Review Article

Breast cancer-related lymphedema: risk factors, precautionary measures, and treatments

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Abstract: Breast cancer-related lymphedema (BCRL) is a negative sequela of breast cancer treatment, and well-established risk factors include axillary lymph node dissection (ALND) and regional lymph node radiation (RLNR). BCRL affects approximately 1 in 5 patients treated for breast cancer, and it has a significant negative impact on patients' quality of life after breast cancer treatment, serving as a reminder of previous illness. This paper is a comprehensive review of the current evidence regarding BCRL risk factors, precautionary guidelines, prospective screening, early intervention, and surgical and non-surgical treatment techniques. Through establishing evidence-based BCRL risk factors, researchers and clinicians are better able to prevent, anticipate, and provide early intervention for BCRL. Clinicians can identify patients at high risk and utilize prospective screening programs, which incorporate objective measurements, patient reported outcome measures (PROM), and clinical examination, thereby creating opportunities for early intervention and, accordingly, improving BCRL prognosis. Innovative surgical techniques that minimize and/or prophylactically correct lymphatic disruption, such as axillary reverse mapping (ARM) and lymphatic-venous anastomoses (LVAs), are promising avenues for reducing BCRL incidence. Nonetheless, for those patients with BCRL who remain unresponsive to conservative methods like complete decongestive therapy (CDT), surgical treatment options aiming to reduce limb volume or restore lymphatic flow may prove to be palliative or corrective. It is only through a strong team-based approach that such a continuum of care can exist, and a multidisciplinary approach to BCRL screening, intervention, and research is therefore strongly encouraged.

Keywords: Breast cancer-related lymphedema (BCRL); lymphedema; lymphedema precautionary measures; lymphedema risk factors; lymphedema treatment

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Introduction

As advances in the treatment of breast cancer continue to progress, health care providers and patients are increasingly focused on post-treatment quality of life. Accordingly, an in-depth understanding of breast cancer-related lymphedema (BCRL) and its treatments is necessary for all clinical providers (1). BCRL, a much-feared sequela of breast cancer treatment, results from disruption to the lymphatic system that prevents adequate drainage from lymphatic vessels causing protein-rich lymph fluid to accumulate in the interstitial space (2,3). This excess fluid can cause abnormal swelling in the breast, trunk or upper extremity on the side of treatment. Depending on the extent of edema, symptoms of BCRL can include arm tightness, heaviness/fullness, pain, and impaired limb function (3-5). Furthermore, as BCRL progresses, adipose deposition and fibrosis can result (6). BCRL negatively affects a patient's

quality of life, causing elevated rates of depression and anxiety in addition to physical impairment compared to patients without BCRL (7-9). It is imperative to not only understand the risk factors influencing BCRL but also to use this knowledge to inform preventative measures and diagnostic approaches. The purpose of this review is to outline evidence-based risk factors, precautionary measures, and treatment modalities in order to establish an integrative knowledge base from which clinicians and researchers can draw to understand, diagnose, prevent, and treat BCRL.

Incidence of BCRL

In a recent meta-analysis, the overall estimated incidence of chronic arm edema after breast cancer was found to be 21.4%, indicating that BCRL is a widespread problem affecting 1 in every 5 patients following breast cancer treatment (10). Due to the lack of diagnostic criteria for BCRL, the reported incidence varies from less than 5% to more than 50% (10-12). The likelihood of any one individual developing lymphedema depends largely on that patient's individual risk factors. Literature examining these risk factors generally investigates the risk associated with either treatment-related or non-treatment-related risk factors. There are likely other non-modifiable risk factors including genetics and anatomy, which are less researched and not well-understood.

Treatment-related risk factors for BCRL

The main treatment-related risk factors for BCRL literature include axillary lymph node dissection (ALND) and regional lymph node radiation (RLNR). There is strong evidence that both ALND (10,11,13-17), and RLNR (10,11,17-20) are independent risk factors for BCRL. Additionally, emerging evidence indicates lack of breast reconstruction (21-23) as another treatment-related risk factor. Conversely, discord exists in the literature regarding risk posed by taxane-based chemotherapy (*Table 1*).

Type of axillary surgery

Axillary surgery type largely determines an individual's risk for developing lymphedema. Both ALND and the less invasive sentinel lymph node biopsy (SLNB) put patients at life-long risk for developing lymphedema due to the removal of either many axillary, in the case of ALND, or few sentinel, in the case of SLNB, lymph nodes (10,11,13-18,32). However, a recent meta-analysis of BCRL incidence in patients with unilateral breast cancer estimated that patients who receive ALND have a lymphedema incidence four times higher than those who receive SLNB [19.9% (95% CI: 13.5–28.2) and 5.6% respectively] (10). Thus, SLNB is an effective option for staging the axilla while minimizing the risk of lymphedema in patients with clinically node negative breast cancer (33), including a contralateral SLNB for those patients undergoing contralateral prophylactic mastectomy in conjunction with therapeutic mastectomy (24). These results are supported by Kilbreath and colleagues, who prospectively screened for lymphedema and found similar incidence rates when they stratified their data by number of nodes removed. For patients who have had more than five or more nodes removed, the incidence rate was 18.2%; for patients with less than five nodes removed, the incidence rate was 3.3% (18). This suggests that BCRL risk associated with axillary surgery may depend on the number of nodes removed, a metric that is generally accepted as an approximation for overall surgical damage to the lymphatic system (32). Indeed, Kim and colleagues showed that BCRL incidence rates in patients with 10 or more axillary lymph nodes removed were significantly greater than in patients with less than 10 dissected lymph nodes (27% *vs.* 6% respectively; $P<0.001$), and McLaughlin and colleagues found a significant difference in the number of axillary lymph nodes removed for patients who did not develop BCRL compared to those that did (19 *vs.* 22 respectively; $P<0.0001$) (16,32). Together, these data remind clinicians and researchers that the extent of axillary surgery may be an important prognostic factor for BCRL development, one which may be modified with the advancing surgical techniques outlined below. Moreover, De Groef and colleagues cautioned against the assumption that SLNB does not substantially affect arm morbidity irrespective of BCRL. In their prospective study, 50% of patients who underwent SLNB reported pain and 49% of patients experienced impaired shoulder function 1 year after surgery (25). This, and the fact that SLNB itself poses a risk for LE development, must be considered during the development of new treatments and protocols for patients undergoing treatment for breast cancer.

RLNR

Radiotherapy to the regional nodes, or RLNR, has been shown to be a significant risk factor for lymphedema development (11,17-20,26). Warren and colleagues demonstrated that RLNR, either supraclavicular with or

Table 1 Select studies reporting treatment-related risk factors and incidence rates

Risk factor	Article	Relevant findings	Limitations	Strengths
ALND	DiSipio *et al.*, 2013 (10)	(I) Estimated incidence of BCRL was 19.9% in studies examining patients who had ALND (95% CI: 13.5–28.2) (II) Nine studies, including at least two prospective cohort studies and two randomized clinical trials, provided strong evidence that ALND is a risk factor for BCRL	(I) Much of the studies analyzed to assess risk factors were of low or moderate quality (2 and 17 out of 29 respectively)	(I) Meta-analysis of 72 studies published from 2000–2012 used assess incidence rates (II) Meta-analysis of 29 studies published from 2000–2012 used to assess risk factors (III) Risk factors were assessed based on level of evidence
	Kilbreath *et al.*, 2016 (18)	(I) 18.2% of patients with ≥5 axillary LNs removed developed BCRL compared to 3.3% of patients with <5 nodes removed	(I) Only objective data was used in BCRL diagnosis (Impedance ratio increased by ≥0.1 from baseline or exceeded normative values)	(I) Large, prospective cohort study (II) Objective measurement method (BIS) (III) Examined cohort specific risk factors for patients with ≥5 axillary LNs removed
	Miller *et al.*, 2012 (24)	(I) Patients undergoing ALND during mastectomy (i.e., modified radical mastectomy) had significantly greater mean WAC changes than patients undergoing mastectomy alone (P=0.0028) or with SLNB (P<0.0001)	(I) Retrospective, non-randomized selection of patients for SLNB *vs.* no axillary staging during mastectomy (II) Only objective data was used in BCRL diagnosis (RVC ≥10%)	(I) Prospective cohort study (II) Objective measurement method (perometer) (III) Baseline measurement used for standardization (IV) Examined BCRL risk due to ALND and SLNB in patients undergoing bilateral mastectomies
	Tsai *et al.*, 2009 (11)	(I) ALND increases BCRL risk threefold compared to no axillary dissection (RR 3.47; 95% CI: 2.34–5.15) and compared to SLNB (RR: 3.07; 95% CI: 2.20–4.29)	(I) Many different definitions of BCRL were used across the studies analyzed, thereby limiting the comparability between studies (II) Many studies contained potential confounding factors that were not accounted for in the original studies	(I) Meta-analysis of 98 studies published in and before 2008

Table 1 *(continued)*

Table 1 *(continued)*

Risk factor	Article	Relevant findings	Limitations	Strengths
SLNB	De Groef *et al.*, 2016 (25)	(I) SLNB in unilateral, clinically node negative patients treated for breast cancer, with an 8% incidence rate of BCRL 1 year after surgery	(I) The long-term effects of SLNB on BCRL incidence cannot be completely assessed because of short follow up time	(I) Prospective cohort study (II) Objective measurement method (perimeter) (III) Assessed axillary swelling in addition to pain, range of motion, and shoulder function
	DiSipio *et al.*, 2013 (10)	(I) Estimated incidence of BCRL was 5.6% in studies examining patients who had had SLNB	(I) A majority of the studies analyzed to assess risk factors were of low or moderate quality (2 and 17 out of 29 respectively)	(I) Meta-analysis of 72 studies published from 2000–2012 used assess incidence rates (II) Meta-analysis of 29 studies published from 2000–2012 used to assess risk factors (III) Risk factors were assessed based on level of evidence
	Kilbreath *et al.*, 2016 (18)	(I) 3.3% of patients who had less than 5 LNs removed developed BCRL	(I) Only objective data was used in BCRL diagnosis (impedance ratio increased by ≥0.1 from baseline or exceeded normative values) (II) Risk factors for patients with <5 axillary LNs removed could not be examined because of insufficient events of BCRL at 18 mos postoperatively	(I) Large, prospective cohort study (II) Objective measurement method (BIS)

Table 1 *(continued)*

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Risk factor	Article	Relevant findings	Limitations	Strengths
RLNR	Kilbreath *et al.*, 2016 (18)	(I) For patients with ≥5 axillary LNs removed, radiotherapy to the axilla is an independent risk factor for developing BCRL at 18 mos (OR: 2.6; 95% CI: 0.7–8.9)	(I) Only objective data was used in BCRL diagnosis (impedance ratio increased by ≥0.1 from baseline or exceeded normative values) (II) Radiotherapy to the axilla as a risk factor for patients with <5 axillary LNSs removed could not be examined because of insufficient events of BCRL at 18 mos postoperatively	(I) Large, prospective cohort study (II) Objective measurement method (BIS) (III) Examined cohort specific risk factors for patients with ≥5 axillary LNs removed
	Miller *et al.*, 2014 (26)	(I) 19.3% of unilateral or bilateral breast mastectomy patients who received ALND without RT developed BCRL (95% CI: 10.8–33.1) compared to 30.1% (95% CI: 23.7–37.8) of unilateral or bilateral mastectomy patients who received ALND with RT (II) 2.19% of unilateral or bilateral mastectomy patients who received SLNB without RT developed BCRL (95% CI: 0.88–5.40) compared to 10% of mastectomy patients who received SLNB with RT (95% CI: 2.6–34.3)	(I) Only objective data was used in BCRL diagnosis (RVC ≥10%) (II) RT included patients treated with chest wall RT alone and patients treated with chest wall RT + RLNR, thereby preventing assessment of RT *vs.* RLNR as separate risk factors for BCRL	(I) Prospective cohort study (II) Objective measurement method (perometer) (III) Examined the rates of BCRL in unilateral and bilateral mastectomy patients who underwent SLNB or ALND followed by RT or no radiation (IV) Baseline measurement for standardization
	Shaitelman *et al.*, 2017 (17)	(I) Any type of regional nodal radiation in addition to breast/chest wall radiation increased the risk of BCRL (OR: 2.85; 95% CI: 1.24–6.55) (II) Compared to those who had SLNB and breast/chest wall radiation alone, those who had ALND with breast/chest wall RT alone (OR: 3.18; 95% CI: 1.60–6.32) and those who also had breast/chest wall RT and RLNR (OR: 8.70; 95% CI: 4.19–18.09) had increased risk of BCRL	(I) Analysis limited to 21 studies (II) Large differences in BCRL incidence were found across studies, potentially due to methodological differences	(I) Meta-analysis (II) Studies were only included if they were randomized clinical trials, controlled trials without randomization, or prospective comparative cohort trials, thereby offering high levels of scientific evidence

Table 1 *(continued)*

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Risk factor	Article	Relevant findings	Limitations	Strengths
	Tsai *et al.*, 2009 (11)	(I) RT has a risk ratio of 1.92 compared to no RT (95% CI: 1.61–2.28) (II) RLNR *vs.* no RLNR to the carried a 2.97 risk ratio (95% CI: 2.06–4.28)	(I) Many different definitions of BCRL were used across the studies analyzed, thereby limiting the comparability between studies (II) Many studies contained potential confounding factors that were not accounted for in the original studies (III) The RT may have included those with RLNR, limiting the impact of the RT *vs.* no RT result	(I) Meta-analysis of 98 studies published in and before 2008
	Warren *et al.*, 2014 (20)	(I) The 2-year incidence of BCRL was 3.1% for patients only receiving breast/chest wall RT, 21.9% for patients receiving SC RT, and 21.1% for patients receiving SC RT and PAB (II) The hazard ratio for RLNR (SC +/- PAB) compared to breast/chest wall RT was 1.7 (P=0.025)	(I) Only objective data was used in BCRL diagnosis (RVC ≥10%) (II) Nonrandom assignment of radiation fields (III) There were too few patients who underwent SLNB and RLNR to allow for subgroup analysis (IV) The lateral border of the SC field was not investigated	(I) Prospective cohort study (II) Objective measurement method (perometer) (III) Prospective cohort study (IV) Baseline measurement for standardization
Lack of breast reconstruction	Basta *et al.*, 2015 (27)	(I) In a cohort of patients undergoing ALND, 19.2% of patients undergoing reconstruction developed BCRL compared to 20.1% of patients who did not have reconstruction (P=0.82)	(I) Retrospective study (II) Did not use objective measurements of BCRL (III) Patients who underwent reconstruction had higher rates of preoperative radiation therapy (33% *vs.* 14%; P<0.001) and neoadjuvant chemotherapy (52% *vs.* 15%; P<0.001)	(I) Patients in the cohort were propensity-matched for age, BMI, mastectomy laterality, hypertension, cardiovascular disease, and postoperative radiation therapy (II) Used clinical diagnosis of BCRL available in the medical records
	Card *et al.*, 2012 (23)	(I) Patients who did not undergo reconstruction surgery were more likely to develop BCRL (9.9% *vs.* 3.7%; P<0.001)		

Table 1 *(continued)*

Table 1 *(continued)*

Risk factor	Article	Relevant findings	Limitations	Strengths
		(II) In a multivariate regression model, patients who underwent reconstruction were less likely to develop BCRL (OR: 0.37; 95% CI: 0.02–0.63) (III) Patients who underwent reconstruction developed BCRL more slowly than those who did not (HR: 0.39; 95% CI: 0.23–0.65; P<0.001)	(I) Retrospective study	(I) Used subjective as well as objective data documented in the medical records for BCRL diagnosis (II) The first direct cohort comparison between patients who underwent mastectomy alone and patients who underwent mastectomy with reconstruction (III) Patients in the cohort were cross-matched for age, ALND, and axillary irradiation
	Lee *et al.*, 2013 (28)	(I) Patients undergoing immediate autologous reconstruction had significantly lower incidence of BCRL compared to patients undergoing modified radical mastectomy alone (OR: 0.461; 95% CI: 0.236–0.901; P=0.023)	(I) Retrospective study (II) The reconstruction group had a significantly lower BMI (21.9 *vs.* 23.3; P<0.01) (III) Heterogenous cohorts	(I) Used subjective as well as objective data documented in the medical records for BCRL diagnosis
	Miller *et al.*, 2016 (21)	(I) The 2-year incidence of BCRL in a cohort of patients undergoing immediate breast reconstruction was 5.13% (95% CI: 3.50–7.49) compared to 26.66% (95% CI: 20.38–34.43) for patients not undergoing reconstruction (II) Immediate breast reconstruction reduced the risk of BCRL compared to no reconstruction (HR: 0.432; P<0.0001) according to multivariate analysis (III) Patients receiving implant reconstruction had an incidence of 4.08% (95% CI: 2.59–6.41); patients receiving autologous reconstruction had a BCRL incidence of 9.89% (95% CI: 4.98-19.13) (IV) Implant reconstruction significantly reduced the risk of BCRL compared to no reconstruction (HR: 0.352; P<0.0001); autologous reconstruction did not reduce the risk compared to no reconstruction (HR: 0.706; P=0.215)	(I) Only objective data was used in BCRL diagnosis (RVC ≥10%) (II) Nonrandomization for immediate reconstruction *vs.* mastectomy	(I) Prospective cohort study (II) Objective measurement method (perometer) (III) Prospective cohort study (IV) Baseline measurement for standardization (V) Large cohort

Table 1 *(continued)*

Table 1 *(continued)*

Risk factor	Article	Relevant findings	Limitations	Strengths
Neoadjuvant chemotherapy	Kim *et al.*, 2015 (29)	(I) Neoadjuvant CT was not found to be a significant risk factor associated with BCRL (P=0.61)	(I) Retrospective study	(I) Used subjective clinical diagnoses of BCRL available in the medical records (II) Examined patients who had either modified radical mastectomy *vs.* breast conserving therapy, ALND, and RT (SC + PAB)
	Specht *et al.*, 2013 (30)	(I) The comparison between patients undergoing neoadjuvant CT and patients undergoing adjuvant CT was not statistically significant, with incidence rates of 23% and 15% respectively (HR: 0.76; P=0.39) (II) For neoadjuvant CT patients, BCRL risk increased ninefold when there was residual lymph node disease post-CT (P=0.038)	(I) Only objective data was used in BCRL diagnosis (RVC ≥10%)	(I) Prospective cohort study (II) Objective measurement method (perometer) (III) Baseline measurement for standardization
Adjuvant chemotherapy	DiSipio *et al.*, 2013 (10)	(I) At least 75% of studies analyzed, including at least one high-quality study, indicated CT as a risk factor for developing BCRL	(I) A majority of the studies analyzed to assess risk factors were of low or moderate quality (2 and 17 out of 29 respectively)	(I) Meta-analysis of 72 studies published from 2000–2012 used assess incidence rates (II) Risk factors were stratified based on level of evidence (III) Meta-analysis of 29 studies published from 2000–2012 used to assess risk factors
	Kilbreath *et al.*, 2016 (18)	(I) Those who had taxane-based CT were at risk for arm swelling at 6 mos (OR: 2.6; 95% CI: 1.1–6.5) and at 12 mos (OR: 2.1; 95% CI: 0.9–4.9). Those who experienced arm swelling at 6 and 12 mos were at greater risk for BCRL at 18 mos (6 mos OR: 5.6; 95% CI: 2.0–16.9) (12 mos OR: 13.5; 95% CI: 4.8–38.1)	(I) Only objective data was used in BCRL diagnosis (Impedance ratio increased by ≥0.1 from baseline or exceeded normative values)	(I) Large, prospective cohort study (II) Objective measurement method (BIS)
	Swaroop *et al.*, 2015 (31)	(I) Adjuvant taxane-based CT was not associated with increased BCRL risk compared to no CT (HR: 1.14; P=0.62) and compared to non-taxane CT (HR: 1.56; P=0.40) (II) Docetaxel treatment was associated with mild swelling compared to both no CT and non-taxane CT groups (HR: 1.63, P=0.0098; HR: 2.15, P=0.02 respectively), but it did not result in BCRL	(I) Only objective data was used in BCRL diagnosis (RVC ≥10%) (II) Nonrandomization for immediate CT treatment (III) A small percentage of patients received non-taxane based neoadjuvant CT	(I) Prospective cohort study (II) Objective measurement method (perometer) (III) Baseline measurement for standardization (IV) Large cohort

ALND, axillary lymph node dissection; LN, lymph nodes; BCRL, breast cancer-related lymphedema; SLNB, sentinel lymph node biopsy; WAC, weight-adjusted volume change; RVC, relative volume change; RLNR, regional lymph node radiation; RT, radiation therapy; SC RT, supraclavicular radiation therapy; PAB, posterior axillary boost; CT, chemotherapy; mo(s), month(s).

without posterior axillary boost, significantly increased LE risk compared to breast/chest wall RT alone (HR: 1.70; 95% CI: 1.07–2.70) (20). A new meta-analysis by Shaitelman and colleagues calculates the pooled incidence for patients undergoing breast/chest wall radiation alone as 7.4% (95% CI: 5.1–10.0), but the pooled incidence for various combinations of RLNR varies from 10.8% to 15.5% (17). When stratified by type of axillary surgery, patients undergoing ALND and RLNR, had 18.2% pooled incidence (95% CI: 12.4–23.9), which represented a significant increase in lymphedema risk compared to ALND patients who received breast/chest wall radiation only (OR: 2.74; 95% CI: 1.38–5.44) (17). Furthermore, while patients with positive SLNB who receive adjuvant RLNR in lieu of ALND have lower rates of clinically diagnosed lymphedema 5 years after surgery (23% *vs.* 11%, P<0.0001), the risk of RLNR in and of itself should not be underestimated (34). Thus, patients undergoing RLNR, even without ALND, should be considered a high-risk group for developing lymphedema, and all patients undergoing ALND and/or RLNR should be prospectively screened.

Lack of breast reconstruction

The effect of reconstruction on risk of BCRL has become an emerging area of interest in the literature (21-23,28). Recently, in a large prospective cohort study, Miller and colleagues investigated immediate implant reconstruction and immediate autologous reconstruction compared to mastectomy without reconstruction (21). Mastectomy itself has been occasionally cited as a risk factor for BCRL (10,11,18,19,35), and several studies have shown that delayed autologous reconstruction reduced the severity of BCRL (36-38). They found that immediate reconstruction significantly reduced the risk of lymphedema (HR: 0.432; P<0.0001). Specifically, immediate implant reconstruction offered a greater reduction in risk compared to immediate autologous reconstruction (HR: 0.500; P=0.0322) (21). These results are similar to those of an earlier study by Avraham and colleagues who found that those undergoing tissue expander breast reconstruction had significantly lower rates of BCRL (5% *vs.* 18%; P<0.0004) (39). Moreover, a retrospective study by Card and colleagues that found patients who did not undergo reconstruction were more likely to develop BCRL compared to patients who had reconstruction (adjusted OR: 0.37; 95% CI: 0.02–0.63) (23). In a previous study, the same authors acknowledged that immediate reconstruction decreased risk of BCRL, but they found no difference in BCRL incidence based on type of immediate reconstruction (22). In contrast to these studies, Basta and colleagues did not find reconstruction or lack thereof as a significant factor influencing LE risk, but this study's retrospective nature and lack of objective measurement-based diagnostic criteria limit the scope of its findings (27).

Adjuvant and neoadjuvant chemotherapy

Whereas ALND and RLNR are known risk factors for BCRL and lack of reconstruction likely increases the risk of BCRL as well, less conclusive evidence exists to suggest chemotherapy as a risk factor. Some studies indicate adjuvant chemotherapy as a potential risk factor for BCRL (10,18,32,40-42) whereas other studies do not (19,31). In particular, taxane-based chemotherapy is of interest in BCRL literature because of taxane-induced fluid retention in patients during treatment (43-45). In a recent prospective cohort study by Kilbreath and colleagues, arm swelling at 6 and 12 months was associated with adjuvant taxane therapy, and swelling at both time points were independent risk factors for LE development (18). Zhu and colleagues' recent retrospective analysis lends support to Kilbreath *et al.*'s findings. They found that docetaxel-based chemotherapy significantly increased the cumulative incidence of BCRL compared to non-docetaxel based chemotherapy (19.91% *vs.* 32.09%; P=0.011) and was an independent risk factor for BCRL (HR: 1.73; P=0.017) (42). Conversely, Swaroop and colleagues did not find taxane-based chemotherapy as a risk factor for BCRL. They did, however, find docetaxel treatment, but not paclitaxel treatment, to be a risk factor for mild swelling compared to no chemotherapy and non-taxane based chemotherapy (31). Thus, while it is clear taxanes, specifically docetaxel, cause edema, there is not a clear consensus in the literature that taxane-based chemotherapy is a risk factor for BCRL.

The effect of neoadjuvant chemotherapy on BCRL risk is unclear. Neoadjuvant chemotherapy is utilized in breast cancer treatment to decrease the size of the primary tumor and any affected lymph nodes, allowing for less extensive surgery. It has been suggested that neoadjuvant chemotherapy could, in theory, decrease BCRL incidence by reducing the number of positive lymph nodes (29,30). Specht and colleagues found that there was an increased risk of BCRL in patients with residual lymph node disease after neoadjuvant chemotherapy (30). More studies, using objective and standardized BCRL measurement techniques and definitions, are needed to define the role of neoadjuvant and adjuvant chemotherapy in BCRL risk.

Non-treatment-related risk factors for BCRL

Studies have demonstrated several non-treatment-related risk factors for BCRL, including body mass index (BMI) at time of diagnosis, subclinical edema, and cellulitis on the side of treatment (*Table 2*). Efforts aimed at addressing these risk factors may represent a prudent avenue for BCRL prevention.

BMI

High BMI at time of breast cancer diagnosis is a well-established risk factor for developing BCRL (14,16,20,22,40,46,49-55). In a prospective cohort screening for BCRL using perometry, Jammallo and colleagues found a BMI greater than or equal to 30 kg/m^2 was an independent risk factor for BCRL (47). This result was similar to Ridner and colleagues' smaller prospective study using perometry in which they found that patients with a BMI of 30 kg/m^2 or above were 3.6 times more likely to develop lymphedema (95% CI: 1.42–9.04; P=0.007) (55). Similarly, Fu and colleagues investigated BMI's influence on lymph fluid by using bioimpedance spectroscopy (BIS) to screen for lymphedema in a small cohort of 140 women. They found that obese women (BMI ≥30) were more likely to have an L-Dex score of greater than 7.1, which was their operative definition for lymphedema, compared to both the normal/underweight group (18.5–24.9, <18.5 respectively) and the overweight group (25.0–29.9) before surgery and throughout the following year (46). This result supports the previous arm volume studies which indicate BMI ≥30 at time of diagnosis as a modifier of BCRL risk.

In addition to high BMI at diagnosis, there is some supporting evidence suggesting weight fluctuations during and after treatment may be a risk factor for BCRL (15,35,47). Jammallo *et al.* demonstrated that post-operative weight fluctuations greater than 10 pounds per month, either lost or gained, increased BCRL risk (47). Thus, more research regarding weight fluctuation is needed before optimal weight loss and/or management programs can be implemented clinically to modify a patient's risk for BCRL.

Subclinical edema

Subclinical edema has been shown to be a risk factor for BCRL (18,20,48). Specht and colleagues first studied the relationship between subclinical swelling and progression to lymphedema—defined as >10% relative volume change—to assess at what level of swelling would intervention be warranted. They prospectively screened 1,173 patients treated for breast cancer with perometry, and they found small increases in arm volume (≥3% but <5%) as well as larger increases in arm volume (≥3% but <10%) within 3 months of surgery increased BCRL risk. After the third postoperative month, only larger increases in arm volume (≥5% but <10%) were correlated with increased BCRL incidence (48). Additionally, in their large cohort screened prospectively with BIS, Kilbreath and colleagues found that, for women with five or more lymph nodes removed, axillary swelling at 6 and 12 months postoperatively are independent risk factors for BCRL at 18 months. Interestingly, arm swelling at 6 and 12 months were associated with arm swelling in the first month of surgery (18). Together, these studies demonstrate the importance of screening for early postoperative arm volume increases to inform long-term BCRL risk.

Cellulitis

Cellulitis is a well-established BCRL risk factor in the literature (13,14,16,35,49,51,56,57). In their recent large prospective cohort study, Ferguson and colleagues demonstrated that cellulitis infections significantly increased BCRL risk (P<0.001). They also showed that ipsilateral 'risk events', such as blood draws and injections, did not correlate with cellulitis infections, and they further suggest that these routine medical procedures may not expose the axilla to substantial infection risk when done in a sterile environment (14). Nonetheless, patients who have undergone treatment for breast cancer should be wary of the risks of postoperative infections. In a cohort of patients receiving both unilateral and bilateral breast conserving therapy, Indelicato and colleagues found that patients with BCRL were more likely to develop delayed breast cellulitis (56). Thus, cellulitis and BCRL may represent a feedback loop in which cellulitis increases BCRL risk and BCRL increases risk of further infections (13,15). More research is needed to fully delineate the relationship between cellulitis and BCRL to help mitigate risk of both.

Prevention

Precautionary guidelines

The National Lymphedema Network (NLN) outlines precautionary lifestyle recommendations for those at risk of lymphedema, which they define as anyone who has had lymph nodes removed or radiation therapy during treatment for cancer (58). It should be clarified that, for patients treated for breast cancer, RLNR is the specific type of radiotherapy that increases a patient's risk for BCRL.

Table 2 Select studies reporting non-treatment related risk factors and incidence rates

Risk factor	Article	Relevant findings	Limitations	Strengths
Body mass index and weight fluctuation	DiSipio *et al.*, 2013 (10)	(I) Higher BMI was found to have a strong level of evidence as an independent risk factor for BCRL development (RR: 5.5)	(I) A majority of the studies analyzed to assess risk factors were of low or moderate quality (2 and 17 out of 29 respectively)	(I) Meta-analysis of 72 studies published from 2000–2012 used assess incidence rates (II) Meta-analysis of 29 studies published from 2000–2012 used to assess risk factors (III) Risk factors were stratified based on level of evidence
	Fu *et al.*, 2015 (46)	(I) Patients with BMI ≥30 had significantly higher L-Dex ratios at pre-surgery compared to normal/underweight patients (BMI ≤24.9) and overweight patients (BMI 25–29.9) (II) Patients with BMI ≥30 had significantly higher L-Dex ratios at 4–8 weeks post-surgery compared to normal/underweight patients (BMI ≤24.9) and overweight patients (BMI 25–29.9)	(I) Only objective data was used to diagnose BCRL (L-Dex ratio >7.1) (II) Small cohort of 140 patients (III) The long-term effects of high BMI on lymph fluid level and BCRL incidence cannot be assessed because of short follow up time (12 mos)	(I) Prospective cohort study (II) Objective measurement method (BIS)
	Jammallo *et al.*, 2013 (47)	(I) Pre-operative BMI ≥30 was associated with increased risk of BCRL compared to both pre-operative BMIs of <25 (HR: 3.58; P=0.001) and 25–<30 (HR: 2.46; P=0.012) (II) Cumulative absolute fluctuation in weight from pre-operative weight was associated with increased risk of BCRL (HR: 1.07 per lb/month weight change; P<0.0001)	(I) Only objective data was used to diagnose BCRL (RVC ≥10%) (II) Non-standard measurement schedule	(I) Large, prospective cohort study (II) Objective measurement method (perometry) (III) Baseline measurement for standardization
Subclinical edema	Kilbreath *et al.*, 2016 (18)	(I) Patients with ≥5 axillary LNs removed who experienced arm swelling at 6 and 12 mos were at greater risk for BCRL at 18 mos (6 mos OR: 5.6; 95% CI: 2.0–16.9) (12 mos OR: 13.5; 95% CI: 4.8–38.1)	(I) Only objective data was used in BCRL diagnosis (impedance ratio increased by ≥0.1 from baseline or exceeded normative values)	(I) Large, prospective cohort study (II) Objective measurement method (BIS)
	Specht *et al.*, 2013 (48)	(I) Patients with RVCs of ≥5 and <10% more than 3 mos after surgery had increased risk of progressing to RVC ≥10% (HR: 2.97, P<0.0001) (II) RVCs of ≥3% to <5% (P=0.007), ≥5% to <10% (P<0.0001), and ≥10% (P=0.023) 3 or more mos after surgery were significant risk factors for BCRL	(I) Only objective data was used to diagnose BCRL (RVC ≥10%)	(I) Large, prospective cohort study (II) Objective measurement method (perometry) (III) Baseline measurement for standardization

Table 2 *(continued)*

Table 2 *(continued)*

Risk factor	Article	Relevant findings	Limitations	Strengths
Cellulitis	Ferguson *et al.*, 2016 (14)	(I) Cellulitis infections significantly increased arm volume changes by approximately 3% (95% CI: 1.72–3.8, P<0.001) (II) Prior ipsilateral blood draws (HR: 0.977, P=0.91), injections (HR: 1.101, P=0.5), and blood pressure readings (HR: 0.943, P=0.1) were not significantly associated with subsequent cellulitis infections	(I) Only objective data was used to diagnose BCRL (RVC or WAC ≥10%)	(I) Large, prospective cohort study (II) Objective measurement method (perometry) (III) Baseline measurement for standardization
	McLaughlin *et al.*, 2008 (16)	(I) Postoperative infections were associated with higher BCRL incidence compared to those with no infections (28% *vs.* 8% respectively, P<0.0001)	(I) Only objective data was used to diagnose BCRL (<2 cm change in arm circumference in the ipsilateral arm)	(I) Large, prospective cohort study (II) Objective measurement method (circumferential arm measurements) (III) Baseline measurement for standardization

BMI, body mass index; BIS, bioimpedance spectroscopy; L-Dex, lymphedema index; BCRL, breast cancer-related lymphedema; RR, risk ratio; HR, hazard ratio; RVC, relative volume change; LN, lymph node; OR, odds ratio; WAC, weight-adjusted volume change; cm, centimeter; mo(s), month(s).

These precautionary guidelines range from minimally burdensome (e.g., good skin care) to potentially demanding (e.g., potential use of a compression garment during air travel, avoidance of blood pressure cuffs and other forms of limb constriction, and reduction of trauma to the at-risk limb by avoiding venipuncture) lifestyle alterations. Yet, implementation of these guidelines may not significantly reduce a patient's risk of developing BCRL (13,14,18,59). Ferguson *et al.* found that, in their cohort, blood pressure readings, blood draws, and air travel did not significantly increase BCRL risk in patients who underwent unilateral breast cancer surgery (14). In patients who underwent bilateral breast cancer surgery, a recent prospective cohort study by Asdourian and colleagues demonstrated similar results, namely that lifestyle risk factors were not associated with an increased weight adjusted volume change (60). Doubt regarding precautionary guidelines is further enhanced by Kilbreath *et al.*'s recent study, which found that air travel, arm trauma, medical procedures, and arm use did not increase risk of BCRL in women with five or more lymph nodes removed (18). Indeed, evidence for many of these clinically-guided, precautionary guidelines lack high level scientific evidence; however, as Asdourian *et al.* highlighted, there is a need for more rigorous research regarding precautionary behaviors prior to implementing practice changes (13). This recommendation is echoed in the 2016 International Society of Lymphedema Consensus document. They state, "*The recent promulgation of lists of risk factors for secondary lymphedema has become a highlighted issue due to publications of 'do's and don'ts'. These are largely anecdotal and not sufficiently investigated. While some precautions rest on solid physiological principles, others are less supported.*" It goes on to state that "*standard use of some of these 'don'ts' for risk reduction of lymphedema may not be appropriate and possibly subjects patients to therapies which are unsupported until a point in the future when evaluation and prognostication evidence has demonstrated more clearly specific risks and the corresponding preventative measures*" (61).

Screening programs and early intervention

Historically, BCRL has been treated using an impairment-based model which relies on both the patient and the provider to detect visible limb swelling and to accurately diagnose/treat the swelling as lymphedema. However, as the BCRL field has progressed, the consensus has shifted, instead recommending a preventative, prospective screening approach (47,48,52-58). With the advent of better, more

precise diagnostic technology, such as perometry and BIS, patients can be easily screened for BCRL both during and after treatment (12,62-67). Massachusetts General Hospital has successfully established one such prospective BCRL screening program in its multidisciplinary breast cancer clinic, using perometry as a standard objective tool, together with subjective patient reported outcome measures (PROM) (62). Patients with elevated measurements beyond baseline are referred to a certified lymphedema therapist for clinical evaluation and consult. Elements of any successful prospective screening program should include a validated, reliable, objective measurement tool, a standardized measurement protocol, a preoperative baseline measurement, a longitudinal series of follow up measurements that account for natural arm asymmetry and weight changes, and PROM. Such screening should also include clinical examination by a certified lymphedema therapist at the discretion of the team (62,67-73).

Using this model, BCRL can be diagnosed in earlier stages, allowing for earlier intervention (61,74). Stout and colleagues successfully screened 196 patients for BCRL, and patients were given compression garments if there was a >3% increase in arm volume compared to the preoperative measurement and contralateral arm volume changes. After 4 weeks, the patients who received the early intervention had significant volume reduction that was maintained at the four month follow up visit (68). Similarly, Soran and colleagues prospectively screened 186 patients with either BIS or circumferential arm measurements, treating those diagnosed with subclinical lymphedema with physical therapy, compression garments, and education. Of the 33% of patients in the BIS group who were diagnosed with subclinical lymphedema, only 4.4% developed clinical lymphedema compared to 36.4% in the control group, demonstrating the effectiveness of prospective screening and early intervention in reducing BCRL (75). While these studies demonstrate potential efficacy for early intervention, they are limited by their small sample size. Large, randomized trials are needed to fully evaluate the benefits of early intervention for subclinical edema. Nonetheless, the International Society for Lymphology upholds that prospective screening models and early intervention allow for greater treatment success and potential cost savings (61).

Improving treatment techniques

Improving treatment techniques to minimize lymphatic disruption is another avenue of research in BCRL prevention (33). One of the main ways to prevent lymphatic disruption is to perform less invasive nodal surgeries. The concept of removing only the sentinel lymph node(s) (SLN)—or the lymph nodes that first receive drainage from the tumor—was a concept proposed by Cabanas in the 1970s in the treatment of penile cancer (76). By the 1990s, melanoma researchers and breast cancer researchers began using tracers like blue dye and/or radioactive colloids to map the drainage of ducts into the sentinel lymph nodes (77-80), and Krag and colleagues demonstrated that biopsy of the sentinel lymph nodes could accurately predict axillary-node metastasis in patients treated for breast cancer (80). As research further demonstrated the efficacy of using SLNs to indicate nodal metastasis without decreasing survival rates (81,82), modern surgical trends shifted towards using the more conservative SLNB as opposed to ALND to stage the axilla in patients treated for breast cancer. As suspected, the advent of SLNB as an alternative to ALND in clinically node negative patients with breast cancer has drastically reduced the risk of BCRL (83) and arm morbidities (83-86).

For patients who present with node-positive breast cancer, there are fewer options for modifying treatment to reduce BCRL risk. Current clinical practice guidelines recommend that most patients with lymph node metastases undergo ALND (87,88); however, there is compelling evidence that neoadjuvant chemotherapy treatment may downstage the axillary lymph nodes and allow for less extensive surgery (89-91). Both the SENTINA study and the ACOSOG Z1071 clinical trials showed a less than 10% false-negative rate when three or more sentinel lymph nodes were biopsied, demonstrating that at least three negative SLNs reliably indicates absence of further nodal metastases (89,90). In a recent prospective study by Mamtani and colleagues, they avoided ALND for 40% of their patients who presented with nodal metastases by downstaging with neoadjuvant chemotherapy (91). These patients all had three or more negative SLNs and had no contraindications to SLNB. Furthermore, in Mamtani *et al.*'s study, only 14% of patients had fewer than three identified SLNs, which is a much lower proportion than the SENTINA and ACOSOG Z1071 studies. This study provides further evidence that ALND may not be indicated in patients who have been successfully downstaged with neoadjuvant chemotherapy and with three or more negative SLNs. Large trials demonstrating positive long-term

regional recurrence outcomes are needed to validate this novel approach. In addition, results from the AMAROS (34) and the Z0011 (92,93) trials suggest that, for patients with positive SLNB, ALND may not be indicated if it replaced with adjuvant therapy. Compared to ALND, the AMAROS trial demonstrated that RLNR offered comparable locoregional control with significantly less arm morbidity, including significantly less lymphedema comparatively (34).

Moreover, new surgical techniques are being developed to minimize axillary lymphatic disruption in both SLNB and ALND procedures. The first procedure, axillary reverse mapping (ARM), has shown promise in recent years as a new method to map out and preserve axillary lymphatics during surgery and potentially reduce post-surgical lymphedema incidence in patients (94-98). It is based on the hypothesis that, because the axilla and breast have mostly separate drainage pathways, upper extremity lymphedema can be prevented by avoiding the removal of tracer-identified lymph nodes and lymphatics that only drain the axilla. In 2007, the first published reports of ARM demonstrated that blue dye injected into the ipsilateral arm could be used to visualize these axillary lymphatics and lymph nodes, thereby differentiating them from the SLNs that drain the breast (99,100). Since then, other methods of visualizing ARM nodes have developed, including using radioactive colloids and lymphoscintigraphy (95,101,102), using the fluorescent dye IndoCyanine Green with a fluorescence imaging system (103-106), and using combinations of tracers (106-109).

In studies looking at BCRL after ARM procedures, the reduced incidence rates provide evidence for the efficacy of ARM's ability to reduce BCRL (94-96,98,100,102,106, 109-116). One recent study by Tummel and colleagues demonstrated promising results. They measured arm volume using water displacement at baseline and every 6 months, and they characterized objective lymphedema as any increase ≥20% in volume of the affected side over the contralateral side, whilst considering baseline measurements and changes in contralateral arm volume. Six hundred and fifty-four ARM procedures were performed with either an SLNB or an ALND, and, except during the beginning of the study, benign-appearing ARM nodes and lymphatics were preserved during ALND (67.3% of ALND patients with ARM lymphatics identified). In a subset of patients for which ARM lymphatics were identified and preserved, objective BCRL rates at a median of 26 months after surgery were 1.2% for SLNB patients and 6.9% for ALND patients (110). These represent a marked decrease to typical BCRL incidence rates for SLNB and ALND. Yet, it should be noted that their definition of ≥20% increase in arm volume was conservative, and the same cohort of patients might have had a higher incidence of BCRL if other BCRL definitions were used. This highlights an important limitation in BCRL assessment in ARM studies. Because these studies use varying definitions of BCRL and inconsistent methods of measuring edema across studies, it is difficult to compare BCRL incidence rates after sparing ARM nodes, thereby limiting our ability to assess ARM as a surgical tool for BCRL reduction (94,98). The limitations of current ARM studies highlight the need for standard definitions of BCRL that use quantitative measurements, ones which take into account preoperative baseline arm volume and changes in the contralateral arm and/or weight (69-72). Future studies of ARM must include this type of rigorous assessment of BCRL in order to fully understand the potential benefit it could have (98). Nevertheless, the potential of ARM to reduce post-surgical axillary morbidity should not be underestimated.

However, ARM lymph nodes and lymphatics cannot, and potentially should not, always be spared. There have been incidences of the SLN coinciding with the ARM node in some patients (95,96,106,110-113,117-120), and studies have reported ARM/SLN crossover rates anywhere between 0–28% (96,100,101,103,104,106,110-116,118-122). This is not surprising because research has shown that interconnections do exist between the two, relatively independent drainage pathways (123). Any connections between the two pathways potentially allow metastatic breast cancer cells to invade axillary lymphatics, making the pathological status of ARM nodes an important area of investigation to determine oncologic safety. In the case of crossover between the SLN and ARM nodes, the crossover nodes are removed during SLNB, and upon examination, some studies identified metastases in these concordant nodes (96,111,120). Moreover, the rates of metastases in non-crossover ARM nodes are important to consider when assessing oncologic safety. In trials examining ARM during ALND, studies have reported metastatic involvement of ARM nodes anywhere from 0% to 43% (99-101,103-105,107,108,112,114-116,118,121,122,124-128). Because of these varying rates of ARM nodal involvement, it is unclear whether this procedure can be safely used in clinically node positive patients undergoing primary ALND. However, there is evidence indicating that ARM can successfully be implemented into SLNB procedures for clinically node negative patients and that non-crossover ARM nodes can be spared in these patients with positive SLNB (95,96,129).

Yet, larger, randomized clinical trials comparing the efficacy and safety of ARM in conjunction with axillary surgery to SLNB and ALND alone are needed before clinical guidelines can implement ARM for lymphedema reduction in patient populations (94).

Boccardo and colleagues, recognizing that the preservation of ARM lymphatics might not always be feasible or possible due to complications such as extensive axillary disease or failure to find blue lymphatics, established the Lymphatic Microsurgical Preventative Healing Approach (LYMPHA) technique (130-132). LYMPHA involves constructing lymphatic-venous anastomoses (LVAs) between the arm lymphatics and a collateral branch of the axillary vein during axillary surgery. LVAs have been successfully used in the surgical treatment of primary and secondary lymphedema for many years (133,134), but the preventative approach of creating these anastomoses between ARM lymphatics and the axillary vein collateral during axillary surgery represents a creative method of preserving lymphatic function when ARM lymph node removal is necessitated (130). After 4 years, only 3 out of 79 patients demonstrated clinical LE, which corresponds to an incidence rate of 4.05% (132). Feldman and colleagues had similar results in their LYMPHA trial: only 3 out of the 24 patients who had a successful LYMPHA procedure with ALND developed LE after 26 months compared to 4 out of 8 patients (50%) who had unsuccessful LYMPHA procedures due to lack of adequate axillary vein or extensive lymphatic/axillary disease (135). Interestingly, Tummel and colleagues constructed LVAs when blue ARM lymphatics had to be transected during their ARM studies during SLNB and ALND. In the subset of patients who had blue lymphatics transected, the BCRL incidence rate was significantly lower when the lymphatics were reanastomosed (18.7% *vs.* 0%; P=0.009). However, these results are limited because there was a low incidence of ARM lymphatic transection as well as transected ARM reanastomosis (110). LYMPHA in conjunction with ARM procedures may prove to be an effective adjustment to SLNB and ALND, particularly for those in which ARM lymphatics and nodes must be transected or removed. The technique could be implemented with relatively little burden to hospitals in which surgeons trained in microsurgical techniques work, particularly if performed at the time of mastectomy with immediate reconstruction (136). However, as noted by Ahn and Port (59,137), access to surgeons with microsurgical skills is not ubiquitous, limiting the feasibility of this technique as a widespread preventative procedure in the immediate future. Nevertheless, to fully determine the efficacy of ARM in conjunction with LYMPHA as a preventative approach to reducing BCRL, a large, multicenter, prospective cohort study that uses standardized, objective definitions of BCRL along with clinical assessments is needed.

Treatments

Non-invasive treatments

First-line intervention to treat BCRL involves two distinct phases: reduction therapy and maintenance therapy. Reductive therapy typically involves complete decongestive therapy (CDT) administered by a certified lymphedema therapist, whose goal is to decrease symptoms and limb volume. CDT is individualized for each patient, but it typically includes manual lymphatic drainage (MLD), compression bandaging, exercise, skin care, and patient education. There is no consensus on optimal treatment parameters, including frequency, for CDT. Once minimized limb volume is achieved with CDT, typically after several weeks, maintenance therapy begins. This may include self- or caregiver-administered MLD, compression garments, exercise, and skin care.

Research regarding non-invasive treatment for BCRL has focused on CDT in its entirety, but there has been less well-established research regarding the efficacy of each individual CDT component. Compression bandaging as a first line intervention for subclinical BCRL has been used increasingly to prevent swelling progression (68) and it has been shown to reduce arm volume successfully with or without the addition of MLD for BCRL (138,139). However, MLD is an important tool for volume reduction. One recent meta-analysis concluded that MLD is not only safe and well-tolerated, but it may also be most beneficial to patients with mild to moderate BCRL in addition to compression bandaging (140). Current ISL consensus highlights the need for more research regarding MLD as a monotherapy (61).

Furthermore, exercise is an important aspect of CDT as well as a helpful tool in the long-term management of BCRL. An exercise program including both aerobic and resistance exercises, initially supervised to ensure proper technique and progression, does not incite or exacerbate BRCL (141-146). Moreover, there is no limitation on the maximum amount of weight that can be lifted as long as weight-lifting exercises are supervised and progressive (141).

Patients, both with and without BCRL, are encouraged to progress toward meeting the American College of Sports Medicine guidelines for patients who have undergone treatment for breast cancer. These recommendations include 150 min/week of moderate activity (e.g., walking) or 75 min/week of vigorous activity (e.g., running), as well as 6–8 resistance exercises for the major muscle groups of the upper and lower extremities (147).

Other non-invasive, technological treatments for BCRL exist. Intermittent pneumatic compression (IPC) pumps have been used to treat BCRL, but there is unclear evidence demonstrating their efficacy. In their meta-analysis, Shao and colleagues found that the addition of IPC pumps to routine management of BCRL did not significantly improve treatment outcomes (148). However, others have shown IPC to be an effective addition to CDT (149) or an alternative to MLD and compression bandaging when combined with self-lymphatic drainage (150). Rogan and colleagues, in their meta-analysis of different treatment modalities, concluded that while IPC pumps may be useful in the reductive phase of treatment, their utility is limited because they can only stimulate drainage in unaffected lymphatic collectors (146). Additionally, low level laser therapy (LLLT) has become a recent modality of interest to treat BCRL (61,151,152). One small randomized pilot trial demonstrated that 20 minutes of LLLT combined with compression bandaging is just as effective at reducing volume compared to 40 minutes of MLD, potentially offering a time saving treatment that would reduce burdensome treatment (152). A meta-analysis of nine studies examining LLLT as a BCRL treatment modality concluded that LLLT alone or in conjunction with other treatments decreases pain and swelling in patients (151).

Surgical treatments

While non-invasive treatment remains the standard of care for BCRL, surgical management is another avenue to treat persistent lymphedema, particularly for patients who do not respond to non-invasive treatments. There are two main surgical strategies: ablative procedures and physiologic procedures (153-157).

Ablative procedures, also known as debulking procedures, reduce limb volume by surgically removing edematous tissue. Typically, liposuction or suction-assisted protein lipectomy (SAPL) are used as volume reduction treatments because they are less invasive than older debulking procedures and do not require skin grafting. Liposuction/SAPL procedures are best suited for individuals with solid, non-pitting edema whose volume excess is largely due to fat deposits instead of fluid accumulation (61,153,155,158-162). In studies looking at patients with upper and lower extremity lymphedema, liposuction/SAPL has shown significant volume reductions (61,158,162-166). However, because these procedures do not address the underlying physiologic causes of lymphedema, namely the inadequate drainage of lymphatic fluid from the extremity, compression garments must be worn continuously to maintain the decreased volume (158,163,164,167,168).

Conversely, physiologic procedures treat the etiology of BCRL by reestablishing and/or redirecting axillary lymphatic flow. Re-approximation or rerouting of lymphatic drainage pathways can be achieved by establishing unobstructed connections with distal healthy tissue or proximal venous tissues. Because these procedures work to resolve fluid accumulation in the extremity, physiologic procedures are indicated for patients with pitting edema who have not progressed to fibrotic, solid edema (153,158).

Procedures utilizing distal tissues generally involve lymphatic grafts or vascularized flaps containing lymphatic soft tissue. The lymphaticolymphatic bypass procedure is an example of the former, during which healthy lymphatic vessels are harvested from the lower extremity and anastomosed to the affected arm's axillary lymphatics at one end and to healthy supraclavicular lymphatics on the other (169). In reports, these rerouted lymphatic pathways achieved long term patency and improved lymphatic transport, and they have proven effective in reducing upper extremity volume (169-172). However, harvesting the lymphatic graft can potentially cause lymphedema in the donor extremity. In lieu of using lymphatic grafts, autologous venous grafts from donor extremities can be used to bypass the blockage in a similar way to lymphatic grafts without the potential disruption to the donor lymphatic pathways (173,174). The other major surgical treatment involving introduction of distal tissues to the axilla is a vascularized lymph node transfer (VLNT). A VLNT involves harvesting a lymph node flap with its corresponding vascular supply from a donor site and introducing it into the affected extremity (154,175-180). Blood supply is achieved by anastomosing the lymph node flap's blood vessels and the native axillary blood vessels. The donor lymph node flaps can be taken from various areas, but most surgeons typically use lateral groin lymph nodes to treat upper-extremity lymphedema (155,176,178,179). Studies have also shown successful results when harvesting lymph node flaps for VLNT in conjunction with abdominal

flaps, which surgeons then use for simultaneous breast reconstruction (181,182). Furthermore, while this procedure does put the donor site at risk for developing lymphedema (183,184), the mapping of lymphatic drainage patterns allows for the selective removal of lymph nodes not primarily responsible for draining the donor extremity (158,185).

Surgical treatments for BCRL also include physiologic procedures, such as LVA, which utilize proximal tissues instead of grafts or flaps to reestablish lymphatic drainage. In fact, LYMPHA, mentioned above, is a prophylactic LVA performed at the time of axillary surgery between transected lymphatics and the collateral branch of the axillary vein (130). During palliative LVAs, multiple lymphatic vessels are anastomosed to venules, thereby allowing lymphatic drainage into the venous system (133,134, 186-190). Recently, Poumellec and colleagues successfully used a stepped LVA approach, during which three total anastomoses were created at the wrist, forearm, and elbow, to treat upper extremity lymphedema. Of the 31 patients treated, 93.5% showed a decrease in arm circumference with a mean reduction of 24.7%, and of the 3 patients with late-stage BCRL, 1 showed no circumference decrease whereas the other 2 patients had recurrences (186). In their prospective study, Chang and colleagues performed LVAs in 89 women with upper extremity lymphedema, and symptom improvement was reported by 96% of patients. One year after surgery, the mean volume reduction was 42% overall, and patients with less progressive lymphedema (stages 1 and 2) had significantly greater volume reductions compared to patients with stage 3 or 4 lymphedema (187). As with all of the previously mentioned procedures, large, randomized clinical trials are needed to fully evaluate the palliative benefits of LVAs alone and compared to other treatment techniques.

Conclusions

BCRL remains a potentially life-altering sequela of breast cancer treatment that affects approximately one in five patients (10). Well-established risk factors include ALND, RLNR, high BMI at time of diagnosis, edema 3–5% within 3 months of surgery, edema 5–10% at any time after surgery, and cellulitis infections. Nevertheless, research has precipitated significant advances in BCRL screening and treatment. Most notably, establishment of risk factors, evolving evidence around precautionary guidelines, and adapting surgical treatments to reduce lymphatic disruption are powerful areas of evolving BCRL research and care. Techniques such as ARM and LYMPHA have shown promising reductions in post-operative BCRL incidence. Moreover, BCRL treatment offers many therapeutic modalities, including conservative and surgical methods that can be tailored to suit the individual patient. For BCRL research to continue to advance, clinical researchers must utilize objective, standardized measurements that are comparable to other studies in addition to PROM/symptom monitoring and clinical examination. Doing so would allow researchers to better compare individual study results using different preventative/treatment techniques, thereby allowing providers to make informed decisions regarding patient treatment.

One theme that becomes apparent while reviewing the literature is the need for a multidisciplinary approach to diagnose, treat, and prevent BCRL. Success necessitates communication and coordination with a patient's medical, surgical, and radiation oncologists and nurse practitioners as well as with their physical therapists. Fundamental to BCRL screening are pre-operative measurements to determine a patient's natural baseline asymmetry. To successfully diagnose BCRL early, health care providers on the patient's treatment team must make a concerted effort to ensure these measurements are obtained preoperatively. Screening must be longitudinal throughout and beyond treatment for breast cancer, incorporating objective measures, subjective data and clinical examination. Such a screening program allows for early detection and treatment of swelling before it can progress. Ideally, preoperative imaging studies could allow surgeons to identify patients with pre-existing lymphatic disruption and develop individualized surgical plans to minimize BCRL risk. After surgery and treatment, it is imperative to monitor any upper extremity edema, a responsibility that extends beyond the clinical staff. Patients themselves are important components of any treatment team, and clinical providers must educate patients about BCRL and their individual risk for developing it. Quality, comprehensive, individualized patient education should allow a patient to be vigilant, not fearful, in monitoring her at-risk limb. It is a mutual goal of the entire team to maximize every patient's quality of life beyond treatment for breast cancer. A multidisciplinary team-based approach to understanding, screening for, preventing, diagnosing, and treating BCRL is strongly recommended to provide best care for patients who have been treated for breast cancer and who are at risk of BCRL.

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Footnote

Conflicts of Interest: AG Taghian has been loaned equipment from ImpediMed for use in an investigator initiated clinical trial. ImpediMed has had no involvement in the conception or reporting of our research activities. AG Taghian has been a consultant for VisionRT (image-guidance radiation oncology). The other authors have no conflicts of interest to declare.

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