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Review

Integrated Treatment of Breast Cancer-related Lymphedema: A Descriptive Review of the State of the Art

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Abstract. *Background/Aim: Upper limb breast cancer-related lymphedema (BCRL) is a chronic and severe condition affecting a significant percentage of breast cancer survivors. Even though its physiopathology is well-known, there is no worldwide consensus on BCRL evaluation and a gold-standard treatment. This narrative review aims at providing a brief descriptive overview with regard to BCRL treatment modalities. Materials and Methods: We conducted a literature search within the PubMed database, and 33 articles out of 56 were selected, including reviews, systematic reviews, and meta-analyses aiming find the most updated evidence regarding BCRL treatment modalities. Results: Physical exercise (aerobic exercise, resistance exercise, aquatic therapy), bandages, and intermittent pneumatic compression were shown to be most effective in BCRL patients, in terms of swelling reduction in the acute-intensive phase. Furthermore, physical exercise was beneficial also as a maintenance tool. Manual lymphatic drainage demonstrated efficacy in preventing secondary lymphedema if applied immediately after breast cancer surgery or in early phases of BCRL or as a maintenance tool. Complementary procedures such as acupuncture, reflexology, yoga and photo-biomodulation therapy did not show conclusive results in BCRL treatment. Surgery was shown effective in managing symptoms (liposuction), preventing (lymphaticovenular anastomosis) and treating BCRL (vascularized lymph node transfer). Conclusion: BCRL is still a challenging condition either for breast cancer survivors and clinicians, deeply impacting patient functioning and quality of life. Due to the lack of globally accepted criteria in evaluating BCRL, to date a gold standard treatment for this widespread issue is still needed.*

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Improved survival rates in breast cancer patients contribute to an increased number of survivors complaining of upper limb Breast Cancer-Related Lymphedema (BCRL), which is a secondary lymphedema after surgery and radiation therapy (1). BCRL is a common complication occurring after lymph node dissection for breast or upper limb tumors (*e.g.*, melanoma), and it is generally caused by an excessive accumulation of protein-rich fluid (lymph) in tissue extracellular spaces that causes transient or persistent soft tissue swelling (2). Up to 30% (3-5) of breast cancer survivors, may suffer from BCRL and its physical and psychological consequences such as: pain, pitting edema, upper limb heaviness and discomfort, decreased range of motion of the affected joints, recurrent skin infections and ulcers, elephantiasis, cutaneous angiosarcoma, depression, anxiety, body image-related disorder. Quality of life (QoL) is dramatically worsened by BCRL.

Lymphedema (LYE) might be defined as "an increase of more than 10% in volume between the abnormal and normal arm" or "a difference of more than 200 ml in arm volume or more than 20 mm in the circumference between the abnormal and normal arm" (6). All variants of LYE stem from an imbalance between production and drainage of protein-rich fluid, *i.e.*, lymph. Secondary LYE is a consequence of a primary condition that does not directly impair lymphatic function and is the most frequently occurring condition. Primary LYE may be caused by a congenital dysfunction or anomaly of the lymphatic system, and it may be sporadic or hereditary or syndrome-associated and is less common (7, 8) than secondary LYE (9).

Secondary LYE finds its roots in obstruction or disruption of the lymphatic system due to cancer, radiation therapy, chronic venous insufficiency, surgery, trauma, or infections. *Wuchereria bancrofti*, responsible for filariasis, is the most common cause of secondary LYE worldwide (10).

Some risk factors participate in developing secondary LYE, such as obesity and pathological BMI, chemotherapy, the number of lymph nodes removed (1, 11, 12). Some authors advocated physical exercise, but this theory has been rejected, as discussed below (13, 14). However, predisposing factors have not been yet identified. Despite older literature claiming the healthy state of the unaffected side, recent studies advocate the existence of differences between the arms' drainage function in the absence of any cancer or surgical treatment. More specifically, an unaffected lymph node side that non dissected may not be considered "normal" and presenting a slower tracer appearance time. Such differences in lymphatic function between the two limbs may predispose to LYE development (15).

International Society of Lymphology (ISL) classified the limb LYE in 4 stages: stage 0 to indicate subclinical or latent limb LYE with no evident volume gain and swelling but an initially impaired lymphatic network; stage I to indicate mild LYE with visible transient limb swelling and volume gain but with the possibility to be reduced with limb elevation; stage II to indicate non-reducible LYE with poor pitting edema and little to no response with limb elevation, as an indicator of tissue changes; stage III to indicate overt LYE with tissue changes such as fat and tissue fibrosis, hypertrophic thickened skin and limb deformities up to lymphostatic elephantiasis with absent pitting of edema (16).

Diagnosis of LYE is made by physical examination and is aided by linear circumference measurements or volumetric arm measurements based on water displacement. Advanced staging tools are indocyanine green lymphography, US and MRI, lymphoscintigraphy, lymphography, LASER scanning, bioimpedance spectroscopy (L-Dex score or lymphoedema index), perometry and tonometry (17).

Early detection and treatment on BCRL may reduce chronic BCRL rates by >50% (18, 19). Together with the increase of BCRL, the need for treatment is rising. However, BCRL is considered a chronic disease, and its management aims at disease control, prevention of complications and limb function preservation (20). Some medical and surgical solutions have been proposed, including physical exercise and treatment related to Complete (or Complex) Decongestive Therapy (CDT), medical treatment, surgery, complementary and integrative therapies. Here we present a review of literature regarding the state of the art of BCRL treatment in the last five years, with a brief discussion for each modality and its effectiveness in BCRL management.

Materials and Methods

This review aims at analyzing and discussing current knowledge on BCRL based on the last five years-literature. The review was conducted by search within the PubMed database. The authors (PM and SD) independently searched the past studies in the last five years using the following medical subject heading (MeSH) terms and free text words: "breast" AND "cancer" AND "lymphedema" AND "treatment." The following filters were applied: "Clinical Trial", "Meta-Analysis", "Randomized Controlled Trial", "Review", "Systematic Review", "in the last 5 years", "English", "Systematic Reviews", "MEDLINE". Our initial search yielded 56 studies, 23 of which were deemed not to be relevant after screening the titles and the abstract content because they dealt with other topics than BCRL treatment. Afterward, the reviewers screened the full text of the remaining 33 studies and extracted the recommendations that emerged from these papers. The authors discussed any discrepancies before including the conclusive evidence in this paper. Single case-reports and case-series and single RCT were not considered.

Results

The authors displayed 56 articles after the research. Among them, only 33 papers were found relevant to the BCRL treatment topic, as shown in Table I. Manual Lymphatic Drainage (MLD) was discussed in 7 reports, bandage and garments roles were investigated in 2 different papers. Only one paper discussed Kinesio taping and intermittent pneumatic compression. Five articles from Eastern authors described the role of acupuncture. Most articles focused on physical exercise (14 papers on 23), evidencing the prominent and widespread part of physical activity in the treatment of BCRL. Surgical treatment of BCRL was discussed in only four scientific works, suggesting that surgery is not universally considered as a first-choice option in the treatment of BCRL yet. Four articles investigated the role of the emerging photo-biomodulation therapy. Finally, five articles discussed the role of complementary alternative medicine (yoga, reflexology).

Twenty-three articles (Table II) were not relevant to the aim of this work as they concerned topics other than the treatment of BCRL, such as epidemiology, comorbidities and impact of BCRL, diagnostic studies, the effect of

Table I. *Articles found relevant to BCRL treatment*.

Topic	Author	Year	Type
MLD	Jang *et al*. (81)	2020	Systematic review and meta-analysis
	Olsson Möller *et al*. (27)	2019	Systematic review
	Jeffs *et al*. (32)	2018	Systematic review
	Müller *et al*. (26)	2018	Systematic review
	Smile TD *et al*. (31)	2018	Systematic review
	D'Egidio *et al*. (33)	2017	Systematic review
	Shao *et al*. (28)	2017	Systematic review
Bandage and garments	Olsson Möller *et al*. (27)	2019	Systematic review
	Rogan *et al*. (35)	2016	Systematic review and meta-analysis
Kinesio Taping	Kasawara *et al*. (38)	2018	Meta-analysis
IPC	Rogan *et al*. (35)	2016	Systematic review and meta-analysis
Physical Exercise			
Resistance exercise	Montaño-Rojas *et al*. (49)	2020	Systematic review
	Hasenoehrl *et al*. (50)	2020	Systematic review and meta-analysis
	Hasenoehrl *et al*. (46)	2020	Systematic review
	Nelson (52)	2016	Systematic review
	Keilani *et al*. (47)	2016	Systematic review
Nordic walking	Sánchez-Lastra *et al*. (45)	2019	Systematic review
Resistance exercise, yoga	Olsson Möller *et al*. (27)	2019	Systematic review
Aerobic exercise, resistance exercise, stretching	Panchik *et al*. (43)	2019	Systematic review
	Furmaniak *et al*. (39)	2016	Systematic review
Resistance exercise, aquatic therapy	Baumann *et al*. (42)	2018	Systematic review
	Yeung *et al*. (53)	2018	Systematic review and meta-analysis
Non-specific physical exercise	D'Egidio *et al*. (33)	2017	Systematic review
	Rogan *et al*. (35)	2016	Systematic review and meta-analysis
	Runowicz *et al*. (48)	2016	Guideline
Lymphedema surgery	Markkula *et al*. (61)	2019	Meta-analysis
	Siotos *et al*. (69)	2018	Systematic review
	Smile *et al*. (31)	2018	Systematic review
	Ozturk *et al*. (66)	2016	Systematic review
PBMT or LLLT	Chen *et al*. (70)	2019	Systematic review and meta-analysis
	Olsson Möller *et al*. (27)	2019	Systematic review
	Baxter *et al*. (73)	2017	Systematic review
	Greenlee *et al*. (29)	2017	Review
CAM			
Acupuncture	Liang *et al*. (6)	2020	Systematic review and meta-analysis
	Hou *et al*. (84)	2019	Systematic review and meta-analysis
	Chien *et al*. (87)	2019	Systematic review and meta-analysis
	Zhang *et al*. (82)	2019	Systematic review and meta-analysis
	Kim *et al*. (85)	2018	Systematic review
Yoga practice	Wei *et al*. (95)	2019	Systematic review
	Rogan *et al*. (35)	2016	Systematic review and meta-analysis
Yoga practice, Tai Chi practice	Olsson Möller *et al*. (27)	2019	Systematic review
Yoga practice, Qigong, pilates, *etc*	Panchik *et al*. (43)	2019	Systematic review
Reflexology	Wanchai *et al*. (90)	2020	Systematic review

MLD: Manual lymphatic drainage; IPC: intermittent pneumatic compression; PBMT: photobiomodulation; LLLT: low-level laser therapy; CAM: complementary alternative medicine.

Table II. *Studies not relevant to BCRL treatment*.

Topic	Author	Year	Type
Epidemiology, comorbidities, and impact of BCRL	Torgbenu *et al*. (96)	2020	Systematic review and meta-analysis
	De Vrieze *et al*. (97)	2020	Systematic review
	Co *et al*. (98)	2019	Systematic review
	Visser *et al*. (99)	2019	Systematic review
	Zomkowski *et al*. (100)	2018	Systematic review
	Leysen *et al*. (101)	2017	Systematic review and meta-analysis
Diagnostic studies	Abbaci *et al*. (102)	2019	Systematic review
	Sierla *et al*. (103)	2018	Systematic review
	Burnier *et al*. (104)	2017	Review
	Shah *et al*. (18)	2016	Systematic review
Radiotherapy	Liu *et al*. (105)	2020	Systematic review and meta-analysis
	Kanda *et al*. (106)	2020	Systematic review and meta-analysis
	Sheitelman *et al*. (107)	2017	Systematic review and meta-analysis
Chemotherapy	Hugenholtz-Wamsteker *et al*. (108)	2016	Systematic review
Diagnostic and therapeutic surgical procedures causing lymphedema	Demiri *et al*. (109)	2018	Systematic review
	Parks *et al*. (110)	2017	Systematic review
	Bromham *et al*. (111)	2017	Systematic review
	Gebruers *et al*. (112)	2016	Systematic review
	Han *et al*. (113)	2016	Systematic review and meta-analysis
Safety of hand-surgery following prior breast cancer treatment	Paton *et al*. (114)	2020	Systematic review and meta-analysis
Air travel safety in breast cancer patients	Co *et al*. (115)	2018	Systematic review
	Co *et al*. (116)	2018	Systematic review
Generical physical activity recommendation in people with cancer	Shallwani *et al*. (117)	2019	Systematic review

radiotherapy and chemotherapy on LYE onset, diagnostic and therapeutic surgical procedures causing LYE, the safety of hand surgery following prior breast cancer treatment, air travel safety in breast cancer patients, and generic physical activity recommendation in people with cancer. Papers defined by the authors as of major scientific importance according to the topics covered are outlined in Table III.

Discussion

Breast cancer represents the most common cancer among women, with 65.5 cases per 100,000 women (21, 22). BCRL represents a social plague and a stigma of cancer. Its treatment is, therefore, crucial in the physical and psychological rehabilitation of women to enhance QoL. Nevertheless, no globally accepted guidelines exist regarding BCRL treatment because of the insufficient level of evidence reached by most published papers due to small sample sizes, heterogeneity of patients and treatments provided, and treatment adherence. A brief discussion regarding the state of the art of BCRL is presented below, taking into consideration every kind of therapy discussed and investigated in the last five years' systematic reviews and meta-analyses. Physical, surgical, medical, and complementary therapies used in BCRL treatment are described below.

Physical therapy. Physical therapy includes the four pillars of Complete or Complex Decongestive Therapy (CDT): manual lymphatic drainage, bandaging and garments, physical exercise, and skincare practice. CTD is considered the first line and the most widely accepted treatment for patients affected by BCRL (20). However, CDT is characterized by a complexity of protocols, thus needing long treatment duration and expensive costs that often discourage patients. CDT internationally accepted best

practice includes a first phase characterized by an intensive treatment able to decongest the arm through compression bandaging and manual lymph drainage and a second maintenance phase. The patient becomes the main actor of his treatment by wearing compressive garments (23). The mainstays of CDT are listed and discussed below:

Manual lymphatic drainage (MLD) consists of specialized movements that act as a pump on the skin to improve lymph flow and reabsorption. As a result, it reduces the swelling and fibrosis in the affected limb. MLD may be conducted using the Vodder method (24) or Földi's technique (25). It enhances muscle tissue elasticity and beneficially acts on autonomous nervous system activity, increasing parasympathetic tone.

MLD has a beneficial effect but cannot significantly reduce or prevent the risk of long-term LYE, although the literature is not univocal as regards its efficacy (6, 26) and its effect seems inconclusive as it reduces arm volume but does not improve subjective symptoms and arm function (27, 28). Its failure may be attributed to multiple risk factors and patient's heterogeneity, which may influence outcomes. Nevertheless, some authors advocate its effectiveness in preventing secondary LYE when MLD is applied immediately after breast cancer surgery (29, 30), in early phases of BCRL (31), and even in BCRL-affected patients (32, 33), by reducing arm volume. However, it is not completely clear if MLD should be part of the therapy after breast cancer surgery and seems to be related to the severity of BCRL (27).

Bandaging and garments reduce fluid formation by means of compression producing counterpressure, reducing the subsequent swelling (29, 34). Standard sleeves have inconclusive effects in reducing arm volume compared to compression bandages or fitted sleeves, which showed beneficial volume reduction (27). Indeed, a standard sleeve is configured not as a treatment modality for the intensive phase of BCRL but as a maintenance tool for the leanest volume, reducing the risk for regaining volume or early stage after the onset BCRL (35). However, the standard sleeves may have a role in preventing additional swelling. Outcomes deriving from their use must be checked regularly (27). On the other hand, bandages have a role in the intensive phase, as they stimulate the resorption of the interstitial lymph fluid and have a more influential role in reducing volume compared to standard sleeves (35). However, the pressure generated by these devices should be carefully assessed by professional therapists.

Kinesio taping can be added to complete decongestive therapy because it generates a low pressure on the skin, improving lymphatic flow, by applying elastic tapes to the skin. Mechanoreceptors simulation and the elastic action seem to influence the lymphatic system (36, 37). A recent meta-analysis (38) discussed the role of Kinesio taping role in BCRL. Kinesio taping reduced upper limb volume but, compared to other treatments, no significant difference was evidenced. However, the studies investigated by Kasawara presented a low methodological quality and different forms of Kinesio taping application (38); thus, it does not allow to conclude the role of Kinesio taping in BCRL treatment.

Table III. *Most relevant studies on BCRL treatment according to the Authors' opinion.*

Author	Year	Topic
Jang *et al*. (81)	2020	MLD
Rogan *et al*. (35)	2016	Bandage and garments
Kasawara *et al*. (38)	2018	Kinesio Taping
Rogan *et al*. (35)	2016	IPC
Hasenoehrl *et al*. (50)	2020	Physical Exercise
Markkula *et al*. (61)	2019	Lymphedema surgery
Chen *et al*. (70)	2019	PBMT or LLLT
Liang *et al*. (6)	2020	Acupuncture
Rogan *et al*. (35)	2016	Yoga practice

MLD: Manual lymphatic drainage; IPC: intermittent pneumatic compression; PBMT: photobiomodulation; LLLT: low-level laser therapy.

Intermittent pneumatic compression (IPC) refers to a system composed of an air pump and inflatable auxiliary sleeves or gloves (boots when used for lower limbs) to improve venous and lymphatic circulation. Although IPC effectively reduces BCRL volume in the intensive phase, they cannot be considered a maintenance tool because they only stimulate the drainage in working collectors and do not actually seem to reduce interstitial protein-rich fluid resorption (35).

Physical exercise acts as a muscular pump promoting lymph flow and reducing soft tissue swelling (2). Its effectiveness is also proven in patients receiving adjuvant therapy, as it reduces upper limb volume and diameter and lowers the risk of BCRL (35, 39). Devoogdt *et al*. investigated the effect of exercise with or without MLD association, finding no difference among the groups (40).

One of the most frequent physical exercise obstacles is represented by compliance to programs and the lack of healthcare providers' knowledge regarding training type and prescription.

A systematic metanalysis defined aerobic exercise as "any activity that uses large muscle groups, can be maintained continuously and is rhythmic in nature" (41), like cycling, dancing, hiking, jogging/long-distance running, swimming, and walking. It appeared feasible and safe and did not imply increasing BCRL symptoms or development. Furthermore, it has a beneficial effect in reducing upper limb volume (42), improving upper body strength and endurance, reducing body fat and waist and hip circumference, and increasing muscle mass, associated with psychological and emotional benefits (43).

Nordic walking (NW) defines an aerobic physical activity in which poles support walking; it is low-cost and easy to

perform and, thus, it is a safe, attractive, and interesting physical exercise for patients affected by breast cancer sequelae (44). It has been demonstrated that NW provides positive changes in BCRL symptoms, reduces extracellular fluid, the circumference of the arm, and the LYE absolute and relative volumes (27, 35, 45). Furthermore, NW helps in women's perception of BCRL regarding heaviness and tightness and upper limbs disability. However, the most significant difficulty in using NW in BCRL concerns the lack of knowledge of patients and therapists regarding the ground were to perform the exercise, the intensity, and the exercise duration. These concerns make the current studies of low methodological quality and make it challenging to extrapolate exact data regarding NW protocols. Thus, the importance of qualified instructors' interfaces with the physician and the patient and a learning phase of performing NW before they perform it independently. A recent systematic review concluded that a safe prescription to perform NW in women with BCRL might be three times a week exercise, up to 1 hour per session, the intensity of 70-80% maximum heart rate, and 11-14 of perceived exertion scale (Borg rate) (45). Finally, no evidence exists regarding any adverse effect caused by NW (*e.g.*, falls, commonly described in association with chemotherapy due to toxicity and osteoporosis). Therefore, NW may be considered a safe alternative in BCRL rehabilitation.

Resistance training programs performed on strength-training machines have been investigated with regards to their role in BCRL. In addition to determining an improvement in QoL, psychological, cognitive, and social condition, muscle strength, fatigue, pain, and aerobic capacity, resistance training are considered safe as it do not affect the development or worsening of LYE (33, 42, 46-48), if there is control and progression in training (49), as reported by previous literature (14). Hence, resistance exercise should be considered an additional treatment in cancer patient rehabilitation (48). Several authors depict the resistance exercise as beneficial for BCRL treatment due to its significant reduction (35, 42, 43, 50, 51) and increased upper and lower body muscular strength (27, 42, 52). Standardization of intensity training is difficult due to patient heterogeneity, differences in measurements used and patients' compliance. Few patients report negative effects of resistance exercise. Thus, a resistance training program might be of benefit in BCRL treatment (50).

Aquatic therapy refers to a type of physical exercise that takes advantage of water properties. Aquatic therapy acts as activating muscle pump mechanism and, due to the hydrostatic pressure of water, improves lymphatic circulation. Moreover, it facilitates aerobic exercise, helps muscle strengthening due to the water's natural resistance, and reduces the risk of musculoskeletal injuries while performing the exercise. Furthermore, warm water acts on the imbalance of the autonomous nervous system, increasing parasympathetic activity and decreasing sympathetic tone. A single meta-analysis has been found in literature describing the effect of aquatic therapy in BCRL. However, although no adverse events were reported, no significant benefits of aquatic therapy were evidenced, with no significant difference regarding LYE status and volumetric limb change and physical function of upper limb comparing aquatic therapy to conventional physical exercise and standard care for BCRL. Hence, patients should be addressed to the physical activity to which they can be more compliant (53).

Skincare has a role in preventing infection and subsequent complications (2).

Lymphedema surgery. LYE surgery is an expanding and (relatively) recently introduced tool. It is traditionally considered the last option in BCRL treatment when other measures have failed (54), although early treatment might reduce disease prevention. Indications include inadequate BCRL reduction and patient satisfaction after conservative medical or physical therapy, persistent pain, severely compromised limb function, recurrent lymphangitis, and patient accepting a more invasive treatment as surgery (55). Techniques are distinguished in reductive and reconstructive surgeries:

• Reductive surgery

o Liposuction is a reductive technique and aims at reducing the arm's volume by removing the excess fibrotic and circumferentially hypertrophied fat tissue through a liposuction cannula (56). As conventional liposuction, postoperative treatment needs the use of life-long compressive garments to prevent a recurrence. Liposuction demonstrated efficacy in moderate-to-severe BCRL (31), but it does not improve lymphatic drainage and may be considered a symptomatic treatment. Surgical resection is an alternative.

• Reconstructive surgery

o Lymphaticovenular anastomosis (LVA) is a reconstructive method that aims at bypassing the obstruction to lymphatic outflow by creating a direct connection between the lymphatic vessels in the subcutaneous tissue and the veins upstream to the lymphnodes, to redirect the protein-rich fluid (lymph) to the venous circulation (57, 58). This way, the scarred and lymphnode deprived axylla is bypassed.

o Lymphatic-lymphatic bypass grafts takes advantage of an intact and unaffected lymphatic vessel to bypass the obstructed area (59). Different dyes are used to detect lymphatic vessels before performing anastomosis and anastomosis patency checks, and follow-up may be conducted through lymphoscintigraphy (55). LVA demonstrated efficacy in advanced BCRL but might also be

an effective tool in preventing or slowing down disease progression (31).

o Vascularized lymph node transfer (VLNT) aims at reconstructing the resected lymph nodes and at re-connecting lymphatic channels (60). The donor lymph nodes site is often localized in the groin or abdomen, and the harvested nodes are inset into the armpit to replace the native ones. VLNT surgery seems to interrupt a life-long physical and conventional therapy and demonstrated efficacy in advanced BCRL (31).

A recent meta-analysis (2019) (61) compared the efficacy of surgery for prevention and treatment of BCRL by investigating the tissue volume and distribution, the limb composition, and by evaluating the BCRL status through the use of imaging exams (lymphoscintigraphy, lymphangiography, MRI, US, CT scan) (17, 62) after performing LVA (63, 64) and VLNT (65). Despite reporting low-certainty evidence in the effectiveness of LVA and VLNT respectively in preventing BCRL (63, 64) and treating stage II LYE (65), the meta-analyses showed that surgery provides encouraging results. Regarding LVA, it emerged that this technique determined a reduction in the incidence of BCRL compared to a non-operative treatment up to 24 months after surgery (63, 64). VLNT appeared to be effective in limb volume, pain, heaviness sensation reduction, and function score improvement. Indeed, the VLNT group presented a 57% reduction of mean limb volume than the control group that received the conventional treatment (18% limb volume reduction). Furthermore, pain, heaviness sensation reduction, and function score showed improvement after VLNT (65).

Limitations in the paper by Markkula *et al*. (61), consisted in the fact that none of the included studies discussed long-term complications (cellulitis, lymphangitis, lymphadenitis, skin ulcers, lymphorrea), and only the paper on VLNT by Dionyssiou *et al*. (65) reported a reduction with regards to short-term complication (seroma, lymphorrea, wound dehiscence, wound infection) in the VLNT group. Furthermore, only three studies were considered eligible for the review; thus, all results were based on a total of 131 patients. Hence, the small sample size does not allow to identify patients' subgroups to identify factors that may be predictive of failure or success of surgical therapy. Finally, no other techniques have been included in the review, and no comparison was made between the effectiveness of a surgical procedure against another. Therefore, further studies are required to determine the efficacy of BCRL surgery as regards prevention and treatment. However, LVA and VLNT surgery are potentially able to decide on beneficial effects in BCRL affected patients.

A previous systematic review regarding VLNT surgery investigated 18 studies (309 limbs, of which 191 BCRL of the upper limbs) and showed that 91% had improvement in limb circumference, 86% had improvement in limb volume, and 60% had improvement of flow at lymphoscintigraphy/lymphangiography. No donor site persistent LYE was found (66). Hence, VLNT surgery was demonstrated to be a safe and effective tool for BCRL treatment.

Delayed breast reconstruction with autologous tissues deserves special consideration. Indeed, to date, it is unclear whether autologous reconstruction is useful for treating BCRL. A vascularized pedicled or free healthy tissue may provide relief from BCRL (67, 68), as discussed in the paper by Siotos. However, the benefit provided by the addition of VLNT to delayed breast reconstruction appears more effective than the microsurgical breast reconstruction alone. This finding may be explained by the flap acts' nodal component, which acts as the largest contributing factor in BCRL improvement. Nonetheless, it has been demonstrated that a flap introduced into a LYE affected area serves as a trigger to the formation of new lymphatic vessels (68), because providing roots for lymph outflow. Finally, all the studies reviewed by Sotos agree that delayed breast reconstruction does not have a role in worsening BCRL (69).

Photobiomodulation therapy. Only a meta-analysis is available as regards photobiomodulation therapy (PBMT) (70). PBMT is a light therapy (wavelength 650-1000 nm), and it is a type of phototherapy deemed capable of improving lymphatic drainage, stimulating lymphangiogenesis, reducing inflammation and related pain (71), improving the wound healing process (72), and finally softening fibrotic tissue (thus its employ in the modulation of scarring process and improving lymphatic flow) (29). A previous systematic review recommended a dose of 1-2 J/cm^2 per point to treat the fibrotic area and volume reduction effectiveness (27). Other authors compared PBMT to sham laser for limb volume and circumference reduction, pain relief and found a more effective action of the first (73). The most recent meta-analysis (70) included nine RCTs that investigated the effects of PBMT on BCRL, but the conflicting results did not allow to clarify the effectiveness of PBMT. Indeed, no statistically significant difference was found in arm circumference, arm volume, grip strength, and pain related to BCRL between the patients who received PBMT and the control groups receiving other treatments. Furthermore, the previous studies' sample size was limited; thus, no significant effect of PBMT in the management of BCRL was found, and no consensus has been reached yet on the PBMT effect.

Medical pharmacological therapy. Medical pharmacological therapy is mostly represented by drug class benzopyrones, which bind to interstitial proteins, thus inducing phagocytosis and proteolysis. Once being fragmented, they can quickly be reabsorbed by venous capillaries. They may

have a role in reducing interstitial edema, softening the limb affected by BCRL, and reducing infection (74, 75). However, they are characterized by hepatotoxicity, and they do not represent the first-line treatment of BCRL. No recent systematic reviews or metanalyses have been found regarding their use in BCRL treatment.

Not enough evidence exists to form a clinical recommendation (29) on therapies such as Cyclo 3® Fort (Cyclo 3® Fort, Pierre Fabre Medicament Laboratories, Boulogne-Billancourt, France), which is a combination of root extract of the *Ruscus aculeatus* plant, hesperidin methyl chalcone and ascorbic acid (76), electrotherapy (77), *Ginkgo biloba* (78), pentoxifylline and vitamin E (79).

Complementary medicine. Acupuncture is part of the traditional Chinese medicine, is based on the regulation of energy pathways and circulation through stimulation of specific points on the body surface, as evidenced by neurophysiological investigations, and has been shown effective and safe in a variety of conditions and treatment-related side effects (80). Acupuncture treatments may also include bloodletting, puncturing and cupping, moxibustion, laser needle and electric stimulation. As results from our review, some studies reported that acupuncture provided a significant decrease in reducing arm circumference when compared to physical exercise (6, 81-83), but the same conclusion was not found by other authors (84-86). However, it has been reported that acupuncture intervention is safe and tends to improve the efficacy of other BCRL treatments (84, 87), compared to the single physical exercise or conventional medicine alone (84).

One of the most critical issues in evaluating the effectiveness of acupuncture is the difference in the technique used that is not always described in these studies and the heterogeneity in assessing the patient's LYE. Indeed, different LYE measurement tools have been used, including the circumference at the height of the elbow or above it, the rim of the most bulging point, the sum of more circumferences calculated at the level of the upper limb, or through the bioimpedance spectrometry measurement. This heterogeneity makes the studies difficult to compare and, therefore, difficult to assess the overall effectiveness of acupuncture treatment. Furthermore, the absence of hidden grouping and blinding method and the reduced sample size produce multiple biases, leading to insufficient evidence of the effectiveness of the acupuncture role in BCRL treatment. Finally, most of the patients who received acupuncture treatment were Asian; thus, no studies represent different ethnic groups (82, 85).

Reflexology bases are, to date, not clarified yet. However, theories rely on the direct pressure on a peripheral nerve of the foot in stimulating a corresponding area of the body, providing relief to a specific symptom (88). Reflexology is also based on oxytocin's release, improving the circulation through pressure and the input to the central nervous system that perceives the symptoms (89). Regarding BCRL, reflexology has not enough high-level evidence supporting beneficial or detrimental effects on BCRL, despite no adverse effects reported after reflexology intervention. Reflexology seems to improve quality of life acting on fatigue, nausea, and vomiting, but no substantial evidence is available as regards effects on BCRL because of limited numbers and quality of studies (90).

Yoga practice is considered part of the complementary therapies, but also of physical exercise. It is based on meditation, relaxation, breathing, stretching, and posture control exercises to improve muscles and joints status and range of motion. Yoga interventions may help in reducing pain, swelling, limb volume, and tissue fibrosis (27, 35, 91-94). The study by Wei *et al*. (95) described the effect of different yoga programs, including meditation, warm-up, breathing, exercises, and cooldown, practiced from once to twice a week, with an exercise duration of 60 minutes, for a variable duration from 4 weeks to 6 months of yoga practice. This revision aimed to evaluate if yoga and conventional treatments improved BCRL condition. The measured outcomes were the upper extremity volume, upper limb and grip strength, range of motion, and QoL. Results on BCRL status varied between the studies: some reported that 8-week yoga practice improved LYE and spine mobility but did not report QoL changes; others did not find any change or no significant outcome of the 6-month procedure. Concerns emerging from this investigation are the vast heterogeneity of practice (some studies did not report how the yoga practice was conducted) that make the studies incomparable and not conclusive. It can't be clearly demonstrated that a yoga intervention may provide significant benefits when added to usual treatment. However, developing a standard yoga protocol may reveal that yoga practice, with 1-2 times a week class session and remaining days with home practice, with 60-minute sessions, and extended up to 8 weeks, could lead to a significant improvement of BCRL, reducing swelling, disability and improving joints and muscles status and function and related range of motion, with a final positive impact on QoL. Panchik *et al*. described the effect of yoga and other physical exercise practice, claiming a decreased swelling and reduction of BCRL related symptoms (43). However, non-traditional forms of exercise should be further investigated to assess their role in BCRL treatment properly.

Alongside yoga practice, Tai Chi intervention had a beneficial effect on emotional wellbeing and upper limb mobility as well, but the investigated studies presented low methodological quality; thus, careful interpretation of these results is mandatory (27).

Limitations

Almost all conclusions from the studies discussed above should be cautiously taken into account because of the

insufficient quality of most published papers on BCRL treatment. Indeed, only bandages and IPC showed a substantial beneficial effect in reducing LYE volume in the acute-intensive phase. At the same time, MLD demonstrated effectiveness when immediately applied after breast surgery or in the early stage of BCRL, but not in overt BCRL.

Despite being burdened by difficult compliance to the treatment, physical exercise remains a milestone in BCRL regarding almost all its modalities (aerobic exercise, resistance exercise, aquatic therapy), reduced upper limb volume, improved upper body strength, and does not affect the development or worsening of LYE. Kinesio taping, PBMT, pharmacological therapy and complementary procedures do not show conclusive effectiveness in BCRL treatment, but patients often seek complementary medicine for symptom relief as other therapies are not beneficial. Finally, surgery is considered the last resort. It may be a symptom treatment (liposuction, reducing volume but not improving the drainage), preventing treatment (LVA, reducing BCRL incidence, improving drainage, useful in BCRL early phase), and curative treatment (VLNT, reducing volume, improving drainage, useful in overt BCRL). At present, no comparison has been made between the effectiveness of a surgical technique against another. Skincare practice is pivotal to prevent infection in association with all concurrent treatments.

This review has certain limitations since the literature search did not include articles before 2016, although many of these and certainly the most important were discussed in the papers examined. Furthermore, the review does not meet the PRISMA criteria for systematic review and included no statistical evaluation because of the impossibility of comparing all the articles discussing substantially different topics. the review is intended as narrative and aims to be an introductory guide for those new to the treatment of BCRL of the upper limb.

Conclusion

In conclusion, BCRL is still to be considered a challenging issue for breast cancer survivors, and there is not a gold-standard treatment. Furthermore, the lack of clinically globally accepted criteria in evaluating BCRL makes it challenging to evaluate BCRL treatment's effectiveness. As stated by the American Cancer Society and the American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline (48): "It is recommended that primary care clinicians should counsel survivors on how to prevent/reduce the risk of LYE, including weight loss for those who are overweight or obese and should refer patients with clinical symptoms or swelling suggestive of LYE to a therapist knowledgeable about the diagnosis and treatment of LYE, such as a physical therapist, occupational therapist, or LYE specialist." Knowledge about different treatment options deserves diffusion and the role of medical, physical and surgical treatments always considered to improve QoL of breast cancer survivors.

Conflicts of Interest

All Authors declare that they have no conflicts of interest.

Authors' Contributions

Study concept and design: PM and SD. Acquisition, analysis, and interpretation of data: PM, SD, SM, VG. Drafting of the manuscript: PM, SD, DP, SM, VG. Critical revision of the manuscript: all authors. All Authors read and approved the final manuscript.

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