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EDUCATIONAL OBJECTIVES:

After reading the article "Recent Progress in the Treatment and Prevention of Cancer-Related Lymphedema," the learner should be able to:

1. Review the risk factors and pathophysiology of cancer-related lymphedema.
2. Discuss the strengths and limitations of various methods for the diagnosis of lymphedema and assessing its impact on symptoms and quality of life.
3. Review evidence regarding treatment options for patients with cancer-related lymphedema.

ACTIVITY DISCLOSURES

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Recent Progress in the Treatment and Prevention of Cancer-Related Lymphedema

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This article provides an overview of the recent developments in the diagnosis, treatment, and prevention of cancer-related lymphedema. Lymphedema incidence by tumor site is evaluated. Measurement techniques and trends in patient education and treatment are also summarized to include current trends in therapeutic and surgical treatment options as well as longer-term management. Finally, an overview of the policies related to insurance coverage and reimbursement will give the clinician an overview of important trends in the diagnosis, treatment, and management of cancer-related lymphedema. **CA Cancer J Clin 2015;65:55-81.**

Keywords: lymphedema, morbidities, treatment, diagnosis

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Introduction

In 2009, Lawenda et al published an in-depth review of the anatomy of the lymphatic system and the pathophysiology of lymphedema in this journal.[1] In the present review, we build on the foundation established by Lawenda et al and provide updated information on advancements in the field of lymphedema. Specifically, we review the contemporary literature and report lymphedema incidence after treatment for a wide range of cancers, discuss ongoing debates about defining lymphedema, and describe new technologies for visualizing and assessing lymphedema. In addition, we summarize the studies addressing controversies in the optimal treatment and prevention of lymphedema, as well as some current health policy issues related to the condition.

Impact of Lymphedema

Lymphedema is a significant health issue for cancer survivors.[2] The condition can severely affect patients' health-related quality of life (HRQOL), a multidimensional construct that comprises items belonging to a number of domains,

Additional Supporting Information may be found in the online version of this article.

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including emotional, functional, social/family, and physical domains.[3] Emotional well-being measures a person's coping ability and includes the person's perceptions of feelings ranging from joy to distress. Functional well-being identifies a person's ability to perform the activities of daily living, such as dressing, bathing, walking, and performing household tasks. Social well-being includes feelings related to the quality and quantity of relationships with friends and family as well as wider social interactions. Physical well-being, the domain thought to be most affected by lymphedema, includes questions related to pain. A large number of instruments have been developed to assess specific lymphedema symptoms.[4-6] Although these tools are useful in clinical practice, they do not encompass the physical well-being domain as it factors into overall HRQOL.[7]

QOL outcomes have been assessed in patients with various cancers who develop lymphedema and most frequently in patients with breast cancer who have the condition. In 2013, Pusic et al[8] completed a systematic review of QOL outcomes in breast cancer survivors with lymphedema. The authors identified 39 studies that met the review's inclusion criteria. Seventeen different HRQOL instruments were used in the studies; the most commonly used instruments were the 36-item Medical Outcomes Survey-Short Form and the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, which measure overall QOL and do not include lymphedema-specific items. However, the review identified 2 HRQOL instruments that were validated specifically for use in women with breast cancer-related lymphedema: the Wesley Clinic Lymphedema Scale[9] and the Upper Limb Lymphedema-27 questionnaire.[10] The review's findings indicated that exercise and complete decongestive therapy were associated with improved overall QOL in this patient population.

Functional well-being is much more frequently affected in patients with lower extremity lymphedema than in those with lymphedema of the upper extremities.[11] In one study, 789 women with gynecologic cancers were given questionnaires to determine the effect of lymphedema on functional well-being.[11] Of the 616 women who returned completed surveys, 36% reported having lymphedema. Compared with the women who did not report having lymphedema, the women who reported having lymphedema had a lower overall QOL (relative risk [RR], 1.2; 95% confidence interval [95% CI], 1.0-1.4), less satisfaction in functional well-being symptoms including difficulty with sleep (RR, 1.3; 95% CI, 1.1-1.5), and increased urgency to use the restroom (RR, 1.6; 95% CI, 1.2-2.3). Despite the adverse outcomes associated with their lymphedema, less than 30% of the women sought medical care to help manage symptoms.

Pathophysiology of Lymphedema

Lymphedema results from a disequilibrium between the microvascular filtration rate of the capillaries and venules and that of the lymphatic drainage system. Vascular anomalies that could lead to or contribute to lymphedema include vasodilation and/or angiogenesis, which may cause increased vascular flow that cannot be compensated by the existing lymphatic vessels, and venous obstruction, which may cause swelling.[12]

Lymphedema can result from an intrinsic fault in the lymphatic vessels (primary lymphedema) or damage caused to the lymphatic vessels or nodes (secondary lymphedema). Secondary lymphedema is the most prevalent form of lymphedema and is typically caused by obstruction or disruption of the lymphatics due to surgery, radiation, trauma, or infection (typically filariasis).[13] Obesity is a well-known risk factor for the development of secondary lymphedema after oncologic treatment,[14] but the mechanism mediating this association has yet to be elucidated.

Manifestation

Lymphedema typically manifests as swollen, sometimes disfigured, extremities or truncal regions that can be painful and cause functional impairment.[15-17] Electron microscopic examination of damaged lymphatics suggests that their destruction first occurs proximally, at the smooth muscle cells of the vessel walls.[18] Functional studies have demonstrated that drainage from superficial and deep lymphatic vessels is often interrupted, leading to superficial collateralization with retrograde flow to the skin lymphatics (dermal backflow). The retained lymphatic fluid is typically confined to the epifascial space of the skin and subcutaneous tissue and does not involve the deeper muscle.[19] Lymphatic fluid stasis is associated with the accumulation of interstitial fluid in the subcutaneous tissue and skin, and the proteins and glycosaminoglycans in the retained interstitial fluid are thought to subsequently stimulate collagen production, which leads to skin thickening and subcutaneous soft tissue fibrosis.[19] Lymphedema is associated with a greater than 70-fold increase in the risk of cellulitis, which is believed to be due to disturbances in immune cell transport caused by a compromised lymphatic system.[20] Both bacterial infections related to *Streptococcus* and fungal infections have been identified in patients with lymphedema.[21]

Genetics

Why only some patients develop secondary lymphedema due to cancer treatment remains unknown. This uncertainty has made it challenging to appropriately advise patients of their risk of cancer treatment-related lymphedema. One potential explanation may be patients' different

genetic characteristics. Recent studies have identified polymorphisms in multiple candidate genes that appear to be associated with the development of breast cancer-related lymphedema.[22,23]

Additional studies have evaluated genes that are known to impact lymphatic development or have been identified in inherited, primary lymphedema. For example, in a study of 59 women with breast cancer-related lymphedema, 6 individual mutations were identified that led to the truncation or missense changes of hepatocyte growth factor (HGF) and the HGF receptor (HGFR/MET) in a small subset of those with secondary lymphedema.[24] The second study was a case-control study of 188 women, 80 of whom had lymphedema (cases). Mutations in the GJC2 gene, which encodes connexin-47, were identified in 4 patients with lymphedema, but not in any of the 108 breast cancer survivors without lymphedema (controls) ($P = .03$). In the same study, only one of the cases and none of the controls had a HGFR/MET mutation; no HGF mutations were found in either controls or cases.[25] A recent study compared the frequency of genetic polymorphisms among breast cancer survivors with or without lymphedema and found significant associations for 3 genes: interleukin-4, interleukin-10, and nuclear factor-κB2, all of which are involved with the body's inflammatory response.[26] Genetic polymorphisms associated with immune-deficient states have also been linked with lymphedema.[20] Finally, an analysis of skin biopsies and serum from normal controls and patients with lymphedema (the majority of whom had secondary lymphedema related to cancer) identified a panel of candidate serum biomarker proteins involved in the development of lymphedema.[27] All these findings have been reported as preliminary and require validation in large data sets. Such studies hold promise for the early identification and risk stratification of patients likely to develop lymphedema, which would facilitate targeted therapy with molecular and pharmacologic agents.

Incidence

Patients With Breast Cancer

The number of breast cancer survivors living in the United States as of January 2014 was more than 3 million, and is predicted to rise to almost 4 million by January 2024.[28] Given the incidence of breast cancer, the frequency of axillary surgery and irradiation, and the large number of breast cancer survivors, it is not surprising that breast cancer-related lymphedema has received the most attention of all cancer-related lymphedemas. One of the largest population-based prospective studies to date, of 631 women living in Pennsylvania, found that the 5-year cumulative incidence of patient-reported lymphedema among breast cancer survivors was 42%.[29] Although the majority of these women experienced mild lymphedema, an early onset of mild lymphedema symptoms was associated with a significantly higher risk of developing moderate to severe lymphedema. The exact incidence of lymphedema among breast cancer survivors varies and largely depends on the type of treatment received, with patients who undergo axillary lymph node dissection (ALND) having the highest incidence. Our review of the literature has revealed that the pooled incidence of breast cancer treatment-related lymphedema after sentinel lymph node biopsy (SLNB) is 6.3% (range, 0%-23%) (Table 1),[30-46] whereas that after ALND is 22.3% (range, 11%-57%) (Table 2).[30,31,34-37,43,44,46-49]

Lymphedema Beyond Patients With Breast Cancer

Patients with other solid tumors requiring treatment that adversely affects lymphatic function are also at significant risk of developing lymphedema. Unfortunately, relatively few studies have investigated lymphedema in these patient populations. For example, a recent systematic review identified only 47 studies that assessed non-breast cancer-related lymphedema, and most of those studies were retrospective.[50] The following subsections provide an overview of the current body of published literature regarding the incidence of lymphedema as a result of the treatment of nonbreast malignancies.

Patients with melanoma

Our review of the published literature revealed that patients with melanoma who undergo SLNB have a pooled lymphedema incidence of 4.1% (Table 3).[51-56] For patients treated with a therapeutic lymph node dissection, one review of studies enrolling a total of 3676 patients found an overall pooled treatment-related lymphedema incidence of 9% (range, 1%-66%).[50] Interestingly, the pooled lymphedema incidence of patients who underwent inguinofemoral lymph node dissection (18%) was higher than that of patients who underwent ALND (3%) (Table 4).[50,54,55,57-69] This difference may be due to anatomic variability in the number of collateral lymphatic pathways or differences in hydrostatic pressure based on the location of the lymphatic disruption.

Hyngstrom et al conducted a detailed prospective assessment of melanoma-related lymphedema in 182 patients using both objective and subjective measurement tools.[51] After 12 months, the incidence of moderate lymphedema among patients treated with SLNB (14.8%) was substantially lower than that of patients treated with therapeutic lymph node dissection (30.4%). Compared with SLNB alone, lymph node dissection conferred a greater than 3-fold risk of mild to moderate lymphedema. Furthermore, patients with melanoma of the lower extremities were 1.72 times more likely to develop increased limb volume change (LVC) compared with patients with upper extremity melanoma. Compared with patients who had minimal LVC (<5%), patients with volumetrically assessed

TABLE 1. Studies Assessing Lymphedema After SLNB for the Treatment of Breast Cancer

REFERENCE	NO. OF PATIENTS	MEASUREMENT TECHNIQUE	LYMPHEDEMA INCIDENCE, %
Sackey 2014[30]	140	Water displacement	20
Sagen 2014[31]	187	Water displacement	3
Velloso 2011[32]	45	Circumference	4
Goldberg 2010[33]	600	Circumference	5
Lucci 2007[34a]	446	Circumference	7
Langer 2007[35]	449	Circumference	4
Mansel 2006[36]	478	Circumference	5
Francis 2006[37]	26	Circumference	17
Wilke 2006[38]	2904	Circumference	7
Leidenius 2004[39]	92	NR	4
Ronka 2004[40]	57	NR	23
Langer 2004[41]	40	NR	0
Blanchard 2003[42]	683	Circumference	6
Haid 2002[43]	57	Circumference	4
Swenson 2002[44]	169	Subjective	9
Sener 2001[45]	303	NR	3
Schrenk 2000[46]	35	NR	0
Total: 17	6711		Average: 7 Range: 0-23 Pooled incidence: 6.3

SLNB indicates sentinel lymph node biopsy; NR, not reported. [a]Subset of a larger research study which included more extensive nodal surgery.

TABLE 2. Studies Assessing Lymphedema After ALND for the Treatment of Breast Cancer

REFERENCE	NO. OF PATIENTS	MEASUREMENT TECHNIQUE	LYMPHEDEMA INCIDENCE, %
Sackey 2014[30]	194	Water displacement	45
Sagen 2014[31]	204	Water displacement	17
Rutgers 2013[47]	744	NR	28
Ashikaga 2010[48]	1975	Water displacement	14
Teshome 2014[49]	853	Circumference	40
Lucci 2007[34]	445	Circumference	11
Langer 2007[35]	210	Circumference	19
Francis 2006[37]	73	Circumference	47
Mansel 2006[36]	403	Circumference	13
Haid 2002[43]	140	Circumference	27
Swenson 2002[44]	78	Subjective	17
Schrenk 2000[46]	35	NR	57
Total: 12	5354		Average: 28 Range: 11-57 Pooled incidence: 22.3

ALND indicates axillary lymph node dissection; NR, not reported.

TABLE 3. Studies Assessing Lymphedema After SLNB for the Treatment of Melanoma

REFERENCE	NO. OF PATIENTS	MEASUREMENT TECHNIQUE	LYMPHEDEMA INCIDENCE, %
Hyngstrom 2013[51]	84	Perometry	15
Murawa 2013[52]	47	Circumference	2
Palmer 2013[53a]	47	NR	2
de Vries 2006[54]	52	Circumference	6
de Vries 2005[55]	44	Water displacement	11
Roaten 2005[56]	339	NR	0.6
Total: 6	613		Average: 6.1 Range: 0.6-15 Pooled incidence: 4.1

SLNB indicates sentinel lymph node biopsy; NR, not reported. [a]Pediatric melanoma cohort.

TABLE 4. Studies Assessing Lymphedema After Surgical Lymph Node Dissection for Melanoma

REFERENCE	NO. OF PATIENTS	MEASUREMENT TECHNIQUE	LYMPHEDEMA INCIDENCE, %
Axillary lymph node dissection			
de Vries 2005[55]	14	Water displacement	7
Starritt 2004[57]	107	Water displacement/circumference	17
Serpell 2003[58]	33	Subjective	6
Burmeister 2002[59]	56	Subjective	39
Lawton 2002[60]	106	Circumference	5
Bowsher 1986[61]	28	Circumference	3
Urist 1983[62]	98	Circumference	1
Total: 8	2130		Average: 9.9 Range: 1-39 Pooled incidence: 3
Inguinofemoral lymph node dissection			
Brouns 2008[63]	62	Circumference	61
de Vries 2006[54]	66	Water displacement	18
Wrightson 2003[64]	784	Subjective	6
Serpell 2003[58]	27	Subjective	29
Burmeister 2002[59]	33	Subjective	66
Lawton 2002[60]	56	Circumference	14
Baas 1992[65]	151	Water displacement/circumference	20
Bowsher 1986[61]	44	Circumference	35
Karakousis 1983[66]	67	Circumference	21
Urist 1983[62]	58	Circumference	26
James 1982[67]	33	Water displacement/circumference	58
Holmes 1977[68]	84	Circumference	24
Papachristou & Fortner 1977[69]	81	Circumference	30
Total: 13	1546		Average: 31.4 Range: 6-61 Pooled incidence: 18

Adapted from Cormier JN, Askew RL, Mungovan KS, Xing Y, Ross MI, Armer JM. Lymphedema beyond breast cancer: a systematic review and meta-analysis of cancer-related secondary lymphedema. *Cancer*. 2010;116:5138-5149.[50]

TABLE 5. Studies Assessing Lymphedema in Patients With Gynecologic Malignancies

REFERENCE	NO. OF PATIENTS	MEASUREMENT TECHNIQUE	LYMPHEDEMA INCIDENCE, %
Vulvar cancer			
Carlson 2008[70]	137	Circumference	64
Van der Zee 2008[71]	383	Subjective	9
Moore 2008[72]	31	Subjective	0
Zhang 2007[73]	57	Subjective	37
Bellati 2007[74]	14	Subjective	21
Judson 2004[75]	61	Subjective	26
Gaarenstroom 2003[76]	101	Subjective	28
de Hullu 2001[77]	106	Subjective	73
Total: 8	890		Average: 32.3 Range: 0-73 Pooled incidence: 30
Miscellaneous			
Tanaka 2007[78]	184	Subjective	11
Fujiwara 2003[79]	64	Subjective	11
Cervical cancer			
Bergmark 2002[80]	246	Subjective	41
Uno 2000[81]	98	Subjective	19
Kridelka 1999[82]	25	Subjective	12
Logmans 1999[83]	22	Subjective/MRI	23
Snijders-Keilholz 1999[84]	220	Subjective	10
Yeh 1999[85]	179	Subjective	42
Chatani 1998[86]	128	Subjective	49
Werngren-Elgstrom & Lidman 1994[87]	54	Water displacement	41
Fiorica 1990[88]	50	Subjective	2
Bilek 1982[89]	120	Subjective	14
Martimbeau 1978[90]	402	Subjective	23
Total: 11	1544		Average: 25.1 Range: 2-49 Pooled incidence: 27
Endometrial cancer			
Orr 1991[91]	168	Subjective	1

MRI indicates magnetic resonance imaging. Adapted from Cormier JN, Askew RL, Mungovan KS, Xing Y, Ross MI, Armer JM. Lymphedema beyond breast cancer: a systematic review and meta-analysis of cancer-related secondary lymphedema. *Cancer*. 2010;116:5138-5149.[50]

moderate lymphedema had a 7-fold to 9-fold higher rate of lymphedema-associated symptoms. The most common lymphedema-related symptoms patients described included numbness, swelling, tightness, and tenderness.

Patients with gynecologic cancers

The treatment of gynecologic cancers has been reported to be associated with an overall lymphedema incidence of 25%, with specific incidences of 1%, 27%, and 30% for endometrial cancer, cervical cancer, and vulvar cancer, respectively (Table 5).[50,70-91] However, in patients who undergo SLNB as a part of their gynecologic cancer treatment, the overall pooled incidence of lymphedema is reported to be 9.0% (range, 0%-25%) (Table 6).[72,92-95] Such studies may lead to a greater understanding of the lymphatic system's different responses to the assault of oncologic treatment.

Patients with head and neck cancer

Prospective studies of lymphedema in patients with head and neck cancer have been relatively limited. Our review of the published literature revealed a pooled lymphedema incidence

TABLE 6. Studies Assessing Lymphedema After SLNB for the Treatment of Gynecologic Cancer

REFERENCE	NO. OF PATIENTS	MEASUREMENT TECHNIQUE	LYMPHEDEMA INCIDENCE, %
Robison 2014[92]	69	NR	8
Achouri 2013[93]	88	Subjective	11
Novackova 2012[94]	12	Circumference	25
Niikura 2013[95]	23	Subjective	9
Moore 2008[72]	31	NR	0
Total: 5	223		Average: 10.6 Range: 0-25 Pooled incidence: 9.0

SLNB indicates sentinel lymph node biopsy; NR, not reported.

of 4% (range, 0%-8%) in this population (Table 7).[50,59,62,96] Investigators at Vanderbilt University recently published a prospective study of 81 patients with head and neck cancer who were assessed for posttreatment lymphedema.[97] They found that 75.3% of the patients had some degree of lymphedema, as defined by visible swelling in the skin and soft tissues of the head and neck and/or by internal swelling of the mucosa and underlying soft tissue of the aerodigestive tract visualized with flexible fiber-optic endoscopy or mirror examination. By these definitions, 7.4% of patients had external lymphedema, 29.6% had internal lymphedema, and 50.8% had both external and internal lymphedema. Of the patients with external lymphedema, 18.5% had stage I and 27.2% had stage II lymphedema according to Foldi's scale, and of the patients with internal lymphedema, 34.5% had mild, 45.5% had moderate, and 20% had severe lymphedema based on the Patterson scale. Moderate lymphedema most often involved the interarytenoid space, valleculae, and aryepiglottic folds, whereas severe lymphedema most often involved the pyriform sinus and interarytenoid space. This study highlights that detailed physical examination can reveal a strikingly high incidence of lymphedema after treatment of head and neck cancer.

Patients with genitourinary cancers and sarcomas

The lymphedema risk associated with treatment of genitourinary cancers and sarcomas has received relatively little attention. One systematic review identified pooled lymphedema incidences of 4%, 16%, and 21% after treatment for prostate cancer, bladder cancer, and penile cancer, respectively (Table 8).[50,98-105] Notably, the majority of studies included in that review used subjective criteria to measure lymphedema. In another study, the lymphedema incidence among 54 patients treated for sarcoma was 30%.[106]

Impact of Radiation

Relatively few lymphedema studies have included detailed descriptions of radiation targets as a part of treatment. This has made it challenging to separate the effects of radiation from those of surgery on lymphedema genesis. Similarly, although radiation is thought to augment the risk of breast cancer treatment-related lymphedema, isolating radiation's contribution from that of surgery is difficult (Table 9).[34,47,48,107] We recently conducted a systematic literature review and found that the lymphedema incidence based on radiation targets alone was 14.5% for patients treated with breast/chest wall irradiation; 31.5% for patients treated with breast/chest wall and supraclavicular irradiation;, and 41.4% for patients treated with breast/chest wall, supraclavicular, and posterior axillary boost irradiation. The pooled lymphedema incidences among patients who received radiation were 16% for patients with genitourinary cancers, 34% for patients with gynecologic cancers, and 50% for patients with melanoma.[50]

TABLE 7. Studies Assessing Lymphedema in Patients With Head and Neck Cancer

REFERENCE	NO. OF PATIENTS	MEASUREMENT TECHNIQUE	LYMPHEDEMA INCIDENCE, %
Wolff 2009[96]	50	Subjective	8
Burmeister 2002[59]	41	Subjective	5
Urist 1983[62]	48	Circumference	0

Adapted from Cormier JN, Askew RL, Mungovan KS, Xing Y, Ross MI, Armer JM. Lymphedema beyond breast cancer: a systematic review and meta-analysis of cancer-related secondary lymphedema. *Cancer*. 2010;116:5138-5149.[50]

TABLE 8. Studies Assessing Lymphedema in Patients With Genitourinary Malignancies

REFERENCE	NO. OF PATIENTS	MEASUREMENT TECHNIQUE	LYMPHEDEMA INCIDENCE, %
Penile cancer			
Jacobellis 2003[98]	10	Subjective	20
Ravi 1993[99]	234	Circumference	21
Total: 2	244		Average: 20.5 Range: 20-21 Pooled incidence: 21
Bladder cancer			
Henningsohn 2002[100]	224	Subjective	15
Clark 1978[101]	43	Subjective	23
Total: 2	267		Average: 19 Range: 15-23 Pooled incidence: 16
Prostate cancer			
Kavoussi 1993[102]	372	Subjective	1
Greskovich 1991[103]	65	Subjective	3
Rainwater & Zincke 1988[104]	30	Subjective	10
Lieskovsky 1980[105]	82	Subjective	18
Total: 4	549		Average: 8 Range: 1-18 Pooled incidence: 4

Adapted from Cormier JN, Askew RL, Mungovan KS, Xing Y, Ross MI, Armer JM. Lymphedema beyond breast cancer: a systematic review and meta-analysis of cancer-related secondary lymphedema. *Cancer*. 2010;116:5138-5149.[50]

Measuring Lymphedema

Many different objective tools, ranging from external volumetric assessment to minimally invasive lymphatic mapping, as well as subjective tools that involve physician and/or patient input, are available for lymphedema measurement. The differences among these measurement tools and inconsistent measurement criteria contribute to the wide variation in the reported incidence of cancer-related lymphedema. In addition, relatively small sample sizes, a lack of prospective studies, a lack of reliability in many studies,[108] and variability in patient follow-up make it difficult to compare study findings and accurately predict the lymphedema risk associated with various oncologic treatments. Given that early detection and intervention have been shown to provide patients with most appropriate treatment and effective lifelong management of symptoms,[109,110] defining an accurate, reproducible tool with which to measure and quantify lymphedema clinically would have a meaningful impact on millions of cancer survivors.

Objective Measurement Tools

The ideal objective tool for lymphedema measurement would be efficient, easy to use, noninvasive, inexpensive, hygienic, reliable, and adaptable to any part of the body that

TABLE 9. Studies Reporting the Incidence of Breast Cancer Treatment-Related Lymphedema Based on Extent of Lymph Node Surgery and Radiation Therapy

		LYMPHEDEMA INCIDENCE, %				
REFERENCE	FOLLOW-UP TIME	SLNB PLUS WBI	ALND PLUS WBI	SLNB PLUS WBI PLUS RNI	ALND PLUS WBI	ALND PLUS WBI PLUS RNI
NSABP B-32[48]	36 mo	8	14			
ACOSOG Z0011[34]	12 mo	6	11			
EORTC AMAROS[47]	5 y			14	28	
NCIC-CTG MA.20[107]	5 y		4.2			7.3

SLNB indicates sentinel lymph node biopsy; WBI, whole breast irradiation; ALND, axillary lymph node dissection; RNI, regional lymph node irradiation; NSABP, National Surgical Adjuvant Breast and Bowel Project; ACOSOG, American College of Surgeons Oncology Group; EORTC AMAROS, European Organization for Research and Treatment of Cancer After Mapping of the Axilla: Radiotherapy Or Surgery; NCIC-CTG, National Cancer Institute of Canada Clinical Trials Group.

FIGURE 1. Water Displacement Technique for the Measurement of Limb Volume.

could be affected by lymphedema.[108,111,112] Such a tool could be easily implemented clinically and be used to take prospective serial measurements of patients' lymphedema from the time they first present through their care in survivorship clinics. Given differences in limb dominance and changes in body mass index over time, initial preoperative measurement is important for all measurement tools.[111]

Water displacement

Water displacement is generally considered to be sensitive and specific for quantifying limb volume, and the tools required for its clinical implementation are relatively inexpensive (Fig. 1). However, the technique is particularly cumbersome and messy, making it difficult to apply in a clinical setting.[108] Although it provides an accurate overall volumetric measurement, water displacement cannot be used to localize lymphedema to a particular limb segment. Water displacement has also been reported to have a broad standard deviation (up to 25 mL).[113]

FIGURE 2. Circumference Measurement of the Forearm for Quantification of Upper Extremity Lymphedema.

FIGURE 3. Perometry Measurement of the Upper Extremity.

Circumference measurement

Circumference measurement can be taken at set anatomic points along the extremity to assess the extent of lymphedema (Fig. 2). These measurements can be used to track centimeter-sized changes in limb circumference at a particular location or calculate the limb's volume. Ideally, these measurements are obtained using flexible, nonstretching measuring tapes, which are relatively inexpensive and widely available. However, this measurement tool has a high degree of interrater and intrarater variability.[108] In addition, the equations used to calculate limb volume are based on a simplification of actual anatomy, presuming a cylindrical circumference at each point measured. The measurement procedure is also time-intensive and requires substantial training and experience.

Perometry

The perometer is a noninvasive optoelectronic device that uses infrared light to quantify the volume of the limb (Fig. 3). The device is mounted to an open frame; as the frame is moved along the extremity, the perometer creates a computer output based on near-infrared laser sensors and receivers that includes an image of the limb and volumetric measurement. Thus, abnormalities in particular regions of the extremity can be well localized.[114] The estimated standard deviation of the tool's measurements is 8.9 mL.[115] The machine is efficient to use and is hygienic, because it does not require direct contact with the involved limb.

Bioelectrical impedance

Bioelectrical impedance (bioimpedance) measures the opposition of the flow of an electrical current through the body; this impedance is inversely related to the volume of conductive material in the region. Electrocardiography-like electrodes are attached to the skin at 2 points spanning the region of interest. Bioimpedance spectroscopy measures impedance over a range of frequencies and models the

impedance from 0 to infinite frequencies.[116] The path of the electrical current through tissue is frequency-dependent; impedance at 0 frequency takes account of the extracellular water compartment (including lymph), and that at infinite frequency predicts the impedance of total tissue water. The impedance in one extremity is normalized to that in the contralateral limb, and this ratio is compared against other normative values. This ratio is typically reported with 2 or 3 standard deviations.[116-118]

Comparison

Armer and Stewart at the University of Missouri assessed breast cancer treatment-related lymphedema of the upper extremity using 4 distinct diagnostic criteria: 200-mL LVC as measured by perometry, 10% LVC as measured by perometry, 2-cm change in arm circumference via tape measurement, and patient-reported symptoms of heaviness or swelling.[108] The study cohort was 221 patients with stage I to IV breast cancer who received a broad range of therapies. The prevalence of lymphedema at 1 year after treatment as assessed using the 4 measurement techniques were 42% for 200-mL LVC (95% CI, 31%-53%), 21% for 10% LVC (95% CI, 12%-30%), 70% for 2-cm change in arm circumference (95% CI, 60%-79%), and 40% for patient-reported symptoms of heaviness or swelling (95% CI, 30%-59%). These incidences differed significantly. The authors concluded that the most conservative criteria for defining lymphedema was a 10% LVC, whereas the most liberal criteria was a 2-cm change in arm circumference.

In another study, researchers at the Universitair Ziekenhuis Brussel compared perometry with water displacement and arm circumference measurements.[119] The study, which included 80 patients, used each technique to calculate relative arm volumes, and 3 different formulas were used to calculate volume based on arm circumference measurements. The researchers found that arm circumference-based volume calculations using formulas for a truncated cone and a disc model (which divides the extremities into multiple cones) resulted in the largest volume measurements, whereas water displacement measurements resulted in the smallest volume measurements. Three perometer measurements were performed for each patient, with high intrarater reliability (interclass correlation coefficient [ICC] for agreement, 0.997-0.999). The authors deemed a single frustum-based (single truncated cone) calculation less than ideal because it did not account for the typically elliptical shape of edematous arms and thus underestimated arm volume.

Deltombe et al also compared water displacement, arm circumference, and perometry among 30 breast cancer survivors.[120] For both arm circumference and water displacement measurements, intrarater reliability was found to be better than interrater reliability, leading the authors to recommend that the same individual should perform serial measurements on a given patient. The overall ICC ranged from 0.94 to 1. The authors also recommended against the use of a frustum-based model for calculating arm volume based on circumference measurements owing to its relatively high intrarater relative difference (3.2%). In comparing these techniques, the investigators found that perometry had the highest reliability (ICC, 0.997) and was the most efficient of the tools available.[120]

Subjective Measurement Tools

In response to reports that subjective findings of lymphedema are precursors to objective findings of the condition,[121,122] many lymphedema staging systems now include a preclinical stage.[123-125] Indeed, objective and subjective measurement tools may identify distinct aspects of lymphedema; perhaps a particular tool should be selected depending on the goal of the lymphedema assessment (eg, screening for treatment referral, assessing for incidence secondary to cancer treatment, assessing response to lymphedema treatment). Subjective tools may be best used to identify patients for whom lymphedema results in a significant decline in QOL.[126]

Many instruments for assessing subjective reports of lymphedema have been developed. In a study of 577 breast cancer survivors, Bulley et al[126] and Webster et al[127] compared the prevalence of lymphedema as assessed using perometry with the prevalence of lymphedema as assessed using 3 instruments: the Functional Assessment of Cancer Therapy questionnaire with breast cancer and arm function subscales (FACT-B Version 4), the Lymphedema and Breast Cancer Questionnaire (LBCQ), and the Morbidity Screening Tool.[6,126,127] The range of reported lymphedema prevalence based on these measurement tools ranged from 20.5% to 26.3%, with no significant difference in symptoms identified between patients who had lymphedema and those who did not. There was moderate agreement between subjective tools (kappa [κ]=0.531) but only poor agreement between subjective tools and perometry (κ=0.143-0.207). The investigators reported that using an objective limb volume difference of 10% resulted in a higher prevalence of lymphedema; however, whether subjective or objective measurement tools result in a higher lymphedema prevalence remains unclear.[108,126,128,129] The study was limited in that it was a cross-sectional study without baseline (ie, pretreatment) volumetric measurements.

Symptom assessment

One of the earliest and most robust studies to investigate symptoms as early indicators of LVC was conducted by Armer et al. In this study, the investigators sought to determine the predictive and discriminatory validity of a lymphedema symptom questionnaire to predict objective findings of lymphedema.[6] The authors used the LBCQ, a semistructured interview tool that inquires about 19

symptoms present currently or within the past year as well as arm circumference measurements.[130] Questions elicit information concerning the following symptoms: swelling, tenderness, erythema, blistering, tightness, heaviness, stiffness, aching, seroma formation, change in temperature, size, limitations in movement, and weakness. The 2 factors found to be most predictive of objectively measured lymphedema were patient reports of "heaviness in the past year" and "swelling now."

The LBCQ has also been used to assess symptoms in patients with melanoma who were treated with lymph node surgery.[51] One study found that in a cohort of 182 patients, those with lymphedema (defined as a >10% LVC) at 1 year reported increases in a mean of 6 symptoms (range, 4-14 symptoms), whereas those without lymphedema reported an increase in a mean of 3 symptoms (range, 2-5 symptoms). The most commonly reported symptoms were numbness, swelling, tightness, and tenderness. The symptom scores of patients who underwent lymph node dissection were significantly higher than those of patients treated with only an SLNB ($P < .05$).

Building on the LBCQ, the Gynecologic Cancer Lymphedema Questionnaire (GCLQ) was created to identify lower extremity lymphedema symptoms secondary to gynecologic cancer treatment.[5] In a pilot study of the GCLQ, 58 gynecologic cancer survivors completed the 20-item symptom questionnaire and provided leg circumference measurements. Higher scores on the questionnaire were associated with the presence of objectively assessed lymphedema, with an overall area under the receiver operating characteristic curve of 0.95. The symptoms found to be most predictive of objective lymphedema were swelling, numbness, and heaviness. Nearly all patients (95%) reported that the GLCQ was easy to understand, and even more patients (97%) expressed their willingness to complete the 5-minute to 10-minute questionnaire at subsequent visits. The authors presented multiple clinical cutoff scores with their associated sensitivities and specificities. Additional work will need to be done to determine how to best use this tool in the clinical setting to appropriately diagnose and refer patients for lymphedema treatment.

Objective assessment of symptoms of early limb swelling has been studied by Stout et al, who investigated segmental changes in limb volume.[114] The authors have described subclinical, measurable volume changes in segments of the limb that occur prior to and may be predictive of the onset of lymphedema in patients with breast cancer. The authors measured arm segments at 10-cm intervals along the limb. A significant volume increase was measurable at 2 segments of the limb (10-20 cm and 20-30 cm) prior to the diagnosis of subclinical lymphedema. Furthermore, the coefficient of determination (r^2) for these segments was 0.845 and 0.952, respectively, suggesting that these segments predicted total LVCs prior to a diagnosis of lymphedema. The authors provide evidence that serial interval assessment of segmental limb volume may be a clinically important symptom assessment tool in the early detection of lymphedema.

Patient-reported outcomes

Cemal et al recently conducted a systematic review of studies investigating the HRQOL of patients with lymphedema of the lower extremity related to cancer treatment.[131] The authors identified only 6 studies that met the review's inclusion criteria, which included the use of a validated patient-reported outcome questionnaire. None of the studies were considered as level I evidence, and only one study used a patient-reported outcome instrument that was specific to cancer-related lymphedema. Instead, most of the studies used QOL tools that were not developed to evaluate lymphedema, which limited their ability to assess the condition. In contrast, this group of researchers also conducted a systematic review of patient-reported outcome instruments for breast cancer-related lymphedema and identified 39 studies that met the review's inclusion criteria, 8 of which provided level I evidence.[8] This lack of validated lymphedema-specific subjective measurement tools has led to patient complaints of a lack of treatment options and opportunities to partake in research.[132]

Advances in Imaging

Imaging has been used to help visualize lymphatics. Imaging of the peripheral lymphatic vasculature, although still currently under development, can offer a potential new way to detect lymphatic disruption before signs of lymphedema become visible.

Lymphoscintigraphy

The traditional, standard-of-care imaging modality for imaging the lymphatics is lymphoscintigraphy. Although widely clinically available, lymphoscintigraphy has a number of characteristics that limit its clinical and investigational use, including its use of a radioactive tracer that can restrict its "point-of-care" use; its relatively poor spatial resolution, which limits visualization of small lymphatic vessels; and a long integration time that precludes direct imaging of contractile lymphatic pumping.

Near-Infrared Fluorescence Imaging

Near-infrared fluorescence (NIRF) imaging has been developed over the past decade to provide improved, noninvasive, in vivo imaging of the lymphatics in humans and animals. NIRF imaging can image the lymphatics directly and enables in vivo visualization of contractile lymphatic propulsion and thus can be used for diagnosing early lymphedema and assessing lymphatic function and its response to lymphedema therapy.[133] The technique depends upon the

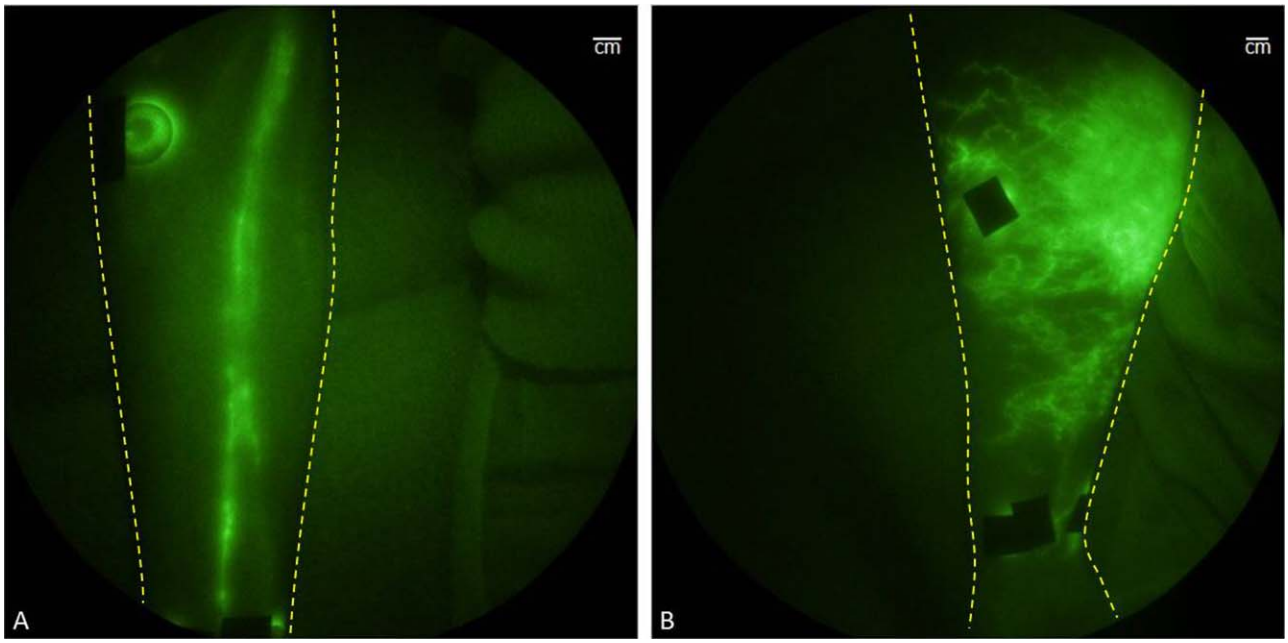

FIGURE 4. Near-Infrared Fluorescence Imaging of Healthy and Affected Limbs.

intradermal administration of indocyanine green (ICG), a green dye that has been approved for intravenous administration in humans since 1956. Off-label, intradermal administration results in immediate uptake into the dermal lymphatics and transit through the collecting and conducting lymphatic vessels. The contractile propulsion of ICG-laden lymph in these conducting vessels can then be imaged noninvasively by illuminating tissue surfaces with dim near-infrared light, and collecting the ICG fluorescence using a charge-coupled device-based system (marketed outside the United States as Photodynamic Eye [Hamamatsu Photonics, Hamamatsu City, Japan]) or an intensified charge-coupled device-based system (considered investigational inside the United States), using the University of Texas frequency-domain photon migration or near-infrared fluorescence lymphatic imaging system. After administering a trace dose of ICG, it is possible to detail fine lymphatic capillaries as well as deeper conducting vessel structures. It is also possible to demonstrate the presence or lack of contractile lymphatic flow through quantitation of the velocity and frequency of contractile events (see Videos 1 and 2 in the online supporting information).[134,135] In clinical practice, NIRF has been used for intraoperative SLN mapping in patients with breast, gastric, gynecologic, and skin cancers.[136-140] In addition, NIRF imaging has been used intraoperatively to guide lymphedema-relieving surgeries such as lymphaticovenular anastomoses and to successfully redirect manual lymphatic drainage (MLD) in a patient with head and neck cancer toward otherwise unknown, newly formed functional lymphatics crossing surgical and radiation scars.[141,142] Comparative NIRF imaging of patients with and without lymphedema has demonstrated notable differences in terms of the architecture of the lymphatic vasculature (Fig. 4) as well as the contractile frequency of the lymphatic vessels.[134,135,143,144] Highlighting another potential clinical application of the technology, NIRF was used to demonstrate improvements in lymphatic contractile function and lymphatic velocity immediately after MLD therapy (see Video 3 in the online supporting information), as well as to assess movement of extravascular ICG-laden lymph proximally with pneumatic compression devices.[145,146] However, there are limitations associated with NIRF imaging: 1) in the United States, the technology is currently investigational and is not yet market-approved; and 2) because NIRF uses low-energy photons that are scattered and absorbed by intervening tissues, it is currently limited to visualizing superficial lymphatic vessels no more than 3 cm to 4 cm below the skin surface.[143] However, the use of a nonradioactive trace dose of ICG; the rapid, "point-of-care" real-time imaging; and the comparatively superficial location of lymph nodes and lymphatic vessels draining the upper and lower extremities make NIRF imaging a potential screening diagnostic tool for the early detection of aberrant lymphatic vascular changes that precede lymphedema symptoms.[134]

Single-Photon Emission Computed Tomography/Computed Tomography

In single-photon emission computed tomography/computed tomography (SPECT/CT), a gamma camera is used to visualize a gamma-emitting radionuclide that is injected into the patient. The lymphatic-imaging ability of SPECT/CT has been directly compared with that of lymphoscintigraphy in a series of 41 patients with lower extremity lymphedema

TABLE 10. Lymphedema Staging Systems

	FOLDI STAGING SYSTEM[123]				
CLINICAL STAGE	PATHOLOGY	SYMPTOMS	INTERNATIONAL SOCIETY OF LYMPHOLOGY[124]	CTCAE VERSION 4.03[151]	MDACC HEAD AND NECK CANCER LYMPHEDEMA RATING SCALE[125]
0	Focal fibrosclerotic tissue alterations	Latency: no symptoms	Latent or subclinical; swelling not yet evident; impaired lymph transport; subtle changes in tissue fluid and/or composition; changes in subjective symptoms		No visible edema but patient reports heaviness
I	High protein edema; focal fibrosclerotic tissue alterations	Reversible: pitting edema; elevation reduces swelling; possibly "congestion pain"	Edema regresses with limb elevation; early accumulation of fluid relatively high in protein content; pitting edema may be present	Trace thickening or faint discoloration	Ia: Soft visible edema; no pitting; reversibleIb: Soft pitting edema; reversible
II	Extensive fibrosclerosis; proliferation of adipose tissue	Spontaneously irreversible: hard swelling that does not respond to elevation	Edema that rarely reduces with limb elevation; initial pitting that subsides secondary to excess fat and fibrosis	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL	Firm pitting edema; irreversible; no tissue changes
III	Extensive fibrosclerosis; proliferation of adipose tissue	Elephantiasis: similar to stage II with a degree of severity involving invalidism	Lymphostatic elephantiasis; trophic skin changes; deposition of fat and fibrosis; warty overgrowths may develop	Severe symptoms; limiting self-care ADL	Irreversible; tissue changes

CTCAE indicates Common Terminology Criteria for Adverse Events; MDACC, The University of Texas MD Anderson Cancer Center; ADL, activities of daily living.

by Baulieu et al.[147] The study demonstrated that SPECT/CT could be used to categorize morphologic abnormalities of the lymphatic vessels and that SPECT/CT localized and defined the anatomic extent of dermal backflow more accurately than lymphoscintigraphy. SPECT/CT has been used clinically to identify the SLN in patients with various cancers.[148] Ongoing studies are investigating the use of SPECT/CT to guide radiation therapy to avoid irradiating the uninvolved lymph nodes that drain the extremities.[149]

Magnetic Resonance Imaging

Magnetic resonance-based lymphangiography, in which a gadolinium-based contrast agent is injected subcutaneously into the patient and visualized using magnetic resonance imaging, is a relatively novel application of an older diagnostic imaging tool to better visualize the lymphatics. Lu et al reported on 40 patients with lymphedema that was related to treatment for gynecologic cancer who underwent magnetic resonance lymphangiography.[150] Compared with lymphatics visualized in the unaffected extremity, those visualized in the lymphedematous extremity demonstrated a large number of dilated vessels with a beaded appearance and irregular blurring in areas of dermal backflow.

Defining Lymphedema

How to best define lymphedema remains a subject of debate. Published studies have significant variability in defining thresholds for diagnosing lymphedema, which makes it challenging to compare lymphedema outcomes. Several oncology and lymphedema organizations have created distinct staging systems to assist clinicians in quantifying lymphedema; 4 of the most commonly used staging tools are summarized in Table 10.[123-125,151] Although these tools are similar, they do not directly overlap.

Patients With Breast Cancer

Even in the relatively well-studied group of patients with lymphedema related to breast cancer treatment, the precise threshold that should be used to define clinically meaningful lymphedema remains uncertain. In one detailed prospective study of 269 patients with breast cancer,[152] lymphedema was measured objectively using perometry, and lymphedema symptoms were assessed using the LBCQ, the Functional Living Index-Cancer, and the RAND 36-Item Health Survey. The investigators classified lymphedema based on the relative LVC from baseline as mild (5.0%-9.9% LVC), moderate (10.0%-14.9% LVC), or severe ($\geq$15.0% LVC). At 12 months, the incidences of mild, moderate, and severe lymphedema were 24.4%, 8.4%, and 7.6%, respectively. Some patients experienced fluctuations in the severity of their lymphedema, and 30.1% of patients had mild, 26.0% had moderate, and 5.2% had severe lymphedema as the highest stage of lymphedema. Increases in limb volume were correlated with worse symptomatology as assessed with the QOL tools. Strikingly, noticeable symptom changes were detected even in patients with only mild lymphedema.

Stout Gergich et al hypothesized that a relatively low threshold for diagnosing and treating lymphedema would improve clinical outcomes.[109] The investigators prospectively followed a cohort of patients with breast cancer and provided

women who had an LVC of more than 3% treatment with a compression garment for 4 weeks.[109] They found that this early intervention provided a meaningful return to a sustained normal LVC, indicating that a diagnosis of early-onset lymphedema may optimize treatment intervention.

Patients With Melanoma of the Lower Extremity

Lymphedema is common in patients who undergo lymph node dissection for melanoma of the lower extremity, but relatively little work has been done to define clinically significant diagnostic thresholds for lower extremity lymphedema. One group of investigators at the Sydney Cancer Centre in Australia prospectively assessed lymphedema in 66 patients who had undergone inguinal or ilioinguinal dissection.[153] The objective measurements were limb circumference measurements at 6 points along the lower extremity and volumetric measurement via perometry; subjective assessments included questions concerning patients' perceptions of functional deficits, obvious increases in the size of the limb, and postoperative complications. The investigators found that a change in perometry-measured LVC from baseline of at least 15% and a change in the sum of limb circumferences from baseline of at least 7% both predicted moderate to severe lymphedema as assessed by patient-reported symptoms. Of note, this same group of researchers had previously reported that a change in arm volume measured via water displacement of at least 16% was meaningfully correlated with postoperative symptoms in patients with melanoma who were treated with ALND.[57] Although both studies used precise volumetric measurements, both were also limited by a relatively short clinical follow-up (minimum, 6 months). Additional studies investigating the long-term trajectory of melanoma treatment-related lymphedema will improve our understanding of how to clinically diagnose the condition and when to offer treatment.

Patients With Head and Neck Cancer

Unlike the lymphedema related to the treatment of other malignancies, lymphedema resulting from the treatment of head and neck cancer should be assessed with an examination of both internal and external anatomy. How to best quantify visible anatomical changes systematically still needs to be determined. Researchers at The University of Texas MD Anderson Cancer Center published a detailed protocol for assessing patients with head and neck cancer for external lymphedema; they also published a lymphedema rating scale that takes into account the fact that most patients with head and neck lymphedema do not have pitting lymphedema and thus benefit from a more nuanced evaluation for milder forms of lymphedema (Tables 7 and 11).[50,59,62,96,125] The algorithm provides directions for taking detailed measurements of the face and neck to be used at baseline assessment and for follow-up measures. How to best categorize lymphedema that is not clinically apparent remains to be defined.

TABLE 11. The University of Texas MD Anderson Cancer Center Head and Neck Lymphedema Evaluation Protocol

FACIAL MEASUREMENTS	NECK MEASUREMENTS
Facial circumferences • Diagonal: chin to crown of head • Submental: <1 cm in front of ear, vertical tape alignment	Neck circumference • Superior neck: immediately beneath mandible • Medial neck: midway between points 1 and 3 • Inferior neck: lowest circumferential level
Point to point • Mandibular angle to mandibular angle • Tragus to tragus • Facial composite ▪ Tragus to mental protuberance ▪ Tragus to mouth angle ▪ Mandibular angle to nasal wing ▪ Mandibular angle to internal eye corner ▪ Mandibular angle to external eye corner ▪ Mental protuberance to internal eye corner ▪ Mandibular angle to mental protuberance	

Adapted from Smith BG, Lewin JS. Lymphedema management in head and neck cancer. *Curr Opin Otolaryngol Head Neck Surg*. 2010;18:153-158.[125]

In a cross-sectional study of 103 patients with head and neck cancer, investigators at Vanderbilt University evaluated 4 distinct lymphedema scales with the aim of determining which best fit the needs of this patient group.[154] The scales were the National Cancer Institute Common Terminology Criteria for Adverse Events Lymphedema Scale-Head and Neck (version 3.0), the American Cancer Society Lymphedema of the Head and Neck Scale, the Stages of Lymphedema scale by Foldi, and the National Cancer Institute Common Terminology Criteria for Adverse Events Lymphedema-Related Fibrosis Scale (version 3.0), each of which captures distinct lymphedema features, such as swelling and fibrosis, and quantifies the lymphedema stage differently. The findings from this study demonstrated that none of the currently available scales accurately identify or classify head and neck lymphedema.

Treatment of Lymphedema

Complete Decongestive Therapy

The optimal treatment protocol for patients with lymphedema remains controversial.[155] The current standard of care is complete decongestive therapy (CDT), which involves the use of MLD, daily bandaging, skin care, exercise, and compression in a 3-phase protocol.[156] One systematic review identified 26 studies of CDT published

between 2004 and 2011, including 9 randomized controlled trials that demonstrated that CDT decreased limb volume and improved overall QOL.[156]

However, another recent randomized controlled trial of 103 women with breast cancer-related lymphedema who were assigned to receive treatment with compression garments only or CDT with daily MLD and short-stretch bandaging reported no significant differences in limb volume between the 2 groups at 6 weeks.[157] Women who were treated with compression garments had a median limb volume decrease of 29%, whereas women treated with MLD and short-stretch bandaging had a decrease of 22%. For experienced lymphedema therapists, the findings are surprising given that elastic compression garments are designed for maintenance therapy and do not provide the same benefits as short-stretch bandages, which enhance lymphatic pumping. The study participants were also asked to complete QOL questionnaires at baseline and at 3, 6, 12, 24, and 52 weeks after the study initiation; no differences in QOL scores between the 2 groups were noted. The study's limitations include its small patient cohort with variability in the length of time since breast cancer treatment and a higher rate of dropout in the compression garment group (16%) compared with the CDT group (2%).[158] A more recent meta-analysis of 10 randomized controlled trials (total of 566 patients) of MLD for the treatment and prevention of breast cancer-related lymphedema reported that MLD was not beneficial for the prevention of postoperative lymphedema.[159] The authors found wide variability in the studies' definitions of lymphedema, and the differences between the affected and unaffected extremities at the time of lymphedema diagnosis ranged from 3% to 20%. In most of the trials, the Vodder method of MLD was used.[160] Significant heterogeneity in the objective measurement and definition of lymphedema among the trials made it difficult to universally define lymphedema.

Tan et al[145] used NIRF imaging to assess the lymphatics in both the affected and unaffected limbs before and after MLD in 10 patients with breast cancer-related lymphedema. The researchers found that the mean increase in lymph system contraction speed after MLD was 23% in the affected limbs and 25% in the asymptomatic, unaffected limbs. They reported that MLD immediately improves lymphatic function. The researchers also reported that MLD increased lymph velocity by a mean of 28% in 12 healthy control participants.

Bandaging and Compression

During the early phases of lymphedema treatment, including CDT, daily bandaging is used to reduce limb volume until maximum limb volume reduction has been achieved and a compression garment can be applied. A systematic review of randomized controlled trials of various interventions for the treatment of breast cancer-related lymphedema identified 14 studies enrolling 658 women who were treated with MLD, pneumatic pumps, compression garments, therapeutic exercises, self-treatment instruction, or a combined regimen.[161] Bandaging as a single therapy was reported to be effective in reducing upper limb volume; however, the best combination therapy could not be identified because of heterogeneity in the patient populations, measured outcomes, follow-up durations, and treatment protocols.

Exercise

Exercise in patients with lymphedema remains a topic of controversy in the current literature.[162,163] With the increase in rates of obesity in the United States, particularly among cancer survivors,[164] specific recommendations for physical activity in this population are critical. The National Comprehensive Cancer Network (NCCN) recently released practice guidelines for "Healthy Lifestyles" to encourage cancer survivors to achieve and maintain a healthy lifestyle. In this document, patients with lymphedema are classified as being at "moderate risk" of exercise-induced adverse events.[165] Recommendations for patients at moderate risk include medical evaluation prior to the initiation of exercise and consideration for referral to an individual specially trained in exercise. The NCCN guidelines recommend compression for patients with lymphedema during exercise as well as baseline and continued evaluation for exacerbation of lymphedema. Strength training in the affected limb should only be done if lymphedema is stable and has not required therapy in the past 3 months.[165]

A systematic review of the literature published between 2004 and 2010 included 19 studies that addressed the use of resistance, aerobic, or other types of exercise by patients with breast cancer who either already had or were at risk of developing lymphedema. The findings from this review indicate that exercise, when completed with proper supervision, can be safe for patients and not increase the risk of lymphedema or exacerbation of symptoms.[162] A recent randomized controlled trial of 25 women with long-term lymphedema related to breast cancer (median duration, 53 months) found those who participated in water-based exercise had improvement in shoulder range of motion over the course of the 8-week program, without any effect on lymphedema status.[166] However, most studies concerning this question have been conducted in populations of breast cancer survivors, and evidence regarding lower extremity lymphedema remains limited. A cross-sectional study of 213 uterine cancer survivors reported that increasing self-reported physical activity and walking was associated with decreased levels of self-reported lymphedema.[167] However, these observational findings were noted by the authors to

TABLE 12. Studies Assessing Excisional Procedures for the Treatment of Lymphedema

REFERENCE	STUDY DESIGN	NO. OF PATIENTS	LYMPHEDEMA SITE	PROCEDURE	FOLLOW-UP TIME, MONTHS	% VOLUME REDUCTION	MEASUREMENT TECHNIQUE
Kim 2004[172]	Retrospective	20	Lower extremity	Excision	17.8	16	Volometer
Modolin 2006[173]	Prospective	17	Penile/scrotal	Excision	72	NR	NR
Lee 2008[174]	Retrospective	22	Lower extremity	Excision	48	NR	Infrared optometric volumetry; circumference
Salgado 2009[175]	Prospective	11	Upper extremity	Excision with preservation perforators	17.8	21	Circumference
van der Walt 2009[176]	Retrospective	8	Lower extremity	Modified Charles procedure	27	8.5 kg	NR
Karri 2011[170]	Retrospective	27	Lower extremity	Charles procedure	48	NR	NR
Sapountzis 2014[171]	Retrospective	24	Lower extremity	Modified Charles procedure with lymph node flap transfer	14	NR	NR

NR indicates not reported.

be hypothesis-generating and should be evaluated in prospective studies. Although evidence remains limited, contemporary evidence indicates that, when done in moderation and under close supervision, exercise is safe in patients with or those at risk of lymphedema.

Surgery

In the past decade, surgery as a treatment option for patients whose lymphedema is refractory to CDT has received significant attention; however, the true efficacy of surgical approaches in this population has yet to be proven.[168] At this point, surgical treatment of lymphedema is reserved primarily for patients who have lymphedema that is refractory to standard treatment modalities. The various surgical treatment options for lymphedema can be broadly categorized as excisional procedures, liposuction, lymphatic reconstruction, and tissue transfer procedures.

Excisional procedures

Historically, patients with chronic, disabling lymphedema have undergone excisional procedures to debulk the affected limb. For example, the Charles procedure, which was first reported in 1912, was initially designed to reduce scrotal lymphedema but has been used most frequently to debulk lymphedematous lower extremities.[169] More recently, these procedures have been modified to improve cosmesis and healing and reduce the rate of postoperative infection.[170,171] Excisional procedures have been reported to be associated with a number of complications, including hematoma, infection, skin or flap necrosis, delayed healing, and loss of limb function. Although the majority of contemporary studies of these procedures do not report volume reduction percentages, historically, the Charles or modified excisional procedures were reported to result in limb volume reductions ranging from 16% to 21% in patients followed for 14 to 48 months (Table 12).[170-176]

Liposuction

Liposuction, a less invasive excisional procedure, was introduced as a means of reducing limb volume by removing excess adipose tissue after all excess fluid has been removed from the limb. Complications such as infection and delayed wound healing have been reported.[168] One systematic review identified 6 studies that investigated the use of liposuction for the treatment of lymphedema.[177,178] Of the 105 patients in these studies, only 4 underwent liposuction as a treatment for lower extremity lymphedema; all other patients had upper extremity lymphedema.[178] Among those patients with lymphedema of the lower extremity, the mean limb volume reduction after liposuction was 87%.[179] Among patients with upper extremity lymphedema, the mean volume reduction after liposuction was 94.7% (range, 18%-123%) (Table 13).[177-182] However, the majority of patients who underwent liposuction continued to wear compression garments after surgery.[178]

Lymphatic reconstruction

Microsurgical reconstruction of the lymphatics has shown promise as a low-risk surgical option for the treatment of lymphedema. This procedure, performed by a plastic surgeon with special training in microsurgery, involves the creation of anastomoses, commonly between the lymphatics and veins.[168] The primary advantage of lymphatic reconstruction is that it is a less invasive surgical procedure and usually only requires one night in the hospital. Seventeen studies enrolling a total of 2251 patients who underwent lymphatic venous anastomosis for lymphedema of the

TABLE 13. Studies Assessing Liposuction Procedures for the Treatment of Lymphedema

REFERENCE	STUDY DESIGN	NO. OF PATIENTS	LYMPHEDEMA SITE	PROCEDURE	FOLLOW-UP TIME, MONTHS	% VOLUME REDUCTION	MEASUREMENT TECHNIQUE
Liu 2005[177]	Prospective	11	Upper extremity	Liposuction	[a]	[a]	Circumference
Brorson 2006[178]	Prospective	35	Upper extremity	Liposuction	12	103	Water displacement
Qi 2009[180]	Prospective	11	Upper extremity	Liposuction, myocutaneous flap transfer	26	18	Circumference
Damstra 2009[181]	Prospective	37	Upper extremity	Suction-assisted lipectomy	12	118	Water displacement
Schaverien 2012[182]	Prospective	12	Upper extremity	Liposuction	36	123	Water displacement
Granzow 2014[179b]	Retrospective	10	Upper extremity (n=6); lower extremity (n=4)	Suction-assisted lipectomy	32	111 (upper extremity); 87 (lower extremity)	Circumference

[a]Abstract available only. [b]The study included a discussion of patients who underwent tissue transfer and lymphatic venous anastomosis.

upper or lower extremities or head and neck reported volume reductions ranging from 2% to 91.7% at follow-up times of between 8.9 to 120 months (Table 14).[140,183-198]

Tissue transfer procedures

Raju and Chang first reported the use of vascularized lymph node transfer for the treatment of lymphedema in an animal model in 1979; by 1982, it was being used in patients.[199] In this procedure, lymph nodes are removed from one part of the body and transferred to the lymphedematous limb. One recent review of lymph node transfer procedures[199] identified 6 studies that reported quantitative data for patients with lymphedema, 4 that reported qualitative data for these patients, and 6 that reported results using animal models. The most common donor sites in the human studies were the inguinal, submental, supraclavicular, and thoracic lymph nodes, which were most commonly transferred to the lymph node basins of the affected upper or lower extremity. Combining the results of this review[199] with those of the review of all surgical procedures for the treatment of lymphedema[168] yields a total of 10 studies that reported outcomes after vascularized lymph node transfer. The LVCs reported in these studies range from an increase of 13% to a decrease of 64% from the presurgical volume (Table 15).[200-209] Complications reported to be associated with tissue transfer include infection at the donor or recipient site and an increased risk of lymphedema at the donor site.[210]

Lymphedema Prevention

SLNB

SLNB, which was introduced in the 1990s, is used to identify the first draining regional lymph nodes from a primary tumor. In patients with a confirmed negative SLN, a completion ALND or inguinofemoral lymph node dissection can be avoided, greatly reducing the chances of lymphedema.

The first evaluation of the impact of SLNB on survival was the Multicenter Selective Lymphadenectomy Trial (MLST-I), a multiinstitutional randomized controlled trial led by Morton.[211] In that trial, patients with melanoma were randomized to undergo a wide local excision and either SLNB or lymph node observation. Ten-year follow-up data for 1661 patients were available for the final analysis, which was published in 2014.[211] The 10-year melanoma-specific survival rates for the patients who received SLNB (81.4% ± 1.5%) were significantly higher than those of the patients who underwent lymph node observation only (78.3% ± 2.0%; P =.01). The NCCN guidelines include recommendations for the pathologic staging of melanoma in patients with primary tumors that are thicker than 0.75 mm or are of any thickness and are ulcerated or have at least 1 mitotic figure per high-power field.[212]

When SLNB was initially introduced, it was thought that this surgical technique would eliminate the risk of postoperative lymphedema in patients spared a completion lymph node dissection. However, recent studies indicate that although the incidence of lymphedema is diminished after SLNB, it has not been eliminated. The incidence of lymphedema after SLNB among breast cancer survivors is approximately 6%.

Breast cancer is the most common cancer among women worldwide; nearly 1.68 million new cases are diagnosed annually.[213] Cervical cancer is the fourth most common cancer among women, with approximately 1.09 million new cases diagnosed each year.[213] Melanoma, one of a few cancers whose annual incidence is increasing, was diagnosed in more than 230,000 men and women worldwide in 2012.[213] Given these figures and lymphedema incidences after SLNB of 6%, 4%, and 9%, respectively, among patients with breast cancer,

TABLE 14. Studies Assessing Microsurgical Procedures for the Treatment of Lymphedema

REFERENCE	STUDY DESIGN	NO. OF PATIENTS	LYMPHEDEMA SITE	PROCEDURE	FOLLOW-UP TIME, MONTHS	VOLUME REDUCTION
Koshima 2004[183]	Retrospective	52	Lower extremity	Lymphatic venous anastomosis	15	42%
Matsubara 2006[184]	Retrospective	9	Lower extremity	Lymphatic venous anastomosis	21-87	>5 cm (n=6); 2 cm (n=2); no effect (n=3)
Damstra 2009[185]	Prospective	10	Upper extremity	Lymphatic venous anastomosis	12	2%
Demirtas 2009[186]	Retrospective	42	Lower extremity	Lymphatic venous anastomosis	11.8	59.3%
Campisi 2010[187a]	Retrospective	1800	Upper and lower extremities	Lymphatic venous anastomosis	120	56% (83% with 67% reduction)
Chang 2010[188]	Prospective	20	Upper extremity	Lymphatic venous anastomosis	18	35%
Maegawa 2010[189]	Retrospective	111	Lower extremity	Lymphatic venous anastomosis	NR	Mean reduction of 872 mL
Mihara 2010[190]	Retrospective	11	Lower extremity	Lymphatic venous anastomosis	23.6	91.7%
Narushima 2010[191]	Prospective	14	Upper extremity (n=2); lower extremity (n=12)	Lymphatic venous anastomosis	809	11.3%
Furukawa 2011[140]	Prospective	9	Upper extremity	Lymphatic venous anastomosis	17	77.8% of patients had >50%
Yamamoto 2011[192]	Retrospective	20	Lower extremity	Lambda-shaped lymphaticovenular anastomosis	8.9	11.3%
Auba 2012[193]	Prospective	12	Upper extremity (n=7); lower extremity (n=5)	Lymphatic venous anastomosis	24	1.18 cm
Mihara 2012[194]	Prospective	6	Lower extremity	Lymphatic venous anastomosis	10	NR
Ayestaray 2013[195]	Prospective	4	Head and neck	Lymphatic venous anastomosis	12	3.7%
Boccardo 2013[196]	Retrospective	23[b]	Lower extremity	Lymphatic venous anastomosis	42	80%
Chang 2013[197]	Prospective	100	Upper extremity (n=89); lower extremity (n=11)	Lymphatic venous anastomosis	12-36	42% (upper extremity); 7%-42% (lower extremity)
Yamamoto 2014[198]	Prospective	8	Upper extremity (n=3); lower extremity (n=5)	Lymphatic venous anastomosis		

NR indicates not reported. [a]Selected among duplicate studies with overlapping patient cohorts. [b]The study included patients receiving preventative care.

melanoma, and gynecologic cancers, approximately 208,000 individuals will be diagnosed with post-SLNB lymphedema annually worldwide. Many more are at a significant lifetime risk.

Although SLNB significantly reduces the risk of postoperative lymphedema compared with completion lymph node dissection, it does not eliminate this risk. Therefore, when obtaining consent for SLNB, one must mention lymphedema as a possible long-term morbidity. Prospective surveillance for lymphedema continues to be an appropriate part of a cancer survivorship care plan.

Axillary Reverse Mapping

Axillary reverse mapping (ARM), which was introduced by Klimberg in 2008, is a modified lymph node mapping technique for identifying the SLN while preserving the functioning upper extremity lymphatics to minimize the risk of lymphedema.[214-216] During ARM, isosulfan blue dye is injected into the ipsilateral upper inner arm along the intramuscular groove[217] and tracks in the lymphatics to the axilla and serves to identify the lymphatic channels of the arm. The driving idea behind ARM is that, owing to variations in anatomy, each patient has distinct lymphatic

TABLE 15. Studies Assessing Tissue Transfer Procedures for the Treatment of Lymphedema

REFERENCE	STUDY DESIGN	NO. OF PATIENTS	LYMPHEDEMA SITE	PROCEDURE	FOLLOW-UP TIME, MONTHS	VOLUME REDUCTION	MEASUREMENT TECHNIQUE
Weiss 2002[200]	Prospective	12	Upper extremity	Autologous lymphatic tissue transplant	96	Range: 22%-31%	Circumference
Wongtrungkapun 2004[201]	Prospective	10	Lower extremity	Lymphonodovenous implantation	4.5	3.5 cm at knee; 7.37 cm at 16 cm below knee; 2.75 at metatarsal level	Circumference
Becker 2006[202]	Retrospective	24	Upper extremity	Lymph node transplant	96	Reduction to normal (n=10); some reduction (n=10); no change (n=2)	Circumference
Belcaro 2008[203]	Retrospective case-control	9	Lower extremity	Autologous lymphatic tissue transplant (n=9) versus control (n=8)	120	Increase of 13%	Water displacement
Hou 2008[204]	Randomized control trial	15	Upper extremity	Autologous bone marrow stromal cell transplant (n=15) versus CDT (n=35)	12	81%	Circumference
Lin 2009[205]	Retrospective	13	Upper extremity	Vascularized lymph node transfer	56	51%	Circumference
Gharb 2011[206]	Prospective	21	Upper extremity	Vascularized lymph node transfer	40	NR	Circumference
Saaristo 2012[207]	Prospective	9	Upper extremity	Vascularized lymph node transfer	6	33.3%	Circumference
Cheng 2013[208]	Prospective	10	Hand	Vascularized lymph node transfer	39.1	40.4%	Circumference
Dancey 2013[209]	Retrospective	18	Upper extremity	Vascularized lymph node transfer	14	NR	Subjective

CDT indicates complex decongestive therapy; NR, not reported.

channels of the breasts and upper extremities. In the initial evaluation of the ARM procedure, 18 patients with breast cancer were injected with 2.5 to 5.0 mL of isosulfan blue dye at the upper inner arm at the time of ALND.[215] In this report, the findings indicated a lymphedema incidence of less than 1%. In a feasibility study of 131 patients undergoing SLNB for breast cancer, a radioactive tracer was injected into the breast for SLN identification, and blue dye was injected into the upper inner arm for ARM. In these patients, only 3% of the lymph nodes with blue dye also contained radioactive tracer,[218] indicating that the lymph nodes that drained the tumor and those that drained the upper extremity were anatomically distinct. Metastases were not detected in any of the blue ARM lymph nodes.

Several other small studies have demonstrated the feasibility of ARM.[215,217,219-221] However, the outcomes after ARM that are specifically related to the long-term reduction of lymphedema have yet to be confirmed. In addition, studies have reported the identification of metastatic disease in up to 18% of blue (ARM) lymph nodes, indicating that these lymph nodes may not be completely distinct from the SLN and may facilitate disease progression if preserved.[219,222] These results have called into question the oncologic safety of ARM. In addition, some patients who have undergone ARM have reported temporary blue tattooing of the injection site that lasts for a few days to several months.[217] Most importantly, ARM has not been longitudinally studied using objective measurements of upper extremity lymphedema; therefore, a primary benefit of ARM in reducing the incidence of lymphedema has yet to be determined.[219]

Surgery

The use of established surgical procedures to prevent lymphedema was introduced in 2008 by Boccardo et al[223] and entails the completion of lymphatic-venous anastomoses at the time of ALND. In one recent study of 78 patients,[224] the procedure could not be completed in 3 patients because afferent lymphatics could not be visualized and in 1 patient owing to bulky metastatic disease. Of the 74 patients in whom the procedure was performed successfully, 71 did not have any lymphedema at the 8-month or 12-month follow-up times, and 3 patients developed chronic edema in the treatment limb. Although promising, these results are not

derived from a randomized controlled trial, which limits their widespread application. Similar techniques have been used in patients with melanoma[196] and vulvar cancer[225]; however, long-term results in those patients are not yet available.

Prospective Surveillance

In 2012, Stout et al introduced a prospective model for rehabilitation and the early identification of swelling in women with breast cancer.[226] The model promotes surveillance for physical issues commonly associated with breast cancer treatment, provides opportunities for education and risk reduction, and facilitates the early identification of lymphedema, which in turn allows for early intervention with physical activity and weight management programs. The model has demonstrable clinical efficacy in the early identification and treatment of lymphedema.[227,228] Between 10% and 64% of women report lymphedema symptoms 6 to 36 months after breast cancer treatment.[229] Identifying and treating lymphedema in its early stages reduces its impact on functional outcomes as well as the costs[230] associated with its treatment and improves patients' QOL.[231] The prospective surveillance model has been studied beyond lymphedema and demonstrates improved outcomes in a variety of cancer-related impairments.[232-234] A model such as this is aligned with comprehensive care delivery for the cancer survivor and consideration should be given to integrating the prospective surveillance model toward the goal of improved health outcomes.[235]

Financial Impact

One of the biggest stressors that patients with cancer report is fear related to the financial impact of their disease both during and after treatment.[2] This stressor is even more significant in cancer survivors who develop lymphedema.[230,236-238] Patients who have lymphedema are not only more likely to have higher treatment costs but are also more likely to spend more time in a hospital because of cellulitis.[230] A study of claims data found that patients with breast cancer-related lymphedema were likely to have higher medical costs ($23,167) compared with breast cancer survivors without lymphedema ($14,877).[230] Compared with patients without lymphedema, patients with lymphedema were also more likely to use mental health services, undergo diagnostic imaging, and receive outpatient therapy.

One recent systematic review highlighted several areas in the delivery and cost of lymphedema treatment that might benefit from changes in health policy. Stout et al[239] identified 8 articles about health care delivery models and 6 articles about economic and cost analyses. They found that although evidence-based care for the diagnosis and treatment of lymphedema is limited, much of the burden to facilitate diagnosis and referral for effective care is placed on the patient. The authors also found that, compared with patients who do not have lymphedema, patients with lymphedema have significantly higher hospitalization rates, higher rates of medical services use, lower QOL, and significantly higher indirect costs. However, the study had a low level of evidence and yielded only speculative findings.

Prospective surveillance for the early identification and conservative, early treatment of lymphedema holds promise as a cost-saving measure. Stout et al compared direct costs of treating early-onset lymphedema with costs of traditional CDT and found a potential savings of greater than $2400 per patient per year when the prospective surveillance model of care is used and lymphedema is detected and treated early using conservative interventions.[240] Although further cost analysis is warranted, a prospective surveillance approach may reduce the financial impact of the condition and conserve vital health care resources.

Insurance Coverage

Despite continuous efforts to advance lymphedema research and treatment, policies requiring that insurance companies provide coverage for services related to the diagnosis and treatment of lymphedema have not yet become widely adopted. Significant headway was made in 2009 when the Medicare Evidence Development and Coverage Advisory Committee assembled a committee to evaluate lymphedema measurement and treatment technology. The group's findings established levels of evidence related to current practices in lymphedema treatment and diagnosis and may lead to improvements in insurance coverage in both the public and private sectors.[239]

Three states currently have passed legislation mandating that health insurance companies provide coverage for lymphedema treatment and diagnosis. Virginia was the first state to pass such legislation; Virginia House Bill 1737, which was proposed in 2003, requires that insurance companies provide coverage for supplies, equipment, CDT, and outpatient self-management training and education by qualified therapists. In 2007, California passed Assembly Bill 213, which requires that insurance companies provide coverage for physician diagnosis and plan of care; medically required compression garments and bandages; and patient education for skin care, self-treatment, self-measurement, and recognition of infection. Similarly, in 2009, Massachusetts passed Bill S.0896, which requires insurance companies to cover equipment, supplies, CDT, and outpatient self-management training and education.

Despite these advances, coverage for lymphedema treatment remains limited. Legislation that would mandate that insurance companies provide coverage for lymphedema treatment based on current best-practice standards, as well as

CDT, compression garments, and at-home aids, has been introduced in Congress (H.R. 3877-Lymphedema Treatment Act) (beta.congress.gov/bill/113th-congress/house-bill/3877). The bill also seeks to amend the Social Security Act (section 1861 [42 U.S.C 1395x]) to allow compression garments to be covered under Medicare's durable medical equipment clause.

Conclusions

Lymphedema after cancer treatment continues to be a frequently reported morbidity. As patients continue to survive longer after the treatment of cancer, it is important to carefully evaluate not only the symptoms of lymphedema, but also its impact on overall QOL and well-being. Recent advances in the treatment of lymphedema include a more accurate genetic profile and more precise imaging of the lymphatics. As progress continues in the field, the ability to precisely identify those patients at highest risk of developing lymphedema for targeted treatment increases.

Aside from advances in the identification of lymphedema, advances in its treatment offer insight and improvements into the management of this chronic, progressive condition. Although lymphedema remains a significant survivorship issue after cancer treatment, more reasonable management plans and potential preventive approaches have allowed for patients to continue to thrive. As a clinician, it is important to be able to identify the early signs and symptoms of lymphedema and facilitate a rapid referral to a certified lymphedema therapist for appropriate treatment. ■

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