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Clinical Staging and Differential Diagnosis of Lymphedema

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Lymphedema is a chronic, progressive disease caused by impaired lymphatic transport, resulting in protein-rich interstitial fluid accumulation, fibrosis, and adipose hypertrophy. Because lymphedema shares overlapping clinical features with venous, cardiac, renal, hepatic, and inflammatory edema, accurate differential diagnosis and staging are essential for guiding management. This review summarizes the pathophysiologic basis, differential diagnosis, and contemporary multimodal staging of extremity lymphedema, with particular emphasis on the Taiwan Lymphoscintigraphy Staging (TLS) system as a reliable, validated framework that addresses the limitations of older lymphoscintigraphic grading schemes. Lymphedema represents "low-output" lymphatic failure and must be distinguished from "high-output" failure (heart failure, hypoproteinemia, venous hypertension) and mixed forms (chronic cellulitis, post-radiation injury). A practical diagnostic algorithm combining careful history, focused physical examination (including the Stemmer sign), screening laboratory tests, and targeted imaging permits separation of true lymphedema from lipedema, chronic venous insufficiency, deep vein thrombosis, complex regional pain syndrome, and systemic causes. For staging, no single modality is sufficient. The International Society of Lymphology (ISL) consensus defines clinical stages 0-III; ultrasound characterizes dermal and subcutaneous structural changes; indocyanine green (ICG) lymphography depicts superficial lymphatic flow patterns; and lymphoscintigraphy-graded by validated systems such as the Taiwan Lymphoscintigraphy Staging-assesses functional transport. Hybrid SPECT/CT lymphoscintigraphy refines this assessment by adding anatomic localization, and recent quantitative SPECT/CT parameters such as maximum lymphatic activity (MLA) and total lymphatic accumulation (TLA) provide objective imaging biomarkers that correlate with treatment response. Comprehensive staging requires integration of clinical examination, structural imaging, and functional lymphatic imaging. Quantitative SPECT/CT lymphoscintigraphy, in combination with established staging frameworks, provides reliable, reproducible information that correlates with clinical severity and supports individualized treatment decisions.

Key Words: Lymphedema · Diagnosis · Differential · Lymphoscintigraphy · Indocyanine Green · Single Photon Emission Computed Tomography Computed Tomography

INTRODUCTION

Lymphedema is a chronic, progressive condition characterized by accumulation of protein-rich interstitial fluid, secondary tissue fibrosis, and adipose hypertrophy that result from impaired lymphatic transport. The fundamental pathophysiologic abnormality is a reduction in lymphatic transport capacity below the lymphatic load ("low-output failure"), which may be congenital (primary lymphedema) or acquired after surgery, radiotherapy, infection, trauma, or chronic venous disease (secondary lymphedema)[1,2]. In Western populations, secondary lymphedema after cancer treatment accounts for the majority of cases, with breast and gynecologic cancers as the most common antecedents[3,4].

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Despite the apparent simplicity of clinical recognition, lymphedema is frequently misdiagnosed in the early phase because limb swelling can result from venous, cardiac, renal, hepatic, endocrine, inflammatory, or adipose pathology[5,6]. Misdiagnosis delays appropriate compression therapy and surgical referral, allowing the irreversible secondary tissue changes that define advanced disease to develop. In addition, the absence of an internationally adopted, multidimensional staging framework hampers communication among clinicians and limits comparability across studies.

Several staging systems have been developed to address these problems. The International Society of Lymphology (ISL) consensus document classifies disease severity according to physical findings[7]. Imaging-based systems-Yamamoto's indocyanine green (ICG) dermal backflow staging [8], lymphoscintigraphic schemes such as those of Lee and Bergan and the more recently validated Taiwan Lymphoscintigraphy Staging (TLS)[9,10], and hybrid SPECT/CT classifications[11]-extend the assessment beyond the skin surface to the structural and functional integrity of the lymphatic system itself. The TLS system, in particular, has emerged as a reliable and reproducible lymphoscintigraphic grading scheme that correlates strongly with both clinical severity and treatment outcomes[9,12].

This review consolidates the pathophysiologic basis of lymphedema, presents a structured approach to differential diagnosis, and discusses the principal staging systems available to the practicing clinician. Special emphasis is placed on lymphoscintigraphic staging using the TLS system because earlier scintigraphic schemes-although still in widespread use-have been criticized for limited inter-observer agreement and weak correlation with clinical severity[9,10].

1. Pathophysiologic Basis: Low-Output, High-Output, and Mixed Failure

An understanding of edema pathophysiology is the foundation for distinguishing lymphedema from its mimics. The Starling principle dictates that net interstitial fluid accumulation occurs when capillary filtration exceeds lymphatic absorption[1]. Edema can therefore arise either from reduced lymphatic transport capacity, increased capillary filtration, or both.

Low-output (mechanical) failure denotes a primary defect in lymphatic transport. Examples include congenital lymphatic dysplasia (Milroy disease, Meige disease, Hennekam syndrome) and acquired injury such as that following axillary or pelvic lymphadenectomy, radiotherapy, recurrent cellulitis, or filarial infection. High-output (dynamic) failure arises when capillary filtration overwhelms an intrinsically intact lymphatic system; this is the mechanism of edema in congestive heart failure, hypoproteinemic states (nephrotic syndrome, hepatic cirrhosis), and chronic venous hypertension[1]. Although the lymphatic vessels are not initially damaged, prolonged high-output overload can ultimately cause secondary lymphatic injury-so-called "safety-valve insufficiency"-leading to a mixed pattern of edema. Recurrent infections, severe burns, and chronic inflammatory states are common settings for this mixed mechanism, and these patients are particularly difficult to treat because both mechanisms must be addressed[1,5].

From a clinical standpoint, true lymphedema is characterized by a high protein content (typically >1.0 g/dL), a positive Stemmer sign in advanced cases, peau d'orange skin, predilection for the dorsum of the hand or foot, and resistance to simple elevation. These features distinguish it from the low-protein edema of cardiac, renal, or hepatic origin[13].

2. Differential Diagnosis of Limb Edema

A systematic approach to differential diagnosis groups potential causes by mechanism, which streamlines the diagnostic workup[3,5,6]. Five major etiologic categories should be considered in any patient presenting with limb swelling: lymphatic, adipose/connective tissue, venous, systemic/metabolic, and inflammatory/miscellaneous (Table 1).

1) True Lymphedema (Lymphatic Insufficiency)

Primary lymphedema results from congenital abnormalities of lymphatic vessels and accounts for approximately 10% of cases. It is subdivided by age of onset

Table 1. Major causes of limb edema and distinguishing features

Category	Representative conditions	Key clinical clues	Useful tests
Lymphatic	Primary (Milroy, Meige); secondary (post-cancer, post-radiation, filariasis)	Asymmetric, includes dorsum of hand/foot, positive Stemmer sign, peau d'orange	Lymphoscintigraphy, ICG lymphography, ultrasound
Adipose	Lipedema, lipo-lymphedema	Symmetric, spares feet/hands, painful, easy bruising, Stemmer negative	Lymphoscintigraphy (normal early), MRI
Venous	CVI, DVT, May-Thurner, phlebolymphedema	Improves with elevation, hemosiderin staining, varicosities, ulcers	Duplex Doppler ultrasound, D-dimer
Systemic	CHF, nephrotic syndrome, cirrhosis, myxedema	Bilateral, pitting, systemic symptoms	CBC, U&E, LFT, TFT, albumin, BNP, urinalysis
Inflammatory/Other	Cellulitis, CRPS, tumor infiltration, drug-induced	Acute onset, erythema, pain, medication history	ESR/CRP, imaging, medication review

BNP, B-natriuretic peptide; CBC, complete blood count; CHF, congestive heart failure; CRP, C-reactive protein; CRPS, complex regional pain syndrome; CVI, chronic venous insufficiency; DVT, deep vein thrombosis; ESR, erythrocyte sedimentation rate; ICG, indocyanine green; LFT, liver function test; TFT, thyroid function test; U&E, urea and electrolytes.

into congenital (Milroy disease, present at or shortly after birth), praecox (Meige disease, typically presenting at puberty), and tarda (after age 35). Identified gene mutations include FOXC2 (lymphedema-distichiasis syndrome), VEGFR-3 (Milroy disease), and SOX18 (hypotrichosis-lymphedema-telangiectasia syndrome)[7,14]. Secondary lymphedema, accounting for approximately 90% of cases, results from acquired injury to the lymphatic system following cancer surgery, radiotherapy, infection (especially filariasis in endemic regions), severe trauma, or chronic venous disease[1,3].

2) Lipedema (Adipose Tissue Disorder)

Lipedema is a disorder of abnormal subcutaneous adipose tissue proliferation that affects almost exclusively women, with onset during periods of hormonal change such as puberty, pregnancy, or menopause. It produces symmetric, bilateral lower extremity (and occasionally upper extremity) enlargement that characteristically spares the hands and feet, creating a "cuff sign" at the ankles and wrists. Pain, tenderness on pinching, and easy bruising are typical, and the Stemmer sign is negative in pure lipedema. Lymphoscintigraphy is generally normal early in the disease, although chronic lipedema can progress to lipo-lymphedema as the lymphatic system becomes secondarily overwhelmed[13,15].

3) Venous Disease

Chronic venous insufficiency (CVI) and deep vein thrombosis (DVT) cause edema through elevated venous pressure and increased capillary filtration. Skin findings include hemosiderin staining, lipodermatosclerosis, varicose veins, and venous ulceration over the medial malleolus. The hallmark of CVI is dependency-related swelling that improves with elevation. Phlebolymphedema describes the mixed condition in which long-standing CVI causes secondary lymphatic dysfunction; lymphoscintigraphy in such cases shows progressive lymphatic transport delay despite an initially venous etiology[5,13].

4) Systemic and Metabolic Causes

Generalized edema typically reflects a systemic process: cardiac failure (reduced cardiac output and venous congestion), nephrotic syndrome and renal insufficiency (proteinuria-induced hypoalbuminemia), hepatic cirrhosis (combined hypoalbuminemia and portal hypertension), and severe hypothyroidism (mucopolysaccharide deposition producing myxedema). These conditions produce bilateral, dependent, pitting edema and are usually accompanied by other systemic manifestations (dyspnea, ascites, hypothyroid symptoms) and abnormal screen-

ing laboratories[5,6].

5) Inflammatory and Miscellaneous Causes

Acute or asymmetric swelling should prompt consideration of cellulitis or erysipelas (especially in patients with prior lymphatic injury), allergic angioedema, malignant infiltration with tumoral lymphatic obstruction, post-radiation or post-surgical fibrosis, complex regional pain syndrome (CRPS), May-Thurner syndrome, Baker's cyst, and medication-induced edema (e.g., calcium channel blockers, gabapentin, NSAIDs)[3,5,16].

3. Practical Diagnostic Algorithm

A staged diagnostic workup begins with a thorough history and focused physical examination, proceeds to screening laboratory tests, and reserves specialized imaging for cases that remain ambiguous or require precise staging.

1) History and Physical Examination

Key historical features include the laterality and pattern of swelling, age at onset, antecedent cancer treatment, recurrent cellulitis, family history, medication review, and travel to filariasis-endemic regions. Physical examination should document limb circumference at standardized levels, the presence of a positive Stemmer sign, skin condition (papillomatosis, hyperkeratosis, lipodermatosclerosis), pitting characteristics, and signs of systemic disease[5,17].

2) Screening Laboratory Tests

Recommended baseline tests for any patient with unexplained limb edema include complete blood count, urea and electrolytes, liver and thyroid function tests, plasma total protein and albumin, fasting glucose, ESR/CRP, B-natriuretic peptide, D-dimer when DVT is suspected, and urinalysis (including chyluria)[5]. Cortisol and ACTH may be added when endocrine disease is suspected.

3) Specialist Investigations

When lymphedema is confirmed clinically or remains likely after initial workup, the following modalities further characterize the disease: bioimpedance analysis (BIA) for early detection of extracellular water shifts; ultrasound and color Doppler ultrasound for assessment of dermal/subcutaneous structure and venous patency; lymphoscintigraphy for functional lymphatic transport; ICG lymphography for real-time superficial lymphatic flow imaging; CT or MRI for detection of honeycomb patterns, tumoral obstruction, and lymphatic anatomy; and electrodiagnostic studies when neuropathic mimics such as CRPS are suspected[3,17,18].

4. Staging Systems for Lymphedema

Staging serves four complementary purposes: (1) distinguishing reversible from irreversible disease; (2) selecting and timing treatment, including conservative therapy, lymphaticovenous anastomosis (LVA), and vascularized lymph node transfer (VLNT); (3) objective monitoring of progression and response; and (4) prognostication. No single modality captures all dimensions of disease, and modern practice combines clinical, structural, and functional staging[7,9,17].

1) ISL Clinical Staging (2020)

The ISL consensus document defines four physical-examination-based stages, supplemented by a severity grade based on inter-limb volume difference (Table 2) [7]. Stage 0 (latent or subclinical) describes patients with impaired lymph transport but no visible swelling; subjective heaviness or tightness may be present, and BIA or tissue dielectric constant (TDC) may detect early fluid shifts. Stage I represents reversible pitting edema that subsides with limb elevation. Stage II features more solid tissue change; pitting may diminish as subcutaneous fat and fibrosis develop. Stage III (lymphostatic elephantiasis) shows non-pitting fibrotic skin with papillomatosis, hyperkeratosis, and gross deformity. Severity

Table 2. International Society of Lymphology clinical staging (2020)

Stage	Definition	Clinical findings
0	Latent/subclinical: impaired lymphatic transport without visible edema	Heaviness, subtle tightness; abnormal BIA/TDC may be detectable
I	Reversible: pitting edema that resolves with elevation	Soft, easily compressible swelling
II	Spontaneously irreversible: tissue fibrosis develops; pitting variable	Skin thickening, decreased pitting in late stage
III	Lymphostatic elephantiasis	Non-pitting fibrosis, papillomatosis, hyperkeratosis, deformity

Severity grading (within each stage): mild (<20% excess limb volume), moderate (20-40%), severe (>40%). BIA, bioimpedance analysis; TDC, tissue dielectric constant.

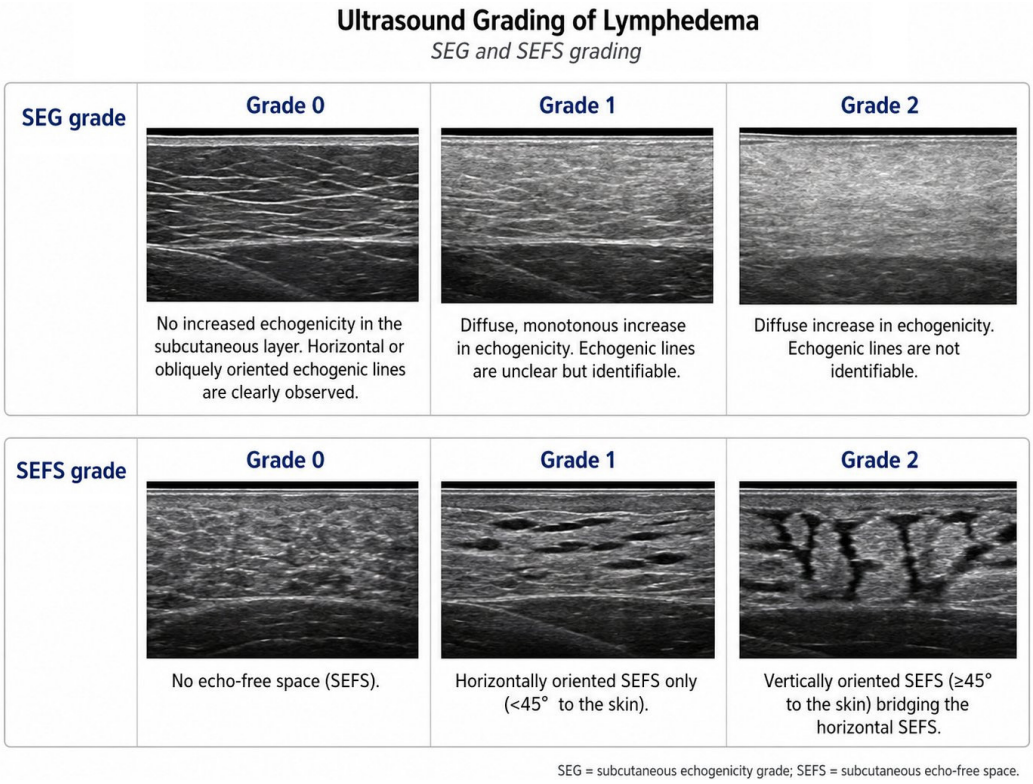


Fig. 1. Ultrasound grading of lymphedema using the subcutaneous echogenicity grade (SEG) and the subcutaneous echo-free space (SEFS) classification proposed by Suehiro and colleagues. The SEG grade reflects inflammatory and fibrotic changes in the subcutaneous layer. SEG Grade 0 shows no increased echogenicity in the subcutaneous layer, with horizontally or obliquely oriented echogenic lines from connective tissue bundles clearly observed. SEG Grade 1 shows a diffuse, monotonous increase in echogenicity, with echogenic lines that are unclear but still identifiable. SEG Grade 2 shows a diffuse increase in echogenicity, with echogenic lines no longer identifiable. The SEFS grade reflects free fluid accumulation between the superficial fasciae. SEFS Grade 0 shows no echo-free space. SEFS Grade 1 shows horizontally oriented echo-free space only (<45 degrees to the skin). SEFS Grade 2 shows vertically oriented echo-free space (45 degrees or greater to the skin) bridging the horizontally oriented echo-free spaces. The grading criteria are adapted from Suehiro et al.[20]. Images are AI-generated schematic representations and do not represent actual patient ultrasound studies. SEG, subcutaneous echogenicity grade; SEFS, subcutaneous echo-free space.

within each stage is graded as mild (<20% excess volume), moderate (20-40%), or severe (>40%)[7].

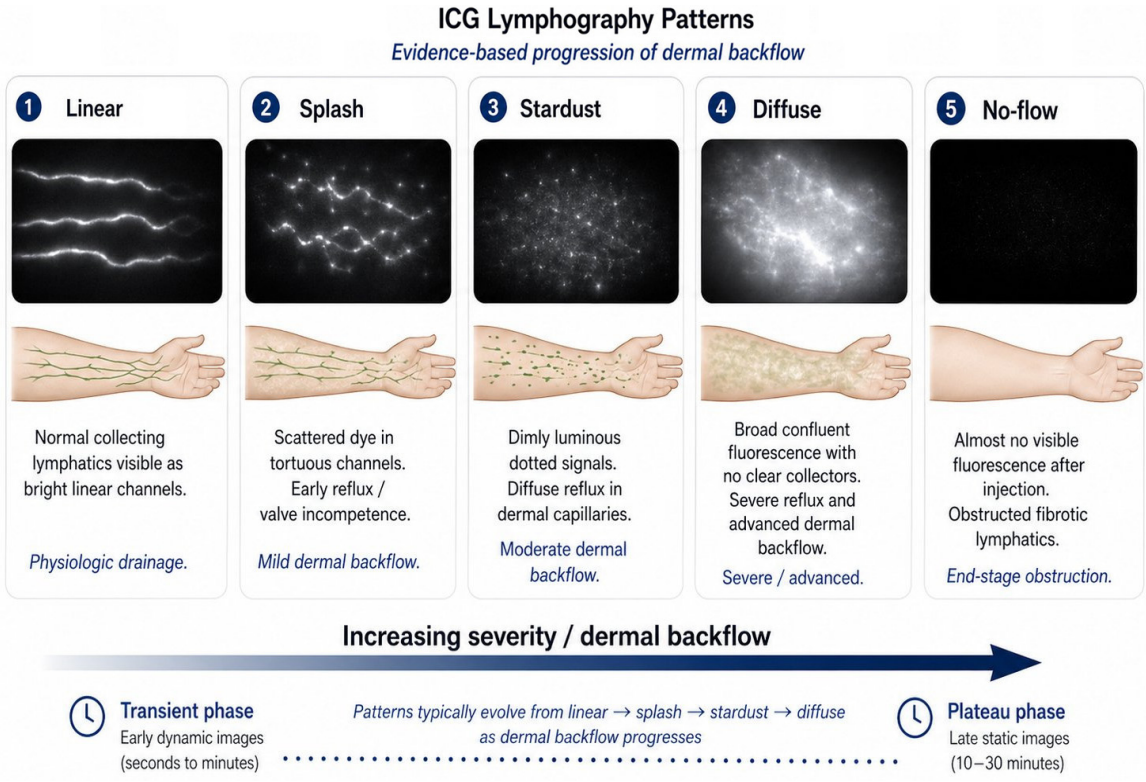


Fig. 2. Indocyanine green (ICG) lymphography patterns of dermal backflow. The five characteristic patterns reflecting progressive lymphatic dysfunction are illustrated. (1) Linear: normal collecting lymphatics visible as bright linear channels, indicating physiologic drainage. (2) Splash: scattered dye in tortuous channels, representing early valve incompetence and partial reflux. (3) Stardust: dimly luminous dotted signals, reflecting diffuse reflux in dermal capillaries. (4) Diffuse: broad confluent fluorescence without clearly identifiable collectors, indicating severe and advanced dermal backflow. (5) No-flow: absent fluorescence after injection, consistent with obstructed and fibrotic lymphatics in end-stage disease. Patterns typically progress in the order of linear, splash, stardust, diffuse, and no-flow as severity increases. The transient phase refers to early dynamic images obtained within seconds to minutes after injection, whereas the plateau phase corresponds to late static images obtained 10-30 minutes after injection. Images are AI-generated schematic representations and do not represent actual patient imaging. ICG, indocyanine green; DBF, dermal backflow.

The principal limitation of the ISL system is that it captures only the cutaneous phenotype and does not reflect the underlying lymphatic anatomy or function[7,9].

2) Ultrasound Findings

High-frequency ultrasound provides an inexpensive, non-invasive structural assessment of dermal and subcutaneous changes in lymphedema. Suehiro et al. proposed two complementary ultrasound grading systems for the subcutaneous tissue (Fig. 1)[19,20]. The subcutaneous echogenicity grade (SEG) reflects inflammatory and fibrotic changes within the subcutaneous layer and ranges from Grade 0 (no increased echogenicity, with horizontally or obliquely oriented echogenic lines from connective tissue bundles clearly observed), to Grade 1 (diffuse, monotonous increase in echogenicity with echogenic lines that are unclear but still identifiable), to Grade 2 (diffuse increase in echogenicity with echogenic lines no longer identifiable). The subcutaneous echo-free space (SEFS) grade reflects free fluid accumulation between the superficial fasciae and ranges from Grade 0 (no echo-free space), to Grade 1 (horizontally oriented echo-free space only, <45 degrees to the skin), to Grade 2 (vertically oriented echo-free space, 45 de-

Table 3. Taiwan Lymphoscintigraphy Staging (TLS) system

Pattern	Grade	Lymphoscintigraphic findings
Normal drainage	L-0	Normal visualization of linear lymphatic ducts and proximal lymph nodes; no dermal backflow
Partial obstruction	P-1	Distal linear lymphatic vessels present without dermal backflow; proximal lymph nodes still visualized
	P-2	Engorged distal linear lymphatic vessels with dermal backflow involving the proximal or distal portion of the lymphedematous limb
	P-3	Engorged lymphatic vessels with dermal backflow involving the entire affected limb
Total obstruction	T-4	Engorged or absent lymphatic vessels with distal-only dermal backflow; proximal lymph nodes not visualized
	T-5	Engorged or absent lymphatic vessels with dermal backflow involving the entire limb; proximal lymph nodes not visualized
	T-6	Absent lymphatic vessels with no dermal backflow; total obstruction with non-functional lymphatics

Adapted from Cheng et al.[9] and Pappalardo et al.[10]. The presence/absence of proximal-intermediate lymph nodes is the principal determinant separating partial (P) from total (T) obstruction.

grees or greater to the skin, bridging the horizontally oriented echo-free spaces). The SEG and SEFS grades distinguish true lymphedema from dependent edema and provide a sensitive marker of tissue changes during complex decongestive therapy[19,20].

3) Indocyanine Green (ICG) Lymphography

ICG lymphography uses near-infrared fluorescence imaging following intradermal injection of ICG dye to visualize superficial lymphatic flow in real time[8,21]. Yamamoto and colleagues described five characteristic patterns reflecting progressive lymphatic dysfunction (Fig. 2): linear (normal collectors visible), splash (scattered tortuous channels reflecting early valve incompetence), stardust (dimly luminous dotted dermal signals indicating diffuse reflux into dermal capillaries), diffuse (broad confluent fluorescence without identifiable collectors representing severe irreversible dermal backflow), and no-flow (absent fluorescence indicating obstructed, fibrotic lymphatics)[8]. The dermal backflow staging system stratifies severity from stage 0 through stage V according to the spatial extent of these patterns[8,21]. ICG lymphography is particularly sensitive for early disease and is now central to surgical planning for LVA [21,22].

4) Lymphoscintigraphy

Lymphoscintigraphy is widely regarded as the gold-standard functional imaging test for lymphedema[10, 23]. After intradermal injection of a Tc-99m-labeled radiocolloid into the interdigital webspace, sequential planar gamma-camera images demonstrate lymphatic transport kinetics, regional lymph node visualization, dermal backflow, and collateral pathways[11,23,24]. Earlier qualitative schemes such as the Lee-Bergan classification (stages I-IV based on main lymphatics, dermal backflow, and collaterals)[25] have been criticized for limited inter-observer reliability and weak correlation with clinical severity[9,10]. The more recently validated Taiwan Lymphoscintigraphy Staging (TLS) system, proposed by Cheng et al., classifies findings into three patterns and seven grades-normal drainage (L-0), partial obstruction (P-1, P-2, P-3), and total obstruction (T-4, T-5, T-6)-based on visualization of proximal/intermediate lymph nodes, linear lymphatic ducts, and the extent of dermal backflow (Table 3, Fig. 3)[9,10]. TLS shows high inter-observer agreement and significant correlations with CT volumetric difference and clinical severity, and it forms one of the four parameters of the composite Cheng Lymphedema Grading system used to guide selection among complete decongestive therapy, lymphaticovenous anastomosis (LVA), and vascularized lymph node transfer (VLNT)[9,10,12].

5) SPECT/CT Lymphoscintigraphy

Conventional planar lymphoscintigraphy is limited by poor spatial resolution and difficulty separating lymphatic from non-lymphatic uptake[11,18]. Hybrid SPECT/

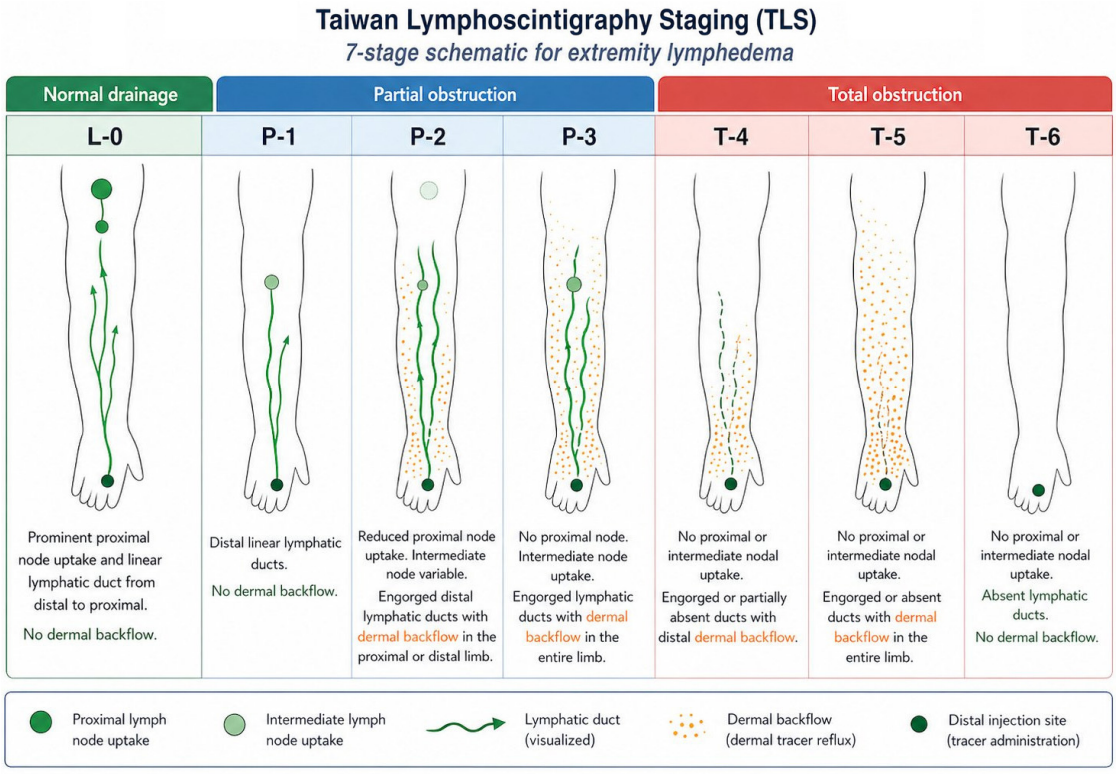


Fig. 3. Schematic representation of the seven grades of the Taiwan Lymphoscintigraphy Staging (TLS) system. The TLS system classifies lymphoscintigraphic findings into three categories and seven grades on the basis of three observations: visualization of proximal lymph nodes, visualization of intermediate (popliteal or epitrochlear) lymph nodes, and the location and extent of dermal backflow. Normal drainage (L-0) shows prominent proximal lymph node uptake and linear lymphatic ducts traveling from distal to proximal, with no dermal backflow. Partial obstruction comprises three grades: P-1, distal linear lymphatic ducts without dermal backflow; P-2, engorged distal lymphatic ducts with dermal backflow in the proximal or distal portion of the limb; and P-3, engorged lymphatic ducts with dermal backflow extending throughout the entire limb. P-3 is classified as partial obstruction because intermediate lymph node uptake remains visible despite reduced or absent proximal nodal uptake. Total obstruction is defined by absent uptake of both proximal and intermediate lymph nodes, comprising T-4 (engorged or partially absent ducts with distal dermal backflow), T-5 (engorged or absent ducts with dermal backflow in the entire limb), and T-6 (absent lymphatic ducts with no dermal backflow, representing end-stage disease). Symbols: dark green circle, proximal lymph node uptake; light green circle, intermediate lymph node uptake; green wavy line with arrow, visualized lymphatic duct; orange dots, dermal backflow (dermal tracer reflux); small dark green circle at the foot, distal injection site of the radiotracer. The schematic is AI-generated and based on the staging system originally proposed by Cheng et al. and Pappalardo et al. TLS, Taiwan Lymphoscintigraphy Staging.

CT overcomes these limitations by combining the functional sensitivity of SPECT with anatomic localization on CT, modifying the TLS stage in approximately 15% of cases compared with planar imaging alone-primarily by detecting otherwise invisible dermal backflow and by distinguishing intermediate lymph node uptake from contamination artifact[11]. Yoon et al. further proposed a hybrid SPECT/CT classification that combines dermal backflow on SPECT with the honeycomb pattern (HP) on CT, demonstrating strong correlations with both clinical severity and TLS stage[11].

Beyond visual classification, recent technical advances have enabled quantitative SPECT/CT analysis using standardized uptake value (SUV)-based parameters. Na

Table 4. Comparison of staging and imaging modalities for lymphedema

Modality	Domain assessed	Strengths	Limitations	Clinical role
ISL clinical staging	Clinical phenotype	Simple, bedside; no equipment; universally adopted	Subjective; cutaneous phenotype only; no lymphatic information	Initial assessment and longitudinal monitoring
Ultrasound (SEG, SEFS)	Dermal/subcutaneous structure	Inexpensive, non-invasive, point-of-care; sensitive to treatment response	Operator-dependent; no functional information	Tissue characterization; treatment monitoring
ICG lymphography	Superficial lymphatic flow	Sensitive for early disease; depicts dermal backflow	Superficial only (1–2 cm); requires NIR equipment	Early detection; LVA mapping
Lymphoscintigraphy (TLS grading)	Whole-limb functional transport	Functional reference test; TLS grading validated for clinical severity and treatment outcomes	Limited spatial resolution; older grading (Lee–Bergan) less reliable	Severity grading; surgical decision-making (CDT/LVA/VLNT/debulking)
SPECT/CT LSG	Functional + anatomic; quantitative SUV (MLA, TLA)	Anatomic co-registration; quantitative biomarkers for early detection	Costly; quantitative parameters need validation	Refines TLS staging; investigational role in early detection and treatment response prediction

CDT, complete decongestive therapy; CT, computed tomography; ICG, indocyanine green; ISL, International Society of Lymphology; LSG, lymphoscintigraphy; LVA, lymphaticovenous anastomosis; MLA, maximum lymphatic activity; NIR, near-infrared; SEFS, subcutaneous echo-free space; SEG, subcutaneous echogenicity grade; SPECT, single photon emission computed tomography; SUV, standardized uptake value; TLA, total lymphatic accumulation; TLS, Taiwan Lymphoscintigraphy Staging; VLNT, vascularized lymph node transfer.

et al. demonstrated in patients with unilateral upper extremity lymphedema that maximum lymphatic activity (MLA) and total lymphatic accumulation (TLA), measured from SPECT/CT, were significantly lower in the affected limb than in the unaffected limb, and that the MLA ratio and TLA ratio (affected/unaffected) showed significant positive correlations with treatment response measured as reduction of relative volume increase at one-month follow-up[27]. These observations suggest that quantitative SPECT/CT-derived metrics may serve as objective imaging biomarkers for early detection of lymphatic dysfunction and prediction of therapeutic outcomes-particularly valuable in bilateral disease, in which contralateral comparison is not feasible[27]. It should be emphasized, however, that quantitative SPECT/CT parameters are not yet established in routine clinical practice for lymphedema staging. Additional multicenter validation, standardization of acquisition and reconstruction protocols, and prospective correlation with established clinical staging systems will be required before these metrics can be incorporated into everyday clinical staging.

5. Why and How to Stage Lymphedema

Staging directs four critical clinical decisions. First, it distinguishes reversible from irreversible disease, identifying patients in whom intensive conservative therapy is most likely to succeed. Second, it selects between conservative and surgical treatment: ICG patterns of stardust or diffuse type, TLS grades P-2 to T-5, and CLG grades II-III generally support consideration of physiologic surgery (LVA or VLNT), while end-stage disease (TLS T-6, CLG IV with non-pitting fibrosis) typically requires debulking procedures such as suction-assisted lymphectomy[9,17]. Third, it provides objective metrics for monitoring disease progression and treatment response. Fourth, it informs prognosis and long-term planning, including infection prophylaxis and compression management[4,7].

No single modality is sufficient. Each test illuminates a different stratum of lymphatic biology: clinical staging characterizes the cutaneous phenotype; ICG lymphography depicts microscopic superficial lymphatic flow in real time; lymphoscintigraphy and SPECT/CT assess functional transport and anatomic structure together; and ultrasound, CT, and MRI describe structural changes in skin, subcutis, and underlying compartments. Comprehensive staging therefore integrates findings across these modalities into a multidimensional assess-

ment (Table 4)[11,17,26].

CONCLUSION

Lymphedema is a heterogeneous, chronic disease whose accurate diagnosis requires careful exclusion of venous, cardiac, renal, hepatic, endocrine, inflammatory, and adipose mimics. A structured diagnostic algorithm-history and physical examination, screening laboratory tests, and selective use of imaging-permits confident differentiation in most patients. Staging should be multimodal: the ISL system characterizes the clinical phenotype, ultrasound and CT describe structural changes, ICG lymphography depicts superficial lymphatic flow, and lymphoscintigraphy-graded by validated frameworks such as the Taiwan Lymphoscintigraphy Staging-assesses functional transport. Hybrid SPECT/CT and emerging quantitative parameters such as MLA and TLA further refine staging by combining functional and anatomic information and offer objective biomarkers for treatment response. Ongoing research integrating quantitative imaging, genetic profiling, and patient-reported outcomes promises to advance lymphedema staging from a primarily morphologic exercise toward a precision-medicine framework.

Conflicts of Interest

The author declares no conflicts of interest related to this article.

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