

BMJ Open Acupuncture in chemotherapy-induced dysgeusia (AcuDysg): study protocol of a randomised controlled trial

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ABSTRACT

Introduction Dysgeusia is a common side effect of chemotherapy in patients with cancer, but to date, there is no effective treatment. Many patients with cancer request complementary medicine treatment in addition to their cancer treatments, and acupuncture is highly accepted for patients with cancer; however, evidence regarding the effectiveness of acupuncture for dysgeusia is scarce. The study investigates the effectiveness of an additional dysgeusia-specific acupuncture plus self-acupressure intervention compared with supportive acupuncture plus self-acupressure intervention alone for chemotherapy-induced dysgeusia in patients with cancer.

Methods and analysis This is a multicentre, randomised, controlled and two-armed parallel-group, single-blind trial involving 130 patients. Both groups will receive eight sessions of acupuncture treatment over a period of 8 weeks and will be trained to perform self-acupressure (eLearning combined with therapist instruction) at predefined acupressure points once a day during the whole treatment period. Patients in the control group will receive supportive routine care acupuncture and self-acupressure treatment only; in addition to this treatment, the intervention group will receive the dysgeusia-specific acupuncture and acupressure within the same treatment session. The primary outcome is the perceived dysgeusia over 8 weeks, measured weekly after the acupuncture treatment. Secondary outcomes include the indices from the objective taste and smell test, weight loss, perceived dysgeusia, fatigue, distress, nausea and vomiting, odynophagia, xerostomia and polyneuropathy, as well as quality of life at the different time points.

Ethics and dissemination The study has been approved by the Cantonal Ethics Committee (CEC) (Kanton Zürich Kantonale Ethikkommission) (approval no. KEK-ZH-Nr. 2020–01900). The results will be submitted to a peer-reviewed journal for publication.

Trial registration numbers DRKS00023348, SNCTP000004128.

INTRODUCTION

Dysgeusia is a common side effect in patients undergoing chemotherapy. It is often described as very disturbing, can vary in intensity depending on the chemotherapeutic medication and often has an impact on the

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study allows for blinding of patients because it provides acupuncture treatment for another common symptom (cancer-related fatigue) in both groups, and the intervention group receives additional points only to treat dysgeusia.
- ⇒ Both subjective and objective outcomes of dysgeusia are used in the study.
- ⇒ All participants, regardless of the treatment arm will receive an evidence-based acupuncture treatment plus self-acupressure via eLearning for cancer-related fatigue.
- ⇒ This is a single-blinded study because the acupuncturist cannot be blinded.

patient's quality of life.¹ The prevalence of dysgeusia during chemotherapy ranges from 56% to 76%.² Affected patients often ask their oncologists or nutritionists for treatment of dysgeusia. However, to date, there is no effective treatment, and the effects of zinc sulphate or amifostin are small.²

Half of patients with cancer ask for complementary medicine as an adjunct to their conventional therapy, and acupuncture is widely used.³ In 2016, a National Cancer Institute symposium in the USA concluded that existing acupuncture studies in oncology show promising results and recommend more research in this field.⁴

To date, there is only one completed acupuncture study for idiopathic dysgeusia with a small sample (n=37). In this trial, the treatment group achieved higher levels in taste discrimination compared with the groups receiving sham acupuncture, but due to the small sample size, the differences were not statistically significant.^{5,6} In a separate single-centre study that is ongoing in Germany, the plan is to include 75 patients with breast cancer, using phantogeusia as the primary outcome, and patients are

randomised to either acupuncture, sham acupuncture or nutrition counselling.⁷

In Switzerland, supportive acupuncture treatment is widely accepted in patients with cancer and is usually reimbursed within the Swiss basic health insurance when provided by a medical doctor with the respective specialisation. There are positive experiences for acupuncture in chemotherapy-induced dysgeusia in practice. However, a randomised controlled trial is needed to support an evidence-based decision regarding the prospective implementation of acupuncture.

Dysgeusia is a side effect that often appears in conjunction with other chemotherapy-related side effects, such as chemotherapy-induced nausea and vomiting (CINV), cancer-related fatigue (CRF) and chemotherapy-induced polyneuropathy (CIPN), for which there is already evidence for acupuncture.^{4 8 9} Although, animal studies provide support for the presence of acupuncture point specificity, particularly for specific outcomes and stimulation parameters,^{10 11} there is to date, no basic research on acupuncture for dysgeusia. Acupressure is another intervention from traditional Chinese medicine, where instead of inserting needles, pressure is applied to the points. In supportive cancer care, there is positive evidence for acupressure as an effective treatment for CRF^{12 13} and CINV.¹⁴⁻¹⁶

Two study design aspects have been discussed widely in acupuncture trials: the choice of the control group and blinding of patients. Previous trials often either used a sham control and blinded patients or used an active control without blinding patients, as this was not possible. The idea of this trial is to not only use an active control but also allow the blinding of the patients.

The study investigates the effectiveness of an additional dysgeusia-specific acupuncture and self-acupressure intervention compared with a supportive acupuncture and self-acupressure intervention only regarding chemotherapy-induced dysgeusia in patients with cancer.

The aim of this study is to use an innovative approach and to

- ▶ Combine acupuncture and acupressure, provided by a health professional and as self-care intervention.
- ▶ Assess both patient-reported and objective outcomes.
- ▶ Use a control group receiving an active treatment while blinded to the study intervention.

METHODS AND DESIGN

Study design and recruitment

The study is planned as a multicentre, randomised, controlled two-armed, parallel-group, single-blind trial in Switzerland with a group sample size of 65 patients in each group (figure 1).

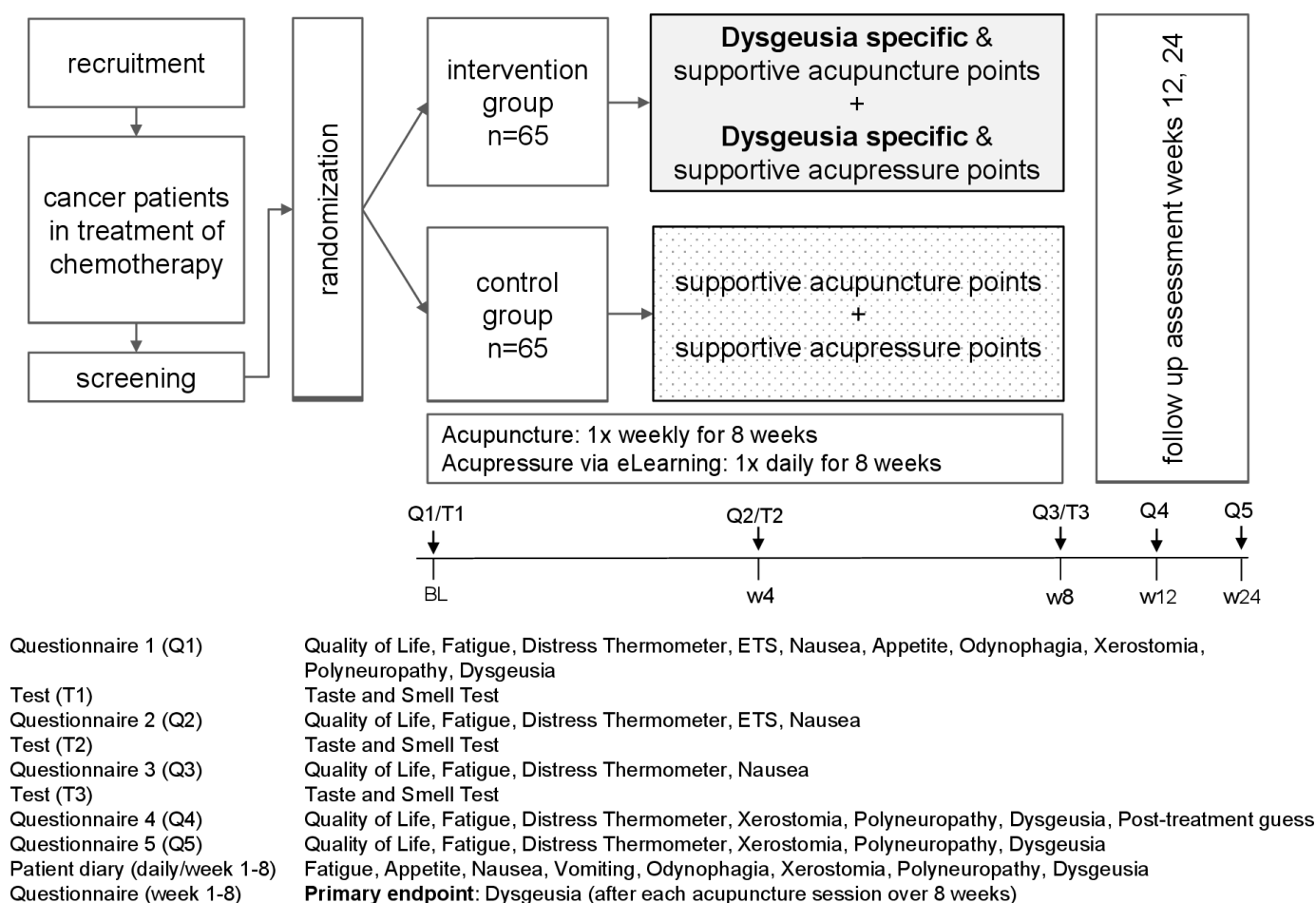


Figure 1 Flow chart of the study. BL, baseline; ETS, expectation for treatment scale.

Patient screening and inclusion will take place in two study centres in Switzerland, the Institute of Complementary and Integrative Medicine of University Hospital Zurich and the Center for Integrative Medicine at the Cantonal Hospital St. Gallen. Health professionals in charge of patients with cancer are informed about the study. Furthermore, patients will be informed about the study via the websites of the study centres and leaflets. Patient recruitment started in February 2021.

Randomisation and blinding

We will use central randomisation with the software REDCap. Randomisation will be conducted at a 1:1 ratio using block randomisation with variable block length, stratified by study centre and cancer type. Stratification according to cancer type will be used to better balance groups for the different chemotherapy regimens. The patients and statistician will be blinded. The randomisation sequence was generated by a statistician not further involved in the study with the software R. To ensure allocation concealment, the study group has no access to the master randomisation list. Only the acupuncturists will be allowed to do the randomisation. The study centre and cancer type must be chosen before randomisation, and those could not be changed or deleted after randomisation.

Patients can be blinded because the intervention group includes only additional dysgeusia-specific acupuncture and acupressure. Patients are not aware of the number of points and which points are dysgeusia-specific.

Inclusion criteria

Patients who fulfil the following additional inclusion criteria can be included:

- ▶ At least 18 years old.
- ▶ Indication of supportive routine care acupuncture treatment for fatigue, with a fatigue intensity of at least three on a Numeric Rating Scale (NRS 1–10).
- ▶ Dysgeusia of at least 5 on the NRS (=moderate dysgeusia (NRS 1–10)) with the screening tool (adapted from Zabernigg *et al.*).¹
- ▶ Currently treated with a chemotherapy regimen that includes taxanes, platinum based antineoplastic drugs or anthracyclines.
- ▶ Plan for chemotherapy treatment to continue at least 8 weeks after the beginning of acupuncture treatment.
- ▶ Breast, ovarian, endometrial, pancreas, colorectal, lung, prostate cancer, urothelial, carcinoma, germ cell tumour or sarcoma.
- ▶ Lymphomas with bone marrow infiltration <50% that are under treatment with anthracyclines.
- ▶ Performance status of Eastern Cooperative Oncology Group (ECOG) 0–1.
- ▶ Able to eat normal food without pain or swallowing problems.
- ▶ Internet access and interest in using eLearning.

Exclusion criteria

- ▶ Currently receive acupuncture treatment.
- ▶ Dysgeusia that occurred independently of the chemotherapy treatments for the current cancer.
- ▶ Confirmed positive COVID-19 test with associated dysgeusia prior to chemotherapy.
- ▶ Increased risk of bleeding, for example, caused by haemophilia or platelets <50 000 μ L.
- ▶ Coexisting myelodysplastic syndromes (MDS).
- ▶ Unable to speak sufficient German.
- ▶ Mucositis and dysgeusia with an impact on nutrition (pain or swallowing problems).
- ▶ Currently receiving or having a plan to receive radiotherapy (within the next 12 weeks) in the head/neck area.

Interventions

Both groups

Acupuncture is provided once a week over 8 weeks, and self-acupressure will be performed daily within these 8 weeks. The routine care treatment applied in both groups uses a modular approach: all patients receive supportive routine care acupuncture for at least CRF. Furthermore, patients who also have CINV and/or CIPN will also receive specific acupuncture points for those symptoms.

Acupuncture: Acupuncturists with more than 3 years of experience in Chinese-style acupuncture will perform the treatment. All of them received specific training for the study acupuncture before the trial started. The intervention and communication with patients will follow standard operating procedures (SOPs). CE certified sterile stainless-steel needles (SEIRIN Shizuoka, Japan; 0.20×15 mm, 0.25×40 mm) will be used. The needles will be inserted into the skin, stimulated manually to achieve de qi and will be retained for 20 min.

Acupressure: Patients will be trained using eLearning, and if necessary, the acupuncturists will show the correct application. The learning objective of eLearning is to enable patients to apply acupressure independently during the study. Access is password protected and individualised via the learning platform Moodlerooms/Open LMS at the study centre in Zurich. Patients will be instructed to perform acupressure following the Chinese style using their thumbs or index fingers daily before noon for 8 weeks, each point in a small circle with medium pressure for 3 min. The points will be the same as those chosen for acupuncture according to the randomisation but without the points for CINV and CIPN.

All patients will receive their cancer treatments (eg, chemotherapy) and routine supportive care therapies (eg, antiemetics). These interventions will be documented.

Intervention group

Patients in the intervention group will receive four additional points, which will be applied directly in combination with the respective supportive routine care points

during the same acupuncture session, where the CRF is treated.

The intervention group will also stimulate the same four additional points during self-acupressure. Because the blinding of the patients depends on the respective acupuncture points, the number of points and the location of the points for the different modules are kept confidential. Therefore, we cannot disclose the exact information of the acupuncture points (eg, names or locations of points used, unilateral/bilateral, number of needle insertions per subject per session, depth of insertion) in this protocol publication. These details will be provided in the publication of the study results.

Outcome measures

Primary outcome

The primary outcome of the study is the perceived dysgeusia over 8 weeks calculated as the mean from two patient-reported items on taste. This is based on a two-item questionnaire from the European Organisation for Research and Treatment of Cancer (EORTC) item database (Question 1: Have you had problems with your sense of taste? Question 2: Did food or drink taste different than usual?). Each item is assessed using an NRS ranging from 1 to 10 (1=no alteration, 10=severe alteration of taste). These questions will be completed by the patients directly after each acupuncture treatment.

Secondary outcomes

In addition, responder rates after 4 and 8 weeks for perceived dysgeusia (50% improvement from baseline) will be calculated. The secondary outcomes are according to the measurements from the following items:

Taste and smell test

For the taste and smell test, measured at baseline and at 4 and 8 weeks directly after the acupuncture treatment, we will use a common standard procedure. The taste test uses filter-paper taste strips (Burghart Messtechnik, Wedel, Germany). The smell test uses sniffing sticks (Burghart Messtechnik, Wedel, Germany) and comprises subtests for odour threshold (THR), odour discrimination (DIS) and odour identification (ID).

Patient diary

Patients will complete a diary during the 8 weeks of acupuncture treatment. The diary contains 9 items (xerostomia,¹⁷ polyneuropathy,¹⁸ dysgeusia,¹ odynophagia,¹⁹ fatigue,²⁰ nausea and appetite (based on the EORTC core quality of life questionnaire (QLQ-C30)) that are assessed on the NRS from 1 to 10, with higher values indicating more severe symptoms. Two additional items on chemotherapy and acupressure have yes or no as the response option.

Patient questionnaire

The questionnaire will be completed at baseline and at 4, 8, 12 and 24 weeks. The patient's quality of life will be assessed using a standard instrument in cancer,

the Functional Assessment of Cancer Therapy-General (FACT-G).²¹ For fatigue assessment, the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT)²² will be used. Distress will be assessed with the Distress Thermometer (Mehnert, Müller, Lehmann and Koch, 2006). The subjective items dysgeusia, xerostomia and polyneuropathy will be included in the questionnaire at baseline and at 12 and 24 weeks using the same questions as in the diary. Nausea will not be assessed at week 12 or 24 because it is closely linked to chemotherapy treatment. At week 12 patients will complete an additional question about post-treatment guess.

Weight and body composition

At baseline and at 4 and 8 weeks, body weight will be measured, and weight loss at 4 and 8 weeks will be calculated. In one centre (Zurich), body composition parameters will also be assessed at baseline and at 4 and 8 weeks using a Bioelectric Impedance Analysis (BIA) scale.

Expectation Measure

Expectation can have an impact on treatment outcome, and although we blind patients to the intervention, we will assess their treatment-related outcome expectation at baseline and at 4 weeks using a validated five-item questionnaire.²³

Safety assessment

In this study, severe adverse events (SAEs) and acupuncture-related adverse reactions (ARs) will be documented. Acupuncture has been shown to be safe, and the possible ARs have been included in the patient consent form.^{24,25} The documentation of ARs will be based on this form.

Given the patient population of this study (patients with cancer receiving chemotherapy), acupuncture will have numerous adverse events (AEs) that are not associated with acupuncture, and the cancer disease and its treatment will explain most of them. This has also been shown in one of the acupuncture studies in our team with patients with cancer under chemotherapy.²⁶ Because of the already available evidence about acupuncture-related side effects, AEs will not be documented.

The outline of the assessment schedule is displayed in figure 1.

Sample size calculation

Based on the primary outcome, a group sample size of 65 patients per group will achieve 90% power to detect a difference of 1.5 in the design with 8 repeated measurements when the SD is assumed to be 3, and the correlation between observations on the same subject is assumed to be 0.6. A difference of 1.5 points is considered to be of clinical relevance. The significance level is set at 0.05 (two sided). Considering dropouts, we plan to include a total of 130 patients. The sample size was calculated with PASS 2008 software (V.08.0.16, Release 27.01.2011; Hintze, J. (2008), NCSS, LLC, Kaysville, Utah, USA).

Statistical analysis

All available baseline data will be analysed descriptively per treatment group and in total. Interval and ratio variables will be reported as the mean and standard deviation (SD), and nominal and ordinal variables will be reported as frequencies and percentages.

The primary analysis of the primary outcome will be performed as a mixed-model analysis of repeated measures data with a compound symmetry covariance model. The model includes treatment as a fixed effect, subject as a random effect and the stratifying variables study centre (random effect) and cancer type (fixed effect), as well as the baseline perceived dysgeusia value as covariates. From this model, the mean of each treatment group over time (with the 95% CI) and the time-averaged difference of the group means (with the 95% CI) will be calculated, as well as the p value for the group difference. The significance level is set at 0.05 (two sided). The population for analysis will be the modified intention-to-treat (mITT) population.

The analysis of continuous secondary outcomes over time (eg, measured or summarised as weekly scores over 8 weeks) will be performed with similar models as those for the primary outcome. The analysis of continuous secondary outcomes for specific time points (eg, at 4 weeks) will be performed by analysis of covariance (ANCOVA). Treatment group (fixed effect), study centre (random effect), cancer type (fixed effect) and the respective baseline value (if available) will be included in the model as covariates. Adjusted treatment group means (with 95% CI) and the (exploratory) p value for the group difference will be presented. Binary secondary outcomes (including responders) will be analysed using logistic regression with treatment (fixed effect), study centre (random effect), cancer type (fixed effect) and the respective baseline value (if available) as covariates in the model. The odds ratio (OR), corresponding 95% CI and (exploratory) p value will be estimated from this model. In addition, secondary outcomes measured daily or weekly will be displayed graphically over time. The evaluation of all secondary outcomes will be performed with the full-analysis set (FAS).

The associations between subjective and objective taste and smell assessments will be explored in scatterplots, and Spearman correlations will be calculated. The population for analysis will be the FAS.

All safety variables will be tabulated (in total and per treatment group). Categorical variables will be reported as the frequency and percentage, and continuous variables will be reported with descriptive measures (mean, SD/SE, quartiles and range). The evaluation of safety outcomes will be performed with the safety population.

As additional analyses of the primary outcome, the following subgroups will be used: cancer type, centre, gender and objective smell/taste test affected (yes/no). Subgroup analyses will be performed by (additionally) including the subgroup variable and the interaction term subgroup*treatment into the model of the primary

outcome using the mITT population. In general, missing values will not be replaced. Sensitivity analyses for the primary outcome will include repeating the primary analysis: imputing missing data; using a different covariance structure (eg, autoregressive order 1 (AR(1))); using the per protocol population; and including additional baseline variables into the model in case of relevant baseline differences between the two treatment groups.

No interim analyses are planned.

Patient and public involvement

We included patient feedback from both routine care clinics on the study intervention in the study design. The eLearning for the acupuncture used a participatory approach during the development, where patients and health professionals participated in this process.

ETHICS AND DISSEMINATION

The study uses interventions that are usually seen as safe.²⁴ Furthermore, all patients will receive their cancer treatment and supportive treatment as usual.

The study was registered at the German Clinical Trials Register (DRKS00023348) and approved by the Cantonal Ethics Committee (CEC) (Kanton Zürich Kantonale Ethikkommission) (approval no. KEK-ZH-Nr. 2020-01900). Study results will be disseminated by publication in a peer-reviewed medical journal and made available via open access at least over the open repository and archive of the University of Zurich (<https://www.zora.uzh.ch>). In addition, an outreach concept will be developed to make the results accessible to the public.

DISCUSSION

Acupuncture has been increasingly included in integrative oncology settings. This is supported by growing evidence as displayed in most recent clinical practice guidelines.⁸ The potential of acupuncture in supportive cancer care is internationally recognised, with suggestions for more research.⁴ This study design takes up this call and focuses on one symptom: dysgeusia. In addition, the study design includes three innovative aspects, which will be discussed here more in depth.

Intervention: combination of acupuncture and acupressure

During the intervention period, patients will receive acupuncture treatment by acupuncturists once a week in the study centre. In addition, patients will perform self-acupressure at home once a day for 8 weeks. From the scientific point of view, there is evidence showing that somatosensory stimulation of cerebral areas is achieved both for acupuncture treatment and, in weaker patterns of brain responses, for tactile stimulation, such as acupressure.²⁷ There is a growing evidence on the understanding of the cortical responses evoked by different somatosensory stimuli, such as acupuncture and acupressure. Both electroacupuncture and acupressure show significantly

decreased response amplitudes following 5 min of stimulation. However, the latency of these decreases occurs much earlier in electroacupuncture than in acupressure.²⁸ Acupuncture, carried out in weekly intervals, provides a stronger stimulus than acupressure. However, acupressure is carried out daily. Acupuncture and acupressure in combination could lead to a higher dose of stimulation.

Furthermore, self-acupressure requires active participation, which can be easily taught via the eLearning platform; once patients have mastered the technique of self-administered acupressure, they can experience self-efficacy by implementing the supportive cancer care intervention.

Outcomes: assessment of patient-reported and objective outcomes

We decided to assess both to obtain a better understanding of the association between patient-reported and objective outcomes regarding dysgeusia and the impact of our intervention on both categories of outcomes. Dysgeusia is one of the most common side effects of the respective types of chemotherapy. Patients describe it as a disturbing feeling, which is often associated with loss of appetite, weight loss and decreased quality of life. Therefore, we chose the perceived dysgeusia item as the primary outcome. However, from the clinical point of view, we already know that dysgeusia does not necessarily correlate with the patient's self-reported taste alteration.²⁹ For this reason, we differentiate between objective taste results and subjective reported taste alterations (primary outcome), representing mainly the patient's disturbing clinical symptoms. The objective taste and smell test results count as the secondary outcomes, where we expect to provide further valuable data for comparison between perceived dysgeusia and actual objective dysgeusia obtained with a standardised taste and smell test.

In our study, we will analyse both subjective and objective data regarding dysgeusia obtained from patient questionnaires and taste/smell tests. As the objective testing is set up by patient feedback regarding presented different taste/smell concentrations, we are aware that the patient's answer is a subjective assessment, though within an objective, standardised setting.

Supportive acupuncture for all patients in the study to allow blinding for the study intervention

This study includes only patients with cancer who have an indication for supportive acupuncture treatment for fatigue. Because of this study design, we are able to blind the patients in both study groups because all participants will receive the same standardised supportive acupuncture treatment for CRF, meeting one of the inclusion criteria. We will also be able to provide additional points for CINV and CIPN in both study groups within the same acupuncture session by including different modules of standardised acupuncture options in our study design. Adding specific treatment for CINV and CIPN, if needed, will not have any repercussions on blinding issues or

altering the primary outcome. Hence, all study participants can benefit from a more personalised acupuncture treatment.

Our study design does not include a sham control group; all patients from both study groups will receive at least specific acupuncture treatment for CRF. Therefore, non-specific effects of acupuncture cannot be ruled out but would be expected to occur in both study groups as a result of blinding.

In addition to the three aspects, we wish to discuss the choice of acupuncture points. Many patients with cancer receive supportive acupuncture treatment at both study centres. In addition, the Breast Cancer Centre at Kliniken Essen-Mitte in Germany has long-term experience with acupuncture. Two acupuncture experts (TM and LZ) developed the supportive acupuncture protocol for CRF, CINV and CIPN based on previously published literature.^{13 14 30–33} The three protocols use only acupuncture points that, according to the theoretical framework of acupuncture, should not have any influence on dysgeusia in the aspects of functions or meridian connections.^{34 35} Those points, which are expected to be associated with dysgeusia, have been removed. Based on the clinical experience in the centres, specific acupuncture points have shown potential for improving dysgeusia symptoms. In traditional Chinese medicine (the great compendium of acupuncture and moxibustion, *Zhen Jiu Da Cheng*), disorders of the tongues are treated with needling of specific acupuncture points. The dysgeusia-specific acupuncture protocol was developed by the consensus of three acupuncture experts (TM, PV and LZ) based on the meridian theory of traditional Chinese medicine.^{34 35}

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Contributors CH, LZ and CMW designed the study and interventions. JB and SR advised on the statistical methods and will perform the statistical analysis. CMW and MS will oversee the overall conduct of the study. TM, PV and CD suggested the study design and interventions. CH and LZ have contributed equally to the paper in terms of research, planning and writing the protocol. CMW edited the manuscript. All coauthors critically reviewed and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Cantonal Ethics Committee (CEC) (Kanton Zürich Kantonale Ethikkommission) (approval no. KEK-ZH-Nr. 2020-01900) Participants gave informed consent to participate in the study before taking part.

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