INPLASY

Zinc Supplementation for the Prevention of Severe Radiation-Induced Oral Mucositis in Patients with Head and Neck Cancer: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202620063

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 February 2026 and was last updated on 20 February 2026.

INTRODUCTION

Review question / Objective The primary objective is to assess the efficacy of zinc supplementation in preventing severe oral mucositis in patients with head and neck cancer (HNC) undergoing radiotherapy or chemoradiotherapy.
Using the PICOS framework:
- Population: Patients with pathologically confirmed HNC receiving radiotherapy.
- Intervention: Administration of zinc supplementation (systemic or topical).
- Comparison: Placebo, standard care, or no treatment.
- Outcome: Incidence of severe oral mucositis (Grade 3–4 according to RTOG/WHO criteria).
- Study design: Randomized controlled trials (RCTs).

A secondary objective is to perform a subgroup analysis comparing the therapeutic potential of topical versus systemic zinc administration.

Rationale Radiation-induced oral mucositis (RIOM) is a distressing and dose-limiting complication in head and neck cancer (HNC) patients, often leading to malnutrition and treatment interruption. Zinc, an essential trace element with antioxidant and anti-inflammatory properties, has been proposed as a preventive agent to mitigate radiation-induced oxidative stress and accelerate mucosal repair. However, previous systematic reviews and trials have yielded inconsistent results regarding its clinical benefit. Furthermore, the optimal route of zinc administration—whether systemic (oral capsules) or topical (mouthwash)—remains controversial. Given the recent accumulation of new randomized controlled trials utilizing different zinc formulations, there is a pressing need for an updated meta-analysis. By synthesizing the latest evidence and conducting a pre-specified subgroup analysis to compare administration routes, this study aims to clarify zinc's efficacy and provide precise guidance for optimizing supportive care in radiation oncology.

Condition being studied Radiation-induced oral mucositis (RIOM) is a severe, dose-limiting complication commonly affecting patients undergoing radiotherapy or concurrent chemoradiotherapy for head and neck cancer. Clinically, it presents with severe erythema, ulceration, and debilitating pain, which can severely compromise oral intake, leading to malnutrition, significant weight loss, and an impaired quality of life. In severe cases (Grade 3-4), it frequently necessitates the unplanned interruption of oncological treatment, which can negatively impact local tumor control and overall survival. Despite advancements in conformal radiation techniques such as Intensity-Modulated Radiotherapy (IMRT), the incidence of severe RIOM remains unacceptably high, highlighting the need for effective prophylactic interventions.

METHODS

Search strategy A comprehensive literature search will be conducted across three major electronic databases: PubMed, Embase, and the Cochrane Library, covering the period from their inception to February 2026. The search strategy will utilize a combination of Medical Subject Headings (MeSH/Emtree terms) and free-text keywords to ensure high sensitivity. The primary search concepts will be combined as follows: ("Zinc" OR "Zinc Sulfate" OR "Polaprezinc" OR "Zinc Gluconate") AND ("Mucositis" OR "Stomatitis" OR "Oral Ulcer") AND ("Radiotherapy" OR "Chemoradiotherapy" OR "Radiation") AND ("Head and Neck Neoplasms" OR "Head and Neck Cancer"). Additionally, the reference lists of all initially included studies and relevant review articles will be manually screened to identify any further eligible randomized controlled trials. No language restrictions will be applied.

Participant or population The population of interest comprises patients with pathologically confirmed head and neck cancer (HNC) of any clinical stage who are undergoing therapeutic radiotherapy. This includes patients receiving radiotherapy either as a definitive single modality or concurrently with chemotherapy (chemoradiotherapy). Patients treated for malignancies located in various head and neck regions (e.g., oral cavity, oropharynx, hypopharynx, larynx, nasopharynx) will be included. There will be no restrictions regarding patient age, gender, or ethnicity.

Intervention The intervention is the administration of zinc supplementation for the prophylaxis of oral mucositis. This includes all formulations and routes of administration, specifically: systemic ingestion (e.g., oral zinc sulfate or zinc gluconate capsules/tablets) and topical application (e.g., polaprezinc swish-and-swallow formulations or zinc sulfate mouthwashes). The intervention must be initiated prior to or concurrently with the radiotherapy regimen.

Comparator The comparator group consists of target populations receiving a placebo, standard supportive care for oral mucositis (such as basic oral hygiene protocols or non-medicated rinses), or no specific prophylactic treatment.

Study designs to be included Only Randomized Controlled Trials (RCTs), including both double-blind and open-label designs, will be included in this systematic review and meta-analysis to ensure the highest level of evidence.

Eligibility criteria

Inclusion Criteria:

Studies must explicitly report the incidence of severe (Grade 3–4) oral mucositis as an outcome, evaluated according to validated clinical scoring systems such as the Radiation Therapy Oncology Group (RTOG) or the World Health Organization (WHO) grading criteria.

Exclusion Criteria:

1. Non-randomized observational studies (cohort, case-control, cross-sectional), case reports, case series, and animal/in vitro experimental studies.
2. Trials from which insufficient or incomplete statistical data can be extracted for quantitative pooling.
3. Studies utilizing combined or complex interventions (e.g., multi-ingredient herbal formulations) where the specific, isolated effect of zinc cannot be independently evaluated.

Information sources The primary information sources will be three major electronic databases: PubMed, Embase, and the Cochrane Library. The systematic search will cover literature from the inception of each respective database up to February 2026. In addition to the electronic database searches, the reference lists of all included studies and previously published relevant systematic reviews will be manually screened to identify any further eligible randomized controlled trials. No language restrictions will be applied during the search process.

Main outcome(s) The primary outcome of this systematic review and meta-analysis is the incidence of severe radiation-induced oral mucositis. Specifically, this is defined as the

development of Grade 3 or Grade 4 oral mucositis, evaluated according to validated and standardized clinical scoring systems such as the Radiation Therapy Oncology Group (RTOG) criteria or the World Health Organization (WHO) scale. The effect measure for this dichotomous outcome will be calculated as the Risk Ratio (RR) with its corresponding 95% Confidence Interval (CI).

Additional outcome(s) None specified.

Data management Two investigators will independently extract data from the included studies using a standardized electronic data extraction form. Any discrepancies between the two reviewers will be resolved through discussion and consensus, or by consulting a third independent reviewer if necessary. The extracted data will include: first author, year of publication, country of origin, sample size, patient characteristics, radiation protocol (technique and total dose), intervention details (zinc formulation, dose, frequency, and route of administration), and the primary outcome data (incidence of Grade 3–4 oral mucositis).

Quality assessment / Risk of bias analysis The methodological quality and risk of bias for each included randomized controlled trial will be rigorously assessed using the Cochrane Risk of Bias Tool for randomized trials (RoB 2.0). Two independent reviewers will evaluate the studies across five distinct domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. The overall risk of bias for each trial will be categorized as "low risk," "some concerns," or "high risk."

Strategy of data synthesis All statistical analyses will be performed using Review Manager (RevMan) version 5.4 software. For dichotomous outcomes, specifically the incidence of severe (Grade 3–4) oral mucositis, the Risk Ratio (RR) along with 95% Confidence Intervals (CIs) will be calculated. Given the anticipated clinical heterogeneity across the included trials regarding zinc formulations, doses, and administration routes, a Random-effects model (DerSimonian and Laird method) will be employed a priori for all data pooling. Statistical heterogeneity among studies will be evaluated using the I square statistic and the Cochrane Q test (Chi-square test). An I square value greater than 50% or a P-value < 0.10 for the Q test will be considered indicative of substantial heterogeneity. A two-sided P-value < 0.05 will be considered statistically significant for the overall effect.

Subgroup analysis To investigate potential sources of heterogeneity and evaluate the clinical impact of different delivery methods, a pre-specified subgroup analysis will be conducted to compare the efficacy of Topical Zinc (e.g., mouthwash, swish-and-swallow formulations) versus Systemic Zinc (e.g., oral capsules or tablets) in preventing severe radiation-induced oral mucositis.

Sensitivity analysis Sensitivity analysis is not planned for this study due to the limited number of included randomized controlled trials.

Language restriction None. No language restrictions will be imposed on the search or study selection to minimize publication bias.

Country(ies) involved Taiwan.

Other relevant information This systematic review and meta-analysis is conducted and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Methodological quality is assessed using the Cochrane Risk of Bias 2.0 tool to ensure high evidence quality.

Keywords Zinc; Mucositis; Radiotherapy; Head and Neck Neoplasms; Meta-analysis; Prophylaxis.

Dissemination plans The findings of this systematic review and meta-analysis will be submitted to a peer-reviewed international journal in the field of clinical oncology or supportive care in cancer. The aim is to contribute updated evidence to the current body of literature and provide clinical insights for healthcare professionals. Furthermore, the results may be presented at academic conferences where appropriate.

Contributions of each author

Author 1 - Chih Sheng Tsao - Author 1 conceived and designed the study, performed the literature search and statistical analysis, interpreted the results, and drafted the manuscript.
Email: sam60104@gmail.com
Author 2 - Kai Yu Wang - Author 2 participated in the study selection, independently performed data extraction and quality assessment, and critically revised the manuscript for important intellectual content.
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