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Comparison of quantitative analysis to qualitative analysis for interpretation of lower-limb lymphoscintigraphy

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Comparison of quantitative analysis to qualitative analysis for interpretation of lower-limb lymphoscintigraphy

ABSTRACT
Qualitative analysis of lymphoscintigrams is subject to wide variability and may miss subtle differences in ilioinguinal uptake between normal and abnormal limbs. This study compared quantitative analysis to qualitative analysis of lower-limb lymphoscintigraphy in diagnosing lymphedema. Fifty-two lymphoscintigrams performed using standardized protocol, 99-metastable technetium nanocolloid intradermal injection at the first interdigital space, were analyzed quantitatively. Fifty-three normal and 51 abnormal limbs were analyzed. For each limb, a region of interest (ROI) was drawn around the injection site, and ilioinguinal nodes on the 1.5 h static images and the counts in these ROIs were recorded. Percentage ilioinguinal nodes uptake was then computed. Analysis of variance (ANOVA) was performed to determine the difference in ilioinguinal uptake between normal and abnormal limbs. Specificity and sensitivity were calculated and the figures were used to plot a receiver operator characteristic (ROC) curve. Thirty-six females and 16 males (104 limbs) were analyzed. ANOVA revealed a significant difference between the mean uptake in normal (19.7%) and abnormal limbs (5.5%) (F = 81, P < 0.001). ROC had a maximal area under the curve of 0.924 (P < 0.001). The significant difference in the means of ilioinguinal uptake between normal and lymphedema limbs infers reduced lymphatic function. Ilioinguinal lymph node uptake is thus a reliable parameter in quantitative analysis of lymphoscintigrams.

Keywords: Lymphedema, lymphoscintigraphy, nuclear medicine, qualitative analysis, quantitative analysis

INTRODUCTION
Lymphedema is a painless, progressive accumulation of protein-rich fluid in the interstitial spaces of the skin, resulting from an anatomic or functional obstruction of the lymphatic system.1,2 It is most common in the lower limbs, about 80% of cases, but can also occur in the arms, trunk, and external genitalia.

The primary pathology leading to lymphedema is dysfunction of the lymphatic transportation system.3 Disruption of the lymphatic systems by pathological processes such as trauma, surgery and radiotherapy, infection, and congenital abnormalities can lead to lymphedema.4 Primary lymphedema is usually as a result of congenital abnormalities in the lymphatic system which can be either aplasia or hypoplasia.5,6 Lymphedema praecox is early-onset lymphedema, typically before 35 years. It is characterized by hypoplastic lymphatic system and is usually unilateral. Lymphedema tarda usually presents after 35 years of age, and there is much debate regarding its etiology. Milroy disease is the autosomal dominant form of typically bilateral primary lymphedema with the very early age of onset and is due to agenesis of the lymphatic system.7 Secondary lymphedema results from obstruction or interruption of the normal lymphatic channels. This can be iatrogenic (surgery and/or radiotherapy) or due to trauma or infections such as filariasis.8

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Lymphoscintigraphy is the primary imaging modality used in determining a diagnosis in patients with suspected extremity lymphedema.\textsuperscript{[5,6,9]} The current protocol in our institution utilizes 20–40 mega-Becquerels (MBq) of 99-metastable technetium (Tc-99m) nanocolloid, injected intradermally, with static image acquisition at 5-min, 15-min, and 1.5-h intervals. Field of view is at the injection site on 5-min images and from the feet to the pelvis for the 15 minutes and 1.5 hour images. The patients walk for at least 5 min before the 15-min image.

Quantitative and semiquantitative analysis parameters can be used to complement visual analysis, to better characterize discrete changes, or to monitor therapeutic assessment in sequential studies.\textsuperscript{[10]}

Quantitative analysis provides a means to unify the interpretation of scintigraphic findings, allowing for the detection of small changes in lymphatic function. Furthermore, the quantitative analysis can facilitate the comparison between studies during follow-up or after

Figure 1: 1.5-h images of normal (a and b) and abnormal (c and d) lymphoscintigrams. 1.5-h images of normal (a and b) and abnormal (c and d) lymphoscintigrams. (a and b). There is fairly uniform migration of tracer to the ilioinguinal lymph nodes. (c) There is dermal backflow in the left lower limb, due to interruption of the lymphatic channels, and although not readily apparent, slightly less tracer reaches the left ilioinguinal nodes compared to the right; hence quantitative analysis would be of value in this case. (d) There is congenital aplasia of the lymphatic channels on the right and no tracer reaches the ilioinguinal nodes.

Figure 3: Bar graph showing distribution of lymphedema by sex and side.

Figure 2: Lymphoscintigraphy image showing the regions of interest drawn around the injection site (A) and ilioinguinal nodes (B) for computation of ilioinguinal uptake.

Figure 4: Bar and whisker plot of uptake in lymphedema limbs and normal limbs.
therapeutic interventions in a patient. Analysis by less experienced radiologists and nuclear physicians can be enhanced by quantitative analysis.

The data obtained would provide a more sensitive and reproducible approach to differentiate normal patients from those with mild lymphedema, more so for the less experienced radiologist.

MATERIALS AND METHODS

This was a prospective cross-sectional study, in which consecutive patients undergoing lymphoscintigraphy at the Nuclear Medicine Department for suspected lymphedema, on the basis of unexplained lower-limb swelling, were recruited.

Patients without images at 1.5 h were excluded from the study.

The sample size was calculated using the formula for studies comparing two means; the equation used for the sample size calculation is as follows:

\[ N = \frac{4\sigma^2 (Z_{\alpha/2} + Z_{\beta/2})^2}{D^2} \]

The study had a power of 80% and with 0.05 margin of error.

The estimated sample size was 102, 51 for the group with lymphedema and 51 for the group with normal limbs.

Patients were positioned supine and the Tc-99m nanocolloid was injected intradermally to the first interdigital web of both limbs – if the dose was uneven, the larger dose was administered to the affected or more edematous limb. A static planar image of the feet with the entire injection site in the field of view was obtained 5-min postinjection, on a 256 × 256 matrix. The patients were then asked to walk up and down the hallway 4–5 times (at least 2 min) and return back for 15-min delay images. A hemi-body planar image (starting from hip to feet) was obtained at 15-min and 1.5-h postinjection, using a 256 × 1024 matrix.

Normal or abnormal limbs were selected on the basis of qualitative analysis by a consultant nuclear medicine physician with a 15-year experience. Normal limbs showed
prompt and uniform migration of the radionuclide through
discrete lymph vessels. Abnormal limbs had a combination
of any of the following findings: interruption of lymphatic
flow, collateral lymph vessels, progressive dermal backflow,
delayed flow, delayed visualization or nonvisualization of
lymph nodes, reduced number of lymph nodes, dilated
lymphatics, and in severe cases no visualization of the
lymphatic system at all [Figure 1].

For all the normal limbs, a region of interest was drawn
around the injection site (B) and inguinal nodes (A) at 1.5-h
static images [Figure 2]. Inguinal node uptake was computed
as follows:

\[
\frac{A}{A+B} \times 100
\]

A similar analysis was done for the abnormal limbs.

Approval for the study was obtained from the institutional
ethics review committee. All the study participants gave
written informed consent. Consent was obtained from
all the adult study participants and from the guardians of
participants aged below 18 years.

This study portends no harm to the participants, and the
standard imaging protocol was not altered. The study
investigators have no conflict of interest to declare.

Table 1: Demographic characteristics of the subjects

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of subject (years)</td>
<td>52</td>
<td>3</td>
<td>90</td>
<td>37.9</td>
<td>37.5</td>
<td>19.7</td>
</tr>
<tr>
<td>Age at onset of edema (years)</td>
<td>52</td>
<td>0</td>
<td>70.0</td>
<td>32.3</td>
<td>30</td>
<td>17.1</td>
</tr>
<tr>
<td>Duration of edema (years)</td>
<td>52</td>
<td>0</td>
<td>30</td>
<td>5.5</td>
<td>3</td>
<td>7.0</td>
</tr>
</tbody>
</table>

SD: Standard deviation

Table 2: Distribution of lymphedema by sex

<table>
<thead>
<tr>
<th>Sex</th>
<th>Outcome (/limb)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lymphedema</td>
<td>Normal</td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>Female</td>
<td>26</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>51</td>
<td>53</td>
</tr>
</tbody>
</table>

SD: Standard deviation; SEM: Standard error of mean

Table 3: Ilioinguinal lymph node uptake among normal and lymphedema limbs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n</th>
<th>Mean (%)</th>
<th>SD</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ilioinguinal node uptake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphedema</td>
<td>51</td>
<td>5.5</td>
<td>4.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Normal</td>
<td>53</td>
<td>19.7</td>
<td>10.2</td>
<td>1.4</td>
</tr>
</tbody>
</table>

SD: Standard deviation; SEM: Standard error of mean

All statistical analysis was performed using SPSS version 17 (SPSS Statistics for Windows, SPSS Inc: Chicago, USA).

RESULTS

Fifty-five bilateral lymphoscintigraphic examinations
were performed between August 2014 and January 2015.
Fifty-two patients (25 males and 26 females) were included
in the final study. Excluded patients included one where
1.5-h images were not acquired and two patients in whom
both injection sites and ilioinguinal nodes were not in the
field of view on the 1.5-h images. The median age was
37.5 years, with a standard deviation (SD) of 19.7; their mean
duration of lymphedema was at least 5.5 years [Table 1].

The proportion of males with positive scans (diagnosis of
lymphedema) was significantly higher (78% vs. 36% \(P < 0.001\)).
Both limbs were equally affected with lymphedema, with no
preference for either side [Figure 3 and Table 2].

Quantitative analysis

The mean for each of the groups is illustrated in [Table 3
and Figure 4].

The data were skewed to the right in both the normal group
and the group with lymphedema [Figure 5]. The Kolmogorov–
Smirnov test for normality, however, showed a lognormal
distribution which is a common finding in many biologic
samples [Figure 6].

Analysis of variance

Following analysis of variance (ANOVA), the difference
of the means between the two groups was statistically
significant (\(P \leq 0.0001\)). An \(F\) value (a measure of
intergroup vs. intragroup variance) of 81.37 indicates a
large difference.
CONCLUSION

Illoinguinal lymph node uptake can be used for the differentiation of normal limbs from limbs with lymphedema. Quantitative analysis if developed and standardized can be an accurate tool in the diagnosis of lymphedema. Quantitative indices would be useful for monitoring of disease progression and efficacy of therapeutic measures.

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Nil.
Conflicts of interest

There are no conflicts of interest.

REFERENCES