Current Diagnostic Measures for Lymphedema
A Comprehensive Review

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Abstract: Lymphedema presents diagnostic challenges due to complex symptomatology and multifaceted onset. This literature review synthesizes diagnostic measures ranging from clinical assessments to advanced imaging techniques and emerging technologies. It explores the challenges in early detection and delves into the disparities in access to advanced diagnostic tools, which exacerbate health outcome differences across populations. This review not only provides insights into the effectiveness of current diagnostic modalities but also underscores the necessity for ongoing research and innovation. The goal is to enhance the accuracy, affordability, and accessibility of lymphedema diagnostics. This is crucial for guiding future research directions and for the development of standardized diagnostic protocols that could help mitigate the progression of lymphedema and enhance the quality of life for affected individuals.

Key Words: lymphedema, diagnostic measures, imaging, lymphatic diseases

(*Ann Plast Surg* 2024;93: S132–S135)

Lymphedema is the buildup of protein-rich fluid in the interstitial spaces, causing swelling and skin changes.[1,2] The lymphatic system drains excess fluid and waste, including white blood cells, triglycerides, bacteria, cell debris, water, and protein.[1,2] When fluid accumulation exceeds the lymphatic system's capacity, lymphedema occurs, which can be primary (congenital) or secondary (acquired).[1,2]

Symptoms include swelling in extremities, breasts, genitals, face, chest, and groin, along with restricted movement, skin discoloration, heaviness, and pain. Primary lymphedema, although rare, is inherited and caused by abnormalities in lymphatic vessels.[1,2] Conversely, secondary lymphedema results from injury or obstruction. Globally, filariasis is the leading cause, whereas, in the US and the other developed countries, cancer treatment either surgical or radiotherapy is common.[1,2] Thus, lymphedema significantly impacts quality of life and imposes substantial healthcare burdens. Achieving timely diagnosis is crucial yet difficult due to the disease's varied nature and lack of standard diagnostic methods. Consequently, healthcare professionals must navigate various tools and strategies to identify lymphedema accurately.

This literature review evaluates current diagnostic measures for lymphedema. It examines the strengths and limitations of clinical assessments, advanced imaging, and emerging technologies. Additionally, it explores diagnostic challenges, improvement opportunities, and future research directions. Ultimately, this review aims to provide a clear understanding of the diagnostic landscape to improve lymphedema patient outcomes.

Received June 6, 2024, and accepted for publication, after revision June 25, 2024.
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Conflicts of interest and sources of funding: none declared.
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ISSN: 0148-7043/24/9303–S132
DOI: 10.1097/SAP.0000000000004084

CURRENT DIAGNOSTIC MEASURES

Clinical Assessment

Lymphedema manifests as swelling caused by lymph fluid buildup, primarily in the extremities, but can also affect the face, neck, and abdomen in severe cases. Evaluating patient symptoms is crucial for accurate diagnosis. Common symptoms include feeling of heaviness and swelling, often the first and most noticeable signs. This swelling may fluctuate and improve with elevation initially but can become persistent in the later stages. Pitting edema, where pressure creates a temporary indentation, indicates early-stage fluid dominant lymphedema. As lymphedema progresses, the skin may thicken, become less pliable, and exhibit a "peau d'orange" texture. Lymph fluid also stimulates adipose tissue deposition in the area, which progresses to a solid dominant disease in the later stages.[3] Patients may also experience more heaviness or tightness, progressing to pain that affects mobility and quality of life. Recurrent infections like cellulitis or lymphangitis are common due to impaired lymphatic function.[1,2]

Physical examination is essential for diagnosing lymphedema and involves several techniques. Inspection of the affected area reveals signs of swelling, skin changes, and asymmetry. Palpation assesses tissue texture, warmth, and fluid presence. The Stemmer sign, difficulty lifting the skin at the base of the second toe or finger, is a key diagnostic indicator.[2] Circumference measurements quantify swelling and monitor changes over time, helping assess severity and progression. Range of motion assessments in affected limbs determine lymphedema's impact on functional mobility.[2] These clinical methods, combined with patient history and symptoms, guide further diagnostic testing and management strategies.

Among these methods, simple circumferential measurements are straightforward for assessing lymphedema. Using a nonstretch flexible tape, measurements are taken at fixed points along the limb, typically at 4 cm or 10 cm intervals from the wrist to the axilla. These measurements are compared to baseline values, crucial for early detection and ongoing monitoring.[4] A 2-cm or greater increase in circumference is defined as lymphedema. The truncated cone formula allows for conversion of circumferential measurements to volume. By comparing to the unaffected side, excess volume is calculated as percentage difference. In general, a 10% or higher volume changes is considered as lymphedema.[5] Baseline measurements are taken before any medical treatment that might cause lymphedema, such as surgery or radiation. Regular measurements can detect subtle changes in limb size, allowing for early intervention. Although simple and cost-effective, the accuracy of this method depends on consistent measurement techniques and the measurer's precision. Despite its limitations, circumferential measurements are widely used due to their practicality in various clinical settings.[4]

Imaging Techniques

Lymphoscintigraphy

Lymphoscintigraphy is the current standard of care imaging technique for diagnosing lymphedema, especially when the cause of limb swelling is unclear. It involves injecting a radiotracer, typically technetium-99m-labeled sulfur colloid, into the spaces between the fingers or toes. Serial imaging tracks the radiotracer's movement through the lymphatic system, allowing for visual mapping and functional assessment of lymphatic drainage and node functionality.[6]

Lymphoscintigraphy is minimally invasive and provides detailed visualization, making it invaluable for differential diagnosis. It is useful for diagnostic confirmation before planning surgical interventions, such as lymphovenous anastomosis (LVA). Compared to direct lymphography, which involves injecting dye directly into lymphatic vessels, lymphoscintigraphy is safer and less invasive and can provide functional data.[7] However, lymphoscintigraphy has limitations. The lack of an internationally standardized technique causes variability in results across different medical centers. Its sensitivity can vary, and early stages of lymphatic impairment may go undetected if anatomical changes have not yet occurred. The test's efficacy is also affected by local factors at the injection site and systemic factors influencing lymphatic function.[6] Despite these limitations, lymphoscintigraphy remains crucial in diagnosing lymphedema.

Indocyanine Green Lymphography

Indocyanine green (ICG) lymphography is a sophisticated imaging technique utilized primarily in the mapping of lymphatic vessels and nodes.[8] This method involves the injection of ICG, a fluorescent dye, into the dermal or subdermal layers of the skin.[8] Once injected, ICG binds to plasma proteins and is transported through the lymphatic system.[8] Under near-infrared (NIR) light, the ICG fluoresces, allowing for real-time visualization of lymphatic flow and structure.[8] The procedure to carry out ICG lymphography is similar to lymphoscintigraphy. ICG is injected into the distal extremity and imaged at intervals to watch its progression through the lymphatic system.[8] Earlier scans provide insight into the local lymphatic anatomy and transport time from one anatomic region to another, whereas later scans provide insight into the overall effectiveness of the lymphatic system based on the distribution of the agent in the limb.[8] This process provides a dynamic and detailed map of lymphatic drainage patterns, highlighting both normal and abnormal lymphatic architecture.

ICG lymphography delivers higher-resolution images than lymphoscintigraphy using near-infrared imaging rather than radiation.[9] Clinically, it aids in diagnosing lymphedema, planning surgical interventions such as LVA, and assessing the effectiveness of these surgeries. ICG lymphography can also visualize pre- and postoperative improvements following operative interventions, create a preoperative map of the lymphatic drainage system in patients about to undergo lymphatic surgery, and serve as an intraoperative imaging tool. Moreover, it is a reliable diagnostic and staging tool, especially in oncologic surgeries for conditions like breast cancer and melanoma, where accurate identification of sentinel nodes is critical for staging and treatment planning.[10–13] The technique's minimally invasive nature, coupled with its relatively high resolution and real-time imaging capabilities, makes ICG lymphography a preferred method over traditional lymphoscintigraphy, providing superior anatomical details and functional insights into the lymphatic system.

MRI and CT Scans

MRI and CT scans provide crucial insights for diagnosing lymphedema by visualizing the lymphatic and surrounding tissues. MRI offers superior soft tissue contrast, identifying subtle changes that indicate lymphedema. For example, it can differentiate lymphedema from other edema types by showing a honeycomb pattern in the subcutaneous layer, which signals fibrosis and fluid accumulation. This pattern is less evident in other edema types.[14] Additionally, gadolinium-enhanced MRI improves the visibility of lymphatic vessels and nodes, aiding in lymphatic drainage assessment.[14]

CT scans, although less sensitive than MRI to soft tissue contrast, are useful for identifying causes of secondary lymphedema, such as neoplasms obstructing lymphatic pathways. CT can also show the honeycombing pattern of fibrotic tissue and fluid, although with less detail than MRI. In advanced lymphedema cases, CT helps assess the extent of fibrosis and structural changes in the affected limbs[14]

Ultrasound

Ultrasound imaging, through high-resolution scans, effectively assesses lymphedema by detecting subcutaneous fluid and tissue density changes, crucial for diagnosing and monitoring lymphedema treatment.[7] Ultrahigh-frequency ultrasound (UHFUS) demonstrates higher sensitivity and specificity compared to conventional high-frequency ultrasound (CHFUS) for detecting lymphatic vessels, particularly those with smaller diameters.[15] UHFUS can visualize lymphatic vessels with unprecedented clarity, including those less than 0.3 mm in diameter, and detect a larger number of vessels in the extremities.[15] Unlike CHFUS, which is limited by difficulty in distinguishing lymphatic vessels from other subcutaneous structures, UHFUS provides clear images and valuable new imaging characteristics.[15] Recently, high-resolution ultrasound has also been used for detecting small lymphatic vessels and veins around these vessels to facilitate LVA surgeries and increase their effectiveness.[15] However, UHFUS's imaging depth is limited to 10 mm, making it less effective for deeper vessels. Further studies are needed to evaluate interoperator reliability and confirm findings through direct intraoperative observation.[16]

Ultrasound elastography, a recent advancement, enhances diagnostic accuracy by evaluating tissue stiffness and elasticity.[17] Changes like increased fibrosis and fluid accumulation affect tissue elasticity, measurable through elastography.[17] In lymphedema, tissues show increased stiffness or decreased elasticity, identifiable with this method.[17] Thus, elastography provides additional diagnostic data beyond traditional ultrasound, offering a nuanced assessment of lymphatic dysfunction.

Integrating ultrasound elastography into clinical practice enhances traditional diagnostic and monitoring methods. It offers detailed insights into the mechanical properties of tissues affected by lymphatic fluid accumulation.[17] As this technology evolves, it may improve lymphedema staging and guide targeted therapies, enhancing patient outcomes.[17]

Bioimpedance Spectroscopy

Bioimpedance analysis (BIA) and modern electrical bioimpedance spectroscopy (EIS) are noninvasive methods used to assess and monitor various medical conditions, particularly lymphedema. BIA measures the electrical impedance of body tissues to indicate fluid and fat composition by passing a small electrical current through the body and measuring the resistance. Water-rich tissues like muscle conduct electricity better than fatty tissues, allowing for the estimation of fluid volume in body compartments, especially extracellular fluid, which increases in lymphedema.[18,19] BIA is effective for early detection of lymphedema because it can identify subtle tissue changes before physical symptoms appear. Studies show that BIA can detect lymphedema at a subclinical level with high sensitivity and specificity, allowing for earlier intervention and better management outcomes.[18] Given these advantages, BIA is recommended for routine monitoring of at-risk patients, such as those post–breast cancer surgery, due to its simplicity, speed, and effectiveness in clinical settings.[20]

A recent multicenter randomized controlled trial provides additional support for the use of BIA in prospective breast cancer-related lymphedema (BCRL) screening. The study demonstrated that BIA, coupled with early intervention using a short 4-week well-fitted compression sleeve and gauntlet, significantly reduced the progression to chronic BCRL compared to traditional methods. Specifically, the use of BIA as part of prospective BCRL surveillance reduced chronic BCRL (C-BCRL) progression rates from 19.2% to 7.9% ($P = 0.016$). This clinically significant outcome suggests that BIA can help reduce a patient's risk of developing C-BCRL and offers a cost-effective intervention option.[20]

The study at the University of Iowa Lymphedema Center from 2015 to 2017 further evaluated BIA's diagnostic accuracy using ICG lymphography as a reference. Although ICG lymphography findings consistently correlated with clinical examinations and other lymphedema indices, BIA demonstrated a false-negative rate of 36%. Despite this limitation, BIA remains a valuable tool as an adjunct for early detection, enabling timely intervention to prevent lymphedema progression.[18]

Given these advantages, BIA is recommended for routine monitoring of at-risk patients, such as those post–breast cancer surgery. Early detection through BIA allows for more effective interventions to prevent lymphedema progression. Its simplicity and speed make BIA ideal for clinical settings, where it can be used repeatedly to monitor lymph fluid status and guide treatment decisions.[21] Although BIA is valuable for detecting and monitoring lymphedema, it is most effective when used alongside clinical evaluations and other diagnostic measures.[21]

Emerging Technologies and Methods

Emerging technologies and methods in lymphedema diagnosis show advances in imaging and genetic studies. NIR is a novel technique that visualizes lymphatic function and structure with minimal invasiveness. This is valuable in complex areas like the head and neck, where NIR can guide traditional management strategies, such as manual lymphatic drainage (MLD), more effectively by targeting functional lymph vessels.[22]

In genetics, research on molecular and genetic markers for lymphedema has expanded but faces challenges. Genetic screening for primary lymphedema often shows low efficacy, with many tests returning inconclusive or negative results despite clinical diagnoses. This highlights the complexity of lymphedema's genetic basis and the need for deeper molecular insights. Promising research has identified key pathways, such as PI3K/AKT and RAS/MAPK, involved in lymphatic development and function, which could be targets for precise diagnostic and therapeutic approaches.[23]

COMPARATIVE EFFICACY OF DIAGNOSTIC TOOLS

Two imaging modalities, lymphoscintigraphy and ICG lymphography, have become the gold standards due to their reliability and low invasiveness. Lymphoscintigraphy involves injecting a radioactive tracer into the lymphatic system, which is then imaged to evaluate lymphatic function. This method has demonstrated high sensitivity and specificity in detecting lymphatic abnormalities, making it a valuable tool for confirming lymphedema diagnosis.[14,24] Studies have shown significant correlations between lymphoscintigraphy findings and clinical severity of lymphedema. For instance, Pappalardo et al[25] demonstrated a statistical correlation between image staging and clinical severity of lymphedema, whereas Maclellan et al[26] described no association between lymphoscintigraphy and the volume of the lymphedematous extremity. The present study found a mild correlation between lymphoscintigraphy staging and preoperative Lymphedema Life Impact Scale (LEL) index, suggesting that lymphoscintigraphy staging can help predict the clinical severity of lymphedema.[27] A systematic review by Nagy et al[24] confirmed lymphoscintigraphy as a highly sensitive and specific diagnostic tool for lymphedema, highlighting its continued relevance in clinical practice.

ICG lymphography provides detailed imaging of superficial lymphatic channels and has proven effective in early diagnosis and severity assessment.[14] The present study demonstrated a strong positive correlation between ICG lymphography and the NECST classification, which is consistent with findings from Garza et al,[10] who reported a mild correlation between ICG lymphography and the volume of the lymphedematous extremity.[27] ICG lymphography provides high-resolution images of superficial lymphatic channels, making it particularly useful for detecting early-stage lymphedema and guiding surgical interventions such as LVA.[27]

Lymphoscintigraphy and ICG lymphography are both invaluable tools for diagnosing and managing lymphedema. Lymphoscintigraphy provides comprehensive imaging of deeper lymphatic channels and correlates well with clinical severity. In contrast, ICG lymphography offers detailed visualization of superficial lymphatic structures and is particularly effective in early-stage diagnosis and surgical planning.[14,24] The integration of these imaging modalities with clinical evaluations enhances the accuracy of lymphedema diagnosis and the effectiveness of subsequent interventions, underscoring the importance of selecting the appropriate technique based on individual patient needs.[14,24,27]

GUIDELINES AND CHALLENGES IN DIAGNOSING LYMPHEDEMA

Diagnosing lymphedema, particularly in its early stages, presents significant challenges that can impede effective management and treatment. Early detection is complicated by the subtle onset of symptoms like slight swelling, which can be easily overlooked or misattributed to less serious conditions, allowing significant lymphatic damage before proper diagnosis. This is further exacerbated by the subjectivity in clinical assessments, such as the Stemmer sign and circumferential measurements, which vary significantly between clinicians due to the lack of standardized protocols. Such variability can lead to inconsistent diagnoses, underdiagnosis, or misdiagnosis.

Access to advanced diagnostic tools, which provide more definitive insights into lymphatic function, is not uniform. Technologies like lymphoscintigraphy, ICG lymphography, MRI, and BIA are often unavailable in all healthcare settings, especially in regions lacking specialized lymphedema care. This disparity restricts timely and accurate diagnosis and worsens health outcome disparities across different populations.

Current guidelines for treating lymphedema advocate a comprehensive, multidisciplinary approach aimed at preventing disease progression, restoring limb function, averting complications such as cellulitis, and enhancing quality of life.[28,29] Treatment strategies, tailored based on the underlying etiology and severity of lymphedema, emphasize patient education and engagement. Complete decongestant therapy (CDT), which includes manual lymphatic drainage, compression therapy, exercise, and skincare, is fundamental in managing both primary and secondary lymphedema. Early intervention with CDT is crucial to optimize outcomes, although evidence supporting its efficacy in primary lymphedema remains limited. Encouraging physical activity and weight management helps mitigate disease progression, particularly in pediatric patients. Regular monitoring for skin complications and prompt treatment of cellulitis are essential. Surgical interventions such as debulking surgeries, LVA, and vascularized lymph node transfer (VLNT) may be considered for patients with progressive disease despite conservative measures, although the timing and indications for these surgeries require careful consideration.[29]

FUTURE DIRECTIONS IN LYMPHEDEMA DIAGNOSIS

The diagnostic landscape for lymphedema is continuously evolving, with significant gaps and opportunities for improvement. One primary area requiring further exploration is the validation of emerging diagnostic technologies, such as near-infrared fluorescence imaging and advanced genetic screening. Comprehensive validation studies are necessary to establish their efficacy and reliability, assessing sensitivity, specificity, and practicality in various clinical settings. There is also a pressing need for long-term studies to evaluate the clinical usefulness of both current and new diagnostic tools, especially in how they influence treatment decisions and patient outcomes.

To enhance the accuracy, affordability, and accessibility of diagnostic measures, developing standardized diagnostic protocols is essential to reduce variability in clinical assessments and ensure consistency across healthcare providers. Technological advancements should focus on cost-effective solutions suitable for implementation in lower-resource settings, reducing healthcare disparities. Integrating digital health technologies like telemedicine and mobile health apps could expand access to specialized diagnostic services, making them more accessible to patients in underserved or rural areas. Lastly, fostering interdisciplinary collaborations between researchers, clinicians, and technology developers can spur clinically relevant innovations aligned with the needs of lymphedema patients.

SUMMARY

This review highlights the complexities of diagnosing lymphedema, emphasizing the need for standardized diagnostic protocols and greater access to advanced imaging techniques. Despite progress in methods like lymphoscintigraphy, ICG lymphography, MRI, and innovative approaches like BIA, challenges in early detection and variability in clinical assessments persist, often leading to underdiagnosis or misdiagnosis. These findings stress the importance of continued research and innovation to enhance diagnostic accuracy and accessibility. Healthcare professionals must remain cognizant of these challenges to improve patient outcomes, and ongoing innovation and research are vital for developing effective diagnostic solutions that ensure equitable healthcare for all lymphedema patients.

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