


# Acupuncture for Radiation-Induced Xerostomia in Cancer Patients: A Systematic Review and Meta-Analysis

Integrative Cancer Therapies  
Volume 19: 1–14  
© The Author(s) 2020  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/1534735420980825  
journals.sagepub.com/home/ict  


Xixiu Ni, MD<sup>1</sup> , Tian Tian, MD<sup>1</sup>, Dan Chen, MD<sup>1</sup>, Lu Liu, MD<sup>1</sup>, Xiao Li, MD<sup>1</sup>, Fengmei Li, MD<sup>1</sup>, Fanrong Liang, PhD<sup>1</sup>, and Ling Zhao, PhD<sup>1</sup>

## Abstract

**Background:** Radiation-induced xerostomia is one of the most common symptoms experienced by cancer patients. The aim of our study is to evaluate the preventive and therapeutic effect of acupuncture for radiation-induced xerostomia in cancer patients. **Methods:** Eight databases were searched for all published randomized clinical trials (RCTs) on acupuncture for radiation-induced xerostomia in cancer patients up to December 31, 2019. Manual searching included other conference abstracts and reference lists. Meta-analysis was conducted using Revman V.5.3, and risks of bias for included studies was assessed following the Cochrane Handbook. **Results:** Eight clinical trials (725 participants) were analyzed, and 3 were included in a meta-analysis. All included trials had a high risk of bias, such as selection, performance, and detection bias. Analysis indicated favorable effects of acupuncture regarding the improvement of xerostomia symptoms (MD  $-3.05$ ,  $P=0.02$ , 95% CI  $-5.58$  to  $-0.52$ ), compared with sham acupuncture. There were no significant differences between real acupuncture and sham acupuncture regarding the stimulated salivary flow rate (MD  $0.37$ ,  $P=0.08$ , 95% CI  $-0.05$  to  $0.79$ ) and unstimulated salivary flow rate (MD  $0.09$ ,  $P=0.12$ , 95% CI  $-0.02$  to  $0.21$ ), which were whole salivary flow rate. Compared with no acupuncture (standard oral care, usual care, or no treatment), acupuncture produced a significant improvement in patient-reported xerostomia, without causing serious adverse effects. However, a Grading of Recommended Assessments analysis revealed that the quality of all acupuncture outcome measures was low. **Conclusion:** The present meta-analysis and systematic review suggests that acupuncture is effective at improving xerostomia symptoms in cancer patients but not at objective salivary flow measurements. The evidence is still limited due to the low quality of the published studies.

## Keywords

acupuncture, cancer, xerostomia, systematic reviews

Submitted August 19, 2020; revised November 3, 2020; accepted November 24, 2020

## Introduction

Xerostomia is associated with reduced salivation that causes a subjective sensation of a dry mouth, and is one of the most common symptoms experienced by patients with cancer.<sup>1-4</sup> Cancer treatments often adversely affect the quantity and quality of saliva. Patients may show clinical signs of dry mouth, such as hypofunction of the salivary glands (SGs) or hyposalivation, or symptoms of dry mouth (xerostomia). The decline in SG function is most severe after radiation therapy of the head and neck.<sup>5-10</sup> Patients with cancer report varying degrees of dry mouth, reduced diet, and somniphathy,<sup>11</sup> and are at higher risk of developing dental complications, dysgeusia, dysphagia, odynophagia, difficulty sleeping and speaking, and oral ulcers, which may

seriously decrease quality of life.<sup>12</sup> Xerostomia may also lead to decreased patient compliance and impact treatment, which can lead to inadequate tumor control<sup>13</sup>; therefore, it is

<sup>1</sup>Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China

### Corresponding Authors:

Fanrong Liang, Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, No. 37 Shi'er Qiao Road, Chengdu, Sichuan 610075, China.  
Email: acu973@126.com

Ling Zhao, Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, No. 37 Shi'er Qiao Road, Chengdu, Sichuan 610075, China.  
Email: zhaoling@cduetcm.edu.cn



important to initiate effective xerostomia treatment. Several methods are available for the management of xerostomia, including stringent oral hygiene, fluoride agents, antimicrobials, saliva substitutes, and sialagogic agents that increase salivary secretion<sup>14-32</sup>; however, these treatments achieve limited effects<sup>23-32</sup> and often induce adverse effects such as headache, dizziness, and sweating.<sup>19-21</sup> Amifostine has been approved by the Food and Drug Administration to reduce the incidence and severity of radiation-induced xerostomia, but it requires parenteral administration, has potential adverse effects, and is not universally available.<sup>33</sup> There is also some low-level evidence that saliva substitutes and stimulants are beneficial for cancer-induced xerostomia.<sup>34</sup>

Acupuncture comprises the needling of specific points of the body, and is one of the most widely used complementary therapies in many countries as a valid palliative intervention modality.<sup>35,36</sup> In 2003, the World Health Organization published a report on the efficacy of acupuncture in the cure or relief of 64 different symptoms, including xerostomia.<sup>37</sup>

There are several hypotheses regarding the mechanism by which acupuncture may increase saliva secretion. Acupuncture stimulates the parasympathetic and sympathetic nervous systems through neuronal activation,<sup>38-41</sup> and causes the release of neuropeptides, such as vasoactive intestinal peptide and calcitonin gene-related peptide.<sup>40,41</sup> These neuropeptides have anti-inflammatory properties and nutritional effects on the SGs, and increase the blood flow in the acini. Acupuncture also directly affects the local blood flow near the SGs, thereby increasing the secretion of saliva.<sup>42</sup> Finally, acupuncture therapy may tap into the neuronal circuit that activates the salivary nuclei in the pons and subsequently the SGs via the cranial nerves.<sup>38</sup>

Some studies have explored the effect of acupuncture on xerostomia and showed that it can effectively treat or prevent dry mouth,<sup>43-56</sup> and xerostomia is most common in cancer patients who were undergoing radiation therapy. However, high quality trials investigating efficacy and safety of acupuncture for radiation-induced xerostomia was limited. And 4 new trials have been published since the publication of previous systematic reviews of acupuncture for radiation-induced xerostomia in patients with head and neck cancer.<sup>57,58</sup> Therefore, the present study aimed to update the evidence base by including the many clinical trials published during the past 10 years. A comprehensive review of acupuncture treatment of radiation-induced xerostomia in cancer patients might be beneficial to patients, practitioners, and healthcare policy-makers. The present systematic review and meta-analysis aimed to evaluate all of the currently available studies of acupuncture as a treatment or prevention for radiation-induced xerostomia in cancer patients.

## Methods

### Protocol and Registration

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>59</sup> The peer-reviewed protocol of this systematic review and meta-analysis was published in PROSPERO (registration no. CRD42019129069).<sup>60</sup>

### Search Method

Two authors independently performed a systematic literature search of the following databases: PubMed, MEDLINE, Cochrane Library, Embase, China National Knowledge Infrastructure, Chongqing VIP Chinese Science and Technology Periodical Database, Wanfang Database, and China Biology Medicine Disc. The search strategy consisted of 3 components: clinical condition (cancer, tumor/tumour, carcinoma, neoplasm AND xerostomia), intervention (manual acupuncture, electroacupuncture, body or auricular acupuncture), and study type (randomized clinical trial). The databases were searched from inception to December 31, 2019. The Pubmed search strategy is shown in Table 1; this strategy was modified appropriately for other databases. The authors also searched the Index to Scientific & Technical Proceedings (Web of Science) and the reference lists of relevant primary and review articles to identify cited articles not detected in electronic searches.

### Study Selection

The abstracts of all identified articles were carefully and independently reviewed for eligibility by 2 investigators. The inclusion criteria were: (1) randomized controlled trials (RCTs) (parallel and/or crossover studies); (2) studies of cancer patients with symptoms of dry mouth caused by radiotherapy or studies that recruited patients with cancer who will be going radiotherapy; (3) studies with adult patients ( $\geq 18$  years of age); (4) studies using invasive acupuncture as an experimental intervention, such as body acupuncture, manual acupuncture, and electroacupuncture; (5) studies with a control group that included patients treated with control interventions such as placebo acupuncture, sham acupuncture (SA), Chinese herbs, Western medicine, no treatment (waiting list control), routine care, or conventional therapy; (6) studies using one or more of the following measurements: (a) objective methods, such as stimulated salivary flow rate (SSFR), unstimulated salivary flow rate (USSFR), saliva collection, whole saliva production, or scintigraphy or functional magnetic resonance imaging of the SGs; (b) subjective measurements comprising observer-based toxicity grading or patient self-reported scoring, such as the visual analogue scale,

**Table 1.** Search Strategy for the PubMed Database.

Number	Search terms
1	Acupuncture. Mesh.
2	Acupuncture*. ti, ab
3	1 or 2
4	Neoplasms. Mesh.
5	Neoplasms. ti, ab.
6	Neoplasia. ti, ab.
7	Tumor. ti, ab.
8	Cancer. ti, ab.
9	Malignancy. ti, ab.
10	4 or 5 to 9
11	Xerostomia. Mesh.
12	Xerostomia. ti, ab.
13	Hyposalivation. ti, ab.
14	Asialia. ti, ab.
15	Mouth dryness. ti, ab.
16	Salivary gland hypofunction. ti, ab.
17	11 or 12 to 16
18	Randomized controlled trial. pt
19	Controlled clinical trial. pt
20	Randomized controlled trials. Mesh.
21	Random allocation. Mesh.
22	Randomized. ti, ab
23	Randomly. ti, ab
24	Double-blind method. Mesh
25	Single-blind method. Mesh
26	Clinical trial. pt
27	18 or 19 to 26
28	3 and 10 and 17 and 27

Abbreviations: ti, ab, title/abstract; pt, article type.

\*There is no limit to the number of matches.

the Xerostomia Questionnaire (XQ), or quality of life scoring<sup>61</sup>; (7) studies published in English or Chinese. The exclusion criteria were: (1) non-RCTs, quasi-RCTs, case series, review articles, meta-analyses; (2) animal studies; (3) mixed interventions (eg, acupuncture in combination with other therapies) when manual acupuncture or electroacupuncture was not considered the main intervention. If the 2 investigators disagreed about the eligibility of an article, the disagreement was resolved by consensus with a third reviewer.

### Data Extraction

Two investigators independently extracted data from the included studies and entered this information into a unified data statistics table. The extracted data included the reference ID, first author's name, publication year, type of cancer, patient age, type of acupuncture intervention, type of control intervention, sample size of each intervention group, intervention duration, randomization, allocation concealment and blinding methods, outcome measures, primary

outcomes and adverse events, duration of follow-up, type and source of financial support, and adherence to the Standards for Reporting Interventions in Controlled Trials of Acupuncture.<sup>62</sup> Any disagreements were solved by consensus. A third investigator made the final judgment when consensus on data extraction could not be obtained through negotiation. Data tables were compared and discussed with a third review author. If a study was missing information, the corresponding author was contacted (if the contact details were available). The methodological quality of included RCTs was assessed in accordance with the Cochrane Collaboration's tool described in the Cochrane Handbook version 5.1.0.<sup>63</sup> If more than 10 trials were included in the meta-analysis, a funnel plot was used to assess the reporting biases. Begg and Egger tests were used to evaluate the asymmetry of the funnel plots, and values of  $P < .05$  were considered to represent significant publication bias.<sup>64</sup>

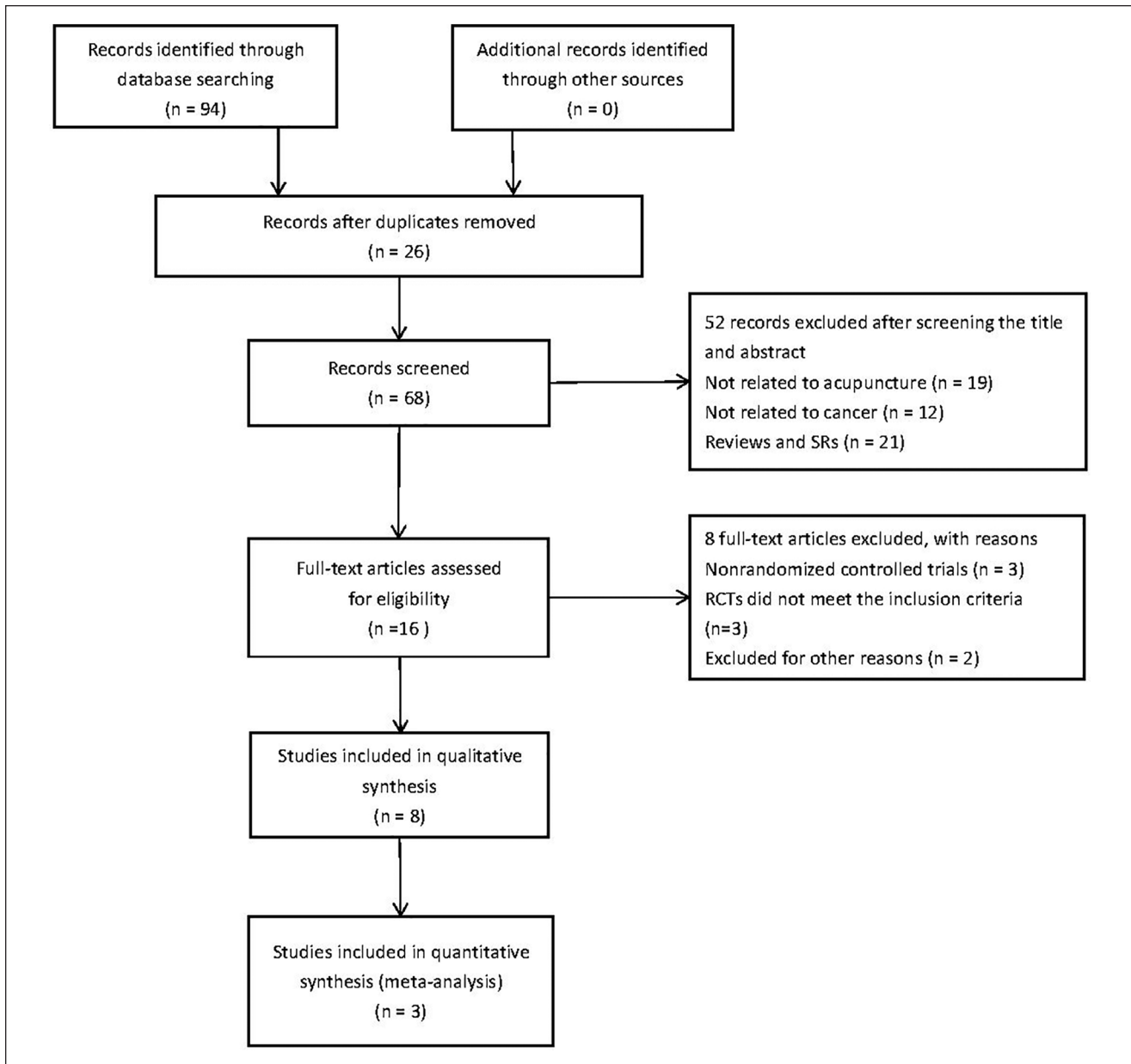
### Statistical Analysis

Data analysis was performed using RevMan software (version 5.3). The effect size was calculated for each study and combined to generate an overall effect size. For categorical variables, the risk ratio or odds ratio and 95% confidence interval (95% CI) were used. For continuous variables, the weighted mean difference (MD) or standard MD and 95% CI were used. A random-effects or fixed-effects model was used for the meta-analysis. In accordance with the Cochrane Handbook for Systematic Reviews of Interventions, heterogeneity was assessed by a visual check of the forest plot, a heterogeneity  $\chi^2$  test, and the Higgins' I2 statistic.<sup>65</sup> If the  $P$  value was  $>.10$  and the I2 value was  $<50\%$ , a fixed-effects model was used to pool the data; otherwise, a random-effects model was used. If there was significant heterogeneity between a set of studies, causes of heterogeneity such as patient characteristics and degree of variation in interventions were explored. Sensitivity analysis or subgroup analysis was used to evaluate heterogeneity if applicable. The Grading of Recommendations Assessment (GRADE) approach was used to describe the quality of the evidence for the results obtained.<sup>66</sup>

## Results

### Study Selection

The initial database searches identified 94 potentially relevant articles. A total of 26 duplicates were excluded, and a further 52 articles were removed based on the title and abstract screening process. The full-text versions of the remaining 16 studies were reviewed, and 8 more studies were excluded in accordance with the eligibility criteria (Figure 1). Eventually, 8 studies<sup>49,67-73</sup> were included in the qualitative synthesis, while 3 studies<sup>67,68,73</sup> were included in the meta-analysis.



**Figure 1.** Flow diagram of the trial selection process.

### Study Characteristics

The study characteristics of the included RCTs are summarized in Table 2. The selection criteria were met by 8 RCTs with 725 participants in total, comprising 304 patients in the acupuncture group and 421 patients in the control group. Three of the included RCTs were conducted in China,<sup>71-73</sup> 2 was conducted in the United States,<sup>69,73</sup> and 1 was conducted in each of Sweden,<sup>67</sup> South Korea,<sup>68</sup> Brazil,<sup>49</sup> and England.<sup>70</sup> Seven studies were 2-armed, while 1 was 3-armed.<sup>73</sup> Seven trials used parallel group designs, while 1 was a cross-over study.<sup>70</sup> Three articles aimed to

explore the preventive effect,<sup>49,71,72</sup> the rest to explore the therapeutic effect of acupuncture on radiation-induced xerostomia in cancer patients.<sup>67-70,73</sup>

**Condition characteristics.** All 8 trials included patients diagnosed with tumors in the head and neck region with a history of radiotherapy. None of the included RCTs specifically identified the types of cancer; therefore, there were no specific diagnostic criteria.

**Patient characteristics.** The average age of patients was 54.15 years (median 55.12; interquartile range (IQR)

**Table 2.** Study Characteristics.

Blom et al <sup>67</sup>	
Methods	Design: RCT Randomization method: unknown Blinding: unknown
Participants	Number of TG/CG: 20/18 Inclusion criteria: patients who had had all or some of their salivary glands irradiated during treatment of malignant tumours in the head and neck region were initially included in the study Demographics: mean age (y): 62.68; 31.58% female Setting: Sweden Duration (mo): TG: 15.5 CG: 13.5
Interventions	TG: acupuncture plus ear acupuncture CG: sham acupuncture Acupuncture points: 1. Acupuncture applied at 5 to 8 local and distal points(ST 3, ST 6, ST 5, DU 20, ST7, SI 17, LI 18, P 6, H 7, ST36, LIV 3, LI 11, LI 10, LI 4, SI 3, SP 8, SP 3, SP 6, KI 7, KI 3, KI 5); 2. Auricular points (Shenmen, kidney mouth, stomach, Gl. parotis, sympathetic, subcortex). Number of treatment sessions: 24 (20 min each,twice weekly) Duration: 14wk Follow-up: 12 mo
Result	SSFR; USSFR
Cho et al <sup>68</sup>	
Methods	Design: RCT Randomization method: block randomization Blinding: single-blind
Participants	Number of TG/CG: 6/6 Inclusion criteria: patients with xerostomia with a history of radiotherapy (minimum dose 38 Gy and exposed volume of parotid gland 50%) for their head and neck cancers were recruited Demographics: mean age (y): 44; 16.67% female Setting: South Korea Duration (mo): TG: 35.5 CG: 6.5
Interventions	TG: acupuncture CG: sham acupuncture Acupuncture points: acupuncture was done at 5 to 8 local and distal points (eg, ST 6, ST 36, LI 4, SP 6) Number of treatment sessions: 12 (20 min each,twice weekly) Duration: 6 wk Follow-up: 0
Result	SSFR; USSFR; XQ
Pfister et al <sup>69</sup>	
Methods	Design: RCT Randomization method: random assignment was implemented via a secure computerized database Blinding: unknown
Participants	Number of TG/CG: 28/30 Inclusion criteria: all had undergone neck dissection for cancer $\geq 3$ mo since neck dissection and radiation; and had moderate or severe pain and dysfunction Demographics: mean age (y):58.93; 34.48% female Setting: The United States Duration (mo): TG: 39 CG: 34
Interventions	TG: acupuncture plus ear acupuncture CG: usual care Acupuncture points: 1. Acupuncture applied at LI-4, SP-6, GV-20, luozhen + various customised points plus LI2; 2. Auricular points (Shenmen). Number of treatment sessions: 4 (30 min each, once weekly) Duration: 4 wk Follow-up: 4 wk
Result	Constant-Murley score; Modified Constant-Murley score; XI; NRS of pain
Braga et al <sup>49</sup>	
Methods	Design: RCT Randomization method: unknown Blinding: unknown

(continued)

**Table 2. (continued)**

Braga et al <sup>49</sup>	
Participants	Number of TG/CG: 12/12 Inclusion criteria: patients were receiving either primary or postoperative external beam RT (>5000 cGy) whose irradiation fields involved $\geq 50\%$ of the major salivary gland volume Demographics: mean age (y): 63; 33.33% female Setting: Brazil Duration (mo): unknown
Interventions	TG: acupuncture plus ear acupuncture CG: no treatment to minimize the irradiation side effects Acupuncture points: 1. Acupuncture applied at ST-3, ST-4, ST-5, ST-6, ST-7, GB-2, SI-19, TB-21, LI-4, LI-11, LR-3, ST-36, KI-3, KI-5, GV-20; 2. Auricular points: Shen-Men, central nervous system, neurovegetative system, kidney, spleen, pancreas, and mouth. Number of treatment sessions: 16 to 20 (20 min each, twice weekly) Duration: 8 to 10 wk Follow-up: 0
Result	RSFR; SSFR; XQ
Simcock et al <sup>70</sup>	
Methods	Design: crossover RCT Randomization method: a combination of simple randomisation in uneven blocks and standard permuted blocks of varying size Blinding: unknown
Participants	Number of TG/CG: 75/70 Inclusion criteria: patients treated with radical radiotherapy (at least 1 parotid gland in the irradiated field) and recurrence free $\geq 18$ mo later were eligible Demographics: mean age (y): 59.4; 24.31% female Setting: England Duration (mo): unknown
Interventions	TG: acupuncture plus ear acupuncture CG: standard care control Acupuncture points: 1. Acupuncture: bilaterally LI2, LI20; 2. Auricular points: salivary gland 2, modified point zero, and Shen Men. Number of treatment sessions: 8 (20 min each, once weekly) Duration: 8 wk Follow-up: 6 mo
Result	QLQC30; (H&N-35)
Meng et al <sup>71</sup>	
Methods	Design: RCT Randomization method: random number table Blinding: unknown
Participants	Number of TG/CG: 40/46 Inclusion criteria: age > 18y; nasopharyngeal carcinoma (NPC); anatomically intact parotid and submandibular glands; and Zubrod performance status of 0, 1, or 2 Demographics: mean age (y): 47.37; 29.76% female Setting: China Duration (mo): unknown
Interventions	TG: acupuncture plus ear acupuncture CG: standard care control Acupuncture points: 1. Acupuncture applied at local (REN 24, LU7, K6); 2. Auricular points (Shenmen, point zero, salivary gland 2-prime, and larynx). Number of treatment sessions: 21 (20 min each, 3 times weekly) Duration: 7 wk Follow-up: 6 mo
Result	XQ; USSFR; SSFR
Meng et al <sup>72</sup>	
Methods	Design: RCT Randomization method: adaptive randomization, minimization Blinding: single-blind

(continued)

**Table 2. (continued)**

Meng et al <sup>72</sup>	
Participants	Number of TG/CG: 11/12 Inclusion criteria: >18y; nasopharyngeal carcinoma (NPC); scheduled for IMRT; intact parotid and submandibular glands; Zubrod performance status of 0, 1, or 2 Demographics: mean age (y): 46.53; 4.76% female Setting: China Duration (mo): unknown
Interventions	TG: acupuncture plus ear acupuncture CG: sham acupuncture Acupuncture points: 1. Acupuncture applied at body points (Shenmen, Ren 24, lung 7, and kidney 6); 2. Ear points (point zero, salivary gland 2-prime, and larynx). Number of treatment sessions: 18 (20 min each, 3 times weekly) Duration: 6 wk Follow-up: 5 wk
Result	XQ; USSFR; SSFR
Garcia et al <sup>73</sup>	
Methods	Design: RCT Randomization method: centralized computer system Blinding: single-blind
Participants	Number of TG/CG: 112/115/112 Inclusion criteria: adult ≥18y of age. Able to give informed consent. Diagnosed with head and neck squamous cell carcinoma (primarily oropharyngeal or nasopharyngeal). Planned intensity-modulated radiation therapy (IMRT), with or without concurrent chemotherapy, at a mean dose of at least 24 Gy to at least 1 of the parotid glands. (The other gland could receive any dose level.) Anatomically intact parotid and submandibular glands. Karnofsky performance status >60. Demographics: mean age (y): 51.3; 23.89% female Setting: China; The United States Duration (mo): unknown
Interventions	TG: acupuncture plus ear acupuncture CG: sham acupuncture; standard care control Acupuncture points: 1. Acupuncture applied at local (REN 24, LU7, K6); 2. Auricular points (Shenmen, point zero, salivary gland 2-prime, and larynx) and the placebo needle at Gb32 on right knee. Number of treatment sessions: 18 to 21 (20 min each, 3 times weekly) Duration: 6 to 7 wk Follow-up: 12 mo
Result	XQ; incidence of clinically significant xerostomia (score > 30), salivary flow, quality of life, salivary constituents

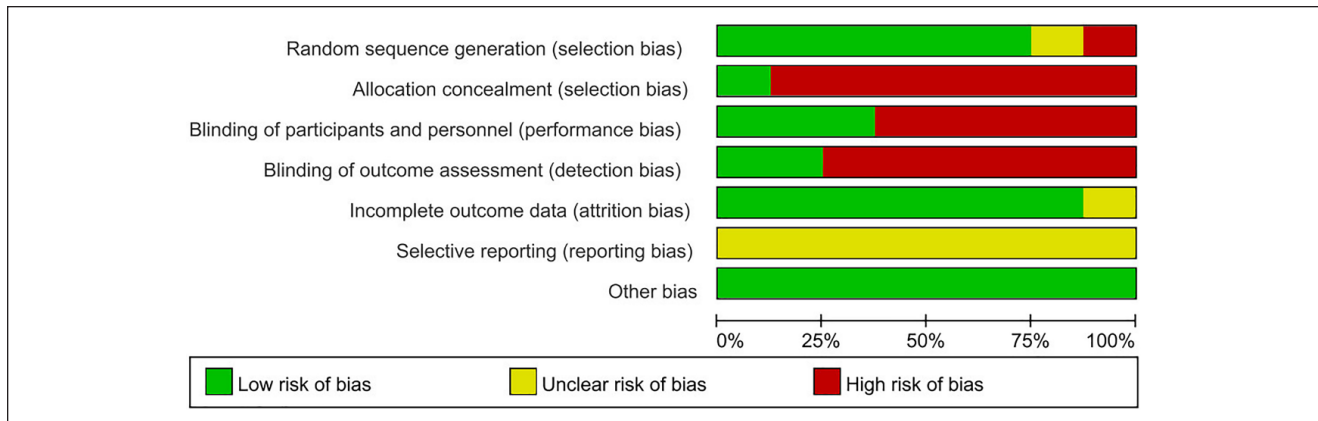
Abbreviations: RCT, randomized clinical trials; TG, treatment group; CG, control group; SSFR, stimulated salivary flow rate; USSFR, unstimulated salivary flow rate; XQ, Xerostomia Questionnaire; XI, Xerostomia Inventory; RSFR, resting salivary flow rate.

46.53-59.4). The proportion of females ranged from 4.76% to 34.48% (median 26.95; IQR 16.67-31.58).

**Intervention characteristics.** The treatment groups in 7 trials received body acupuncture plus ear acupuncture, while 1 trial used body acupuncture alone.<sup>68</sup> The number of treatment sessions ranged from 4 to 24 (median 18; IQR 8-20); the frequency of treatment ranged from 1 to 3 times per week (median 2; IQR 1-3). The treatment period ranged from 4 to 14 weeks (median 7; IQR 6-8). The duration of each acupuncture session ranged from 20 to 30 minutes (median 20; IQR 20-20). The duration of the follow-up period ranged from 4 to 52 weeks in 6 studies, while 2 RCTs did not perform any follow-up.<sup>49,68</sup> The number of needle

insertions ranged from 4 to 24 (median 19.5; IQR 8-24). The number of acupoints ranged from 2 to 15 (median 3.5; IQR 3-5).

**Control characteristics.** The most commonly used control intervention was SA comprising either needle puncture at sham locations (eg, sham points, pseudo points, inactive points) or sham insertions (eg, superficial insertion, pseudo insertion, or electroacupuncture without electric stimulation).<sup>74</sup> The control intervention was SA in 4 trials,<sup>67,68,72,73</sup> standard oral care in 3 trials,<sup>70,71,73</sup> usual care (entailing no specific treatment, physical therapy, analgesia, and/or anti-inflammatory drugs) in 1 trial,<sup>69</sup> and no treatment in 1 trial.<sup>49</sup>



**Figure 2.** Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

**Outcomes**

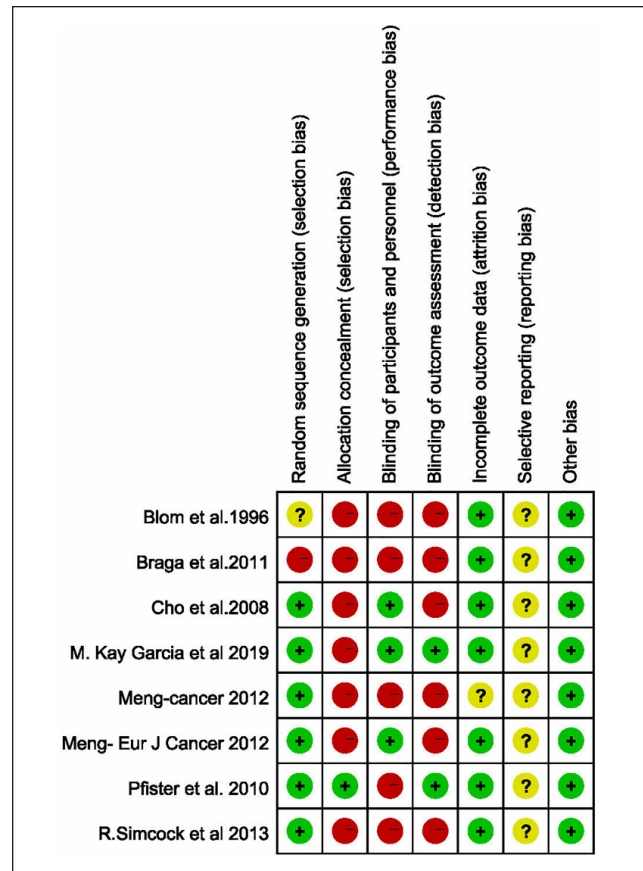
Most studies used the XQ as a subjective outcome to assess the effect of acupuncture,<sup>49,68,71-73</sup> while the objective outcomes included the SSFR and USSFR.<sup>49,67-69,71,72</sup> Other outcomes included the Modified Constant-Murley score and Xerostomia Inventory in 1 trial,<sup>69</sup> the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire in 1 trial,<sup>70</sup> and the incidence of clinically significant xerostomia (score >30), salivary flow, quality of life, and salivary constituents in 1 trial.<sup>73</sup>

**Risk of Bias**

Figure 2 shows the risk of bias in each of the 6 domains for all included studies. Most included studies were classified as having a high risk of bias. Most studies explicitly reported the randomization method, while 2 study failed to provide a detailed description of the randomization process.<sup>49,67</sup> Only 1 trial provided information about allocation concealment via the use of sealed envelopes or by computer.<sup>69</sup> Due to the special nature of acupuncture, there was no blinding of the acupuncturists in all trials. There was no blinding of the participants in 5 trials,<sup>49,67,69-71</sup> while the other 3 were single-blind.<sup>68,72,73</sup> In 6 studies,<sup>49,67,68,70-72</sup> the outcome assessors were not blinded, suggesting a risk of measurement bias. In addition, only 1 RCT reported the number of dropouts,<sup>71</sup> but did not mention the reasons. All studies had comparable baseline characteristic data. A summary of the risk of bias in each of the included trials is presented in Figure 3.

**Results of Individual Studies**

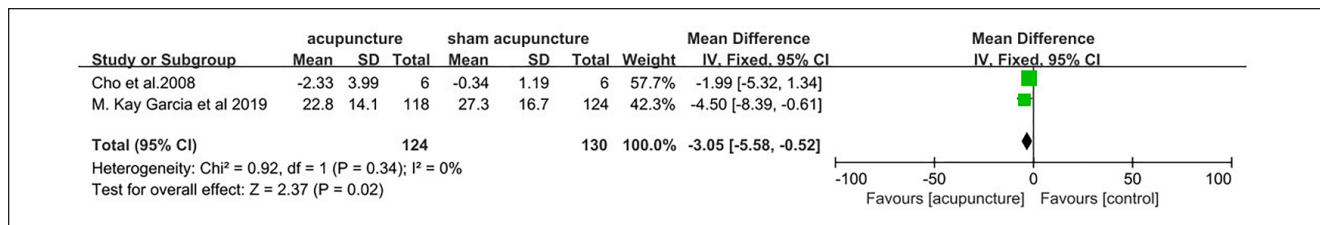
**Acupuncture Versus Sham Acupuncture.** Four RCTs used SA as a control treatment; 2 used superficial needling at non-acupoints,<sup>67,68</sup> 1 used nonpenetrating needling at nonacupoints,<sup>72</sup> and 1 used a mixture of real needling at a real acupoint not indicated for xerostomia, real needling at sham



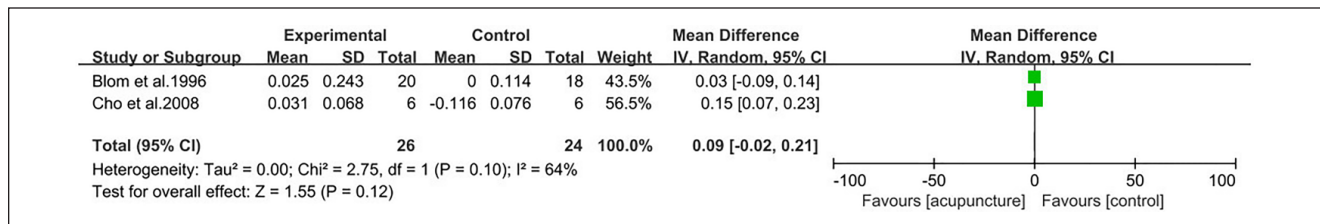
**Figure 3.** Risk of bias summary: review authors' judgments about each risk of bias item for each included. +, low risk of bias; ?, high risk of bias; -, unclear risk of bias.

points, and placebo needling at sham points.<sup>73</sup> Three RCTs reported significantly increased salivary flow rates after treatment in all groups, although the changes in the SA group were smaller and appeared after a longer latency phase compared with the real acupuncture (RA) group,<sup>67</sup>





**Figure 4.** Forest plot of the Xerostomia Questionnaire scores for real acupuncture versus sham acupuncture.



**Figure 5.** Forest plot of the stimulated salivary flow rate results for real acupuncture versus sham acupuncture.

and RA improved the XQ score for dry mouth.<sup>68,72</sup> However, one study found no differences between the RA and SA groups in the USSFR and SSFR.<sup>72</sup> One study reported that the XQ scores of the RA group were marginally lower but not significantly different from those of the SA group, and that the incidence of clinically significant xerostomia at 1 year after radiation therapy ended was significantly different in the RA group versus the SA group only at one of the participating research centers.<sup>73</sup>

**Acupuncture versus no acupuncture.** Three studies used standard oral care as a control intervention.<sup>70,71,73</sup> One study showed that compared with oral care, acupuncture produced significant reductions in patient-reported severe dry mouth, while there were no significant changes in the SSFR and USSFR over time.<sup>70</sup> Two studies reported that the XQ scores of the acupuncture group were significantly lower than those of the control group,<sup>71,73</sup> and found a significant difference between the acupuncture and standard oral care groups in the incidence of clinically significant xerostomia at 1 year after radiation therapy ended.<sup>73</sup> One trial reported that acupuncture produced greater improvement in patient-reported xerostomia compared with usual care (entailing no specific treatment, physical therapy, analgesia, and/or anti-inflammatory drugs).<sup>69</sup> One study showed that acupuncture treatment significantly minimized the severity of radiation-induced xerostomia compared with no treatment.<sup>49</sup>

### Safety

Six of the included RCTs assessed the adverse effects, while 2 did not.<sup>68,71</sup> No serious adverse events were attributed to acupuncture, although somnolence, tiredness, tiny hemorrhages, and minor bruising or bleeding at the puncture site

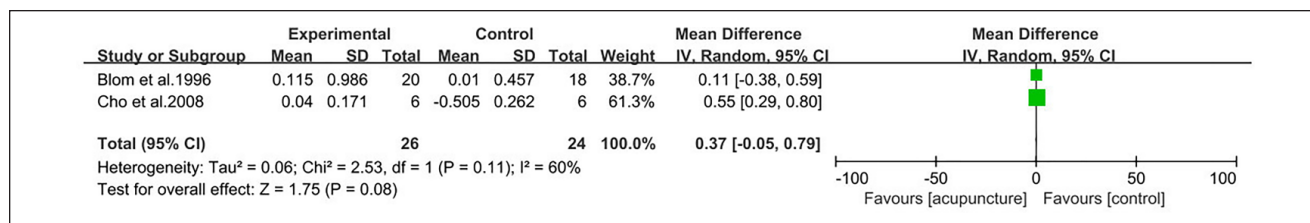
were reported. One trial reported that 2 patients were treated for coronary syndrome during the 8-week acupuncture treatment period<sup>70</sup>; however, both of these patients had multiple risk factors for cardiac disease, and therefore the events were unlikely to be related to the acupuncture treatment. During the oral care intervention period, 1 patient suffered a traumatic hip fracture, while another was hospitalized for aspiration pneumonia.<sup>70</sup> One RCT reported no adverse event.<sup>72</sup>

## Meta-Analysis

### Acupuncture Versus Sham Acupuncture

**Xerostomia Questionnaire.** Three studies used the XQ as an outcome to measure the effect of acupuncture on radiation-induced xerostomia in cancer patients, but only 2 of these studies contained adequate data for inclusion in the present meta-analysis.<sup>68,73</sup> Meta-analysis showed no heterogeneity between these 2 trials ( $I^2 = 0\%$ ,  $P = .34$ ), and so a fixed-effects model was used (Figure 4). RA had favorable effects on the improvement of xerostomia symptoms compared with SA ( $n = 254$ ,  $\text{MD} = -3.05$ ,  $P = .02$ , 95% CI  $-5.58$  to  $-0.52$ ).

**Stimulated salivary flow rate.** Three studies evaluated the SSFR to measure the effect of acupuncture on radiation-induced xerostomia in cancer patients. Two of these studies contained adequate data for inclusion in the present meta-analysis.<sup>67,68</sup> There was significant heterogeneity between the 2 studies ( $I^2 = 60\%$ ,  $P = .11$ ), and so a random-effects model was used (Figure 5). The SSFR did not significantly differ between the RA and SA groups ( $n = 50$ ,  $\text{MD} = 0.37$ ,  $P = .08$ , 95% CI  $-0.05$  to  $0.79$ ).



**Figure 6.** Forest plot of the unstimulated salivary flow rate results for real acupuncture versus sham acupuncture.

**Unstimulated salivary flow rate.** Three studies used the USSFR to assess the effectiveness of acupuncture in treating radiation-induced xerostomia in cancer patients. As the original data were not available for one of these studies, only the data from the other 2 studies were included in the present meta-analysis.<sup>67,68</sup> There was significant heterogeneity between the 2 trials ( $I^2=64%$ ,  $P=.10$ ), and so a random-effects model was used. The USSFR was not improved in the RA group compared with the SA group ( $n=50$ ,  $MD=0.09$ ,  $P=.12$ , 95% CI  $-0.02$  to  $0.21$ ) (Figure 6).

## Discussion

### Summary of the Main Results

The present systematic review included 8 studies involving 725 patients. Sample sizes ranged from 12 to 339 patients. The main findings were that there was no significant difference between RA and SA for treating radiation-induced xerostomia in cancer patients in terms of the salivary flow rate, but RA showed better results in resolving the symptoms of dry mouth. Compared with no acupuncture (standard oral care, usual care, or no treatment), acupuncture produced a significant improvement in patient-reported xerostomia. There were no serious acupuncture-related adverse reactions in all groups, except for some normal phenomena such as bleeding or slight pain due to needling. However, the present meta-analysis findings were insufficient to support a clinical recommendation due to the generally low methodological quality of the included studies.

### Possible Explanations for the Present Findings

Similar to previous reviews, the present review found limited evidence to suggest that acupuncture was beneficial for radiation-induced xerostomia in cancer patients, especially compared with SA. Three factors might explain these findings. First, SA might have direct physiological effects on the mechanisms associated with dry mouth symptoms. Second, a placebo effect may occur in the SA group due to patient expectations, conditioning, anxiety reduction, and social support.<sup>75,76</sup> Third, acupuncture itself might be a particularly effective placebo.

### Quality of Evidence

The Cochrane Collaboration Network GRADE approach was used to perform a systematic review of the results (Figure 7). The systematic analysis comprised 3 outcomes in the acupuncture group and the SA group. Relief of the symptom of dry mouth was the key outcome, while the SSFR and USSFR were important secondary outcomes. The GRADE profile indicated that the quality of evidence was low for all outcomes, mainly due to methodological limitations, unexplained inconsistencies, and variations in sample sizes.

### Limitations of Included Studies

**Methodological quality.** The methodological quality of the included trials was low, especially regarding allocation concealment and blinding. Of the 8 included RCTs, 2 did not describe the randomization process in detail.<sup>49,67</sup> In addition, only 1 RCT provided information about allocation concealment.<sup>69</sup> Patients were blinded to treatment allocation in only 3 RCTs,<sup>68,72,73</sup> and were blinded to the outcome assessment in 2 RCTs.<sup>69,73</sup> In addition, no descriptions could be used to determine whether the included studies had selective reporting bias. These different types of bias may have led to false positive results. Furthermore, only 2 RCTs reported the methods used to calculate the sample sizes,<sup>71,73</sup> and so the included RCTs might have extremely low statistical analysis power.

**Inconsistent interventions.** The 8 included RCTs used different experimental groups, such as RA versus SA, and acupuncture versus standard oral care control, usual care, and no treatment. The included RCTs also differed regarding the frequency, number of sessions, and duration of acupuncture, the selection and number of acupoints, needling depth, acupuncture process, and needle retention time; all of which might have caused bias. There is often a lack of standardization and transparency in complementary and alternative medicine research. This problem is difficult to solve because there is no “gold standard” for acupuncture in treating dry mouth. In fact, as traditional Chinese acupuncture and complementary and alternative medicine does not advocate the use of a standardized, 1-size-fits-all acupuncture regimen,<sup>77</sup>

acupuncture compared to sham acupuncture for xerostomia						
Patient or population: patients with xerostomia						
Settings: treat time:						
Intervention: acupuncture						
Comparison: sham acupuncture						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Sham acupuncture	Corresponding risk Acupuncture				
XQ		The mean xq in the intervention groups was <b>3.05 lower</b> (5.58 to 0.52 lower)		254 (2 studies)	⊕⊕⊕⊕ moderate <sup>1</sup>	
SSFR		The mean ssfr in the intervention groups was <b>0.09 lower</b> (0.02 lower to 0.21 higher)		50 (2 studies)	⊕⊕⊕⊕ very low <sup>2,3</sup>	
USFR		The mean usfr in the intervention groups was <b>0.37 higher</b> (0.05 lower to 0.79 higher)		50 (2 studies)	⊕⊕⊕⊕ very low <sup>2,3</sup>	

\*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval;  
GRADE Working Group grades of evidence  
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.  
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.  
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.  
**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup> None of the trials described allocation concealment; half of them were not blinded to analysts.  
<sup>2</sup> Only one experiment described the random method, and the rest did not mention the random method and allocation concealment; except one trial which was blinded to patients, the rest were not blind  
<sup>3</sup> Confidence intervals with minimal overlap, the heterogeneity is significant.

**Figure 7.** Grading of recommendations assessment of evidence regarding the effects of acupuncture for cancer-induced xerostomia.

personalized treatment for each person is considered an important part of care. Skilled practitioners may therefore consider the use of any single “gold standard” acupuncture regimen to be restrictive and counterproductive.

**Limited outcomes.** The subjective outcome measures used in most of the included trials were not uniform, and studies that used the same indicators also used different individualized scales. In addition, a meta-analysis using a subjective outcome measure such as the XQ yielded positive results for treatment, while a meta-analysis using an objective outcome measure such as the salivary flow rate yielded no significant difference between treatment and control interventions. Thus, future studies should consider using more objective outcome indicators to evaluate the effect of acupuncture on dry mouth.

**Lack of economic data.** No economic data or relative economic analysis has been reported.

**Limitations of the Current Study**

Although a considerable amount of effort was spent in retrieving RCTs and evaluating data quality, and the GRADE framework was applied to assess the quality of evidence for certain outcomes, the current study still had several limitations. (1) The literature search was limited to articles published in Chinese or English, which excluded studies published in other languages (such as Japanese, Korean, and German). This language limitation may have induced biased outcomes. (2) The risk of assessment bias varied between

studies based on the study authors’ subjective views and diligence. (3) The total sample size was small (n=725), as few RCTs have investigated the effect of acupuncture on radiation-induced xerostomia in cancer patients. (4) A Funnel plot was not generated for the outcomes due to the limited number of included RCTs. Therefore, publication bias might exist. (5) The quality of the evidence was poor due to the limited number of included trials and the imperfect study design.

**Comparison With Other Reviews**

Two systematic reviews that included a small number of studies have evaluated the effects of acupuncture for radiation-induced xerostomia in patients with head and neck cancer.<sup>57,58</sup> They concluded that there was not enough evidence to judge whether acupuncture was safe and whether it was effective in preventing or treating radiation-induced xerostomia. We identified 4 new RCTs and updated the evidence. Although the evidence for the effectiveness of acupuncture for radiation-induced xerostomia in cancer patients was still limited, the present meta-analysis of relevant outcome indicators concluded that acupuncture alleviates patient-reported subjective symptoms of dry mouth. The present review used the GRADE framework to assess the quality of evidence for certain outcomes.

**Suggestions for Trials**

As the quality and quantity of literature concerning the efficacy of acupuncture for cancer-induced xerostomia are

limited, a potentially beneficial effect might exist, and future rigorous RCTs with appropriate controls should be conducted. Clinical trials should be registered in the World Health Organization International Clinical Registry Platform or ClinicalTrials.gov, and reported in detail in accordance with the Consolidated Standards for Reporting of Trials<sup>78</sup> or Standards for Reporting Interventions in Controlled Trials of Acupuncture<sup>62</sup> guidelines. Randomization, allocation concealment, and blinding should be designed and rigorously conducted, and the duration of follow-up should be based on the research objectives. Furthermore, in addition to patient-reported subjective symptom relief, future clinical trials should introduce more objective outcome indicators. Finally, more attention should be paid to the reporting of adverse events.

## Conclusion

There was a lack of evidence for objective salivary flow of acupuncture on xerostomia according to the present meta-analysis. Although acupuncture improves the symptoms of cancer-induced xerostomia, this intervention cannot be recommended due to the limited number of included RCTs and the low quality of evidence. Acupuncture cannot yet be recommended for radiation-induced xerostomia in cancer patients until more solid evidence is produced.

## Acknowledgments

Thanks to all the participants and clinical researchers involved in the publications cited in this review. Thanks to all the peer reviewers who contributed to the continuous improvement of this article.

## Author Contributions

XXN conceived and designed the article. XXN and TT searched the databases and screened the articles. XXN and DC extract information and analyzed the data. XXN and TT assess the quality of included literature. XL and FML made figures and tables. XXN analyzed the data. All the authors contributed to the composition of the manuscript. LZ and FRL monitor each procedure of the review and are responsible for the quality control. All authors read and approved the manuscript.

## 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: The review is financially supported by the National Natural Science Foundation of China (Grant No. 81722050, 81973962) and Project of Science and Technology Department of Sichuan Province (Grant No. 20ZDYF1199). Funders and sponsors have no role in the design of this review.

## ORCID iD

Xixiu Ni  <https://orcid.org/0000-0001-7359-6173>

## References

- Guggenheimer J, Moore PA, Yin XM. Xerostomia: etiology, recognition and treatment. *J Am Dent Assoc.* 2003;134:61-69.
- Heiskanen V, Zadik Y, Elad S. Photobiomodulation therapy for cancer treatment-related salivary gland dysfunction: a systematic review. *Photobiomodul Photomed Laser Surg.* 2020;38:340-347.
- Yin XM, Feng LX, Feng LN, et al. Study on the intervention effect of traditional Chinese medicine prescription on dry mouth symptoms caused by chemotherapy. *J Nurs Train.* 2018;33:1712-1713.
- Twycross R, Wilcock A, Toller C. Alimentary symptoms. In: Twycross R, Wilcock A, Toller C, eds. *Symptom Management in Advanced Cancer.* 4th ed. Palliativedrugs.com Ltd; 2009:62-65.
- Chen AM, Farwell DG, Lau DH, Li BQ, Luu Q, Donald PJ. Radiation therapy in the management of head-and-neck cancer of unknown primary origin: how does the addition of concurrent chemotherapy affect the therapeutic ratio? *Int J Radiat Oncol Biol Phys.* 2011;81:346-352.
- Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys.* 1991;21:109-122.
- Franzén L, Funegård U, Ericson T, Henriksson R. Parotid gland function during and following radiotherapy of malignancies in the head and neck: a consecutive study of salivary flow and patient discomfort. *Eur J Cancer.* 1992;28:457-462.
- Wijers OB, Levendag PC, Braaksma MMJ, Boonzaaijer M, Visch LL, Schmitz PI. Patients with head and neck cancer cured by radiation therapy: a survey of the dry mouth syndrome in long-term survivors. *Head Neck.* 2002;24:737-747.
- Eisbruch A, Ten Haken RK, Kim HM, Marsh LH, Ship JA. Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. *Int J Radiat Oncol Biol Phys.* 1999;45:577-587.
- Wynn RL, Meiller TF. Artificial saliva products and drugs to treat xerostomia. *Gen Dent.* 2000;48:630-636.
- Feng LN, Feng LX. Investigation of symptom groups in patients with lymphoma chemotherapy. *Zhongguoshiyonghulizazhi.* 2017;33:2130-2133.
- Bertram U. Xerostomia: clinical aspects, pathology and pathogenesis. *Acta Odontol Scand.* 1967;25:1-126.
- Van den Bogaert W, Van der Leest A, Rijnders A, Delaere P, Thames H, van der Schueren E. Does tumor control decrease by prolonging overall treatment time or interrupting treatment in laryngeal cancer? *Radiother Oncol.* 1995;36:177-182.
- Jellema AP, Langendijk H, Berghenhenegouwen L, et al. The efficacy of Xialine in patients with xerostomia resulting from radiotherapy for head and neck cancer: a pilot-study. *Radiother Oncol.* 2001;59:157-160.
- Momm F, Volegova-Neher NJ, Schulte-Mönting J, Guttenberger R. Different saliva substitutes for treatment of xerostomia following radiotherapy. *Strahlenther Onkol.* 2005;181:231-236.

16. Epstein JB, Loh R, Stevenson-Moore P, McBride BC, Spinelli J. Chlorhexidine rinse in prevention of dental caries in patients following radiation therapy. *Oral Surg Oral Med Oral Pathol.* 1989;68:401-405.
17. Epstein JB, McBride BC, Stevenson-Moore P, Merilees H, Spinelli J. The efficacy of chlorhexidine gel in reduction of *Streptococcus mutans* and *Lactobacillus* species in patients treated with radiation therapy. *Oral Surg Oral Med Oral Pathol.* 1991;71:172-178.
18. Johnson JT, Ferretti GA, Nethery WJ, et al. Oral pilocarpine for postirradiation xerostomia in patients with head and neck cancer. *N Engl J Med.* 1993;329:390-395.
19. Chambers MS, Posner M, Jones CU, et al. Cevimeline for the treatment of postirradiation xerostomia in patients with head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2007;68:1102-1109.
20. Simcock R, Shields P. Management of radiation induced xerostomia in the UK. *Clin Oncol.* 2011;23:S53.
21. Davies AN, Daniels C, Pugh R, Sharma K. A comparison of artificial saliva and pilocarpine in the management of xerostomia in patients with advanced cancer. *Palliat Med.* 1998;12:105-111.
22. Mercadante S, Calderone L, Villari P, et al. The use of pilocarpine in opioid-induced xerostomia. *Palliat Med.* 2000;14:529-531.
23. Fox PC, Van der Ven PF, Baum BJ, Mandel ID. Pilocarpine for the treatment of xerostomia associated with salivary gland dysfunction. *Oral Surg Oral Med Oral Pathol.* 1986;61:243-248.
24. Greenspan D, Daniels TE. Effectiveness of pilocarpine in postradiation xerostomia. *Cancer.* 1987;59:1123-1125.
25. Johnson JT, Ferretti GA, Nethery WJ, et al. Oral pilocarpine for post irradiation xerostomia in patients with head and neck cancer. *N Engl J Med.* 1993;329:390-395.
26. Zimmerman RP, Mark RJ, Tran LM, Juillard GF. Concomitant pilocarpine during head and neck irradiation is associated with decreased posttreatment xerostomia. *Int J Radiat Oncol Biol Phys.* 1997;37:571-575.
27. Horiot JC, Lipinski F, Schraub S, et al. Post radiation severe xerostomia relieved by pilocarpine: a prospective French cooperative study. *Radiother Oncol.* 2000;55:233-239.
28. Brizel DM, Wasserman TH, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol.* 2000;18:3339-3345.
29. Rudat V, Meyer J, Momm F, et al. Protective effect of amifostine on dental health after radiotherapy of the head and neck. *Int J Radiat Oncol Biol Phys.* 2000;48:1339-1343.
30. Wasserman T, Mackowiak JI, Brizel DM, et al. Effect of amifostine on patient assessed clinical benefit in irradiated head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2000;48:1035-1039.
31. Lindegaard JC, Grau C. Has the outlook improved for amifostine as a clinical radioprotector? *Radiother Oncol.* 2000;57:113-118.
32. Jha N, Seikaly H, Harris J, et al. Phase III randomized study: oral pilocarpine versus submandibular salivary gland transfer protocol for the management of radiation-induced xerostomia. *Head Neck.* 2009;31:234-243.
33. Brizel DM, Wasserman TH, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol.* 2000;18:3339-3345.
34. Hanchanale S, Adkinson L, Daniel S, Fleming M, Oxberry SG. Systematic literature review: xerostomia in advanced cancer patients. *Support Care Cancer.* 2015;23:881-888.
35. Lu W, Rosenthal DS. Recent advances in oncology acupuncture and safety considerations in practice. *Curr Treat Options Oncol.* 2010;11:141-146.
36. Bodeker G, Ong CK, Grundy C, Burford G, Shein K. *WHO Global Atlas of Traditional, Complementary and Alternative Medicine.* WHO Center for Health Development; 2005.
37. Lin J-G, Chen Y-H. The role of acupuncture in cancer supportive care. *Am J Chin Med.* 2012;40:219-229.
38. Naik PN, Kiran RA, Yalamanchal S, Kumar VA, Goli S, Vashist N. Acupuncture: an alternative therapy in dentistry and its possible applications. *Med Acupunct.* 2014;26:308-314.
39. O'Regan D, Filshie J. Acupuncture and cancer. *Auton Neurosci Basic Clin.* 2010;157:96-100.
40. Dawidson I, Angmar-Månsson B, Blom M, Theodorsson E, Lundeberg T. Sensory stimulation (acupuncture) increases the release of vasoactive intestinal polypeptide in the saliva of xerostomia sufferers. *Neuropeptides.* 1998;32:543-548.
41. Dawidson I, Angmar-Månsson B, Blom M, Theodorsson E, Lundeberg T. Sensory stimulation (acupuncture) increases the release of calcitonin gene-related peptide in the saliva of xerostomia sufferers. *Neuropeptides.* 1999;33:244-250.
42. Blom M, Lundeberg T, Dawidson I, Angmar-Månsson B. Effects on local blood flux of acupuncture stimulation used to treat xerostomia in patients suffering from Sjögren's syndrome. *J Oral Rehabil.* 1993;20:541-548.
43. Blom M, Lundeberg T. Long-term follow-up of patients treated with acupuncture for xerostomia and the influence of additional treatment. *Oral Dis.* 2000;6:15-24.
44. Dawidson I, Blom M, Lundeberg T, Angmar-Månsson B. The influence of acupuncture on salivary flow rates in healthy subjects. *J Oral Rehabil.* 1997;24:204-208.
45. Deng G, Hou BL, Holodny AI, Cassileth BR. Functional magnetic resonance imaging (fMRI) changes and saliva production associated with acupuncture at LI-2 acupuncture point: a randomized controlled study. *BMC Complement Altern Med.* 2008;8:37.
46. List T, Lundeberg T, Lundström I, Lindström F, Ravald N. The effect of acupuncture in the treatment of patients with primary Sjögren's syndrome: a controlled study. *Acta Odontol Scand.* 1998;56:95-99.
47. Johnstone PAS, Peng YP, May BC, Inouye WS, Niemtzow RC. Acupuncture for pilocarpine-resistant xerostomia following radiotherapy for head and neck malignancies. *Int J Radiat Oncol Biol Phys.* 2001;50:353-357.
48. Wong RKW, Jones GW, Sagar SM, Babjak AF, Whelan T. A phase I-II study in the use of acupuncture-like transcutaneous nerve stimulation in the treatment of radiation-induced xerostomia in head-and-neck cancer patients treated with radical radiotherapy. *Int J Radiat Oncol Biol Phys.* 2003;57:472-480.

49. Braga FDPF, Lemos Junior CA, Alves FA, Migliari DA. Acupuncture for the prevention of radiation-induced xerostomia in patients with head and neck cancer. *Braz Oral Res.* 2011;25:180-185.
50. Rydholm M, Strang P. Acupuncture for patients in hospital-based home care suffering from xerostomia. *J Palliat Care.* 1999;15:20-23.
51. Meidell L, Holritz Rasmussen B. Acupuncture as an optional treatment for hospice patients with xerostomia: an intervention study. *Int J Palliat Nurs.* 2009;15:12-20.
52. Sagar SM. Acupuncture as an evidence-based option for symptom control in cancer patients. *Curr Treat Options Oncol.* 2008;9:117-126.
53. Deng G, Cassileth B. Acupuncture in cancer care. *Integr Oncol.* 2011;173:744.
54. Standish LJ, Kozak L, Congdon S. Acupuncture is underutilized in hospice and palliative medicine. *Dtsch Zeitschrift fur Akupunkt.* 2009;52:54-55.
55. Lu W. Acupuncture for side effects of chemoradiation therapy in cancer patients. *Semin Oncol Nurs.* 2005;21:190-195.
56. Deng G, Vickers A, Yeung KS, Cassileth BR. Acupuncture: integration into cancer care. *J Soc Integr Oncol.* 2006;4:86-92.
57. Zhuang L, Yang Z, Zeng X, et al. The preventive and therapeutic effect of acupuncture for radiation-induced xerostomia in patients with head and neck cancer. *Integr Cancer Ther.* 2013;12:197-205.
58. O'Sullivan EM, Higginson IJ. Clinical effectiveness and safety of acupuncture in the treatment of irradiation-induced xerostomia in patients with head and neck cancer: a systematic review. *Acupunct Med.* 2010;28:191-199.
59. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Open Med.* 2009;3:e123-e130.
60. Xixiu N, Yang Y, Tian T, et al. Acupuncture for patients with cancer-induced xerostomia: a systematic review protocol. *BMJ Open.* 2019;9:e031892.
61. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85:365-376.
62. MacPherson H, White A, Cummings M, Jobst KA, Rose K, Niemtzow RC. Standards for reporting interventions in controlled trials of acupuncture: the STRICTA recommendations. *J Altern Complement Med.* 2002;8:85-89.
63. Deeks JJ, Higgins JPT, Altman DG. Chapter 9: analyzing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* The Cochrane Collaboration; 2011.
64. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315:629-634.
65. Higgins JPT, Thompson SG. Quantifying heterogeneity in a metaanalysis. *Stat Med.* 2002;21:1539-1558.
66. Guyatt GH, Oxman AD, Vist GE, et al. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336:924-926.
67. Blom M, Dawidson I, Fernberg JO, Johnson G, Angmar-Månsson B. Acupuncture treatment of patients with radiation-induced xerostomia. *Eur J Cancer B Oral Oncol.* 1996;32:182-190.
68. Cho JH, Chung WK, Kang W, Choi SM, Cho CK, Son CG. Manual acupuncture improved quality of life in cancer patients with radiation-induced xerostomia. *J Altern Complement Med.* 2008;14:523-526.
69. Pfister DG, Cassileth BR, Deng GE, et al. Acupuncture for pain and dysfunction after neck dissection: results of a randomized controlled trial. *J Clin Oncol.* 2010;28:2565.
70. Simcock R, Fallowfield L, Monson K, et al. ARIX: a randomised trial of acupuncture v oral care sessions in patients with chronic xerostomia following treatment of head and neck cancer. *Ann Oncol.* 2013;24:776-783.
71. Meng Z, Garcia MK, Hu C, et al. Randomized controlled trial of acupuncture for prevention of radiation-induced xerostomia among patients with nasopharyngeal carcinoma. *Cancer.* 2012;118:3337-3344.
72. Meng Z, Garcia MK, Hu C, et al. Sham-controlled, randomised, feasibility trial of acupuncture for prevention of radiation-induced xerostomia among patients with nasopharyngeal carcinoma. *Eur J Cancer.* 2012;48:1692-1699.
73. Garcia MK, Meng Z, Rosenthal DI, et al. Effect of true and sham acupuncture on radiation-induced xerostomia among patients with head and neck cancer: a randomized clinical trial. *JAMA Netw Open.* 2019;2:e1916910-e1916910.
74. Chen YJ, Shimizu Bassi G, Yang YQ. Classic Chinese acupuncture versus different types of control groups for the treatment of chronic pain: review of randomized controlled trials (2000–2018). *Evid Based Complement Alternat Med.* 2019;2019:6283912.
75. Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H. The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review. *Health Technol Assess.* 1999;3:1-96.
76. Benedetti F. Mechanism of placebo and placebo-related effects across diseases and treatments. *Annu Rev Pharmacol Toxicol.* 2008;48:33-60.
77. Chien TJ, Liu CY, Fang CJ. The effect of acupuncture in breast cancer-related lymphoedema (BCRL): a systematic review and meta-analysis. *Integr Cancer Ther.* 2019;18:1534735419866910.
78. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med.* 2010;7:e1000251.