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Meta-analysis of the effect of non-pharmacological interventions on the development of dysgeusia in patients undergoing radiotherapy for head and neck squamous cell carcinoma

Yuyang Li[1], Lili Hou[2]✉, Xing Gan[1] & Xi Yang[3]

This study was conducted by searching electronic databases from January 1, 2000 to August 8, 2023: Web of Science, PubMed, Cochrane Library, Embase, Scopus, Google Scholar, China Biomedical Literature Database (CBM), China National Knowledge Network (CNKI), China Science and Technology Journal Database (VIP) and Wan-fang Database were included in 14 studies with a total sample size of 1630 cases. This study conducted a meta-analysis of the literature published in recent years on the occurrence of dysgeusia in Head and neck squamous cell carcinoma (HNSCC) patients with non-pharmacological treatment, in order to provide the latest evidence-based evidence for medical staff and provide a basis for further intervention of dysgeusia in HNSCC patients. Compared with conventional care in the control group, In the experimental group, the non-pharmacological intervention reduced the score of dysgeusia [*MD* = −0.76, 95% CI (−1.04, −0.48), *P* < 0.00001] and the incidence of dysgeusia [*MD* = 0.17, 95% CI (0.09, 0.31), *P* < 0.00001].

Keywords Dysgeusia, Squamous cell carcinoma of head and neck, Non-pharmacological interventions, Meta-analysis

Head and neck squamous cell carcinoma (HNSCC) is an umbrella term for a group of cancers with similar incidence and treatment options, including various types of oral cavity cancers, oropharyngeal cancers, laryngeal cancers, hypopharyngeal cancers, and salivary gland tumors[1,2]. HNSCC is the seventh most common cancer in the world, with more than 660,000 new cases and 32.5 million deaths annually[3,4]. At present, the main clinical treatment for patients with head and neck tumors is a combination of surgery and radiotherapy. However, due to the characteristics of radiation and the anatomical location of the head and neck tumor primary focus involving or adjacent to the oral cavity, radiotherapy-induced oral mucositis (RTOM) is one of the common and serious complications of head and neck tumor radiation, which is manifested as congestion, erythema, vesicles, ulcers, and fibrosis of the oral mucosa, and the patients suffer from pain, difficulty in nearsightedness, dryness of the mouth, and dysgeusia, etc.[5]. Gunn et al.[6] noted that dysgeusia is more common when the oral cavity, especially the anterior two-thirds of the tongue, is irradiated. Taste is one of the important physiological senses in the human body, which plays an important role in the regulation of intake, nutrition and metabolism of the body[7]. The receptors of taste are taste buds, which are mainly distributed on the surface and margin of the tongue, and scattered on the surface of the oral and pharyngeal mucosa. Since head and neck radiotherapy usually irradiates the area where the taste buds are located, altered taste, loss of taste, and decreased taste sensitivity are very common in patients with head and neck cancer receiving radiotherapy. According to the relevant literature, 60–95% of HNSCC patients have problems with their diet[8], and the incidence of dysgeusia in patients receiving head and neck radiotherapy or concurrent radiochemotherapy is as high as 70–100%, which usually occurs

[1]School of Nursing, Chengdu University of Traditional Chinese Medicine, Chengdu, China. [2]Nursing Department, Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China. [3]Department of Oral Maxillofacial Head and Neck Oncology, Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China. ✉email: pisces_liz@163.com

2–4 weeks after the start of radiotherapy, and the damage reaches its maximum at 4–6 weeks, although the recovery time is still controversial[9]. One study[10] noted that 51–100% of patients developed dysgeusia at the end of radiotherapy, and still up to 23–50% 1–2 years after the end of radiotherapy. Radiotherapy accelerates the metabolic rate of patients, and at the same time leads to a series of acute adverse reactions, such as dry mouth, dysgeusia, difficulty in chewing, and other symptoms, which directly affects the feeding and intake of patients, leading to malnutrition and low immunity[11]. Dysgeusia can reduce patients' appetite and weaken absorption and digestion, which has a profound impact on patients' quality of life. A study[12] found that 70.95% of patients with dysgeusia experienced weight loss. Dysgeusia also have a serious impact on patients' mental and psychological well-being, which decreases their adherence to cancer treatment[2]. In addition, several studies have shown[13–15] that patients with dysgeusia have varying degrees of anxiety, depression and other negative moods, leading to the expansion of abnormal sensations on the body, which has a direct impact on the body. However, clinical attention is mostly focused on the treatment and prevention of RTOM, often ignoring the disturbance caused to patients by the dysgeusia that occurs in the treatment of the disease, and there are fewer studies aimed at the prevention and alleviation of radiotherapy-induced dysgeusia[16]. In this study, we conducted a meta-analysis of the literature published in recent years on the occurrence of dysgeusia in patients with HNSCC by non-pharmacological treatments, with the aim of providing healthcare professionals with the latest evidence-based evidence for further interventions against taste disorders in the population of patients with HNSCC. The meta-analysis has been registered on the International Prospective Register of Systematic Reviews (PROSPERO), and the trial registration number is CRD42023453374. This meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Methods

Search strategy

The following electronic databases were searched in this study: Web of Science, PubMed, Cochrane Library, Embase, Scopus, Google Scholar, Chinese Biomedical Literature Database (CBM), Chinese National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP), and Wan-Fang Database from 1 January 2000 to 8 August 2023, independently by two researchers. The search is a combination of subject terms combined with free words. There were no limitations on publication status, but the language was limited to Chinese and English. Using the terms: Head and Neck Neoplasms/Head and neck cancer/Head and neck tumor/Head and neck squamous cell carcinoma/HNSCC, Dysgeusia/Dysgeusias/Taste, Distorted/Distorted Taste/Taste, Altered/Altered Taste/Parageusia/Parageusias, intervening measure/management/nursing.

Search for additional sources

Two researchers rechecked the reference lists of the included literature to find potential literature that met the inclusion criteria; articles that were not available via the Internet were hand-searched, and unpublished studies were searched through conference reports; when information on the included literature was incomplete, the researchers tried to contact the authors to obtain the information.

Selection criteria

Inclusion criteria

① The study subjects were patients (age ≥ 18 years, gender, radiotherapy dose and frequency) with radiotherapy for head and neck tumors diagnosed by pathological tissue examination; ② The interventions were either conventional interventions given to the control group and non-pharmacological interventions applied on top of the conventional interventions to manage taste disorders in the test group; or comparisons were made between the non-pharmacological interventions; ③ The ending indicators are those related to the symptoms of taste disorders, and the tools used to evaluate them include M.D. Anderson Symptom Inventory-Head and Neck Module (MDASI-H&N); Toxicity criteria of the Radiation Therapy Oncology Group (RTOG); Simple Oral Comfort Scale; NCI scale; Taste Loss Visual Analog 4-point Scale (VAS), etc.; ④ The type of study was a randomized controlled trial.

Exclusion criteria

① Study subjects combined with serious complications, such as acute cardiovascular and cerebrovascular accidents, serious infections, etc.; ② Incomplete raw data or inability to extract data; ③ Duplicated published literature; ④ Non-RCT studies, such as cohort studies, cross-sectional studies, and clinical pre-tests; ⑤ Literature with quality of C grade.

Literature screening and extraction of data

Relevant data information was extracted by 2 evidence-based trained researchers who independently screened the literature and cross-checked. Literature screening was done first by reading the title and abstract for initial screening. All randomized controlled trials on non-pharmacological interventions in radiotherapy patients with HNSCC were included and then read in full text to exclude irrelevant literature and literature for which full text and complete data were not available. Data extraction included the basic characteristics of the literature (first author's name, year of publication, and type of study), the basic characteristics of the study population (age, sample size), the intervention protocol reported by the study (intervention, duration of the intervention), the outcome indicators, the duration of the outcome indicator detection, and the key elements of the risk of bias evaluation.

Bias and quality assessment

The risk of bias of all the included literature was assessed using Cochrane collaboration's tool for assessing risk of bias[17], which mainly evaluates the risk of bias in 6 domains and 7 indicators, and "low bias", "unclear" and "high bias" were used to determine the risk of bias for each indicator, "High bias" was used for each indicator. The assessment was cross-checked by two researchers. This study included only the literature with grade A or B in terms of quality.

Statistical analysis

Data merger

The data of this study were continuous and dichotomous variables, and were analyzed using RevMan 5.4 for Meta-analysis. The data of continuous variables were expressed as mean difference (*MD*) and dichotomous variables as odds ratio (*OR*) and 95% confidence interval (*CI*).

Heterogeneity test

The χ^2 test was used to analyze the heterogeneity of the included literature, with the significance level α set at 0.1, and combined with the I^2 statistic for quantitative description of heterogeneity to quantify the magnitude of heterogeneity. When $P > 0.1$ and $I^2 < 50\%$ were met, good homogeneity was considered between the results of the studies, and the combined statistics were used in a fixed effects model (FD). If $P \leq 0.1$ or $I^2 \geq 50\%$, it is considered that there is obvious heterogeneity between the results of each study, and if the heterogeneity is not eliminated even after excluding the effect of obvious heterogeneity, the combined statistics are combined using the random effects model (REM).

Results

Studies search results

In total, 1279 published articles were collected from online databases, including Web of Science (n = 22), PubMed (n = 202), Cochrane Library (n = 60), Embase (n = 811), Chinese Biomedical Literature Database (CBM) (n = 100), Chinese National Knowledge Infrastructure (CNKI) (n = 16), Chinese Scientific Journal Database (VIP) (n = 8), and Wan-Fang Database (n = 60). After deleting duplicates by EndNote, 923 studies were obtained. After the review of the titles and abstracts, 51 articles were chosen for full-text review. Based on the inclusion and exclusion criteria screening and articles quality evaluation criteria, 14 articles were selected for the qualitative synthesis. Finally, 14 articles[18–31] were included in the quantitative synthesis (meta-analysis). The PRISMA flow diagram of study selection is shown in Fig. 1.

Characteristics of the included studies

A total of 14 studies were included, comprising 1630 patients, of which 834 were in the experimental group and 796 in the control group, involving 14 interventions. All 14 studies were two-armed studies. The characteristics of the included studies can be found in Table 1.

The quality appraisal of the included studies

9 studies[18,19,21–24,29–31] had descriptions related to randomized grouping, of which 4 articles[19,21,24,29] were grouped using the randomized numeric table method, 5 studies[18,22,23,30,31] did not describe the specific randomization method, but only mentioned randomization as "unclear". 14 studies[18–31] were unclear about the implementation of the allocation concealment scheme. 1 paper[30] was a double-blind trial; and the quality of the 14 included studies was graded B. The quality assessment of the included studies shown in Fig. 2.

Results of meta-analysis

5 studies[19,21,22,24,29] used scales to score patients undergoing radiotherapy for HNSCC, including 508 participants. 3 papers using the M.D. Anderson Symptom Inventory-Head and Neck Module (MDASI-H&N), 1 study[24] used the Simple Oral Comfort Scale, 1 article[21] used a three-tiered rating scale of the hospitals' own scale to assess the degree of symptoms. The post-intervention scale scores were combined using *MD*, and the results of the heterogeneity test suggested that heterogeneity among the included studies was more pronounced ($P < 0.1$, $I^2 = 81\%$), so our study used random effects model. The results (Fig. 3) show that the addition of non-pharmacological treatments to the trial group reduced dysgeusia scores in patients undergoing radiotherapy for HNSCC compared to the control group [$MD = -0.76$, 95% CI (-1.04, -0.48), $P < 0.00001$]. Sensitivity analysis: There was no inversion in the meta-analysis results after removing articles one by one, and the analysis results were relatively stable.

The other 9 studies[18,20,23,25–28,30,31] used scales to count the number of dysgeusia occurring in patients undergoing radiotherapy for HNSCC, involving 1122 participants. The number of post-treatment interventions occurring in the 2 groups was statistically combined using *MD*, and there was good homogeneity between studies ($P > 0.1$, $I^2 = 0\%$), so the fixed effects model was used. The results (Fig. 4) show that the addition of non-pharmacological treatments to the trial group reduced dysgeusia scores in patients undergoing radiotherapy for HNSCC compared to the control group [$MD = 0.17$, 95% CI (0.09, 0.31), $P < 0.00001$]. Sensitivity analysis: There was no inversion in the meta-analysis results after removing articles one by one, and the analysis results were relatively stable.

Publication bias analysis

A publication bias test of the included studies using multiple dysgeusia scales found that the included studies was concentrated in the middle of the funnel plot with a generally symmetrical distribution (Fig. 5), suggesting that there is a low possibility of publication bias in the current study.

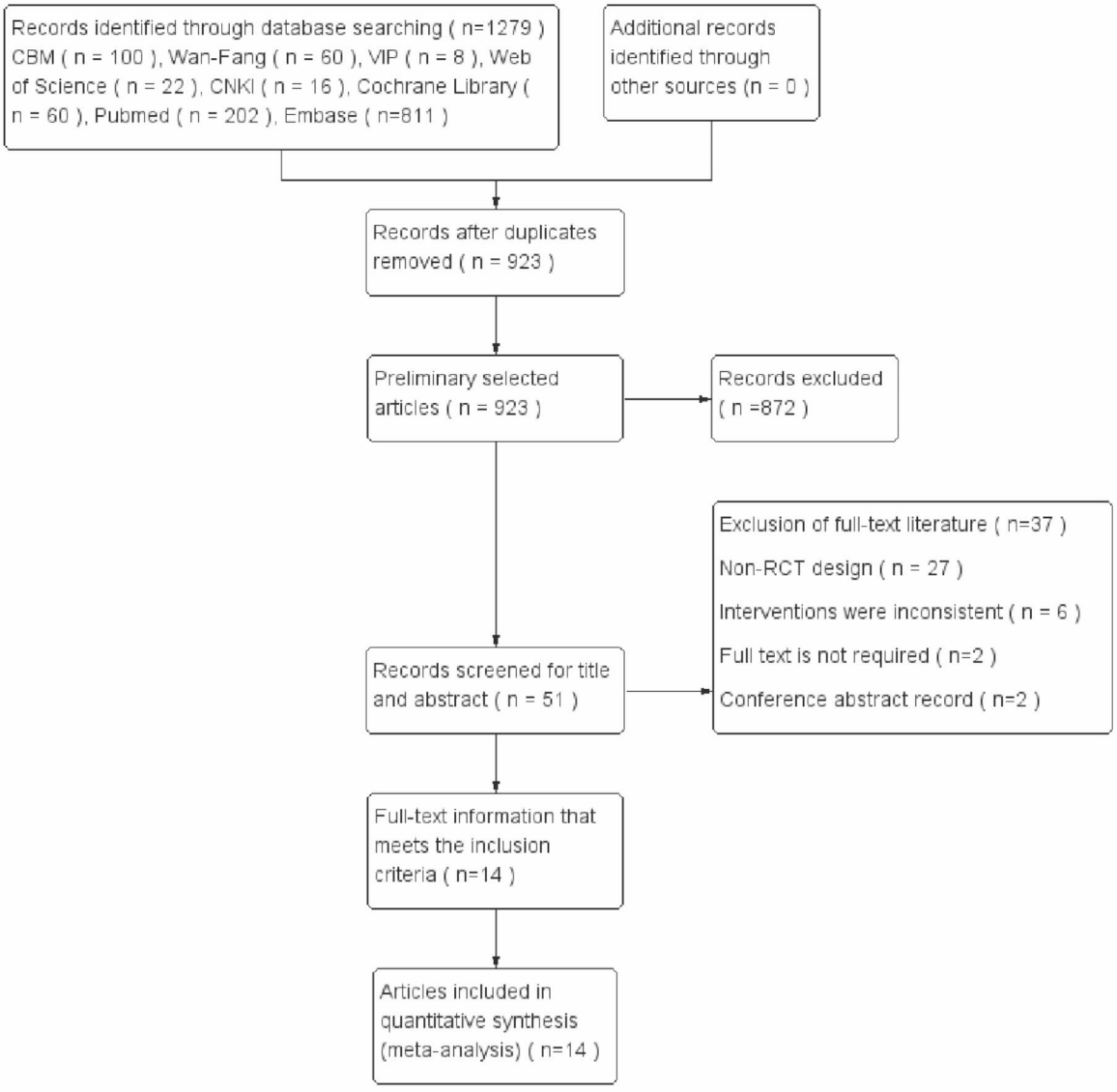

Fig. 1. Flow diagram of study selection.

Discussion

Quality analysis of the included studies

The 14 studies included in this paper had clear inclusion and exclusion criteria, which were consistent with the inclusion and exclusion criteria of this study. The measurement tools used were more varied and of unclear reliability. All 14 studies used randomized grouping, 4 articles reported on the generation of randomized sequences, and most of the papers lacked a description of the allocation concealment and blinding protocols, which increased risk of bias. The overall quality of the literature was poor, and the rigor of non-pharmacological intervention study design and reporting needs to be further improved.

Studies	Sample size		Age(years)		Intervention measures		Outcome indicator
	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group	
Cheng-Qiong Jiang et al.[19], 2020	44	45	57.55 ± 7.01	57.11 ± 7.42	Routine nursing + Multiple-modality exercise	Routine nursing	①
Hitoshi et al.[31], 2021	25	26	64.2 ± 10.6	62.4 ± 8.01	Dietary supplementation with monosodium glutamate	No monosodium glutamate supplementation in the diet	⑤
Hong-Zhen Zhang et al.[25], 2013	54	56	46.4 ± 13.5	48.4 ± 13.5	Enteral nutrition + Parenteral nutrition	Normal diet	②
Li-Chan Zhu et al.[28], 2014	50	50	46.5 ± 12.7	47.3 ± 11.2	Comprehensive nursing intervention	Routine nursing	⑦
Li-Chun Zhou et al.[27], 2014	23	23	47.9 ± 13.8	48.4 ± 12.5	Phenomenon analysis of nursing intervention	Routine nursing	⑦
Na Zhang et al.[26], 2019	72	68	54.78 ± 11.19	55.65 ± 11.19	Intensive nutrition management	Routine nursing	②
Patrícia et al.[30], 2022	32	28	58 ± 9.7	59.5 ± 10.2	Propolis	Placebo	④
Qian-Qian Ma et al.[22], 2023	53	51	54.40 ± 11.03	56.29 ± 11.95	Routine nursing + symptom management log + Intervention effect of symptom management dynamic model	Routine nursing + symptom management log	①
Wei Liao et al.[20], 2016	247 (47 deaths)	213 (31 deaths)	41.6	43.1	Whole course intervention of dentist	No whole course intervention	–
Wen-Juan Qin et al.[23], 2015	29	32	Data cannot be extracted		Wearing individual dental stent	Not wearing individual dental stent	⑦
Xiao-Xia Xu et al.[24], 2021	80	80	52.86 ± 6.31	53.19 ± 5.85	Routine nursing + Ice saline wash	Routine nursing	③
Yi-Xin Zhu et al.[29], 2022	48	47	57.32 ± 8.24	55.76 ± 8.35	Routine nursing + Objective management in mouth opening training	Routine nursing + Mouth opening training	①
Yue Gu et al.[18], 2016	47	47	51. 85 ± 6.72	51. 28 ± 6.54	Routine nursing + Local hypothermia care	Routine nursing	③
Yu-Tong Liu[21], 2022	30	30	42.69 ± 4.15	42.48 ± 4.11	Routine nursing + Green tea ice cubes combined with systemic nursing intervention	Routine nursing	⑥

Table 1. Basic characteristics of the included studies ($n = 14$). ① M.D. Anderson Symptom Inventory-Head and Neck Module, MDASI-H&N; ② Toxicity criteria of the Radiation Therapy Oncology Group (RTOG); ③ Simple oral comfort scale; ④ NCI (Version 2.0, 1999) scale; ⑤ 4-point visual analogue scale for taste loss (VAS); ⑥ Self-made hospital scale; ⑦ Oral comfort self-assessment.

The non-pharmacological intervention reduces the occurrence of dysgeusia in patients undergoing radiotherapy for HNSCC

Dysgeusia is very common in patients undergoing radiotherapy for HNSCC, with up to 75% of patients reporting loss of taste, which is particularly pronounced during radiotherapy[32]. As one of the adverse effects of radiotherapy, taste disturbance affects patients' quality of life and even disease prognosis. Currently, there is no assessment tool specifically for taste alteration in radiotherapy patients, and foreign researchers[33–36] mostly used objective evaluation methods, which can accurately measure the threshold and sensitivity of basic taste. Domestic studies[37] are few, and they are also dominated by observable measurements or single-entry assessments. Multidimensional assessment tools that can comprehensively reflect patients' dysgeusia is rarely used, in addition to the fact that taste disorders can be easily overlooked by patients or physicians, and changes in the intensity of taste loss or abnormality can only be assessed by patient-reported outcomes at present. Without specific tests, it is even more difficult to recognize loss of function or abnormal function. The inclusion and exclusion criteria of this study were strict, and through 14 studies, the results showed that non-pharmacological interventions had a positive effect in improving dysgeusia in both HNSCC radiotherapy patients compared to the control group.

Hypothermia nursing can reduce the occurrence of dysgeusia in patients undergoing radiotherapy for HNSCC

Hypothermia promotes sustained vasoconstriction of the oral mucosa, which in turn reduces the oxygen content in the oral mucosal tissues, ultimately prolonging the process of necrosis or apoptosis of the mucosal cells and decreasing the mucosal radiolucent damage. A study[38] found that the metabolic processes of oral tissues are related to oral temperature, and that hypothermia reduces the oral kinase content, which is a factor that influences the development of oral mucositis.

The kinesitherapy can reduce the occurrence of dysgeusia in patients undergoing radiotherapy for HNSCC

Heath et al.[39] reported that multimodal exercise in a variety of forms allows patients to exercise with their attention focused on the movements, eliminating the interference of external factors on the brain and allowing mental relaxation and rest, thus improving the symptoms of taste disorders and loss of appetite in patients. The integration of exercises such as warm-up training, tai chi, resistance training, and stretching exercises into positive thinking meditation, followed by physical training and then transferring to intentional association improves the immune function of the body while also increasing the excitability of the cerebral cortex and vagus nerve, thus improving the patient's spirit and appetite[40].

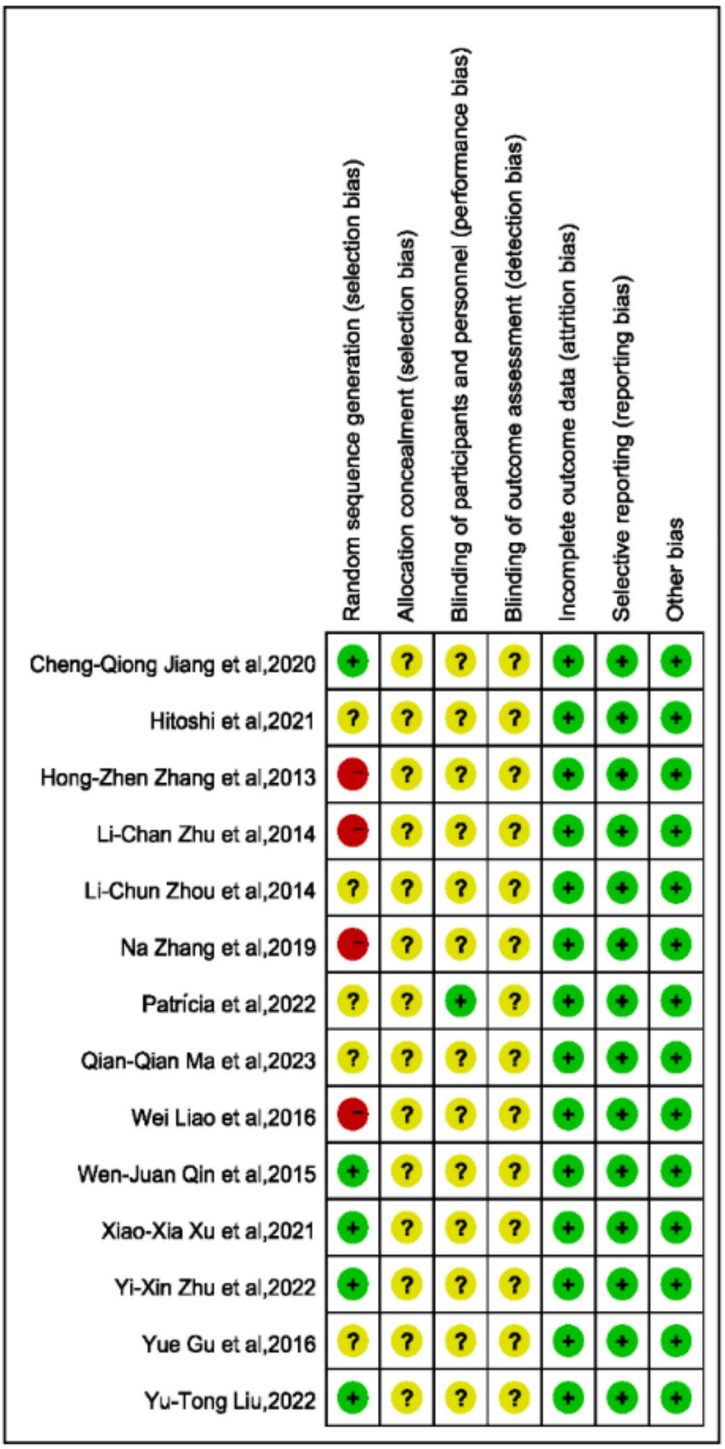

Fig. 2. Risk of bias assessment for included studies.

Diet or nutrition management can reduce the occurrence of dysgeusia in patients undergoing radiotherapy for HNSCC

In the process of treating head and neck malignant tumors, radiation has a toxic effect on normal tissues and cells, leading to the occurrence of toxic side effects, which in turn affects the nutritional status, and malnutrition in turn affects the ability of cells and tissues to repair, aggravating toxic side effects. Some studies have shown that early nutritional intervention can improve patients' immunity and reduce the severity of toxic side effects[41]. Several studies have shown[42,43] that MSG induces the expression of T1R1 and T3R3 in the tongue, and oral

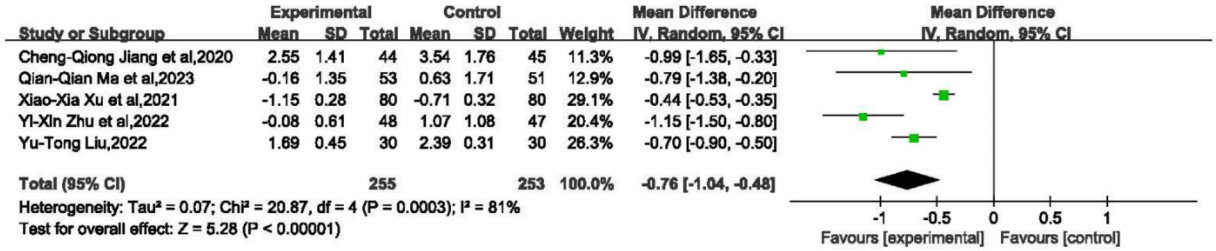

Fig. 3. Comparison of MDASI-H&N scores between Experimental group and Control group. *MDASI-H&N* M.D. Anderson Symptom Inventory-Head and Neck Module.

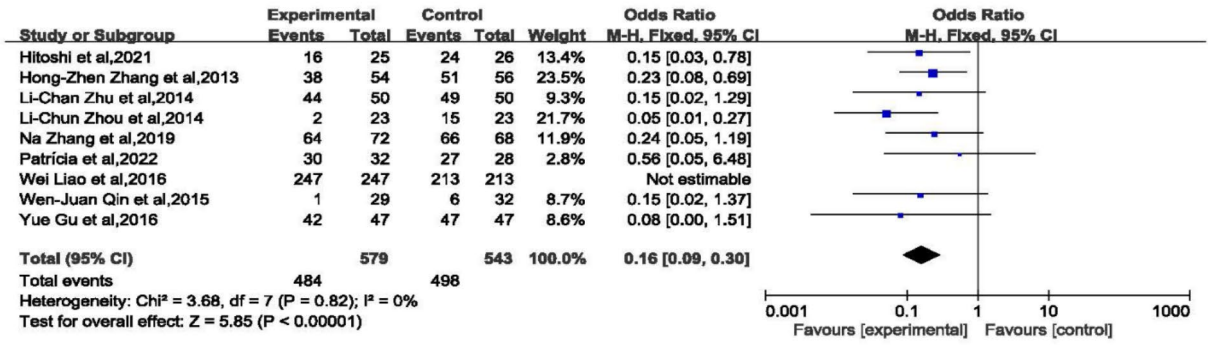

Fig. 4. Comparison of other scales scores between Experimental group and Control group

administration of MSG also increases T1R1 and T1R3 mRNA and protein levels in the gastrointestinal tract of piglets. Dietary addition of MSG could inhibit taste impairment in HNSCC patients by attenuating the down-regulation of T1R3 expression. In addition, propolis use reduced the incidence of patients suffering from oral mucositis by 11.1%, lowered the mean scores of dysgeusia, and reduced episodes of candidiasis[30], this finding

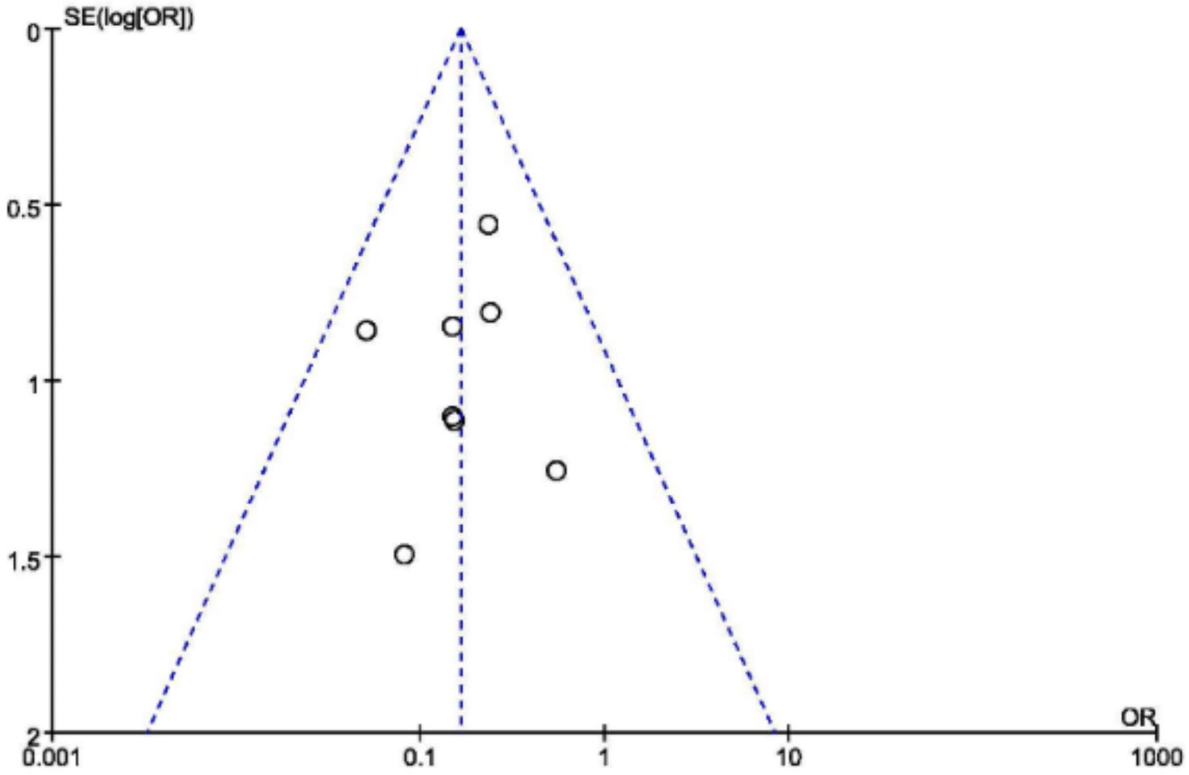

Fig. 5. Funnel plot of other scales scores.

that may be a result of the radioprotective ability of propolis extracts against taste buds present in the tongue and soft palate[44,45].

Nursing management intervention can reduce the occurrence of dysgeusia in patients undergoing radiotherapy for HNSCC

The 4 studies included in this article[22,27–29] discussed the implementation of nursing professional information guidance and dynamic care management intervention strategies targeted to help patients with symptom management and nursing interventions to improve motivation and initiative in treatment. A study[46] found that anticipatory nursing interventions for patients with head and neck tumors during radiotherapy can

reduce the adverse effects of patient symptoms and improve quality of life. Based on the theoretical model, a professional nursing management team was set up to enhance the communication and contact between healthcare professionals and patients through individualized symptom assessment, development of specialized nursing intervention standards, development of whole process quality nursing services, synchronized health education for family members, strengthening of disease-related education, and improvement of patients' self-management ability, which is conducive to alleviating the patients' adverse reactions and negative emotions during the treatment period. After the patients were discharged from the hospital, the health education process was improved through WeChat, telephone follow-up and other follow-up channels to ensure the continuity of nursing interventions. WeChat is an indispensable communication tool for people nowadays, and WeChat punch card, as an online check-in mode, can grasp the dynamics of patient self-management in a timely manner[47]. Patients were discharged from the hospital using the network communication platform for intervention to ensure the continuity and effectiveness of the implementation of the intervention program. In addition, the full participation of the patient's family members is conducive to strengthening the patient's social support, urging the patient's symptom management, and improving treatment adherence.

Limitations of this study

Due to the interventional nature of the studies, most of the included studies did not use proper randomization methods, allocation concealment, and blinding of patients, which may have had an impact on the results, and the methodological quality was generally low. This study focused on exploring the interventional effects of non-pharmacological interventions on taste disorders in patients undergoing radiotherapy for HNSCC, so only dysgeusia scores of the studies were included, and an overall rating for dynamic monitoring of symptom clusters was lacking such as fatigue, poor appetite, dry mouth, oral/pharyngeal mucus, etc. In addition, because there is no specific taste disorder measurement tool, there are multiple outcome indicator measurement scales in the included literature, whose reliability and validity are uneven, with selectivity and publication bias, and which need to be continuously improved in subsequent studies. Finally, because there is still no uniform recommendation for non-pharmacological interventions, and there is a diversity of intervention modalities, intervention times, and intervention frequencies in different studies, meta-analysis can only prove the effectiveness of each program, and cannot compare the strengths and weaknesses of the effects horizontally, so further studies are needed to compare the efficacy differences of each intervention modality.

Conclusion

Our meta-analysis indicated that hypothermia nursing, kinesitherapy, dietary or nutritional management, and care management interventions are more effective than conventional interventions in alleviating dysgeusia in patients with squamous carcinoma of the head and neck. However, due to limitations such as the quality or quantity of the original literature, direct comparative studies between interventions and more high-quality, multicenter, large-sample, randomized, controlled trials are needed to validate the effectiveness of these interventions.

Relevance of clinical practice

This study conducted a meta-analysis of the literature published in recent years on the occurrence of dysgeusia in HNSCC patients with non-pharmacological treatment, in order to provide the latest evidence-based evidence for medical personnel and provide a basis for further intervention in the population of HNSCC patients with dysgeusia.

Data availability

All data included in this study are available upon request by contact with the corresponding author. The meta-analysis has been registered on the International Prospective Register of Systematic Reviews (PROSPERO), and the trial registration number is CRD42023453374.

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Author contributions
Yuyang Li (First Author): Conceptualization, Methodology, Software, Investigation, Formal Analysis, Writing–Original Draft, Data Curation, Visualization, Investigation; Lili Hou (Corresponding Author): Conceptualization, Funding Acquisition, Resources, Supervision, Writing—Review and Editing; Xing Gan: Resources, Supervision, Software, Validation; Xi Yang: Visualization, Writing—Review and Editing.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval and informed consent
Ethical approval and informed consent were not required for this study.

Additional information
Correspondence and requests for materials should be addressed to L.H.

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