EFFECTIVENESS OF COMPLEX PHYSICAL THERAPY (CPT) OF LYMPHEDEMA IN A PROSPECTIVE BASELINE-CONTROLLED STUDY IN ELEVEN DOMESTIC FACILITIES

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ABSTRACT

Objective: In a domestic prospective multicenter study, the effectiveness of complex physical therapy（CPT）of lymphedema was evaluated.

Materials and Methods: Adult outpatients who required lymphedema therapy after cancer surgery were registered in eleven lymphedema outpatient facilities. CPT was conducted according to the study protocol, and data（body measurements to calculate the edema volume, quality of life（QOL）questionnaire）on the effectiveness of the therapy were recorded.

Results: Two hundred and thirty-three cases were analyzed. Significant decrease in edema volume was achieved in the intensive decongestion phase. No significant change in limb volume was seen in the maintenance phase. The significant improvement of QOL over the course of treatment was observed in the QOL assessment using the health survey SF-36（Medical Outcomes Study 36-Item Short-Form Health Survey: SF-36）and the questionnaire regarding skin condition（Skindex 29）.

Conclusion: CPT's effectiveness in decreasing edema volume in the intensive decongestion phase was shown, and the maintenance of limb volume was confirmed in the maintenance phase. Moreover, it was shown that QOL was improved after CPT as compared to pretreatment scores.

Key words: lymphedema, complex physical therapy, multicenter study, edema volume, quality-of-life assessment

Introduction

Complex physical therapy（CPT）was introduced to Japan from Germany in 1995 as a conservative medical treatment for lymphedema. Full-scale implementation of CPT began in 2000. CPT is recognized as standard therapy by the International Society of Lymphology, [1,2] and a large number of theses on its effectiveness and safety have been released in Europe and North America.[3-8] In Japan, despite the research on CPT has been publicized thus far [9,10] its effectiveness has only been evaluated in single facilities. Therefore, in order to verify the effectiveness of CPT in multiple domestic facilities, a prospective multicenter study was performed.

Materials and Methods

This study was conducted as a prospective multicenter epidemiological study（prospective open study）pertaining to the effectiveness of complex physical therapy of lymphedema, using as its study subjects the outpatients who visited the lymphedema departments of the lymphedema multicenter study group during a period from February 2009 through March 2010. The study was based on the standard diagnostic and treatment methods for lymphedema specified in the protocol, as devised by the lymphedema multicenter study group（see 1. and 2.）.

The subjects of the study were adult patients who required lymphedema therapy after cancer surgery. Of those patients, the ones who satisfied the following selection/exclusion criteria and signed the informed consent, were registered in this study.

Subject Selection Criteria:

・Patients who received cancer surgery; and

・Patients who had been diagnosed with upper- or lower-limb lymphedema based on the results of interview and visual examinations, palpation and ultrasound imaging, and who required lymphedema treatment

・male or female of at least 20 years old or older upon

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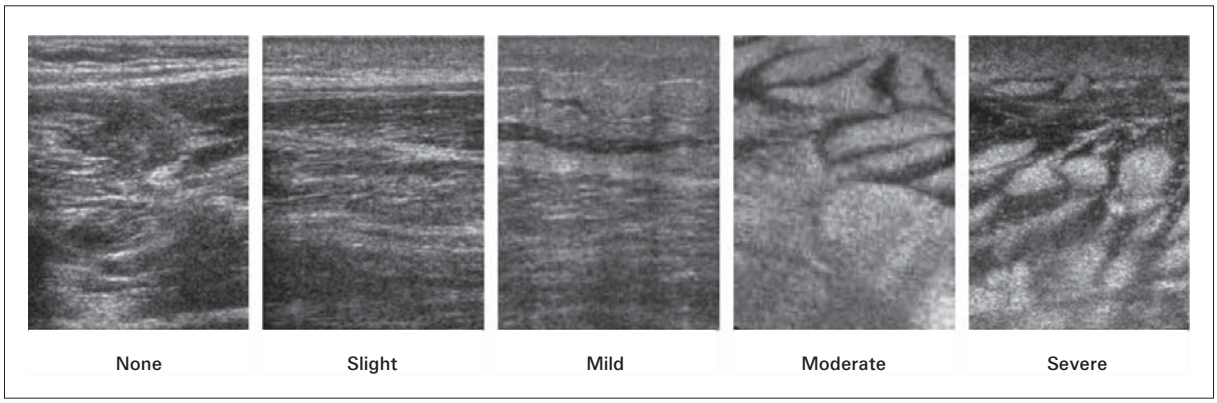

Fig. 1 Ultrasound imaging of EFS

registration.

Subject Exclusion Criteria:

・Primary lymphedema patients;

・Patients in whom edema developed during the proliferation of cancer cells in the lymphoreticular system (e.g., edema caused by lymph-node metastasis);

・Patients whose life expectancy was a year or less;

・Patients who were/were going to be participating in clinical trials of pharmaceuticals and/or medical equipment pertaining to lymphedema;

・Venous edema accompanied by acute phase thrombus, generalized edema such as cardiac and renal edemas, or mixed edema caused by multiple factors;

・Patients whose lymphedema treatment was contraindicated due to their pathological conditions or other reasons; and

・Patients whose physicians had determined that the continuous data collection would be difficult due to their physical/mental conditions and/or living environments.

Additionally, it was determined that initiation of the study must be approved by the Ethics Committee of each participating hospital.

1. Diagnostic Method of Lymphedema

The diagnostic method and the staging specified in the protocol of this study were as follows:

1.1. Diagnosis Based on Ultrasound Imaging

Using the linear probe (center frequency of 7.5 MHz and maximum depth of field of 4 cm as the standard), the subcutaneous adipose tissue structure of the limbs was examined in order to confirm the presence of the destruction of the layer structure (decrease in tissue contrast, increase in echogenicity) and increase in adipose tissue as well as the Echo-Free Space (EFS) in the subcutaneous adipose tissue. Eight points, generally used as measuring points of the circumference of the limbs, were used as observation points for the respective upper and lower limbs. The level of free water in the subcutaneous adipose tissue was evaluated using the EFS as an index with the following five-grade scale (Figure 1):

None: No EFS is observed in the subcutaneous adipose tissue.

Slight: EFS is observed in the form of dots or lines.

Mild: The EFS lines further expanded and show an obvious belt-like shape.

Moderate: Several lines of belt-like EFS are observed, and those belts begin to align in the vertical direction.

Severe: It can be observed that the subcutaneous adipose tissue is floating in a cobblestone-like state in EFS.

1.2. Staging in combination with Ultrasound Findings

This study conformed to the staging determined by the International Society of Lymphology. [1,2] Additionally, a clearer staging was achieved by adding the evaluation criteria based on the ultrasound imaging, aiming for more objective evaluation.

Stage 0: Although no obvious edema is observed during the interview and visual examinations and palpation, a slight tension is present on the surface of skin. The decrease in the tissue contrast within the subcutaneous adipose tissue (increased echogenicity) is observed on the echo. No increase is observed either in the adipose tissue or in the EFS in the adipose tissue. (EFS = None)

Stage 1: Although a slight degree of skin tension can be seen during interview and visual examinations and palpation, no hardness is present on the skin. A slight increase in adipose tissue is observed, as well as the decrease in tissue contrast in the subcutaneous adipose tissue on the echo. No EFS can be seen. (EFS = None)

Stage 2: The edema is evident during interview and visual examinations and palpation, and it is partially accompanied by skin hardness. The structural destruction on the subcutaneous adipose tissue and the increase in the adipose tissue are evident on the echo. EFS can or cannot be observed. (EFS = None – Moderate / Severe)

Stage 3: This stage can be determined by the fact that an obvious lymphedema is accompanied by skin complications. The obvious structural destruction of the subcutaneous adipose tissue, the increase in the adipose tissue and belt-like or cobblestone-like EFS can be

observed on the echo as well.（EFS = Moderate – Severe）

2. Treatment Methods

The following four programs were conducted as complex physical therapy（CPT）:（1）skincare;（2）manual lymphatic drainage（MLD）;（3）compression therapy using elastic bandages（Bdg.）or elastic compression garments; and（4）kinesitherapy under compression. The treatment period was divided into two phases: the intensive decongestion phase and the maintenance phase. However, in Japan lymphedema is treated mostly in the outpatient setting. Because it was difficult to conduct intensive care on a daily basis as recommended in the guidelines of overseas countries,[11, 12] the definitions of intensive decongestion and the maintenance phases were determined specifically for this study and are described below. Treatment was administered by nurses, physiotherapists, occupational therapists and massage therapists with expert knowledge in lymphedema treatment and under the supervision of a physician.

2.1. Intensive Decongestion Phase

MLD at least for 60 minutes, skincare, compression therapy and kinesitherapy were given by a single practitioner to stage 2 patients with moderate to severe EFS and/or significant skin hardness and stage 3 patients. This treatment was repeated at least once a week based on the standard of three days a week. During the intensive decongestion phase the QOL evaluation form was filled out at two occasions.

2.2. Maintenance Phase

MLD for at least 40 minutes and Bdg.（as required）were conducted by a single practitioner to stage 0, 1 and stage 2 patients with none to mild EFS and no significant skin hardness. These procedures were performed at least twice a month when introducing treatment to a new patient. For all other occasions the above procedures were performed once in a period of one month to three months. The QOL evaluation form was filled out once a month.（However, if the treatment interval was longer than one month, the form was filled out upon each treatment.）In addition to the treatment self-care guidance was given to the patients at the outpatient department.

Regarding the intensive decongestion – maintenance phase transition, after giving treatment several times, a therapist of each facility confirmed that the conditions of the affected limbs had changed through visual examination and palpation. Subsequently, a physician performed ultrasound diagnosis in order to determine whether or not there was a shift to the maintenance phase. When the condition of the ultrasound observation points had been recognized as "Mild or less" the intensive decongestion phase changed to maintenance phase.

3. Evaluation of Treatment Effects

The lymphedema treatment effects were evaluated by measuring the limb circumferences. The limb volume was calculated as an approximate volume of a circular truncated cone, and the volume change caused by the treatment was evaluated. The volumes were calculated using the equation $V = h\,(C2+Cc+c2) / 12\pi$, which was reported by Casley-Smith.[13] Furthermore, for the evaluation of treatment effects on QOL, SF-36 was used to evaluate health-related QOL and Skindex 29 was used to evaluate skin-condition-related QOL.

4. Statistical Analysis Method

4.1. Upper and Lower Limb Volumes

Investigation in multiple facilities concerning the effectiveness of lymphedema treatment in terms of edema volume involves various kinds of patient data. Due to such diversity, a random-effects linear regression analysis[14] was conducted using Stata SE（Release 11.2）, considering the upper- and lower-limb volume values（including the unaffected control limbs）of the patient who received treatment at least once as dependent variables.

As the factors that may possibly affect the volumes, six independent variables of the regression model were determined as: 1）Upper or lower limbs, 2）Left and right, 3）Staging of lymphedema before treatment, 4）Elapsed period since the first measurement, 5）The first treatment phase classification and 6）The interaction（reciprocal action）between the treatment type × elapsed period

The first three items of the list were specified as the major items, of which effects to the volume values were already known or could be predicted. Chronological comparison between before and after treatment served as the most important index of effectiveness. Because the effectiveness of treatment in each treatment phase is a combination of treatment phase and the elapsed period, it can be shown as an item of interaction of treatment phase × elapsed period. The patient functioned as random-effects.

4.2. QOL Evaluation

QOL data were obtained from answers to the SF-36 and Skindex 29 questionnaires, which were comprised of eight and four subscales, respectively. The subscale scores of the first and last surveys for each patient were calculated, including mean values and SD. Calculations for the SF-36 subscales were based on the norm-based scoring method. For the statistical analysis, the Wilcoxon signed-rank test was conducted on each scale for each questionnaire separately.

Results

1. Outline of Subject Patients

At eleven facilities 233 cases of adult patients, who

Table 1 Effect of the factors on the volumes (liters) of upper and lower limbs (random-effect linear regression of limb volumes in 233 patients)

Factor (Variable)	Regression coefficient and standard error (L)	p-value
Stages (initial edema volume compared to unaffected limbs)		
Stage 0	− 0.20 ± 0.12	0.1
Stage 1	− 0.26 ± 0.13	0.05
Stage 2	0.16 ± 0.14	0.2
Stage 3	1.33 ± 0.15	< 0.0005
Phases (initial edema volume compared to unaffected limbs)		
Intensive decongestion phase (Phase I)	1.04 ± 0.15	< 0.0005
Maintenance phase (Phase II)	0.32 ± 0.13	0.01
Elapsed period (rate of limb volume change of not-treated unaffected limbs, liters per year)	− 0.14 ± 0.13	0.3
Interaction: treatment phase × elapsed period (compared to unaffected limbs)		
Phase I × elapsed period (rate of limb volume change with intensive phase, liters per year)	− 0.52 ± 0.19	0.007
Phase II × elapsed period (rate of limb volume change with maintenance phase, liters per year)	− 0.09 ± 0.18	0.6

Random-effect linear regression intercept: volume of unaffected left arm

required lymphedema treatment after cancer surgery, were eligible for this study. Out of the 233 cases, 229 were female and four were males. The average age was 59.5 years old (29 - 88). The major cancer types that caused lymphedema were 103 cases (44%) of uterine cancer (including one case with ovarian cancer); 86 cases (37%) of breast cancer; and 31 cases (13%) of ovarian cancer (including one case with uterine cancer).

2. Effectiveness of Lymphedema Treatment in Terms of Edema Volume

Volume changes were calculated on the basis of 233 cases. Stage 2 was most frequently seen, accounting for more than 70% of all cases. Neither the upper limbs nor the lower limbs showed laterality in the distribution tendency. With respect to the patients' treatment-phase distribution, patients with the maintenance phase alone accounted for more than half of the subjects. Of the patients who were in the intensive decongestion phase, more than half transitioned to the maintenance phase, because their conditions had improved during the course of treatment.

The average treatment period was 93 ± 74 days, ranging from one day to 304 days. The number of treatments for each affected limb was widely spread from once to 20 times in both treatment phases. However, patients who received treatment ten times or less accounted for 91% in the maintenance phase, while it was 80% in the intensive decongestion phase.

Table 1 shows the results of the random-effects linear regression analysis. At the time of the first circumference measurement the initial edema volumes of the affected limbs were compared to those of the unaffected limbs and divided into each stage and each treatment phase. Results for each stage were as follows: − 0.20 ± 0.12 L ($p = 0.1$) in stage 0; − 0.26 ± 0.13 L ($p = 0.05$) in stage 1; 0.16 ± 0.14 L ($p = 0.2$) in stage 2; and 1.33 ± 0.15 L ($p = 0.0005$) in stage 3. Here, only the affected limbs in stage 3 showed a significant increase in volume. The different treatment phases showed both a significant increase in volumes with 1.04 ± 0.15 L ($p < 0.0005$) for the intensive decongestion phase and 0.32 ± 0.13 L ($p = 0.01$) for the maintenance phase.

Volume changes during the study period have been converted to an annual basis showing no significant chronological change of the non-treated unaffected limbs (− 0.14 ± 0.13 L, $p = 0.3$). As a result of CPT, a significant chronological decrease of − 0.52 ± 0.19 L ($p = 0.007$) was observed in the volumes of the affected limbs that received treatment for the intensive decongestion phase. No significant chronological change was observed in the volumes of the affected limbs that received treatment for the maintenance phase (− 0.09 ± 0.18 L, $p = 0.6$).

Figure 2 depicts the actual volume change in each treatment phase for each of the upper and lower limbs. The x-axis indicates the volume of each limb upon the initial measurement, and the y-axis indicates the volume

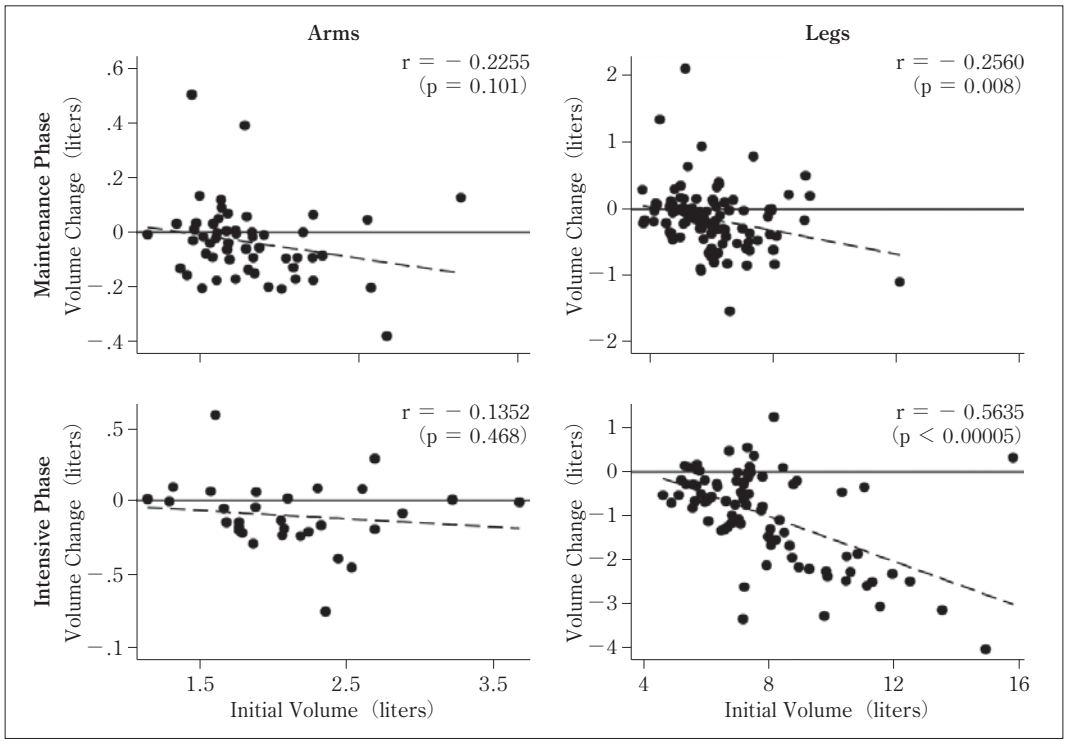

Fig. 2　Correlation between initial volume (x-axis) and volume change at the last visit (last - initial, y-axis)

change upon the final measurement. Generally, from these results it was observed that the volume change had a correlation with the volume at the initial measurement. Particularly, during the intensive decongestion phase the lower limbs showed a significantly high correlation with the initially measured volume ($r = -0.5635$, $p < 0.00005$).

3. Effectiveness of Lymphedema Treatment on QOL

181 out of 233 possible answers to the questionnaires could be obtained and evaluated, accounting for 78% of all cases. Regarding the changes in the SF-36 norm-based scores between the first and last visits all the subscale items showed an increase after treatment. According to Wilcoxon signed-rank test significant differences were observed in all items except for "physical functioning, PF" ($p = 0.065$), "role (physical), RP" ($p = 0.199$) and "general health, GH" ($p = 0.313$). The scores±SD for the remaining subscales before treatment were for "body pain, BP" 46.2±10.1, "vitality, VT" 46.4±9.7, "social functioning, SF" 42.5±12.6, "role (emotional), RE 40.3 ± 13.7 and "mental health, MH" 46.3±10.3. Those scores increased after treatment to BP 47.8±9.5 ($p = 0.022$), VT 49.0±9.1 ($p = 0.000$), SF 46.0±11.9 ($p = 0.000$), RE 42.9±12.8 ($p = 0.017$) and MH 48.4±9.9 ($p = 0.002$). Furthermore, regarding the changes of the Skindex 29 scores between the first and last visits, according to Wilcoxon signed-rank test, all the subscale items demonstrated a significant decrease after treatment, thus indicating a significant improvement in QOL related to skin condition. Scores±SD before treatment were "symptoms" 22.3±16.5; "functioning" 23.8±18.5; "emotions" 34.8±19.4 and overall score 27.0 ± 16.2. Those decreased after treatment to "symptoms" 19.0±14.2 ($p = 0.001$); "functioning" 19.2±16.4 ($p = 0.000$); "emotions" 24.3±18.0 ($p = 0.000$) and overall score 20.7±14.7 ($p = 0.000$).

Discussion

The prospective multicenter study conducted in eleven domestic facilities reported in this paper was planned because no report had been made about a multicenter study on effects of treatment using a standardized lymphedema diagnosis method and CPT. This study was conducted in order to investigate the effectiveness of CPT, focusing not only on the decrease in the edema volume but also on the improvement in patients' QOL in terms of their overall health and skin condition.

Regarding the decrease in lymphedema using CPT, it is difficult to directly compare absolute volume deduction values and rates of decrease from different publications to the results of this study, because the results can differ between upper and lower limbs, stages of the disease and treatment phases, as well as the difference between the CPT standards of foreign countries and those of Japan (where such treatment is mainly conducted in outpatient departments). Furthermore, this study did not evaluate a particular treatment method employed by a single facility for a certain period of time but instead included data pertaining to various pathological conditions or situations

of various types of patients in multiple facilities with different treatment phases. In order to investigate the effectiveness of CPT in terms of limb volumes using such diverse data, it is necessary to use an evaluation method for the effects of major factors that might possibly affect the limb volumes. Therefore, it was necessary to analyze the influential factors using a random-effects linear regression model. This analysis can also show the diversity in patients' treatment phases as the standardized annual base volume change rate of each treatment phase. The analysis results showed the following facts: Lymphedema volume can be significantly reduced by the intensive decongestion phase of CPT and through further treatment in the maintenance phase, the upper and lower limb volumes can be maintained without any change for a long period of time. It can be concluded that the results of this study show the more universal clinical effectiveness of CPT treatment in Japan because, despite diverse patient conditions, different therapists and treatment phases in multiple facilities, the data collected has clearly demonstrated that the goals of CPT treatment（i.e. reducing lymphedema during the intensive congestion phase and maintaining limb volume during the maintenance period）have been achieved.

Regarding SF-36, as used in this study to evaluate the QOL related to lymphedema patients, improvement was recognized in all the subscales with statistically significant difference in five of the subscales. It therefore indicates that the improvement in health-related QOL has been observed over a broad range. Moreover, in Skindex 29, which indicates skin-condition-related QOL, significant improvement was recognized in all subscale items（emotions, functions, symptoms and overall scores）. It can therefore be surmised that CPT improves QOL in various aspects by improving not only limb volumes but also the patient's overall health and skin condition.

Conclusion

The prospective multicenter study conducted in eleven domestic facilities showed the effectiveness of CPT in the intensive decongestion phase in terms of lymphedema reduction. It also confirmed the maintenance of the upper and lower limb volumes in the maintenance phase. Moreover, the patients' QOL evaluation using SF-36（QOL related to overall health）and Skindex 29（QOL related to skin condition）showed that patients' QOL was significantly improved after CPT, as compared to their QOL before treatment.

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Disclosure Statement

None of the authors have any conflict of interest to disclose.

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リンパ浮腫の複合的理学療法の有効性に関する国内 11 施設の前向きベースライン試験

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要　旨

【目的】国内多施設研究において，リンパ浮腫の複合的理学療法（Complex Physical Therapy：CPT）の有効性を確認する。

【方法】11 施設のリンパ浮腫外来において，悪性腫瘍術後にリンパ浮腫治療を必要とする成人患者が登録された。実施計画書に基づき CPT を実施し，治療の有効性に関するデータ〔浮腫容積の計算に必要な身体計測値，生活の質（Quality of Life: QOL）質問票〕を記録した。

【結果】233 例を解析した。集中排液期の患者では，浮腫容積の有意な減少がみられた。維持治療期の患者では，上下肢容積の有意な変化はみられなかった。SF-36 健康調査（Medical Outcomes Study 36-Item Short-Form Health Survey: SF-36）および皮膚の状態についてのアンケート（Skindex 29）を用いた QOL 評価では，治療による有意な改善が認められた。

【結論】CPT により集中排液期では浮腫容積が有意に減少した。また，維持治療期においては，上下肢容積の維持が確認された。さらに，治療前と比較して，CPT 後の患者の QOL が有意に改善されていることが示された。