Lymphology 41 (2008) 1-10

RELATIONSHIP BETWEEN LYMPHOSCINTIGRAPHY AND CLINICAL FINDINGS IN LOWER LIMB LYMPHEDEMA (LO): TOWARD A COMPREHENSIVE STAGING

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ABSTRACT

Although radionuclide lymphoscintigraphy (RNL) is widely used diagnostically for patients with lymphedema (LE), it has not been utilized for LE staging, which is still based upon clinical findings. The aim of this work is to establish whether the results of both conventional RNL and fusion imaging obtained from hybrid detectors may be used for a comprehensive clinicoimaging staging in LE. Radiolabeled nanocolloids (0.2 ml) were subcutaneously injected in 4,328 patients (23-78 years) with clinical lower limb LE and without venous disease. Patients were classified according to the ISL classification and had a minimal follow-up of 2 years. Images were taken 60 minutes after the injection as a whole body scanning and fusion images of functional SPET and anatomical CT. Clinical and RNL results were not in accordance, and a specific RNL staging was established. The association of clinical and functional staging yields a new method to grade LE patients, and this staging correlated with treatment efficacy. RNL is an important tool in lymphology, and its association with the clinical evaluation offers a new grading system which may be able to delineate patients with good prognosis, patients at risk for a complex decongestive physiotherapy (CDP) failure, and patients who may benefit from other therapeutic protocols.

Keywords: lymphoscintigraphy, lymphedema, imaging, grading, staging, prognosis, treatment

Since 1958 (1), radionuclide lymphoscintigraphy (RNL) has progressively superseded lymphangiography and is now established as the most advanced method to assess the limb lymphatic system particularly in lymphedemas (LE). As a safe, non-invasive and physiological method, RNL is giving either morphological or objective functional information useful to clinical lymphologists (2,3). However, these results are not currently used for LE staging which is still based upon the clinical findings (4). During the past 5 years, introduction of hybrid detectors resulting in fusion imaging of tomoscintigraphic and computed tomographic findings have elicited a better understanding of molecular lymphatic imaging in lower limb LE (5). The aim of this work is to establish whether the results of both conventional RNL and fusion imaging obtained from hybrid detectors could be used for a comprehensive clinico-imaging staging in LE of extremities.

MATERIAL AND METHOD

Patients

4,328 patients (age range 23-78 years) with a clinical lower limb LE (transient or

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fixed, distal or proximal, uni- or bilateral) without venous disease (by venous evaluation) were entered in this study. The study was approved by the institutional radiation committee and the regional ethical committee. All patients included gave their informed consent to the study. They were classified according to the 4 stage clinical classification (4).

Stage 0: no clinical sign and symptom of impaired lymphatic function.
Stage I: spontaneous, reversible, soft and doughy tissue swelling, pitting edema, extensive regression with limb elevation, no fibrous tissue, negative or borderline Stemmer sign.
Stage II: spontaneous, irreversible, hard edema which may or may not be pitting in relation to a moderate to marked fibrosis, no regression with limb elevation, positive Stemmer sign.
Stage III: lymphostatic elephantiasis, hard and non-pitting edema, skin lesions, relapsing infections, no regression with elevated positioning of the extremity, pronounced fibrosis, positive Stemmer sign.

All patients with a clinical swelling (i.e., stages I to III) were treated with a standard complex decongestive physiotherapy (CDP) (6), while patients classified stage 0 were only treated with manual lymphatic drainage without bandaging and exercise. The clinical and the functional responses were evaluated by limb volume and on RNL obtained before and one year after this treatment was applied by certified physiotherapists in a single comprehensive lymphology center. Limb volumes were calculated using limb circumference taken every 5 centimeters. A good clinical response was established when a decrease in volume of more than 30% compared to baseline was observed in stages I, II and III, or when subjective and objective improvements were noted in all symptoms of stage 0. All patients had a minimal follow up of 2 years and more.

RNL Protocol

LEs of extremities are mainly located in the superficial compartment of the limb, so we have used a subcutaneous injection dedicated to only assess the superficial lymphatic system of the limb (2,3). Radiolabeled colloids of albumin (Nanocoll, GE healthcare) were used. Their mean diameter ranged between 35 to 55 nm preventing any venous diffusion and providing a total lymphatic resorption (7). A small volume (< 0.2 ml) of calibrated nanocolloids labeled with technetium 99m was used. The standard procedure involves a bilateral and simultaneous single subcutaneous injection performed into the first web space of each foot. This easy and reproducible protocol is designed to only visualize the superficial lymphatic vessels and the corresponding lymph nodes.

Imaging Protocol

The protocol involves first a dynamic study with the continuous registration of the injection sites for 10 minutes in frame mode (30 sec per frame) to assess a lymphatic speed of the radiocolloid. Then after a ten minute walk, all patients had a whole body detection performed within 60 minutes after injection using a large and rectangular field of view dual detector gamma camera (Millenium VG, GE medical system). Anatomic results are obtained on scintigraphic images of the ankles, legs, knees, thighs and pelvis. The lymphatic system is considered to be normal when lymph node uptake is seen within 60 minutes with visualization of the superficial lymphatic channels running along the saphena magna (8). We choose 60 minutes in accordance with the paper published by Franco et al (8). This group has established that for all patients without lymphatic

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disease, inguinal lymph nodes are always visualized while inguinal nodes were not or poorly visualized in patients with lymphatic disorders. It has been decided that 60 minutes is a good time to determine if a patient does or does not have a lymphatic problem. In some cases, delayed images after 2 hours were obtained in patients with very slow lymphatic progression. RNL images are more accurate in demonstrating lymphatic blockade and dermal backflow; however, the diagnosis of lymphatic disorder or lymphatic disease was in all instances obtained on images performed at 60 minutes. In this paper, we have systematically used images obtained at 60 minutes. LE patients with clinical stage 0 and I were systematically assessed with a hybrid system combining a dual-detector, variable angle gamma camera with a low-dose radiograph tube, mounted on the same gantry (Millennium VG & Hawkeye GE Healthcare). Fusion images of functional single photon emission tomography (SPET – 3° angle step, 20 s per frame) and anatomical computerized axial tomography (CT – 3.5 mm slices) data were acquired over 360° in a 128 x 128 matrix size. Reconstruction was performed by filtered back-projection or iteratively using the ordered subsets expectation maximization (i.e., OSEM) technique. Transaxial, coronal and sagittal fusion images of the superimposed anatomical maps (CT) and functional (SPET) data were finally obtained (5). In addition, all patients had a CT at the baseline but CT was not systematically performed one year later.

Statistical Analysis

The non-paired Student's t test was used to compare the clinical staging and the RNL grading obtained for each patient. A two tailed p value <0.05 was considered statistically significant. We did statistical analysis using the SPSS package version 12.0.

RESULTS

In general, RNL usually demonstrated different situations *(Fig. 1)* combining 3 main types:

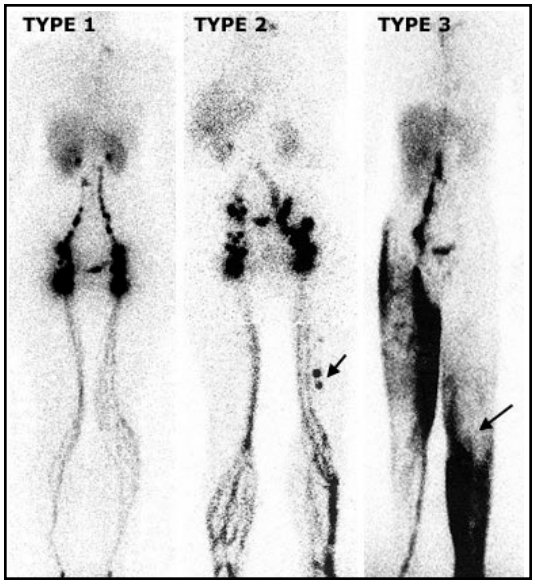

Fig. 1. Different types of RNL morphological results. Type 1: Normal; Type 2: Superficial lymphatic insufficiency balanced by the deep lymphatic system (arrow); Type 3: Dermal back flow and lymphatic blockades (arrow) with failure to detect inguinal lymph nodes.

- Type 1: Normal lymphatic system with visualization of the superficial lymphatic system and normal inguinal lymph nodes.
- Type 2: Radiolabeled colloid carried out through the superficial and/or the deep lymphatic system with visualization of popliteal nodes and normal, few, or no detection of the superficial femoro-unguinal nodes in the pelvis. This type is related to a superficial lymphatic insufficiency balanced or not by the deep lymphatic system.
- Type 3: No or partial visualization of the superficial lymphatic collecting ducts with stasis of the isotopic material in certain areas (dermal back flow) and lymphatic blockades, few or lack of detection of inguinal lymph nodes.

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A direct correlation between the RNL types and the clinical classification was studied. According to clinical evaluation, there were: 115 patients classified as stage 0; 518 classified as stage I; 2,509 classified as stage II; and 1,186 classified as stage III. The clinical stage and the RNL result were significantly different (p=0.045). 76 out of the 115 patients (66%) classified as stage 0 (clinically normal) presented lymphoscintigraphic abnormalities. Moreover, when looking at the other clinical stages, 71 (13.7%) of stage I, 401 (15.9%) of stage II, and 312 (26.3%) of stage 3 did not present expected RNL results.

These results suggested that RNL was bringing specific additional information which is not obtained from the clinical examination. In order to have a better understanding of the RNL results, we performed a precise analysis of the functional and the anatomical results of the lower limb RNL leading to a new lymphoscintigraphic classification using the same method as the clinical one and focusing on the following parameters:

- The transport efficacy evaluated from the quantitative functional results and classified as fast or slow.
- The drainage route of the radiocolloid: superficial and/or deeper transport.
- The occurrence of lymph stasis: slight, dermal back flow, blockade.
- The status of inguinal nodes: functional and visualized or not visualized.

This analysis of RNL imaging developed a 4 step classification (stage 0 to 3) with a sub classification for the stages 1 and 2.

Stage L_0: Fast lymphatic transport within the superficial lymphatic system. No lymph stasis. Normal lymph nodes in the pelvis *(Fig. 2)*.

Stage L_{1A}: Fast lymphatic transport within the superficial lymphatic system. Slight distal or intraductal

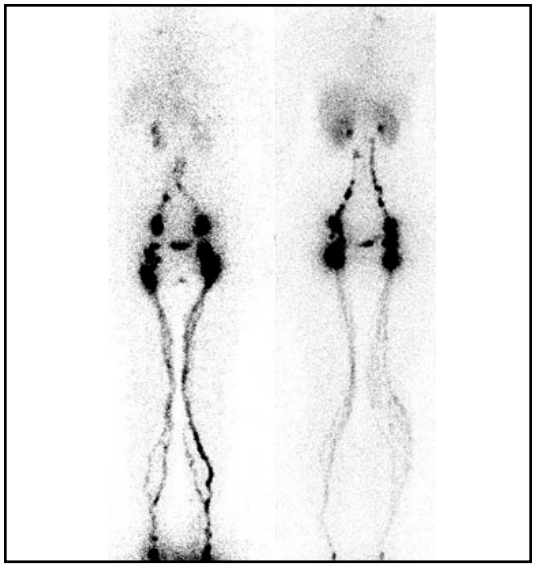

Fig. 2. RNL Staging. Stage L_0: Fast lymphatic transport within the superficial lymphatic system. No lymph stasis. Normal lymph nodes in the pelvis.

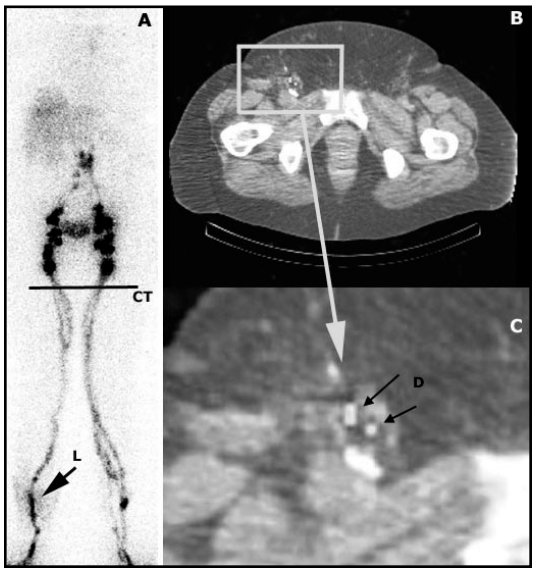

Fig. 3. RNL staging. Stage L_{1A}: A: Uni- or bilateral slow lymphatic transport within the superficial and visualization of the deep lymphatic system as a compensatory route (A,B). Distal lymph stasis and no blockade. Normal inguinal lymph nodes and visualization of functional popliteal lymph nodes (black arrows). C: Visualization of the lymphatic pathway between the superficial and the deep lymphatic systems on the SPET-CT fusion image (white arrow).

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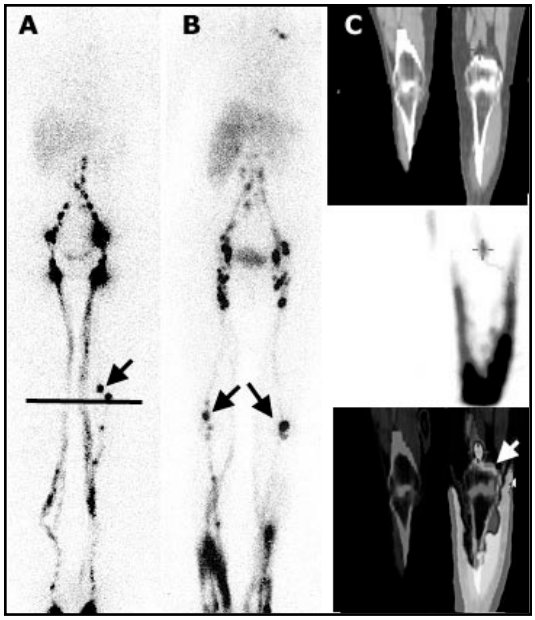

Fig. 4. RNL staging. Stage L_{1B}: Uni- or bilateral slow lymphatic transport within the superficial and visualization of the deep lymphatic system as a compensatory route (A,B). Distal lymph stasis and no blockade. Normal inguinal lymph nodes and visualization a functional popliteal lymph nodes (black arrows). C: Visualization of the lymphatic pathway between the superficial and the deep lymphatic systems on the SPET-CT fusion image (white arrow).

lymph stasis (SPET-CT). Normal inguinal lymph nodes *(Fig. 3)*.

Stage L_{1B}: Uni or bilateral slow lymphatic transport within the superficial and visualization of the deep lymphatic system as a compensatory route (SPET-CT). Distal lymph stasis and no blockade. Normal inguinal lymph nodes and visualization of functional popliteal lymph nodes *(Fig. 4)*.

Stage L_{2A}: Slow lymphatic transport within the superficial and visualization of the deep lymphatic system as a compensatory route. Distal lymph stasis and no blockade.

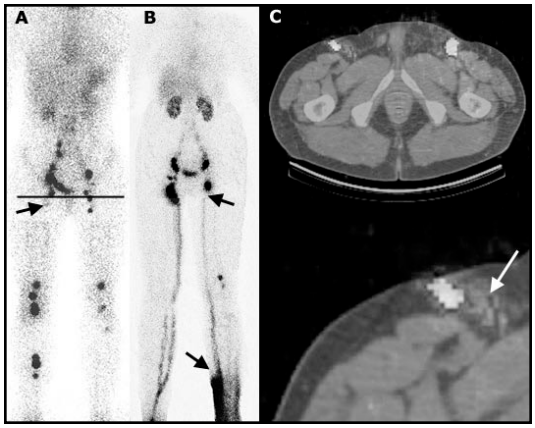

Fig. 5. RNL staging. Stage L_{2A}: Slow lymphatic transport within the superficial and visualization of the deep lymphatic system as a compensatory route (A,B). Distal lymph stasis and no blockade. Visualization of superficial non-functional inguinal lymph nodes at the SPET-CT fusion image (white arrow), but normal deep system with functional popliteal and retrocrural nodes.

Visualization of superficial not functional inguinal lymph nodes (SPET-CT) but normal deep system with functional popliteal and retrocrural nodes *(Fig. 5)*.

Stage L_{2B}: Slow lymphatic transport of the radiocolloid within the superficial and the deep lymphatic systems. Distal or proximal lymph stasis or lymphatic blockage with dermal back flow. Lack of visualization of superficial inguinal lymph nodes, but normal deep system with functional popliteal and retrocrural nodes (*Fig. 6*).

Stage L_3: No transport through the main superficial system and very slow lymphatic transport within the subcutaneous and/or the deep lymphatic system. Any kind of lymphatic blockade with dermal back flow. Lack of visualization of inguinal and pelvic lymph nodes. No visualization of popliteal nodes *(Fig. 7)*.

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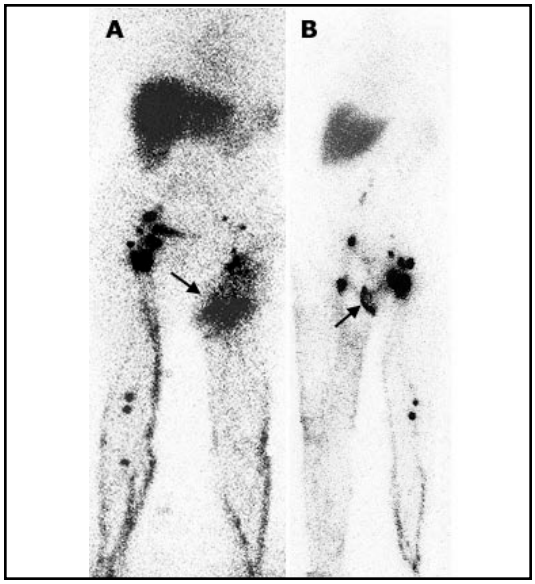

Fig. 6. RNL staging. Stage L_{2B}: Slow lymphatic transport of the radiocolloid within the superficial and the deep lymphatic systems. Distal or proximal lymph stasis or lymphatic blockage with dermal back flow (arrows). Lack of visualization of superficial inguinal lymph nodes but normal deep system with functional popliteal and retrocrural nodes.

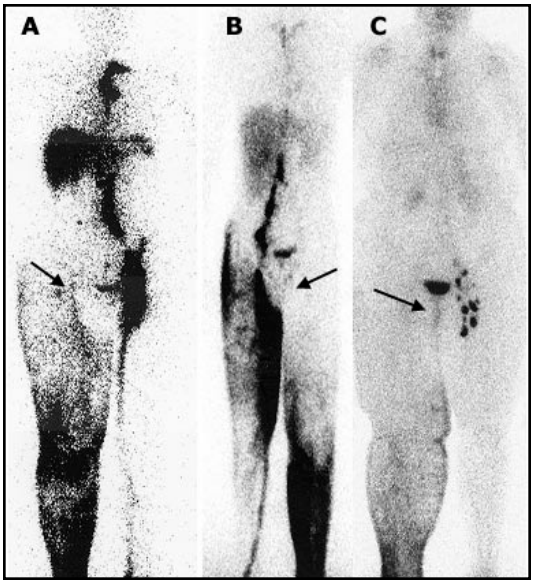

Fig. 7. RNL staging. Stage L_3: 3 cases (A,B,C) with no transport through the main superficial system and very slow lymphatic transport within the subcutaneous lymphatic system, lymphatic blockade with dermal back flow and lack of visualization of inguinal and pelvic lymph nodes (arrows). No visualization of popliteal nodes.

This method to classify RNL results is very simple and is currently used in our Nuclear Medicine Department by all the nuclear medicine physicians after a learning curve performed on 50 RNL. All RNL were staged by well-trained nuclear medicine physicians using these parameters, and the inter-observer variation was very low as the staging was not in accordance for only 32 cases (i.e., 0.7%).

The clinical and the RNL stages *(Table 1)* for study cases are significantly different (p=0.038, student test) *(Table 1)*. These results confirm that RNL and clinical examination are identifying different information of the lymphatic diseases. In each clinical stage, a significant number of patients who are considered identical from a clinical point of view have distinctly different functional imaging results. The combination of clinical and RNL results lead to a comprehensive new method for staging mimicking the TNM (tumor, node, metastasis) staging usually performed in oncology: clinical staging + imaging staging are associated in grades. We suggest a 4-step grading in LE of extremities:

Grade 0:	Stage 0 + L_0 - Stage I + L_0 (any clinical stage with a L_0 imaging result)
Grade I:	Stage 0 + L_{1A} - Stage I + L_{1A} - Stage I + L_{1B} - Stage II + L_{1B} (any clinical stage with an L_1 imaging result)
Grade II:	Stage I + L_{2A}- Stage I + L_{2B} - Stage II + L_{2A} - Stage II + L_{2B} - Stage III + L_2 - Stage III + L_{2B} (any clinical stage with an L_2 imaging result)
Grade III:	Stage III + L_3 - Stage II + L_3 (any clinical stage with an L_3 imaging result)

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TABLE 1
Correlation Between the Clinical and the RNL Classification

		Stage 0	Stage I	Stage II	Stage III
Clinical stages		115	518	2,509	1,186
RNL stages	L_0	92	6	0	0
	L_{1A}	23	279	0	0
	L_{1B}	0	218	15	0
	L_{2A}	0	11	1,451	14
	L_{2B}	0	4	1,038	178
	L_3	0	0	5	994

TABLE 2
Correlation Between the Clinical and the Grading System

	0	I	II	III	Total
RNL Grades	98	535	2,696	999	4,328
Clinical stages	115	518	2,509	1,186	4,328
Changed status	23	25	20	192	260
Upstaged	23	19	5	0	47
Downstaged	0	6	15	192	213

The correlation between the clinical staging alone and the grading associating clinical and RNL staging is reported in *Table 2*. We observed that 260 patients have a different grading when compared to the clinical classification. Forty seven patients have more lymphatic abnormalities and 213 patients have fewer lymphatic abnormalities than the clinical examination suggested.

All patients with clinical swelling (i.e., clinical stages I to III) were treated with standard CDP while patients classified clinical stage 0 were only treated with manual lymphatic drainage without bandaging and exercise. *Table 3* gives the rates of good responses in each group and compares the distribution according to the clinical staging or the clinico functional grading. It is clear that patients in low clinical stages gain advantages from the grading system as good responder patients can easily be identified.

DISCUSSION

Lymphedema of the extremities is usually classified using the clinical recommendation published by the International Society of Lymphology (4). It is generally accepted that the diagnosis of lymphatic dysfunction is largely a clinical diagnosis and that

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TABLE 3
Rate of Good CDP Responders in Each Group According to the Clinical Staging or the Clinico-Functional Grading

	# patients	Improved patients (rate in %)
Clinical		
Stage 0	115	99 (86.1)
Stage I	518	327 (63.1)
Stage II	2,509	1,262 (50.3)
Stage III	1,186	489 (41.2)
Clinico-functional		
Grade 0	98	90 (91.8)
Grade I	535	336 (62.8)
Grade II	2,696	1,342 (49.7)
Grade III	999	409 (40.9)

additional assessments are only used when the diagnosis is not completely clear. However, for the past 20 years RNL has become an increasingly valuable tool in wide use around the world. Unfortunately, RNL has not been standardized except for the concept of a standardized, informative image, and many different imaging protocols are used. We recommend a protocol with both kinetic evaluation and imaging 60 min after the injection as an easily reproducible method for a first analysis of a lymphatic disorder (2,3). With the RNL anatomic images, lymphatic dysfunction is uniformly detected (except in case of a wrong technique) when no visible nodes are visualized or if the isotopic material is abnormally concentrated in certain areas (dermal backflow, blockage). The lymphatic kinetic studies only assess the transport velocity. RNL is always useful in case of unilateral swollen limb demonstrating a lymphatic dysfunction in a clinically normal contralateral limb, at the very beginning of the lymphatic dysfunction during the few weeks or days when the edema first appears, or when the patient is in a transitory edema phase without any clinical edema appearing at the time of examination. Moreover, RNL provides objective and reproducible quantitative parameters necessary to assess lymphatic changes under therapy (decongestive physiotherapy, surgery, drugs) and may be useful in the evaluation of new treatments developed in lymphology. Lymphologists can all recall a large number of cases where their clinical findings were not really correlated with an expected therapeutic result. The clinical examination only takes into account the clinical manifestation of a lymphatic dysfunction and does not provide any information on the underlying lymphatic status of the lower limbs. RNL is mainly useful as an additional tool for the clinician and has not been associated to any classification. We have suggested such an association between the clinical and the RNL finding in a single grading analogous to the TNM staging in oncology. This goal is possible, and it will provide a more precise clinical classification. Using this grading method, the classification appears to be more predictive of the treatment efficacy, particularly for the low clinical

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stages. In these patients with rather good prognosis, RNL delineates unsuspected lymphatic disturbances which may explain the failure of conventional treatment to define patients who will benefit from CDP in contrast to those at risk for CDP failure or those who may benefit from other therapeutic protocols. Moreover, in comparisons of RNL results obtained prior to and after CDP, it is rare to observe a dramatic change in the RNL results, suggesting that other aspects of LE need to be evaluated. Using computerized X-ray tomography (CT) and standard or high resolution magnetic resonance (MR) imaging, it is possible to demonstrate the presence of tissue changes related to the lymph stasis (9-13). A competent clinical exam is not able to evaluate these underlying tissue changes. It is easy to assess the volume, the degree of pitting, and to postulate a slight or marked fibrosis. Clinically, the limb is swollen but it is difficult to dissociate fat deposition from simple edema or fibrosis. A precise evaluation of the swollen limb is essential to evaluate such fat deposition and fibrosis as treatment efficacy is dramatically altered depending of these tissue changes. In our study, CT showed tissue abnormalities in a large number of these low stage patients where treatment was not really effective. Tissue changes and particularly fat deposition are likely reasons for explaining failure of the conventional treatment. These are exactly the patients where the clinical and the clinico-functional staging is not well correlated. As an example, a patient classified stage 0 at the clinical evaluation and grade I after the RNL is a patient at risk for tissue changes related to the lymph stasis. These selected patients are those where limb MR or CT imaging should be performed in order to detect the earliest signs of these tissue changes including particularly fat deposition.

CONCLUSION

Lymphoscintigraphy is an established and evolving method and an important tool for research and clinical use in lymphology. The procedure involving only one subcutaneous injection per limb into the first web space (superficial compartment) and images obtained at 60 minutes provides reliable data on the lymphatic status of a swollen limb whatever the radiocolloid used. A recommended protocol with both kinetic evaluation and whole body imaging 60 min after the injection is an easily reproducible method for analysis of a lymphatic condition. RNL results associated with clinical evaluation provide a new classification which may be able to delineate patients with good prognosis, patients at risk for CDP failure, and patients who may benefit from other therapeutic approaches. In other words, patients with lower limb LE should have first an extensive clinical examination and then a lower limb RNL and depending on the grading of the lymphatic disorder, high resolution CT scan or MR imaging should be helpful to assess the tissue changes related to the lymph stasis.

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