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Review

Tackling the diversity of breast cancer related lymphedema: Perspectives on diagnosis, risk assessment, and clinical management

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ABSTRACT

Breast cancer related lymphedema (BCRL) develops as a consequence of surgical treatment and/or radiation therapy in a significant number of breast cancer patients. The etiology of this condition is multifactorial and has not yet been completely elucidated. Risk factors include high body mass index, radical surgical procedures (i.e. mastectomy and axillary lymph node dissection), number of lymph nodes removed and number of metastatic lymph nodes, as well as nodal radiation, and chemotherapy. However, these predisposing factors explain only partially the BCRL occurrence, suggesting the possible involvement of individual determinants. Despite the implementation of conservative approaches, BCRL still remains in a proportion of cases an incurable and progressive condition with major physical and psychological implications. To date, diagnostic methods and staging systems lack uniformity, leading to a possible underestimation of the real incidence of this condition, decreasing early detection and thus the possibility of an effective treatment. Several preventive and therapeutic options are available, both conservative and surgical, but are not included in a standardized intervention protocol, tailored on patient's specific characteristics. In this review, we provide a comprehensive overview of the current state-of-knowledge of BCRL management, novel advantages in the assessment of pre-operative evaluation and risk prediction and discuss strengths and weaknesses of diagnostic and treatment strategies currently accessible in clinical practice.

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1. Introduction: definition and historical considerations

Breast cancer related lymphedema (BCRL) is a localized fluid retention and tissue swelling which occurs after surgical procedures and/or radiotherapy in a substantial proportion of breast cancer patients [1]. This condition is due to the impaired transport capacity of the lymphatic system of the arm, resulting in the stasis of the lymph in the interstitial space [2]. The clinical manifestations of BCRL include augmented volume of the upper limb with subsequent reduced functionality, increased risk of comorbidities, psychophysical frailty, and detrimental impact on social life, work, and career [2,3]. Given its protracted time of onset, BCRL is a lifelong threat to breast cancer survivors [2].

The first case of *elephantiasis chirurgica* after operation for breast cancer was formally described by William Stewart Halsted as a report from around 1880 [4], when the surgical treatment of breast cancer, previously considered a systemic and inoperable disease, was at its beginning [5]. At that time, and for most of the 20th century, the *en bloc* removal of the breast along with the skin, nipple, pectoralis muscles, and axillary lymph nodes was the standard treatment for breast cancer [5,6]. These mutilating procedures were often troubled by multiple complications, including lymphedema [6]. In the second half of the 20th century, the widespread exploitation of radiation therapy opened new avenues for the use of less aggressive approaches in surgical oncology [7–9]. Randomized clinical trials were launched to compare the therapeutic effects and the complications of radical mastectomy with those of simple mastectomy plus local radiotherapy (i.e. McWhirter approach) and of simple mastectomy plus pectoral node histologic examination with or without concomitant radiotherapy (i.e. Forrest approach) [10]. Both these approaches showed not only significantly better survival but also less postoperative complications, including swelling and lymphedema. Further reduction of BCRL incidence was made in the modern era, with the advent of the sentinel lymph node dissection (SLND), with or without radiation [11–15]. Longer term survival, however, has meant more patients at risk for lymphedema.

During the past few years, many efforts have been made by multiple professional organizations and consensus groups (e.g. American Society of Clinical Oncology, National Comprehensive Cancer Network, National Lymphedema Network, International Society of Lymphology, Lymphoedema Framework, Dutch Working Group on Lymphedema, European Society for Medical Oncology) to define recommendations and guidelines for the management of BCRL [16–22]. Regrettably, none of these guidelines are widely adopted. As a result, this condition is often managed using locally-developed empiric strategies.

2. Epidemiology and clinical features

It is estimated that among the 1.7 million women worldwide diagnosed with breast cancer every year, approximately 20% of them will develop BCRL, with increasing risk up to 2 years after diagnosis or surgery [23]. The clinical signs of BCRL are the consequence of protein-rich fluid accumulation in the interstitial space of the upper limb, which causes a chronic inflammatory response associated with connective tissue overgrowth, and ultimately fat deposition and fibrosis [24]. A paradigmatic example of BCRL is portrayed in Fig. 1. Pathological changes manifest initially as swelling and enlargement of the affected limb, with pitting edema that often disappears with night rest. Later, non-pitting edema increased skin thickness, trophic changes such as acanthosis and skin color alterations appear [1,24]. Other physical symptoms associated with BCRL include a limited range of motion, diminished strength, and function, the sensation of tingling, heaviness, and pain [24]. Women with BCRL have to face great physical and psychological handicaps and may be prevented from returning to the level of activity prior to their diagnosis [3]. Frustration, anxiety, depression, decreased self-esteem, and distorted body image are

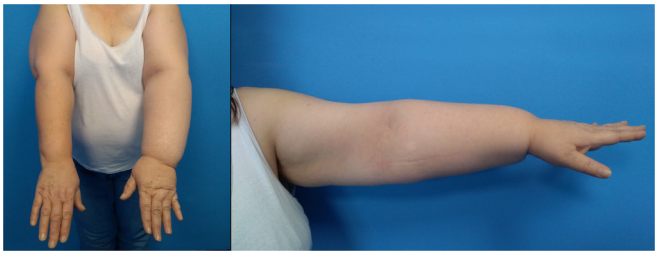

Fig. 1. Representative images of upper limb lymphedema of the left arm in a patient with previous axillary dissection for a metastatic invasive carcinoma. In this patient, lymphedema occurred after 1 year from surgery; review of the pathology report revealed that the metastatic deposits in 3 out of 19 lymph nodes showed diffuse images of extracapsular extension.

frequently reported by patients who survived breast cancer but have to confront BCRL [25,26].

3. Risk indicators, prognostic factors, and predictive tools

The etiology of BCRL is multifactorial and not entirely understood, albeit strictly related to axillary therapeutic procedures, including axillary lymph node dissection (ALND) and radiotherapy. In particular, the risk of BCRL increases both with the number of lymph nodes removed and the number of lymph nodes found to be metastatic, probably due to the increased use of axillary radiations in patients with multiple lymph node metastasis [23,27]. Hence, it has been demonstrated that radiation therapy can promote BCRL by blockade or compression of the lymph vessels through radiation fibrosis [28]. Furthermore, regional radiotherapy after ALND is associated with two times increased risk of BCRL compared to no irradiation or breast/chest wall irradiation alone, suggesting that these treatments might be synergistic in their negative impact on the lymphatic system integrity [29,30]. Of note, up to 6% of pN0 (sn) women are reported to experience BCRL, with higher frequency when more than one sentinel lymph nodes are excised [23,28]. Furthermore, patients who undergo radical mastectomy are at higher risk compared to those treated with breast-conserving surgery[31]. The role of chemotherapy is more controversial, given that only the taxanes seem to increase BCRL risk, particularly in women subjected to ALND [32,33]. Many studies have demonstrated a significant correlation with high BMI (>25 kg/m^2) and large post-operative weight fluctuations [34].

There is recent evidence that tumor-specific biological features, such as peritumoral lymphovascular invasion (LVI) and extranodal extension (ENE) of the metastasis have a negative impact on BCRL-free survival [27]. Despite these patients can be treated with more aggressive radiotherapy protocols, this correlation was found to be independent from the use of irradiations, suggesting that the assessment of LVI and ENE can be integrated with clinical and surgical data to improve BCRL risk stratification. In recent years, several germline alterations in genes involved at variable levels in lymphangiogenesis and angiogenesis have been documented in BCRL patients (Table 1) [35–46]. However, no highly recurrent molecular alterations have been identified to date.

4. Diagnosis: from empirical procedures to cutting-edge technologies

Precise arm volume measurement is capital in the follow-up of breast cancer patients, as an early detection of BCRL can reduce the incidence of irreversible stages [47]. Several approaches have been proposed, as summarized in Table 2. All of them require a pre-treatment baseline measurement and/or comparison with the contralateral arm.

4.1. Water displacement

For long, the volume of the limb has been measured by immersing it in a tank of water [23,48]. The diagnosis of lymphedema can be made in the presence of a displacement of 10% in volume or 200 mL of fluid[23]. Nowadays, this method is considered imprecise, complex, time-consuming, and contraindicated in several cases, such as those with skin lesions and infections [49].

4.2. Circumferential measurement

Given that the truncated cone solid can be considered as a proxy of the arm shape, the measurement of several circumferences across the arm can be used to estimate its total volume as the sum of all truncated cones volumes [49,50]. Different measurement techniques have been proposed but the optimal approach remains a matter of controversy [51,52]. A variant of the circumferential method is the so-called “figure-of-eight” (Fig. 2) [53]. Despite its reliability, many authors question the sensitivity and reproducibility of the circumferential measurement, particularly in case of arm shape irregularity and gibbousness [49,53].

4.3. Perometry

Optoelectronic limb volume measurement (also known as

Table 1
Genes showing germline alterations in BCRL patients.

Gene (location)	Encoded protein	Function
LCP2 (5q35.1)	Lymphocyte cytosolic protein 2	T-cell activation.
NRP2 (2q33.3)	Neuropilin-2	Cardiovascular development axon guidance.
SYK (9q22.2)	Spleen tyrosine kinase	Adaptive immune receptor signaling; Cell proliferation, differentiation, and phagocytosis; Separation of newly formed lymphatic vessels from the blood vasculature.
VCAM1 (1p21.2)	Vascular cell adhesion molecule 1	Leukocyte-endothelial cell adhesion and signal transduction.
HGFR (7q31.2)	Hepatocyte growth factor receptor/c-MET	Mitogenesis and morphogenesis; Embryonic development; Myocardial development; Epithelial-mesenchymal transition; Gastrulation, angiogenesis, myoblast migration, bone remodeling, and nerve sprouting; Liver regeneration
VEGFC (4q34.3)	Vascular endothelial growth factor-C	Angiogenesis and endothelial cell growth; Permeability of blood vessels.
RORC (1q21.3)	Nuclear receptor ROR- γ	Lymphoid organogenesis (in mice).
GJC2 (1q42.13), *GJA4* (1p34.3)	Connexins 47 and 37	Arteriogenesis; Oocyte survival; Oligodendrocyte development.
NFKB2 (10q24.32)	Nuclear Factor κ B subunit 2	Inflammation and immune response.
IL4 (5q31.1) *IL10* (1q32.1)	Interleukins 4 and 10	Apoptosis and cell proliferation; Immunoregulation and inflammation; Expressed also in endothelial cells.
KCNA1 (12p13.32), *KCNJ3* (2q24.1), *KCNJ6* (21q22.13), *KCNK3* (2p23.3)	K channel proteins	Electrochemical gradient across cell membranes In the lymphatic system facilitate lymph flow.

Table 2
Overview of the main diagnostic strategies in BCRL, with a focus of their strengths and weaknesses.

Diagnostic method	Strengths	Limitations
Circumferential measurements	• Cheap; • Easily accessible; • High portability; • Non-invasive.	• Unable to detect lymphedema in subclinical settings; • Low intra- and inter-rater reproducibility; • Time consuming; • Left-right dominance, muscle atrophy, fibrous tissue deposition, or weight gain may affect the measurement.
Water displacement	• Current gold-standard method; • Evaluation of hand volume changes; • Cheap.	• Unable to detect lymphedema in subclinical settings; • Cumbersome; • Low portability; • Time consuming; • Not indicated in case of wounds/skin infections
Perometry	• Detection of subclinical forms; • Rapid, accurate and precise.	• Changes in fat or muscle composition can affect arm volume; • Low portability; • Expensive equipment.
Bioimpedance spectroscopy	• Detection of subclinical forms; • Rapid and easy to use; • High inter- and intra-rater reproducibility; • Selective measurement of water content.	• Not yet well established in clinical practice; • False negative results in late stage BCRL and segmental/superficial swelling; • Low portability.
Tissue dielectric constant	• Early diagnosis; • Applicable in almost any body site.	• Lack of full characterization of differences between Lymphedematous and non-lymphedematous tissue
Ultrasonography	• Cheap; • Easily accessible; • Analysis of physical properties and structural alterations of tissue in real time.	• Difficulties in achieving deep tissue penetration; • Operator'dependent; • No interpretation guidelines.
Magnetic resonance imaging	• Early diagnosis; • Evaluation of lymphatic function; • Assessment of morphologic tissue changes.	• Expensive; • Time consuming; • Possible adverse events to contrast agents; • Contraindications: claustrophobia and metal implants/devices. • Low portability
Lymphoscintigraphy	• Early detection of lymphatic impairment; • Direct visualization of the lymphatic system.	• Lack of standardized procedures and radiopharmaceuticals; • Need for consistent criteria to interpret the results; • Prolonged times.
3D photogrammetry	• Evaluation of hand volume changes; • Safe and non-invasive; • Portable; • Cheap	• Requires trained technicians; • Requires access to a 3D camera system.

perometry) employs an optical scanner to calculate the arm volume [54]. A perometer operates using infrared light bulbs inside of a square-shaped frame; as the frame moves along the length of a fully extended arm, horizontal and vertical shadows are cast and used to compute the arm volume. Despite this method is extremely sensitive, it requires expensive and not portable equipment, making its clinical use demanding [49,55].

4.4. Bioimpedance spectroscopy

Using multiple-frequency spectroscopy, resistance can be measured when alternating electrical current passes through the limb (Fig. 3) [56]. The higher the interstitial fluid, the lower the resistance. Bioimpedance spectroscopy has demonstrated good performance in the detection of subclinical BCRL and in terms of inter and intra-observer variability [57]. Furthermore, it can selectively measure the amount of edema, irrespective of the presence of adipose or fibrous tissue in the limb [58]. Single frequency bioimpedance analysis (SFBIA), which measures the impedance at a single constant frequency in the low-frequency range, is a less expensive alternative [59]. It should be noted, however, that SFBIA does not allow for the selective measurement of the extracellular fluid, questioning its use in BCRL follow-up, where fibrous tissue deposition occurs. Furthermore, abnormalities in bioimpedance are not always correlated with an underlying BCRL [60].

4.5. Ultrasonography

BCRL can be reliably diagnosed with ultrasonography by comparing the thickness of skin and subcutaneous tissue and also evaluating the compliance of subcutaneous tissue in clinical settings [61]. Ultrasonography provided previously unavailable evidence that BCRL is not only the result of the tissue edema but also of the chronic inflammation involved [62]. This method is cheap, easily accessible, safe from radiation exposure, and noninvasive.

4.6. Magnetic resonance imaging

Due to its ability in recognizing both extracellular water and adipose tissue, magnetic resonance imaging (MRI) is a safe and noninvasive technique for visualizing the dermal and subcutaneous changes associated with BCRL [63–66]. Due to the expensiveness, individual contraindications, and lack of portability, however, the role of MRI in BCRL diagnosis and follow-up is extremely limited.

4.7. Lymphoscintigraphy

This method offers an objective and reliable approach to diagnose and characterize the severity of BCRL, with the visualization of regional lymph nodes, lymphatic channels, collateral lymphatic channels, interrupted vascular structures, and the deep lymphatic nodes [67,68]. However, this method is has issues of reliability in clinical practice.

4.8. Stereophotogrammetry/laser scanner 3D

The three-dimensional (3D) stereophotogrammetry is an augmented reality diagnostic technique, which is emerging as an extremely reliable non-invasive and cost-effective tool in the early

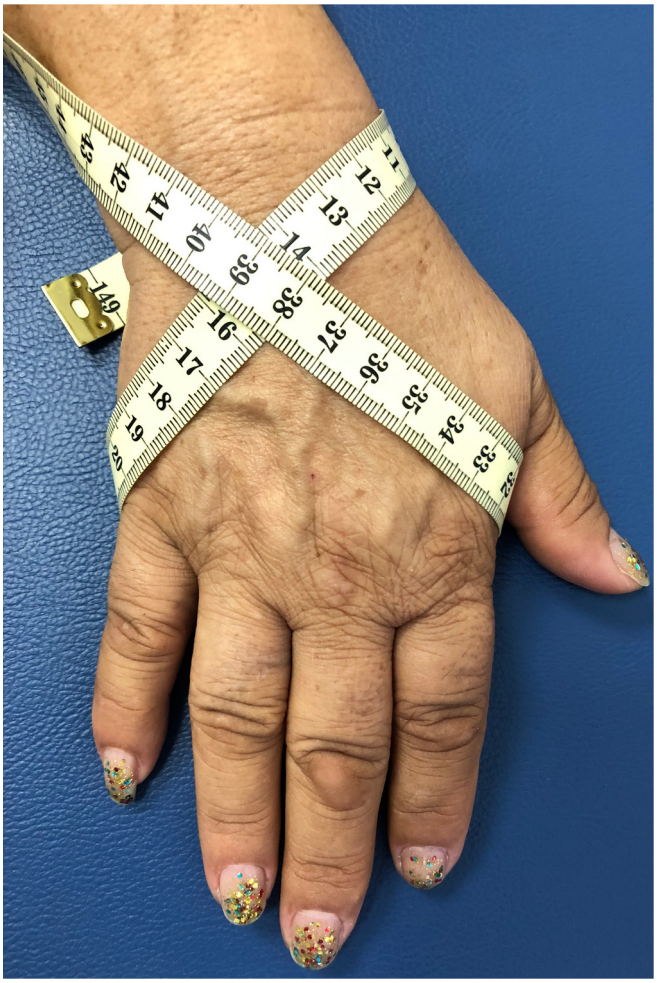

Fig. 2. Circumferential measurement according to the figure-of-eight method in a patient with initial lymphedema of the right upper limb. The patient's right forearm should reste pronated on the treatment table; the hand should extend over the end of the table. The tester instructs the woman to maintain a position of wrist neutral flexion/extension and radial/ulnar deviation, with fingers adducted. The medial aspect of the wrist just distal to the ulnar styloid process is used as the starting point for the measurement. The tester aligns the zero point of the tape measure on this starting point with the blackened side visible. The the tape is then wrapped across the ventral surface of the wrist to the most distal point of the radial styloid. Then, the tape is placed diagonally across the dorsum of the hand to the fifth metacarpophalangeal joint. The tape is wrapped across the ventral surface to the second metacarpophalangeal joint. The final step involves placing the tape diagonally across the dorsum of the hand back to the starting point.

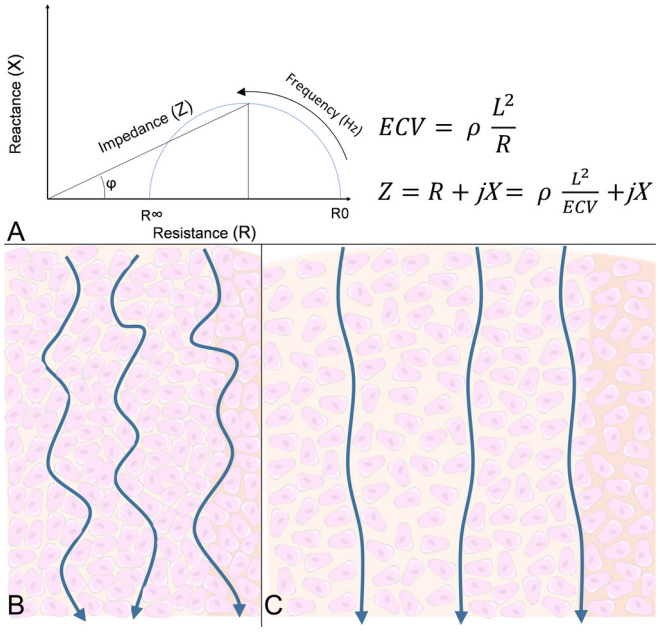

Fig. 3. Graphic representation of impedance and current propagation in tissues with different fluid content. Bioimpedance spectroscopy (BIS) measures the opposition that a circuit presents to a current when a voltage is applied. At low frequencies (<5 Hz) the current travels through extracellular fluid (ECW) only, allowing a direct measurement of ECW. A. Impedance is determined by the reactance (X) and resistance (R). B. Given the assumption that impedance is inversely proportional to fluid volume, tissues with low ECW have higher impedance rates. C. As fluid accumulates, impedance to the current flow decreases.

diagnosis and follow-up of BCRL [69]. This method allows for the accurate real-time volume measurements of several regions of the human body.

5. Staging systems and prognostic stratification: does one size fit all?

Over the past few years, several methods have been proposed for BCRL staging. Which system is the most consistent in clinical practice, however, still represents a matter of great controversy among lymphedema specialists. The International Society of Lymphology classifies lymphedema into a four-stage scale, as summarized in Table 3 [70]. In clinical practice, the severity of BCRL can also be determined by measuring circumference or volume changes of the affected limb in comparison to the contralateral normal limb. However, many authors consider the currently available staging methods to be arbitrary, given that they only refer to physical parameters (pitting, swelling, circumference, volume) [71]. Lately, it has been proposed to quantify the lymphatic function using imaging techniques [72]. Regrettably, none of the proposed staging systems for BCRL takes into account patients' clinicopathologic features and tumor-specific biologic characteristics.

6. Primary prevention

Preventing BCRL is one of the great challenges in breast cancer clinical multidisciplinary management. Several strategies have been proposed, with vastly heterogeneous results.

6.1. Patient's education

Education regarding the signs and symptoms of BCRL in patients with breast cancer treated with surgical procedures and radiations is mandatory to promote early identification and to improve patient outcomes [15]. All women who received treatment for breast cancer should be made aware of the importance to contact a healthcare provider immediately if they begin to experience feelings of heaviness, tightness, or burning sensation in the homolateral arm, as well as if they notice swelling and/or reddening in the affected area [73]. According to the National Lymphedema Network, patients at risk should follow some precautionary behaviors, such as healthy lifestyle (e.g. healthy diet and exercise), skin care (e.g. keep at-risk arm clean and dry, pay attention to nail care, do not cut cuticles, protect exposed skin with sunscreen and insect repellent), medical check-ups with lymphedema therapists [74]. Furthermore, they should be educated to avoid possible BCRL triggers, including injury or trauma (e.g. wear gloves while doing activities that may cause skin injuries, such as washing dishes, gardening, using chemicals), limb constriction (e.g. wear loose

Table 3
Lymphedema staging system according to the International Society of Lymphology.

Stage	Term	Characteristics
0 (Ia)	Latent	Latent or subclinical edema, swelling is not clinically evident despite impaired lymph transport, subtle alterations in tissue fluid/composition, and changes in subjective symptoms.
I	Spontaneously reversible	Early accumulation of fluid with high protein content compared to "venous" edema. Pitting may occur.
II	Spontaneously irreversible	Non-pitting edema and spongy consistency. Fat deposition and fibrosis starts to occur; the affected limb shows progressive hardening and increases in size.
III	Lymphostatic elephantiasis	Irreversible swelling unresponsive to conservative treatment. Tissue is hard and fibrotic, with trophic skin changes, such as acanthosis, fat deposits and warty overgrowth.

jewelry and clothing, avoid carrying heavy bags), extreme temperatures (e.g. hot tubs, saunas), prolonged inactivity [3].

6.2. Axillary reverse mapping

There is evidence that the lymphatics draining the proximal part of the arm are distinct (i.e. unjoining) from those of the breast [75]. Based on this assumption, the injection of a visual marker (e.g. blue dye, fluorescent dye, ^{99m}Tc) allows for the intraoperative identification and subsequent preservation of the arm lymphatics during axillary surgery [76]. Given the lack of randomized clinical trials, however, the efficacy of this axillary reverse mapping in preventing BCRL need further investigations [76,77].

6.3. Lymphedema microsurgical preventive healing approach (LYMPHA)

This microsurgical technique is based on performing multiple lymphatic-venous anastomoses between lymphatics identified by axillary reverse mapping and axillary vein branches during axillary dissection in high-risk patients [78]. Specifically, the patent blue dye is injected into the patient approximately 10 min before skin incision, allowing for the lymphatic channels mapping and bypass sites identification. The node dissection is then performed with preservation of the axillary vein by suturing the afferent lymphatic vessels into a branch of the axillary vein distal to a competent valve. Thanks to the reduced regional intra-lymphatic pressure, LYMPHA-treated patients have shown a significantly lower risk of BCRL and other lymphatic complications, such as lymphorrhea and lymphocele [78,79].

7. Building up individualized therapeutic schemes

For decades BCRL has been considered as an incurable condition but several therapies are now available [80]. However, the ultimate therapeutic strategy for BCRL has yet to be identified, particularly for patients with advanced stage, where fibrous tissue deposition stabilizes the increased arm volume.

7.1. Physical therapy

Mechanical force and mobilization (e.g. manual therapy, exercise therapy, and electrotherapy), have long been used in BCRL treatment and remain cornerstone tools to date. In particular, the complex decongestive therapy (CDT) is the first-line treatment for lymphedema [18]. It consists of four physical approaches that should be integrated into an individualized program, namely compressive therapy, manual lymph drainage (MLD), physical exercise, and skin care (Fig. 4) [81]. Overall, CDT is used both to reduce the arm volume and consolidate the results obtained [82]. MLD is based on the manual stimulation of lymph nodes in adjacent drainage regions followed by manual decongestion of the affected

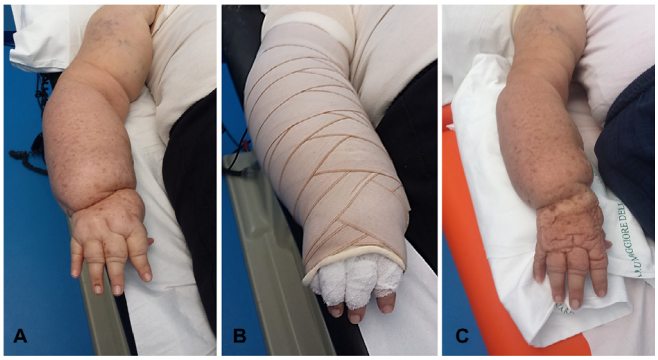

Fig. 4. Severe chronic lymphedema of the upper right arm before (A), during (B), and after (C) Complete Decongestive Therapy (CDT).

arm [81]. This procedure has shown significant results in improving lymph flow with an additive effect, in particular for patients with low/moderate BCRL [81]. The safety of physical exercise has been questioned until recently, when a systematic review provided evidence that slowly progressive exercise is not associated with an increased risk of BCRL occurrence and/or exacerbation [83]. Physical exercise, particularly resistance training protocols, provide major benefits for BCRL, with the advantage of improving also arm strength and range of motion, compared to the aerobic training alone [84].

7.2. Complementary therapies

Society for Integrative Oncology (SIO) guidelines, endorsed by the American Society of Clinical Oncology (ASCO), provided recommendations about the use of integrative therapies to manage symptoms and adverse effects during or after breast cancer treatment. Qigong exercise is a rather popular self-help mean of relieving the signs and symptoms related to conventional cancer treatments [85]. Some evidence suggested its potential role in improving microcirculation, suggesting that it could be helpful to manage BCRL and improve poor circulatory status in breast cancer survivors. However, benefits may not be sustainable over a long period, requiring repeated practice to maintain the results [85]. Temporary benefits, particularly in terms of quality of life, result also from yoga [86]. However, these approaches have never been confirmed in randomized clinical trials.

7.3. Laser therapy

Low-level laser therapy (LLLT) applies low-power lasers to the surface of the affected arm [87]. This method can be employed in association with CDT in selected groups of BCRL patients, although there are relatively few studies supporting its efficacy.

7.4. Medical strategies

The first attempts to evaluate *anti*-BCRL drugs were performed more than a decade ago [88]. A randomized placebo-controlled trial of combined pentoxifylline and tocopherol showed that six months of treatment could significantly reduce superficial radiation-induced fibrosis [89]. On the basis of these findings, a placebo-controlled trial investigated if the same drugs could prevent radiation-induced side effects in women with breast cancer, including BCRL [88]. The combination of pentoxifylline and vitamin E has been demonstrated to be safely associated with less volume increase [89]. In our opinion, however, pharmacologic treatment of BCRL is not ready for prime time, requiring further preclinical studies.

7.5. Shockwave therapy

Several studies have investigated the role of extracorporeal shock wave therapy, already used in several musculoskeletal conditions, in the treatment of BCRL, due to its effects in promoting lymphangiogenesis [90]. A pilot study including patients with BCRL resistant to CDT, provided circumstantial evidences to suggest that extracorporeal shock wave therapy might provide benefits in terms of decrease in arm volume, skin thickness, and severity of subjective symptoms [91].

7.6. Excisional procedures

Surgical removal of the excess of skin, fibrous, and adipose tissue that forms as a response to the increased fluid volume in interstitial space can be performed in chronic non-pitting stage II/III BCRL [92]. Among the various methods evaluated in multiple studies, liposuction is the most commonly used excisional procedure in BCRL [92]. Its efficacy in reducing limb volume, coupled with the good esthetic and functional results and the low rate of postoperative complications, make liposuction a reliable strategy, both in monotherapy and in combination [93,94]. This method is based on the removal of the hypertrophic adipose tissue that results from a response to chronic lymphedema via suction, using particular cannulas [92]. A prospective study showed that the volume reduction in women treated with liposuction for BCRL resistant to conservative therapy was maintained 12 months after surgery without any specific complication, in particular in those patients with less fluid accumulation.

7.7. Derivative microsurgery and microsurgical reconstruction

These methods are used to restore the normal lymphatic flow by creating connections between lymphatic and venous vessels; today the most commonly used procedure is multiple lymphatic-venous end-to-side or end-to-end anastomoses [95]. Derivative microsurgery consists in creating an anastomosis between afferent and efferent lymphatics with the interposition of autologous lymphatics or, more often, venous segments, usually taken from the same affected side or alternatively from the arm volar surface [96]. Significant improvement has been observed after microsurgery, particularly in early stages, with more than 80% volume reduction compared with preoperative conditions. In this perspective, preoperative risk stratification and early diagnosis play an important role in the identification of patients with a higher probability of developing this complication after surgery. Advantage of these techniques is that they also seem to reduce the rate of infections, such as cellulitis, and consequently the morbidity of this disorder. Recently, excellent results have been shown by the super-microsurgical lymphaticovenous anastomosis, a new technique which creates fine connections (i.e. 0.5–0.8 mm) between lymphatic vessels and subdermal venules [97].

7.8. Tissue transfer procedures

Vascularized lymph node transfer (VLNT) is a microsurgical procedure based on the relocation of a lymphatic-containing soft-tissue flap with its arteriovenous supply from an autologous donor site to the affected limb [98]. The lymph nodes can be removed from different regions, such as the lateral groin, chest wall or neck, and then transplanted into the lymphedematous area and connected to local lymph vessels by end-to-end anastomosis in order to bypass the site of discontinuation of the lymphatic flow [98]. The main concern regarding the VLNT procedure is the donor-site morbidity and development of lymphedema in the site of lymph node removal, which is an unlikely but still a possible complication.

7.9. Block of sympathetic innervation

Stellate ganglion block with the combination of local anesthetics (e.g. Bupivacaine) and corticosteroids (e.g. Triamcinolone) has shown promising results in reducing arm swelling. Similar were shown by the thoracic block, which allows for a complete interruption of the sympathetic innervation to the arm [99]. Further studies are needed in order to validate effectiveness, side effects, and risk linked to these procedures.

8. Conclusion

Despite the clinical relevance of BCRL, its management remains burdened by heterogeneous and institution-dependent approaches. A universal agreement in defining, measuring, and quantifying lymphedema, in association with an accurate preoperative stratification of patient's individual risk, could ease the identification of the most appropriated therapeutic strategy. Practitioners should also shift the attention to the early detection, screening, and prevention of BCRL through the active involvement and education of the patients. Moreover, there is a chance that clarifying the molecular mechanisms involved in the pathogenesis and progression could offer new perspectives on risk assessment and treatment. Recent findings challenge the traditional view that BCRL is solely due to a mechanical damage of lymphatics vessels. Several lines of evidence suggest the presence of an individual susceptibility. Future research should be addressed towards the understanding of the genetics underlying this condition. This would allow not only a better characterization of patients, but it could also provide molecular targets for medical therapy in order to realize a full implementation of precision medicine.

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