

Effect of Acupuncture on Lung Cancer-Related Fatigue: Study Protocol for a Multi-center Randomized Controlled Trial

Zhaoqin Wang

Yueyang Hospital of Integrated Traditional Chinese and Western Medicine

Shanshan Li

Shanghai Municipal Hospital of Traditional Chinese Medicine

Luyi Wu

Shanghai Research Institute of Acupuncture and Meridian, Shanghai University of Traditional Chinese Medicine

Qin Qi

Yueyang Hospital of Integrated Traditional Chinese and Western Medicine

Huirong Liu

Shanghai Research Institute of Acupuncture and Meridian, Shanghai University of Traditional Chinese Medicine

Xiaoming Jin

Stark Neurosciences Research Institute, Indiana University School of Medicine

Jianhui Tian

Longhua Hospital, Shanghai University of Traditional Chinese Medicine

Ming Zhang

Shanghai Chest Hospital

Xiaopeng Ma

Shanghai Research Institute of Acupuncture and Meridian, Shanghai University of Traditional Chinese Medicine

Deli Sun

Longhua Hospital, Shanghai University of Traditional Chinese Medicine

Shifen Xu

Shanghai Municipal Hospital of Traditional Chinese Medicine

Huangan Wu (✉ wuhuangan@126.com)

Key Laboratory of Acupuncture and Immunological Effects, Shanghai University of Traditional Chinese Medicine

Study protocol

Keywords: Acupuncture; Lung cancer; Cancer-Related Fatigue; RCT; multi-center randomized controlled trial

Posted Date: October 12th, 2019

DOI: <https://doi.org/10.21203/rs.2.10295/v2>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published on November 9th, 2019. See the published version at <https://doi.org/10.1186/s13063-019-3701-0>.

Abstract

Background Fatigue is one of the primary symptoms of lung cancer patients, with a prevalence of 88.0% in cancer survivors, and even higher post resection surgery. Effective fatigue control after lung cancer surgery is important for patient recovery and quality of life. Some studies have shown that acupuncture might be effective in treating cancer-related fatigue, however, randomized controlled trials of suitable sample size are limited. **Method/Design** This is a multi-center, patient-blind, randomized controlled trial (RCT). A total of 320 eligible patients will be recruited in four centers (Shanghai Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai Chest Hospital and LongHua Hospital Shanghai University of Traditional Chinese Medicine) and randomly assigned to either the acupuncture group or the sham acupuncture group in a 1:1 ratio. Treatment will be given twice per week for 12 sessions. Treatment will consist of acupoints GV20, GV29, CV12, CV6, CV4, and bilateral LI4, LR3, SP6, ST36. The primary outcome will be assessed using the Chinese version of Brief Fatigue Inventory-Chinese (BFI-C), the secondary outcomes will be measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), and Hamilton Rating Scale for Depression (HAMD). The primary outcome will be assessed at all main points (baseline, the 3rd week, the 6th week and follow-ups), the secondary outcomes will be assessed at baseline and the 6th week. Intention-to-treat (ITT) analysis will be used in this RCT. **Discussion** This trial protocol provides an example of clinical application for the management of lung cancer-related fatigue using acupuncture treatment. If the acupuncture treatment protocol confirms that acupuncture is an effective and safe option for lung cancer-related fatigue, it can be adopted as a standardized treatment.

Background

Cancer is a worldwide health epidemic with ever increasing morbidity and mortality rates. Partially driven by the modern lifestyle, cancer is currently the second leading cause of death worldwide [1-3]. Lung cancer ranks first in the incidence of malignant tumors in China; about 781,000 people suffer from lung cancer per year [4]. Cancer-Related Fatigue (CRF) is a common comorbidity of oncological disease which seriously affects the quality of life and mental health of patients. In 2000, the National Comprehensive Cancer Network (NCCN) guidelines note [5], CRF is characterized by feeling of fatigue and lack of energy that includes physical, emotional or cognitive fatigue. It is persistent and is not relieved through rest. It may be caused by cancer itself or cancer-related treatments, and is not proportional to activity [5, 6]. A study has shown that the prevalence of CRF is 88.0% in cancer survivor [7]. In lung cancer patients, their respiratory function decreases significantly after lung cancer resection, which can lead to worsening fatigue. Symptomatic treatment may be helpful for lung cancer-related fatigue, such as regulating immunity, anti-depression, nutritional support, improving sleep and exercise. Yet there are few effective therapies available for treating CRF. Therefore, finding effective and no side-effect treatment is imperative.

Acupuncture therapy has been successfully used to treat many various diseases for thousands of years. In fact, some research on acupuncture for lung CRF has revealed its advantages [8-10], include relieving symptoms, improving patient quality of life and delaying the progression of cancer. However, most of these studies are low value because of some flawed methodology, such as improper treatment times, sample size and lack of blinding. The deficit of objectivity makes the findings of those reports unreliable.

Faced with the limitations of current research, high quality evidence is needed to confirm the effectiveness and safety of acupuncture for lung cancer related fatigue. Therefore, through this proposed multi-center randomized controlled trial (RCT), we aim to obtain evidence for the use of acupuncture in treatment of lung CRF. The findings of this trial will provide useful information, it will be shared through publication and form an optimal acupuncture treatment protocol for lung CRF.

Hypotheses:

This trial aims to prove that acupuncture is an effective intervention that can relieve fatigue and improve the life quality of lung cancer patients after lung cancer resection surgery.

Objectives:

1. To assess whether acupuncture is cost-effective in improving the Brief Fatigue Inventory-Chinese (BFI-C) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), when compared with sham acupuncture.
2. To compare the differences in improvement of mood, measured by the Hamilton Rating Scale for Depression (HAMD), between the intervention group and control group.
3. To determine the influence of acupuncture credibility on acupuncture treatment, assessed by the Credibility of Treatment Rating Scale (CTRS).

Methods/design

Study Design:

We proposed this study is a multi-center, randomized, sham-controlled, patient and assessor blind trial. The trial will be commenced in 4 centers, after ethical approval has been obtained from the Institutional Review Board. The clinical trial is designed and reported following the Consolidated Standards of Reporting Trials[11] and Standards for Reporting Interventions in Clinical Trials of Acupuncture guidelines[12]. Eligible patients will be randomly divided into the acupuncture group and the sham acupuncture group in a 1:1 allocation ratio. All participants will sign the informed consent before proceeding with the trial. The flow chart of the study process is as follows in Fig.1.

Sample size:

The sample size calculation was based on the change of BFI-C scores. According to previous studies[13], we assume the change is -2.35 in acupuncture group, while -2.0 in sham-acupuncture group; therefore, the mean difference between two group is 0.35 with standard deviations of 1.03 and 1, a sample size of 133 per group can provide 80% power to reject the null hypothesis with a significance level of 0.05 using a 2-sided, 2-sample, unequal-variance t test. Considering the dropout rate of 20%, a total of 320 participants should be recruited for this trial.

Recruitment:

This multi-center, randomized, sham-controlled, patient and assessor blind trial will be conducted in the Shanghai Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai Chest Hospital and LongHua Hospital Shanghai University of Traditional Chinese Medicine. Participants of the study will be recruited through the outpatient clinic or inpatient, hospital-based Wechat advertising, and posters in the hospital. Any interested patients will be screened either via telephone or on-site and consented for the study. After being informed of the details of this RCT, participants will be asked to sign the informed consent, and deliver it to an independent research assistant. Patients will be randomly divided into two groups: acupuncture group (n=160) and sham acupuncture group (n=160). All participants will undergo six-week treatment of acupuncture (or sham-acupuncture) and a series of assessments on CRF free of charge. Timing of treatment assessments and data collection are as follows in Table 1.

Inclusion Criteria: Participants with the following conditions will be included:

- (1) Participants in line with Interpretation of Chinese lung cancer treatment guidelines (2015 edition) for the diagnosis of lung cancer[14];
- (2) Participants who have imaging evidence that supports Lung adenocarcinoma diagnosis;
- (3) Participants whose resection surgery took place within the last 3-6 months and did not receive chemotherapy;
- (4) Participants who meets the diagnostic criteria of CRF[15], and BFI-C score is higher than 4;
- (5) Participants aged 18-75 years old;
- (6) Participants whose KPS (Karnofsky Performance Status) score is higher than 80[16];

(7) Participants with the ability to understand the nature of the study and willing to give informed consent;

(8) Participants capable of providing responses during outcome measurement.

Exclusion Criteria: Participants with the following conditions will be excluded:

(1) Participants with comorbidities such as serious heart, kidney or liver disease;

(2) Participants who have severe mental disorders such as cognitive impairment;

(3) Participants with other physiological or pathological fatigue such as chronic fatigue syndrome (CFS);

(4) Participants who have received acupuncture within the past 6 months;

(5) Participants who are pregnant or currently lactating.

Randomization and Allocation concealment

Stratified block randomization will be used in this experiment. The randomization sequence will be generated by an independent statistician using SPSS 23.0. The participants who meet the criteria will be randomly assigned to 1 of the 2 groups in 1:1 ratio by computer-generated random sequences after completion of baseline assessment. Block randomization with a random block size ranging from 4-8 will be applied in each center. Randomization concealment is realized by opaque envelope method. The treatment allocation codes will not be revealed until the participants have finished all baseline assessments and before the first acupuncture treatment. In order to minimize breaks in coding, the principal investigator (PI) who designed the trial and research personnel who perform the outcome assessments will be blinded to the treatment assignment. Only the acupuncturists will know which participants belong to which groups.

Blinding:

Participants will be informed that they will be randomly assigned to either acupuncture treatment or acupuncture-like simulation treatment. Participants will be asked to wear an eye-patch when they receive treatment, the 2 groups will receive identical treatment except no skin penetration will be involved in the sham acupuncture group. Therefore, Participants and other researchers (the principal investigator, the data analysts, the outcome assessors and statistician) will be blinded to the group allocation. To ensure the successful implementation of the blinding method, all researchers will be trained before the trial begins.

Intervention protocol:

The acupuncture treatment will be conducted after all participants have given informed consent. All patients will receive 12 treatments, either acupuncture or sham acupuncture treatment twice times per week for 6 weeks. In each treatment session, every patient will be placed in a separate space and asked to wear an eye-patch. Each procedure will be 30 minutes and performed by a trained acupuncturist who will be a registered practitioner with more than 3 years of experience in clinical practice. The acupuncturist will confirm that the participant has undergone the assigned procedure. To improve patients' compliance, all patients will receive the intervention and assessments by telephone reservation.

The acupuncture procedure will be performed following the Guidance of Clinical Practice of Acupuncture^[17]. Before the treatment, all patients will be skin sterilization with alcohol wipes, then the experienced acupuncturists will begin to treat. In the treatment group, acupuncture needles will be standard stainless steel, sterile, and disposable (0.25 × 40 mm and 0.30×40mm in length; Jia Jian, China). The control group will use the Streitberger Placebo-needle at the same acupoints. Each session treatment will last for 30-min. The treatment methods of acupuncture and acupoints are shown in Table 2. Any concomitant care or intervention which has the effect of supplementing Qi (Traditional Chinese Medicine term) is not allowed to be use during the treatment and follow up period, including using some special herbs and exercising Qi-Gong et al.

The acupuncture group:

The acupuncture group will receive a real acupuncture treatment throughout the 6 weeks. According to our previous experience, Baihui (GV20), Yintang (GV29), Zhongwan (CV12), Qihai (CV6), Guanyuan (CV4), bilateral Hegu (LI4), bilateral Taichong (LR3), bilateral Sanyinjiao (SP6), bilateral Zusanli (ST36) will be used as the acupoints for treatment. Patients in the supine position, GV20, CV12, CV6, CV4 and LI4 (with the needle tip pointing towards the ground), CV29 and LR3 (with the needle tip pointing towards the feet), while SP6 and ST36 (with the needle tip pointing towards the limb extremities), all the points will be punctured perpendicularly to the respective depth 10-30mm. Manipulating manually (including lifting, thrusting, and rotating) until the patient reports needling sensations (Deqi sensation). The needles on the bilateral Zusanli (ST36) will be connected to an SDZ-III Electronic Acupuncture Treatment Instrument (Hwato, China), using continuous wave type stimulation, with a frequency of 2Hz, and intensity of 2~3 mA. Needles will be retained for 30 minutes.

The control group:

The control group will undergo treatment with a special sham acupuncture. We will use a non-invasive placebo control, the Streitberger Placebo-needle. Acupoints are the same as with acupuncture group, without insertion. Similarly, the electroacupuncture apparatus (SDZ-III Electronic Acupuncture Treatment Instrument) will be set beside the patients and connected to the bilateral Zusanli (ST36), without electrical pulse. This set up will remain in place for the next 30 minutes.

Outcome measures

We will assess the primary outcome at baseline, week 3, post-treatment (week 6), and with follow-ups at the 4th and 12th weeks after the end of treatment. Secondary outcomes will be assessed at baseline and week 6.

Primary outcome

Brief Fatigue Inventory-Chinese version (BFI-C):

The change of BFI-C scores will be used to evaluate the degree and impact of fatigue. The Brief Fatigue Inventory scale is designed by Mendoza[18] and translated by Wang[19], and it is comprised of 2 parts, (the first part consists of 1-3 items, the second part consists 4-9 items), questionnaire items 1-3 are used to assess the individual's overall fatigue level over the past 24 hours. The items 4-9 are designed to evaluate the effects of fatigue on general activities, emotions, walking ability, normal work (including work and housework), relationship with others and enjoyment of life. The scale uses the 10-point scoring method, 0 points means no fatigue, 10 points for the most severe fatigue. A higher score indicates more severe fatigue. According to the average score, it could be divided into 4 grades, that is no fatigue (score 0), mild fatigue (score 1-3), moderate fatigue (score 4-6), and severe fatigue (score 7-10). The BFI scale has been validated in different cancer patients all over the world[19-21], the structural validity is 0.81-0.92, and the Cronbach's coefficient of the total scale is 0.96. The Chinese version of BFI has been proven to have good reliability and validity[19]. The mean of the changed score in BFI-C at week 6 will be analyzed as a primary outcome.

Secondary outcomes:

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30):

EORTC QLQ-30 is a core scale for the determination of quality of life in all cancer patients by the European Organization for Research and Treatment (EO RTC)[22]. It includes a total of 30 entries, which are divided into 15 domains. Of those are 5 functional domains (body, role, cognition, mood and social function), 3 symptom domains (fatigue, pain, nausea and vomiting), 1 overall health status / quality of life area and 6 single entries (each as a domain). The higher the score for the functional domains and overall health status, the better the functional status and quality of life. The higher the score for the symptom domains, the worse the quality of life. The mean of any changed score at week 6 will be analyzed.

Hamilton Rating Scale for Depression (HAMD):

The HAMD developed in 1960[23, 24], is the questionnaire used to describe the severity of cognitive and bodily symptoms of depressive disorders.

Each item is rated in 3- or 5- point scales. According to the total score, the depression could be divided into 4 grades: normal (total score <7); may be depression (total score 7-17); depressed (total score 17-24); severe depression (total score >24). The higher the total score, the more significant the depression tendency. The mean of any changed score at week 6 will be analyzed.

Safety assessment:

Any adverse events occurring during the trial will be recorded by the patients and doctors. Any discomfort, symptoms or any other diseases will be assessed. All details of adverse events will be reported in the Case Report Form. The researcher will interview participants and write an adverse event report after treatment. The Data and Safety Monitoring Board and ethic review board will assess its correlation with the intervention, and make the final decision as to whether to continue the study or not. We will analyze the influence of all events at the end of the trial.

Credibility of Treatment Rating Scale (CTRS) □

The CTRS is a scale for assessing the credibility of the acupuncture treatments. It consists 4 items and is used to assess the participants as “perceived logic of the treatment,” “confidence in recommending the treatment to their friends who have similar complaints,” “confidence in the treatment to alleviate their complaint,” and “likelihood that the treatment would alleviate their other complaints.” A lower score indicates a greater confidence toward the received treatment [25, 26].

Blinding success assessment□

After the final treatment session, the success of blinding will be tested by asking the participants the following question “When you volunteered for the study, you were informed that you had an equal chance of receiving traditional acupuncture or acupuncture-like simulation treatment. Our study is finished now, which style acupuncture do you think you are received?” The participants will be provided with 3 choices: acupuncture treatment group, acupuncture-like simulation treatment group and uncertain group. If participants do not chose uncertain, we will ask the reason why they have made that assumption [27].

Quality control:

The Clinical Research Center of Drugs of Shanghai University of Traditional Chinese Medicine will response for the data monitoring team to control bias and identify problems in the project. In order to guarantee the quality of this study, every acupuncturist in this trial will be registered practitioners with 3-5 years of clinical experience in acupuncture practice. Meanwhile, a qualified clinical trial expert will monitor every trial center, and regular board meetings will be held to ensure the study process.

Monitoring:

According to the National Institutes of Health (NIH) to monitor the trial progress and review safety and quality of data, A Data and Safety Monitoring Board (DSMB) will be formed[28]. The committee consists of 3 members, including a senior acupuncturist, an oncologist and a statistician. The DSMB is independent of the proposed trial and all members will have to declare any conflict of interest in the trial. Regular meetings will be held during the trial, to ensure the data are collected scientifically and ethically. Moreover, DSMB could avoid participants exposure to by unnecessary risks, it has the right to unblinding if serious adverse events related to the intervention occur. The DSMB committee will provide data monitoring with access to any interim results and will make the final decision to terminate the trial if necessary. It also will identify problems in the project, if any, will make decisions to change the details of this protocol, apply for approval from ethics review board by written application, and announce the persons conducting the trial by written notice after approval is received from the ethics committee. Besides this, a qualified clinical trial expert will be invited to monitor this study, and the PI will take full responsibility and make any final decisions.

Clinical trial registration:

This RCT was registered in the Chinese Clinical Trial Registry (ChiCTR1900022831), Date: 2019-04-27.

URL: <http://www.chictr.org.cn/showproj.aspx?proj=37823>

Data management:

The participant will be interviewed at each time point, and further cancer care advice will be given at the interview. This procedure will promote retention and completion of follow-up assessments. All the original data will be collected by blinded assessors and double-entered into the Electronic Data Capture System (EDC). The system will be tested before it is officially launched to ensure that system meets the trial requirements. The original data recorded in case report forms will be entered within 1 week when the participants finished the all treatment and follow-ups. In case report forms, the codes and initials will be used instead of the participant's information to protect the participant's privacy. If the data is found to be uncertain, the data supervisor will notify the researcher to respond with a data question form. If necessary, the statistician will send a data question form to the researcher and the researcher's answer should be filled in the form. The question form is then returned to the statistician by the inspector.

Statistical analysis:

Statistical analysis of data will be carried out by SPSS 23.0 software. We will use multiple imputation to address any missing data. All data including the data from any participants who drop out of the RCT during the trial will be analyzed by Intention-to-Treat (ITT) analysis by an independent statistician who will be blinded to group allocation. Descriptive analyses will be done on baseline demographics. To compare changes in BFI-C between 2 groups as the primary analysis, a repeated measure ANOVA (General Linear Model) will be used. For the secondary outcomes, scores in QLQ-C30, HAMD and CTRS between the two groups will be compared with Student's t test or the Wilcoxon rank-sum test. All reported *P* values will be 2-sided, and a *P* value of less than 0.05 is considered statistically significant. The mean difference and confidence intervals at the 95% level will also be calculated using SPSS.

Discussion

Fatigue is a typical symptom common with lung cancer patients and can seriously affect a patient's quality life and emotional health [29, 30]. CRF is a common disease that occurs in different stages (after surgery, treatment with target therapy, et.al.) with oncological disease[29-31]. With the development of complementary and alternative medicine, more and more cancer patients tend to choose acupuncture as a main treatment method to treat fatigue. Recently, several studies have shown that acupuncture can effectively improve the symptom of CRF[32-36]. However, there is currently a lack of multi-center, large sample and sham-controlled, randomized clinical trials for CRF[29, 37]. In this study protocol, we designed a randomized, multi-center, sham-controlled, patient and assessor blind trial. If the protocol confirms that acupuncture is effective and safe, it can be implemented for relieving CRF and improving quality of life in lung cancer patients.

Because of the nature of acupuncture, there are many factors that can affect the clinical outcomes, including the individual differences, the needle insertion techniques and the times of the sessions. Our study protocol is based on textbooks, related literature reports, and our previous clinical experience. Traditional acupoints will be selected for treatment (GV20, GV29, CV12, CV6, CV4, and bilateral LI4, LR3, SP6, ST36). Another advantage is the same trained acupuncturists will be used to implement a standardized protocol for point selection and for the needle insertion, minimizing factors that might affect the clinical outcomes. The nature of acupuncture treatment made double blinding impossible, so our designed of sham acupuncture allowed blinding of the patient and assessor. Only the acupuncturist will know the treatment allocation, but they will know nothing about the results, and assessors are not clear of the treatment allocation before and after the evaluation treatment efficacy, avoiding any potential bias. Another innovation in this study protocol is the assessment of the influence of acupuncture credibility on acupuncture treatment by the CTRS.

However, this study protocol still faces several limitations and challenges. Firstly, the blinded method. Because of the nature of the clinical trials of acupuncture it is inevitable that the acupuncturist will know the treatment allocation. However, the acupuncturists will be blind to the results. In order to prevent the acupuncturist from accidentally revealing the group allocation, their interactions with the patients will be limited. All patients will be asked to wear an eye-patch and arranged in a separate space during treatments. Overall, both groups will receive string blinding to balance the efficacy between the 2 groups. Secondly, the application of the acupuncture method. Before the study begins, all acupuncturists will receive a standardized protocol for point selection and the needle insertion through several training sessions to ensure the acupuncture techniques. Thirdly, the challenge of compliance. To solve this problem, we will provide patients outreach over the Wechat or phone to arrange the

treatment time to improve the attendance of the patients. Following completion of the trial, researchers will conduct follow-ups by phone to collect data on patient's final outcomes.

Though there are many challenges, we will strive to standardize the steps of the trial and the quality of the trial will be monitored by the Data and Safety Monitoring Board (DSMB). We hope that this trial will provide strong-quality evidence on the efficacy and the safety of acupuncture for lung cancer-related fatigue (CRF). We expect that our findings will advance knowledge on effectiveness of acupuncture in usual for lung cancer patients who with CRF in China.

Trial status:

The first investigators' meeting took place on 18 November 2018. The protocol version 2.0 which revised on 15 April 2019 was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine. The RCT is in preparation now and will launch on 1 June 2019. Recruitment is expected to end in late 2021.

List Of Abbreviations

CRF: Cancer-Related Fatigue

NCCN: National Comprehensive Cancer Network

RCT: Randomized Controlled Trial

BFIC: Brief Fatigue Inventory-Chinese

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

HAMD: Hamilton Rating Scale for Depression

CTRS: Credibility of Treatment Rating Scale

KPS: Karnofsky Performance Status

CFS: Chronic Fatigue Syndrome

GV: Governor vessel

CN: Conception vessel

LI: Yangming Large Intestine Channel of Hand

LR: Liver channel of foot Jueyin

SP: Spleen meridian of foot Taiyin

ST: Stomach Channel of Foot-Yangming

EO RTC: European Organization for Research and Treatment

NIH: National Institutes of Health

DSMB: Data and Safety Monitoring Board

EDC: Electronic Data Capture System

ITT: Intention-to-Treat

ANOVA: General Linear Model

Declarations

Ethics approval and consent to participate:

This multi-center RCT was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine on 25 April 2019 (certificate number 2019-034). The purpose, procedures, and potential risks of the RCT will be explained clearly to the participants. All participants shall give their written informed consent to the research assistant before joining the RCT.

Statement:

Central ethical approval has been confirmed from the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine (ref approval no. 2019-034) and we will not begin recruiting at other centres in the trial until local ethical approval has been obtained. The final version identifier of this protocol is 2.0, which was modified on 15 April 2019.

Consent for publication:

Not applicable.

Availability of data and material:

The trial results will be published through publication in a peer-reviewed scientific paper and poster or oral presentations in conferences. All data and protocol will be available beginning 3 months and ending 3 years following publication of the results with researchers who provide a methodologically sound proposal to achieve aims in the approved proposal. The trial data will be available from the corresponding author upon reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

This work was supported by National Basic Research Program of China (973 Program) [grant number 2015CB554500]. The funding body has no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Authors' contributions:

The trial was designed and developed by HGW and SFX. The manuscript was prepared by ZQW, SSL and LYW. MZ, JHT, and SFX were responsible for the methodology and design of the intervention. QQ wrote the tables and figures. The protocol was carefully revised, edited by XPM and HRL, XMJ and DLS contributed the discussion. All authors read and approved the final manuscript.

Acknowledgements:

We would like to thank Dr. Philippa Hazlewood from the International Education College, Shanghai University of Traditional Chinese Medicine, for her language editorial support.

Publisher's note:

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A: **Global cancer statistics, 2012**. *CA Cancer J Clin* 2015, **65**(2):87-108.

2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J: **Cancer statistics in China, 2015**. *CA: A Cancer Journal for Clinicians* 2016, **66**(2):115-132.
3. Siegel RL, Miller KD, Jemal A: **Cancer statistics, 2018**. *CA: A Cancer Journal for Clinicians* 2018, **68**(1):7-30.
4. Chen W, Sun K, Zheng R, Zeng H, Zhang S, Xia C, Yang Z, Li H, Zou X, He J: **Cancer incidence and mortality in China, 2014**. *Chin J Cancer Res* 2018, **30**(1):1-12.
5. M. Berger A, Abernethy AP, Atkinson A, Barsevick AM, Breitbart WS, Cimprich B, Cleeland C, Eisenberger MA, Escalante CP, Jacobsen PB *et al*: **NCCN Clinical Practice Guidelines in Oncology on Cancer-Related Fatigue**. *Journal of the National Comprehensive Cancer Network* 2010, **8**.
6. Dodd M: **Cancer-Related Fatigue**. *Cancer Investigation* 2009, **18**(1):97-97.
7. Sha FEI, Zhuang S, Zhou LI, Zhang L, Yang Y, Zhang S, Jiang YI, Qiu G, Chen C, Zheng J *et al*: **Biomarkers for cancer-related fatigue and adverse reactions to chemotherapy in lung cancer patients**. *Molecular and Clinical Oncology* 2015, **3**(1):163-166.
8. Cheng C-s, Chen L-y, Ning Z-y, Zhang C-y, Chen H, Chen Z, Zhu X-y, Xie J: **Acupuncture for cancer-related fatigue in lung cancer patients: a randomized, double blind, placebo-controlled pilot trial**. *Supportive Care in Cancer* 2017, **25**(12):3807-3814.
9. He X-R, Wang Q, Li P-P: **Acupuncture and Moxibustion for Cancer-related Fatigue: a Systematic Review and Meta-analysis**. *Asian Pacific Journal of Cancer Prevention* 2013, **14**.
10. Moran JM, Puerto-Parejo LM, Leal-Hernandez O, Sánchez Fernández A, Pedrera-Zamorano JD: **Acupuncture for cancer-related fatigue in lung cancer patients: methodological and statistical issues**. *Supportive Care in Cancer* 2018, **27**(1):1-2.
11. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG: **CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials**. *Bmj* 2010, **340**(mar23 1):c869-c869.
12. MacPherson H, Altman DG, Hammerschlag R, Li Y, Wu T, White A, Moher D: **Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): Extending the CONSORT Statement**. *Chinese journal of Evidence-Based Medicine* 2010, **10**(10):1228-1239.
13. Lian W: **Clinical Research of Traditional Chinese Medicine(TCM) Syndrom Differentiation and Acupuncture Treatment on Cancer Related Fatigue(CRF)**. Guangzhou: Guangzhou University of Chinese Medicine; 2015.
14. Xiuyi Z, Yuankai S, Jinming Y: **Chinese lung cancer treatment guidelines (2015 edition)**. *Chinese journal of Oncology* 2015, **37**(1):67-79.
15. Plummer AL: **International Classification of Diseases, Tenth Revision, Clinical Modification for the Pulmonary, Critical Care, and Sleep Physician**. *Chest* 2015, **148**(5):1353-1360.
16. Mor V, Laliberte L, Morris JN, Wiemann M: **The Karnofsky Performance Status Scale: An Examination of its Reliability and Validity in a Research Setting**. *Cancer* 1984, **53**(9):2002-2007.
17. Witt CM: **Clinical research on acupuncture - Concepts and guidance on efficacy and effectiveness research**. *Chin J Integr Med* 2011, **17**(3):166-172.
18. Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Judy K, Wendt M, Stephen L, Huber MS: **The Rapid Assessment of Fatigue Severity in Cancer Patients**. *American Cancer Society* 1999, **85**(5):1186-1196.
19. Wang XS, Hao XS, Wang Y, Guo H, Jiang YQ, Mendoza TR, Cleeland CS: **Validation study of the Chinese version of the Brief Fatigue Inventory (BFI-C)**. *J Pain Symptom Manage* 2004, **27**(4):322-332.
20. Catania G, Bell C, Ottonelli S, Marchetti M, Bryce J, Grossi A, Costantini M: **Cancer-related fatigue in Italian cancer patients: validation of the Italian version of the Brief Fatigue Inventory (BFI)**. *Support Care Cancer* 2013, **21**(2):413-419.
21. Paramita N, Nusdwiningtyas N, Nuhonni SA, Atmakusuma TD, Ismail I, Mendoza TR, Cleeland CS: **Validity and Reliability of Brief Fatigue Inventory (BFI)-Indonesian Version in Cancer Patients**. *Journal of Pain and Symptom Management* 2016, **52**(5):744-751.
22. Chie WC, Yang CH, Hsu C, Yang PC: **Quality of life of lung cancer patients: validation of the Taiwan Chinese version of the EORTC QLQ-C30 and QLQ-LC13**. *Qual Life Res* 2004, **13**(1):257-262.
23. Hamilton M: **A rating scale for depression**. *J Neurol Neurosurg Psychiatry* 1960, **23**:56-62.

24. Cusin C, Yang H, Yeung A, Fava M: **Rating Scales for Depression**. In: *Handbook of Clinical Rating Scales and Assessment in Psychiatry and Mental Health*. edn.; 2009: 7-35.
25. Devilly!!; GJ, Borkovec TD: **Psychometric properties of the credibility expectancy questionnaire**. *Journal of Behavior Therapy and Experimental Psychiatry* 2000, **31**:73-86.
26. Vincent C: **Vincent C 1990-Credibility assessments in trials of acupuncture**. *Complementary Medical Research* 1990, **4**.
27. Lao; L, Bergman; S, Hamilton;; Langenberg; P, Beran. B: **Evaluation of acupuncture for pain control after oral surgery: a placebo-controlled trial**. *Arch Otolaryngol Head Neck Surg* 1999, **125**:567-572.
28. **Data and Safety Monitoring Board (DSMB) Guidelines** [<https://www.nidcr.nih.gov/research/human-subjects-research/interventional-studies/data-and-safety-monitoring-board-guidelines>]
29. Lau CH, Wu X, Chung VC, Liu X, Hui EP, Cramer H, Lauche R, Wong SY, Lau AY, Sit RS *et al*: **Acupuncture and Related Therapies for Symptom Management in Palliative Cancer Care: Systematic Review and Meta-Analysis**. *Medicine (Baltimore)* 2016, **95**(9):e2901.
30. Aggarwal AN, Iwase S, Kawaguchi T, Tokoro A, Yamada K, Kanai Y, Matsuda Y, Kashiwaya Y, Okuma K, Inada S *et al*: **Assessment of Cancer-Related Fatigue, Pain, and Quality of Life in Cancer Patients at Palliative Care Team Referral: A Multicenter Observational Study (JORTC PAL-09)**. *Plos One* 2015, **10**(8).
31. Dagnelie P, Pijls-Johannesma M, Lambin P, Beijer S, De Ruyscher D, Kempen G: **Impact of fatigue on overall quality of life in lung and breast cancer patients selected for high-dose radiotherapy**. *Annals of Oncology* 2007, **18**(5):940-944.
32. Deng G, Chan Y, Sjoberg D, Vickers A, Yeung KS, Kris M, Straus D, Cassileth B: **Acupuncture for the treatment of post-chemotherapy chronic fatigue: a randomized, blinded, sham-controlled trial**. *Supportive Care in Cancer* 2013, **21**(6):1735-1741.
33. Berger AM: **Does the strength of evidence support recommending acupuncture to relieve cancer-related fatigue?** *Ann Palliat Med* 2013, **2**(1):11-13.
34. Grant SJ, Smith CA, de Silva N, Su C: **Defining the Quality of Acupuncture**. *Integrative Cancer Therapies* 2015, **14**(3):258-270.
35. Johnston MF, Hays RD, Subramanian SK, Elashoff RM, Axe EK, Li JJ, Kim I, Vargas RB, Lee J, Yang L *et al*: **Patient education integrated with acupuncture for relief of cancer-related fatigue randomized controlled feasibility study**. *BMC Complement Altern Med* 2011, **11**:49.
36. Molassiotis A, Bardy J, Finnegan-John J, Mackereth P, Ryder DW, Filshie J, Ream E, Richardson A: **Acupuncture for Cancer-Related Fatigue in Patients With Breast Cancer: A Pragmatic Randomized Controlled Trial**. *Journal of Clinical Oncology* 2012, **30**(36):4470-4476.
37. Javdan B, Cassileth B: **Acupuncture Research at Memorial Sloan Kettering Cancer Center**. *J Acupunct Meridian Stud* 2015, **8**(3):115-121.

Tables

Table 1. Timing of treatment assessments and data collection

TIMEPOINT	STUDY PERIOD					
	Enrollment	Baseline	Treatment phase		Follow-up phase	
	-1week	0week	3week	6week	4week	12week
ENROLMENT						
Eligibility screen	X					
Informed consent	X					
Medical history	X					
Allocation		X				
INTERVENTIONS						
Acupuncture		X	X	X		
Sham Acupuncture		X	X	X		
ASSESSMENTS						
Primary outcome						
BFI-C		X	X	X	X	X
Secondary outcomes						
EORTC QLQ-C30		X		X		
HAMD		X		X		
Others						
Adverse events		X	X	X		
Patients's satisfaction				X		
Success of blinding				X		

Table 2. Details of intervention

	Intervention group	Control group			
Acupoints	GV20, GV29, CV12, CV6, CV4, LI4, LR3, SP6, ST36	GV20, GV29, CV12, CV6, CV4, LI4, LR3, SP6, ST36			
Depth of insertion	GV20, GV29, LI4, LR3 10mm	No insertion			
	CV12, SP6, CV6, CV4, ST36 30mm				
Needle type	Steel needle (Wuxi Jiajian Medical Co. Ltd. Wuxi, China)	Blunt-tip needle (Streitberger Placebo-needle)			
Needle sensation	With de-qi sensation	Without de-qi sensation			
Electric stimulation	Needle on Bilateral ST36 connected to SDZ-III Electronic Acupuncture Treatment Instrument (Hwato, China). with electric pulse at a frequency of 2.5 Hz and an intensity of 45 mA	Needle on Bilateral ST36 connected to SDZ-III Electronic Acupuncture Treatment Instrument (Hwato, China). without electric pulse	Frequency and duration	Twice per week for the 6 weeks	Twice per week for the 6 weeks

Figures

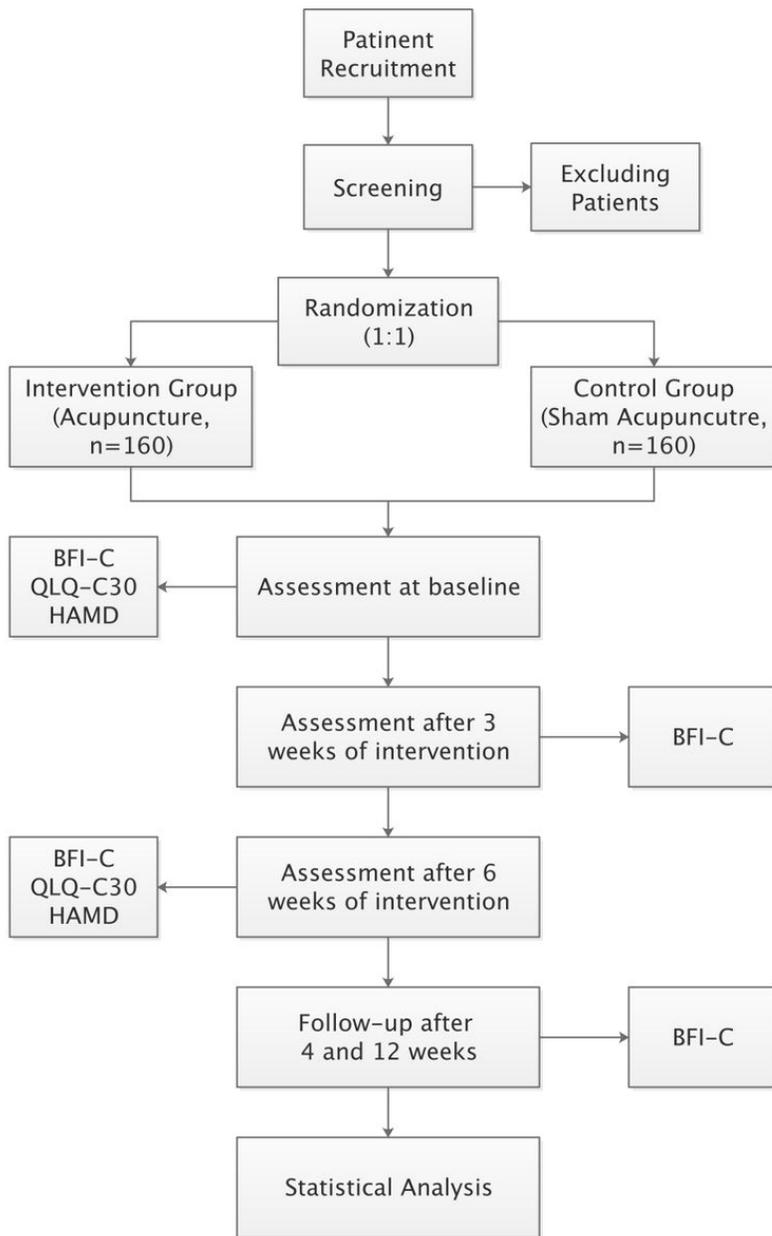


Figure 1

Flowchart of the study process

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SPIRITchecklist.pdf](#)
- [DataandSafetyMonitoringBoardmemberslist.pdf](#)