Combined Clinical and Laboratory (Lymphoscintigraphic) Staging

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Summary of Basic Concepts

Lymphedema is a dynamic disease involving the lymphatic system and soft tissue. Staging the disease requires attention to physical exam and clinical and radiographic findings. Accurate staging of patients with chronic lymphedema is essential to provide a reliable method of classifying patients to guide proper treatment and management.

Accurate staging of patients with chronic lymphedema is essential to provide a reliable and objective method of classifying patients to guide proper treatment and management [1, 2]. In particular, staging is critical when reconstructive or ablative surgical therapy is considered as a supplement in a patient who has failed to respond to complex decongestive therapy (CDT) [6, 7]. Appropriate timing of surgical intervention is crucial to avoid irreversible progression of disease [8, 9].

Throughout the last decade, our understanding of chronic lymphedema has undergone significant change. While previously considered a «static» condition of simple lymph fluid stasis, we now understand the condition to be a dynamic, ever-evolving interplay between the lymphatic system and the entire soft tissue [8, 10]. Chronic lymphedema is not a benign process, rather a progressive and degenerative disease which can portend significant disability. Quality of life (QoL) assessment has become an increasingly recognized important factor in the treatment of chronic lymphedema [11, 12]. As such, contemporary management of lymphedema [8, 9] includes the improvement of QoL to facilitate better social interaction and improved functional and psychological well-being.

The radiographic options for diagnosis and treatment of lymphedema have also improved substantially. Various noninvasive to minimally invasive tests have been developed over the last decade to better assess the progression of lymphedema, of which the most commonly utilized is lymphangioscintigraphy (LAS) [13–16]. This study provides detailed images of the lymphatic system following isotope injection. By estimating the uptake of the radiolabeled tracer, useful information about the mechanism and pathophysiology of lymphatic failure can be gleaned [3, 17]. For instance, diagnostic data can be obtained from radiographic delay or absence of lymphatic transport from injection site, asymmetric or absent visualization of regional lymph nodes, and/or the presence of radiotracer uptake in dermal lymphatics called dermal backflow [3]. More recently, indocyanine green lymphography has been explored as a more accurate diagnostic tool, especially in the early diagnostic periods of lymphedema [18]. This method facilitates a real-time examination without radiation exposure that can provide both morphologic and functional data. Utilizing this technique, noninvasive methods of measuring lymphatic pumping have also been explored to provide further functional diagnostic information [19].

Despite the large advancement in our understanding and diagnostic abilities in lymphatic disorders, the staging published in the International Society of Lymphology (ISL) Consensus Document from 2013 utilizes only physical exam to stage lymphedema [4]. Although this society first published in 1995 [20], staging was not described until 2001 [21, 22] with an updated yet still antiquated staging system in 2013. As

Table 15.1 ISL staging of lymphedema [4]

	Clinical characteristics
Stage 0 (or Ia)	Subclinical condition where overt swelling is not present; however, impaired lymph transport exists with subtle changes in tissue fluid/composition with changes in subjective symptoms
Stage I	Early accumulation of fluid high in protein content Pitting may occur
Stage II	Limb elevation alone rarely reduces tissue welling Pitting is present
Stage III	Lymphostatic elephantiasis Pitting absent Trophic skin changes such as acanthosis, wary overgrowth, and deposition of fat and fibrosis

acknowledged by the consensus statement, these stages detail a crude approach to classification with several shortcomings [4]. These staging criteria fail to consider the pathophysiologic mechanisms of lymphedema and underlying genetic contributions as well as QoL factors.

The current system utilizes three stages (Table 15.1). Many clinicians also recognize a stage 0 (or Ia) which refers to a subclinical condition where swelling is not yet evident despite impaired lymph transport (Table 15.1). 2 A functional severity assessment has also been designed to define minimal (<20% increase in limb volume), moderate (20–40% increase), or severe (>40% increase) disease within each stage [4].

In line with the ISL staging, other systems have been developed based on physical descriptors such as the Földi staging system, pitting edema scale, and staging by limb size [2]. Staging by clinical symptoms is also a common methodology particularly in those with lymphedema secondary to parasitic disease. The LVF scale (location, volume fibrosis) method has also been used to collect numerical data for lymphedema grading; however, this method does not comment on the clinical condition of the patient [2].

More recently, volumetry-based staging based on CT, MRI images, and water displacement methods has been used for evaluation. Circumference measurements of the extremity are simple; however, comparison between individuals is difficult as well as the lack of «normal» extremity for comparison in patients with bilateral lymphedema. A more detailed lower extremity lymphedema index (LEL) utilizing cross-sectional area and BMI to stage lymphedema has also been described and validated [23, 24].

Overall, the current staging methods fail to inclusively describe and consider the clinical, radiographic, and pathogenic components of lymphedema [25, 26]. An updated staging system is needed. Recognizing that LAS is not ubiquitously available, we propose two staging systems, one clinical and the other using laboratory (lymphoscintigraphy) data. Together, these two staging systems seek to classify the clinical manifestation and/or progress of the lymphedema more precisely based on two independent criteria (Table 15.2).

Table 15.2 Guideline criteria for the new clinical and laboratory staging system (I–IV)

Laboratory (lymphoscintigraphic) staging		Clinical staging	
Grade I (stage)	Lymph node uptake (LN): decreased (±)	Edema (swelling): mild and/or easily reversible (+)	Stage I
	Dermal backflow (DBF): none (–)	Skin change: none without dermatofibrosclerosis (DFS) (–)	
	Collateral lymphatics (CL): good visualization (+)	Sepsis (systemic and/or local): none (–)	
	Main lymphatics (ML): decreased visualization (±)	Daily activity limitation (DAL): no limitation (–)	
	Clearance of radioisotope from injection site (CR): decreased lymphatic transport (±)	Quality of life (QOL): good with minimal and/or occasional limitation (e.g., exercise, hobby) physically, psychologically, and/or socioeconomically	
Grade II (stage)	LN: decreased to none (–)	Edema: moderate and/or reversible with effort (+)	Stage II
	DBF: visualization (+) [a]IIA – extent of DBF does not exceed half of each limb [a]IIB – exceeds half of each limb	Skin change: none to minimum without DFS (±)	
	CL: decreased visualization (±)	Sepsis: none to occasional (±)	
	ML: poor to no visualization (±)	DAL: occasional and/or moderate limitation (±)	
	CR: more decreased (±)	QOL: fair with moderate limitation physically, psychologically, and/or socioeconomically	
Grade III (stage)	LN: no uptake (–)	Edema: moderate to severe and/or minimally reversible to irreversible (±) to (–)	Stage III
	DBF: visualization (+)	Skin change: moderate with significant DFS (+)	
	CL: poor visualization (–)	Sepsis: common (+) – less than four times a year	
	ML: no visualization (–)	DAL – frequent and significant (+)	
	CR: no clearance (–)	QOL – poor with significant limitation	

Table 15.2 (continued)

Laboratory (lymphoscintigraphic) staging		Clinical staging	
Grade IV (stage)	LN: none (–)	Edema: severe and/or irreversible (–)	Stage IV
	DBF: poor to no visualization (–)	Skin change: severe with advanced DFS (++)	
	CL: no visualization (–)	Sepsis: very frequent (++) – four times or more a year	
	ML: no visualization (–)	DAL: constant and severe (++)	
	CR: no clearance (–)	QOL: bad with severe limitation	

[a]Minimum two or more lymphoscintigraphic findings for laboratory staging and three or more clinical findings for clinical staging

Of note, we initially attempted to incorporate lymphoscintigraphic data of chronic lymphedema patients into the conventional clinical-ISL-staging system. Integrating the clinical findings with those of laboratory findings (e.g., radionuclide lymphoscintigraphy) was too complicated, and in cases in which a significant mismatch between clinical and laboratory findings was observed, more confusion was added to the staging system. We therefore proposed two separate staging systems.

The new clinical staging classifies the clinical manifestation and progression of lymphedema using a four-stage system (clinical stages I through IV). Systemic and local clinical conditions associated with lymphedema are included along with QoL measures. The limitations of the ISL system (three stages) based on clinical data, mostly local factors (edema and skin change), are by and large fully compensated for by the inclusion of various systemic factors including sepsis, daily activity limitation, and QoL parameters – physical, functional, socioeconomic, and psychological [5, 27].

Clinical stage is determined based on a total score of the clinical factors involved: edema (swelling), skin change, sepsis, daily activity limitation, and QoL (Table 15.2). The subjective and objective findings of the local condition of the skin and subcutaneous soft tissue are assessed with the degree of skin change (dermatofibrosclerosis) [10, 28], swelling, and natural reversibility. The presence of local and/or systemic sepsis is assessed along with the presence of erysipelas and cellulitis. Functional limitation of daily activity as a result of the various subjective symptoms is assessed, including pain, uncomfortable sensory complaints (heaviness, tightness, numbness) and skin texture, feeling of the swollen limb, and difficulty wearing clothes because of the swelling The evaluation of daily activity limitation was originally included in the QoL assessment with sepsis; however, this arrangement made interpretation of the clinical status more complicated; therefore, both items were removed from the QoL assessment. Only a limited part of the physical condition was left for the QoL assessment which incorporates the physical factors, including strength, movement, restriction of duties at home and work, and psychological and socioeconomic factors [1, 2, 5, 27].

Table 15.3 Quality of life (QOL)

Excellent	No limitation or difficulty with extra activity (e.g., hobby) physically, psychologically, and/or socioeconomically in addition to daily activity
Good	Some limitation of extra activity, but occasionally, physically, psychologically, and/or socioeconomically, but with no limitation of daily activity
Fair	Significant limitation of extra activity, but no limitation of daily activity physically, psychologically, and/or socioeconomically, or occasionally some limitation of both daily and extra activity
Poor	Significant limitation of both daily activity and extra activity, frequently physically, psychologically, and/or socioeconomically
Bad	Profound limitation of daily activity as well as extra activity or no daily activity feasible without assistance physically, psychologically, and/or socioeconomically

The QoL was evaluated by the impact of the lymphedema on the patient's physical, psychological, and socioeconomic limitations and well-being (Table 15.3). The physical factors for the QoL include strength of the affected limb, restriction of movement compared with the unaffected limb, as well as further additional impact on duties at home and work and recreational activity. The psychological factors included feelings of depression, frustration, anger due to the lymphedema, and difficulty sleeping. The socioeconomic factors included difficulty with intimate relationships and social activities. This new clinical staging system could not separate and exclude the economic factors in the review of the QoL. We learned that patient economic issues have both social and psychological implications for overall patient well-being.

The separate laboratory staging system using four grades (stages) was developed based on lymphoscintigraphic findings of the lymphedema [29–31]. Laboratory stage was determined by the sum total of various normal and abnormal findings on lymphoscintigraphy. These findings include the lymph node (LN) uptake status, the dermal backflow (DB) status, the collateral and main lymphatic visualization status, and the clearance of the radioisotope (CR) from the injection site as a parameter of the lymphatic transport ability [1, 2].

Several revisions of the new staging systems have been made by a multidisciplinary team through the years, in order to make them more user-friendly. This diagnostic tool allows better assessment of the progression of disease thus allowing better treatment and prevention of complications.

15.1 Clinical Experience [1, 2]

Among a total of 840 chronic lymphedema patients, 220 patients (85 primary and 135 secondary (169 female and 51 male, mean age 41.3 years)) were randomly selected during the period 1995 through 2004 to be evaluated using new clinical and laboratory staging systems (Table 15.2).

Table 15.4 Demographic data of the initial clinical and laboratory stage of chronic lymphedema

			Laboratory (L) stage (grades I–IV)				
			I	II	III	IV	Unidentified[b]
Clinical (C) stage[a]	I	77	53	19	1	0	4
	II	98	6	66	24	1	1
	III	29	0	2	15	10	2
	IV	16	0	1	6	9	0
	Total	220	59	88	46	20	7 (total)

220 patients, selected for a 4-year follow-up assessment (1995–2004)
[a]Based on the new four-stage system
[b]Unavailable for the comparison study

Table 15.5 Demographic data of the clinical (C) stage of chronic lymphedema in progress (deterioration or improvement)

			Final (progress) C stage				
			Clinical stage				
			I	II	III	IV	Further deterioration
Initial C stage Clinical stage	I	77	70	6	1	0	0
	II	98	3	81	11	2	1
	III	29		2	14	12	1
	IV	16			1	6	9

The patients underwent various combinations of standard CDT and compression therapy. Periodic clinical evaluation was made with an average interval of 6 months, but no longer than a year's interval. Lymphoscintigraphic study was performed on an annual basis, except in situations where recurrent sepsis was present. In these cases, an additional study was performed whenever feasible.

A comparison of clinical (C) stage and laboratory (L) stage during the initial diagnosis of 220 patients showed a broad overlap between the two different stagings; each group of patients with the same C stage had various L stages, and patients with the same L stage also had a wide range of C stages. In general, a more advanced L stage patient was more likely to have a more advanced C stage (Table 15.4).

Clinical implementation of this new staging system (Table 15.5) demonstrated reliable staging regarding both the progression of lymphedema and improvement of the clinical status following therapy.

Among 220 patients, 49 patients were appropriately classified by this new staging, 43 had deterioration, and 6 showed improvement in their clinical stage. Deterioration of the clinical stage occurred despite adequate therapy in various C stages, but was more frequent among patients with advanced C stage, which was mainly related to decreased compliance.

The majority of patients who deteriorated at the same clinical stage were among the higher L stage accompanying group: 5 out of the 7 in C stage I who progressed had L stage II (4/5) and III (2/5) initially, while 10 out of the 14 in C stage II who progressed also had a higher L stage III (9/10) and IV (1/10) from the beginning. Another 11 out of the 13 in C stage III, who progressed, had L stage IV or higher before treatment.

Maintenance of the initial clinical stage throughout the 4-year follow-up period was achieved in the majority of patients (171/220) with good to excellent compliance. Further improvement in the C stage was observed in a limited number of patients, particularly among the excellent compliance group with a good motivation, reversing the C stage (Table 15.4). Two out of the three converted from C stage II to I and showed a concomitant improvement in the L stage from II to I.

This limited experience with a new, combined, clinical and laboratory staging system appears to be useful in guiding surgical therapy. Using the staging system allowed earlier determination of treatment failure in patients with minimal clinical improvement with CDT and allowed optimal timing of various surgical therapies during the appropriate stage of chronic lymphedema as a supplement to failed CDT.

Patients experiencing progression of lymphedema by C stage, despite maximum CDT, benefited from reconstructive surgery [8, 9, 32] when surgery was added during an earlier C stage, before a minimum of 2 years in order to become a surgical candidate when C stage patients were also classified as having advanced L stage. The excisional surgery [32–35] was also added to the lymphedema in C stage III and IV, based on the same principle.

The addition of laboratory staging in the development of this new clinical staging system has improved the overall predictability of treatment outcome with regard to clinical response to various therapies and progression of the lymphedema. A patient with an advanced L stage, compared with lymphedema patients in the same C stage, demonstrated a tendency to progress faster in this study. L stage has therefore been used to help determine which lymphedema patients would benefit from different treatment modalities, particularly surgical therapy in order to prevent further disease deterioration.

15

Four-year follow-up evaluation of the complex decongestive physiotherapy (CDP)-based therapy results among 220 patients.

Conclusion

Current staging systems are inadequate to describe the clinical and radiographic factors affecting patients with lymphedema. We propose two separate staging systems that can be utilized in combination that may be useful in establishing guidelines for the treatment of chronic lymphedema and in the decision-making process for supplemental surgical therapy. Further clinical implementation of the staging systems and new radiographic techniques is still needed to prove its clinical efficacy, especially in defining the role of surgical therapy.

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