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REVIEW

Decision-Making for Lymphedema Diagnostic and Surveillance Measures: A Case-Based Approach

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Abstract

Purpose of review An expanding array of diagnostic techniques for lymphedema detection and monitoring constitutes a growing aspect of lymphedema care. This discipline includes both the development and the clinical integration of methods to optimize and tailor clinical care for individuals affected by (or at risk for) lymphedema. A case-based approach highlights the practical application of these diagnostic modalities.

Recent findings A recent critical review synthesized the evidence base for a range of techniques used to diagnose, characterize and quantify lymphedema, including current and emergent methods. Available modalities include traditional methods, such as clinical examination and circumferential tape measurement, as well as recently developed digitally-based techniques. Their availability ranges widely from ubiquitous office-based approaches to advanced imaging tools. Evaluation of assessment approaches should emphasize their capacity to enhance clinical practice by advancing the core aims of lymphedema evaluation: screening, diagnosis, individualizing management, and monitoring treatment response.

Summary The use of cases illustrates how lymphedema assessment modalities are being integrated into clinical care, including their strengths and limitations, while highlighting the necessity of a person-centered approach, for each of the aims noted above.

Keywords Lymphedema · Diagnosis · Surveillance · Screening · Cancer · Lipedema · Imaging

Introduction

Management of lymphedema encompasses highly diverse clinical presentations, and requires an approach that is both versatile and consistent. A previous critical evidence review outlined priorities to guide evaluation and clinical application of lymphedema assessment techniques. Specific diagnostic tools, from traditional modalities to newer and emerging tests, were described, and clinical integration tables were created [1]. This approach suggested a means for identifying preferred diagnostic modalities for specific clinical situations, and highlighted overarching clinical applications for which evidence is relatively strong or weak.

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Aims of lymphedema evaluation include screening, diagnosis, individualization of treatment, and monitoring treatment response. Each of these categories contain various subdomains.(Table 1) Some assessment tools have well-established applications and have been integrated, to a varying extent, in lymphedema research and clinical management. These include history and physical, tape measure (TM), water displacement, perometry, and lymphoscintigraphy. A rapidly expanding collection of novel tools span the translational continuum from development and refinement to commercialization and clinical implementation. These include bioimpedance spectroscopy (BIS), tissue dielectric constant (TDC), three-dimensional (3D) camera, patient reported outcome measures (PROMs), ultrasound, indocyanine green (ICG) lymphography, computed tomography (CT), and magnetic resonance imaging (MRI), including specialized techniques. The expanding range of assessment modalities brings promise, yet also raises challenges as to how they may be best implemented, given diverse clinical contexts, a multiplicity of choices inherent within some of the approaches, and evolving clinical evidence regarding their strengths and limitations [2–5]. Contextual differences across settings will affect decision-making, especially regarding feasibility.

A key challenge in the evaluation of both established and novel tools is lack of a gold standard comparator by which to gauge their performance [6]. Tools may measure distinct or complementary properties of lymphedematous tissues and affected areas. For example, lymphedema may be assessed with respect to limb dimension and contour, degree of skin metaplasia, rate of lymph transport, or interstitial fluid volume, among other features. More generally, understanding continues to evolve regarding the importance of the lymphatic system in the pathogenesis and sustainment of various etiologies of chronic edema [7].

Table 1 Aims of lymphedema assessment and relevant subdomains of each

Aims of Lymphedema Assessment
1. Screening
a. Measures “at risk” territory
b. Sensitive to early change
c. Longitudinal discrimination
d. Independent of normal comparator
e. Easy to perform and interpret
2. Diagnosis
a. Discriminates from other edema or limb enlargement etiologies
b. Discriminates across full severity range
c. Distinguishes affected and unaffected areas (focality)
d. Identifies contributing factors
3. Individualizing Management
a. Distinguishes degree of involvement in affected territory
b. Informs treatment type, dose and frequency
c. Directs compression requirements
d. Guides follow-up cadence, encounter type and provider
e. Stratifies risk, predicts adverse clinical events
4. Monitoring Treatment Response
a. Volume
b. Dysmorphism
c. (shape, contour)
d. Tissue composition/fluid content
e. Lymphatic anatomy
f. Lymphatic function
g. Metaplasia (skin)
h. Symptoms
i. Function
j. Quality of life

Clinical scenarios (with names changed) related to these diagnostic aims are presented to enable the reader to discern how these diagnostic tools may be applied.

Screening

Michelle

Breast cancer related lymphedema. Use of bioimpedance spectroscopy (BIS).

Case description A 43 year old woman was diagnosed with breast cancer and referred to the prospective surveillance and early intervention program by her surgeon. Michelle underwent surgery for Stage IIIA right breast cancer including a right mastectomy with 2-stage reconstruction and axillary lymph node dissection (14+lymph nodes/30). Michelle received doxorubicin, cyclophosphamide and taxane chemotherapy, 5 weeks of radiotherapy to her breast and supraclavicular fossa, then tamoxifen for 5 years.

Diagnostic strategies Clinical history indicated lymphedema risk factors including axillary lymph node dissection, radiation therapy, and taxane-based chemotherapy [8–15]. Michelle underwent prospective surveillance for five years with BIS and TM, as well as a PROM, the Lymphedema Symptom, Intensity & Distress Survey - Arm (LSIDS-A**).** [16] While undergoing her paclitaxel chemotherapy, Michelle's BIS measurement, the lymphedema index, or L-Dex score, became elevated. Self-reported symptoms and distress on the LSIDS-A increased for symptoms of heaviness, tightness and aching, corresponding to her BIS scores. These symptoms settled when she was effectively managed with a compression sleeve.(Fig. 1) During this time, her volumetric measurements by TM remained unchanged.

Rationale BIS assesses extracellular fluid status via application of a multifrequency current of 0-1000khz to the limbs, examining for deviation in extracellular fluid content from the normal range in the identified at-risk limb.Bioimpedance devices gauge resistance to electrical current flow, with an inverse relationship existing between impedance and tissue fluid volume. Low frequency current flows primarily through extracellular fluid, whereas higher frequency current passes through both extracellular and intracellular fluid. BIS has robust support for use in Stage 0 (subclinical) lymphedema [2]. BIS may signal need to intervene and thereby reduce progression to Stage 1 lymphedema [17, 18]. (See "Laura" case regarding lymphedema stages.) BIS is easy to perform and interpret. In this case BIS discriminated across repeated measures. An L-Dex score≥6.5 (≥2 standard deviations from population average), or a score increase of ≥6.5 from an individual's pre-treatment baseline indicates subclinical lymphedema [19].

The SOZO ™ is currently the most common BIS device, and the L-dex score is specific to its manufacturer [20]. Limitations of the SOZO ™ device can occur in the setting of bilateral arm lymphedema, truncal lymphedema, and lymphedema affecting a focal area. It can be used for bilateral leg edema, but is not yet interpretable for bilateral arm edema. Utility of BIS for established and chronic lymphedema is under-researched. BIS should be avoided in individuals with pacemakers or other electrical implants (albeit, a case series of individuals with pacemakers who received BIS found no instances of malfunction or harm) [21]. Measurements can be conducted in the sitting position if needed, including when the device weight limit

Fig. 1 BIS screening during breast cancer treatment. Michelle's L-Dex scores were tracked every 3 months over 5 years. In the second year post-treatment, Stage 0 lymphedema was detected, with L-Dex score of 12.5 which subsequently increased to 29.7, and responded to use of a compression garment. Subsequent but milder L-Dex score elevations again responded to compression garment use. Dates are approximately relative to time 0

is exceeded; individuals must be able to make good contact with both feet and hands on the device. Related techniques include multifrequency bioimpedance analysis (MFBIA) and single frequency bioimpedance analysis (SFBIA) [22]. MFBIA obtains bioimpedance data at different points from 1 to 1000 kHz and also is available in a stand-on device; at this time BIS has the larger body of research and is in most common use but the extent to which one or the other is more advantageous is unknown. Bioimpedance techniques can also assess other aspects of body composition such as fat and muscle.

Possible alternatives TDC (See "Susie"), which measures percent free water in the dermis, can be used for screening, but the need to manually measure multiple side-to-side measurements (similar to earlier versions of BIS, before the stand-on technique was developed) makes TDC less efficient for screening than the SOZO™ device. Limitations of TDC use include bilateral disease, as well as atypical cases in which peripheral lymphedema affects predominantly deep tissues. Delfin's Lymphscanner's™ "scan" function allows for potential identification of focal within-limb variances, but published norms are based on side-to-side ratios [23–26]. Perometry (Pero-System), a measure of limb volume (unlike BIS or TDC which assess fluid) employing an infrared scanner, is validated, reliable, repeatable and can be quickly performed [27]. Feasibility limitations include higher initial start-up cost of the device, as well as floor space requirement. Tape measure of limb circumference is slightly less sensitive or reliable than the above technologically-based evaluations, but remains feasible in most clinical settings, alone or in combination with other methods [28].

3D imaging, a computerized approach to limb volume measurement, utilizing multiple views from a stereo camera, holds promise for overcoming some feasibility limitations of other volumetric methods. While it has demonstrated validity and reliability, it's research base is still developing [29–32]. ICG lymphography is used to visualize lymph collection and dynamics in the tissue, and has been found to detect breast cancer related lymphedema months before clinically evident, but has limited current feasibility for screening [33]. MRI measurement of subcutaneous adipose tissue in the limbs may aid detection of lymphedema, and when available could add specific information about limb tissue composition changes in a surveillance program, but also lacks feasibility for routine screening [34].

General points of emphasis for screening Precision can vary across tools. Reported standard error values include 3.6% for water displacement, 5.6% for perometry, and 6.6% for TM [6]. Pre-treatment baseline readings should be obtained, with one study utilizing perometry finding 40% risk of both underdiagnosis and overdiagnosis without a baseline value [35]. Subject-specific and contextual factors may affect volumes and fluid status, e.g., body habitus, hemodynamic or hydration variations, salt consumption, and recent exertion. Bilateral disease can pose interpretation challenges for all of these methods (except imaging modalities), though a baseline reading mitigates this problem. None of the above techniques (except ICG lymphography and MR lymphangiography) are specific for a lymphatic system etiology versus other causes of limb swelling. All individuals at risk of lymphedema following a cancer diagnosis should have access to a prospective surveillance and early intervention model of care using whichever tool is available in the clinical setting [11, 36].

Diagnosis

Laura

Primary lymphedema. Use of lymphoscintigraphy and ultrasound.

Case description Laura, a 24 year old woman with fuller ankles since her teens, presented after left leg swelling worsened acutely overnight, in association with heaviness and ache.

Diagnostic strategies Laura likely has primary lymphedema, but the sudden worsening was not explained. On a clinical basis, her lymphedema was classified as Stage I, characterized by early fluid accumulation which is characteristically pitting, per International Society of Lymphology (ISL) criteria [2]. In more advanced stages, increased fibrosis and fatty tissue deposition develop, with loss of pitting (Stage II), and further progression can lead to lymphostatic elephantiasis (Stage III) with trophic skin changes which can be deforming. Laura's diagnostic testing included ultrasound which showed increased skin thickness, and hyperechogenicity of the subcutaneous space. Lymphoscintigraphy was also performed which showed nearly complete absence of left inguinal lymph nodes, and moderate to severe dermal backflow with retention of tracer in her left calf.(Fig. 2).

Rationale This case demonstrates the utility of ultrasound, which exhibited a characteristic appearance of lymphedema with thickening of dermal and subdermal layers, and subcutaneous hyperechogenicity [37]. Lymphoscintigraphy, the traditional gold standard tool for verifying lymphedema, portrayed the scope of abnormality [38].

Possible alternatives ICG lymphography or MR lymphangiography (see "Brianna") could illuminate the condition of Laura's lymph vasculature. BIS or TDC could inform about

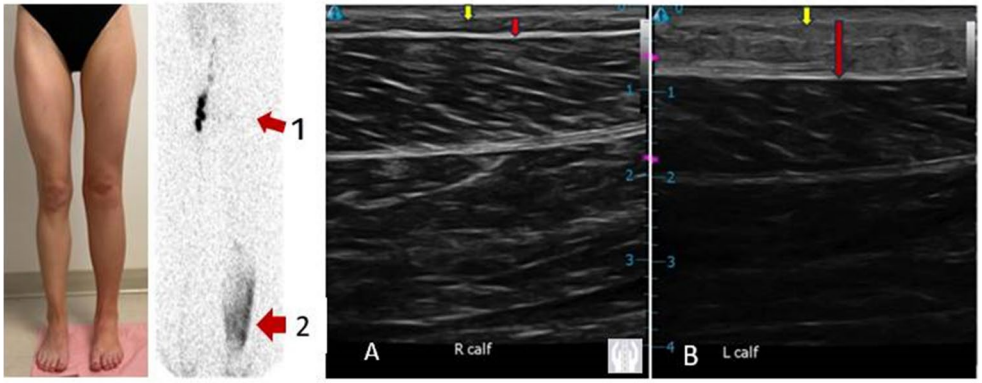

Fig. 2 Laura's lymphoscintigraphy revealed (1) absence of the lymph structures in the left inguinal space, and (2) dermal backflow in the distal lower extremity. A. Transverse ultrasound image of Laura's normal right calf findings. B Left calf ultrasound showed increased skin thickness (yellow arrow) and expansion of the hyperechogenic subcutaneous space (red arrow), consistent with lymphedema

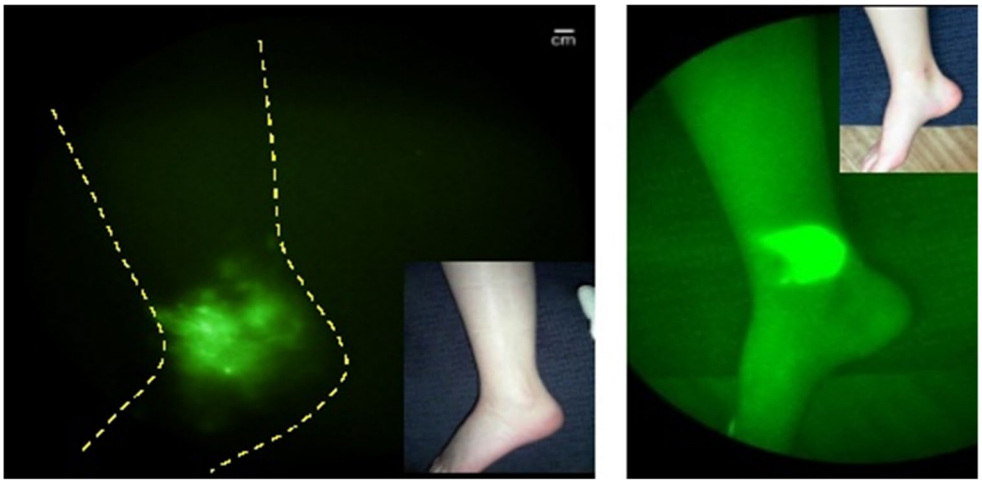

Fig. 3 Brianna's NIRF-LI study showed dermal backflow bilaterally, which is in contrast to normal findings in which linear flow can be visualized in the lymphatic vessels. Left: Right foot. Right: Left foot

fluid status, but would not distinguish a primary lymphatic system problem from other possible etiologies.

Brianna

Primary lymphedema. Use of indocyanine green (ICG) lymphography.

Case description An 18 year old female cross country runner developed relatively acute onset of left ankle swelling that progressed over time to affect both ankles. Brianna had been prescribed an antidepressant (citalopram) starting at age 15. Physical examination showed slightly fibrotic skin overlying both ankles. Her physician initially suspected a hairline bone fracture, but did Brianna not improve over 3 months of wearing a boot.

Diagnostic strategies Lymphoscintigraphy testing appeared normal. She underwent ultrasound study, which showed dermal thickening at the ankle. Physical examination and ultrasound testing supported a preliminary diagnosis of primary lymphedema, despite the normal lymphoscintigraphy. Brianna was enrolled in a research study of near-infrared fluorescence lymphatic imaging (NIRF-LI). NIRF-LI is a variant of ICG lymphography which allows real time imaging of the lymphatic flow [39]. The signal-to-noise ratio and contrast is higher with NIRF-LI than with commercially available ICG [40]. Dermal backflow was visualized in both of her ankles, confirming the lymphedema diagnosis.(Fig. 3).

Rationale This case illustrates the utility of physical examination, ultrasonography, and ICG lymphography to diagnose primary lymphedema in the setting of a negative lymphoscintigram. Lymphoscintigraphy is less sensitive in early and lower stage (milder) lymphedema, yet highly specific. When comparing limbs affected by lymphedema to unaffected comparator limbs, lymphoscintigraphy has a sensitivity of 0.62 and a specificity 1.0 [41]. Limitations of lymphoscintigraphic testing include variability of protocols (several hours duration can be needed for reliable assessment) and low image resolution [38, 42, 43].

Brianna's antidepressant use is of uncertain significance regarding lymphedema, however there have been multiple reports of antidepressants, especially escitalopram, being associated with leg swelling [44, 45]. Medications should always be reviewed in the evaluation of a patient with limb swelling. Commonly prescribed medications that may

contribute to leg swelling include pregabalin and calcium antagonists such as amlodipine. Many other medications may cause leg swelling [46, 47]. Leg swelling due to amlodipine may be less pronounced with lower doses and combination antihypertensive treatments [46, 48, 49].

Possible alternatives MRI techniques may prove to be useful in such situations, as they can also visualize tissue composition related to volume changes or tracer dynamics through lymphatics [50]. While genetic testing was not performed in this case, nor did Brianna have a family history of lymphedema, about 30% of individuals with primary lymphedema have a mutation that can be detected using currently available genetic screening [51–53].

Elizabeth

Lipedema and lymphedema. Use of lymphoscintigraphy and ultrasound.

Case description A 54-year-old woman presented with progressive bilateral leg enlargement associated with heaviness, tension, and pressure, as well as easy bruising, fatigue, and brain fog. Her leg symptoms worsened at the end of each day. Elizabeth's lower body has been disproportionately larger than her upper body since she was a teenager. Physical examination showed tenderness of the lower limbs. Her bilateral thighs were soft to touch, with a "squishy" and "lumpy" tissue consistency.

Elizabeth clinically exhibited irregular skin characteristic of Stage II lipedema [54]. Smooth skin is seen in Stage I lipedema, along with small nodules within the fat. Larger fat-forming lobules characterize Stage III lipedema [55, 56]. As lipedema progresses, lymph transport can be secondarily affected, causing the combined condition of lipolymphedema [56, 57].

Diagnostic strategies Lymphoscintigraphy showed minimal soft tissue retention of tracer in both distal lower extremities. However, ultrasound examination (Fig. 4) showed findings consistent with lipedema at Elizabeth's thigh, with thickened subcutaneous adipose layer containing angulating fascia. In contrast, lymphedema was found distally at her ankle, with dermal thickening and hyperechoic tissues.

Rationale Ultrasound study captured the mixed findings of lipedema and lymphedema in this case, despite the inconclusive lymphoscintigraphy.

Possible alternatives BIS could have assessed extracellular fluid status, but would not have captured the patient's lipedema [58]. In one application of BIS to lipedema, the ratio of leg compared to arm extracellular fluid was shown to increase with lipedema stage consistent with tissue edema in later stages of disease (lipolymphedema) [59]. ICG lymphography studies could have evaluated Elizabeth's lymphedema, but not the lipedema. MRI can evaluate for lymphedema as well as for lipedema, the latter by measuring subcutaneous adipose tissue volume or thickness, which is most differential, relative to muscle mass, in the thighs [60]. The presence of subcutaneous edema consistent with lymphedema has been demonstrated in patients with lipedema by non-tracer heavily T2-weighted MR lymphangiography [61, 62]. Emerging noninvasive sodium imaging

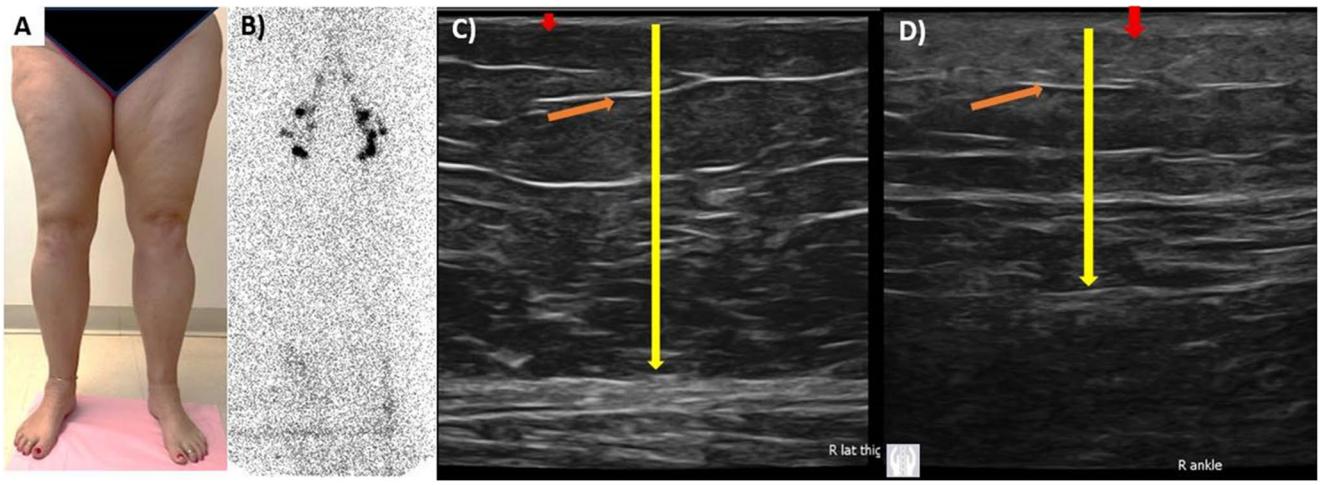

Fig. 4 (**A**) Elizabeth's clinical presentation of Lipedema Stage II. (**B**) Lymphoscintigraphy of lower extremities revealed intact migration of tracer in both legs with good inguinal nodal uptake bilaterally, and minimal soft tissue retention of tracer in both distal lower extremities. (**C**) Ultrasound image of the right lateral thigh exhibited thin skin (red arrow), thick subcutaneous space (yellow arrow), and angulating subcutaneous fascia (orange arrow), compatible with lipedema. (**D**) The right ankle ultrasound image showed increased skin thickness (red arrow), and hyperechoic superficial subcutaneous space (yellow arrow), compatible with lymphedema

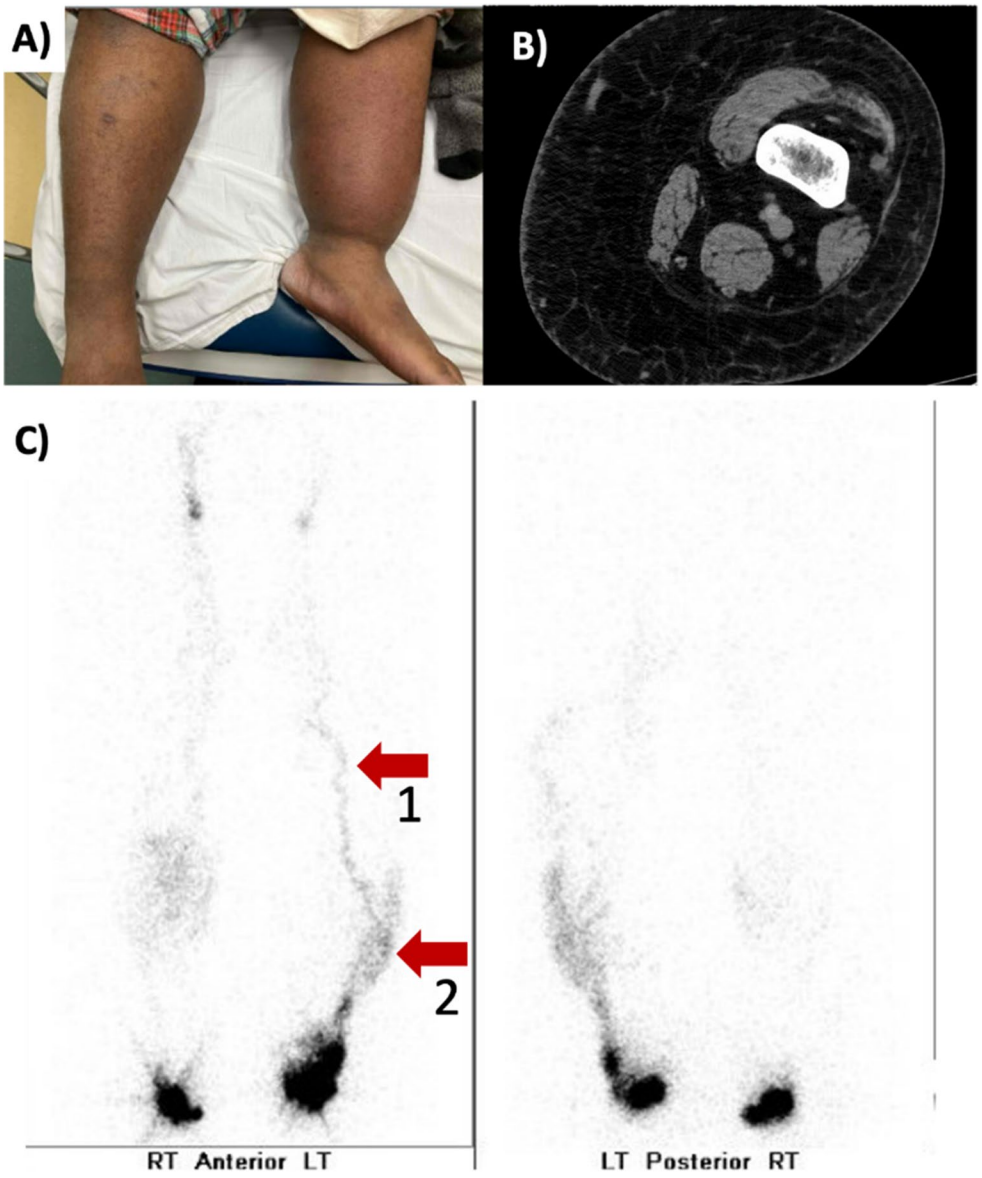

Fig. 5 Damon. (**A**) Photo demonstrating left leg enlargement especially at the calf. (**B**) CT scan showing honeycomb subcutaneous tissues consistent with lymphedema. (**C**) Lymphoscintigraphy with evidence of collateralization in the left lower limb lymphatics, and left worse than right dermal backflow

by 23Na MRI demonstrates higher tissue sodium in the calves of patients with lipedema [63, 64].

Damon

Traumatic lymphedema, morbid obesity. Use of lymphoscintigraphy, CT.

Case description A 27 year old man presented with a history of multiple episodes of left leg cellulitis, and morbid obesity (body mass index 58). Damon had sustained a stab wound to the left groin 5 years earlier, requiring hospitalization for left leg cellulitis. CT imaging at the time showed diffuse edema and skin thickening of his leg, as well as enlarged inguinal and iliac lymph nodes, consistent with the cellulitis. His leg swelling became chronic, initially pitting, then nonpitting. Venous duplex ultrasound studies were consistently negative. Physical examination showed evidence of Stage II lymphedema, marked left calf enlargement (11 cm side-to-side difference by TM), and a healed laceration distal to the left inguinal crease.

Diagnostic strategies Lymphoscintigraphy showed asymmetric lymphatic flow in the lower extremities, with moderately delayed flow in the left leg compared to the right and presence of collateral lymphatic circulation. (Fig. 5) Bilateral subcutaneous pooling of radiotracer consistent with dermal lymphatic backflow was noted in the calf. CT imaging of Damon's left leg showed a honeycomb pattern in his subcutaneous tissue, consistent with lymphedema [65–67].

Rationale Lymphoscintigraphy was pursued given the history of stab wound, which raised concern for lymphatic injury.

Lymphoscintigraphy results suggested a mixed lymphedema etiology implicating both groin trauma and morbid obesity. Collaterals may be more common in secondary lymphedema, as in this case, than in primary lymphedema.

Possible alternatives Venous insufficiency studies could have been considered to assess for possible venous component, but would not likely have affected near-term management. Soft tissue imaging (CT or MRI) around the groin might allow more precise examination of the laceration, such as extent of scar tissue, fat, and fluid composition. Interventional radiologic techniques such as MR lymphangiography or X-ray based fluoroscopy can help visualize how collaterals are forming with higher resolution than lymphoscintigraphy [68–70]. Information about presence and location of functioning collaterals may prove to be useful in decision-making for lymphovenous anastomotic surgeries [70].

Susie

Breast cancer-related lymphedema. Use of tissue dielectric constant (TDC) device to measure percent water content (PWC) of tissues.

Case Description A 55 year old woman was referred by her rheumatologist due to complaint of bilateral hand pain and swelling. Susie's history included Stage 1 A triple negative left breast cancer at age 40, treated with lumpectomy, adjuvant radiation, and chemotherapy with docetaxel and cyclophosphamide. She also had chronic heart failure, presence of a pacemaker, diabetes, carpal tunnel syndrome, osteoarthritis, and trigger fingers. Physical examination showed slight hand edema, worse on the left than right, most evident at the left index finger.

Diagnostic Strategies While the clinical impression was primarily of neuropathic and arthritic impairments, mild left lymphedema was possible. Susie's TM circumferences were symmetric within measurement standards, though with slight fullness at the left index finger (6.5 cm left, 6 cm right), wrist (18 cm left, 17 cm right), and proximal forearm (28 cm left, 27 cm right). TDC measurements suggested lymphedema at her left medial elbow, with percent water content (PWC) ratio 1.23 compared to the right elbow. (Reported threshold ratios for abnormality include 1.2 for upper limb, 1.28 for breast, and 1.35 for a leg to arm ratio in the setting of bilateral lower extremity lymphedema.) [24–26] While other sites did not reach diagnostic significance, the PWC raw scores of her left arm all improved after a course of decongestive therapy, and her PWC ratio at the left medial elbow improved to 0.94. Separately, she also had electrodiagnostic study consistent with polyneuropathy and bilateral carpal tunnel syndrome.

Rationale Susie's symptoms related to multiple diagnoses. This is common as cancer is most prevalent in older populations with comorbidities, and cancer treatment may cause morbid late effects [71–75]. In this case, the TDC measurements supported the presence of lymphedema, and lymphatic decongestive therapy resulted in measurable response. TDC can be especially useful when lymphedema is focal, including either limb or axial sites. While it is possible that inflammation from her osteoarthritis or neurovascular changes from her polyneuropathy were impacting her fluid status, this was considered less likely given the left-sided predominance.

Possible Alternatives BIS was contraindicated due to Susie's pacemaker. Perometry may have been sensitive to volume asymmetry, since TM values were suggestive but not definitive. Expensive testing such as lymphoscintigraphy or other advanced imaging was not necessary given that Susie's swelling was mild and responsive to treatment.

Individualizing Management

Caroline

Axial (breast) lymphedema. Use of multiple modalities.

Case Description A 68 year old left handed woman and retired nurse presented with left breast discomfort and enlargement two years after being treated for left Stage 1 A breast cancer with partial mastectomy, sentinel lymph node biopsy, and adjuvant radiation therapy. Caroline had had a stroke one year after cancer diagnosis with persistent right spastic hemiparesis and moderate expressive aphasia. Physical examination showed modest enlargement of her left breast, but no appreciable skin or soft tissue changes. No swelling was evident at her upper limbs by gross observation or upon TM.

Diagnostic Strategies Imaging including CT scan of the chest, ultrasound of the breast and axilla, and MRI of the breast were negative for tumor recurrence. BIS unexpectedly showed abnormality in her hemiparetic side, with left arm L-Dex score of −12.2. TDC readings were normal over the four quadrants of the the left breast with ratios (compared to the contralateral side) ranging from 0.84 to 1.07. (See "Susie" for normal values.) Caroline underwent ICG lymphography of bilateral arms; findings were normal on the right, but on the left she had normal linear channels

reaching the elbow but not crossing into the upper arm, with overall impression of mild lymphedema.

Rationale Breast lymphedema was clinically suspected, but the diagnosis could not be confirmed. Challenges included the axial location, the possibility of deeper tissue predominance, and her stroke-related sequelae. BIS detected more fluid on the unaffected side, possibly due to dependent edema in her hemiplegic arm. Few BIS studies have focused on focal lymphedema, and its measurement properties are ill-defined in these settings [76]. TDC has advantages in the setting of focal lymphedema (such as breast lymphedema), however, this was also normal in Caroline's case. TDC is not sensitive to abnormalities deeper than approximately 2.5 mm, which may have been a limiting factor here. ICG lymphography of the upper limb did support the likely presence of lymphedema. Caroline had a surgical consultation with continued conservative care recommended.

Possible Alternatives Caroline had received advanced diagnostic imaging early in her workup, including ultrasound, CT and MRI, but these studies had been performed with the aim of evaluating for tumor recurrence rather than assessing for tissue composition and edema, and no lymphedema-related observations had been made. MRI can evaluate tissue changes related to lymphedema, including examining for fat asymmetry in chest areas, and tissue edema on long- T2-weighted MRI; a body coil or torso coil are best used to acquire a bilateral exam for lymphedema assessment, rather than a breast coil which would not capture the axilla [61, 77]. In the future, 3D camera may be useful in evaluating breast volumes and truncal regions which are difficult to assess with other in-office measures. Indocyanine green dye injections around the left breast, imaged by ICG lymphography, could reveal dermal backflow indicative of breast lymphedema [78]. The function-based PROM Caroline completed reflected disability from her stroke. A symptom-based measure more specific to lymphedema or postmastectomy pain might provide more discrimination for her breast-related concern [79, 80].

Monitoring Treatment Response

Robert

Rectal cancer, obesity, renal insufficiency. Use of tape measure, patient reported outcome measure (PROM).

Case Description A 70 year old man with underlying morbid obesity and renal insufficiency presented with seven-month history of bilateral leg swelling. Three years previously he was treated for rectal cancer with surgical resection and neoadjuvant chemoradiation. Physical examination showed features of mixed stage lymphedema with pitting, rubor, and skin thickening including verrucous hyperpigmentation. Clinically Robert had an excellent response to decongestive lymphedema therapy and intentional weight loss of 25 lbs.

Diagnostic Strategies In Robert's case, differential diagnosis included a lymphatic system abnormality, comorbid venous disease (thrombosis or insufficiency), and/or systemic factors. Recurrent tumor was clinically less likely but possible. He underwent venous duplex ultrasound, and CT of the abdomen and pelvis, which were unremarkable.

TM circumferences effectively monitored Robert's response to treatment, which demonstrated reduction in upper calf circumferences by 4.2 cm left and 2.3 cm right. Robert also underwent surveillance with a PROM, the PROMIS Cancer Function Brief Three Dimensional Profile (PROMIS CF 3D). Over the course of treatment, his physical function domain raw scores improved from 22/30 to 28/30, exceeding the minimally important change threshold [81].

Rationale In this case, the traditional surveillance method of TM, coupled with longitudinal PROM administration, proved sufficient from a clinical monitoring standpoint. His bilateral disease adds to the challenge of quantifying lymphedema, given the lack of an unaffected, contralateral comparator.

Even with the availability of emerging technologies, practical considerations such as cost, space, time, and operator expertise remain relevant in the clinical evaluation of lymphedema. TM is the most widely researched method, has been used in multiple trials, and is considered to be the most commonly employed measure in clinical settings [41].

Inclusion of a PROM offers an encompassing and patient-centered assessment of this patient's edema and treatment response. Regarding choice of PROMs, options vary greatly. In this case a cancer-specific assessment tool was used to assess three distinct domains, physical function, fatigue and social participation. Lymphedema-specific tools are also available. The benefits of PROM-based assessment include low cost, ease of administration, and feasibility of longitudinal and remote administration. Downsides include respondent burden and PROM scores' inconsistent correlation with lymphedema severity. It is important to employ valid measures which are pertinent to the population being evaluated [1, 82].

Possible Alternatives As with Damon, venous insufficiency testing was not pursued as unlikely to influence clinical decision making or management. Of note, a pilot study employing NIRF-LI found evidence of lymphatic dysfunction in patients with early venous insufficiency, suggesting

these processes develop concurrently, but with further study needed into causality [83]. BIS could have been considered for evaluation and monitoring. On the research frontier, tissue sodium imaging of the extremity by 23Na sodium MRI would be interesting in this setting of lymphedema with renal disease. It would be expected that tissue sodium retention would be compounded from both morbidities, potentially exceeding expected values from renal disease alone [84].

Nora

Breast cancer related lymphedema. Use of ICG, BIS.

Case Description A 48 year old right-handed woman had diagnosis of right breast cancer fourteen years earlier, treated with neoadjuvant chemotherapy (doxorubicin, cyclophosphamide, and paclitaxel), mastectomy with axillary lymph node dissection (24 nodes negative), and chest wall radiation therapy. Nora was subsequently seen for longstanding follow-up care of right upper limb postmastectomy lymphedema, as well as myofascial pain of her neck and right upper shoulder. Initially her clinical findings of lymphedema were mild (2 cm or less side-to-side differences by TM), but with gradual worsening over the years despite semi-consistent use of compression garments. By 5 years after cancer treatment, Nora's lymphedema severity had worsened to the moderate-severe range with 4–5 cm differences at her upper arm and forearm. Nora eventually underwent plastic surgical evaluation and received the MITESE procedure (minimally invasive tissue excision with possible redundant skin excision) 12 years after her breast cancer treatment, with clinically excellent correction of her arm asymmetry [85]. However, Nora continued to experience subjective dissatisfaction with the control of swelling around her elbow, and difficulty finding a compression sleeve that is both tolerable and effective.

Diagnostic Strategies Nora originally received standard clinical surveillance including TM. Preoperative ICG lymphography showed a stardust pattern, consistent with a diffuse abnormality of lymph transit, whereas a linear pattern is normal. When she returned for surgical follow-up one year post-surgery, pitting edema was noted; ICG lymphography was repeated and continued to exhibit the stardust pattern. BIS showed L-Dex score of 29.3 which had yet worsened from her pre-MITESE abnormal value of 21.1. (See "Michelle" case, Screening section for discussion of normal values.)

Rationale Nora's TM values were nicely corrected by tissue excision but she continued to experience symptomatic arm heaviness, especially around her elbow, so further investigation was warranted. ICG lymphography showed that significant remodeling of Nora's lymphatic circulation had not yet occurred despite the one year time interval, though the extent to which improvement might be expected is uncertain as she had received an excisional surgery, not a physiologic procedure such as lymphovenous anastomosis (LVA) or vascularized lymph node transplant (VLNT) [86]. (Though, improvement in lymphatic function per lymphoscintigraphy has been reported with excisional surgery such as lipectomy.) [87] Additionally, Nora's BIS studies (L-Dex scores) had uptrended. At present, physiologic surgery is being considered for Nora.

The combined value of diagnostic information lay in demonstrating the continued need for optimizing treatment in spite of stable limb circumference measurements. This case emphasizes that while lymphedema management has historically focused on volume reduction, a better understanding of how underlying lymphatic anatomy and function affect symptom control is important.

Possible Alternatives Perometry might have demonstrated volume changes in Nora's affected limb before TM, including evaluation for segmental change around the elbow. TDC could have provided fluid assessment at the elbow and other sites. Advanced imaging including CT or MRI can provide additional anatomical detail of lymphedema.

Conclusion

Emerging technologies are enabling increasingly systematic and comprehensive evaluation of lymphedema. This case series has aimed to illustrate how lymphedema diagnostic strategies can be incorporated into clinical care. We have also mentioned alternative options, since few institutions will have all available technologies at their disposal. Assessment tools measure a variety of components of lymphedema and they need to be interpreted carefully. Furthermore, measurement comprises but one aspect of overall lymphedema care and surveillance processes.

Emerging themes include the evolution from an impairment-recognition model to a screening model for at-risk individuals, including importance of obtaining a baseline measurement, and that a layering of multiple modalities can be appropriate in certain instances to enhance diagnostic confidence [88]. For screening and monitoring, methods need to be used consistently, not interchangeably, in any given patient over time. Further research is needed regarding risk stratification (especially for screening) and cost effectiveness. Advanced imaging, biomarker, genetic, and artificial intelligence approaches hold promise for the future [89, 90]. Person-centered care, including evaluation of all health factors that may be contributing to a person's lymphedema risk, and individualized goals remain crucial to the assessment process.

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  Lymphedema staging is described, as well as consensus information on diagnosis and treatment of lymphedema.

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  This systematic review if BRCL risk factors pointed to a combination of treatment related risk factors as well as impact of health comorbidities and socioeconomic factors in lymphedema risk.

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  Post hoc analysis of a randomized controlled trial population found lymphedema risk factors of axillary lymph node dissection, taxanes, regional lymph node irradiation, body mass index > 30, and rurality, but not mastectomy, age, hypertension, diabetes, seroma, smoking, or air travel.

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  Population study from Korea found a hazard ratio for BCRL of 1.95 for patients receiving chemotherapy, with the effect most pronounced with taxanes (hazard ratio 3.38).

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  Survey of lymphedema experts was conducted, generating data on favored tools for office-based surveillance in lymphedema patients, including PROMs and physical examination approaches.

- Vargo M, Aldrich M, Donahue P, Iker E, Koelmeyer L, Crescenzi R, Cheville A. Current diagnostic and quantitative techniques in the field of lymphedema management: a critical review. Med Oncol 2024:41(10):241. https://doi.org/10.1007/s12032-024-02472-9.

  This critical review outlines diagnostic approaches to lymphedema, and current status of evidence for their applicability to a range of clinical contexts, for purposes including diagnosis, screening, monitoring treatment response, and individualizing management.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Competing Interests The authors declare no competing interests.

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