Would complex decongestive therapy reveal long term effect and lymphoscintigraphy predict the outcome of lower-limb lymphedema related to gynecologic cancer treatment?

Young Bum Kim, Ji Hye Hwang, Tae Won Kim, Hyun Ju Chang, Sang Gil Lee

Abstract

Objective. The aims of this study were to investigate the long-term effect of complex decongestive therapy (CDT) on lymphedema volume reduction, especially considering the proximal and distal parts of the leg, and to evaluate the utility of pre-therapy lymphoscintigraphy in predicting the response to CDT in patients with lower-limb lymphedema after surgery for gynecologic cancer.

Methods. Medical records of 158 patients with secondary lymphedema of unilateral leg after surgery for gynecological cancer were reviewed retrospectively. They were treated with two weeks of CDT along with self-administered home therapy and were followed up for 24 months. Whole, proximal and distal leg volume was serially measured by using an optoelectric volumeter prior to and immediately after therapy, and follow-up visits at months 3, 6, 12 and 24. Lymphoscintigraphy was performed prior to therapy.

Results. The percent volume reduction was 22.1% in the whole leg, 30.9% in the distal leg and 18.4% in the proximal leg immediately after CDT. The volume reduction was maintained for 24 months, but the distal leg was significantly well maintained better than the proximal leg. Extremity radioisotope uptake ratio (EUR) among lymphoscintigraphic findings could predict the improvement of lymphedema volume in the distal, proximal and whole leg.

Conclusions. This study suggests that the long-term edema reducing effects of CDT are better maintained in the distal leg than in the proximal part, and initial lymphoscintigraphic quantitative finding may usefully predict the short and long-term response to CDT.

Introduction

Chronic lymphedema that arises as a consequence of impaired lymphatic drainage causes symptomatic, functional and aesthetic defects as well as psychological sequelae, thereby reducing the quality of life for gynecological cancer survivors [1–3]. The reported frequency of lower limb lymphedema secondary to treatment of gynecological cancers ranges from 10% to 49% [4,5].

Upper-limb lymphedema is a frequent complication following breast cancer treatment with estimated frequency of 12%–28% [6–8]. Recently sentinel lymph node biopsy (SLNB) reduces the incidence of lymphedema compared with axillary lymph node dissection (ALND) in patients with breast cancer. One study reported that lymphedema was found in 5% of patients who underwent SLNB alone and 16% of patients who underwent SLNB/ALND [9].

In the treatment of gynecologic cancers (cervical cancer, endometrial cancer, ovarian cancer etc.), knowledge on lymph node metastatic pathways and mechanism has emphasized the need for radical lymph node dissection and adjuvant radiotherapy. And unlike the treatment of breast cancer, clinical studies on SLNB in gynecologic cancer continue to be conducted, so it is limited for SLNB to be widely applied in clinical area. The above reasons can make a difference of lymphedema frequency between breast cancer and gynecologic cancer patients.
The affected patient with lower-limb lymphedema can experience pain, swelling of the leg with increased dermal turgor and hyperkeratosi, tightness and heaviness in the leg and recurrent skin infections, so the patient has problems with walking, running, and fitting shoes. When combined with genital lymphedema, patients can be devastated. These problems tend to be worse in the patients with lower limb lymphedema than upper limb lymphedema when considering our clinical experience and ongoing research.

Current management of lymphedema is based on complex decongestive therapy (CDT), and it includes manual lymph drainages, low-stretch bandaging, exercises and skin care. There are many studies to describe the effect of CDT in patients with upper limb lymphedema after breast cancer treatment [10–13], but there has been limited study of lower-limb lymphedema after CDT. While some studies have reported a reduction in edema after CDT during the first 12 months or less following cancer treatment [12,14], little is known regarding the long-term edema reducing effect of CDT in lower-limb lymphedema.

Conventional treatment such as sequential pneumatic compression pump reduces edema volume of the distal leg well, but greatly reduces the degree of edema reduction or rather increases edema volume in the proximal leg because it let edema fluid translocate to the proximal territory [12,14]. In contrast, CDT has been suggested to make little difference in the volume reducing effect of CDT between the proximal and distal legs because it reflects more normal physiologic mechanism in the way that improves the functionality of the remaining lymphatic system. But, maintenance effect of long-term follow up is not known. Therefore, in this study, lower limb was divided into the proximal and distal legs, and we investigated the difference between them.

The response to CDT is not uniform in patients with secondary lymphedema of the lower-limbs. One study reported that age, lymphedema duration, and radiotherapy did not affect lymphedema severity and CDT efficacy, but factors such as lymphoscintigraphy findings that influence the outcome of therapy have not yet received sufficient study [14].

Lymphoscintigraphy offers objective evidence to distinguish lymphatic pathology from non-lymphatic causes of extremity edema [15–17]. Qualitative and quantitative lymphoscintigraphies has been widely used in the assessment of therapeutic interventions for lymphedema, ranging from microsurgery and liposuction to manual lymphatic massage, and pneumatic compression [18–22], and it may predict the outcome of lymphedema therapy. In a recent study of women undergoing therapy for post-mastectomy lymphedema, Szuba et al. found that the degree of lymphatic function impairment before treatment correlated with the outcome of manual lymphatic therapy [23]. Also, Hwang et al. suggested that qualitative lymphoscintigraphy is potentially useful for predicting the response of patients with early unilateral leg lymphedema to CDT [12]. However, there has been no study analyzing the relationship between the quantitative findings of lymphoscintigraphy and the edema reducing effect of CDT for lower-limb lymphedema.

Therefore, the purpose of this study was to investigate the long-term edema reducing effect of CDT especially considering the proximal and distal parts of the leg separately and to evaluate the utility of pre-therapy lymphoscintigraphy in predicting the response to CDT in patients with lower-limb lymphedema.

Methods

Patients

A retrospective chart review was performed for 273 patients treated for lower-limb lymphedema between 1 January 2000 and 30 October 2009. The inclusion criteria for this study were as follows: 1) unilateral lower-limb lymphedema after surgery for gynecological cancer of clinical stage II (spontaneously irreversible non-pitting edema) or IIILymphostatic elephantiasis) diagnosed based on clinical assessment and lymphoscintigraphic findings; 2) fully attended decongestive treatment five times per week for two weeks once over follow up period; and 3) clinical follow-up longer than two years after CDT. The exclusion criteria were as follows 1) cancer recurrence during follow-up; 2) combined vascular disease of the extremities (arterial insufficiency, deep vein thrombosis, chronic venous insufficiency); 3) past history of attempted lymphedema reduction by any method; and 4) heart or kidney disease. One hundred and fifteen patients were excluded for primary lymphedema, bilateral lymphedema, or non-gynecological cancer. Therefore, 158 patients were enrolled in this study.

A chart review was undertaken to obtain the following clinical information: patient age, body mass index, cancer related therapy (chemotherapy and radiotherapy), infection of the lower limb(s), age of onset, period from surgery to lymphedema onset, lymphoscintigraphy findings, and lymphedema volume. This study was approved by governing Institutional Review Board (IRB) of our hospital.

Complex decongestive therapy

CDT was divided into two phases consisted of decongestive phase and maintenance phase. In decongestive phase, two certified skilled physical therapists performed the 2-week CDT program which included 1 hour of manual lymphatic drainage (MLD), multilayered and low-stretch compressive bandages and specific remedial exercises for five times per week. After 2 weeks of decongestive phase, patients followed the maintenance program. The at-home maintenance therapy consisted of high pressure compression stocking worn during the day, a daily session of self-administered MLD, and skin care as well as exercise programs. Additionally, it was recommended that at least three bandages be worn during the nighttime per week. During the maintenance phase, follow-up visits were scheduled at 3, 6, 12 and 24 months post-CDT. At each follow-up visit, we measured lymphedema volume and checked self-control activities for compliance of patients.

Lymphoscintigraphy

Lymphoscintigraphy was performed prior to the institution of therapeutic interventions for lymphedema. One hundred and forty-eight MBq 99mTc-filtered phytate colloid (total 3 mCi) was administered subcutaneously on the dorsum of the both feet in the inter-digital spaces using a 27-gauge needle. The patient performed a stress activity of walking for 30 minutes after injection, and then the imaging was repeated. Static images were obtained immediately after exercise and one and two hours after injection.

The uptake percentages of the radioisotope in the inguinal lymph nodes and the extremity in question, in addition to the clearance from the injection site on the feet were measured with the gamma camera. Both qualitative and quantitative parameters were measured, including the inguinal lymph node radioisotope uptake ratio (IUR), extremity radioisotope uptake ratio (EUR), and the radioisotope clearance ratio (CR). The IUR was established by placing symmetrical regions of interest (ROIs) over the groin on each lymphoscintigraph. The counts in each ROI were measured, and the ratio of the affected to the non-affected side was calculated for each patient. The analysis was performed using static images 2 h after injection of the radiotracer. The EUR was measured by placing the symmetrical ROIs below the groin lymph node and above the injection site on each lymphoscintigraph. The counts in each ROI were measured, and the ratio of the affected to the non-affected side was calculated for each patient. The analysis was performed using static images 2 h after injection of the radiotracer.

The CR was measured by placing the symmetrical ROIs on the radiotracer injection site on the feet. The counts in each ROI were measured, and the ratio of the affected to the non-affected side was
calculated for each patient. The analysis was performed using static images 2 h after injection of the radiotracer.

**Limb volume measures**

Limb volume was serially measured using an optoelectric volumeter (Perometer®, Pero-system; Wuppertal, Germany). An attempt was made to obtain two measures from the same site and these measurements were averaged. In addition to whole leg volume, we also measured the volume of the proximal portion of the leg (above knee) and the distal portion of the leg (below knee). Measurements were taken by a physical therapist experienced in lymphedema treatment before CDT (baseline), immediately after CDT, and at months 3, 6, 12, and 24 after CDT.

In calculations of limb volume reduction, the unaffected limb was used as a normal control for the affected limb (% excess volume). Limb volume reduction was calculated using the following formula:

\[
\% \text{ excess volume} = \left(\frac{V_a - V_u}{V_u}\right) \times 100.
\]

where \(V_a\) is the volume (ml) of the affected lower-limb, and \(V_u\) is the volume (ml) of the unaffected lower-limb.

The outcome of CDT was quantified as the difference between the affected lower-limb volumes before and after therapy, and the percent reduction in lower-limb volume was calculated using the following formula:

\[
\% \text{ volume reduction} = \left(\frac{\text{preV} - \text{postV}}{\text{preV}}\right) \times 100.
\]

where \(\text{preV}\) is the percent excess volume of the affected lower limb prior to CDT, and \(\text{postV}\) is the percent excess volume of the affected lower-limb after CDT.

**Statistical analysis**

All variables were tested for normality using the one-sample Kolmogorov–Smirnov test and all variables a normal distribution. The paired t-test was used to detect the significant effects of CDT on lymphedema before CDT (baseline), right after CDT, and at months 3, 6, 12, and 24 after CDT. Spearman’s rank correlation coefficient analysis was used to assess correlations between the lymphoscintigraphic findings (IUR, EUR, CR) and the clinical volume measures. To find the prognostic factor of lymphoscintigraphy for predicting the outcome of CDT, multiple logistic regression analysis was adopted for the statistical analysis.

The results were presented as means with standard deviations. P-values less than 0.05 were considered as statistically significant. The collected data were analyzed using SPSS version 18.0 (SPSS, Inc., Chicago, USA).

**Results**

**Descriptive characteristics**

Table 1 shows the patients' characteristics at inclusion. A total of 158 women with an average age of 53.0±11.2 years were included in our study. Body mass index ranged from 19.8 to 40.1 (mean=25.9; SD=4.7). Among these patients, 89 patients (55.8%) had lymphedema of left leg and 69 lymphedema of right leg. When the patients classified according to primary cancer sites, cervical cancer (71.1%) was the most. With regard to their cancer-related treatment, all patients had surgery, 63 patients (38.6%) underwent chemotherapy, and 78 patients (47.8%) received radiotherapy. The length of time between surgery and the onset of lymphedema varied from 1.0 to 237.0 months (mean=55.3; SD=57.8).

**Edema reduction**

When compared to the unaffected leg, data for the mean percent excess volume difference of the affected proximal leg, distal leg, and whole leg pre-CDT, immediately after CDT, and 3, 6, 12, and 24 months post-CDT are shown in Table 2. The percent excess volume in the distal leg and whole leg immediately after CDT, and at 3, 6, 12, and 24 months post-CDT was significantly lower than at baseline (P<0.01; Fig. 1), but no significant difference was seen at 12 and 24 months in the proximal leg (Fig. 2). This result indicated that the percent excess volume tends to increase with time after CDT in the proximal leg, distal leg, and whole leg. The mean percent volume reduction of the affected leg at 3, 6, 12, and 24 months post-CDT was shown in Table 3 when compared with the pre-CDT volume.

**Quantitative lymphoscintigraphy**

There was a significant negative correlation between the IUR and the percent excess volume in the proximal leg, distal leg, and whole leg in pre-CDT. The outcome of CDT (quantified as the percent volume reduction compared to the pre-CDT percent excess volume) negatively correlated with the IUR in the distal leg and whole leg immediately after CDT and at 3 and 6 months post-CDT, but not with the IUR of the proximal leg at any of the follow-up times. There was a significant positive correlation between the EUR and percent excess volume in the proximal leg, distal leg, and whole leg, pre-CDT. The EUR correlated positively with the percent volume reduction in the distal leg immediately after CDT and at 3, 6, 12 and 24 months post-CDT, and in the whole leg at 3 and 6 months post-CDT, but not with the percent volume reduction in the proximal leg at any of the follow-up times. No correlation was observed between CR and the percent volume reduction in the distal leg, proximal leg, or whole leg at any of the follow-up times. Multiple linear regression analysis revealed that EUR

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study group</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>53.0 (11.2)</td>
</tr>
<tr>
<td>Range</td>
<td>28.0–77.0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.9 (4.7)</td>
</tr>
<tr>
<td>Range</td>
<td>19.8–40.1</td>
</tr>
<tr>
<td>Site of lymphedema (n)</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>69</td>
</tr>
<tr>
<td>Left</td>
<td>89</td>
</tr>
<tr>
<td>Site of cancer (n)</td>
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<tr>
<td>Uterus</td>
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<tr>
<td>Ovary</td>
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<tr>
<td>Liposarcoma</td>
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<td>Cancer-related treatment (n)</td>
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<td>Surgery</td>
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<tr>
<td>Chemotherapy</td>
<td>63</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>78</td>
</tr>
<tr>
<td>Lymphedema onset delay since surgery (months)</td>
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</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
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<tr>
<td>Range</td>
<td>1.0–237.0</td>
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</tbody>
</table>

**Table 2**

Patient characteristics at inclusion (before CDPT) (n = 158).

<table>
<thead>
<tr>
<th>Time</th>
<th>Proximal leg</th>
<th>Distal leg</th>
<th>Whole leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-CDT</td>
<td>31.6 ± 29.6</td>
<td>32.4 ± 39.1</td>
<td>31.5 ± 29.7</td>
</tr>
<tr>
<td>Post-CDT</td>
<td>27.8 ± 25.6</td>
<td>22.6 ± 30.3</td>
<td>24.0 ± 24.1</td>
</tr>
<tr>
<td>3 months</td>
<td>24.6 ± 24.3</td>
<td>22.2 ± 27.8</td>
<td>22.9 ± 22.5</td>
</tr>
<tr>
<td>6 months</td>
<td>25.3 ± 21.8</td>
<td>23.1 ± 26.8</td>
<td>23.7 ± 21.5</td>
</tr>
<tr>
<td>12 months</td>
<td>25.5 ± 23.3</td>
<td>23.7 ± 30.7</td>
<td>26.2 ± 24.6</td>
</tr>
<tr>
<td>24 months</td>
<td>31.0 ± 23.8</td>
<td>24.7 ± 30.0</td>
<td>26.8 ± 21.6</td>
</tr>
</tbody>
</table>
could predict the improvement of lymphedema volume in the distal leg and proximal leg immediately after CDT and at 3, 6, 12 months post-CDT, and in the whole leg immediately after CDT and at 3, 6, 12 and 24 months post-CDT, but IUR and CR couldn’t predict that in the distal leg, proximal leg, or whole leg at any of the follow-up times.

**Discussion**

This is the first study to investigate the long-term effect of CDT in the lower leg divided into the proximal and distal portions and analyze quantitative lymphoscintigraphy to predict the outcome of CDT in lower-limb lymphedema following surgery for gynecological cancer. In this study, changes in lower-limb volume reduction were compared with the subjects’ normal lower-limb as a control for their affected lower-limb.

Our results show that percent reduction volume was 22.1 ± 28.6% immediately post-CDT, 27.4 ± 24.9% 3 months post-CDT, 24.7 ± 23.8% 6 months post-CDT, 19.7 ± 17.2% 12 months post-CDT, and 16.3 ± 19.5% 24 months post-CDT in the whole leg, and the greatest decrease in lymphedema volume was at 3 months after CDT, with lymphedema volume tending to increase over time thereafter.

It is pointed out that CDT can make little difference in the volume reducing effect of CDT between the proximal and distal legs rather than the effect of sequential pneumatic compression pump. In our results, the percent excess volume pre-CDT, immediately post-CDT, and at 3, 6, 12, and 24 months post-CDT was significantly lower than at baseline for the distal leg and whole leg (P < 0.01), but there was no significant difference between the percent excess volume pre-CDT and at 12 and 24 months post-CDT in the proximal leg. An important finding in our study is that there was no significant difference in the percent excess volume at 12 and 24 months compared to that pre-CDT for the proximal leg, indicating that the management of lower-limb lymphedema for the proximal portion of the leg is more difficult than the distal portion. Therefore, we recommend paying more attention to the management of proximal leg lymphedema.

The results of this study correspond with the results of earlier studies. They reported a variety of percent lymphedema volume reduction, and this difference may be related to patient factors (different clinical stage of lymphedema, compliance, therapy factors (skill of the therapist, therapy time and duration), and differing formulas used for limb volume calculation [24–27]). One study reported that compliance of patients has an influence on the persistence of reduced lymphedema volume [28]. Foldi et al. found that the initial reduction in lymphedema obtained after the decongestive phase was maintained in more than 50% of the patients maintained during a three-year follow-up program [24].

Lymphoscintigraphy is a noninvasive, effective and safe technique to determine the functional status of peripheral lymphatic vessels, and now has been advocated as the preferred diagnostic test for peripheral lymphedema [17,29,30].

Criteria defining lymphatic dysfunction include delay, asymmetric or absent visualization of regional lymph nodes, and the presence of “dermal backflow.” Additional findings include visualization of asymmetric lymphatic channels, collateral lymphatic channels, interrupted vascular structures, and lymph nodes of the deep lymphatic system (i.e., popliteal lymph nodes after web space injection in the lower extremities) [15]. Quantitative analysis may increase the sensitivity and specificity of lymphoscintigraphy in the diagnosis of lymphatic disorders [17]. The protocol for lymphoscintigraphy is not standardized and differs among diagnostic centers. Differences include the choice of radiotracser, the type and site of injection, the use of dynamic and static acquisitions, and the acquisition times themselves.

In this study, there was a significant, negative correlation between the IUR and percent excess volume in the proximal leg, distal leg, and whole leg, pre-CDT. This result indicates that the higher the IUR is, the smaller the edema volume will be pre-CDT. Although there was a weak correlation between IUR and the volume reducing effect by six months, it is thought that this result was due to the smaller volume pre-CDT performed in patients with a higher IUR. We suggest that IUR is not a significant predictor of the outcome of CDT in lower-limb lymphedema after surgery for gynecologic cancer.

Our results indicated a significant, positive correlation between the EUR and percent excess volume in the proximal leg, distal leg, and whole leg pre-CDT. The EUR also correlated positively with the percent volume reduction in the distal leg immediately post-CDT, and at 3, 6, 12, and 24 months post-CDT, and in the whole leg immediately post-CDT, and at 3, and 6 months post-CDT. This indicates that the greater the edema volume pre-CDT is, the larger the dermal back flow will be on lymphoscintigraphy. As the EUR increased, the edema volume reduction in the distal leg was more pronounced by 24 months.

### Table 3

<table>
<thead>
<tr>
<th>Time</th>
<th>Proximal leg</th>
<th>Distal leg</th>
<th>Whole leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-CDT</td>
<td>18.4 ± 14.3%</td>
<td>30.9 ± 38.4%</td>
<td>22.1 ± 28.6%</td>
</tr>
<tr>
<td>3 months</td>
<td>21.0 ± 28.6%</td>
<td>34.2 ± 29.1%</td>
<td>22.1 ± 24.9%</td>
</tr>
<tr>
<td>6 months</td>
<td>20.1 ± 34.5%</td>
<td>35.8 ± 33.1%</td>
<td>27.3 ± 23.8%</td>
</tr>
<tr>
<td>12 months</td>
<td>9.5 ± 17.5%</td>
<td>25.2 ± 21.0%</td>
<td>19.7 ± 17.2%</td>
</tr>
<tr>
<td>24 months</td>
<td>10.3 ± 24.8%</td>
<td>16.9 ± 22.8%</td>
<td>16.3 ± 19.5%</td>
</tr>
</tbody>
</table>

*P < 0.05, **P < 0.01.
and that of the whole leg was more pronounced by 6 months. Our study showed that only EUR among lymphoscintigraphic findings is a significant predictor on the outcome of CDT in lower-limb lymphedema after surgery for gynecologic cancer.

Results of CR in the present study correspond with the results of earlier studies, which show that radioisotope clearance from the foot is not a reliable indicator and is less sensitive for the diagnosis of lymphatic impairment compared with lymph node uptake percentages [31,32]. The current investigation identified a role of lymphoscintigraphic imaging in predicting the initial volume at onset of lymphedema and the responsiveness of lymphedema to CDT. The main strengths of our study were that it was monocentric and dealt only with patients with unilateral lower-limb lymphedema occurring after surgery for gynecologic cancer. This is also the largest study to date, comprising 158 patients followed over a period of two years.

In conclusion, this study shows that the long-term edema reducing effect of CDT is well maintained for 24 months on whole leg, and is better maintained in the distal portion of the leg than in the proximal portion. Pre-treatment quantitative lymphoscintigraphy can help to predict the initial edema volume and therapeutic outcome in patients with lower-limb lymphedema and represents a potentially useful tool for the clinical assessment of lower-limb lymphedema.

Conflict of interest statement
The authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2012.09.015.

References