Ann Surg Oncol
DOI 10.1245/s10434-017-5982-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Considerations for Clinicians in the Diagnosis, Prevention, and Treatment of Breast Cancer-Related Lymphedema: Recommendations from a Multidisciplinary Expert ASBrS Panel

Part 1: Definitions, Assessments, Education, and Future Directions

Sarah A. McLaughlin, MD[1], Alicia C. Staley, MBA, MS, BS[2], Frank Vicini, MD, FACR, FABS[3], Paul Thiruchelvam, BSc, MD, PhD, FRCS[4], Nancy A. Hutchison, MD, CLT-LANA[5], Jane Mendez, MD[6], Fiona MacNeill, FRCS, MD, FEBS[7], Stanley G. Rockson, MD[8], Sarah M. DeSnyder, MD[9], Suzanne Klimberg, MD, PhD[10], Michael Alatriste, LMT, CLT[11], Francesco Boccardo, MD, PhD, FACS[12], Mark L. Smith, MD, FACS[13], and Sheldon M. Feldman, MD, FACS[14]

[1]Department of Surgery, Mayo Clinic, Jacksonville, FL; [2]Patient Advocate, Akari Health, Boston, MA; [3]Radiation Oncology, UCLA School of Medicine, Los Angeles; [4]Imperial College Healthcare, London, UK; [5]Courage Kenny Rehabilitation Institute of AllinaHealth, Minneapolis, MN; [6]Miami Cancer Institute, Miami, FL; [7]Association of Breast Surgery Great Britain and Ireland, Royal College of Surgeons of England, London, UK; [8]Center for Lymphatic and Venous Disorders, Stanford University School of Medicine, Stanford, CA; [9]Department of Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [10]Winthrop P. Rockefeller Cancer Institute, Little Rock, AR; [11]Lymphedema Alliance of New York, New York, NY; [12]Department of Surgery, Unit of Lymphatic Surgery - S. Martino University Hospital, University of Genoa, Genoa, Italy; [13]Hofstra Northwell School of Medicine, Northwell Health Cancer Institute, Lake Success, NY; [14]Division of Breast Surgery and Breast Surgical Oncology, Department of Surgery, Montefiore Medical Center, The University Hospital for the Albert Einstein College of Medicine, New York, NY

Lymphedema is a chronic, debilitating disease defined as an abnormal, generalized, or regional accumulation of protein-rich interstitial fluid resulting in edema formation and change in tissue structure. Lymphedema reflects the "relative" imbalance between the rate of interstitial fluid generation (lymphatic load) and the degree to which the lymphatic vasculature (lymphatic transport capacity) is underdeveloped or damaged.[1]

Breast cancer-related lymphedema (BCRL) is a common but underreported complication of breast cancer treatment because few studies have baseline and follow-up measurements or long-term (>5 year) follow-up evaluation adequate to record the incidence accurately. Furthermore, lymphedema has negative impact on overall quality of life and represents a financial burden for patients, caregivers, and society.[2–4]

Recent prospective randomized trials continue to document the incidence of lymphedema after any axillary treatment (Table 1). This risk increases after combination therapy with axillary surgery and radiation, reaching 25–40%.[5] With the National Cancer Institute (NCI) predicting more than 4 million breast cancer survivors in the United States by 2024[6] and nearly 2 million women with a diagnosis of breast cancer annually worldwide, lymphedema represents a significant burden to global public health.

Controversy has existed for decades concerning the diagnosis and treatment of lymphedema, but in the last 5 years, the volume of literature addressing BCRL has

Electronic supplementary material The online version of this article (doi:10.1245/s10434-017-5982-4) contains supplementary material, which is available to authorized users.

First Received: 26 May 2017

S. A. McLaughlin, MD
e-mail: Mclaughlin.sarah@mayo.edu

Published online: 01 August 2017

TABLE 1 Incidence of breast cancer-related lymphedema by objective measures based on axillary intervention

	SLNB (%)	ALND (%)	Axillary radiation (%)	ALND and RNI (%)
B-32[52]	8	14		
AMAROS[61]		13	5	
MA.20[101]		4.5		8.4
Z0010[102,103]	7	14		
Z0011[104]	2	13		
IBCSG 23-01[105]	3	13		

SLNB sentinel node biopsy, *ALND* axillary node dissection, *RNI* regional nodal irradiation

increased significantly. Furthermore, because breast cancer survivors are living longer, issues of survivorship are moving to the forefront in patients' minds. Therefore, the American Society of Breast Surgeons (ASBrS) assembled an international, multidisciplinary panel of experts to acknowledge and raise awareness of lymphedema and to review current lymphedema teachings, data, and guidelines in hopes of collating the vast heterogeneous data into clear, meaningful recommendations for surgeons and clinicians caring for breast cancer patients. The broad topic of lymphedema was divided into components for initial individual literature review. Each panel member researched, summarized, and then exchanged his or her research topic summary electronically. This was followed by an in-person meeting at the 2017 annual ASBrS meeting. The recommendations were presented at the meeting, posted for public comment, and reviewed and approved by the ASBrS board of directors. These recommendations consist of two parts. Part 1 focuses on definitions, assessments, patient concerns, and future directions, whereas part 2 focuses on preventive and therapeutic options currently available.

DEFINING AND DIAGNOSING LYMPHEDEMA: OBJECTIVE AND SUBJECTIVE ASSESSMENTS

Objective

Diagnosing lymphedema is challenging, especially in the early stages (stage 0 or 1; Table 2) of the disease, with varying definitions and objective tools available for diagnostic assessment. The National Lymphedema Network (NLN), the International Society of Lymphology (ISL), the National Accreditation Program for Breast Centers, and the National Comprehensive Cancer Network (NCCN) recommend preoperative assessment and ongoing surveillance of the ipsilateral and contralateral arms at regular standardized intervals as best practice, but their guidelines, like many others,[7–10] do not recommend one particular technique as the gold standard screening option.[11,12]

The ideal anthropometric measuring tool should be easy to use, noninvasive, hygienic, cost effective, reliable, reproducible, and quantifiable.[13–15] Each contemporary method has advantages and disadvantages, as listed in Table 3. No head-to-head comparison trials are currently available that validate one technique over another, although a few studies are ongoing. Further details on the specifics of each method can be found online in Appendix 1.

Existing guidelines suggest that circumferential tape measurements are acceptable as a minimum standard provided they are completed with a non-stretch tape measure and at multiple points on each arm. A 2 cm increase in circumference is most commonly used to define lymphedema.[16] However, when multiple measurements are obtained, arm volumes also can be calculated using the formula of a truncated cone (frustum).[17] The NLN and ISL highlight the ability of bioimpedance spectroscopy (BIS), tissue dielectric constants, and infrared perometry to detect subclinical lymphedema, and these may be superior

TABLE 2 Lymphedema staging according to the 2016 consensus document of the International Society of Lymphology[7]

Stage	Evidence
0	Subclinical; absence of edema in "risk" development patient despite impaired lymph transport
1	Presence of edema reduced by treatment or arm elevation (pitting edema)
2	Edema partially reduced by treatment (pitting and non-pitting edema), intractable and progressive
3	Elephantiasis with skin lesions and relapsing infections

TABLE 3 Subjective and objective measures of BCRL[19,22,106–112]

Diagnostic technique	Advantages	Disadvantages
Self-reported symptoms	Inexpensive	Subjective
Bioimpedance spectroscopy (BIS)	Quick	Potentially limited to unilateral patients
	Accurate	Requires disposable electrodes, which may add expense
	Portable	No role in established fatty/fibrous lymphedema
	Identifies subclinical BCRL	
	FDA approved	
Circumferential tape measure	Reliable with extensive training	Time-consuming and cumbersome
	Inexpensive	Requires rigorous training to achieve reproducible results
	Easily accessible	Inter/intra rater variability
Perometry	Quick	Expensive
	Highly reproducible	Large footprint for perometer
	Accurate	Does not measure hand
	Provides segmental volumes	
	Identifies subclinical BCRL	
Tissue dielectric constant	Quick	Standard thresholds not definitively established
	Portable	
	Identifies subclinical BCRL	
	Provides segmental or unilateral measures	
Ultrasound	Quick	High- and low- (dual) frequency machines have greatest accuracy
	Portable	Standard thresholds not definitively established
	Identifies subclinical liquid as well as fibrofatty changes	Operator training and experience required
	Provides segmental or unilateral measures	
Water displacement	Accurate	Time-consuming
	Inexpensive	Requires a strict protocol
		Unhygenic
		Does not isolate site of swelling

BCRL breast cancer-related lymphedema, *FDA* Food and Drug Administration

methods for limiting the risk of false-negative or false-positive results of circumferential tape measures.

A paradigm shift in lymphedema surveillance has occurred, with increased vigilance for identifying subclinical[18] or early-stage lymphedema (relative volume changes of 5–10%) because an early-stage diagnosis offers the best opportunity for early intervention and treatment.[19–22] In addition, data suggest that surveillance and early identification strategies are more cost effective than waiting for symptoms or obvious swelling to occur.[23]

Ongoing trials are assessing the impact and importance of subclinical lymphedema.[24,25] The ideal detection tools for subclinical lymphedema should be objective and reproducible, providing a standardized metric that supports treatment decisions (4 tools described in Table 2). For surveillance, an initial preoperative measurement should be obtained followed by regularly scheduled postoperative measurements for 3–5 years. Unfortunately, available data do not standardize interventions or provide adequate long-term follow-up evaluation to clarify how patients should be treated in these settings. Long-term outcome studies are needed to determine whether more favorable or equivalent outcomes are associated with lymphedema detection at a subclinical or early clinical phase and to determine thresholds at which lymphedema is reversible and when it becomes irreversible.[26–28] Regardless, surgeons should incorporate appropriately trained health care professionals early in the process for assessment and treatment planning.

Subjective

Existing guidelines advocate for subjective symptom assessment and physical examination as well as objective measures because a combination of assessments improves

the diagnosis of lymphedema.[9,29,30] Therefore, BCRL should be evaluated with patient-reported outcomes (PRO) and an objective measure because health-related quality-of-life (HRQOL) impact does not directly correlate with measured limb volume,[30–34] and BCRL is a multifaceted condition.[33,35] However, the long-term pathophysiology of the condition relates to clinical factors.[35,36]

The effect of BCRL on one's life is dependent on one's vocation and usual activities (i.e., participation restriction), a core measure of the World Health Organization (WHO) International Classification of Functioning, Disability, and Health (ICF), together with the overall symptom burden for the affected extremity.[37–40] The usual PROs for BCRL are swelling, pain, heaviness, aching, numbness, stiffness, and impaired arm mobility.[33,40–42] The NCCN Survivorship Guidelines list lymphedema as a cancer pain syndrome.[43] However, many patients with clinical lymphedema do not have subjective symptoms, suggesting that at-risk patients without symptoms still need to be screened.[44,45] Research indicates that PROs should be evaluated at benchmarks during an extended period (2–6 years after treatment).[41,46] Early symptoms can be more intense, and symptom burden may decrease over time. Patients with prolonged symptom burden are at risk for employment loss, depression, increased medical costs, and loss of ability to perform daily life tasks and recreation.[4,31,32]

A number of tools have addressed the totality of upper quadrant symptom burden in BCRL.[37–41,47–49] The research on BCRL PROs concludes that BCRL is a multifaceted pathologic condition including immune dysfunction, swelling, physical impairment, and psychosocial impact, which cannot be accurately defined only by clinically reported outcomes (CRO). Recent attempts have been made to find an all-inclusive tool that will evaluate self-reported swelling, other common BC symptoms, and the impact of these on HRQOL with one tool instead of multiple separate tools.

Recommendation 1 The panel agrees that clinicians should establish a surveillance plan because early diagnosis leads to early treatment and increases the likelihood for limited disease burden.

Recommendation 2 The panel agrees that baseline and follow-up measurements of the ipsilateral and contralateral arms of all breast cancer patients are critical. All measurement techniques have advantages and disadvantages that should be considered when a comprehensive measurement strategy is developed that includes a combination of objective and subjective measures.

RISK FACTORS

Multiple treatment and patient-specific precipitating factors have been associated with the development of BCRL. Extensive breast or axillary surgery is consistently cited. Nesvold et al.[51] performed multivariate analysis and found a significant increase in BCRL (20 vs. 8%; $p = 0.02$) with the use of mastectomy compared with breast conservation (BCS).[50] Similarly, review of randomized trials assessing the validity of sentinel lymph node biopsy (SLNB)) supports the conclusion that axillary lymph node dissection (ALND) is associated with higher rates of BCRL.[50,52–55] Specifically, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 data show rates of BCRL at 3 years to be 8% for SLNB and 14% for ALND patients when a 10% relative volume increase is used as the diagnostic criteria.[53] Furthermore, the removal of many nodes is associated with BCRL, although no consistent cut point has been defined.[56,57]

Receipt of radiation therapy, particularly additive regional nodal irradiation,[58–61] increases BCRL.[50,52] Although limited data comparing the relative risk of BCRL development across interventions are available, the After mapping of the axilla: radiotherapy or surgery (AMAROS) trial reported that ALND is associated with a higher risk of BCRL than axillary radiation without ALND.[62] Finally, specific systemic therapies, especially taxane-based regimens, have been associated with both transient and persistent lymphedema.[60,61,63–65]

The most well-recognized precipitating factor for BCRL is obesity or elevated body mass index (BMI),[50,55,61,65–67] which has been consistently noted, even with NSABP B-04, demonstrating an association between BMI and arm edema. The current prospective Pathways study corroborates these findings.[65,68]

Recommendation 3 The panel agrees that clinicians should practice personalized medicine strategies to minimize axillary surgery, should question the routine use of postmastectomy or regional nodal irradiation, and should use genomic tests to guide the use of chemotherapy to collectively minimize the additive effects of multimodality therapy. Patients should maintain a healthy body weight/BMI.

NEED FOR EDUCATION

The current lack of patient educational standards as well as patient and clinician low awareness of risks and treatments makes lymphedema a critical concern for patients and patient advocates. Unfortunately, surveyed patients consistently show lack of understanding about the risks, recall no clinical discussions, and express generalized fear of lymphedema,[69,70] which persists after treatment.[70]

The NCCN Breast Cancer Panel adopted new standard recommendations in 2015 stressing the importance of lymphedema education as a key component of long-term follow-up care for breast cancer survivors.[71] Current

survivorship plans with long-term follow-up evaluation provide an opportunity for structured educational resources addressing lymphedema and lifestyle risk factors.

It is difficult to provide a personalized risk for BCRL because of numerous contributing variables including cancer treatments, genetics, physiology, and individual anatomy.[72] Guidelines emphasize the crucial role of patient education in encouraging risk-reducing lifestyle changes and early self-detection[43,73] because when these are combined with prompt interventions, significant improvements in outcomes and quality of life are achievable.[71,74]

The goals of patient education are threefold. First, clinicians must raise awareness of the lifetime risk for lymphedema, especially in the 3–5 years after surgery.[72] They should inform patients of concerning early signs and symptoms (unilateral/ipsilateral aching, heaviness, tightness, fullness, or stiffness) that often precede visible swelling[75] and should ask about clothing or jewelry becoming tighter or patient-perceived swelling. Second, clinicians should educate patients on critical risk-reducing strategies that are practical and evidence based.[76] Finally, clinicians should provide patients with a reliable specialist as a point of contact should they experience symptoms.

Patient education reduces BCRL risk and associated symptoms,[69,77,78] probably because of risk-reducing lifestyle changes such as exercise and weight loss. A prospective randomized trial demonstrated significantly lower rates of BCRL with education and active intervention compared with education only.[21] Also, a 10 year follow-up study showed that patients with a diagnosis of low-volume/early lymphedema had better long-term outcomes.[19] Further research is required to optimize BCRL educational program content, delivery method, and timing.

Recommendation 4 The panel agrees that surgeons should admit and accept that lymphedema risks exist and educate themselves and their patients about these risks at preoperative and follow-up visits. Education should continue into survivorship and be incorporated into survivorship care plans.

NEW RESEARCH, PROMISING TARGETS, AND FUTURE DIRECTIONS

Historically, the problem of lymphedema has been addressed as a mechanical one, emphasizing edema as a passive consequence of the disordered convection of fluid from the lymphedematous limb. In this context, it has been attractive to consider the therapeutic potential offered by the identified lymphatic growth factors (therapeutic lymphangiogenesis).

The first experimental application of therapeutic lymphangiogenesis was reported in an experimental model of acquired lymphedema in the rabbit ear, with direct administration of either recombinant vascular endothelial growth factor-C (VEGF-C)[79] or VEGF-C plasmid[80] to ameliorate the chronic acquired lymphedema. Subsequent studies investigating the murine tail reported similar efficacy.[81] Furthermore, the administration of adenoviral VEGF-C or -D in a large animal model reduced edema and invoked lymphatic vascular remodeling, with evidence of newly formed collecting vessels.[82]

In addition to VEGF-C and -D, a multiplicity of additional growth factors are recognized to stimulate lymphangiogenesis both in vitro and in vivo including angiopoietin-1, fibrobast growth factor (FGF)-2, hepatocyte growth factor, insulin-like growth factor (IGF)-1 and -2, platelet-derived growth factor, and VEGF-A.[83]

Although growth factor-induced and growth factor-dependent gene therapies show promise, concerns persist regarding the temporal limitation of the therapeutic effect, the potential for adverse blood vascular responses, and the likelihood of limited functionality inherent in the lymphatic hyperplasia response.[84,85] Thus, there has been an incremental focus on cell-based therapies with lymphatic endothelial progenitor cells.[86] For example, adipose-derived stem cells, when exposed to VEGF-C, express Prox-1, VEGF-C, and VEGF-A.[87] In experimental lymphedema, adipose-derived stem cells produce a lymphangiogenic response to the paracrine effects of their secreted VEGF-C.[88] Parallel efficacy can be demonstrated in a wound-healing model of lymphangiogenesis.[89]

Newer surgical approaches to lymphedema resolution incorporate a reliance upon the biology of lymphatic regeneration, without reliance upon exogenous growth factors or genetic materials. In particular, there is growing reliance upon vascularized lymph node transfer as a treatment strategy for acquired lymphedema.[90,91] Although this is promising, failure of lymphatic engraftment of the transplant may compromise surgical outcome.[92] To circumvent this treatment limitation, investigators have recently elaborated biologic scaffolds that, when surgically implanted at the time of lymph node transfer, are designed to accelerate lymphatic engraftment.[93] These scaffolds, composed of highly aligned nanofibrillar mammalian collagen, potentiate cellular migration and growth[94] between the existing lymphatics and the transplanted lymph node. The efficacy of these scaffolds has already been demonstrated in a porcine model of postsurgical lymphedema,[93] and clinical studies of the device in human lymphedema are underway.

Historically, studies have shown little proven utility for pharmacologic approaches to lymphedema.[95,96] However, in recent years there has been incremental interest in the role of inflammation in the generation and maintenance of lymphedema,[97,98] with significant potential implications

for human therapeutics. In lymphedema, there is remarkable upregulation of the gene expression related to acute inflammation, immune response, complement activation, wound healing, fibrosis, and oxidative stress response.[97] In the experimental setting, targeted inflammatory inhibition is responsible for substantial structural and functional improvement.[99,100] Clinical trials of focused inhibitory therapeutics are currently underway.[100]

The future of lymphedema therapeutics has been enhanced by the recent, substantial surgical, developmental, mechanistic, and molecular achievements in research. From the foregoing discussion, it can be envisioned that, for example, the preemptive use of biologic scaffolds, with or without adipocyte stem cell seeding, might promote lymphatic healing after the breast cancer therapeutics are concluded and thereby serve as a minimally invasive preventive strategy for acquired lymphedema. Continued investigation into the inflammatory substrate of lymphedema, as well as other molecular approaches, is likely to yield ever more effective pharmaceuticals and molecular therapeutics.

Recommendation 5 To acknowledge the pathophysiology of lymphedema as a mechanical insufficiency alone is likely simplistic. Lymphatic obstruction, inflammation, immune response, complement activation, wound healing, and fibrosis to the development of lymphedema. Therapeutic lymphangiogenesis and targeted inflammatory inhibition may aid structural and functional lymphatic improvement.

ACKNOWLEDGEMENTS This work was funded via an unrestricted educational Grant from ImpediMed.

DISCLOSURE Frank Vicini is a research adviser for ImpediMed. Sarah A. McLaughlin, Alicia C. Staley, Paul Thiruchelvam, Nancy A. Hutchison, Jane Mendez, Fiona MacNeill, Stanley G. Rockson, Sarah M. DeSnyder, Suzanne Klimberg, Michael Alatriste, Francesco Boccardo, Mark L Smith, and Sheldon M. Feldman have no conflicts of interest to report.

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