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Acupuncture for breast cancer-related lymphedema: a randomized controlled trial

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Abstract

Purpose—Approximately 20% of breast cancer survivors develop breast cancer-related lymphedema (BCRL), and current therapies are limited. We compared acupuncture (AC) to usual care wait-list control (WL) for treatment of persistent BCRL.

Methods—Women with moderate BCRL lasting greater than six months were randomized to AC or WL. AC included twice weekly manual acupuncture over six weeks. We evaluated the difference in circumference and bioimpedance between affected and unaffected arms. Responders were defined as having a decrease in arm circumference difference greater than 30% from baseline. We used analysis of covariance for circumference and bioimpedance measurements and Fisher's exact to determine the proportion of responders.

Results—Among 82 patients, 73 (89%) were evaluable for the primary endpoint (36 in AC, 37 in WL). 79 (96%) patients received lymphedema treatment before enrolling in our study; 67 (82%) underwent ongoing treatment during the trial. We found no significant difference between groups for arm circumference difference (0.38 cm greater reduction in AC vs. WL, 95% CI – 0.12 to 0.89, $p = 0.14$) or bioimpedance difference (1.06 greater reduction in AC vs. WL, 95% CI – 5.72 to 7.85, $p = 0.8$). There was also no difference in the proportion of responders: 17% AC versus 11% WL (6% difference, 95% CI – 10 to 22%, $p = 0.5$). No severe adverse events were reported.

Conclusions—Our acupuncture protocol appeared to be safe and well tolerated. However, it did not significantly reduce BCRL in pretreated patients receiving concurrent lymphedema treatment. This regimen does not improve upon conventional lymphedema treatment for breast cancer survivors with persistent BCRL.

Keywords

Breast cancer; Lymphedema; Acupuncture; Breast cancer-related lymphedema; BCRL

Introduction

Breast cancer-related upper arm lymphedema (BCRL) is a frequent and devastating complication after surgery. Lymphedema is caused by interruption of the lymphatic drainage system after axillary lymph node dissection or sentinel lymph node biopsy, resulting in local

accumulation of excess lymphatic fluid in the upper arm, forearm, and hand [1]. This leads to symptoms of heaviness, skin thickening, arm swelling, and decreased range of motion. These symptoms can have a significant negative impact on daily functions and fine motor skills, causing limitations in daily activities, and leading to distress, anxiety, and depression [2–6]. A recent meta-analysis suggests that the average incidence of arm lymphedema after breast cancer treatment is about 21% among breast cancer survivors [7]. The incidence continues to increase for at least 2 years after initial diagnosis or surgery. The risk factors for lymphedema are axillary dissection, radiation therapy, chemotherapy, postoperative seroma or infection, a BMI of ≥ 30 , and older age [8–14].

The severity of lymphedema is often determined using arm circumference measurements and related symptoms are assessed by patient-reported outcomes [15]. Notably, even patients with mild lymphedema can experience many symptoms. The optimal treatment for lymphedema remains unclear. Currently, the standard care is complex decongestive therapy (CDT), which includes manual lymphatic drainage (MLD), bandaging, skin care, exercise, and use of a compression sleeve [16]. The efficacy of CDT is highly variable based on different studies [17–21]. It has been reported that the combination of MLD and compression bandaging is probably the most effective maneuver, with up to 38% excess volume reduction based on two randomized controlled trials [22, 23]. However, these maneuvers have limitations [24]. MLD requires regular and frequent intense physical therapy and results are highly dependent on the physical therapist's level of experience. Furthermore, treatment must be repeated once lymphedema recurs. Bandaging requires wearing tight uncomfortable elastic wraps. The efficacy of skin care, exercise, and compression sleeves is largely dependent on the patient's compliance. Additionally, CDT is less effective in moderate to severe BCRL [17]. Other treatments such as laser vacuum may be effective in certain patients, but can be quite costly. Surgery is reserved for patients with severe lymphedema for whom standard therapy has failed. Therefore, additional treatments for BCRL are needed.

Acupuncture is a component of traditional Chinese medicine in which practitioners use thin metal needles to stimulate specific points on the body to relieve pain and other symptoms. Increasing evidence demonstrates that acupuncture is safe and effective in treating many cancer and cancer treatment-related symptoms such as chronic pain, hot flashes, fatigue, neuropathy, nausea and vomiting, xerostomia, and dysphagia [25–27]. It has been suggested that acupuncture stimulates the body to drain “dampness,” a traditional Chinese medicine concept similar to edema. Early clinical trials have demonstrated that acupuncture can reduce lymphedema and associated symptoms [28–30]. Our published pilot study of acupuncture for the treatment of upper limb lymphedema after breast cancer treatment showed that 11 of 33 patients demonstrated a more than 30% reduction in arm circumference difference between the affected and unaffected arm after completing a course of acupuncture treatment [31]. The mean reduction in arm circumference difference was 0.90 cm (95% CI 0.72–1.07; $p < 0.0005$). There were no infections or other serious adverse events reported. Based on this evidence, we performed a randomized, waitlist controlled clinical trial using the same acupuncture protocol to evaluate the potential effectiveness of acupuncture to treat lymphedema.

Methods and materials

Following Memorial Sloan Kettering Cancer Center (MSK) Institutional Review Board (IRB) approval, we conducted a randomized prospective wait-list controlled clinical trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01706081) identifier NCT01706081) to test the hypothesis that acupuncture is a safe and effective treatment for BCRL. Inclusion criteria were women age 18 or older with lymphedema as a result of surgery, chemotherapy, and/or radiation for breast cancer; lymphedema diagnosed as stage II or higher using International Society of Lymphology (ISL) criteria within at least 6 months and no more than 5 years of developing lymphedema; and affected arm circumference > 2 cm larger than the unaffected arm in at least one of two sites. Women with bilateral lymphedema; prior acupuncture treatment; concurrent diuretic use; history of primary lymphedema, pregnancy; or history of an implanted electronically charged medical device were ineligible. Patients receiving other lymphedema treatments were allowed to continued treatment throughout the trial. We identified and enrolled patients in the study following informed consent. All patients were monitored for side effects at each visit. All adverse events were reported according to the standard procedures.

Randomization

Randomization was conducted using MSK's secure Clinical Research Database system, which ensures full allocation concealment. Patients were randomized in a 1:1 ratio to the acupuncture (AC) or wait-list control (WL) group and stratified by the extent of baseline lymphedema (≥ 5 cm difference vs. < 5 cm) using blocks of randomly permuted length.

Acupuncture treatment technique

Certified licensed MSK staff acupuncturists with more than 5 years of experience delivered all acupuncture treatments. We adapted the acupuncture procedure and points used from our pilot study, which has been described previously [31]. Briefly, acupuncturists delivered manual acupuncture at CV12 and CV3, and at bilateral TE14, LI15, LU5, LI4, ST36, and SP6 points. Five acupuncturists with 9–14 years of experiences provided acupuncture treatments using 32–36 gauge, 30- to 40-mm length Serin needles. De-qi sensation was achieved at certain acupoints such as LI4 and ST36. Participants received acupuncture treatments twice a week for six consecutive weeks. Each treatment lasted 30 min. Patients randomized to the acupuncture group were treated for the first 6 weeks of the study. Patients randomized to the wait-list control group waited approximately 6 weeks from baseline and then crossed over to receive acupuncture treatment. Patients continued their standard lymphedema treatments such as exercise and compression garments if they were using them prior to enrolling in the study. No off-study acupuncture treatments were allowed.

Outcomes assessment

Pretreatment and treatment evaluation included lymphedema staging, arm circumference measurement, and bioimpedance measurement. For patients in the acupuncture treatment group, we performed lymphedema assessments after 6 weeks of acupuncture treatment and 3 months after the conclusion of treatment. For patients in the wait-list control group, we performed lymphedema assessments after 6 weeks (before the onset of acupuncture

treatment), following 6 weeks of acupuncture treatment, and 3 months after the conclusion of treatment. The research staff was not blinded to treatment group.

Lymphedema staging was based on the International Society of Lymphology (ISL) staging system and performed by a Certified Lymphedema Therapist (CLT). Arm circumference measurements were performed by trained research staff 10 cm above and 5 cm below the olecranon process using non-stretch tape. They were used to determine the extent of lymphedema at each time point. We measured bioimpedance using the Impedimed L-Dex U400, which measures the rate of electrical current transmission through tissues and estimates fluid content in a lymphedematous limb compared with the normal limb. Bioimpedance was an excellent method for confirming our objective findings because it has high inter- and intra-rater reliability, is highly sensitive and specific for lymphedema (100 and 98%, respectively), and is highly correlated with circumference measurements [32]. We defined the extent of lymphedema as the greatest difference between the circumference of the affected and unaffected arm, at either the forearm or the upper arm. The extent of lymphedema post-treatment and at the 3-month follow-up time point was measured at the same site determined at baseline.

Statistical methods

Our primary aim was to establish the difference in the extent of lymphedema between patients receiving acupuncture and patients receiving no treatment. The difference in the extent of lymphedema between groups was assessed with an analysis of covariance (ANCOVA) model, with the extent of lymphedema after 6 weeks as the outcome and the treatment group and baseline extent of lymphedema as covariates.

We used ANCOVA models to assess differences between treatment groups for bioimpedance. The six-week score was the outcome; we included the treatment group and baseline score as covariates. To assess how the effects of acupuncture on lymphedema changed after the cessation of acupuncture, we calculated a difference in the extent of lymphedema and 95% confidence interval (CI) after 6 weeks of treatment and 3 months after the cessation of acupuncture. This analysis included data from patients randomized to acupuncture and patients who crossed over after the initial waiting period. To determine whether time since diagnosis affected response to acupuncture, we entered chronicity and an interaction between chronicity and treatment group into the ANCOVA models for both arm difference and bioimpedance. All analyses were performed using Stata 13 (StataCorp, College Station, TX).

Sample size

Based on our pilot study, we expected the baseline mean extent of lymphedema (defined as the largest difference, measured at two sites, between affected arm and non-affected arm circumference) to be 4 cm. In the sample size calculation, we assumed the baseline lymphedema extent to be 3.6 cm due to regression to the mean. In the pilot study, the observed correlation between the extent of lymphedema at baseline and after 6 weeks of acupuncture was approximately 0.95 cm [31]. The standard deviation was 2.1 cm. Using bootstrap methods, we estimated the 75th percentile of the standard deviation to be 2.23 cm.

To be conservative, we used this inflated standard deviation in the sample size calculation. To detect a minimally clinically significant difference of 0.5 cm in the extent of lymphedema, we determined that a trial with 90% power and an alpha of 5% would require 41 patients per treatment arm.

Results

A total of 82 eligible patients were enrolled and participated in the study, with 40 patients in the acupuncture group and 42 patients in the wait-list control group (Fig. 1). We recruited patients between January 2013 and June 2016, and completed follow-up in December 2016. The majority of patients completed all 12 acupuncture treatments: 30 of 40 (75%) in the AC group and 27 of 42 (64%) in the wait-list group after crossover. Patient characteristics for both groups are presented in Table 1. The majority of patients in both groups had undergone mastectomy and axillary lymph node dissection and had a history of prior lymphedema treatment. There was no evidence of a difference in the use of concurrent lymphedema therapy between groups (85% in AC and 79% in WL, $p = 0.6$). The median duration of lymphedema was 2.5 years in AC (quartiles 1.4, 3.4) and 2.2 years in WL (quartiles 1.3, 3.0). See Table 2 for measurements of lymphedema before and after treatment.

The reduction in the extent of lymphedema was not statistically greater in the AC group than the WL control, either as measured by the difference in arm circumference (0.38 cm greater reduction in AC group, 95% CI – 0.12, 0.89, $p = 0.14$) or bioimpedance (1.06 greater reduction in AC group, 95% CI – 5.72, 7.85, $p = 0.8$) after controlling for baseline measurements. There was also no difference in the proportion of patients in each group who were considered responders (a decrease in arm difference of greater than 30% from baseline), with $N = 6$ (17%) in AC and $N = 4$ (11%) in WL difference of $N = 2$ (6%, 95% CI – 10%, 22%, $p = 0.5$).

Among all patients who received acupuncture treatment, including wait-list patients after crossover, we assessed whether acupuncture had a sustained effect on lymphedema over the 3 months post-treatment. We found that the reduction in difference between arm measurements lessened from immediately post-treatment to 3 months post-treatment, suggesting an increase of close to 10% in the size of the affected arm relative to the unaffected arm (mean difference 0.31 cm, 95% CI 0.02, 0.60, $p = 0.039$). Therefore, we did not find evidence that the effects of acupuncture, if any, persisted.

We also found no evidence that the prior duration of lymphedema modified the effect of acupuncture on lymphedema based on either arm measurements ($p = 0.8$) or bioimpedance measurements ($p = 0.4$). An interaction analysis to determine whether the severity of lymphedema (baseline arm difference) modified the effect of acupuncture demonstrated no evidence that the effect of acupuncture on arm circumference at week 6 differed based on baseline severity ($p = 0.8$).

We have summarized adverse events (AE) reported during the study in Table 3. No adverse events were reported in the wait-list group at week 6 and no severe adverse events were reported in either arm throughout the course of study. Adverse events were well balanced

between the acupuncture group and the wait-list group that crossed over to acupuncture for weeks 6–12. Grade 1 treatment-related AEs such as bruising (58%), hematoma (2%), and pain (2%) were reported in patients who received acupuncture. Among the 837 acupuncture treatments provided, one possibly related grade 2 skin infection was reported.

Discussion

In this phase IIB randomized controlled trial, we found no statistically significant difference in either arm circumferences or bioimpedance in patients with moderate to severe BCRL who had received 12 sessions of acupuncture over 6 weeks when compared with the wait-list control group.

When compared with baseline, the acupuncture group had a 0.45 cm reduction in the difference in arm circumferences (a decrease from 4.74 to 4.29 cm), as compared to WL control, which was a 0.06 cm reduction (a change from 4.82 to 4.76 cm). The difference in reductions was 0.38 cm (95% CI, -0.12 to 0.89 ; $p = 0.14$). The extent of lymphedema reduction is less than what we observed in our pilot study in which the mean reduction in arm circumference difference was 0.90 cm (95% CI 0.72–1.07; $p < 0.0005$) among 33 patients with concurrent usual lymphedema care [31]. The clinical significance of this degree of lymphedema reduction remains unknown. But because associated symptoms might improve with even modest lymphedema reduction, this finding may be clinically relevant.

There are several possible reasons that we observed less reduction in lymphedema in our current randomized control trial when compared with our pilot single arm study, despite the fact that patient demographics and characteristics (including age, BMI, type of breast and axillary surgery, acupuncture treatment points selection, and schedule) were similar between these two studies. Importantly, both studies allowed concurrent usual lymphedema care. The pilot study accrued patients from November 2009 to May 2011, whereas our current randomized controlled trial recruited patients from January 2013 to June 2016. Over the past decade, there has been an increase in both awareness of breast cancer lymphedema and referral to physical therapy treatment. Therefore, it is conceivable that if our current study captured a group of patients undergoing more effective treatment, the benefit of acupuncture would be more difficult to discern. In the current study, 97% of the patients in the acupuncture arm had a history of prior lymphedema treatment as compared to 88% of patients in the pilot study. Most patients (85% in the AC arm and 79% in the WL arm) used concurrent lymphedema treatments such as massage, garments, wrap, exercise, or pump/pneumatic compression. Similarly, in the pilot study, such concurrent treatments were used by 89% of patients.

It is challenging to compare the effects between our study and prior published work because of differences in study design and specific types of acupuncture treatment. So far, five clinical trials have evaluated the effects of acupuncture on treating patients with BCRL and we have summarized these studies and ours in Table 4. Alem et al. reported a case series study of 29 women who had BCRL post-surgery and underwent acupuncture once per week for 24 weeks. They experienced significantly improved symptoms associated with their

lymphedema and the study team reported statistically significant differences in arm circumference [28]. A small randomized controlled trial compared 12 acupuncture treatments in 8 weeks to usual care in 20 patients with BCRL. Usual care—but no CDT—was allowed. The results showed that acupuncture was safe and no severe adverse events were reported. Although lymphedema symptoms did not worsen, no reduction in arm circumference was observed [33]. A single arm pilot study ($n = 9$) by Jeong et al. from Korea showed that *Saam* acupuncture (a traditional Korean acupuncture method) was safe and reduced symptoms and severity of lymphedema ($p < 0.001$); in addition, acupuncture did not aggravate the lymphedema [34]. In a recently published randomized controlled trial from China, 30 patients were randomized to either warm acupuncture four times a day for 30 days or 900 mg of diosmin taken orally three times daily. Warm acupuncture uses moxibustion, a traditional Chinese medicine method in which the acupuncturist heats acupuncture needles with a burning mugwort stick during treatment. Diosmin is a flavonoid analog that may improve limb edema. The results demonstrated that warm acupuncture was safe and led to significant reductions in lymphedema compared with the diosmin group (51.5% vs. 26.3% measured by index of effectiveness, which is the ratio between difference in upper arm circumference after lymphedema treatment and the difference in upper arm circumference between affected upper arm and unaffected upper arm, respectively, $p < 0.00001$) [35]. Therefore, acupuncture utilizing moxibustion may be more effective in treating lymphedema. Future studies may need to determine the optimal way to stimulate acupuncture points—via heat (moxibustion) or electricity (electro-acupuncture)—to improve the potential therapeutic effects of acupuncture. In addition, the timing of the intervention may be important. Patients treated earlier in the course of their BCRL may have more opportunity to prevent worsening of lymphedema than those with persistent BCRL.

Our study is limited in that almost all of our patients had received prior lymphedema treatment, and acupuncture was offered concurrently with other ongoing lymphedema treatments, which makes it difficult to discern the effect of acupuncture alone on BCRL. In addition, because we did not include other patient-reported outcomes, we were not able to demonstrate whether acupuncture alleviated the symptoms associated with lymphedema such as pain, limited range of motion of the affected arm, distress, and anxiety. These outcomes should be included in future studies.

This study has a number of strengths. To the best of our knowledge, to date, it is the largest prospective randomized wait-list controlled trial to determine acupuncture's effectiveness in treating patients with moderate to severe BCRL. Ours is the only acupuncture study to use bioimpedance as an objective measurement of lymphedema. It is one of two studies to allow acupuncture needles to be directly applied to the lymphedema site, and our results suggest that it is safe and feasible to include the affected lymphedema limb in acupuncture treatments.

BCRL remains a challenging complication for breast cancer survivors and current treatments are suboptimal. Acupuncture is safe with minimal adverse effects. However, based on this and other existing evidence, our acupuncture-based protocol should not be recommended to breast cancer survivors with heavily pretreated moderate to severe BCRL outside of clinical trials.

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Fig. 1.
Study design

Table 1

Patient characteristics

	Acupuncture (N = 40)	Wait-list (N = 42)
Age (years)	65 (54, 71)	58 (49, 70)
Breast cancer status		
Non-metastatic	33 (83%)	39 (93%)
Metastatic	7 (17%)	3 (7%)
Type of breast cancer surgery		
Lumpectomy	10 (25%)	11 (26%)
Mastectomy	30 (75%)	31 (74%)
Type of axillary surgery		
Sentinel lymph node biopsy	2 (5%)	0 (0%)
Axillary lymph node dissection	37 (93%)	42 (100%)
Unknown	1 (2%)	0 (0%)
Lymphedema stage		
2A	3 (8%)	4 (10%)
2B	23 (57%)	16 (38%)
2, unknown substage	14 (35%)	22 (52%)
Baseline lymphedema extent measured by arm difference		
5 cm	14 (35%)	17 (40%)
< 5 cm	26 (65%)	25 (60%)
Number of acupuncture treatments attended (N = 77)	12.0 (11.5, 12.0)	12.0 (11.0, 12.0)
Affected arm		
Left	22 (55%)	20 (48%)
Right	18 (45%)	22 (52%)
Time since lymphedema diagnosis in years	2.5 (1.4, 3.4)	2.2 (1.3, 3.0)
Prior lymphedema treatment at baseline	39 (98%)	40 (95%)
Concurrent lymphedema treatment	34 (85%)	33 (79%)
Intensive massage	3 (8%)	1 (2%)
Daytime garments	33 (83%)	31 (74%)
Nighttime garments	15 (38%)	14 (33%)
Bandage/wrap	10 (25%)	11 (26%)
Self massage/lymphatic drainage	24 (60%)	22 (52%)
Exercises	17 (43%)	15 (36%)
Pump/pneumatic compression	5 (13%)	4 (10%)
Other, home therapy	2 (5%)	1 (2.4%)

Data are presented as frequency (%) or median (quartiles)

Table 2

Extent of lymphedema before and after treatment in acupuncture (AC) and wait-list (WL) groups

	<u>Acupuncture (N = 36)</u>		<u>Wait-list (N = 37)</u>		Adjusted difference between AC and WL groups at week 6 (95% confidence interval)	p value
	Baseline	Week 6	Baseline	Week 6		
Difference in arm circumference (cm)	4.74 (2.23)	4.29 (2.67)	4.82 (2.32)	4.76 (2.68)	– 0.38 (– 0.89, 0.12)	0.14
	<u>Acupuncture (N = 34)</u>		<u>Wait-list (N = 35)</u>		Difference with 95% confidence interval	p value
	Baseline	Week 6	Baseline	Week 6		
Bioimpedance	38.6 (30.4)	35.9 (27.4)	42.2 (32.2)	40.3 (35.6)	– 1.06 (– 7.85, 5.72)	0.8

Extent of lymphedema assessed using difference in arm circumference between affected and unaffected arms and bioimpedance measurements. The unadjusted mean (SD) is reported at baseline and week 6 for both acupuncture and wait-list groups. The adjusted mean difference (95% CI) for extent of lymphedema is presented as the difference in week 6 measurement (arm circumference difference or bioimpedance) between acupuncture and wait-list groups, adjusted for the baseline measurement. A negative difference in arm circumference between groups indicates a greater reduction in arm circumference among acupuncture patients. A negative difference in bioimpedance between groups indicates a greater reduction in lymphedema in the acupuncture groups

Table 3

Adverse events among all patients who received at least one acupuncture treatment ($N = 77$)

	Number of events (%)
Bruises	45 (58)
Hematoma	2 (2.6)
Pain	2 (2.6)
Skin infection	1 (1.3)

Summary and comparison of current acupuncture studies in patients with BCRL

Table 4

Author year	Study design	Primary end-point	Sample size	Patient/demographics	Pre-existing lymphedema	Lymphedema measures	Control arm	Current therapy	Acupuncture frequency and duration	Acupuncture techniques	Safety	Lymphedema reduction	Lymphedema-associated symptoms
Alem [5]	Case series	Improvement of ROM	29	Brazil	2 cm arm circumference differences between two arms	Palpation and visual inspection	None	Not allowed	Weekly × 24 weeks	Manual acupuncture at CV12, CV3, CV2 and LI15, TE14, LU5, TE5, LI4, ST36, SP9 and SP6 on the unaffected side	Not reported	Yes $p = 0.016$	Improved ROM $p < 0.001$
Cassileth [30]	Single arm	Safety and tolerability	33	United States	2 cm arm circumference differences between two arms	Two-point arm circumference	None	CDT allowed	Twice weekly × 4 weeks	Manual acupuncture at CV12, CV3, and bilateral TE14, LI15, LU5, LI4, ST36, and SP6	Yes	Yes 35% had more than 30% reduction	Not reported
Smith [33]	Randomized controlled	Safety and feasibility	20	Australia	10 cm segment by bioimpedance	Bioimpedance	Yes	Usual care No CDT allowed	Twice weekly × 4 weeks then once weekly × 4 weeks	Manual acupuncture at CV12, CV3, CV2, LI15, TE4, LI15, and LI4 on unaffected side; bilateral ST36, SP9, and SP6	Yes	No difference	No difference
Jeong [34]	Single arm observational	Safety and feasibility	9	Korea	2 cm arm circumference differences between two arms	Visual Analog Scale	None	Emelon	Three times per week × 6 weeks	Individualized manual acupuncture based on 4 syndromes. No needles on the affected side.	Yes	Yes $p < 0.001$	Not aggravated
Yao [35]	Randomized controlled	Reduction of lymphedema	30	China	3 cm arm circumference differences between two arms	One-point arm circumference	Yes; Diosmin	Moxibustion	Three times per week × 30 days	Manual acupuncture at LI10, LI11, LI14, LI15, ST36, and SP6 on the affected side; Moxa applied at ST5, LI15, and ST14	Yes	Yes $p < 0.00001$	Improved ROM $p < 0.05$
Our study 2017	Randomized, wait-list-controlled	Reduction of lymphedema	82	United States	2 cm arm circumference differences between two arms	Two-point arm circumference	Yes; CDT	CDT allowed	Twice weekly × 6 weeks	Manual acupuncture at CV12, CV3 and bilateral TE14, LI15, LU5, LI4, ST36, and SP6	Yes	No difference, but trend favored acupuncture	Not reported