer tracking capabilities, ranging from subclinical to more advanced stages, compared with lymphoscintigraphy (77,80-82). Of note, the greatest advantage of lymphography is that it can be used for the real-time monitoring of lymphatic vessels during surgery, albeit not in a perfect way (82). For example, if the lymph vessels beneath the subcutaneous level of the skin are thicker than 2 cm, observation cannot be achieved by ICG lymphography (82). The advantages and disadvantages of all the diagnosis tools for lymphedema are summarized in Table II.

Lymphedema surveillance can be used to identify and diagnose subclinical or early-stage disease, providing the opportunity for early intervention and treatment of BCRL (83). Prospective interval surveillance greatly optimizes the costs (84), reduces the observed incidence (72) and can reverse and prevent the progression of BCRL (85-87). Data using direct provider costs of surveillance demonstrate that it has potential to reduce direct treatment costs of BCRL management (84); however, for improving assessment, further data on the indirect costs must be reported. At present, there are four main techniques for the surveillance of BCRL: Water displacement, perometry, tonometry and BIS. Water displacement is laborious, time-consuming and not suitable for massive, continuous surveillance. Perometry, optical assessment of limb volume, is less time-consuming but more expensive. Tonometry is a noninvasive method that can detect subclinical interstitial edema via continuously measuring the dielectric constant in affected tissue and evaluating moisture content (88). BIS is more specific, but lacks sensitivity, and it may be the most frequently utilized modality (71). However, no widely adopted consensus has been reached regarding which technique is the best for the surveillance of BCRL.

Table II. Advantages and disadvantages of diagnosis tools for LE.

Diagnosis tools	Advantages	Disadvantages
Perometry; LC; WD	Standard method for diagnosing LE	Results vary widely and are not highly reliable, with no evaluation of arm tissue composition
Radionuclide lymphoscintigraphy	Diagnose LE in its early stage	Radiation exposure, low resolution, high cost, increased invasiveness, no real-time monitoring
Indocyanine green lymphography	Real-time monitoring without radiation exposure, high specificity and sensitivity, tracking ranging from subclinical to more advanced stage	Cannot observe deep lymphatics when the thickness of subcutaneous tissue covering them is ≥2 cm
Magnetic resonance imaging	Diagnoses LE coupled with edema in adipose tissue, high specificity and sensitivity	High cost without real-time monitoring
Computed tomograph toring	Assess LE coupled with the excessive growth of fibrous tissue	Low sensitivity, no real-time monitoring
Color Doppler imaging toring	Assess LE coupled with venous obstruction	Low sensitivity, no real-time monitoring
Bioimpedence spectroscopy	Real-time monitoring, high objectivity and specificity, tracking ranging from subclinical to more advanced stage	Wide range of sensitivity, high false-negative rate
Dual energy X-ray absorption	Quantify the soft-tissue masses and composition of arms; more repeatable to measure volume of LE arm than LC and WD	Unknown

LC, limb circumference; WD, water displacement; LE, lymphedema.

6. Treatment

It is widely believed that the optimal management to efficiently relieve lymphedema is complex decongestive treatment (CDT), lymphatic physiotherapeutic intervention including manual lymph drainage (MLD), skin care, physical exercise, long-term education on self-management of lymphedema, compression bandages and sleeve or stocking compression (1). Lymphoscintigraphy of upper limbs is a valid tool to predict the prognosis of this combined strategy. CDT can be provided with a commercialized product called Linfadren®, which is a mixture of diosmin, coumarin and arbutin, to further improve its efficacy without any adverse events (89). Obesity reduces the effectiveness of CDT (90). Every treatment method for lymphedema has been gradually defined into explicitness.

MLD, a universal treatment for lymphedema is a massage technique that uses a special rhythmic pumping through gentle, directed stretching of skin to massage the affected area and stimulate lymphatic contractility, thus enhancing lymphatic drainage (1). A meta-analysis found that, compared with other treatments such as physical exercise, skin care and compression therapy, additional MLD was unlikely to achieve a significant reduction in the volume of the affected limb (91). Of note, heterogeneity across the analyzed studies was considerable and the sample size was limited. Paradoxically, a subgroup analysis in a Cochrane systematic

review demonstrated that MLD was safe and, when used in combination with compression bandages, may provide additional benefits of swelling reduction for BCRL compared with the use of compression bandages alone, particularly for patients with mild-to-moderate disease (92). Compression bandages used with a compression garment can significantly reduce the volume of the edematous limb compared with the usage of a compression garment alone (1). Generally, the bandaging method involves a spiral-bandaging method and a figure-of-eight method (93). The figure-of-eight method is a more effective approach in maintaining the correct position, is more comfortable for the patient and has a replacement frequency of either 5 times per week over a 4-week period or once per 2 days over a 3-week period (93). Precast adjustable compression systems, a novel technique that can be easily used and removed by patients, may be an effective alternative to compression bandages due to similar effects on reducing excess limb volume (94). When the affected limb reaches a minimum volume, self-care can be accepted by the patient (1). A myriad of advantages is attained by a CDT approach that reduces edema volume, intensity of pain and arm heaviness, reinforces lymphatic function, improves quality of life and lowers the incidence of cellulitis (95-97).

The use of adjuvant tools such as a pneumatic compression device (PCD) provides additional benefits in managing lymphedema that is associated with reduction of outpatient

Table III. Characteristics of current treatment strategies for LE.

Treatment method	Characteristics
Complex decongestive therapy	Reinforces lymphatic function; improves quality of life; reduces edema volume, intensity of pain and arm heaviness and the incidence of cellulitis
Pneumatic compression device	Reduces frequency of outpatient services and hospitalizations; reduces the usage of LE-related manual therapy, LE-related costs and incidence of cellulitis
Physical exercise	Does not cause or worsen LE in patients; ameliorates patients psychosocial and physical conditions; results in patients having active lifestyles with optimized survival
Lymphatic-venous 'end-to-end' anastomoses	Can only be used in the early-stage of LE; reduces limb volume or circumference; improves quality of life; minimizes trauma; lowers the risk of complications; can be performed under local anesthesia
Vascularized lymph node transfer	Can only be used in the moderate-to-advanced stage of LE; reduces limb volume or circumference and the incidence of cellulitis; improves quality of life; donor-site lymph edema is a potential complication
Liposuction	Removes excess adipose tissue; improves lymph flow; increases blood flow to the skin; reduces the incidence of erysipelas and cellulitis

LE, lymphedema.

services and hospitalizations (1). The initial volume reduction of a swollen limb can be maintained over a long period of time by the use of PCD followed by the use of a flexible and suitable compression garment. A meta-analysis of 7 randomized controlled trials (RCTs) showed that PCD can alleviate lymphedema, however, there was no significant reduction in limb volume between conventional management of lymphedema with or without the usage of PCD (98). These RCTs had limitations such as small sample sizes of 12-56 participants with considerable heterogeneity among them (98). Currently, the most advanced PCD uses a calibrated, gradient compressor, and it is designed for home use with multiple inflatable compartments to deliver external pneumatic compression, more garment chambers and a higher level of adjustability and programmability (99). A retrospective analysis demonstrated that this adjunctive modality yields significant clinical and economic effectiveness in treating cancer-related and non-cancer-related lymphedema, demonstrated by a reduction in the adjusted rate of cellulitis, the usage of lymphedema-related manual therapy, outpatient visits and total lymphedema-related costs per patient, excluding medical equipment costs (99).

It is widely known that a sedentary lifestyle leads to being overweight or obese, factors that are associated with an increased incidence of BCRL (14). Participation in physical exercise during and after treatment for breast cancer can ameliorate psychosocial and physical conditions, resulting in active lifestyles with optimized survival (100). Traditionally, patients with lymphedema or who are at risk for lymphedema tend to reduce physical exercise due to concerns about disease exacerbation (100). Some preliminary studies have indicated that exercise neither causes lymphedema nor worsens the disease (101-105). A slowly progressive weight-lifting program does not increase the rate of lymphedema compared with no exercise, and aerobic exercise, resistance training, stretching, yoga, qigong and pilates are also safe (101,105). Under specific circumstances, resistance training can even substantially improve the lymphedema state and may prevent the development of secondary lymphedema in patients (106).

There are a variety of surgical techniques for lymphedema, including debulking resection, liposuction, lymphatic-venous 'end-to-end' anastomoses (LVA) and vascularized lymph node (VLN) transplantation with the advent of microsurgery (1). Typically, LVA is only used in the early-stage of the disease, but despite this limitation it reduces limb volume or circumference effectively and improves quality of life (107-109). LVA also has other advantages such as reducing trauma, lowering the risk of complications and it can be performed under local anesthesia (110,111). After a 1-year follow-up of women undergoing LVA, >56.5% of anastomoses are still patent (109).

A new program, called the 'Lymphedema Microsurgical Preventive Healing Approach (LYMPHA)', combines the LVA technique with the surgery of ALND, which anastomoses the collateral branch of the axillary vein to the lymphatics of the arm, with a low incidence rate of lymphedema of 4.05% (112,113). An altered and simplified version of LYMPHA used during the surgery of ALND dramatically decreases the lymphedema rate to 3% compared with ALND alone, which has a higher rate of 13% (114). Two pilot studies proposed a new technique called 'dynamic-lymphaticovenular anastomosis,' which uses preoperative dynamic imaging of the forearm to determine the incision points followed by microsurgery of LVA (115,116). This technique achieves significant reduction of excess limb volume compared with conventional LVA and results in no swelling rebound after postoperative degradation or removal of compression garments in a 12 month follow up period (115,116).

VLN transfer is a promising technique for treating moderate-to-advanced stage lymphedema, and it has the ability to lower the clinical grade, attenuate limb circumference, reduce the incidence of cellulitis and improve the quality of life in patients (117). However, it requires a strict observation

of the donor site because donor site lymphedema is the most serious complication after this surgery (117). Patient selection and scrupulous assessment of donor and recipient sites prior to VLN transplantation are key factors for surgical success. This concern may be removed by the technique of vascularized groin lymph node (VGLN) flap transplantation (118). Findings revealed VGLN flap harvesting does not cause iatrogenic lymphedema at the donor site, but this surgery cannot be performed in patients with a high risk of lower limb lymphedema due to obesity, pre-existing lower limb edema or previous pelvic surgery (118). Of note, the limitations of LVA and VLN procedures have to be emphasized, as they are complex and can only be provided by experts at tertiary care centers.

CDT is not an effective treatment for chronic massive lymphedema with excess adipose tissue, as adipose tissue cannot be eliminated through compression alone (1). Microsurgery often fails to attain complete limb reduction because the newly formed adipose tissue persisting under the skin of the patient with longstanding non-pitting lymphedema is not resected. These perplexities are solved by the use of liposuction, which can remove excess adipose tissue, resulting in complete reduction of lymphedema (1). Liposuction is effective in removing chronic non-pitting limb lymphedema with a large volume, which can be completely attenuated in 1-3 months, with no recurrence of arm swelling observed in long-term follow-up (119-123). Ample evidence suggests that women with lymphedema who undergo liposuction followed by compression bandages or compression garments achieve significant benefits, as the mean reduction of excess limb volume ranges from 101-118% (124-126) and can be maintained at >100% during 21 years of follow-up (127). In addition, liposuction improves lymph flow (128), increases blood flow to the skin so that it is approximately equal to the flow in a normal arm (129), and it does not injure the existing lymphatic vessels within the affected limb (122,130). These characteristics significantly reduce the incidence of erysipelas and cellulitis (131). The complications from liposuction are limited, with a very low incidence rate; paresthesia of the skin is the most typical complication and fades away within 3-6 months (132), and fibrous tissue increases in some cases, specifically in women with a male distribution of body fat (132). The characteristics of current treatment scenarios for lymphedema are summarized in Table III.

Previous findings illustrated that no medication has the capacity to reduce lymphedema, as the lymphatic flow could not be improved by any drugs, including diuretics that change microvascular fluid filtration by increasing the excretion of sodium chloride and water (96). With a greater understanding of the molecular mechanisms that control lymphatic function, lymphedema may be reversed. The first potential medication for the treatment of BCRL is reported to be in phase I trials (133). An increasing number of lymphedema therapy-related preclinical investigations are performed in animal models of lymphatic disease in which the genes encoding VEGF-C or VEFG-D are transferred into the animal by adenoviruses or adeno-associated viruses (134,135). This technique results in the development of many new lymphatic capillaries and reduces edema following an initial promotion of lymphatic extravasation (136). Following VEGF-C

therapy, the injured collecting lymphatic vessels in mice undergo regeneration of lymphatic capillaries, which subsequently remodel, differentiate and mature into functional vessels (137). Similarly, surgery-based damage of lymphatic vasculature in pigs can be effectively repaired by VEGF-C therapy, which greatly enhances the function and structural stability of transferred lymph nodes (138). The combined program of the microsurgery of VLN transfer followed by VEGF-C treatment may be also equally beneficial in patients with lymphedema to foster lymphatic microvascular anastomoses.

The success of stem cell therapy involving the transplantation of autologous mesenchymal stromal cells derived from adipose tissue, muscle and bone marrow to alleviate lymphedema has been reported in certain preclinical studies (139-141), and this has opened up a potential new field of treatment for this disease. In two pilot studies, injection of adipose-derived regenerative cells into the axillary region with fat grafting was well-tolerated, and only a paucity of liposuction-related adverse events occurred transiently (142,143). After 6-12 months of follow-up, lymphedema was alleviated, without rebound of the swelling limb (143). However, these promising results of autologous stem cell therapy from the two studies must be investigated in humans with RCTs. If the results in humans are positive, increasing number of patients with lymphedema could benefit from this surgery.

7. Conclusions

BCRL exerts a negative impact on the quality of life of survivors of breast cancer. Precautionary measures and earlier lymphedema surveillance combined with effective diagnostic tools, such as BIS or ICG lymphography, are effective in reducing the incidence of lymphedema and providing more opportunities for intervention and treatment in subclinical and early-stages, especially in high-risk patients. In a variety of treatment strategies, the combination of CDT, PCD and appropriate physical exercise can contribute to women having an apparent reduction of excess limb volume and improvement of quality of life. Of the surgical techniques, the usage of LVA in the early-stage of disease, VLN transplantation in the moderate-to-advanced stage and liposuction when lymphedema is coupled with excess adipose tissue can reduce swollen limb volume to normal, and be maintained long-term without rebound of swelling. Recently, molecular therapy and autologous stem cell transplantation have been shown to successfully alleviate lymphedema in preclinical studies, which may lead to the development of novel targeted therapies for BCRL in the future.

Availability of data and materials

Not applicable.

Authors' contributions

LH made substantial contributions to the conception of the review, HQ produced software that was used in the work, QW drafted the manuscript and substantively revised it, and YS contributed to the writing of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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