

Treatment of Postmastectomy Lymphedema with Low-Level Laser Therapy

A Double Blind, Placebo-Controlled Trial

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BACKGROUND. The current study describes the results of a double blind, placebo-controlled, randomized, single crossover trial of the treatment of patients with postmastectomy lymphedema (PML) with low-level laser therapy (LLLT).

METHODS. Participants received placebo or one cycle or two cycles of LLLT to the axillary region of their affected arm. They were monitored for reductions in affected limb volume, upper body extracellular tissue fluid distribution, dermal tonometry, and range of limb movement.

RESULTS. There was no significant improvement reported immediately after any of the treatments. However, the mean affected limb volume was found to be significantly reduced at 1 month or 3 months of follow-up after 2 cycles of active laser treatment. Approximately 31% of subjects had a clinically significant reduction in the volume of their PML-affected arm (> 200 mLs) approximately 2-3 months after 2 cycles of treatment. There was no significant effect of placebo treatment, or one cycle of laser treatment, on affected limb volume. The extracellular fluid index of the affected and unaffected arms and torso were reported to be significantly reduced at 3 months after 2 cycles of laser therapy, and there was significant softening of the tissues in the affected upper arm. Treatment did not appear to improve range of movement of the affected arm.

CONCLUSIONS. Two cycles of laser treatment were found to be effective in reducing the volume of the affected arm, extracellular fluid, and tissue hardness in approximately 33% of patients with postmastectomy lymphedema at 3 months after treatment. *Cancer* 2003;98:1114-22. © 2003 American Cancer Society.

KEYWORDS: lymphedema, low-level laser therapy (LLLT), breast neoplasms, treatment.

Upper limb lymphedema is a common and distressing complication of breast carcinoma surgery.^{1,2} The reported incidence after surgery is approximately 5%, increasing to 30% with the administration of adjunctive radiotherapy. It is a chronic and progressive condition in which there is swollen limb deformity, often accompanied by a brawny edema. Patient discomfort is common, with symptoms of limb heaviness, weakness, pain, restricted shoulder mobility, burning pains and elevated skin temperature, obvious deformity, social isolation, and psychologic morbidity. Traditional treatments for this condition have included compression bandaging, manual lymphatic drainage, and extended limb elevation.³ Because of the nature of these treatments, none have been validated with placebo-controlled trials. In addition, these treatments are expensive, time-consuming and labor-intensive.⁴

Low-level laser therapy (LLLT) is reported to have beneficial

effects on cells and tissues; remarkable effects are reported for the treatment of a surprisingly broad range of conditions, from acne to myocardial infarction. In particular, recent reports indicate an efficacy for LLLT in the treatment of lymphedema,⁵ with both practitioners and clients reporting remarkably rapid improvement of lymphedema, often within hours of irradiation. LLLT has been examined for the treatment of fibrous scar tissue⁶ and has been shown to affect cultured fibroblasts.⁷ These effects most likely are important both in treating the surgical scars associated with postmastectomy lymphedema (PML) and in treating the brawny edema that often develops in lymphedematous limbs. It also has been suggested that LLLT encourages lymphangiogenesis and stimulates lymphatic motoricity.^{8,9} Finally, LLLT is reported to stimulate macrophage cells¹⁰ and to stimulate the immune system.¹¹ All these actions indicate that LLLT could be an appropriate treatment for patients with PML.

Preliminary evidence using a multifrequency scanning laser demonstrated a beneficial effect when the PML arm and the anterior chest were treated.⁵ We sought to test the efficacy of a single wavelength laser applied in the axillary zone only. The axillary zone is the location of the lymph nodes through which the upper limb lymph principally drains, and is the supposed site of blockage of lymphatic drainage from the PML limb. We reasoned that the laser might reduce fibrosis and activate surviving lymphatic drainage pathways, stimulate the growth of new pathways, and/or stimulate a localized lymphocyte response that may assist in resolving the lymphedema. Furthermore, the laser can be deactivated without changing its apparent operation, thus permitting a double blind placebo trial. In the current study, we report the results of what to our knowledge is the first double blind, placebo-controlled trial for the treatment of PML using treatment of any kind; in this study, we used localized LLLT targeted to the axilla of the affected limb.

MATERIALS AND METHODS

Design

There were two components to this trial. First, there was a prospective, double blinded, placebo-controlled, randomized single crossover trial of a single cycle of laser treatment. In parallel, there was a within-group comparison of one cycle versus two cycles of laser-treatment. All clients already attending, or those newly presenting to, the Flinders Medical Centre Lymphedema Assessment Clinic over the period 2001–2002 were considered for entry into the trial. All participants signed written consent forms after being fully informed about the trial, which was approved by the

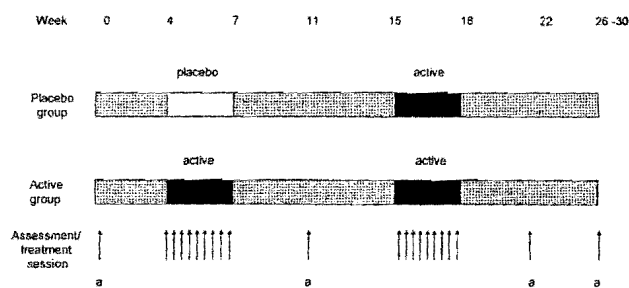


FIGURE 1. Study protocol; treatment regimen. Participants in the "Placebo" group received 1 block of Sham therapy (when the laser had been disabled with no apparent change in its function), which was followed by an 8-week rest period and then 1 block of low-level laser therapy (LLLT). The "active" group received 2 blocks of LLLT, separated by an 8-week rest period. a: assessment only.

Clinical Ethics Committee of Flinders Medical Centre, Adelaide, South Australia. The trial was conducted over a 24-month period, with data collected through all seasons.

The trial was designed to allow comparisons between placebo treatment and one cycle of LLLT, or between one cycle and two cycles of LLLT. Participants were allocated into a "active" or "placebo" group using sequential reference to a random number table (if the participant got 0–4, they went into the active group; those with 5–9 went into the placebo group). Neither participants nor the study coordinator/therapist knew who was in which group. Those participants entering the placebo group received 1 block of sham therapy (in which the laser had been disabled without affecting its apparent function), followed by an 8-week rest period and then 1 block of active LLLT (Fig. 1). The active group received 2 blocks of LLLT, separated by an 8-week rest period. Because statistical analysis demonstrated no ongoing effect from placebo treatment, all placebo participants then were offered a second block of active laser therapy.

Patient Selection

A standard procedure was used to screen patients for inclusion. The following criteria had to be met before a patient was entered into the trial: age of at least 18 years, female gender only; diagnosis of clinically manifest PML (> 200 mL difference between arms or ≥ 2 cm difference in arm circumference at ≥ 3 positions), and assurance that the patient understood the trial and was able to provide informed consent.

Participants were excluded on the following criteria: presence of certain comorbidities (current metastases, history of severe trauma/disruptive surgery to the arm), instability of their condition (significant

changes to the arm in the past 3 months, including change in treatment regime or the occurrence of cellulitis), clinical (inability to abduct arm sufficient for measuring purposes, and diagnosis (presence of primary lymphedema in the lower limbs).

Laser Unit

The LLLT unit used in the trial was the RianCorp LTU 904H (RianCorp Pty Ltd., Henley Beach, South Australia, Australia). This is a portable, rechargeable, battery-powered unit that emits a pulsed 904 nanometer beam with an average output of 5 milliwatts from a treatment head measuring 0.2 cm² in size; treatment is by contact of the treatment head with the skin. Because the RianCorp LTU-904H is a Class 1 laser (ASNZ 4672), added safety precautions such as protective eyewear are not required. One unit was deactivated, such that switching on the laser did not activate the laser diode, and thus no laser irradiation was delivered. This unit was indistinguishable from the active unit.

Study Protocol

Treatment was delivered in blocks of 9 sessions (active laser or placebo), in which 1 block was comprised of treatment 3 times per week for 3 weeks. A plastic guide with a grid of 17 treatment points centered at 2-cm intervals was placed in the axilla to guide application. The laser treatment head was held in contact with, and at right angles to, the skin adjacent to each point in the grid, and switched on for 1 minute, making the treatment time 17 minutes per session. The total energy applied at each point was 300 mJoules over 17 points (5.1 Joules in total), giving a dosage of 1.5 Joules/cm² in the active group; no laser irradiation was delivered in the placebo group.

Patient Assessment

Objective measures initially were taken at the beginning, and at the end of every LTU-904H session for the first treatment or placebo cycle. Statistical analysis demonstrated there was no difference in parameters between the start and end of any individual session; therefore, subsequently, parameters were measured only at the start of every session.

Perometry uses infrared sensors to measure the limb circumference at every 4 mm, with the limb volume calculated via a truncated cone method (Perometer 350S and Pero Plus v1.4 software; Perosystem Meßgerät, Wuppertal, Germany). This is regarded as a very accurate assessment of limb volume.¹²

Bioimpedance measures electrical impedance to alternating electrical currents (100 microamps [μ A], over a range of frequencies up to 50 Kilohertz [kHz]),

thereby providing an objective measure of fluid distribution levels in various parts of the body.^{13,14} We used the Inbody 3.0 system (Biospace, Seoul, South Korea), which provides whole body, trunk, torso, and limb extracellular fluid (ECF) values.^{13,15} Body weight and mass index also were monitored using the Inbody 3.0 system. The bioimpedance at a frequency of 5 kHz as used was an index of ECF only. This measurement has been validated in the detection and treatment of lymphedema.¹⁵

Tonometry measures tissue resistance to pressure, giving an indication of the compliance of the dermis and extent of fibrotic induration in a limb.¹⁶ The tonometer (BME; Flinders Medical Center, Adelaide, South Australia, Australia) is comprised of a central plunger (1 cm in diameter weighted to a gravitational load of 275.28 g/cm², operating through an annular footplate that rests on the surrounding skin and applies a load of 12.2 g/cm². Thus, the plunger applies a differential pressure of 263 g/cm², and the degree of penetration of the plunger is measured by a micrometer in mm. Tonometry of the upper and lower affected and unaffected arm, as well as the anterior and posterior torso, was measured.

Shoulder range of movement was assessed using a goniometer (Jamar, Miami, United States of America)

Subjectively, participants were asked to self-report on three domains:

- 1) Perceptual symptoms of their affected limb were scored from 1 (no symptoms)–10 (worst imaginable sensation) for pain, tightness, heaviness, pins and needles, cramps, burning feelings, limb size difference, limb temperature difference, and range of movement limitation. The perception scores were averaged to provide a summary statistic: the mean perception score.
- 2) The ability to perform specific activities of daily living (ability to put on bra, tie shoes, wash hair, hang out washing) were scored as yes (1) or no (2), and a composite index was derived by calculating the mean score.
- 3) Overall feelings regarding quality of life as assessed on a scale from 1 (good) to 5 (bad).

The subjective questionnaire was administered before and after each 3-week treatment block and at each follow-up visit.

Data Analysis

Data were analyzed using SPSS version 10.55 or 11 (SPSS Inc., Chicago, IL) using analysis of variance and multiple regression. All data were checked for outliers and normality of distribution. Comparisons were made between or within participant groups receiving

TABLE 1
Demographic Details of Participants in Each Treatment Group^a

	Placebo	Active
Age (yrs)	65 ± 2 (42-87)	63 ± 2 (35-83)
Weight at start of trial (Kg)	76 ± 3 (48-113)	76 ± 2 (60-105)
Type of surgery (%)		
Partial mastectomy with axillary clearance	57.1	33.3
Total mastectomy with axillary clearance	42.9	66.7
Received radiotherapy (%)	92.9	90.9
Received chemotherapy (%)	46.4	33.3
Time since onset of LO (mos)	43 ± 9 (3-180)	98 ± 15 ^b (2-336)
Limb volume at start of trial (mLs)	3429 ± 151 (2268-5511)	3579 ± 130 (2181-4993)
Excess limb volume at start of trial (affected limb volume—unaffected limb volume)	645 ± 72 (131-1378)	888 ± 108 (104-2730)

LN: lymph node; LO: lymphedema.

^a Shown as the mean ± the standard error of the mean (range).

^b A significant statistical difference was found between the groups using the Student *t* test ($P < 0.01$).

placebo only, or one or two cycles of active laser treatment. All comparisons between treatments were made at the same time point relative to the end of treatment. Significance (at $P < 0.05$) was determined using the Student *t* test or Fisher exact test for comparisons between groups; comparisons within groups were performed using the Student *t* test for paired data. To assess the change in any parameter, the mean of the first two visits was subtracted as a baseline measurement.

RESULTS

Demographic Details

Twenty-eight participants entered the placebo group and 33 were entered into the active group. The groups were matched for age and weight at the start of the trial (Table 1). The randomly chosen active group had a significantly longer duration since onset of lymphedema, which may explain why their affected limb volumes tended to be higher. There was no significant correlation found between duration of symptoms (range, 2-336 months) and change in affected limb volume immediately after, 1 month after or 3 months after placebo or 1 cycle or 2 cycles of treatment (i.e., there was no significant effect found for duration of lymphedema and outcome of treatment in the current trial). Data regarding the type of surgery performed is provided in Table 1, but data on the number of lymph nodes removed and their precise location was difficult to obtain, which prevented appropriate analysis of these data between groups, or of correlational analysis of the severity of surgery versus outcome measures of laser treatment. On the basis of what data were available, there appeared to be little difference between the groups.

One participant withdrew from the placebo group (because of metastases) and seven withdrew from the active group, one with metastases, one with a deep vein thrombosis of the lower limb, one with dermatitis, and the remainder for personal reasons not associated with the trial). There were no adverse reactions or side effects reported among any participants.

Preliminary statistical analysis demonstrated that there were no significant differences between participants who received one cycle of active laser treatment after placebo treatment in the placebo group compared with those receiving the first cycle of active treatment in the active group (i.e., the placebo treatment did not affect the outcome of a single cycle of active laser treatment). Consequently, 11 of the 27 participants from the placebo group chose to undergo a second cycle of 3 weeks of active laser therapy (and thus were no longer blinded to the trial) and completed the treatment, making a total of 37 participants (33 who started the trial subtracted by 7 who withdrew + 11 'crossovers') who underwent 2 cycles of active laser therapy under the 'active' protocol. There were no differences found between those who were blinded to the trial and the 11 participants who crossed over and, consequently, their data were pooled. A total of 64 participants (27 in the placebo group and 37 in the active group) completed the trial. Of these, 26 patients and 29 patients, respectively, were available for follow-up at 2-3 months after treatment in the placebo and active groups.

Effect of LTU-904H Treatment on Arm Volume

There was no apparent significant effect of placebo treatment only, or one cycle of laser treatment only, on mean affected limb volume (Fig. 2A). The mean

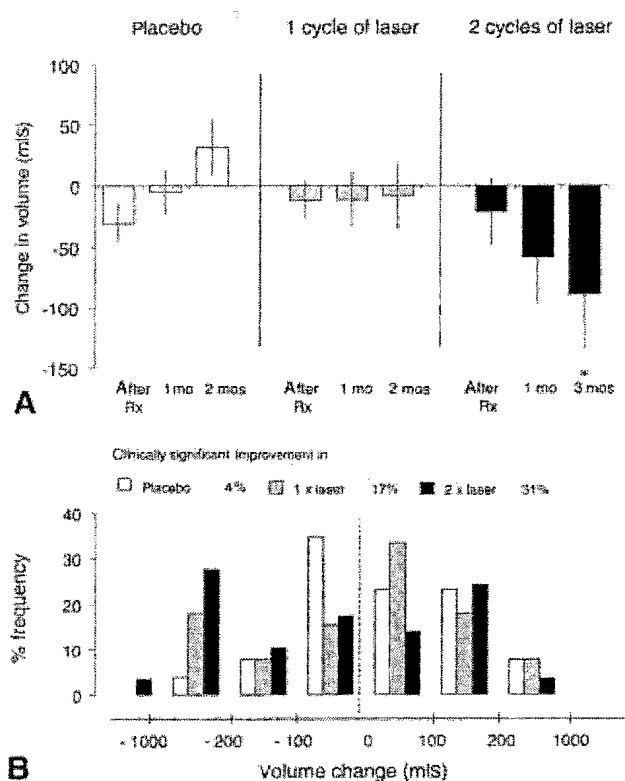


FIGURE 2. (A) Mean change in affected limb volume immediately after treatment with low-level laser therapy (LLLT) (after radiotherapy [Rx]) and 1 month (mo) or 2–3 months after treatment (means \pm Standard error; $P < 0.05$, which indicates it was significantly different from placebo values). (B) Frequency distribution of individual changes in affected limb volume 2–3 months after LLLT treatment.

affected limb volume was not found to be significantly reduced below pretreatment mean values immediately after 2 cycles of active laser treatment ($P = 0.442$, Student *t* test for paired data), but continued to decrease at 1 month ($P = 0.119$) and 3 months ($P = 0.061$) of follow-up after the cessation of treatment. The mean affected limb volume at 3 months after 2 cycles of treatment was significantly less than after placebo treatment ($89.7 \text{ mL} \pm 46 \text{ mL}$ reduction vs. $32.1 \text{ mL} \pm 23.4 \text{ mL}$ increase; $P = 0.017$).

The criterion for effectiveness of the LTU-904H treatment was defined as a 200-mL reduction in the lymphedema-affected limb volume (from the mean of the 2 initial measures). There were no significant differences found using this criterion between active and placebo groups immediately after cessation of the treatment. However, both 1 and 2 cycles of treatment were found to be significantly better than placebo treatment 1 month after the cessation of treatment, and 2 cycles of treatment were found to be significantly better than 1 cycle of treatment 2–3 months

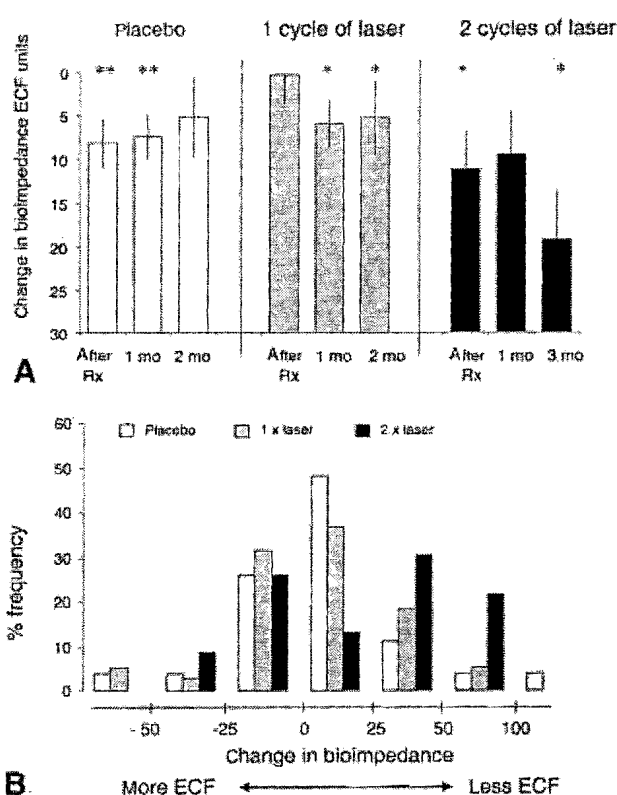


FIGURE 3. (A) Mean change in bioimpedance (arbitrary units) after treatment (after radiotherapy [Rx]) and 1 month (mo) or 2–3 months after treatment (means \pm Standard error; * $P < 0.05$; ** $P < 0.01$, which indicates a significant difference from pretreatment values-). (B) Frequency distribution of individual changes in extracellular fluid (ECF) in affected limb 2–3 months after treatment.

after the cessation of treatment (Fig. 2B). Approximately 31% of subjects had a clinically significant reduction in their affected limb volume 2–3 months after treatment with 2 cycles of LTU-904H treatment (significantly better than 2–3 months after placebo, $P = 0.01$ according to the Fisher exact test).

Effect of LTU-904H Treatment on ECF Distribution

ECF was measured using arbitrary bioimpedance machine units; an increase in these units indicates a decrease in ECF. The mean ECF of both the affected (Fig. 3A) and unaffected limb was significantly reduced by placebo or one cycle of LTU-904H treatment. However, the mean ECF was found to be reduced most after 2 cycles of LTU-904H therapy, in the following regions: 1) the affected limb, immediately after the course of treatment ($P = 0.014$, Student *t* test for paired data) and maintained at 1 month ($P = 0.060$) and 3 months of follow-up ($P = 0.02$) (Fig. 3A); 2) the unaffected limb, immediately after treat-

TABLE 2
Self-Reported Indices of Perceptual Scores, Activities of Daily Living, and Quality of Life for Each of the Treatment Groups^a

	Baseline	Immediately after treatment	1 mo after treatment	2-3 mo after treatment
Placebo cycle (n = 26)				
Mean perceptual scores	2.8 ± 0.2	2.1 ± 0.1 ^b	2.1 ± 0.2 ^b	2.2 ± 0.2 ^c
Activities of daily living	1.08 ± 0.02	1.06 ± 0.03	1.04 ± 0.02 ^c	1.05 ± 0.2
Quality of life	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2
One active cycle (n = 37-42)				
Mean perceptual scores	2.8 ± 0.2	2.2 ± 0.1 ^b	2.4 ± 0.2 ^b	2.5 ± 0.2
Activities of daily living	1.09 ± 0.02	1.06 ± 0.02 ^c	1.09 ± 0.03	1.09 ± 0.03
Quality of life	1.9 ± 0.1	1.8 ± 0.1	1.9 ± 0.1	1.8 ± 0.2
Two active cycles (n = 29-39)				
Mean perceptual scores	2.8 ± 0.2	2.0 ± 0.2 ^b	2.3 ± 0.2 ^b	2.1 ± 0.2 ^b
Activities of daily living	1.09 ± 0.03	1.06 ± 0.02	1.05 ± 0.02 ^c	1.07 ± 0.04
Quality of life	1.9 ± 0.1	1.7 ± 0.1	1.8 ± 0.1	1.6 ± 0.1 ^c

^a Shown as the mean ± the standard error of the mean. Comparisons were made against baseline values using the Student *t* test for paired data.

^b *P* < 0.01.

^c *P* < 0.05.

ment (*P* = 0.009) and maintained at 3 months of follow-up (*P* = 0.015), and 3) the trunk, at 1 month (*P* = 0.007) and 3 months (*P* = 0.009) of follow-up.

A greater proportion of participants demonstrated reductions in ECF of the affected limb at 3 months after 2 cycles of LTU-904H treatment, compared with 1 cycle or placebo treatment. Approximately 52% of participants receiving 2 cycles of treatment had changes in bioimpedance of ≥ 25 units at 3 months of follow-up (Fig. 3B), a finding that was significantly better than that for those receiving 1 cycle (23%; *P* = 0.029 by the Fisher exact test) and/or placebo (24%; *P* = 0.017 by the Fisher exact test).

Effect of LTU-904H Treatment on Tonometry

Tonometry assesses the "hardness" of the tissue, and is an index of fibrotic induration. The lower the tonometry reading, the "harder" the tissue. If untreated, lymphedema causes hardening of the limb over time. There were significant decreases in tonometry readings (indicating increased tissue hardness) in participants receiving placebo or one cycle of LTU-904H treatment over the duration of the trial. Participants receiving 2 cycles of LLLT tended to have softening of the tissues (as measured by increased tonometry readings).

Significant hardening of the affected arm and torso were reported immediately after treatment with 2 cycles of LTU-904H, but at 3 months after treatment there was a significant increase in tissue tonometry (indicating softening of the tissues) reported in the affected upper arm (*P* = 0.025).

Effect of LTU-904H Treatment on Range of Movement

There was no reported consistent effect of any treatment on range of movement in the affected limb.

Effect of LTU-904H Treatment on Subjective Measures

Mean perceptual scores of symptoms and the index of activities of daily living demonstrated improvement after treatment in all groups, but there was no difference found between placebo or either of the active treatment regimens (Table 2). There was a significant improvement in the quality of life index at 3 months after 2 cycles of treatment that was not observed in the other 2 groups.

DISCUSSION

Two cycles of LTU-904H treatment improved the condition of the lymphedema-affected limbs of participants in the current trial, as assessed by a number of criteria. The mean affected limb volume demonstrated a trend toward reduction over time after 2 cycles of LLLT, and was significantly better than placebo or 1 cycle of treatment, but it did not quite reach statistical significance at 3 months compared with baseline. However, comparisons against pretreatment baseline values are less valid than those against the placebo group, because lymphedema is a condition that will significantly worsen over time if left untreated, with increases in limb volume and/or tissue hardening.¹⁷ Szuba et al.¹⁸ recently described the progression of lymphedema in a group of patients who received decongestive lymphatic therapy followed by maintenance treatment (daily self-massage and com-

pression garments); this is a reasonably aggressive and standard current practice in the treatment of lymphedema. The patients had a mean increase in limb volume of 32.7 mL 1 month after decongestive lymphatic therapy, and a further increase of 35 mL at 6 months. Thus, over a 6-month period, patients treated with reasonably aggressive management demonstrated increases in their limb volume of approximately 65–70 mL compared with a mean decrease of 82 mL in the group receiving 2 cycles of LLLT in the current study. More noteworthy was the clinically robust reduction in limb volume of ≥ 200 mL reported at 3 months of follow-up in 31% of participants receiving 2 cycles of LLLT compared to 3.8% in the placebo group, because this statistic better reflects the results for individuals rather than for the groups as a whole. This finding was corroborated by similarly sustained reductions in ECF in the affected arm and torso region, and improvements in dermal tissue "hardness". Although no one parameter measured is definitive of successful treatment of lymphedema, taken together they suggest that repeated LTU-904H treatment is a promising approach to the management of this condition in approximately one-third of patients.

Subjective assessment of symptoms, activities of daily living, and quality of life were improved in all the groups in the current study, including the placebo group. The improvements were modest and variable, and most likely represent a statistical regression to the mean rather than any significant effect. The quality of life index in the group receiving two cycles of treatment demonstrated a significant trend toward improvement, but the use of subjective parameters as reliable outcome measures must be treated with caution. The effect of treatment on lymphedema patients' sense of well-being and perception of symptoms needs to be rigorously assessed; to our knowledge, the current study is the first report of placebo-controlled assessment of subjective parameters in the treatment of lymphedema, and we are studying this phenomenon further.

To our knowledge, the current trial is one of only two published reports on the use of LLLT in the treatment of lymphedema. The sample size in the current trial is modest, but the trial's strength is its robust design to test a novel concept; to our knowledge this is the first report of a placebo-controlled trial of any form of treatment for lymphedema, let alone a cost-effective, easy-to-use treatment that may have long-term effects. The first reported use of laser in lymphedema involved an expensive scanning laser in a clinical setting with each of a number of treatments lasting for a period of up to one hour.⁵ The LTU-904H costs < \$US5000, and can be operated by the patient

at home with ease for short periods (< 20 minutes) a few days a week, or as a minor addition to a clinical consultation. Further work is required to confirm and extend the finding of the current study and to optimize the treatment regimen; parameters such as site, duration, repeatability, and characteristics of the laser application need to be investigated further. In addition, it is important to determine the duration of effect after treatment. In 7 lymphedema patients, the beneficial effect of LLLT in reducing limb volume was sustained for up to 2.5 years, although bioimpedance measurements of ECF and subjective assessments of symptoms had returned to pretreatment levels.⁵ Whether additional laser treatments would have enhanced the effect was not addressed. An investigation of the longer-term effects, and alternative regimens, of LLLT on a larger population is warranted, but the potential for a long-term effect of laser therapy is intriguing.

Possible hypotheses for the beneficial effect of LTU-904H treatment include:

- Restoration of lymphatic drainage through the axillary region, due to stimulation of new lymphatic pathways. We currently have no data regarding this.
- Restoration of drainage through reduction of fibrosis and scarring of tissues in the axillary region. There was evidence of tissue softening after treatment with LTU-904H.
- Systemic effects of LLLT, because the response of the limb occurs despite the laser being applied to tissue that is upstream of the lymphedematous arm. In addition, there also appeared to be sustained changes in the ECF volume in the upper torso and the unaffected limb. To our knowledge, the reasons for this are not clear, but the observation is consistent with similar findings in a previous study of the use of a scanning laser for the treatment of lymphedematous limbs.⁵ It also is consistent with the reported need to clear fluid from truncal lymphatic territories prior to successfully clearing limb edema fluid during manual lymphatic drainage for lymphedema.^{3,4}
- Reduction in tissue fluid accumulation through changes in blood flow, either directly via an effect of blood vessels or by neural or humoral regulation of vessels in the limb. We currently have no data concerning this.

Further improvements in the use of LLLT, in the treatment of a range of conditions rest on a better understanding of its mode of action. The mechanism (s) of action of LLLT in tissues remains elusive, and most likely is complex, involving many aspects of tissue physiology. Furthermore, it is likely dependent on

the wavelength, pulse duration and frequency, dose and dose rate, duration of treatment, and repetition of the LLLT applied. At the molecular level, there are suggestions that LLLT affects cells by interacting with cytochromes of the mitochondrial electron transport chain,¹⁹ and/or may produce local gradients in energy because of laser speckle, resulting in local gradients in cellular heating.²⁰ At the cellular level, LLLT is reported to stimulate mitogenic activity, adhesion, synthetic activity, and viability of fibroblasts,^{7,21-24} although this may be true only for systems that are operating under physiologic stress or in pathologic conditions.²⁵ Macrophages were stimulated by LLLT to produce factors that increased or decreased fibroblast proliferation, depending on the wavelength of laser used.¹⁰ LLLT stimulated lymphocytes to proliferate and to become activated, both in vitro and in vivo,^{11,26,27} although again this may be true only in pathologic settings, in which LLLT "primes" lymphocytes to be more responsive to natural stimulatory products induced by pathophysiologic conditions.²⁸ All these cell types may be compromised in lymphedema, and may respond to LLLT sufficiently to play a role in resolution of the lymphedema.

At the microcirculatory level, there may be stimulatory/protective effects of LLLT on endothelial cells and vascular endothelium in situ.²⁹ This may involve angiogenic factor production by T-lymphocytes (associated with endothelial cell proliferation³⁰ or increased vascular endothelial growth factor (VEGF) production by smooth muscle cells or fibroblasts.³¹ Use of LLLT is reported to enhance endothelial regeneration after damage in animal models,^{32,33} and in humans after coronary arterial stent implantation.³⁴ We have not found any reports of LLLT affecting lymphangiogenesis, but it appears reasonable to propose that lymphatic vessels may respond similarly to blood vessels because members of the VEGF family, VEGF-C and VEGF-D, stimulate lymphangiogenesis.³⁵ There are reports of stimulation of local fluid circulation,²⁰ and stimulatory effects on lymphatic vessels,⁹ perhaps in response to increased fluid mobility in laser-irradiated tissues. There does not appear to be a consistent effect of LLLT on *normal* mesenteric lymphatic vessel contractility when it is applied directly to the vessels alone either in vivo³⁶ or in isolated lymphatic preparations (unpublished data).

Considerably more work needs to be done to better understand the mechanism of action and improve the efficacy of LLLT in a range of applications, but the results of the current study demonstrate that laser treatment for lymphedema may have some clinical benefit. In the current study, two cycles of axillary LLLT treatment (LTU-904H) were found to be effective

in reducing whole arm volume, ECF, and dermal tissue hardness in patients with PML in 31% of participants 3 months after treatment.

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