review articles

Breast Cancer–Related Lymphedema: Risk Factors, Screening, Management, and the Impact of Locoregional Treatment

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INTRODUCTION

Patients fear lymphedema as an unpredictable daily reminder of breast cancer treatment. The medical community has assumed for years that the development of breast cancer–related lymphedema (BCRL) stemmed solely from the primary surgical extirpation of the axillary lymph nodes. However, contemporary data suggest that BCRL development is multifactorial, influenced by multimodality locoregional and systemic treatment strategies and perhaps by the individual patient's ability to form collateral lymphatic pathways after injury, as well as potentially modifiable risk factors such as body mass index (BMI). Understanding the interaction between comprehensive locoregional treatment strategies and their collective impact on overall survival and long-term adverse effects such as BCRL is critical to providing patients individualized treatment recommendations. Herein, we review important factors for the development, diagnosis, prevention, and treatment of BCRL that should be considered when determining the contemporary locoregional management of breast cancer.

RISK FACTORS

Axillary Surgery

The precise incidence of BCRL is difficult and complicated to determine as a result of the prolonged period of latency from breast cancer treatment to initial BCRL signs or symptoms. There is no doubt that the extent of axillary surgery is a significant risk factor.[1] Axillary lymph node dissection (ALND) results in greater lymphatic disruption than sentinel lymph node biopsy (SLNB) and can quadruple the rate of BCRL.[1-4] Removal of more lymph nodes and the total number of positive lymph nodes are consistently cited as BCRL risk factors but are likely corollaries for extent of dissection or need for multimodality therapy, respectively. Currently, the progression of breast cancer clinical trial development has focused on strategic de-escalation of locoregional therapy, particularly to the axilla.[2,5,6] Although primary outcomes for these trials have been survival or local recurrence related, many have included secondary aims focusing on BCRL, providing contemporary insight into incidence.

Collectively, the risk of BCRL after SLNB is between 3% and 8% based on prospective randomized trials.[1,3] Single-institution series corroborate these data. Byun et al[7] observed 7,617 patients for a median of 60 months, reporting BCRL in 3% of patients who underwent SLNB. Similarly, Belmonte et al[8] reported BCRL in 3.4% of SLNB-negative patients. Regarding ALND, the B-32, IBCSG, Z1071, and AMAROS trials documented BCRL risk to range from 13% to 60%, with most studies using a > 10% relative volume change (RVC) as diagnostic for BCRL.[1-3,6] Importantly, length of follow-up and criteria for diagnosis can sway incidence rates and mandate critical synthesis when broadly comparing BCRL incidence across studies. For example, Wetzig et al[9] defined BCRL as > 15% volume change, finding BCRL in only 5% of ALND patients noting progressive swelling changes over 5 years. When their definition changed to include any swelling, 26% of ALND patients were categorized as having BCRL.[9]

In the prospective American College of Surgeons Oncology Group Z1071 trial, all patients proceeded to ALND and 87% had additional radiation.[2] At a median follow-up of 3 years, 37.8% of patients reported symptoms of arm swelling, 58.4% had measured BCRL > 10%, and 36.9% had > 20% RVC in the ipsilateral arm. In this trial, however, BCRL was not confirmed by clinical exam, nor is it clear whether training was provided to those performing the measurements to limit interrater variability. Others have also found a relationship between ALND and regional lymph node radiation (RLNR) but document lower BCRL rates ranging from 31.2% to 38.7%. Because these BCRL rates are higher than with either ALND or RLNR alone, they too support the additive influence of multimodality regional nodal therapies.

RLNR

Positive data from MA.20 and the European Organisation for Research and Treatment of Cancer trials have increased the number of lymph node–positive and high-risk node-negative patients receiving RLNR,[10,11] a significant risk factor for BCRL. Warren et al[12] evaluated 1,476 patients, finding that the supraclavicular (SCV) field regardless of posterior axillary boost (PAB) significantly increased BCRL.

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Chandra et al[13] reported that the extent of the lateral border of the nodal field, dose per fraction, energy used, and tangent types were not correlated with BCRL incidence. Conversely, Gross et al[14] found higher BCRL rates when the lateral border of the nodal field encompassed more than one third of the humoral head. Interestingly, this study also showed that covering the SCV field using anterior oblique beams with and without PAB yielded similar BCRL rates to treatment with parallel opposed beams to include upper level I, II, and III axilla. Unfortunately, this study lacked preoperative baseline arm measurements and quantified BCRL using tape measurements only to completion of radiation sessions. Gross et al[14] found that the axillary-lateral thoracic vessel juncture (superior to level I) dose was most associated with BCRL risk ($P < .001$). These results have not been prospectively validated.

Finally, Naoum et al[15] prospectively observed 1,811 patients and showed that BCRL risk depends mainly on the extent of axillary surgery. The authors classified patients according to extent of axillary surgery with or without RLNR; SLNB alone, SLNB plus RLNR, ALND alone, and ALND plus RLNR yielded cumulative incidences of BCRL of 7.7%, 10.8%, 29%, and 38.7%, respectively, at 5 years. Multivariable analysis showed no significant difference in BCRL risk between SLNB groups and ALND groups regardless of use of RLNR; both ALND groups had higher BCRL risks than those who underwent SLNB. Local control rates were similar across the 4 groups. These data, together with a recent meta-analysis,[4] validate the AMAROS trial data,[6] suggesting the significant reduction of BCRL rates if RLNR replaces ALND in patients with 1-2 positive sentinel lymph nodes.

BMI

BMI of $\geq$ 30 kg/m^2 at breast cancer diagnosis is an independent BCRL risk factor.[16] Weight gain or loss during or after treatment and its effect on BCRL risk is evolving. In a recent randomized trial involving overweight survivors of breast cancer with BCRL, effects of weight loss were examined. Although women in the weight loss group and the combined weight loss and home-based exercise group lost −7.37% (95% CI, −8.90% to 5.84%) and −8.06% (95% CI, −9.82% to −6.29%) of their baseline weight, respectively, weight loss did not improve BCRL outcomes[17] (clinical assessment, symptoms, BCRL exacerbations, cellulitis, or limb volume). The exact impact of postoperative weight fluctuation warrants more study to effectively inform patient education.

Cellulitis

Cellulitis is a well-established BCRL risk factor.[18-20] Cellulitis exacerbates preexisting BCRL, leading to a recurrent cellulitis-BCRL flare cycle.[20] The pathophysiologic relationship between cellulitis and BCRL remains unclear.

Low-Level Limb Volume Changes

Low-level arm volume changes after breast cancer surgery increase progression to BCRL.[21,22] One study found that patients developing RVC increases of 3% to < 5% from baseline within 3 months of surgery or 5% to < 10% from baseline at any point after surgery were more likely to progress to BCRL (RVC $\geq$ 10%).[23] Another study found similar results in patients who had $\geq$ 5 lymph nodes removed and arm swelling at 6 or 12 months.[22]

TIMING OF BCRL ONSET

In a cohort of 2,171 prospectively screened women, BCRL onset peaked between 12 and 30 months postoperatively; however, timing of onset varied with treatment (Fig 1). Early-onset BCRL (< 12 months postoperatively) was associated with ALND (hazard ratio [HR], 4.75; $P < .0001$) but not RLNR (HR, 1.21; $P = .55$). Late-onset BCRL (> 12 months) was associated with RLNR (HR, 3.86; $P < .0001$) and ALND (HR, 1.86; $P = .029$). BCRL risk was highest at 6-12 months in the ALND group (no RLNR), at 18-24 months in the ALND plus RLNR group, and at 36-48 months in the SLNB plus RLNR group. The

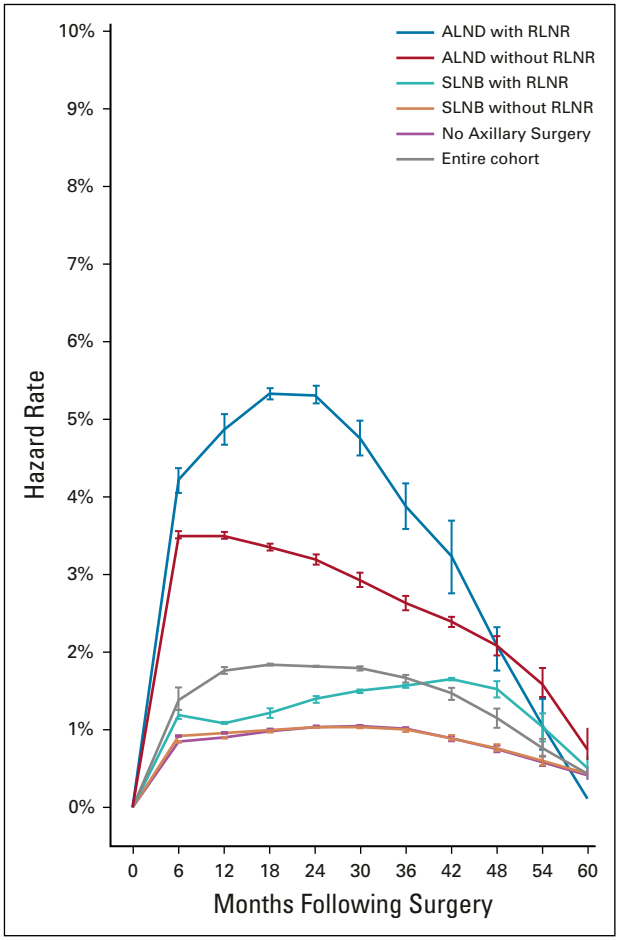


FIG 1. Semiannual hazard rate for development of breast cancer–related lymphedema for the entire cohort and by axillary surgery and radiation groups. ALND, axillary lymph node dissection; RLNR, regional lymph node radiation; SLNB, sentinel lymph node biopsy. Reprinted from McDuff et al,[23] with permission of Elsevier.

understanding of the onset of BCRL will inform screening practices and education.[23]

BCRL SCREENING

Widespread support is emerging for a prospective screening model using objective measures, symptoms, and clinical exam for early diagnosis and prevention of BCRL progression.[24,25] The American Society of Breast Surgeons (ASBrS),[26] the National Comprehensive Cancer Network (NCCN),[27] the National Lymphedema Network (NLN),[28] and the International Society of Lymphology (ISL)[29] all endorse prospective screening beginning at the time of breast cancer diagnosis.

Critical Preoperative Baseline Measurement

Objective limb measurements should be performed at baseline and at regular follow-up intervals for best diagnostic accuracy.[24,29,30] Lack of baseline measurements results in incorrect diagnoses of BCRL because arm asymmetry naturally exists. A prospectively screened cohort of 1,028 patients demonstrated that 28.3% and 2.9% of patients had preoperative arm asymmetry of ≥ 5% and ≥ 10%, respectively (Fig 2).[31] Misdiagnosis occurred in 40%-50% of patients when a postoperative pseudo-baseline was substituted for a true preoperative baseline measurement in a cohort of 1,028 patients prospectively screened for BCRL from preoperative baseline.[31]

RVC

BCRL diagnosis should incorporate volume changes in the affected limb when compared with preoperative baseline, while taking into account weight fluctuations.[32] Formulas for determining RVCs are listed in Table 1. For patients who have undergone unilateral surgery, the contralateral arm functions as the control. For patients who have undergone bilateral surgery and therefore lack a control arm for comparison, the weight-adjusted change (WAC) equation was developed (Table 1),[33] accounting for weight fluctuations relative to baseline.

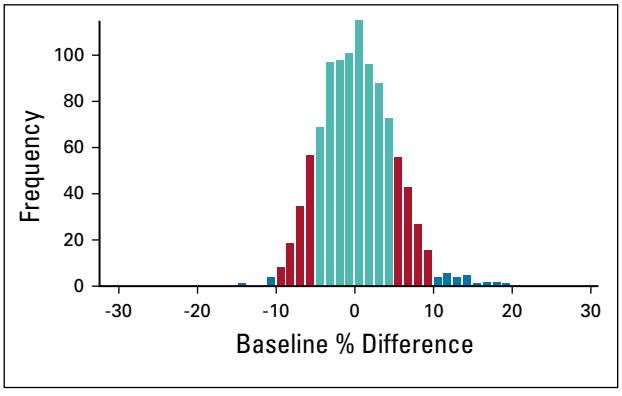


FIG 2. Histogram of baseline arm asymmetry. Magnitude of baseline asymmetry > 5% and > 10% is shaded; 28.3% and 2.9% of the study cohort have magnitude of baseline asymmetry > 5% and > 10%, respectively. Reprinted from Sun et al,[31] by permission from Springer Nature.

BCRL Definition

BCRL is defined as RVC ≥ 10% or WAC ≥ 10% more than 3 months after breast surgery. Although RVC or WAC ≥ 10% is generally accepted as a diagnostic threshold for intervention, some studies have shown treatment effectiveness at RVC as low as 3%[25]; however, these studies lacked a control group not receiving treatment.

Historically, an increase in volume of 200 mL or in circumference of 2 cm in the at-risk arm[32] has been used to diagnose BCRL, which is fraught with error. This does not take into account baseline arm volume or common weight fluctuations. In one study, an absolute volume increase of ≥ 200 mL corresponded to RVC from 2.9%-15.7%, depending on preoperative arm volume (Fig 3),[32] whereas BCRL defined as a 2-cm increase in the affected arm relative to baseline resulted in an RVC from 6.0%-9.8%.[32]

Objective Screening Measures

The lack of standardization in measurement has significantly hindered research in BCRL. Several methods of capturing objective data are reported, each with unique strengths and limitations (Table 2 and Fig 4). Limb circumferences taken with a tape measure at regular intervals along the arm may be used to calculate limb volume. Although 4-cm and 10-cm intervals are frequently used, a minimum of 6 anatomic landmarks may also be used.[30] Commercially available calculators can aid in calculating total limb volume from girth measures, which may then be entered into the RVC or WAC equations (Table 1). Although time consuming, this method is inexpensive and the most commonly used. However, significant training and practice are required to ensure ongoing reliability of this method.[34]

A perometer is a reliable, valid, and diagnostically accurate limb volume measurement system consisting of a frame containing infrared lamp-light receiver pairs. The patient sits in an upright position abducting her arm to 90 degrees while the frame is moved along the arm length. Each arm is measured 3 times, which is completed in < 3 minutes.[24] Perometry identifies subclinical BCRL.[25,35,36] Volumes calculated from perometry are then entered into the WAC or RVC equations (Table 1).

Bioimpedance spectroscopy (BIS) assesses tissue resistance to an electrical current and converts it into a score reflecting interstitial fluid content.[37] The newest BIS technology, SOZO (ImpediMed, Carlsbad, CA), takes < 1 minute, with the patient standing on a platform without shoes, socks, or jewelry holding the machine handles.[37] Although BIS is effective in detecting established BCRL,[37] it may not detect early- or late-stage BCRL when tissues become fibrotic.[38,39]

Lymphoscintigraphy is a gold standard for BCRL diagnosis, allowing for direct visualization of lymphatic function.

TABLE 1. Formulas for Calculating Breast Cancer-Related Lymphedema Volume Changes in Patients With and Without an Unaffected Control Limb

Unilateral At-Risk Limb[36]	Bilateral At-Risk Limbs[33]
Relative volume change (RVC)	Weight-adjusted change (WAC)
RVC = ([A2 × U1]/[U2 × A1]) − 1	WAC = ([A2 × W1]/[W2 × A1]) − 1
A1 = volume of the affected limb at baseline	A1 = volume of the affected limb at baseline
A2 = volume of the affected limb at given time point	A2 = volume of the affected limb at given time point
U1 = volume of the unaffected limb at baseline	W1 = body weight at baseline
U2 = volume of the unaffected limb at given time point	W2 = body weight at given time point

Radiotracer injected into the hand or wrist is taken up by the lymphatic vessels and nodes, and single-photon emission computed tomography assesses dermal backflow and lymphatic blockages. Although accurate, lymphoscintigraphy is not feasible for routine screening as a result of cost and logistics.

SYMPTOMS RELATED TO BCRL

Patients suffering from BCRL report lower quality of life than those without BCRL,[40] and symptoms may be the earliest predictor of BCRL.[41] Armer et al[41] found that BCRL was predicted by patient report of "heaviness in past year" and "swelling now." Fu and Rosedale[42] found that, upon interview, patients reported up to 10 symptoms daily classified into the following 4 psychosocial themes: living with perpetual discomfort; confronting the unexpected; losing prelymphedema being; and feeling handicapped. The study also confirmed the nonlinear relationship between type and number of symptoms and limb volume.[40]

The ASBrS, NCCN, ISL, and NLN[26-29] recommend incorporating longitudinal symptom assessment into BCRL screening alongside objective measurements.[41] Educating at-risk patients on BCRL symptoms facilitates self-screening, even in the absence of formal screening programs.

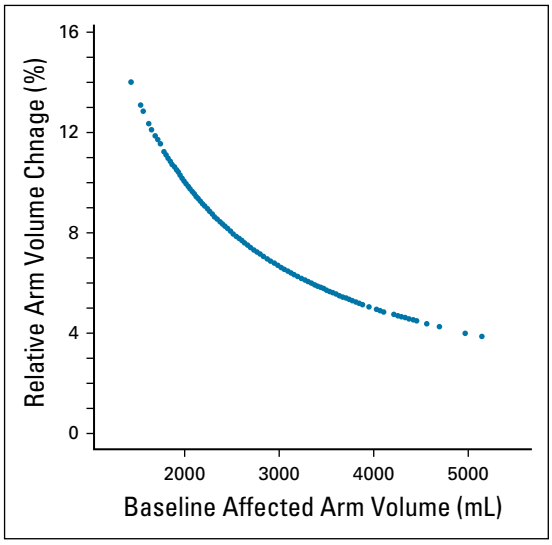


FIG 3. Relative arm volume change corresponding to arm volume increase by 200 mL in the unaffected arm of 677 patients. Reprinted from Ancukiewicz et al,[32] by permission from Springer Nature.

CLINICAL EXAM

Examination should include a basic history (considering individual BCRL risk factors, swelling onset, location, inciting factors, and symptoms) and vascular exam. Other potential causes of swelling such as deep vein thrombosis should be ruled out. The Cancer-Related Lymphedema of the Upper Extremity (CLUE) tool was developed and validated to standardize clinical examinations for lymphedema, providing a single score accounting for multiple constructs.[43] Subscores include obscuration of anatomic architecture, deviation from normal anatomic contour, tissue texture, and edema (pitting). Swelling in early BCRL (ISL stage 0, I, or early II)[29] is pitting, because it is mostly fluid, but in chronic BCRL, swelling becomes fatty and fibrotic, and therefore, there is less pitting.[29] Each CLUE subscale is scored from 0-18, with a scoring system for each subscale. This tool showed good intrarater reliability (intraclass correlation coefficient [ICC], 0.88; 95% CI 0.71 to 0.96), good interrater reliability (ICC, 0.90; 95% CI, 0.79 to 0.95), and moderately strong concurrent validity with perometry (Pearson $r = 0.79$) and subjective measurements (Pearson $r = 0.52$).[43] Of note, patients with subclinical BCRL (ISL stage 0)[29] may have minimal to no edema on clinical examination but report symptoms that may or may not progress to BCRL.

DEVELOPING A BCRL SCREENING STRATEGY

Optimal BCRL screening consists of both objective and subjective assessments.[24] The objective screening modality used will vary by institution based on resources and workflow. Providers must understand advantages and disadvantages of each potential modality and ensure a strict measurement protocol is consistently followed regardless of the modality used. Baseline measurements of both arms are critical for accurate BCRL diagnosis[24]; RVC should be used (if using volumetric measures) and screening should continue longitudinally every 6-12 months for a minimum of 2-3 years.

REFERRAL TO A CERTIFIED LYMPHEDEMA THERAPIST

Patients should be referred to a certified lymphedema therapist (CLT) for treatment when RVC from baseline is ≥

TABLE 2. Advantages and Disadvantages of Common Objective Measurement Techniques for Diagnosing BCRL

Objective Measure	Advantages	Disadvantages
Water volumetry	Reliable, validated	Hygienic standards limit clinical utility
Girth measures	Reliable, validated, inexpensive	Requires strict measurement protocol and training
Perometry	Reliable, accurate, validated Identifies subclinical BCRL	Expensive Not portable Requires dedicated space
Bioimpedance spectroscopy	Efficient and accurate in measuring established BCRL	Expensive with monthly fee for software and data management May not detect subclinical or late-stage BCRL
Lymphoscintigraphy	Diagnostically accurate Assesses lymphatic flow and function	Invasive Requires skilled personnel and dedicated resources

Abbreviation: BCRL, breast cancer–related lymphedema.

10%,[44] when the bioimpedance score changes 7 L-Dex units from baseline using BIS,[45] or when patients at risk experience symptoms or focal edema on clinical exam. CLTs may be found through the Lymphology Association of North America,[46] the NLN,[47] and an international directory through the Vodder School.[48]

CONSERVATIVE MANAGEMENT

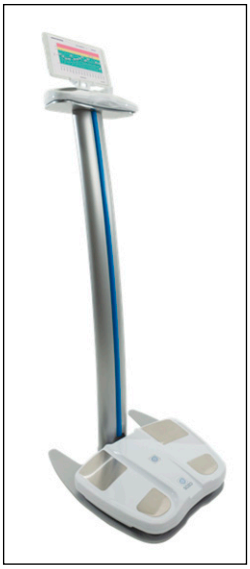
Conservative management consists of a reduction phase and a maintenance phase. The reduction phase aims to decrease limb volume and symptoms through complete decongestive therapy (CDT), which is a combination of manual lymphatic drainage (MLD), multiple layer compression bandaging, exercise, skin care, and patient education. The reduction phase continues for several days per week over several weeks. Once maximal volume and symptom reduction is achieved, treatment shifts to maintenance of limb volume and symptom reduction. Maintenance typically includes a transition from multiple-layer bandaging to compression garments, self-MLD, exercise, and skin care.

Compression alone may be used to prevent swelling progression in patients with subclinical BCRL, and it may reduce limb volume with or without MLD in those with BCRL.[49] Advanced BCRL, however, requires CDT.

Intermittent pneumatic compression (IPC) pumps have been used to treat BCRL since the 1950s. The IPC pump and corresponding appliance are placed on the limb, inflating and deflating in pressure gradients, mimicking MLD performed by a CLT. Whether IPC improves BCRL outcomes is unclear.[50] IPC may be considered for patients unable to attend clinic regularly for CDT or as an adjunct to CDT. It is not recommended for first-line or stand-alone BCRL treatment.

EXERCISE

Exercise has emerged as a crucial survivorship recommendation after breast cancer treatment.[51] Schmitz



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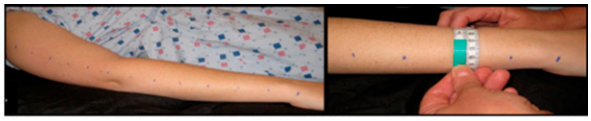
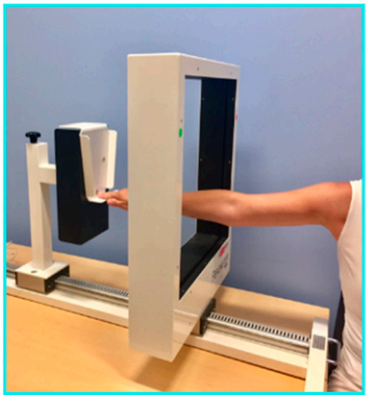


Girth Measures With Tape Measure



Perometry

FIG 4. Common objective measurement tools for breast cancer–related lymphedema screening: bioimpedance spectroscopy[37] (SOZO Bioimpedance Spectroscopy Device; ImpediMed, Carlsbad, CA). Copyright © ImpediMed Limited and ImpediMed, Perometry, Girth Measures.

et al[52,53] conducted the Physical Activity and Lymphedema Trial (PAL), a 12-month, randomized controlled trial of twice-per-week weight lifting or standard care in survivors of breast cancer both at risk for and with BCRL. They found that a slowly progressive facility-based weight lifting program decreased BCRL by 35%.[52] Patients with BCRL participating in the weight lifting program had fewer BCRL flare-ups and reduced symptoms compared with those in the control group.[53] They concluded that an individually prescribed, initially supervised, and slowly progressed aerobic and resistance exercise program does not incite or worsen BRCL.[52,53] More recently, the Women in Steady Exercise Research (WISER) trial[17] evaluated 351 overweight survivors of BC with BCRL. Patients were randomly assigned to a control group, an exercise group (52 weeks; 2 sessions per week of home-based resistance training and 180 minutes walking per week), a weight loss group (20 weeks of meal replacements, 52 weeks of lifestyle modification counseling), or a combined exercise and weight loss group. The study found no significant differences in BCRL between groups in clinical values or symptoms at 12 months. The authors concluded that the home-based exercise program was not enough to elicit a physiologic effect on BCRL and that a facility-based, supervised, progressive program as in the PAL trial[52,53] may be superior to a home-based program for patients with BCRL.

PREVENTION

Precautionary Measures

There are several precautionary recommendations made by the NLN intended to decrease risk of BCRL.[54] These guidelines include skin care; preferential avoidance of blood pressure cuffs, venipuncture, and trauma; and wearing a compression garment during air travel.[54] These guidelines were developed based on an abundance of caution; however, following these guidelines has not been shown to reduce BCRL risk.[19,20,55] In 632 prospectively screened patients, Ferguson et al[19] reported that blood pressure readings, blood draws, and air travel were not associated with arm volume increase. Later, the same group reported similar results from 327 patients who underwent bilateral breast cancer surgery.[55] Others have reported that in women with ≥ 5 lymph nodes removed, air travel, arm trauma, medical procedures, and arm use did not increase BCRL.[56] ASBrS recommendations state the following: "Within the context of an early detection/surveillance program incorporating baseline and follow-up assessments, the routine application of many risk-reducing behaviors is not supported. Use of the ipsilateral arm for IVs or blood pressures is not contraindicated."[57(p2828)] This recommendation is echoed by the ISL.[29] Nevertheless, at this point, there is no universal agreement on precautionary measure guidelines because this issue is evolving.

Surgery for Lymphedema Prevention

There is increased focus on prophylactic surgical techniques performed at initial axillary surgery intending to prevent BCRL. Axillary reverse mapping (ARM) hypothesizes that blue dye injected into the volar aspect of the upper arm can map upper extremity lymphatic drainage.[58] At surgery, the surgeon then seeks to protect the blue lymphatics or nodes.

A systematic review of 8 studies each with at least 50 patients having ARM plus SLNB or ARM plus ALND found that BCRL occurred in 0%-6% of ARM plus SLNB and 5.9%-24% of ARM plus ALND patients.[59] Concern remains over the risk of crossover nodes (node draining both breast and upper extremity), which occurs in up to 10% of patients, of whom 0%-20% had metastases in the crossover nodes. In addition, ARM nodes were unable to be preserved in 11%-18% of patients, of whom up to 19% of patients had metastases in the ARM node.[59] A recent prospective trial in which the patient and assessor were blinded to the surgical intervention randomly assigned 107 patients needing ALND to ARM or no ARM.[60] With 24 months of follow-up, no difference in objective BCRL existed (ALND, 32.3%; ARM plus ALND, 23.5%; $P = .43$); however, patients who underwent both ARM and ALND had significantly less patient-reported symptomatic BCRL than patients who underwent ALND alone (6.1% *v* 26.7%, respectively; $P = .025$).[60] The Alliance for Clinical Trials has recently opened a prospective randomized trial (A221702) evaluating SLNB or ALND with and without ARM to formally evaluate ARM.

Yuan et al[61] sought to build upon the principles of ARM and upper extremity nodal identification and preservation. They described the Identification and Preservation of Arm and Lymphatic (DEPART) technique. After identification of the ARM node, the ARM node was further injected intraoperatively to map and therefore protect the next echelon of lymph nodes involved in upper extremity lymphatic drainage. Proving feasibility in their technique, they subsequently randomly assigned 1,354 patients needing ALND to DEPART plus ALND or ALND alone. Overall, more ALND patients developed BCRL (defined as $>$ 10% RVC) than those undergoing DEPART plus ALND (15.3% *v* 3.3%, respectively; $P < .001$). ARM nodes were not identified in 17% of patients and contained metastases in 6.8%. Regional recurrence rates did not differ between the groups, with both being $< 1.4\%$ ($P = .39$).

Another technique, the Lymphatic Microsurgical Preventative Healing Approach (LYMPHA), seeks to maintain lymphatic flow into the venous system using microsurgical techniques to "dunk" transected axillary lymphatics into a nearby vein with a competent valve. Although fewer patient series have been published affirming this procedure, limited data suggest it may be valuable. In the initial publication, Boccardo et al[62] reported BCRL in 30% of patients with ALND without LYMPHA but in only 4% of

patients with LYMPHA. More recently, Feldman et al[63] found BCRL in substantially more standard ALND patients (50%) than LYMPHA patients (12.5%); however, those in the standard ALND cohort were ineligible for LYMPHA as a result of extensive disease or inability to identify usable lymphatics, suggesting the cohorts may not have been evenly matched. Further study on the role of LYMPHA is needed.

Breast Reconstruction

An emerging body of data indicates that breast reconstruction does not adversely affect the risk of BCRL. Unfortunately, few studies stratify breast reconstruction and BCRL rates by type or timing of reconstruction. In a prospective single-institution series, Miller et al[64] analyzed 616 patients undergoing reconstruction. Multivariable analysis suggested implant-based reconstruction may reduce BCRL risk (HR, 0.35; $P < .0001$).[64] Others find that autologous reconstruction may provide more effective BCRL risk reduction; for example, Lee et al[65] found the BCRL incidence to be 4.2% after autologous reconstruction and 9.3% after implant reconstruction (HR, 0.39; 95% CI, 0.19 to 0.82; $P = .012$). A meta-analysis of 19 studies concluded that fewer women with breast reconstruction developed BCRL (odds ratio [OR], 0.66; 95% CI, 0.55 to 0.79; $P < .001$), with no difference in rates between autologous or implant-based techniques (OR, 0.92; 95% CI, 0.48 to 0.1.77).[66] These data collectively support that breast reconstruction is safe and will not adversely influence BCRL risk.

SURGICAL MANAGEMENT OF BCRL

Advances in microsurgical skills and microsurgical technology have reenergized the discussions surrounding surgical intervention for symptomatic and progressive BCRL. Broadly, interventions are classified as reductive (resection of fibrotic lymphatic tissue) or reconstructive (reanastomosis of lymphatic vessels to veins, other lymphatics, or lymph node transfer). Suction-assisted protein lipectomy, the contemporary reductive technique, is effective at removing nearly 100% of excess limb volume in advanced stages of BCRL.[67] However, it subsequently mandates strict adherence to lifelong compression therapy to maintain volume reductions because it does not improve lymphatic function. Reconstructive techniques aim to restore lymphatic flow and are predicated on some level of existing residual lymphatic function. As a result, they are more effective in earlier stage I or II BCRL.[67] Emerging data are heterogeneous with respect to indications, benefit, follow-up, and outcomes, making standard implementation difficult. It is clear though that, when considered, these patients should be assessed by a multidisciplinary team that has an understanding of BCRL and aftercare where surgery is considered part of a multimodality treatment plan.[57]

THE FUTURE OF BCRL

Exciting contemporary science postulates alternative inherent risk factors for BCRL, specifically genetic predisposition and biomarker identification. Individual genetic variations may explain why only a percentage of patients undergoing the same locoregional and systemic treatments ultimately develop BCRL. Some variations may afford protection from BCRL, whereas others negatively contribute to risk.[68,69] Visser et al[70] recently identified 18 genes influencing BCRL risk, adding to the mechanistic theory of BCRL development. Evolving data also suggest that inflammatory,[71] immunologic,[72,73] and extracellular matrix modulator[73] biomarkers may influence BCRL risk. In fact, pilot studies demonstrate promise for oral anti-inflammatory medications such as ketoprofen in lymphedema treatment.[74] Hopefully, these data can complement existing clinicopathologic and treatment variables to better inform on risk stratification or future patient selection for therapeutic intervention.

CONCLUSION

The development of BCRL is multifactorial, and modern-day breast cancer physicians must acknowledge the contribution and synergism of individual local, regional, and systemic therapies on BCRL risk. Screening for BCRL should be standard practice, including baseline bilateral objective measurements. Patient education should start at the time of breast cancer diagnosis, and longitudinal screening programs,[24] including subjective and objective measures and clinical exam, are imperative for early diagnosis and possible effective management. BCRL as a treatment adverse effect must be considered by the breast cancer community at large.

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SUPPORT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Breast Cancer–Related Lymphedema: Risk Factors, Screening, Management, and the Impact of Locoregional Treatment

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