Current Breast Cancer Reports (2019) 11:365–372
https://doi.org/10.1007/s12609-019-00341-3

HOT TOPICS IN BREAST CANCER (K HUNT, SECTION EDITOR)

The Diagnostic Approach to Lymphedema: a Review of Current Modalities and Future Developments

Anjali C. Raghuram[1] · Roy P. Yu[1] · Cynthia Sung[1] · Sherry Huang[1] · Alex K. Wong[1]

Published online: 25 November 2019
© Springer Science+Business Media, LLC, part of Springer Nature 2019

Abstract

Purpose of Review Breast cancer–related lymphedema (BCRL) is a chronic disease that results from a disruption or obstruction in the lymphatic system and affects 15 in 100 individuals in the USA with newly diagnosed breast cancer. As no curative therapy exists for lymphedema, early detection is crucial in order to reduce the risk of developing late stage symptoms, such as swelling, decreased limb flexibility, disfigurement, and impaired function of the extremity. The objective of this review is to discuss current modalities and devices as well as highlight promising advancements intended to aid in diagnosing secondary lymphedema in breast cancer patients.

Recent Findings Imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) can offer high resolution of the lymphatics but are expensive and time-consuming. Single photon emission computed tomography (SPECT) is an alternative that reveals organ function as opposed to organ structure. Other imaging methods, such as color duplex ultrasound (CDU), laser scanner 3D (LS3D), and dual-energy X-ray absorptiometry (DXA), are relatively easy to use, reproducible, and fast to perform. However, the disadvantages of these techniques include lower sensitivity and specificity compared with CT and MRI. Of note, direct imaging techniques are highly effective for the diagnosis of lymphedema because they utilize dyes or radiotracers in order to directly visualize lymphatic vessels. Fluorescent microlymphography (FMLG) and near-infrared imaging (NIR) involve injection of fluorescent dyes that can be excited with light. Lymphoscintigraphy has effectively replaced lymphangiography as the method of choice for the diagnosis of lymphedema because it is safer, less invasive, and has no risk of causing an allergic reaction in patients. Novel approaches that are currently in development include bioimpedance spectroscopy, ultra-high-frequency ultrasound systems (UHFUS), and magnetic resonance lymphography (MRL).

Summary The wide range of diagnostic methods for BCRL exhibit the tradeoff between simplicity and sensitivity; some techniques provide high resolution but are expensive and time consuming. On the other hand, other modalities are easy to use, reliable, and relatively fast in execution yet lack the ability to precisely visualize the lymphatic system. In review of these various techniques, lymphoscintigraphy serves as a clear gold standard for diagnosing secondary lymphedema while more advanced and promising techniques continue to emerge as newer alternatives in clinical practice.

Keywords Lymphedema · Diagnostics · Devices

This article is part of the Topical Collection on *Hot Topics in Breast Cancer*

✉ Alex K. Wong
Alex.Wong@med.usc.edu

[1] Division of Plastic and Reconstructive Surgery, Department of Surgery, Keck School of Medicine, University of Southern California, 1510 San Pablo Street, Suite 415, Los Angeles, CA 90033-4580, USA

Introduction

As a result of aging and the growth of the world's population, the global burden of breast cancer continues to increase. In the USA alone, the incidence of new breast cancer cases in 2016 was 15 in 100 individuals [1]. The steady increase in the number of breast cancer survivors has provided for a new-found emphasis on the treatment of long-term complications of cancer and cancer-related treatment, such as breast cancer–related lymphedema (BCRL). BCRL results from either a disruption or obstruction in the lymphatic system as a result of removal of lymph nodes, receipt of radiotherapy, and/or patient-specific factors such as obesity, higher body mass index (BMI), infections, or trauma [2–4]. While the functionally intact lymphatic system drains lymph fluid, consisting of water, protein, cellular debris, toxins, and other macromolecules, and returns this fluid to the intravascular circulation, compromised drainage results in accumulation of lymph fluid in the interstitial space. Upper extremity lymphedema secondary to breast cancer treatment causes enlargement and a sensation of heaviness in the limb [5]. As a result, lymphedema affects patient function, psychosocial adjustment after cancer, and overall quality-of-life.

In addition to the lymph nodes, the lymphatic system is comprised of both central and peripheral components. The central lymphatic system consists of the cisterna chyli and the thoracic duct that return lymph collected from peripheral lymphatic vessels to venous circulation in the neck [6•, 7]. Central lymphatic system dysfunction results in a varied host of disorders, encompassing congenital malformations (i.e., the absence of the cisterna chyli), iatrogenic creation of lymphoceles, and even acquired chylothorax [6•]. In order to identify central lymphatic dysfunction and provide for appropriate management, Pamarthi et al. studied the role of magnetic resonance lymphangiography as a diagnostic tool [6•]. The peripheral lymphatics play a role in regulating the immune response; consequently, immune dysfunction resulting in increased susceptibility to infection or inflammatory disease can be linked to poor function of the peripheral lymphatic system [8]. Though infection and inflammatory disease result from peripheral lymphatic dysfunction, a very common clinical manifestation of this dysfunction is lymphedema [9]. Primary lymphedema is a congenital disorder due to developmental defects in the lymphatics and consequent inability to sufficiently drain lymph fluid. Secondary lymphedema is attributable to a wider range of causes and risk factors, such as surgery, inflammation, and/or fibrosis. Clinical manifestations of lymphedema include elephantiasis, upper or lower extremity lymphedema, and chyluria [9].

The diagnosis of lymphedema is generally made based on a detailed patient history and characteristic physical exam findings. Though lymphedema almost always affects the distal extremity, some patients with primary lymphedema can have genital involvement. In the vast majority of cases, primary lymphedema affects the lower extremities, with 50% of patients having unilateral disease and 50% having bilateral disease [10]. Physical exam techniques that can be used to quantify a patient's degree of lymphedema include tissue tonometry, circumferential limb measurements, and the measurement with the greatest demonstrated accuracy, water displacement tonometry [11]. The severity of lymphedema is stratified clinically as mild, corresponding to a < 20% increase in extremity volume, moderate, corresponding to an increase of 20–40% in extremity volume, or severe, corresponding to an increase of > 40% in extremity volume [12]. Furthermore, patients with lymphedema tend to exhibit pitting edema early on in their disease. Over time, the body reacts to lymphedematous fluid stasis by producing subcutaneous fibrous adipose tissue. Thus, patients with long-standing edema will not benefit from compressive therapy [10]. Other pathognomonic findings associated with lymphedema include the Stemmer sign, an inability to pinch the skin on the dorsum of the hand or the foot, scarring in the axillary or inguinal regions that contributes to lymphedema development, and associated cutaneous findings such as vesicular bleeding, hyperkeratosis, and lymphorrhea [10, 13].

In complementing and further supplementing the diagnostic approach conferred by physical exam and patient history, there are an array of techniques to image and assess the anatomy and function of the lymphatic system. Along with improvements in understanding of lymphatic function and pathophysiology, these technological advances have enriched the clinician's algorithm for the diagnosis of lymphedema, recommendations for treatment, and assessment of therapeutic efficacy. The purpose of the following review is to examine the variety of lymphedema diagnostic tests that have been employed to date and discuss ongoing diagnostic developments that may soon be added to clinical practice.

Lymphedema Diagnostic tests

Computed Tomography, Magnetic Resonance Imaging, and Single Photon Emission Computed Tomography

Computed tomography (CT) has been employed to image the affected skin, subcutaneous tissue layers, and underlying musculature in patients with lymphedema. With a characteristic honeycomb pattern of edema detectable by CT, subcutaneous tissue in patients with lymphedema is engulfed by fibrosis and fluid [10]. Other imaging findings include thickened skin, fluid lakes, and direct obstruction of the lymphatics, such as by cancer. With enhanced resolution capabilities over CT, magnetic resonance imaging (MRI) can display the size and number of lymph nodes, helping to identify the type of primary lymphedema. In a retrospective review of CT findings in 19 patients with confirmed diagnosis of lymphedema, Shin et al. found that patients demonstrated imaging findings of honeycombing edema and tall fat globules [14]. Though the honeycombing edema was not found to be specific for lymphedema, CT complemented by three-dimensional MRI with contrast can identify additional findings of dilated superficial lymphatic vessels and deep lymphatic trunks with abnormal dynamics due to stagnant lymph or chyle [15]. While both CT and MRI offer visualization of the tissues and lymph nodes and are generally readily available in most hospital or clinic-based settings, their cost tends to exceed that of other lymphedema diagnostic imaging approaches, precluding their universal application.

Presently, many apparatuses used in lymphoscintigraphy combine single photon emission computed tomography dual-headed devices (SPECT) with X-ray computed tomography (CT or SPECT-CT). SPECT-CT enables evaluation of intra-abdominal lymph node status in lower limb edema and localization of various potentially important lymph nodes in upper extremity edema, such as those in the humeral, axillary, apical, retroclavicular, or supraclavicular regions [16]. Furthermore, SPECT-CT lymphoscintigraphy has demonstrated benefits in patients with chylous reflux and/or leakage, abdominal metabolic activity that does not correspond with classic anatomic localization of the infra-diaphragmatic lymph nodes, and lymphatic reflux and dermal backflow in the genital organs and/or at the abdominal wall level [16, 17]. Unlike conventional lymphoscintigraphy, SPECT-CT increases patient radiation exposure and has increased cost. However, SPECT-CT notably provides clearer anatomic resolution.

Color Duplex Ultrasound

As another contribution to the array of imaging techniques available for the diagnosis of lymphedema, color-duplex ultrasound (CDU) has been recognized as a modality since 1986 [18]. Moreover, this technology has the advantages of being safe, easily reproducible, and relatively inexpensive, allowing for information about a patient's management of lymphedema to be collected prior to, during, and after initiation of treatment. CDU employs high frequency (10–20 MHz) ultrasound probes to detect fluid in suprafascial and subfascial planes, ectatic lymphatic vessels, alterations in lymph node morphology and vascularization, and nodules and cysts in the lymphedematous limb [18–20]. Suehiro et al. demonstrated that duplex ultrasound can identify cellular changes in lymphedema, such as connective tissue hypertrophy, increase in fat cell number and fat cell hypertrophy, and interstitial fluid buildup [21]. Importantly, lymphedema severity as approximated by duplex ultrasound has demonstrated consistency with the International Society of Lymphology (ISL) staging system.

Lymphoscintigraphy

With a growing role in clinical medicine, lymphoscintigraphy (LSG) is used to diagnose lymphedema and determine lymphatic drainage patterns in cancer patients [22]. LSG generates different scan findings in patients depending on the original cause of the lymphedema, the duration of the swelling, and the mechanisms compensating for the altered flow dynamics [23]. LSG provides information about the clearance of a radiolabeled colloid after interstitial injection and also details the patterns of flow to regional lymph nodes, enabling visualization of sites of lymphatic obstruction and leakage. LSG has the advantage of being a relatively non-invasive diagnostic study, but this technique lacks standardization such that radionuclide types employed, dosage, injection sites, exercise and massage protocols to disperse the radionuclide, and timing of imaging are not uniformly performed in all patients [24••]. Additionally, for patients who present with defects in lymphatic function early on, LSG findings can be unrevealing prior to the onset of more significant dermal backflow and edema [24••].

Fluorescent Microlymphography

Developments in imaging technology have allowed for the precise visualization of microlymphatic vessel morphology, diameter, and permeability. These details, when coupled with an assessment of the number of microlymphatic loops and the extravasation of contrast from an injection site, constitute the basis of fluorescent microlymphography (FMLG). FMLG thereby offers application in many microcirculatory and macrocirculatory diseases [25]. Early on in lymphedema, there is both a high number of microlymphatic loops and higher than normal range microlymphatic pressure. With fibrosis over time, microlymphatics fail to visualize on FMLG. Notably, microlymphography can be used in patients with chronic venous disease and other vascular conditions, in addition to those with lymphedema.

Bioimpedance

In contrast to previously mentioned diagnostic modalities for lymphedema, bioimpedance is considered a relatively novel approach. Focused on the administration of a weak, alternating electrical current at one or more radiofrequencies through leads attached to surface electrodes to identify the conductive and nonconductive bodily tissue and fluid components, bioimpedance has had a traditionally established role in assessing body composition and patient nutritional status at the bedside [26]. There is growing interest in the application of segmental bioimpedance spectroscopy (BIS) for the evaluation of lymphedema. BIS has demonstrated applicability in monitoring and detecting early stages of lymphedema in breast cancer patients by enabling creation of an interlimb ratio of resistance values between an affected and unaffected limb [27–32]. Qin et al. examined the ability of single-segmental bioimpedance (SSB) and multi-segmental bioimpedance (MSB) to assess patients with unilateral and bilateral lymphedema, when compared with the reference standard of indocyanine green lymphography (ICG) [33•]. For patients with unilateral disease, SSB had higher sensitivity than MSB. In contrast, in patients with bilateral disease, MSB had higher sensitivity than SSB. Nonetheless, both bioimpedance technologies performed with lower sensitivity and specificity when compared with ICG. While lymphedema diagnostic information provided by bioimpedance is helpful, this information is best considered in conjunction with other patient attributes such as history, exam findings, quality-of-life assessments, and ICG lymphography [33•].

Near-infrared Imaging

As ICG has been established as a standard for visualization of lymphatic anatomy and function, this technique employs excitation by near-infrared light and has unique clinical uses. ICG imaging can be used to guide manual lymphatic drainage via visualization of functional lymphatic vessels [34]. Additionally, ICG imaging can be used to evaluate success of intermittent pneumatic compression in patients with either lymphedema or unilateral venous stasis ulcers [35]. This technique of near-infrared imaging of ICG in the lymphatics does however require greater standardization in practice and consistency in measurement device design [36].

Laser Scanner 3D Method

As upper limb lymphedema is a feared complication of breast cancer and associated treatment, the early detection of and quantification of this lymphedema is essential for appropriate intervention [37, 38]. Commonly used methods in the clinical setting include water displacement and circumferential method (CM) measurements, but a more recent addition to these maneuvers is the laser scanner 3D method (LS3D). Though water displacement has been considered a gold standard in arm measurements, this technique is limited by its inability to recognize nonuniform distributions of lymphedema in contrast with uniform arm swelling [39]. Though CM measurements are easier to obtain, this approach is limited by formulaic errors in volume calculation, particularly when the limb has a more protuberant shape as a result of lymphedema [39]. As an improvement in ability to detect limb volume and shape, the LS3D combines precision, reproducibility, and generates measurements in a short duration of approximately 5 min [40]. Furthermore, LS3D-associated costs are limited to scanner purchase and personnel training, indicating a favorable cost-benefit ratio in clinical use. While the LS3D method has shown promise in characterizing upper limb lymphedema, this modality remains to be explored in lymphedema of the lower limbs and other anatomic regions [39].

Dual-Energy X-ray Absorptiometry

A technique that has been explored in the dynamics of lower limb lymphedema, dual-energy X-ray absorptiometry (DXA) allows for detection of physiological changes in lean mass, fat, and bone mineral content as well as reproducibility in volume measurements [41]. A consideration when employing this technique is patient positioning, as scan performance immediately after ambulation versus after relaxation in the supine position can result in different calculations of lower extremity lean mass. Nonetheless, the absolute difference in these measurements is minimal and does not impede reliability of measurement reproducibility [41]. Additionally, DXA has evidenced improved measurement reproducibility when compared with the water displacement and CM methods of assessing upper extremity lymphedema secondary to breast cancer [42]. DXA functions well as another member of the arsenal of noninvasive lymphedema diagnostic and monitoring techniques.

Future Considerations

While there are several lymphedema diagnostic modalities, each uniquely informing the clinical perspective with visualization, qualification, and quantification data of lymphedema severity, some recently proposed novel modalities may emerge as new contenders in clinical practice. Conventional high-frequency ultrasound (CHFUS) has traditionally substituted ICG lymphography in patients with severe lymphedema, but technique limitations such as operator dependence and difficulty discerning small lymphatic vessels less than 0.3 mm have necessitated an improvement in ultra-high-frequency ultrasound systems (UHFUS) [43, 44]. These improved systems permit frequencies as high as 70 MHz and capillary resolution as fine as 30 μm, permitting more precise imaging of small anatomical structures [45]. When compared with CHFUS, UHFUS has enhanced sensitivity and specificity for detection of lymphatic vessels. Encouraged by favorable animal studies [46, 47], UHFUS has recently been approved for human use with preoperative imaging of functional lymphatic vessels prior to lymphedema surgery. Furthermore, the improved resolution with UHFUS may be able to permit assessment of lymphosclerosis severity and even replace ICG lymphography for detection of lymphatic vessels in lymphedematous limbs [45].

Consistent with this vein of improvements in lymphatic imaging, the technique of magnetic resonance lymphography (MRL) has evidenced improved lymphatic resolution with gadolinium-based nanoparticles in animal models. The gadolinium-based nanoparticle AGuIX offers anatomic localization and has even been proposed as a radiosensitizer for the treatment of brain metastases [48, 49]. In a rat hindlimb lymphedema model, the investigational nanoparticle AGuIX was incorporated as contrast with MRL, demonstrating slow but specific transit through the lymphatic system, allowing for afferent lymphatic vessel detection up to 30 min after injection with minor contrast enhancement [49]. This technique yielded higher spatial and temporal resolution than radionuclide imaging for lymphatic vessels with diameters around 200 μm. Notably, AGuIX-based MRL is suitable for preclinical lymphatic imaging at high field and has the potential to assess lymphatic regeneration post-reconstructive lymphedema surgery [49].

Although lymphedema can have a profound impact on patients' quality of life, most of the current treatments for lymphedema can only aim to help alleviate and manage the symptoms because there is no cure for this disease. Some modalities such as pneumatic compression implement physical, non-invasive ways to attempt to restrict and drain the excess fluid by exerting external pressure on the limbs [50]. Intermittent pneumatic compression (IPC) is performed with a pneumatic massage device, compression garments, and limb bandaging. Taradaj et al. examined the effects of two frequently used pressures in IPC, namely a high of 120 mmHg and a low of 60 mmHg, in the treatment of 81 patients with primary phlebolymphedema. These patients simultaneously received multilayer bandaging, lymph drainage, and pharmacotherapy [50]. Consistent with previously conducted studies, at a pressure of 120 mmHg, IPC reduced phlebolymphedema in patients significantly more so than at a pressure of 60 mmHg. In spite of these favorable findings, there is still a need to further investigate both the pressure setting and treatment duration in patients receiving IPC with the goal of maximizing patient comfort with this procedure.

In the past few years, the FDA approved an advanced pneumatic compression device (PCD), The Flexitouch System, for at-home management of lymphedema [51]. Adams et al. investigated the benefits of using advanced PCD therapy in six patients with BCRL [51]. One of the main causes of lymphedema treatment failure is due to difficulty with patient adherence to prescribed manual lymphatic drainage (MLD) therapy at home. PCDs were therefore proposed as a better alternative to self-MLD treatment in order to improve treatment efficacy and patient compliance [51]. Of note, when compared with control patients, patients with BCRL displayed a statistically significant difference between pre- and post-treatment lymphatic propulsive rates in the untreated arm. This finding could suggest systemic compensation taking place. Furthermore, lymphatic propulsion increased in both arms of BCRL patients, indicating an improvement in overall lymphatic function [51]. Additionally, other studies have shown that PCD improves lymphatic function, decreases limb volume, provides for some weight loss, and reduces healthcare costs when compared with self-MLD [51, 52].

The gold standard for the treatment of lymphedema is complete decongestive therapy (CDT), which consists of multiple steps, including manual lymphatic drainage, compression therapy, rehabilitation exercise, and skin care [53]. CDT aims to reduce lymphedema volume, improve the condition of affected overlying skin, and maintain a long-lasting reduction in lymphedema volume [54]. Melam et al. found that early lymphedema identification and patient education regarding a CDT home program reduced pain and improved quality of life in post-mastectomy breast cancer patients [55]. Furthermore, when used in conjunction with other treatment modalities such as IPC and MDL, CDT has shown to be even more effective in reducing arm volume in BRCL patients, with IPC having an additional protective effect against thrombosis formation [54, 56]. Szuba et al. observed that among 50 patients with BCRL, CDT with IPC led to a 20% greater reduction in mean volume when compared with CDT alone. In fact, CDT alone led to a mean increase in volume during the maintenance phase after initial volume reduction, suggesting that the combination of CDT and IPC provides for enhanced long-term therapeutic results [56].

Conclusions

Secondary lymphedema is a potential complication of utmost importance for breast cancer patients due to its debilitating and disfiguring effects, as well as the absence of a definitive curative modality. Selecting a diagnostic method that is accurate, reliable, and easily accessible remains an ongoing challenge in clinical practice. Lymphoscintigraphy is generally the accepted technique of choice for diagnosing lymphedema because it is less invasive than other diagnostic methods but can still directly measure lymphatic dysfunction with relative ease [24••]. Alternatively, near-infrared imaging is a non-invasive procedure, involving the injection of a fluorescent dye, such as indocyanine green, to provide imaging of deep tissues with high sensitivity [34]. Nonetheless, a major pitfall of diagnostic methods that require injection is that protocols may differ in fluorescent dye or radionuclide type and dosage, the injection site, and the timing of imaging [24••].

Other imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), are performed with equipment that is generally available at hospitals but is too expensive to be used universally in practice. More cost-effective methods, such as color duplex ultrasound (CDU), laser scanner 3D (LS3D), and dual-energy X-ray absorptiometry (DXA), can also be utilized but result in a tradeoff with diminished visual acuity. In addition, several new diagnostic methods are currently being explored. Bioimpedance is a promising new development that measures the water content of the body by administering weak, alternating electrical current at one or more frequencies [26]. Ultra-high-frequency ultrasound systems (UHFUS) offer more precise imaging of small lymphatic vessels and thus may eventually replace ICG lymphography [45]. Lastly, magnetic resonance lymphography (MRL) in combination with a gadolinium-based nanoparticle contrast allows higher resolution than radionuclide imaging for lymphatic vessels [49]. As novel approaches continue to be refined, it is important that physicians understand and appropriately incorporate diagnostic modalities to optimize early detection of breast cancer–related lymphedema (BCRL) with the goal of sparing patients from advanced-stage disease sequelae.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Group USCSW. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999-2016). U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. https://gis.cdc.gov/Cancer/USCS/DataViz.html. Accessed 6 Aug 2019.
2. Lawenda B, Mondry T, Johnstone P. Lymphedema: a primer on the identification and management of a chronic condition in oncologic treatment. CA Cancer J Clin. 2009;59:8–24. https://doi.org/10.3322/caac.20001.
3. Mak S, Yeo W, Lee Y, Mo K, Tse K, Tse S, et al. Predictors of lymphedema in patients with breast cancer undergoing axillary lymph node dissection in Hong Kong. Nurs Res. 2008;57:416–25. https://doi.org/10.1097/NNR.0b013e31818c3de2.
4. McLaughlin S, Bagaria S, Gibson T, Arnold M, Diehl N, Crook J, et al. Trends in risk reduction practices for the prevention of lymphedema in the first 12 months after breast cancer surgery. J Am Coll Surg. 2013;216:380–9. https://doi.org/10.1016/j.jamcollsurg.2012.11.004.
5. Morrell R, Halyard M, Schild S, Ali M, Gunderson L, Pockaj B. Breast cancer-related lymphedema. Mayo Clin Proc. 2005;80:1480–4. https://doi.org/10.4065/80.11.1480.
6.• Pamarthi V, Pabon-Ramos W, Marnell V, Hurwitz L. MRI of the central lymphatic system: indications, imaging, technique, and pre-procedural planning. Top Magn Reson Imaging. 2017;26:175–80. https://doi.org/10.1097/RMR.0000000000000130 **This review describes advances in magnetic resonance (MR) software that allow improved visualization of the lymphatics. In providing helpful visualization of central lymphatic system anatomy and pathology, this technology can be utilized for both lymphedema diagnosis and pre-procedural planning.**
7. Scallan J, Zawieja S, Castorena-Gonzalez J, Davis M. Lymphatic pumping: mechanics, mechanisms and malfunction. J Physiol. 2016;594:5749–68. https://doi.org/10.1113/JP272088.
8. Hancock D, Potezny T, White P. The peripheral lymphatics as an active player in the immune response. J Clin Cell Immunol. 2014;5:268. https://doi.org/10.4172/2155-9899.1000268.
9. Padera T, Meijer E, Munn L. The lymphatic system in disease processes and cancer progression. Annu Rev Biomed Eng. 2016;18:125–58. https://doi.org/10.1146/annurev-bioeng-112315-031200.
10. Greene A. History and physical examination. In: Greene A, Slavin S, Brorson H, editors. Lymphedema. Cham: Springer; 2015.
11. Gerber L. A review of measures of lymphedema. Cancer. 1998;83:2803–4. https://doi.org/10.1002/(sici)1097-0142(19981215)83:12b+<2803::aid-cncr29>3.3.co;2-n.
12. Lymphology ISo. The diagnosis and treatment of peripheral lymphedema: 2013 Consensus Document of the International Society of Lymphology. Lymphology. 2013;46:1–11.
13. Schook C, Mulliken J, Fishman S, Grant F, Zurakowski D, Greene A. Primary lymphedema: clinical features and management in 138 pediatric patients. Plast Reconstr Surg. 2011;127:2419–31. https://doi.org/10.1097/PRS.0b013e318213a218.
14. Shin S, Lee W, Park E, Shin C, Chung J, Park J. Comparison of characteristic CT findings of lymphedema, cellulitis, and generalized edema in lower leg swelling. Int J Card Imaging. 2013;29:135–43. https://doi.org/10.1007/s10554-013-0332-5.
15. Liu N, Wang C, Sun M. Noncontrast three-dimensional magnetic resonance imaging vs lymphoscintigraphy in the evaluation of lymph circulation disorders: a comparative study. J Vasc Surg. 2005;41:69–75. https://doi.org/10.1016/j.jvs.2004.11.013.
16. Bourgeois P. Combined role of lymphoscintigraphy, x-ray computed tomography, magnetic resonance imaging, and positron emission tomography in the management of lymphedematous disease. In: Lee B, Bergan J, Rockson S, editors. Lymphedema. London: Springer; 2011.
17. Nishiyama Y, Yamamoto Y, Mori Y, Satoh K, Takashamia H, Ohkawa M, et al. Usefulness of Technetium-99m human serum albumin lymphoscintigraphy in chyluria. Clin Nucl Med. 1998;23:429–31. https://doi.org/10.1097/00003072-199807000-00006.
18. Cavezzi A. Duplex ultrasonography. In: Lee B, Bergan J, Rockson S, editors. Lymphedema. London: Springer; 2011.
19. Cammarota T, Pinto F, Magliaro A, Sarno A. Current uses of diagnostic high-frequency US in dermatology. Eur J Radiol. 1998;27:S215–S23. https://doi.org/10.1016/S0720-048X(98)00065-5.
20. Matter D, Grosshans E, Muller J, Furderer C, Mathelin C, Warter S, et al. Sonographic imaging of lymphatic vessels compared to other methods. J Radiol. 2002;83:599–609.
21. Suehiro K, Morikage N, Murakami M, Yamashita O, Samura M, Hamano K. Significance of ultrasound examination of skin and subcutaneous tissue in secondary lower extremity lymphedema. Ann Vasc Dis. 2013;6:180–8. https://doi.org/10.3400/avd.oa.12.00102.
22. Krasnow A, Elgazzar A, Kazem N. Lymphoscintigraphy. In: Elgazzar A, editor. The pathophysiologic basis of nuclear medicine. Berlin, Heidelberg: Springer; 2006.
23. Ohtake E, Matsui K. Lymphoscintigraphy in patients with lymphedema: a new approach using intradermal injections of technetium-99m human serum albumin. Clin Nucl Med. 1986;11:474–8.
24.•• O'Donnell T, Rasmussen J, Sevick-Muraca E. New diagnostic modalities in the evaluation of lymphedema. J Vasc Surg Venous Lymphat Disord. 2017;5:261–73. https://doi.org/10.1016/j.jvsv.2016.10.083 **This review examines new diagnostic modalities for evaluating lymphedema and evaluates the utility of each modality. The strength of the literature in support of each modality offers helpful context for physicians to decide which modality to apply in individual patient cases.**
25. Allegra C, Bartolo M, Carlizza A. Fluorescent microlymphaniography. In: Lee B, Bergan J, Rockson S, editors. Lymphedema. London: Springer; 2011.
26. Mulasi U, Kuchnia A, Cole A, Earthman C. Bioimpedance at the bedside: current applications, limitations, and opportunitie. Nutr Clin Pract. 2015;30:180–93. https://doi.org/10.1177/0884533614568155.

27. Cornish B, Chapman M, Hirst C, Mirolo B, Bunce I, Ward L, et al. Early diagnosis of lymphedema using multiple frequency bioimpedance. Lymphology. 2001;34:2–11.
28. Czerniec S, Ward L, Lee M, Refshauge K, Beith J, Kilbreath S. Segmental measurement of breast cancer-related arm lymphoedema using perometry and bioimpedance spectroscopy. Support Care Cancer. 2011;19:703–10. https://doi.org/10.1007/s00520-010-0896-8.
29. Ward L. Bioelectrical impedance analysis: proven utility in lymphedema risk assessment and therapeutic monitoring. Lymphat Res Biol. 2006;4:51–6. https://doi.org/10.1089/lrb.2006.4.51.
30. Cornish B, Thomas B, Ward L. Improved prediction of extracellular and total body water using impedance loci generated by multiple frequency bioelectrical impedance analysis. Phys Med Biol. 1993;38:337–46. https://doi.org/10.1088/0031-9155/38/3/001.
31. Cornish B, Bunce I, Ward L, Jones L, Thomas B. Bioelectrical impedance for monitoring the efficacy of lymphoedema treatment programmes. Breast Cancer Res Treat. 1996;38:169–76. https://doi.org/10.1007/BF01806671.
32. Ward L, Dylke E, Czerniec S, Isenring E, Kilbreath S. Confirmation of the reference impedance ratios used for assessment of breast cancer-related lymphedema by bioelectrical impedance spectroscopy. Lymphat Res Biol. 2011;9:47–51. https://doi.org/10.1089/lrb.2010.0014.
33.• Qin E, Bowen M, James S, Chen W. Multi-segment bioimpedance can assess patients with bilateral lymphedema. J Plast Reconstr Aesthet Surg. 2019. https://doi.org/10.1016/j.bjps.2019.06.041 **This single institution study examined the role of bioimpedance spectroscopy as a lymphedema diagnostic modality. Single-segment bioimpedance (SSB) was more sensitive than multi-segment impedance (MSB) for diagnosing unilateral lymphedema, while MSB had greater sensitivity and specificity for diagnosing bilateral lymphedema. Moreover, MSB was found to be easier to perform and therefore adapted in the authors' department practice.**
34. Maus E, Tan I, Rasmussen J, Marshall M, Fife C, Smith L, et al. Near-infrared fluorescence imaging of lymphatics in head and neck lymphedema. Head Neck. 2012;34:448–53. https://doi.org/10.1002/hed.21538.
35. Rasmussen J, Aldrich M, Tan I, Darne C, Zhu B, O'Donnell TJ, et al. Lymphatic transport in patients with chronic venous insufficiency and venous leg ulcers following sequential pneumatic compression. J Vasc Surg Venous Lymphat Disord. 2016;4:9–17. https://doi.org/10.1016/j.jvsv.2015.06.001.
36. Zhu B, Rasmussen J, Litorja M, Sevick-Muraca E. Determining the performance of fluorescence molecular imaging devices using traceable working standards with SI units of radiance. IEEE Trans Med Imaging. 2016;35:802–11. https://doi.org/10.1109/TMI.2015.2496898.
37. Deltombe T, Jamart J, Recloux S, Legrand C, Vandenbroeck N, Theys S, et al. Reliability and limits of agreement of circumferential, water displacement, and optoelectronic volumetry in the measurement of upper limb lymphedema. Lymphology. 2007;40:26–34.
38. Stout Gergich N, Pfalzer L, McGarvey C, Springer B, Gerber L, Soballe P. Preoperative assessment enables the early diagnosis and successful treatment of lymphedema. Cancer. 2008;112:2809–19. https://doi.org/10.1002/cncr.23494.
39. Cau N, Galli M, Cimolin V, Grossi A, Battarin I, Puleo G, et al. Quantitative comparison between the laser scanner three-dimensional method and the circumferential method for evaluation of arm volume in patients with lymphedema. J Vasc Surg Venous Lymphat Disord. 2017;6:96–103. https://doi.org/10.1016/j.jvsv.2017.08.014.
40. Cau N, Galli M, Cimolin V, Aranci M, Caraceni A, Balzarini A. Comparative study between circumferential method and laser scanner 3D method for the evaluation of arm volume in healthy subjects. J Vasc Surg: Venous and Lymphat Disord. 2016;4:64–72. https://doi.org/10.1016/j.jvsv.2015.05.005.
41. Gjorup C, Zerahn B, Juul S, Hendel H, Christensen K, Holmich L. Repeatability of volume and regional body composition measurements of the lower limb using dual-energy x-ray absorptiometry. J Clin Densitom. 2017;20:82–96. https://doi.org/10.1016/j.jocd.2016.08.009.
42. Gjorup C, Zerahn B, Hendel H. Assessment of volume measurement of breast cancer-related lymphedema by three methods: circumference measurement, water displacement, and dual energy X-ray absorptiometry. Lymphat Res Biol. 2010;8:111–9. https://doi.org/10.1089/lrb.2009.0016.
43. Hayashi A, Yamamoto T, Yoshimatsu H, Hayashi N, Furuya M, Harima M, et al. Ultrasound visualization of the lymphatic vessels in the lower leg. Microsurgery. 2016;36:397–401. https://doi.org/10.1002/micr.22414.
44. Hayashi A, Hayashi N, Yoshimatsu H, Yamamoto T. Effective and efficient lymphaticovenular anastomosis using preoperative ultrasound detection technique of lymphatic vessels in lower extremity lymphedema. J Surg Oncol. 2018;117:290–8. https://doi.org/10.1002/jso.24812.
45. Hayashi A, Giacalone G, Yamamoto T, Belva F, Visconti G, Hayashi N, et al. Ultra high-frequency ultrasonographic imaging with 70 MHz scanner for visualization of the lymphatic vessels. Plast Reconstr Surg Glob Open. 2019;7:e2086. https://doi.org/10.1097/GOX.0000000000002086.
46. Grassi R, Lagalla R, Rotondo A. Genomics, proteomics, MEMS and SAIF: which role for diagnostic imaging? Radiol Med. 2008;113:775–8. https://doi.org/10.1007/s11547-008-0309-y.
47. Grassi R, Cavaliere C, Cozzolino S, Mansi L, Cirillo S, Tedeschi G, et al. Small animal imaging facility: new perspectives for the radiologist. Radiol Med. 2009;114:152–67. https://doi.org/10.1007/s11547-008-0352-8.
48. Lux F, Mignot A, Mowat P, Louis C, Dufort S, Bernhard C, et al. Ultrasmall rigid particles as multimodal probes for medical applications. Angew Chem Int Ed Eng. 2011;50:12299–303. https://doi.org/10.1002/anie.201104104.
49. Muller A, Fries P, Jelvani B, Lux F, Rube C, Kremp S, et al. Magnetic resonance lymphography at 9.4T using a gadolinium-based nanoparticle in rats: investigations in healthy animals and in a hindlimb lymphedema model. Investig Radiol. 2017;52:725–33. https://doi.org/10.1097/RLI.0000000000000398.
50. Taradaj J, Rosinczuk J, Dymarek R, Halski T, Schneider W. Comparison of efficacy of the intermittent pneumatic compression with a high- and low-pressure application in reducing the lower limbs phlebolymphedema. Ther Clin Risk Manag. 2015;11:1545–54. https://doi.org/10.2147/TCRM.S92121.
51. Adams K, Rasmussen J, Darne C, Tan I, Aldrich M, Marshall M, et al. Direct evidence of lymphatic function improvement after advanced pneumatic compression device treatment of lymphedema. Biomed Opt Express. 2010;1:114–25. https://doi.org/10.1364/BOE.1.000114.
52. Brayton K, Hirsch A, O Brien P, Cheville A, Karaca-Mandic P, Rockson S. Lymphedema prevalence and treatment benefits in cancer: impact of a therapeutic intervention on health outcomes and costs. PLoS One. 2014;9:e114597. https://doi.org/10.1371/journal.pone.0114597.
53. Mayrovitz H, Ryan S, Hartman J. Usability of advanced pneumatic compression to treat cancer-related head and neck lymphedema: a feasibility study. Head Neck. 2018;40:137–43. https://doi.org/10.1002/hed.24995.
54. Chang C, Cormier J. Lymphedema interventions: exercise, surgery, and compression devices. Semin Oncol Nurs. 2013;29:28–40. https://doi.org/10.1016/j.soncn.2012.11.005.

55. Melam G, Buragadda S, Alhusaini A, Arora N. Effect of complete decongestive therapy and home program on health- related quality of life in post mastectomy lymphedema patients. BMC Womens Health. 2016;16:23. https://doi.org/10.1186/s12905-016-0303-9.
56. Szuba A, Achalu R, Rockson S. Decongestive lymphatic therapy for patients with breast carcinoma-associated lymphedema: a randomized, prospective study of a role for adjunctive intermittent pneumatic compression. Cancer. 2002;95:2260–7. https://doi.org/10.1002/cncr.10976.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.