

Published in final edited form as:

Contemp Clin Trials. 2012 July ; 33(4): 700–711. doi:10.1016/j.cct.2012.02.017.

Acupuncture for Dysphagia after Chemoradiation in Head and Neck Cancer: Rationale and Design of a Randomized, Sham-Controlled Trial

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Abstract

Introduction—Dysphagia is a common side effect following chemoradiation therapy (CRT) in head and neck cancer (HNC) patients. Current dysphagia management includes swallowing therapy and dilation procedures, but these treatments have limitations. While acupuncture has been reported to positively impact swallowing function and quality of life (QOL) in patients with dysphagia, current evidence is inconclusive.

Material and Methods—In an ongoing trial, 42 squamous cell carcinoma HNC patients, who are receiving platinum-based CRT with curative intent, are being recruited from a comprehensive cancer center. They are randomized to 12 sessions of either active acupuncture or to sham acupuncture during and following CRT over a 24-week period. Blinded research staff assesses outcomes at baseline, 20 weeks post-CRT (end of acupuncture), and 12 months after baseline (6-month follow-up). The primary outcome is change in M.D. Anderson Dysphagia Inventory score from baseline to 12 months. Secondary outcomes include QOL measures pertaining to HNC patients. In addition, a subset of study patients are tested for salivary flow rates and cytokines, including plasma transforming growth factor- β 1 and interleukin 6 (n=10 per arm), to preliminarily explore the biological mechanisms of acupuncture for dysphagia.

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Discussion—This paper addresses unique challenges related to study design in nonpharmacological, sham-controlled acupuncture trials including development of evidence-based credible verum and sham treatment protocols, blinding, and assuring fidelity of treatment. Results of this study will inform the feasibility of conducting a large scale trial and will provide preliminary evidence regarding the value of acupuncture for dysphagia in HNC patients.

Keywords

Acupuncture; chemoradiation therapy; radiation therapy; head and neck cancer; dysphagia; TGF- β 1; IL-6; MDADI; randomized sham-controlled trial

1. Introduction

Dysphagia, or difficulty with swallowing, is a common and expected side effect following chemoradiation therapy (CRT) in patients with head and neck cancer (HNC). It is reported to occur in up to 50% of patients after CRT[1–3]. Dysphagia and its related clinical presentation, aspiration, can significantly impact quality of life in cancer patients recovering from CRT. Many factors contribute to dysphagia, including prolonged mucositis, diffuse fibrosis, contracture and loss of flexibility of the pharyngeal constrictor muscles, xerostomia, and pain[4]. A significant proportion of HNC patients are feeding tube dependent for many months after completion of CRT[5]. A number of studies suggest that quality of life related to swallowing function for HNC patients fails to improve 12 months after therapy[6–8]. Consequently, innovative non-pharmacologic therapies offer an attractive option that may increase the rate and magnitude of recovery from dysphagia in HNC patients.

Acupuncture is an ancient Chinese medical technique that is growing in popularity in the United States. Previous research suggests that acupuncture may reduce symptoms and side effects that are associated with primary cancer therapy, such as chemotherapy-induced nausea[9, 10], hot flashes in women with breast cancer[11], and dysfunction and pain after neck dissection[12].

The uses of acupuncture for dysphagia are well documented in ancient Chinese medicine texts[13]. More recently, research using both animal models and human trials has begun to evaluate the efficacy and underlying mechanisms through which acupuncture may positively impact dysphagia.

Three published studies have characterized the responses of HNC patients with dysphagia to acupuncture[14–16]. In addition, our group has reported a case series of 10 HNC patients who had received acupuncture treatment and appeared to have a shorter duration with percutaneous endoscopic gastrostomy (PEG) tube[17]. Besides these HNC-related dysphagia reports, a significant body of literature exists that characterizes the efficacy of acupuncture for stroke-related dysphagia[18, 19]. While the etiology of dysphagia related to HNC and stroke are quite different, from a traditional Chinese medicine (TCM) perspective, many components of stroke-related acupuncture needling techniques are still relevant to radiation-induced dysphagia[18, 20, 21].

There are several pathologic changes affected by CRT that may impact dysphagia in the post CRT phase, namely vascular and nerve damage, xerostomia and fibrosis. Preliminary evidence suggests that acupuncture promotes the recovery of impaired swallowing function by inhibiting pro-inflammatory cytokines and growth factors[22–25]; stimulating peripheral and central nerve coordination[21, 26, 27]; increasing salivary production[28–30] and promoting tissue repair[31]. The hypothesized biological effects of acupuncture on

dysphagia and the supporting evidence are summarized and presented in Table 1 and Figure 1.

This paper addresses some of unique challenges related to study design and development of protocols in nonpharmacological, sham controlled acupuncture trials. The primary aims of this study are to collect preliminary data on the efficacy of acupuncture on dysphagia-related quality of life in HNC patients receiving chemoradiation therapy, while assessing the feasibility of recruiting and retaining patients into a randomized sham-controlled acupuncture trial. The secondary aim of the study is to preliminarily explore the biological mechanisms of acupuncture on dysphagia.

2. Materials and Methods

2.1 Overview of study design

This study is a pilot randomized, sham-controlled trial of acupuncture for HNC patients with dysphagia after chemoradiation therapy.

Participants who are diagnosed with squamous cell carcinoma of the head and neck receiving CRT, with or without neck dissection, and who are already undergoing swallowing therapy are randomized to 12 sessions of either active acupuncture (n=21) or sham acupuncture (n=21), over a period of 24 weeks. The primary aims of this study are to collect preliminary data on the efficacy of acupuncture in changing scores of quality of life in post CRT head and neck cancer patients. The primary outcome is change in M.D. Anderson Dysphagia Inventory score from baseline to 12 months, i.e. 6 month follow-up after completion of acupuncture treatment[32]. The feasibility of recruiting and retaining patients into a randomized sham-controlled acupuncture trial will also be assessed. Feasibility is evaluated with respect to our ability to recruit subjects, administer interventions and outcome measurements, elicit subjects' compliance, and retain subjects in this trial. A secondary aim of the study is to preliminarily explore, in a subset of 20 participants, the biological mechanisms of acupuncture on dysphagia, through evaluation of salivary flow production, and plasma TGF- β 1 and IL-6 levels.

Study participants randomized to the sham acupuncture will be offered a series of active acupuncture treatment as a courtesy at the end of the trial. Figure 2 summarizes the overall design and the flow of the patients through the study.

2.2 Sponsors

This trial is funded by the National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health. The grant is awarded to Dana-Farber Cancer Institute (DFCI), Boston, Massachusetts, and all clinical work will be performed there. Acupuncture will be administered at the Leonard P. Zakim Center for Integrative Therapies (Zakim Center), DFCI. Institutional Review Boards of Harvard Medical School and the Dana-Farber/Harvard Cancer Center have approved the study and the study is registered at clinical trials.gov (Identifier: NCT00797732).

2.3 Study population and enrollment procedures

2.3.1 Study population—Participants are recruited through the Head and Neck Cancer Program at DFCI, which has a large population of HNC patients in the Boston area. Over 500 new cases of HNC are seen each year. The potential study patients are mainly squamous cell carcinoma HNC patients who are receiving curative intent CRT for stage II, III or IV, without distant metastasis. Eligibility criteria for the study are presented in Table 2.

The identification of potential study subjects is primarily done during weekly tumor board meeting. Identified patients who initially meet eligibility criteria, are sent an introductory letter describing the study, inviting participation, and outlining initial eligibility requirements. In the letter, those who are interested in the study will be encouraged to call or send back a permission letter to the clinical research coordinator (CRC) for more information. A face-to-face contact at regular clinical visits is another way to recruit patients; interested patients names are then forwarded to the CRC.

During the initial interview, the CRC reviews the purpose of the study and required commitment for participation, and preliminarily confirms eligibility criteria. If at the end of this interview the participant is deemed preliminarily eligible and expresses interest, the CRC schedules a meeting with one of medical oncologists at the HNC unit. The oncologist confirms all eligibility criteria and asks subjects to sign the informed consent form to participate in the study. Eligible and interested subjects are then registered and randomized to either active or sham acupuncture treatments.

The consent form specifically states that all study patients will be invited to participate in additional “mechanistic tests” (salivary flow rate and cytokine tests) during the acupuncture study. Twenty patients interested in completing the mechanistic tests are randomly selected to perform the salivary flow rate assessment and have blood drawn for plasma TGF- β 1 and IL-6 at the baseline visit and at the 20-week post CRT visit, i.e. the end of acupuncture treatment.

2.3.2 Randomization and blinding procedures—Treatment assignments (active or sham acupuncture) are generated by the study statistician using a permuted block design with randomly varying block size. During the study, only treating acupuncturists and a designated unblinded study staff know the true treatment assignments of the patients. The study patients and the rest of the team members, including patients’ treating oncologists, speech-language pathologists and study CRCs are blinded to the treatment assignments throughout all follow-up visits. All information that might indicate treatment assignment, including Clinical Research Forms (CRF) with data on acupuncture needling protocols, will not be accessible by the CRC.

At a patient’s first acupuncture visit, the treating acupuncturist will not be aware of the randomized treatment assignment until the completion of the initial interview and explanation of the acupuncture procedure. They will obtain results of randomization by calling the central trial quality office immediately prior to beginning the first needling procedure.

2.4 Overview of acupuncture interventions

The acupuncture protocol outlined below is based on a comprehensive and systematic review of the published evidence, in combination with the clinical experience of our Zakim Center oncology acupuncture group. The reviewed literature includes: 1) an English- and Chinese-language peer-reviewed clinical and basic studies of acupuncture used for dysphagia; and 2) English- and Chinese-language acupuncture text books that describe treatment strategies for dysphagia[33, 34]. Our Zakim Center clinical team includes 5 practitioners with an average of 15 years of training, all of whom have specific expertise in oncology and who have participated in prior NIH studies evaluating acupuncture for cancer patients.

Our systematic review identified 7 papers with information on protocols and 6 primary text books. Data from this review were summarized and synthesized, presented to and

extensively discussed by study team, with the resulting protocol arrived at by consensus [15, 16, 19, 33–43].

As indicated by the results of the review, according to TCM, key imbalances of HNC-related dysphagia include local “heat toxin” from radiation, weakness in muscles, and “stagnation of Qi and blood” (inflammation). Consequently, our treatment strategy includes acupuncture points and needle stimulation strategies that “sedate fire”, “clear heat”, “invigorate blood” and “reduce stagnation”. These classical concepts coincide with the purported anti-inflammatory and neuromuscular stimulation effects of acupuncture discussed in the previous section[21–23, 25, 26, 44] (Figure 1) . A summary of acupuncture points, locations and related nerve innervations for the study of dysphagia is presented in Table 3.

There is currently no consensus regarding the ideal sham acupuncture intervention[45–48]. We have chosen to use a minimally invasive, shallow insertion control for a number of reasons. First, compared to our active TCM protocol, we believe our sham intervention is relatively inert. As discussed below in more detail, we employ very small and thin needles, and insert them shallowly, away from acupuncture points and meridians, and with minimal stimulation. Preliminary results from our previous study with cancer patients[49] suggest a significant difference between this sham approach and more vigorous active needling. Second, we have previously demonstrated that this method results in patients remaining blinded with respect to treatment allocation[49]. Therefore, the particular sham intervention we are using allows us to test the effect of active, clinically relevant treatments from non-specific effects of needle insertion and patient-practitioner interaction.

To assure consistent and high quality treatment and high fidelity to protocols, all treatments take place in the Zakim Center at DFCI and are administered by experienced, licensed and credentialed staff acupuncturists. All acupuncturists graduated from TCM medical schools in China with the same acupuncture training, and have a minimum of 10 years experience in practice. They have also participated in prior NIH-funded acupuncture trials for cancer patients. Protocol-specific trainings for treating acupuncturists are conducted prior to the study and throughout the study period. The study principal investigator periodically audits the study records to ensure the fidelity of acupuncture performance.

2.4.1 Active acupuncture procedure—The active protocol uses a unique, three-phase step-up protocol to gradually increase treatment area and treatment intensity. Based on our experiences in prior trials and in the Zakim Clinic, this protocol reduces the initial anxiety of patients to the treatment and maximizes the treatment intensity. The three phases of treatment are presented in Table 4.

Patients lie supine on a massage table with their arms and legs exposed. The skin on the acupuncture points is prepared with 70% ethyl alcohol. Acupuncture needles (Vinco, Helio Medical Supplies, 36 or 32 gauge, 0.20–0.25 x 25–40 mm) are inserted into acupuncture points bilaterally. The depth of insertion at each point is between 5–10 mm, except for points on the head and neck, which are between 2–5 mm. After insertion, acupuncture needles are manually manipulated in order to obtain the De Qi sensation. The De Qi sensation is defined as the acupuncturist feeling a tugging or grasping sensation from the needle manipulation and the patient feeling mild soreness, fullness, heaviness or local distension at local needling sites. The De Qi sensation is required on at least 2 points bilaterally on the lower extremity and at least 1 point bilaterally on the upper extremity. During the treatment protocol, and after De Qi is obtained, electroacupuncture is administered to a subset of acupuncture points. One pair of microalligator clips from the AWQ-104L electroacupuncture machine (Lhasa OMS, Inc.) is connected with the needles at

GV20 and Yintang, with the negative pole on the GV20 and the positive pole on the Yintang. The stimulation frequency is set at 4 Hz and the pulse width at 350 μ s, with a continuous wave pattern that is well-tolerated by the patient. The patient is asked to report sensations and should feel comfortable with the intensity of the electrostimulation. A TDP CQ-27 infrared heat lamp (Lhasa OMS, Inc) is turned on and is placed about 30 cm above the legs of the patient for warmth. The needles remain in place for 30 minutes. The patient is left alone in the treatment room with dimmed lights. A call bell is available to the study patient during the treatment period. After 30 minutes of treatment, needles are manually manipulated again before removal. De Qi sensation is not required at this time. A complete list of points that are used in active treatments is listed in Table 3. A total of 13, 22 and 27 needles are used during each acupuncture session at each of three phases respectively. Acupuncture point selection will remain at phase one until the 4th week post CRT, regardless of the number of acupuncture sessions received. This ensures that no needles are placed around the chin and neck area during CRT. Electrostimulation starts at the 3rd visit.

2.4.2. Sham acupuncture protocol—The sham intervention is designed to be maximally inert and minimally invasive while simulating most aspects of the active protocol. To minimize stimulation, very thin acupuncture needles (Seirin brand J type, size #02; 0.12 mm x 30 mm) are used. Seirin brand needles are manufactured with a special silicon coating on the tip and body of the needle to ensure smooth insertion. According to a needle test report published by Material Research & Testing Institute, Bauhaus University, Weimar, the Seirin needle requires approximately 30% of the force to insert the needle into a skin-like dermafoil as compared with other acupuncture needles. The #02 needle is the thinnest acupuncture needle available on the market. Needle insertion is limited to 0.2 mm to 0.5 mm in depth, and no needle manipulation is performed after the needle insertion; eliciting De Qi is prohibited. Sham needles are inserted at 14 locations paralleling the same body regions needled in the active group. Point locations include: 2 on each arm; 2 on the top of the head; 1 on the neck; and 3 on each leg.

All the sham points are administered bilaterally except No. 6. and No. 7. All sham acupuncture locations are off the pathways of meridians and acupuncture points according to TCM theory. The number of needles used mirrors the phases of treatment in the active arm. Table 5 presents the locations of the sham acupuncture points.

An electroacupuncture stimulation device identical to the one used in the active treatment arm is used. The internal electrical wires are disconnected so that no electric current will pass through. The green light on the device that indicates an “on” status is activated during each treatment. The wires are connected to the needles at sham points No. 6 and No. 7. The sham procedures related to the use of the heat lamp include the placement of the lamp at a greater distance from the body to minimize the therapeutic effect. These methods have been used in other studies[49–51].

2.4.3 Effective masking of treatment allocation and blinding—A number of measures will be taken to assure effective patient masking and blinding of treatment allocation. To draw attention away from the treatments, an eye pillow will be used in both the active and sham arms during each visit. To minimize differences between sham and active group, all treating acupuncturists are trained to follow a scripted standard operating procedure. Discussing treatment procedures with study subjects is prohibited.

To monitor one key aspect of quality of the needling technique, the treating acupuncturist verbally asks the patient the following questions right after the completion of the needling procedure at each session: “Would you please tell me the level of overall sensation you just experienced during the needling process, where zero (0) is you did not feel the needling

sensation at all and ten (10) is the strongest you could imagine? Please account for all sensations you experienced, e.g. tingling or numbness, not just pain.” The patient’s answer is documented on the CRF.

2.5 Outcome measures

All outcome measures are assessed by a CRC, blinded to treatment assignment. The primary clinical outcomes are changes in MDADI score from baseline to 12 months from baseline (i.e. 6 months follow-up after acupuncture). We have chosen this time frame because other studies suggest that swallowing function after CRT reaches a steady state that is representative of long-term outcome at approximately 12 months after therapy. Additional outcome measures include changes from baseline in MDADI at 20 weeks post CRT, i.e. end of acupuncture treatment, and other QOL questionnaires with changes from baseline in scores at 20 weeks post CRT; changes from baseline in weight at 20 weeks post CRT; and time-to-removal of feeding tube from baseline to the event. Table 6 summarizes all outcomes measurements.

2.5.1 M.D. Anderson Dysphagia Inventory (MDADI)—Our primary outcome is dysphagia-related QOL as measured by the MDADI. The MDADI is a validated, self-administered questionnaire specifically for dysphagia in HNC patients[32]. It is considered the best measure of QOL for this specific population, with a high reliability and sensitivity (Cronbach α =0.85–0.93), and has been used in a number of prior studies[32, 52–56]. This questionnaire is designed to characterize how patients view their swallowing ability as a result of treatment and how the swallowing dysfunction affects their quality of life. The MDADI can be used to track the longitudinal course of individual patient’s outcomes.

The MDADI has four sub-scales: global, emotional, physical, and functional, which were developed to characterize effects of dysphagia on different aspects of QOL. Five responses to items on the MDADI are printed for each item: strongly agree, agree, no opinion, disagree, and strongly disagree, and are scored on a scale of 1–5. Total scores range from 20 to 100, with 20 being low-functioning and 100 being high functioning.

2.5.2 Xerostomia Questionnaire (XQ)—The XQ is a validated 8-item questionnaire that specifically measures radiation-induced xerostomia in HNC patients. It has been used in a number of studies evaluating treatment effects in HNC patients[57–59]. It has been shown to have high reliability and sensitivity (test-retest correlation coefficient γ =0.82, p <0.01). Patients rate each symptom on an 11-point ordinal Likert scale from 0 to 10, with higher scores indicating greater dryness or discomfort due to dryness. The questions are equally divided into 4 items related to dryness while eating or chewing and 4 items related to dryness while not eating or chewing. Each item score is added, and the sum is transformed linearly to produce the final summary score ranging between 0 and 100, with higher scores representing greater level of xerostomia.

2.5.3 The Functional Assessment of Cancer Therapy-Head and Neck Scale (FACT-H&N)—The FACT-G (General) is a multidimensional quality of life instrument specifically designed for use with cancer patients[60]. The FACT-G consists of a 28-item core that can be supplemented by site and /or treatment specific subscales, including a HNC specific subscale (FACT-H&N)[60, 61]. The FACT-H&N has been shown to be reliable in HNC patients (coefficient α =0.70 for 9-item HNS). The FACT-H&N is a self-reported instrument consisting of 28 general plus 11 head and neck specific items, each rated on a 0 to 4 Likert-type scale. Items are combined to describe patient functioning in six areas: physical well-being, social and family well-being, relationship with doctor, emotional well-

being, functional well-being and head and neck related symptoms including dysphagia. Higher scores represent better quality of life.

2.5.4 Expectation and Treatment Credibility Scale—Patients' beliefs or expectations regarding the efficacy of acupuncture for treating dysphagia are assessed using a self-administered Treatment Credibility Scale (TCS) (scale 0–4, 4=greatest expectancy) developed by Borkovec and Nau, and modified for acupuncture studies[62, 63]. The instrument is administered at the baseline, second visit, and end of the study to assess the effectiveness of blinding.

2.5.5 Mechanistic Measurements

2.5.5.1 Salivary flow rate evaluation: Tests are done with unstimulated as well as stimulated methods following standard protocols[64]. During unstimulated saliva collections, patients are seated with eyes open and head tilted slightly forward and given instructions to minimize orofacial movements and to avoid sucking or swallowing, to prevent the influence on salivary flow[64]. Collections are performed between 9:00 am and noon to minimize diurnal variation. Patients are asked to refrain from eating, drinking, and performing oral hygiene for a minimum of 90 min before saliva collection. Just before collection, patients are instructed to swallow and then spit accumulating saliva into a preweighed 50-mL polycarbonate vial continuously for 5 min without swallowing. Stimulated collections consist of an initial swallowing, then the swabbing of 2% citric acid with cotton-tipped applicators to the lateral tongue bilaterally 5 times over a 2-min period, emptying the mouth, then collecting saliva into a polycarbonate tube, as above. Unstimulated and stimulated whole-mouth salivary flow rates are measured at the baseline visit and after the completion of 12th acupuncture treatment.

2.5.5.2 Plasma TGF- β 1 and IL-6: Plasma TGF- β 1 is a cytokine that reflects tissue fibrosis process. IL-6 is a major pro-inflammatory cytokine that is especially important in the initiation, development and prognosis of head and neck cancer[65, 66].

Study samples of plasma TGF- β 1 and IL-6 are sent to R&D Systems, Inc. for testing results. Briefly, for each sample, 5 mL of venous blood are collected into polypropylene tube on ice using EDTA as an anticoagulant. The plasma is centrifuged for 15 minutes within 30 minutes of collection and stored at $<-70^{\circ}\text{C}$ [67]. Plasma TGF- β 1 and IL-6 level are determined by ELISA using monoclonal anti-human TGF- β 1 and IL-6 antibodies according to manufacturer's instructions (R&D Systems, Inc. USA). Samples are collected at the baseline visit and at the completion of the 12th acupuncture treatment. All study samples for a given individual will be deidentified and analyzed in batch; each batch includes a quality control (QC) sample.

2.5.6. Other secondary outcomes—Other secondary outcomes including changes of weight, PEG tube duration, and dietary consistency. These data will be extracted from patients' medical records by the study CRC. In addition, data from a video fluorographic swallowing study will be exploratory measured in patients who are required to undergo the study as part of clinical practice.

2.5.6 Adverse Events—The safety of the acupuncture intervention is evaluated by documenting any symptoms possibly related to acupuncture at each acupuncture visit, which includes bleeding, bruising at needling sites, pain level, and fatigue. The treating acupuncturist records these items and documents them in a toxicity form. All adverse events will be reported to the DFCI IRB and the protocol sponsor.

Care will be available for any sequelae that may occur. Each patient will have usual access to their primary physician and oncologist. All intervention sessions will be held in DFCI where an emergency code cart and hospital code team are immediately available at all times.

To minimize risks, this trial requires all acupuncturists to have high standards of education and experience, and to observe the state requirement of using one-time-use disposable sterile needles.

2.6 Statistical Analysis Size and Power

2.6.1 Statistical analysis—The primary outcome is change in M.D. Anderson Dysphagia Inventory score from baseline to 12 months (6 month post acupuncture treatment) between the active acupuncture and sham acupuncture arms. This study will provide preliminary estimates of the differences between sham and active acupuncture as well as estimates of the standard deviations of change (from baseline) for each of the outcome measures. This information will inform the design and sample size for a definitive study. A secondary aim of the analyses is to compare both groups with respect to changes between baseline and 20 weeks post CRT for MDADI scores and all other QOL questionnaires; and to compare groups with respect to time-to-removal of feeding tube.

To assess the feasibility of conducting a trial of acupuncture for HNC patients, we use screening logs to determine the proportion of screened patients who are eligible and the proportion of eligible patients who enroll in the study. We track factors that make subjects ineligible, and for unwilling eligible subjects, reasons for not participating. We measure compliance through attendance at treatments. Participants who attend at least 80% of the target number of treatments are considered protocol compliant. Overall, we will consider further study feasible if at least 75% of intervention participants are compliant and at least 80% of participants in each group complete all study evaluations (i.e., baseline, 2nd treatment, 4 weeks, 8 weeks, 12-weeks, 20 weeks post CRT, and at 6 months post acupuncture, i.e., 12 months from baseline), and we are able to recruit patients at the anticipated rate.

We will conduct all primary analyses according to the intention-to-treat paradigm using the Wilcoxon rank-sum test. As a non-parametric test, the Wilcoxon test is conservative, less sensitive to outliers in smaller samples, and does not require the assumption of normality. Exploratory secondary analyses include fitting ordinary least squares regression models to evaluate the association between the primary outcomes and a variety of possible predictors (e.g., severity of dysphagia, age, tumor site, radiation dose, etc). We will also test blinding, expectancy and perceived intensity of acupuncture needling and other effect modifiers. The goals are to identify factors that need to be included in the design of a definitive study (i.e., stratification factors) and to identify interesting associations for further investigation (i.e., hypothesis generation). Individual missing items in multi-item scales will be handled as recommended by the scale developers. For missing data due to loss to follow-up or other reasons for non-response, we will employ multiple imputation methods to adjust for the missing data. We will use an imputation model that accounts for the longitudinal structure of the missing data.

2.6.2 Sample Size and Statistical Power—Sample size calculations are based on the primary outcome, MDADI. According to Chen, the lead developer of the MDADI[32], a difference of 20 points is considered clinically significant (AY Chen, personal communication). Only one study provides data on the standard deviation of change in MDADI[53], but in a different subpopulation of HNC, and at 12 months follow-up rather than 6 months. The observed standard deviation in their study was 17.1 points. Allowing for a 20% loss to follow-up and a 10% loss in efficiency for the nonparametric test (relative to a

t-test), we estimate that a sample size of 21 per treatment group will provide 90% power to detect a 20 point difference between active and sham acupuncture.

3. Discussion

The design of this study takes into account a number of unique aspects of nonpharmacological trials, particularly issues for sham controlled acupuncture trials[47]. This includes developing an evidence-based standardized active treatment protocol, selecting an appropriate sham control, and maintaining the effectiveness of blinding.

Developing a standardized active treatment protocol of acupuncture is an imperative step for clinical trials[68]. Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) provides an excellent guidelines[69]. Although acupuncture has been practiced for several thousand years, standardized or validated treatment protocols for most biomedical conditions do not exist. In this study, we used a systematic and evidence-based approach, combined with a consensus building process, to develop both active and sham protocols. Our approach not only identify acupuncture points most relevant for treating HNC patients undergoing CRT, but also identified other key protocol components such as depth of needling, intensity of needling stimulation, frequency of treatments, and strategies to gradually escalate the treatment intensity. The resulting protocol thus represents a strong test of the potential effects of acupuncture for this population.

There is substantial debate regarding the optimal sham control for an acupuncture trial. Sham intervention ideally should mimic the procedure of acupuncture without eliciting therapeutic effects[48]. However, it has been suggested that sham acupuncture needling also evokes physiological responses that are similar to real acupuncture needling, and this may explain why effect sizes in many sham controlled studies are small[45, 46, 70, 71]. For this reason, some have argued that using non-invasive acupuncture needles as sham control is a better approach than the minimally invasive needling approach we are employing[71, 72]. Because of the smaller needle diameter, softer needle body, and very shallow insertion we are employing in this study, we believe the stimulation will be quite minimal, and perhaps even less strong than non-insertive controls that often apply significant surface pressure. The intent of our method is to minimize stimulating effects of needling and to avoid the activation of sensory receptors. Nevertheless, the subtle effect of needling procedure on the system cannot be completely discounted. Therefore, this study represents a rigorous test of specific effects of acupuncture needling.

Sham-controlled acupuncture trials closely resemble many aspects of sham surgical trials[73]. While sensory acuity of study participants is usually suppressed by anesthesia in sham surgical trials, participants in sham controlled acupuncture trials are fully aware of the entire needling process. Therefore, maintaining an effective blinding in acupuncture procedure poses a great challenge. This is particularly important since our IRBs request explicit statements in the consent form to inform study participants regarding the use of sham acupuncture. Therefore, all study participants clearly understand that there is a chance to be randomized into a “sham control”. Because of possible bias that may develop due to incomplete blinding, we will assess the effectiveness of blinding by using the credibility scale in our secondary analysis[50], and these blinding outcomes will be used as potential confounders in secondary analyses.

Overall, our protocol design follows three principles: 1. collecting the best evidence available to determine a valid and maximally effective acupuncture protocol for a specific clinical condition; 2. minimizing the variability of acupuncture performance by using standardization operation procedures, repeat protocol training, and constant monitoring; and,

3. maximizing the potentially therapeutic differences between protocol parameters in the active acupuncture and the sham acupuncture.

The preliminary evidence generated from this study will be used to evaluate the value of acupuncture as an intervention for radiation induced dysphagia in head and neck cancer patients. If the results are positive, the data collected from this study will be used to design and inform a larger definitive study to fully evaluate the clinically meaningful effects of acupuncture for this group of patients and an exploratory study to further evaluate the mechanisms underlying acupuncture's effect on HNC-related dysphagia.

Acknowledgments

This study is supported by grant 1K01 AT004415 from the National Center for Complementary and Alternative Medicine (NCCAM).

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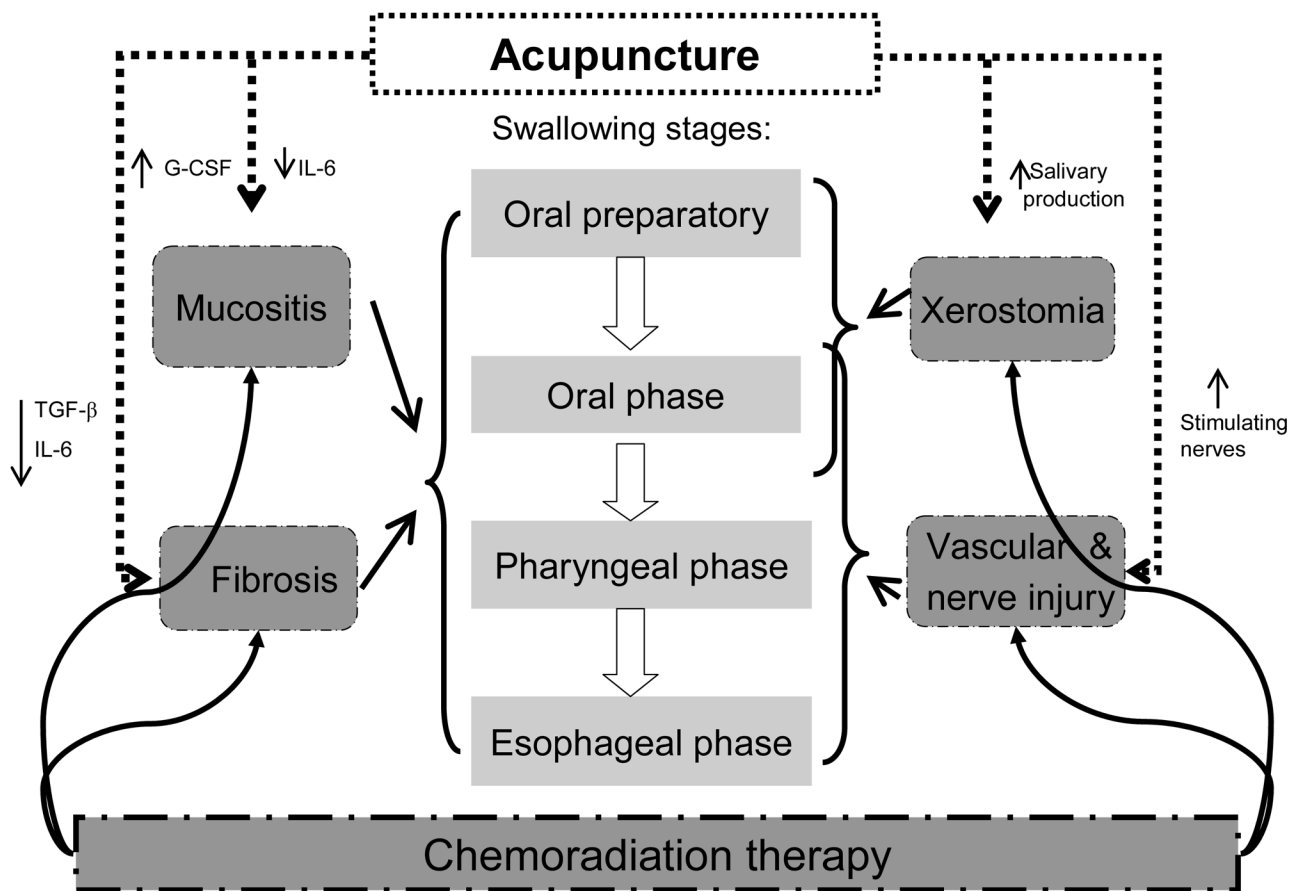


Figure 1. Hypothesized effects of acupuncture for dysphagia in head and neck cancer
 Solid curve lines: pathological damage of chemoradiation therapy;
 Dash lines: potential effects of acupuncture on pathological factors of dysphagia;
 Downward small arrows: inhibitory effects of acupuncture;
 Upward small arrows: stimulating effects of acupuncture.

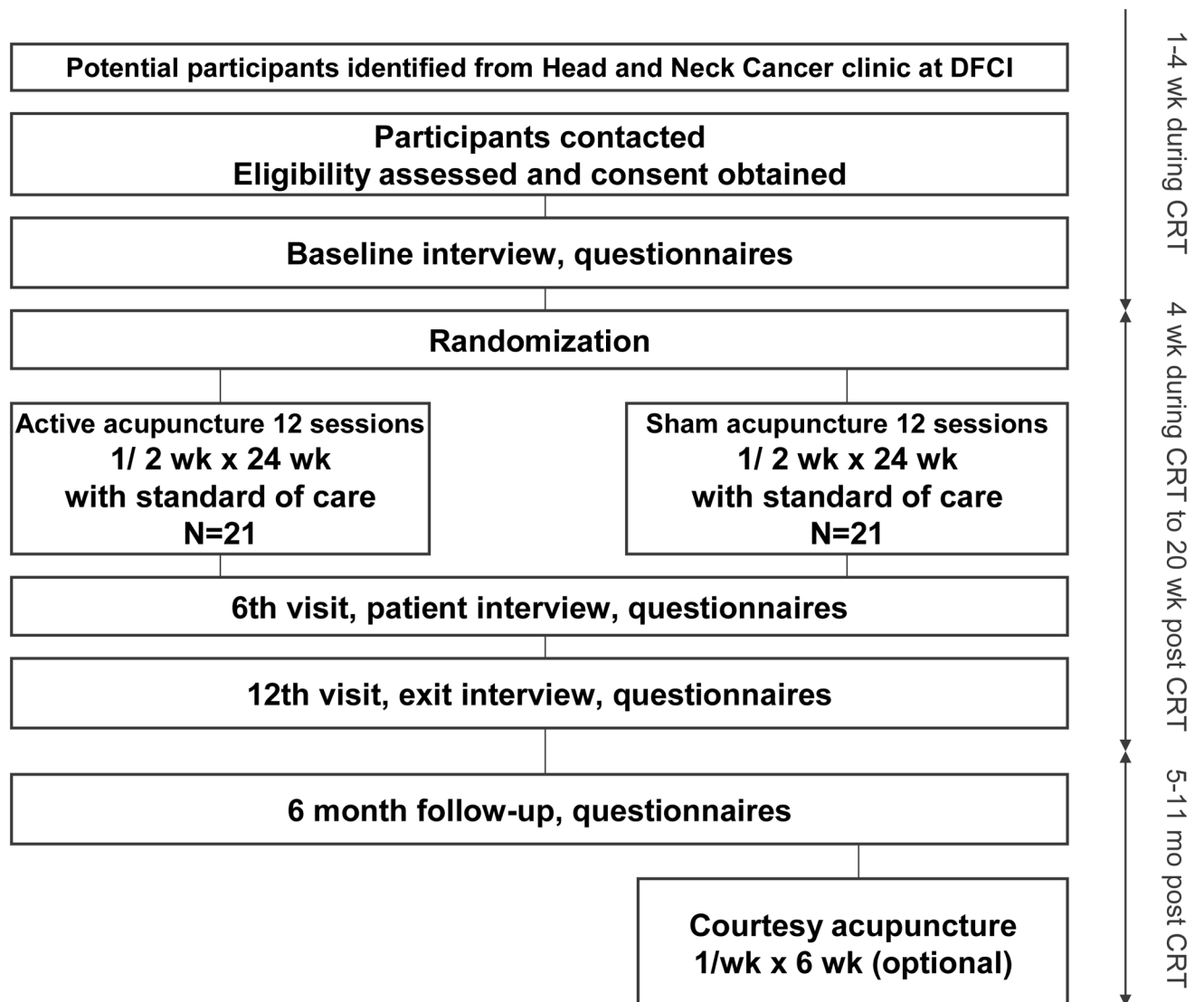


Figure 2.
The study design and the flow of the participants through the trial

Table 1

Supporting evidence for biological effects of acupuncture on dysphagia.

Author/Year	Subjects	N	Groups*	Conditions	Interventions	Relevant Measurements	Results
Cui 2007[31]	rats	60	6	cyclophosphamide induced leukopenic rats	EA [†] vs. rat model	serum GM-CSF [‡]	EA significantly increased GM-CSF level at day 11 compared with model group (p<0.01)
Chen 2006[22]	humans	120	2	acute cerebral infarction	MA [§] plus medications vs. medications	serum IL-6 ^{**}	IL-6 level significantly decrease in acupuncture group compared with medication group at day 14 (p<0.05)
Zhuang 2006[25]	rats	36	3	chemical radiculitis	MA vs. no treatment	plasma IL-6	IL-6 level significantly decreased in the acupuncture group compared with model group at day 30 (p<0.05)
Ma 2009[23]	rats	40	4	carbon tetrachloride induced hepatic fibrosis	EA vs. model	tissue TGF-β1 ^{††}	Protein expression of TGF-β1 significantly decreased in EA-treated group vs. model group at week 8 (p<0.01)
Xiao 2002[24]	rats	72	4	acute ischemic myocardial infarction	EA vs. model	tissue TGF-β1	TGF β1 expression in myocardium less in EA group than model group (+++ vs. +) at week 1
Zhang 2002[26]	humans	30	1	chronic stroke related dysphagia	MA	evoked potential in brainstem and swallowing related muscles	Amplitude and time duration of citrothyroid and tongue muscles decreased after acupuncture (p<0.05)
Seki 2003[21]	humans	41	1	chronic cerebral infarction related dysphagia	MA	latency time in swallowing (LTSR)	Significant improvements in LTSR 30 minutes after MA; continued for up to 7 days
Seki 2005[20]	humans	32	2	poststroke with dysphagia	MA+ usual care vs. usual care	videofluoroscopic swallow study	Mean swallowing time significantly shorter in MA group vs. usual care group at week 4 (p<0.05)
Deng 2008[27]	humans	20	1	healthy volunteers	true MA vs. sham MA	fMRI ^{‡‡}	True MA associated with bilateral activation of the insula and adjacent operculum; induced more saliva production than sham MA
Braga 2008[29]	humans	12	1	radiation induced xerostomia	MA	objective resting and stimulated whole salivary flow rates	Statistically significant improvement for salivary flow rates found at week 6 (P<0.05)
Blom 1992[28]	humans	21	2	xerostomia	MA vs placebo MA	salivary flow rates	MA group showed significant persistent increase of salivary flow rates vs. placebo MA
Dawidson 1997[30]	humans	8	1	healthy volunteers	MA and EA	stimulated and unstimulated salivary flow rates	Significant increase of unstimulated salivary flow both during and after MA

* Randomization assignments were applied in all groups except single arm studies

⁷EA: electroacupuncture

[#]GM-CSF: granulocyte-macrophage colony-stimulating factor

[§]MA: manual acupuncture

^{**}IL-6: interleukin 6

^{††}TGF- β 1: transforming growth factor beta 1

^{††}fMRI: functional magnetic resonance imaging

Table 2

Eligibility criteria of the acupuncture study for dysphagia in HNC patients

Inclusion criteria	Exclusion criteria
Histologically or cytologically proven squamous cell carcinoma of the head and neck at stage II, III or IV, without evidence of distant metastasis Stage I disease will also be permitted if the patient is receiving CRT Primary tumor sites eligible: nasopharyngeal, oropharynx, hypopharynx or larynx, and tumors of the nasal and paranasal cavities Unknown primary squamous cell carcinoma in the neck Receiving chemoradiation Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 Adequate hematological function: neutrophil count $>1.0 \times 10^9/L$, platelet count $>50 \times 10^9/L$ Age 18 years Signed informed consent	Unstable cardiac disease or myocardial infarction within 6 months prior to study entry Wearing a pacemaker or implantable cardioverter-defibrillator History of significant neurologic disorder that affects swallowing, including stroke, neurodegenerative disease, advanced dementia, or uncontrolled seizure disorder Active clinically significant uncontrolled infection Prior use of acupuncture for dysphagia Patients with uncontrolled major psychiatric disorders, such as major depression or psychosis

Table 3

Acupuncture points, locations and related nerve innervations for the study of dysphagia

Name	Chinese Pinyin Name	Location	Innervations
GV24	Shenting	0.5 cun ^{§§} directly above midpoint of anterior hairline.	The branch of the frontal nerve.
GV20	Baihui	On the midline of the head; 7 cun directly above posterior hairline; approximately on midpoint of line connecting apexes of two auricles.	The branch of the great occipital nerve.
SI16	Tianchuang	In the lateral aspect of the neck, in the posterior border of m. sternocleidomastoideus, posterosuperior to Futu.	The cutaneous cervical nerve, the emerging portion of the great auricular nerve.
GB20	Fengchi	In the depression between the upper portion of m. sternocleidomastoideus and m. trapezius, on the same level with Fengfu.	The branch of the lesser occipital nerve.
CV24	Chengjiang	In the depression in the centre of the mentolabial groove.	The branch of the facial nerve.
CV23	Lianquan	Above the Adam's apple, in the depression of the upper border of the hyoid bone.	The branch of the cutaneous cervical nerve, the hypoglossal nerve, and the branch of the glossopharyngeal nerve.
ST7	Xiaguan	At the lower border of the zygomatic arch, in the depression anterior to the condyloid process of the mandible. This point is located with the mouth closed.	The zygomatic branch of the facial nerve and the branches of the auriculotemporal nerve.
ST6	Jiache	One finger-breadth anterior and superior to the lower angle of the mandible where m. masseter attaches at the prominence of the muscle when the teeth are clenched.	The great auricular nerve, facial nerve and masseteric nerve.
ST5	Daying	Anterior to the angle of mandible, on the anterior border of the attached portion of m. masseter, in the groove-like depression appearing when the cheek is bulged.	The facial and buccal nerves.
LI2	Erijian	On the radial side of the index finger, distal to the metacarpal-phalangeal joint, at the junction of the red and white skin. The point is located with the finger slightly flexed.	The dorsal digital nerve of the radial nerve, and the palmar digital properal nerve of the median nerve.
LI11	Quchi	When the elbow is flexed, the point is in the depression at the lateral end of the transverse cubital crease, midway between Chize and the lateral epicondyle of the humerus.	The posterior antebrachial cutaneous nerve; deeper, on the medial side, the radial nerve.
ST36	Zusanli	3 cun below Dubi, one finger-breadth from the anterior crest of the tibia, in m. tibialis anterior.	Superficially, the lateral aural cutaneous nerve and the cutaneous branch of the saphenous nerve; deeper, the deep peroneal nerve.
Sp9	Yinlingquan	On the lower border of the medial condyle of the tibia, in the depression on the medial border of the tibia.	Superficially, in the medial crural cutaneous nerve; deeper, the tibial nerve.
Sp6	Sanyinjiao	3 cun directly above the tip of the medial malleolus, on the posterior border of the medial aspect of the tibia.	Superficially, the medial crural cutaneous nerve; deeper, in the posterior aspect, the tibial nerve.
K3	Taixi	In the depression between the medial malleolus and tendo calcaneus, at the level with the tip of the medial malleolus.	The medial crural cutaneous nerve, on the course of the tibial nerve.
Extra	Yintang	Midway between the medial ends of the two eyebrows.	N/A

^{§§} cun, a measuring unit in acupuncture, approximately 1 inch

Table 4

Acupuncture treatment strategy and treatment phases for HNC patients with dysphagia

Phases of Treatment	Treatment Intention	Treatment Visits	Points, Stimulation and Number of Needles
1	Reduce anxiety regarding needling; familiarize patient with procedure; initiate body response	1 st and 2 nd	ST36, SP9, K3, LI11, GV20, GV24, Yintang; mild; 13 needles ^{***}
2	Increase intensity; expand to facial area; continue body response	3 rd -7 th	Add LI2, ST7, ST5, CV24; Add electroacupuncture moderate; 22 needles
3	Increase intensity; expand to the back and front of neck; maximize body response	8 th -12 th	Add SI16, GB20, CV23, continue electroacupuncture; 27 needles

^{***}Acupuncture point selection will remain at phase one until the 4th week post CRT, regardless of the number of acupuncture sessions received.

Table 5

Sham acupuncture point locations

Sham points	Anatomical Locations
No 1.	3 cun above the tip of the medial malleolus, 2 cun posterior to the posterior border of the medical aspect of tibia.
No 2.	2 cun above the superior lateral border of the patella and 2 cun posterior to the line of connecting with the Anterior Superior Iliac Spine (ASIS)
No. 3	1 cun above the superior medial border of the patella and 1 cun posterior.
No. 4	3 cun above crease of wrist on the posteriorlateral aspect of the forearm, midway between TW 6 (Zhiguo) and LI 6 (Pianli).
No. 5	On the lateral side of the upper arm, 1 cun above LI11(Quchi), midway between LI12(Zhouliao) and the pathway of Lung meridian.
No 6.	3 cun directly above the midpoint of the anterior hairline and 1 cun lateral to the midline on the right side.
No 7.	3 cun directly above the midpoint of the anterior hairline and 1 cun lateral to the midline on the left side.
No 8.	1 cun directly below the depression posterior and inferior to the mastoid process, GB12 (Wangu)

Table 6

Summary of outcome measures and testing schedule

Assessment	Description	Baseline	@2 nd Tx	@ 4 wk post CRT	@ 8 wks post CRT	@ 12 wk post CRT	@20 wk post CRT	@ 12 mos from baseline
History/physical	Cancer history and treatment	x						
Weight	Weight changes	x		x	x	x	x	x
Feeding Tubes	Presence and absence of feeding tube and time-to-removal	x		x	x	x	x	x
QOL: MDADI	Dysphagia specific QOL	x		x	x	x	x	x
QOL: FACT-H&N	General cancer plus HNC QOL	x		x	x	x	x	x
QOL: XQ	Xerostomia specific QOL	x		x	x	x	x	x
Dietary Consistency	Monitor dietary continuum	x		x	x	x	x	x
TCS	Monitor treatment expectation and credibility		x				x	
Blinding	Assess treatment blinding effect		x				x	
VFSS study*	Assess the oral pharyngeal and esophageal stages of deglutition						x	
Salivary flow rate*	Assess salivary flow production	x					x	
TGF- β 1/IL-6*	Assess TGF- β 1/IL-6 levels	x					x	

MDADI: The M.D. Anderson Dysphagia Inventory

FACT-H&N: The Functional Assessment of Cancer Therapy-Head and Neck

XQ: Xerostomia Questionnaire

TCS: Treatment Credibility Scale

VFSS: Videofluorographic swallowing study

* only patients who participate the mechanistic tests need to take these tests.