Laustsen-Kiel *et al. Plast Aesthet Res* 2024;11:17
DOI: 10.20517/2347-9264.2024.32

Plastic and Aesthetic Research

Review

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Breast reconstruction and breast cancer-related lymphedema: insights and perspectives

Cecilie Mullerup Laustsen-Kiel[1,2], Laura Hansen[1], Elisabeth Lauritzen[1], Tine Engberg Damsgaard[3]

[1]Department of Plastic Surgery and Burns Treatment, Copenhagen University Hospital, Copenhagen 2100, Denmark.
[2]Department of Plastic and Breast Surgery, Roskilde, Zealand University Hospital, Roskilde 4000, Denmark.
[3]Department of Plastic and Reconstructive Surgery, Odense and Vejle Hospital, University of Southern Denmark, Vejle 7100, Denmark.

Correspondence to: Cecilie Mullerup Laustsen-Kiel, MD. Department of Plastic Surgery and Burns Treatment, Copenhagen University Hospital, Copenhagen East, Inge Lehmannsvej 8, Copenhagen 2100, Denmark. E-mail: Cecilie.mullerup.laustsen-kiel@regionh.dk

How to cite this article: Laustsen-Kiel CM, Hansen L, Lauritzen E, Damsgaard TE. Breast reconstruction and breast cancer-related lymphedema: insights and perspectives. *Plast Aesthet Res* 2024;11:17. https://dx.doi.org/10.20517/2347-9264.2024.32

Received: 1 Mar 2024 **First Decision:** 10 Apr 2024 **Revised:** 24 Apr 2024 **Accepted:** 14 May 2024 **Published:** 28 May 2024

Academic Editor: Roberto Cuomo **Copy Editor:** Yanbing Bai **Production Editor:** Yanbing Bai

Abstract

An estimated 500,000 women were diagnosed with the debilitating breast cancer-related lymphedema (BCRL) in 2022. Lymphedema is not just fluid, but a complex disease characterized by low-grade inflammation, fat deposition, and fluid accumulation, severely affecting patients' quality of life (QoL). The impact of surgical and adjuvant breast cancer treatment on BCRL has been investigated, and treatments have been modified to maintain a high cancer-free survival while addressing the late effects. In addition, the demand for breast reconstruction has increased in the last two decades, leaving a gap in the understanding of the association between BCRL and breast reconstruction. Early detection and treatment of BCRL is crucial in preventing advancement into an impairing chronic stage, making reliable diagnostic modalities necessary. This review is an updated overview of the various diagnostic tools and the established and evolving treatment approaches for BCRL, providing insight into the research findings published since 2017 on breast reconstruction and BCRL through a systematic literature search. Based on the reviewed literature, the authors could not conclude any sure causality between BCRL and breast reconstruction. Studies suggest that breast reconstruction contributes to lower BCRL rates, but prospective observational studies are recommended for future research.

Keywords: Breast reconstruction, breast cancer-related lymphedema, late morbidity, cancer survivor

INTRODUCTION

Nearly 2.3 million women were diagnosed with breast cancer in 2022[1]. As mortality rates have decreased[2,3], a growing number of women suffer from the long-term effects of breast cancer and its treatment. As an oncologist, plastic-, or breast surgeon treating women diagnosed with breast cancer, it is crucial to understand the relationship between cancer treatment, patient-related outcomes, and pertinent strategies to prevent or treat long-term effects, such as BCRL. This narrative review aims to provide insight into BCRL following breast reconstruction, addressing current knowledge about the association between breast reconstruction and BCRL. The scope is perspectives on the pathophysiological and clinical implications of BCRL, including a discussion on how oncologic breast surgery and adjuvant treatment impact the risk of developing BCRL. The review also highlights advancements in diagnostics and treatment over the last decade. Literature was systematically searched from EMBASE, Pubmed, Cochrane, and BASE databases from January 2017 to December 2023 for breast reconstruction and BCRL articles. Since no international checklist is published for narrative reviews, we adhered to the Scale for the Assessment of Narrative Review Articles (SANRA)[4].

BREAST CANCER-RELATED LYMPHEDEMA

Secondary lymphedema may arise from surgical procedures, radiation, trauma, or infection. Nevertheless, the predominant cause is breast cancer[5]. The incidence of BCRL exhibits considerable variability throughout the literature[6-9]. The most recent systematic review reports an incidence of 21.9%[10]. Thus, approximately half a million women diagnosed with breast cancer in 2022 may potentially be diagnosed with lymphedema during their lifetime.

PATHOPHYSIOLOGY

Lymphedema is characterized by the accumulation of protein-rich fluid, resulting in swelling of the affected body part. The lymphatic vessels return around 2-4 L of fluid to the venous system daily[11]. An imbalance occurs when the lymphatic load exceeds the transport capacity, resulting in lymphedema. However, the pathophysiology of lymphedema is more complex than excess fluid in the interstitial space.

The collecting lymphatic vessels are located in the subcutaneous adipose layer. Thus, lymph fluid accumulates between adipocytes, resulting in adipose hyperplasia or hypertrophia[12]. The exact pathway from increased lymph fluid to hyperplasia or hypertrophia of adipocytes is not fully understood[13], and consensus on whether adipocytes increase in size due to lymphedema is absent[13-15]. Nevertheless, lymphedema leads to the deposition of adipose tissue[16].

Non-linear lymphatic anatomy and early disturbance in lymphatic transport are risk factors for the development of BCRL[17,18]. The role of growth factors, such as vascular endothelial growth factor (VEGF)-C, has been debated[19,20], and treatment with VEGF-C adenovirus was applied in a randomized clinical trial, with ambiguous results[12,21]. The deposition and remodeling of adipose tissue in lymphedema patients may contribute to increased low-grade local inflammation due to the secretion of pro-inflammatory cytokines[22,23]. This chronic inflammation, in which $CD4^+$ cells play a crucial role[21,24,25], has been demonstrated to facilitate fibrosis during the progression to more advanced stages of lymphedema. Pathohistological studies have identified hyperplasia of collagen fibers and smooth muscle cells, causing thickening of the lymphatic vessels. This contributes to the hardening of the lymphatics, compromising their peristaltic ability and[26-28], lastly, exacerbating the accumulation of lymph. In summary, the pathophysiology of lymphedema results from an inappropriate circle of stasis, causing an imbalance in the interstitial fluids, lymphatic vessel remodeling and function, and adipose tissue deposition.

CLINICAL AND PSYCHOLOGICAL IMPLICATIONS OF BREAST CANCER-RELATED

LYMPHEDEMA

Symptoms of arm lymphedema may manifest as swelling, stiffness, pain, heaviness, and restricted movement[29,30]. When examining chronic pain after breast cancer, BCRL was found to be the highest risk factor for developing chronic pain[31,32]. A recently published study on breast reconstruction and upper-extremity function found patients who developed lymphedema to be approximately four times more likely to report high scores on the disabilities of the arm, shoulder, and hand (DASH) questionnaire, signifying upper extremity dysfunction that affect the activity of daily living (ADL)[33]. A systematic review of QoL showed that breast reconstruction improves QoL after mastectomy[34]. However, another study found that BCRL possibly negates the positive effect of breast reconstruction[35].

Psychological stress after breast cancer is reported with a range between 22% and 50% in the literature[36,37]. In a recent German study, 67.3% of patients reported high stress levels, associating BCRL with increased distress[38]. In addition, a matched cohort study from 2023 confirmed that patients with BCRL exhibited lower levels of psychosocial well-being[39]. Consequently, BCRL and upper limb morbidity emerge as the primary complications that negatively impact work activity with increased sick leave days and, lastly, increased socioeconomic burden[40-44].

DIAGNOSTIC MODALITIES

Lymphedema may manifest several years after breast cancer surgery. A study published in 2017 found that 13.5% presented with lymphedema at their two-year follow-up[45], which increased to 41.1% when patients were examined after ten years[45]. A recent cross-sectional study found the median time from breast cancer diagnosis to lymphedema to be four years[46], suggesting both a potential delay in diagnosis and an evolution in limb physiology.

Various diagnostic criteria are present in the literature, encompassing highly advanced technologies, such as 3D live images of lymph flow with SPECT-CT lymphoscintigraphy[47,48], to simple methods, such as circumference measurements and patient-reported outcome measures [Table 1][49-72]. Reliable and valid assessment tools for BCRL are imperative for diagnosing, monitoring, and comparing treatment responses[73]. Lymphoscintigraphy has replaced water displacement as the gold standard, and indocyanine green angiography (ICG-A) is likely the next modality[74]. While the presence of dermal backflow in lymphoscintigraphy is accepted as one of the diagnostic criteria for lymphedema, newer imaging techniques have yet to establish their clear diagnostic criteria for lymphedema. However, a 10% difference between the ipsilateral arm, forearm, or both compared to the contralateral side or baseline measurements is often used as a cut-off value. Notably, the validity of lymphedema diagnosis without baseline measurements is questionable, as studies have shown a significant variation in volume between the two arms at baseline[75,76]. In conclusion, a missing baseline measurement can lead to misdiagnosis in around 40% of patients[75], making baseline measurements imperative in clinical and academic settings to minimize the risk of under or over-diagnosing lymphedema.

Multiple staging systems for lymphedema exist, with the International Society of Lymphedema (ISL) staging system being the most widely used [Table 2][12,76-78].

ONCOLOGIC BREAST SURGERY - SURGICAL INTERVENTION FOR THE TREATMENT OF BREAST CANCER

Oncologic breast surgery has evolved significantly since Halsted's initial introduction of the radical mastectomy in 1882[79]. Breast-conserving surgery (BCS) is widely used instead of mastectomy for early

Table 1. Diagnostic methods of arm lymphedema in recent literature

Diagnostic method	Description	Advantages	Limitations
Water displacement	Immersion of whole limb in water, measuring the volume of water displaced by the submerged limb	Sensitive and specific High interclass correlation	Messy and difficult Inability to localize to specific limb segments It cannot be used if there are open wounds
Tape circumferential measurement	Measurement of limb circumference, often multiple places along the arm	Inexpensive In-home application is possible Easy	High intra- and inter-rater variability Volume calculation assumes a circular arm form, which is seldom the case
Perometry	Infrared light measures limb volume and collects two-dimensional information from each arm	Hygienic Creates a 3D image of the limb, enabling localization of swelling Can detect a 3% volume change Useful for bilateral lymphedema	Requires specialized equipment Cost Can only measure limb edema (e.g., Not breast edema)
Bioimpedance spectroscopy (BIS)	Uses electrical current to scan the upper extremities, measuring resistance	Requires minimal training Rapid Accurate Quantitative assessment	Equipment availability Requires trained personnel Not applicable for bilateral lymphedema Limitations in advanced lymphedema due to fat-dominant composition
Dual-energy X-ray absorptiometry (DEXA)	Measures chemical limb composition	Quantitative assessment Distinguishes fat and fluid	Radiation exposure Limited availability
Lymphoscintigraphy	Radioactive tracer imaging of the lymphatic system	Visualizes lymphatic flow and lymph nodes Identifies lymphatic damage	Invasive Radiation exposure Limited availability
Magnetic resonance imaging	Uses magnetic fields and radio waves	Excellent soft tissue contrast Detailed anatomical images of fat, muscle and water Can be used as MR lymphangiography Can detect changes in edema much earlier than most other modalities	Expensive Limited availability MR cannot resolve smaller lymphatic channels due to limitations in resolution
Indocyanine green (ICG)	Intradermal injection of fluorescent ICG visualizes lymphatic vessels with a near-infrared camera (NIR)	Real-time imaging Assesses lymphatic function No radiation Visualizes dermal backflow	Limited penetration depth of 1.5 cm Operator-dependent With NIR: Depth visualization of 3-4 cm
Photoacoustic imaging	Light energy generates ultrasound waves, which a transducer depicts as an image	Real time Portable	Needs imaging contrast, such as ICG or Evans blue, to view lymphatics
Computed tomography (CT)	X-ray technology for cross-sectional images	Detailed images 3-D representation Evaluates anatomical structures	Radiation exposure Limited sensitivity for lymphedema
Three-dimensional laser scanner	Laser-based scanning for surface measurements	Precise surface mapping Higher intra-rater reliability compared to water displacement	Limited to surface measurements May not assess deep tissues High cost of the device Time-consuming
Ultrasound	High-frequency sound waves for imaging and blood flow	Can measure texture and characterize edema Few limitations to depth perception Easy to transport	Operator dependence Limited depth perception for ultra-high frequency (rarely used)
Tissue dielectric constant (TDC)	300 MHz is emitted into the tissue, and a wave is returned with information on local water content	Provides a better understanding of arm spatial variability in relation to girth measures Convenient Non-invasive	Interpretation of values may depend on location and total body water percentage

breast cancer. A meta-analysis including 25 studies[80] concluded that BCS is superior to mastectomy for early breast cancer. Still, mastectomy is the surgical choice for many patients, especially in low and middle-income countries, where access to adjuvant therapy is limited[81,82]. Conversely, western countries are

Table 2. Staging of lymphedema according to ISL

	Clinical presentation	Pathophysiology
Stage 0 Latent or subclinical	No visible sign of swelling Subjective symptoms might be present	Lymphatic insufficiency/impaired lymph transport Subtle changes in fluid composition
Stage 1 Spontaneously reversible	Pitting may occur Possibly hyperkeratosis	Early accumulation of fluid High in protein ICG shows dilated lymphatics with irregular pulsation Dermal backflow
Stage 2 Spontaneously irreversible	Pitting is still present, but the arm is firmer than in stage 1	Increased fibrosis and tissue changes, including accumulation of adipocytes
Stage 3 Lymphostatic elephantiasis	No pitting Skin changes: thickening and hyperkeratosis Possible warty overgrowths	Irreversible swelling with significant tissue fibrosis Chronic inflammation ICG will often show diffuse accumulation of dye in the skin

increasingly aiming to avoid breast deformities and achieve contralateral symmetry by applying oncoplastic surgery with volume displacement or replacement techniques.

LYMPH NODE DISSECTION

Assessment of the lymph nodes is a crucial part of breast cancer treatment. The risk of developing lymphedema and other arm morbidities is highly dependent on the extent of the axillary surgery, as demonstrated by a recent study analyzing the risk of BCRL[83]. Studies indicate that women undergoing axillary lymph node dissection (ALND) - both with and without adjuvant radiotherapy - have a significantly higher incidence of lymphedema compared to patients undergoing sentinel lymph node biopsy (SLNB) under the same conditions[10,70,83-86]. However, BCRL is still reported after SLNB with postmastectomy radiation therapy (PMRT)[87] and increasing BMI as reported risk factors[83].

RADIOTHERAPY

PMRT and lymphedema have been extensively examined, with multiple trials assessing the difference in toxicity of different radiation schedules[88-94]. A review and meta-analysis from 2020 showed that while PMRT serves its purpose of decreasing local and regional recurrence of breast cancer, it also plays a key role in the development of lymphedema[95].

The impact of radiation on breast reconstruction was recently investigated; a meta-analysis found immediate autologous free flap reconstruction to be associated with superior flap survival compared to delayed autologous reconstruction, indicating that autologous immediate breast reconstruction (IBR) is safe even when PMRT is planned[96]. However, a large cohort study from 2020 found PMRT to increase the 5-year cumulative complication rate for both autologous, two-stage implant-based, and direct-to-implant reconstruction types[97]. The outcome of a direct-to-implant breast reconstruction relies on the mastectomy skin flap viability, and even though modalities - such as ICG-A - lowered the rate of mastectomy skin necrosis[98], the intraoperative decision to deter from one-stage implantation to an expander could potentially bias the complication outcome. Ultimately, the decision on the type of reconstruction should not solely rely on a single factor, such as PMRT.

BREAST RECONSTRUCTION

Breast reconstruction surgery has become a significant part of the breast cancer pathway, with the primary aim of breast reconstruction to improve QoL and breast-related satisfaction for the patient. Increased information, a rise in risk-reducing mastectomies[99], changes in legislation in some countries, such as the United States[100], and the suggestion that breast reconstruction increases health-related QoL outcomes after mastectomy[34], all contribute to the explanation behind the worldwide increase in demand for breast reconstruction during the last two decades[101-103]. The number of patients opting for reconstruction has generally risen but varies between countries, with rates of approximately 18% in Australia[104], 30% in Sweden[105], 40% in Denmark[106], and 50% in South Korea[103].

TIMING OF THE RECONSTRUCTION

Several studies have investigated the timing of breast reconstruction and found IBR to be preferable when looking at the psychosocial impact, as well as the socioeconomic cost of breast reconstruction[107-112]. Considering the rate of complications, IBR has been associated with significantly higher complication rates than delayed procedures[113]. Nevertheless, Saheb-Al Zamani *et al.* could only confirm the higher complication rate for implant-based but not autologous reconstructions[114], and other studies found no significant difference in flap loss between IBR and delayed breast reconstruction (DBR)[115,116]. The latest meta-analysis concluded that IBR generally increases the risk of complication, but additional prospective and observational studies are needed to assess if one reconstructive technique is superior to another[117]. QoL has increasingly been examined as an outcome in studies assessing the difference between IBR and DBR, and no difference in postoperative QoL between IBR and DBR was found[118,119].

AUTOLOGOUS AND IMPLANT-BASED BREAST RECONSTRUCTION

Autologous reconstruction was found to improve upper extremity outcomes in patients undergoing breast reconstruction[33]. Dauplat *et al.* found latissimus dorsi (LD) flaps to have the lowest risk of major complication compared to implant alone, LD flap with implant, or the transverse rectus abdominus myocutaneous (TRAM) flap[31]. There are multiple options for reconstruction. However, the right choice of reconstruction method depends on several factors, including donor-site availability, medical history, previous oncologic treatment, and most importantly, the patient's preferences. Reports have shown that implant-based reconstruction is the more commonly used technique[120,121].

One of the more dreaded complications in free flap breast reconstruction is venous congestion. Therefore, additional venous drainage using the cephalic vein is sometimes incorporated into the flap. It is currently unclear if this increases the risk of ipsilateral lymphedema, although Svee *et al.* did not find an increased risk[122]. In this relation, it is, however, relevant to note that their sample size was small and that another group found lymphedema to develop or worsen when using the cephalic vein[123].

BREAST CANCER-RELATED LYMPHEDEMA AND BREAST RECONSTRUCTION

The most recent systematic review on the impact of breast reconstruction on BCRL from 2017 concluded that breast reconstruction was associated with lower rates of lymphedema[124]. However, due to high heterogenicity in the included studies, further prospective studies were deemed necessary to identify the mechanism by which breast reconstruction contributes to reduced rates of lymphedema.

In our systematic literature search, 23 studies, including a total of 85,584 patients, were published since the review by Siotos *et al.* on BCRL and breast reconstruction[124]. In various studies, the incidence of lymphedema was found to be lower in cases with breast reconstruction compared to mastectomy alone[125-134], while other studies did not specify the incidence of lymphedema for breast reconstruction[31,122,135-139], type of reconstruction[128,129,140], or BCRL incidence at all[31]. Figure 1 presents an overview of the incidence reported for BCRL in the different studies, where possible, by reconstruction type. Further aspects emerged from the studies:

	No breast reconstruction		Breast reconstruction			
	Mastectomy	Breast-conserving surgery	Immediate implant-based	Immediate autologous	Delayed implant-based	Delayed autologous
Alba et al.[142]			65.6 %	34.4 % (DIEP)		
Almailabi et al.[125]	7.85 %		5 %		7.89 %	
Asdourian et al.[140]	13 %		13 %			
Byun et al.[133]	↑		↓ §			
Clegg et al.[128]	8.4 %		↓ (OR 0.43) §			
Clegg et al.[128]	8.4 %		↓ (OR 0.54)		↓ (OR 0.54)	
Humar et al.[33]			↑	↓ §	↑	↓ §
Jeon et al.[126]	12.2 %		9.6 % §			
Lauritzen et al.[134]						↓
Lee et al.[130]			10.9 %	3.7 % (LD) §		
Lee et al.[130]			10.9 %	10.6 % (DIEP) ‡		
Park et al.[129]	6.67 %	9.09 %	3.65 %			
Polat et al.[70]	33.3 %	20.5 %	60 %			
Slavin et al. †[131]	↑			↓ (DIEP + LD) §		
Slavin et al. †[131]				↑ (DIEP)		↓ (DIEP) §
Taghioff et al. †[127]	↑		↓ §			
Taghioff et al. †[127]					↓ §	↑
Zhang et al.[132]	10.8 %	6.8 %				

Figure 1. Incidence of BCRL in included studies from 2017-2024 reporting incidence of BCRL for breast reconstruction. § Significantly reduced (↓) incidence of BCRL compared to other selected groups with a higher incidence of BCRL (↑); ‡ Significantly reduced incidence of BCRL for patients who had ALND and chemotherapy; † Full text not available. Data are based on the abstract. BCRL: breast cancer-related lymphedema; ALND: axillary lymph node dissection; LD: latissimus dorsi; DIEP: deep inferior epigastric perforator; OR: Odds Ratio.

Two recent large cohort studies published only as abstracts have found that delayed breast reconstruction (DBR) is significantly associated with reduced BCRL within ten years[127,131]. Both cohorts were extracted from the same 85,776,922 de-identified patient records. In one cohort, 60,157 patients met the inclusion criteria; in the other cohort, only 24,136 patients did. As the smaller of the two cohort studies analyzed both implant *vs.* autologous and delayed *vs.* immediate breast reconstruction, while the larger study analyzed only autologous flaps, we question the inclusion criteria for the two studies. A recent prospective study of delayed and immediate autologous reconstruction found that out of the seven patients with pre-reconstruction lymphedema[134], three patients experienced an improvement that could also be measured, and one patient felt the lymphedema worsened.

A 2021 study investigating arm volume increase also explored the difference between lumpectomy, mastectomy, and IBR on lymphedema and found a lower BCRL incidence for the IBR group compared to the mastectomy and lumpectomy group[129]. Follow-up was limited to one year, and it would be interesting to study how many patients in the low-volume group will develop clinical lymphedema and assess if this impacts the relative incidence of surgery type. The study was one of the few with baseline measurements of lymphedema, as only six out of 23 studies reported baseline measurements[70,122,134,140,141]. All six studies were prospective cohort studies with smaller cohort numbers compared to the three largest retrospective cohorts that included 24,136[127], 60,157[131], and 5,497[126] patients, respectively. The largest of the prospective studies was performed by a research group from Massachusetts General Hospital and included 327 patients with a total of 578 reconstructed breasts[140]. Here, the researchers did not find any significant impact of breast reconstruction on BCRL.

In a more recently published cross-sectional study, the average follow-up of 38 months was surpassed[135], with a mean long-term follow-up of 10.5 years. Laws *et al.* examined the disparities between implant-based and autologous IBR in their analysis, stratifying the results based on axillary intervention and PMRT.

However, the study did not specify the arm symptoms present in the different groups, precluding an opportunity to report the incidence of BCRL.

Two studies reported a relatively high incidence of BCRL for patients treated with breast reconstruction compared to other studies[70,142]. However, the study with the highest BCRL incidence after breast reconstruction only included five patients with breast reconstruction and concluded there was no significant difference in the effect of surgery type on BCRL[70]. The other study included 72 patients but did not describe how or when they measured lymphedema[142] - only that the diagnosis was based on physical examination[142]. Unfortunately, this lack of description of measurement methods or diagnostic criteria was observed for some of the studies[131,138]. Diagnostic methods used in other studies were circumference[126,136,143], bioimpedance spectroscopy (BIS)[70,134,141], and perometry[129,140]. Several studies also included patient symptoms in evaluating whether lymphedema was present [128,132,135].

A study from 2017 investigated the effect of IBR on lymphedema and further elaborated on the difference between implant-based and autologous IBRs[144]. Here, the researchers found a statistically lower rate of BCRL for immediate DIEP and LD flaps compared to patients receiving implant-based breast reconstruction despite a higher rate of ALND in the LD flap group. Women in the autologous group had a higher BMI, had more radiotherapy preoperatively, and were older, which all are demographic factors associated with an increased risk of BCRL. When correlating to ALND, the researchers found that autologous breast reconstruction significantly reduced BCRL for patients who had ALND and received chemotherapy. Only one study reported the effect of oncoplastic surgery, where no arm lymphedema was found[141].

EVOLVING TREATMENT APPROACHES FOR LYMPHEDEMA

Early detection and management of lymphedema, clinical as well as subclinical, at an early stage, is imperative in preventing its advancement to a chronic stage. However, this narrative review has unveiled the disparity among criteria used to diagnose lymphedema, leading to delayed detection and subsequent treatment initiation. Clinicians lack superior treatment options considering patient preferences, resources, and clinical settings. The following subsections address the currently available treatment modalities and emerging treatment strategies.

Decongestive techniques

Treatment of subclinical lymphedema with compression garments, as seen in Figure 2, was shown to be effective[145]. Compression garments are often combined with manual lymphatic drainage (MLD), therapeutic exercise, moisturizing skincare, and patient education; This combination of five modalities is referred to as complex decongestive physical therapy[146]. Several randomized trials and systematic reviews with meta-analyses found that manual lymphatic drainage, a compression pump, or exercise do not lead to volume reduction[147-150]. Conversely, several systematic reviews with meta-analyses present significant volumetric changes due to MLD[151,152], complex physical/decongestive therapy (CDT)[153], compression pump[154], and laser therapy[155]. In addition, a systematic Cochrane review found MLD to be safe and beneficial to compression bandaging for volume reduction in patients with mild-to-moderate BCRL[156].

Rafn *et al.* presented a statistically significant effect in volume reduction across all interventions (MLD, compression pump, exercise, kinesio taping, laser, and acupuncture) compared to any control. Notably, most of the systematic reviews had chosen volumetric changes as their primary outcome and not the most frequently reported arm symptom associated with BCRL, namely pain. However, no systematic reviews and meta-analyses found an effect of either MLD[153,157], laser therapy[152,155,157,158], CDT[153], kinesio taping[159], or

Figure 2. Treatment of subclinical lymphedema with compression garments.

water-based exercise on pain or discomfort[146,160]. In conclusion, no clear advantage was seen for any treatment methods, regardless of whether the comparison was made with active or non-active control conditions.

Surgical treatment modalities and emerging therapies and research

Complete decongestive therapy has for many years been the primary treatment[161]; however, microsurgical techniques were implemented in the treatment of lymphedema in the seventies, where lymphatic venous anastomosis (LVA) was first used to treat postoperative lymphedema[162]. Since then, multiple studies on LVA have been undertaken[163-165]. A smaller study involving ten patients undergoing LVA from 2008 showed minimal reduction in lymphedema volume and only minimal improvement in QoL[166]. However, a case series of 20 patients by Chang *et al.* showed a reduction in lymphedema volume of 35% and a 95% improvement in lymphedema symptoms after one year[167]. A larger study involving 169 BCRL patients undergoing autologous lymph vessel transplantation from the ventromedial lymphatic bundle at the patient's thigh to the upper limb found that microsurgical technique significantly and persistently improved lymph drainage in patients with lymphedema[168]. Recently, a systematic review found 102 studies investigating LVA, concluding that LVA can reduce the severity of secondary lymphedema[169]; however, standardization of reporting is needed to allow further comparability between methods and studies. LVA has recently emerged as a preventive therapy, where axillary reverse lymphatic mapping and immediate lymphaticovenous bypass are increasingly used in the operating room worldwide[170]. Several studies report a lower prevalence of BCRL in cohorts where lymphaticovenous bypasses were performed as a preventive approach[171-177]. Nevertheless, not all studies confirmed the long-term effects of the Lymphatic Microsurgical Preventive Healing Approach (LYMPHA) on BCRL[178].

Another surgical technique is the vascularized lymph node transfer (VLNT) from other areas in the body. Inguinal lymph node transfer was first shown to reduce lymphedema of the leg in 1982[179], and later, Becker *et al.* reported a decrease in lymphedema after inguinal lymph node transfer to the axilla in 20 out of 22 patients[180]. The vascularized omental lymph node transfer (VOLT) flap to the axillae was first published by Nakajima in 2006[181]; a systematic review has found VOLT improves lymphedema, but it highlights that further studies are needed to identify appropriate patients for the technique[182]. One advantage of the VOLT flap is that the removal of the omentum does not induce iatrogenic lymphedema at the donor site[183], which is a risk with lymph node transfer from the inguen or axillae[184]. This risk can potentially be reduced using ICG-A and lymphoscintigraphy preoperatively, as proposed by Pons *et al.*[185]. Recently, Teven *et al.* performed a minimally-invasive approach utilizing the da Vinci Single-Port robotic system, only requiring two port holes[186], but there is an ongoing debate on the appropriate method of harvesting the flap[183].

Combining surgical and decongestive approaches has recently been investigated, where a study found LVA combined with compression therapy to improve cellulitis in early-stage BCRL[187]. Another study combined CDT and MLD with either LVA or VLNT, dependent on patient anatomy, for stage I and II lymphedema[188]. For stage III lymphedema, patients also had suction-assisted lipectomy, which previous studies showed to reduce lymphoedema in the arm and be an effective technique in end-stage lymphedema[189,190]. 10 of the patients included had combined breast reconstruction with DIEP flaps and VLNT[188]. No difference in complication rate between GE-VLNT and GE-VLNT combined with DIEP was found in seroma, dehiscence, and lymph node flap loss[188].

In recent years, the combination of breast reconstruction with lymphedema surgery in a single surgery has been explored. A retrospective chart review found VLNT to have a similar complication profile with or without autologous breast reconstruction[191]. A 2020 study by Chang *et al.* showed that combining the DIEP flap with VLNT combined with lymphaticovenous anastomosis was safe and might be superior to VLNT alone[192]. The patients were followed up 12 months post-operatively, both cohorts improved their lymphedema symptoms. A recent review found a higher risk of seroma, wound problems, and donor site pain when comparing VLNT combined with autologous breast reconstruction and isolated VLNT[193]. However, as they report, surgical expertise with VLNT is increasing, and the incidence of seroma has decreased for their own cohort during the last five study years[193]. Taranto *et al.* compared delayed breast reconstruction using DIEP flaps with and without VLNT and found no significant difference in donor site complication rate, no difference in BREAST-Q scores, but a notable circumference reduction in the lymphedema arm and statistically significant improvement in lymphedema QoL questionnaire (LYMQOL) after surgery[194].

PERSPECTIVES

When deciding what kind of treatment and follow-up program breast cancer patients should follow in a specific country, economics and feasibility will naturally influence the decision, as resources are divided unevenly around the world. Newer prediction strategies, such as the utilization of artificial intelligence (AI), could help physicians decide on which patients should be monitored more closely[195], or perhaps benefit from preventive BCRL surgery. However, AI is limited by the data it is built on, and it is therefore essential to produce and publish data of high quality, both negative and positive findings, to strengthen these computational tools.

CONCLUSION

Based on the current review of the literature, no certain causality between BCRL and breast reconstruction was found. The surgical and oncologic treatment modalities for breast cancer, as well as patient BMI, are likely factors impacting the advent of BCRL. Recent studies suggest that breast reconstruction may contribute to lower rates of lymphedema compared to mastectomy alone. The increased awareness of BCRL should encourage the reporting and publishing of data on this dreaded complication, providing the clinical and scientific community with the opportunity to perform meta-analyses. Further research, especially prospective studies with baseline measurements, is needed to fully address the impact of breast reconstruction treatment modalities on lymphedema, thus providing the breast reconstruction team with an increased insight into the complexity of lymphedema.

DECLARATIONS

Acknowledgments

Thanks to Professor Andreas Hougaard Laustsen-Kiel for English proofreading.

Authors' contributions

Contributed substantially to the study's conception and design: Laustsen-Kiel CM, Hansen L, Lauritzen E, Damsgaard TE

Wrote the main manuscript, and performed data acquisition, data analysis and interpretation: Laustsen-Kiel CM, Hansen L

Read, critically appraised, and approved the final manuscript: Laustsen-Kiel CM, Hansen L, Lauritzen E, Damsgaard TE

Availability of data and materials

Not applicable.

Financial support and sponsorship

This work was supported by the Vissing Foundation, grant number: 519140 AHO/LAX.

Conflicts of interest

All authors declare that there are no conflicts of interest. Tine Engberg Damsgaard is an Editorial Board member of the journal *Plastic and Aesthetic Research.* AI and AI-assisted technologies have been used in the writing process of the manuscript.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Written permission was obtained from the patient for the use of photographs.

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