*Study Protocol*

# The Adjunctive Effect of Acupuncture for Advanced Cancer Patients in a Collaborative Model of Palliative Care: Study Protocol for a 3-Arm Randomized Trial

Integrative Cancer Therapies
Volume 20: 1–10

DOI: 10.1177/15347354211012749
journals.sagepub.com/home/ict
SAGE

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## Abstract

**Background:** Cancer is the second leading cause of death before the age of 70. Improved cancer survival has put increasing demands on cancer care. Palliative care is the specialized multi-disciplinary care providing relief from the pain, symptoms, and stress of serious illness. The study aims to evaluate the adjunctive effect of acupuncture for advanced cancer patients in a collaborative model of palliative care. **Methods/Design:** This is a single-blinded, randomized, sham-controlled trial. One hundred twenty advanced cancer patients undergoing palliative care will be randomized in a ratio of 2:1:1 to manual acupuncture plus standard care group (ASC), sham acupuncture plus standard care group (SSC), and standard care group (SC). Patients in ASC and SSC will receive 9 sessions of acupuncture or sham acupuncture for 3 weeks, and will be followed up for 2 months. The primary measure is the change from baseline score of the Edmonton Symptom Assessment System at 3 weeks. The secondary measures include the Brief Fatigue Inventory, Hospital Anxiety and Depression Scale, Insomnia Severity Index, Numeric Rating Scale, and European Organization for Research and Treatment of Cancer Quality of Life 15 items Questionnaire for Palliative Care. **Discussion:** The finding of this trial will provide high-quality evidence on the adjunctive effect of acupuncture to standard care on advanced cancer patients undergoing palliative care.

**Trial Registration**

Clinicaltrials.gov, NCT04398875 (https://www.clinicaltrials.gov/ct2/show/NCT04398875), Registered on 21 May 2020.

**Keywords**

acupuncture, cancer related symptoms, palliative care, quality of life, randomized controlled trial

Submitted December 3, 2020; revised March 24, 2021; accepted April 7, 2021

## Background

Cancer is the second leading cause of death before the age of 70 (World Health Organization 2018), and 1 in 5 men and 1 in 6 women worldwide will develop cancer during their lifetime. In 2018, there were an estimated 18.1 million new cases of cancer and 9.6 million cancer deaths, and the total number of patients still alive within 5 years of a cancer diagnosis was approximately 43.8 million.[1] Cancer has heavy social and economic burdens, particularly with an aging population.[2] In Hong Kong, the lifetime risk of cancer is 1 in 4 men or 1 in 5 women according to the Hong Kong

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Cancer Registry. In 2016, there were 31 468 new cases of cancer and 14 209 cancer deaths in Hong Kong. Among all cancers, the top 3 were colorectal (17.3%), lung (15.7%), and breast (13.1%) cancers, which accounted for half of the cancer burden.

Cancer survival is improving which puts increasing demands on cancer care. In the UK, cancer survival has doubled in the past 40 years and 50% of patients diagnosed with cancer will survive for 10 or more years.[3] In the USA, the 5-year survival rate of all cancers has risen from 49% (1975-1977) to 67% (2007-2013).[4] Similarly, survival rates have increased in many developing and developed countries worldwide.[5,6]

Palliative care is the specialized multi-disciplinary care of patients and is defined as "team-based care that focuses on providing relief from the pain, symptoms, and stress of serious illness."[7] Palliative care is a key component of oncologic care providing relief from symptom, pain, and mood distress to improve the quality of life of patients and their families.[8] In a randomized controlled trial of 151 patients with newly diagnosed advanced lung cancer, patients who received early palliative care integrated with standard oncologic care had significantly improved quality of life and mood, as well as a longer median survival.[9,10] Uncontrolled physical symptoms (eg, pain, fatigue, nausea, and vomiting) and psychological symptoms (anxiety and depression) are likely associated with increased mortality.[9,11] Studies indicate that improving the control of symptoms by palliative care might reduce mortality and enhance the ability of patients to tolerate cancer regimes, which in turn would increase survival.[9,11]

Palliative care services have been continuously strengthened in Hong Kong, but there is still room for improvement.[12] In 2017, the Hospital Authority developed a strategic service framework for palliative care that aims to build up a sustainable service model and improve the quality of palliative care in public hospitals and clinics.[12] Currently, 16 public hospitals offer adult palliative care, which includes palliative care specialists from either the Department of Medicine or the Department of Clinical Oncology.[12] However, the integration of complementary and alternative medicines (CAM) in palliative care services is not well established in public hospitals and clinics.

Acupuncture has shown promise for cancer-related symptom control.[13,14] Our systematic review and meta-analysis found that acupuncture could improve quality of life, Karnofsky performance status, and pain control as well as reduce nausea and vomiting in patients with lung cancer.[13] Our pilot randomized controlled trial and systematic review suggested that acupuncture might benefit insomnia disorders,[15,16] indicating a potential positive role in cancer patients. Randomized controlled trials from other groups indicated acupuncture could relieve symptoms of pain, fatigue, nausea, depression, anxiety, and dyspnea, and enhance quality of life and sense of well-being.[17,18] A retrospective analysis of 375 cancer patients showed acupuncture relieved cancer-related symptoms.[19] A systematic review and meta-analysis concluded that acupuncture could be considered for cancer-related symptom management in palliative care without serious adverse effects, although evidence from high-quality clinical trials are still needed to verify these acupuncture effects.[20,21]

We hypothesize that traditional manual acupuncture (MA) has adjunctive effects in relieving cancer-related symptoms in patients under palliative care. The proposed study aims to evaluate the adjunctive effect of MA with standard care (ASC) for relieving cancer-related symptoms in a collaborative model of the palliative care compared to sham MA plus standard care (SSC) or standard care alone (SC).

## Methods/Design

### Study Design

This is a randomized, subject- and assessor-blind, 3-arm, controlled trial. The study protocol follows the Declaration of Helsinki, and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline, and was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB, UW 19-822) on January 2020.

### Patient Recruitment

Advanced cancer patients undergoing palliative care will be recruited at the 2 clinical centers of the School of Chinese Medicine and the Palliative Care Units of public hospitals in Hong Kong. After being informed about the study, and potential risk/benefits, patients are required to give written informed consent, followed by eligibility screening. The eligible subjects will be enrolled and randomly assigned into the 3 arms, MA plus standard care (ASC), sham MA plus standard care (SSC), and standard care (SC), according to a pre-generated random sequence. The subjects in ASC and SSC groups will receive up to 9 sessions of acupuncture or sham acupuncture for 3 weeks, respectively, followed by an 8-week follow-up. The manual acupuncture will be performed by acupuncturists with at least 3 years of acupuncture experience. All subjects in the 3 groups will receive standard supportive care. The study flowchart is shown in Figure 1. The proposed project schedule is shown in Table 1.

### Inclusion Criteria

Patients with the following criteria with respect to their physical condition:

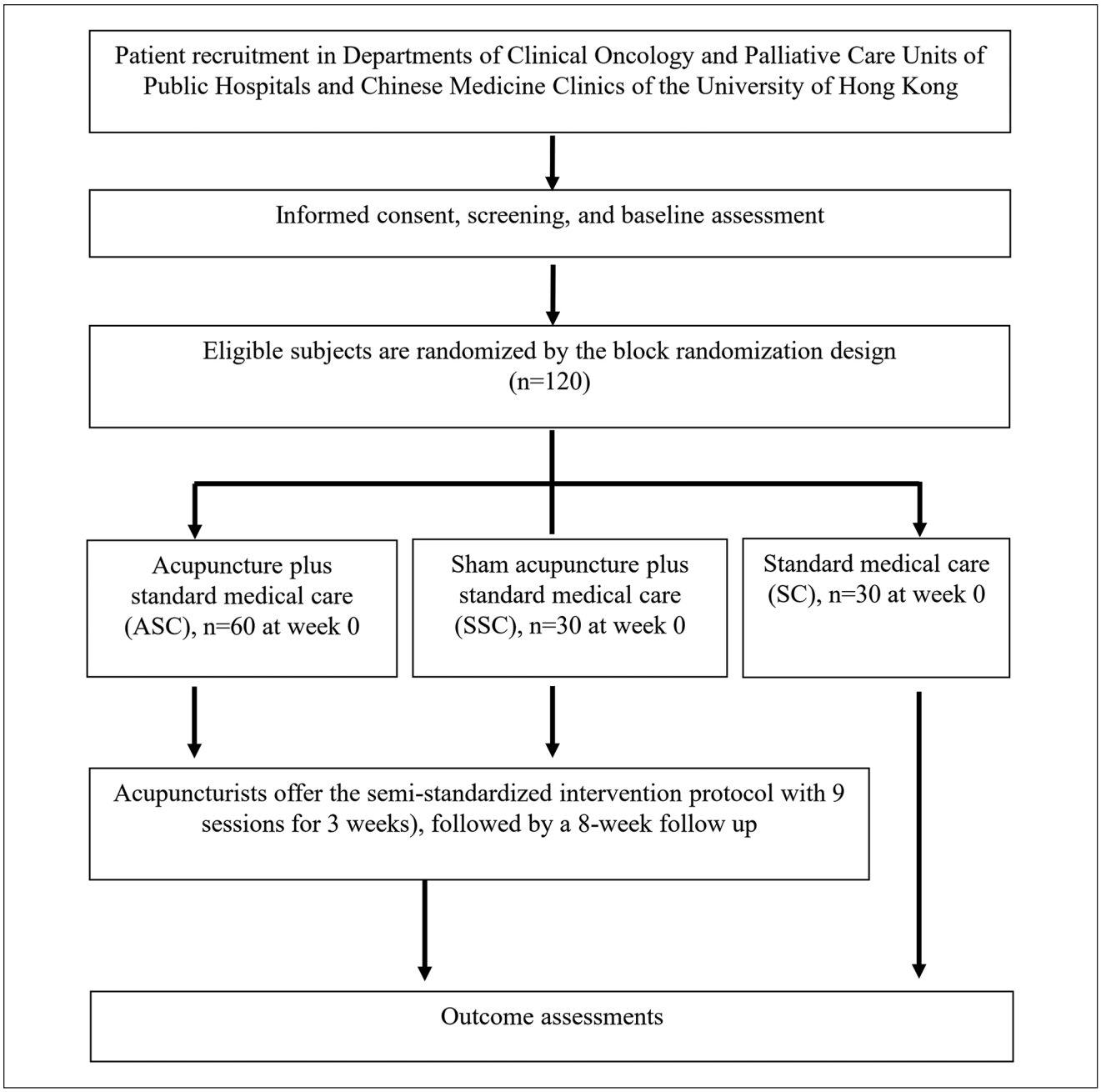


**Figure 1.** Flow diagram of the study protocol.

(1). All cases are subject to pathology and (or) cytology for a diagnosis of malignant solid tumour (pathological type is not restricted) at stage IIIB or IV (the TNM Classification of Malignant Tumors[22]);
(2). Aged 18 years or above;
(3). Expected survival time longer than 16 weeks;
(4). Out-patients or hospice patients with palliative cancer care;
(5). Total symptom distress score in the Edmonton Symptom Assessment System (ESAS) $\geq 27$

### *Exclusion Criteria*

Patients with the followings will be excluded from the study:

(1). Disseminated intravascular coagulation or severe thrombocytopenia with a bleeding tendency, that is, low platelet count $<35\,000/\mu L$; INR $>1.5$; hemoglobin $\leq 90$ g/dL; white blood cell count $\leq 4 \times 10^9/L$;
(2). Uncontrolled active skin infection;

**Table 1.** Study Assessment Schedule.

| | | | Intervention | | | Follow up | |
|---|---|---|---|---|---|---|---|
| Assessment | Screening | Baseline | Wk 1 | Wk 2 | Wk 3 | Wk 7 | Wk 11 |
| Day (D) | −21 to −14 | −7 to 0 | D7 | D14 | D21 | D49 | D77 |
| Visit window (D) | | | ±1 | ±2 | ±2 | ±3 | ±5 |
| Basic information | | | | | | | |
| Informed consent | √ | | | | | | |
| Review inclusion/exclusion criteria | √ | √ | √ | √ | √ | √ | √ |
| Medical history | √ | | | | | | |
| Vital signs | √ | √ | √ | √ | √ | √ | √ |
| Demographics | √ | | | | | | |
| Physical examination | √ | | | | | | |
| Primary outcome | | | | | | | |
| ESAS | | √ | √ | √ | √ | √ | √ |
| Secondary outcomes | | | | | | | |
| EORTC-QOL-C15-PAL | | √ | | | √ | √ | √ |
| NRS | | √ | | | √ | √ | √ |
| BFI | | √ | | | √ | √ | √ |
| HADS | | √ | | | √ | √ | √ |
| ISI | | √ | | | √ | √ | √ |
| Other measures | | | | | | | |
| Blinding success | | | √ | | √ | | |
| Treatment credibility | | √ | √ | | √ | √ | √ |

Abbreviations: BFI, Brief Fatigue Inventory; ESAS, Edmonton Symptom Assessment System; HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; NRS, Numeric Rating Scale; QOL-C15-PAL, European organization for research and treatment of cancer quality of life 15 items questionnaire for palliative care; Wk, week; "√" indicates the assessment schedule.

(3). Needle phobia;
(4). Inability to read and understand Chinese;
(5). Not signed written informed consent.
(6). Receiving surgery during the whole study period;
(7). Receiving acupuncture treatment in last 3 months.

## *Randomization and Allocation Concealment*

The allocation sequence will be generated according to a block (n=4 or 6) randomization design in a ratio of 2:1:1 (ASC, n=60: SSC, n=30: SC, n=30) using SPSS 22.0 by a statistician who will not be further involved in the study. The randomized codes will be sealed in sequentially numbered opaque envelopes. When an eligible patient is recruited, a research assistant will open the next envelope and the randomized unique code will then be assigned to the subject. Within the research team, only the research assistant and acupuncturist will know the subjects' group assignments.

## *Blinding*

Subjects randomly assigned to either ASC group or SSC group will be blinded to their group assignment, whereas subjects in the SC group will know their group assignment. Acupuncturists will not be blinded to subject allocation as they will be performing the treatments. The acupuncturists will not be involved in the data collection and data analyses. The assessor will be blinded to subject allocation and will assess cancer-related symptoms, quality of life, and safety of the acupuncture during the study. Research personnel who will perform the outcome assessments will all be blinded to the treatment assignments. Subject codes rather than subject identities will be used in all assessments and data analyses.

## *Intervention*

*Selection of acupuncture points and justifications.* To reflect clinical practice in the real world and for methodological rigor in a randomized controlled trial, a semi-standardized treatment protocol (combined fixed acupoints with additional acupoints by symptom differentiation) will be employed. All acupuncture points to be used in the treatment are common points for symptoms recommended by textbook[23] and literature,[24,25] and confirmed by senior acupuncturists. The fixed acupuncture points including, Guanyuan (CV4), Xuanzhong (GB39), Sanyinjiao (SP6), Yinlingquan (SP9), Zusanli (ST36), Yingtang (EX-HN3), Baihui (GV20), and Qihai (CV6) will be used in every session. The base protocol is designed to boost qi and replenish

the spleen (SP6, SP9, ST36, GB39, CV4, and CV6) and regulate mood/sleep disorders (EX-HN3, GV20). The additional acupuncture points will be pragmatically selected in line with symptoms and syndrome-differentiation of pain, fatigue, nausea, anxiety and depression, dyspnea, insomnia, and constipation. A total of 2 to 4 acupoints for each symptom will be needled according to the severity of the symptoms. The acupuncturist will avoid needling acupoints at the site of cyst and tumor, varicose veins, and skin infections. All acupuncture points will be recorded in the case report form. The acupoints selection criteria are shown in Table 2.

*Intervention procedures.* Subjects in the ASC and SSC groups will be offered up to 9 sessions of acupuncture or sham acupuncture within 3 weeks. To mimic the real-world clinical practice, subjects can reduce intervention sessions or increase intervention frequency during the intervention period. The number of acupuncture sessions will be analyzed as a covariate. In addition, a semi-standardized protocol adoption of the intervention into real clinical practice will be employed.

*Acupuncture treatment.* Participants will be in a supine position or lying on 1 side. An eye mask will be used for the participant to make better blinding. The skin on top of and around the points will be sterilized with 75% alcohol. Sterilized disposable needles (0.22 mm × 40-60 mm) will be inserted at each point. The needles will be twisted and lifted until a slight "De qi" sensation is produced. Needle retention will be continued for 20 minutes (according to usual practice). The needles will then be removed and cotton wool will be used to compress the points to prevent bleeding.

*Sham acupuncture treatment.* The procedure in SSC group will be as similar as possible to that in the ASC group. An eye mask will be used for the participant so as to make a blinding. A validated non-insertion sham acupuncture (Streitberger sham acupuncture) will be applied in the study,[26] which was validated in Chinese population as well.[27] Briefly, the Streitberger sham acupuncture has the same appearance to real acupuncture. But the tip of the Streitberger needle is blunt, and when it touches the skin a pricking sensation is felt by the patient, simulating the puncturing of the skin. The needle is not fixed inside the copper handle. When the acupuncturist taps the handle, the needle moves inside the handle, and appears to be shortened. A plastic ring covered with plastic sheet will be used to place the needle.[26] The fixed points in the treatment protocol will be used for patients in SCC group. Other procedures will be the same as in the ASC group.

*Waitlist.* In the SC group, participants serving as waitlist controls will receive neither real acupuncture nor sham acupuncture for the first 3 weeks. After 3 weeks, the participants will have compensation treatments in 3 weeks and follow by an 8-week follow-up.

*Concomitant treatment/standard cancer care.* Standard cancer care (eg, physical, emotional, and coping) and medications as the standard operation will be applied to all subjects in the 3 arms (ASC, SSC, and SC groups). The dose of analgesics will be recorded for further analysis. Other regimens, except acupuncture, will not be restricted in this pragmatic study. The concomitant treatment will be recorded during the study period. Additionally, to avoid the nocebo effect and to enhance adherence, subjects in the SSC and SC groups will be offered compensation treatment with acupuncture after subjects complete the trial.

## Outcome Measurements

*Primary outcome.* The cancer-related symptoms will be assessed using the ESAS at week 0, and during and after treatments at weeks 1, 2, 3, 7, and 11. The change from baseline score at 3 weeks will be the primary outcome. The ESAS is a well-validated rating scale (scored on a scale of 0-10) which assesses 9 symptoms common in cancer patients including pain, tiredness (fatigue), nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath. The total distress score (range 0-90) consists of 6 physical symptoms (pain, fatigue, nausea, drowsiness, appetite, and dyspnea), 2 emotional symptoms (anxiety and depression), and wellbeing. Subjects are required to circle the score that best describes their symptoms, with 0 corresponding to absent symptom and 10 the worst degree of symptom.

### *Secondary outcomes*

(i) Quality of life

Quality of life will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life 15 items Questionnaire for Palliative Care (EORTC QLQ-C15-PAL) at weeks 0, 3, 7, and 11. The QLQ-C15-PAL is a shortened 15-item questionnaire for cancer patients in palliative care.[28]

(ii) Pain

The analgesic effect of acupuncture will be measured using the Pain Severity NRS at weeks 0, 3, 7, and 11. The NRS is a rating scale from 0 to 10 (on a 10-cm line) that reflects the overall pain intensity. Subjects are required to indicate the pain intensity at the assessment.

(iii) Fatigue

**Table 2.** A Semi-Standardized Treatment Protocol of Acupuncture.

| | |
|---|---|
| Fixed acupoints | |
| Guanyuan (CV4), Xuanzhong (GB39), Sanyinjiao (SP6), Yinlingquan (SP9), Zusanli (ST36), Yingtang (EX-HN3), Baihui (GV20), and Qihai (CV6) | |
| Additional acupoints based on the symptoms and symptom-differentiation of Chinese medicine | |
| Symptom | Syndrome-differentiation |
| Pain | Excess syndrome |
| | Qi stagnation: Ashi acupoints, Gongsun (SP4), Qimen (LR14), Zhongwan (CV12), Zhigou (TE6), Neiguan (PC6) |
| | Phlegm and blood stasis: Ashi acupoints, Xuehai (SP10), Zhongwan (CV12), Fenglong (ST40), Neiguan (PC6) |
| | Deficiency syndrome |
| | Qi and blood deficiency: Zhongwan (CV12), Geshu (BL17), Pishu (BL20), Dazui (GV 14) |
| Tiredness (fatigue) | Qi and blood deficiency: Danzhong (CV17) |
| | Kidney-essence deficiency: Taixi (KI3), and Shenshu (BL23) |
| Nausea | Excess syndrome |
| | Phlegm congealing: Neiguan (PC6), Zhongwan (CV12), Fenglong (ST40) |
| | Heat-evil invading the stomach: Neiguan (PC6), Zhongwan (CV12), Neiting (ST44) |
| | Cold-evil invading the stomach: Neiguan (PC6), Zhongwan (CV12), Liangqiu (ST34) |
| | Deficiency syndrome |
| | Neiguan (PC6), Zhongwan (CV12), Gongsun (SP4) |
| Depression | Excess syndrome |
| | Liver qi stagnation: Hegu (LI4), Taichong (LV3), Shenmen (HT7) |
| | Liver fire flaming: Xinjian (LR2), Shenting (GV24) |
| | Deficiency syndrome |
| | Heart and spleen deficiency: Shenmen (HT7), Zhangmen (LR13), Juque (CV14) |
| | Heart-sprit disturbance: Shenmen (HT7), Tongli (HT5), Shaofu (HT8) |
| | Yin deficiency with effulgent fire: Shenmen (HT7), Taixi (KI3), Shenshu (BL23) |
| Anxiety | Excess syndrome |
| | Phlegm-fire harassing the heart: Laogong (PC8), Fenglong (ST40), Shangwan (CV13) |
| | Qi and blood stasis: Shenmen (HT7), Daling (PC7), Xuehai (SP10) |
| | Deficiency syndrome |
| | Yin damaged by yang excess: Shenmeng (HT7), Daling (PC7), Dazui (GV14) |
| Shortness of breath (dyspnea) | Deficiency syndrome |
| | Danzhong (CV17), Gaohuangshu (BL38), Shenshu (BL23) |
| Drowsiness | Excess syndrome |
| | Zhaohai (KI6), Fenglong(ST40) |
| | Deficiency syndrome |
| | Mingmen (GV4) |
| Insomnia | Excess syndrome |
| | Liver yang excess: Shenmen (HT7), Xinjian (LR2) |
| | Heart fire flaming: Shenmen (HT7), Shaofu (HT8) |
| | Deficiency syndrome |
| | Heat and spleen deficiency: Shenmen (HT7), Xinshu (BL15), Jueyinshu (BL14), Pishu (BL20) |
| | Heat and kidney disharmony: Shenmen (HT7), Taixi (KI3), Xinshu (BL15), Shenshu (BL23) |
| | Heat and gall bladder deficiency: Shenmen (HT7), Qiuxu (GB40), Xinshu (BL15), Danshu (BL14) |
| Loss appetite | Excess syndrome |
| | Zhongwan (CV12), Neiguan (PC6) |
| | Deficiency syndrome |
| | Zhongwan (CV12) |
| Constipation | Excess syndrome |
| | Qi stagnation: Tianshu (ST25), Zhigou (TE6), Shangjuxu (ST37) |
| | Deficiency syndrome |
| | Qi and Yin deficiency: Tianshu (ST25), Zhigou (TE6), Shangjuxu (ST37), Taixi (KI3) |
| | Yang deficiency: Mingmen (GV4), Dachangshu (BL25), Ciliao (BL32) |

Fatigue will be measured by the Chinese version of Brief Fatigue Inventory (BFI)[29] at weeks 0, 3, 7, and 11. The BFI is a 9-item questionnaire used to rapidly assess the severity and impact of cancer-related fatigue during the past 24 hours. Subjects are required to circle the score (0-10) that best describes their level of fatigue.

(iv) Mood status

Mood status (anxiety and depression) will be assessed by the Chinese version of Hospital Anxiety and Depression Scale (HADS)[30] at weeks 0, 3, 7, and 11. The HADS is a 14-item measure designed to assess psychological distress on a 4-point severity scale for non-psychiatric patients. It consists of 2 subscales, Anxiety (HADS-A) and Depression (HADS-D). Subjects are required to report the severity (0-3) of distress.

(v) Sleep

Sleep conditions will be assessed by the Chinese version of Insomnia Severity Index (ISI)[31] at weeks 0, 3, 7, and 11. The ISI is a 7-question measure to assess the insomnia severity in the past 2 weeks on a 5-point scale for each item. Subjects are required to report the severity (0-4) of insomnia.

## Assessment for Acupuncture Safety

*Adverse events (AE) and serious adverse events (SAE).* After each intervention, subjects will be asked about any AEs according to the monitoring form. All AEs and the perceived causal relationship to the intervention will be recorded. Any SAEs resulting in death, threat to life, hospitalization or prolonged hospitalization, disability or permanent damage, or any condition the investigator deems to present a significant hazard will be reported to the IRB, DSMB and the regulatory authorities within 48 hours. The investigator will follow up the subject's AE/SAE until the event has resolved, subsided, or stabilized; the event is otherwise explained; or the subject is lost to follow-up.

*Reasons for withdrawal.* When a subject withdraws before completion of the study, the reasons for withdrawal will be recorded.

## Quality Assurance of Intervention

To ensure the quality of the acupuncture treatment and to minimize intervention bias, the acupuncturist involved in this study will be a registered Chinese Medicine Practitioner with at least 3 years of experience in acupuncture. The acupuncturist will be trained by the senior acupuncturists for both the real and sham acupuncture interventions, and will be assessed to ensure the locations of the acupoints and needling procedures are accurate.

## Assessment for Treatment Credibility

The Credibility of Treatment Rating Scale (CTRS) will be used to assess the patient's degree of confidence on the acupuncture treatments at weeks 1 and 3. The 4-item scale (from 0, no credibility, to 6, maximum credibility) is adopted to assess the patient's confidence on acupuncture.[32] The following questions will be asked to each subject by the assessors at the first treatment: (1) Do you believe this treatment will reduce the symptoms you are suffering? (2) Does the treatment seem to be a logical one? The follow questions will be asked by the assessors at the last treatment: (1) Would you recommend this treatment to a friend or relative with the same problem? (2) Do you believe this treatment could be applicable to treat other problems?

## Data and Safety Monitoring Plan

A data and safety monitoring board (DSMB) comprising 3 members, an acupuncturist, an oncologist or related physician, and a statistician, will be formed to monitor the study progress and to review the safety and quality of the data. The DSMB will be independent from the proposed study to ensure there is no conflict of interest for any board members. Regular board meetings (every 6 months) will be held to ensure that the data are scientifically and ethically collected and that subjects are not exposed to any unnecessary risks. All AEs or SAEs will be reported to the DSMB within 48 hours. The DSMB will determine whether the trial should be terminated in the event that an SAE occurs.

## Statistical Methods

*Sample size.* Sample size was estimated based on the scores of global ESAS before the first treatment and the first follow-up (the longitudinal effect of acupuncture) in a retrospective study.[19] The observed effect sizes of acupuncture adjunctive to standard palliative care in global ESAS were 1.294.[19] The needle-insertion sham acupuncture and non-insertion sham acupuncture are the commonest types of sham acupuncture.[33] Studies including ours have revealed that sham acupuncture is not an inert placebo; the non-penetrating sham acupuncture has a smaller non-specific effect than the needling-insertion (superficial needling) sham acupuncture.[33-36] We have systematically reviewed literature in Pubmed. However, no studies reported values of ESAS scales for estimating the effect size of sham acupuncture. Here, we estimated the non-insertion sham acupuncture produced a nonspecific effect with 0.45 (a medium effect size) according to a meta-analysis.[34] So the effect size of real acupuncture versus sham acupuncture is 0.844. According to a previous study and our clinical experience, patients prefer to receive real acupuncture rather than sham acupuncture and waitlist control, we designed a 3-arm study

with a ratio of 2:1:1.[37] Ninety-six patients (48:24:24) will achieve 90% power (1-β) with $\alpha = .05$ (2-sided). Assuming a 20% dropout rate, the total sample size will be 120 (ASC, n = 60: SSC, n = 30: SC, n = 30). The estimation of effect size between real acupuncture and sham acupuncture may be optimistic. We will perform interim analysis yearly and the first analysis will be performed at the end of the 3-month recruitment period. Sample size will be adjusted based on the effect size of sham acupuncture on ESAS.

*Statistical analysis.* All data will be double-entered and checked for consistency before conducting the analyses. The data will be analyzed based on the intent-to-treat (ITT) population. Missing data on the primary outcome will be imputed using the multiple imputation method under the assumption of missing-at-random. For secondary outcomes, no imputation will be performed. The results for the per-protocol (PP) population will be used as the sensitivity analysis. We assume that longitudinal data (ESAS, QLQ-C15-PAL, NRS, BFI, HADS, and ISI scores) from a single patient are correlated. Hence, we will perform between-group comparisons of acupuncture group with sham acupuncture group, as well as waiting list group. Differences in mean changes from baseline for each longitudinal outcome at each time point will be compared between groups with mixed-effects linear regression model using baseline as a covariate; group, visit, and group × visit interaction as a fixed effect; site as random effect. Changes in the scores from baseline within treatment groups will be assessed using the Wald test on the treatment effect parameters specified in the linear mixed model. Response rate will be dichotomized as improved (ESAS $\geq +3$ in total distress score) or not and compared between groups using mixed-effects logistic regression model with site as a random effect. Comparisons of other categorical data between groups will be tested using the Fisher exact test or Wilcoxon rank-sum test. All statistical analyses will be assessed using a 2-tailed test at a 5% significance level, with SAS software, version 9.4 (SAS Institute Inc).

## Discussion

The patients in palliative care may experience various unpleasant symptoms, including pain, fatigue, nausea, anxiety and depression, dyspnea, insomnia, and constipation, which significantly decrease the quality of life. There is limited evidence on the adjunctive effect of acupuncture treatments for advanced cancer patients in a palliative care setting in Hong Kong. Previous trials mainly assessed the effects of acupuncture on single symptoms in cancer patients. The proposed study will assess the adjunctive effect of EA with standard care across all cancer-related symptoms in a palliative care setting compared to sham acupuncture with standard care or standard care only. Using a 3-arm pragmatic trial, the study will identify the extent of adjunctive effects of acupuncture, and its minimal and maximal effects by comparing with 2 controls.[33] The pragmatic trial may deliver the real-world evidence on the added value of acupuncture compared with standard cancer care and inform decision making earlier in development.

The study will contribute to the methodological design of clinical trials on acupuncture. Individualized acupuncture treatment guided by symptom/pattern differentiation is a key principle of Chinese medicine doctrine. However, individualized treatment has been omitted from many randomized controlled trials (RCTs) on acupuncture, which may be one of the reasons for the failure in demonstrating their effectiveness. For the proposed research, we have designed a semi-standardized treatment protocol that considers subjects' individual symptoms/patterns. This design meets the requirements of RCT design rigor and the clinical reality of acupuncture treatments. The 3-arm design in the trial will enable us to distinguish a therapeutic effect and placebo effect as a sham acupuncture may result in treatment effect described in our publications.[33] These approaches will make a major contribution to the design of RCTs on acupuncture.

The study will recruit advanced cancer patients without limiting cancer types because of the limited patients. It increases the heterogeneity among groups though the randomization may reduce the heterogeneity. The study will provide the preliminary data of acupuncture for different types of cancer patients, and enable us to estimate the acupuncture effect for a specific type of cancer in a future clinical trial.

The study will also test the feasibility and safety of acupuncture to advanced cancer patients under palliative care. Findings will benefit the implementation of acupuncture to standard care in the palliative care setting.

### Authors' Contributions

HC conceived of the study. HC, THS, WCSC, CHM, SGL, ZY, JW, ZJZ, FMK, and LXL initiated the study design and protocol development. ZQ and FJ provided the advice for statistical analysis. HC sought funding and ethical approval. HC drafted the manuscript. All authors contributed to the refinement of the study protocol and approved the final manuscript.

### Availability of Data and Materials

Access to the protocol and the dataset may be provided upon request to the authors.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This

work was supported by the Health and Medical Research Fund (HMRF), Food and Health Bureau, Hong Kong SAR Government (ref. 17181831). The funding plays no role in study design, collection, management, analysis, interpretation of data, writing of the report, or the decision to submit the report for publication.

## Ethical Approval and Consent to Participate

The trial will be initiated after approval has been obtained from the Institutional Review Board. Any changes in protocol will be sent to the IRB for approval. All participants will provide written informed consent prior to participation in the study and have the right to withdraw at any time with or without a reason. All data management will comply with the Personal Data (Privacy) Ordinance (CAP 486). The insurance will be purchased to cover potential harms for all participants in the study.

The study protocol was reviewed and approved the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB, UW 19-822) on January 2020.

## Trial Status

This study protocol version number is 1.1, dated 5 December 2020. The participants will be recruited on February 2021. The recruitment is estimated to be completed on 30 September 2022.

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