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INPLASY

Oral metastatic carcinoma: clinical characteristics and prognosis - a protocol for systematic review and meta-analysis of observational studies

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Li, R.

Corresponding author:
Ruotong Li

3576619147@qq.com

Author Affiliation:
The First Affiliated Hospital of Chongqing Medical University, Chongqing, China.

ADMINISTRATIVE INFORMATION

Support - This study received no external funding. It is a self-selected project of the graduate student and is supported by the student's own research budget (CNY 9,000-21,000).

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 October 2026 and was last updated on 30 October 2026.

INTRODUCTION

Review question / Objective Oral metastatic carcinoma (OMC) refers to an epithelial malignancy originating outside the oral cavity that metastasizes to oral soft tissues or jaw bones via hematogenous or lymphatic routes. This systematic review and meta-analysis aims to: (1) delineate the clinicopathological spectrum of OMC, including the distribution of primary tumor types, oral metastatic sites, and the sex and age composition of patients; (2) estimate overall and primary-specific 1-year and 2-year survival rates; and (3) evaluate the methodological quality of the included primary studies and the completeness of reporting of key variables.

The review question is defined using the PECOS framework. Population (P): patients with epithelial malignancies metastatic to oral soft tissues or jaw bones, confirmed pathologically or by clinical imaging; oral primary carcinomas, non-epithelial tumors (sarcoma, lymphoma, melanoma, leukemia), and metastases to non-target sites (salivary glands, facial skin, orbit) are excluded. Exposure (E): primary tumor type, oral metastatic site, timing of oral metastasis discovery (oral-first presentation, metachronous metastasis after the primary tumor, synchronous presentation), and treatment modality. Comparator (C): no traditional parallel control group; comparisons will be made between prespecified subgroups. Outcomes (O): primary outcomes are the proportions of the primary tumor spectrum, metastatic sites, sex and age distribution, and 1-year and 2-year survival rates; secondary outcomes include the proportion of oral-first presentation, misdiagnosis, clinical warning signs, treatment distribution, reporting completeness of primary tumor tracing, survival time and treatment details, and the methodological quality of included studies. Study designs (S): observational studies providing original individual patient data, including case reports, case series, and retrospective or prospective cohort studies.

Rationale Oral metastatic carcinoma is rare, accounting for 1%-3% of all oral malignancies;

however, approximately 20%-30% of patients present with an oral lesion - local swelling, a non-healing ulcer, or a gingival mass - as the first clinical manifestation of a systemic malignancy. Oral clinicians are often the first providers to encounter these patients, and the lesions are easily misdiagnosed as primary oral benign or malignant conditions, delaying the diagnosis and treatment of the underlying systemic cancer. With continuous advances in comprehensive cancer therapy prolonging the survival of patients with advanced malignancies, the detection of atypical oral and maxillofacial metastatic lesions is increasing. Some scholars have proposed that oral metastatic carcinoma may serve as a 'window lesion' reflecting the biological status of systemic tumors, but this hypothesis still lacks large-sample evidence.

Existing international systematic reviews adopted broad inclusion criteria, pooling non-epithelial malignancies (sarcoma, lymphoma, melanoma) and non-oral anatomical structures (facial skin, salivary glands, orbit) together with oral cavity lesions, which dilutes the evidence specific to oral lesions. Domestic studies are mostly small single-center retrospective series or case reports with inconsistent data-reporting standards, and key variables such as primary tumor tracing, survival time, and treatment details are frequently missing. To date, no meta-analysis has strictly restricted the pathological type (carcinoma) and the anatomical scope (oral cavity) while preventing duplicate counting of patients across studies. By systematically integrating published original case data, quantitatively pooling clinical characteristics and key prognostic indicators, and exploring subgroup effects of primary tumor type and metastatic site through GLMM-based meta-analysis with prediction intervals, this review will provide more robust evidence to improve clinicians' vigilance, reduce misdiagnosis, and inform multidisciplinary, individualized diagnosis and treatment decisions for patients with oral metastatic carcinoma.

Condition being studied Oral metastatic carcinoma denotes an epithelial malignancy originating outside the oral cavity that spreads through hematogenous or lymphatic routes to oral soft tissues or jaw bones. It is an uncommon condition, comprising approximately 1%-3% of all oral malignancies. The jaw bones - particularly the mandible - are the most frequently involved sites, while the gingiva is the most common soft-tissue location. The lung, kidney, breast, and digestive tract are the leading primary sources, and the distribution of involved sites differs by primary tumor type. Approximately 20%-30% of patients present with an oral lesion as the first sign of a hidden systemic malignancy, and the lesions frequently mimic primary oral disease clinically and radiographically, leading to misdiagnosis and delayed oncologic care. Overall prognosis is generally poor and varies substantially by primary tumor type and the timing of metastatic discovery. Because of its rarity and heterogeneity, evidence remains fragmented across case reports and small case series, making a rigorously defined systematic synthesis necessary.

METHODS

Search strategy The following electronic databases will be searched: PubMed, Embase, Cochrane Library, Web of Science Core Collection, CNKI, Wanfang Data, and VIP.

MeSH/Emtree terms combined with free-text terms will be used for literature retrieval, and search terms will be harmonized across databases.

No restrictions on publication language or publication date will be applied. The formal search is planned in October 2026, and the search will be updated before thesis submission.

Reference lists of included studies and relevant reviews will be hand-searched, and forward citation tracking will be performed in Web of Science to capture additional eligible studies.

Participant or population Patients with epithelial malignancies (carcinomas) confirmed pathologically or by clinical imaging as metastatic to oral soft tissues or jaw bones, with the primary tumor located outside the oral anatomical region. Oral primary carcinomas, non-epithelial malignancies (sarcoma, lymphoma, leukemia, melanoma), and metastases confined to non-target structures (salivary glands, facial skin, orbit) are excluded.

Intervention Not applicable. This is a systematic review of observational studies without an experimental intervention. The exposures of interest are primary tumor type, oral metastatic site, timing of oral metastasis discovery (oral-first presentation, metachronous after the primary tumor, or synchronous), and treatment modality.

Comparator No traditional parallel control group. Comparisons will be made between prespecified subgroups: different primary tumor types; jaw bone versus oral soft-tissue metastasis; oral-first presentation versus non-first presentation; and different treatment modalities.

Study designs to be included Observational studies providing original individual patient data:

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case reports (at least 1 case), single- or multi-center retrospective case series, and retrospective or prospective cohort studies. No minimum case number per study is required. Excluded: reviews, systematic reviews/meta-analyses, secondary aggregated case series, conference abstracts, duplicate publications, and studies with non-extractable data.

Eligibility criteria Inclusion criteria: (1) Study type: any study providing original individual case data of oral metastatic carcinoma, including case reports (at least 1 case), single- or multi-center retrospective case series, and retrospective cohort studies; no minimum case number per study. (2) Population: pathologically confirmed epithelial malignancy (carcinoma) metastatic to oral soft tissues or jaw bones, with the primary tumor outside the oral cavity. (3) Outcomes: the study reports at least one of the following - distribution of clinical characteristics, survival rate, or survival status.
Exclusion criteria: (1) Aggregated (secondary) case series in which the authors did not collect original cases but compiled previously published cases; for traceable original cases in such publications, the original source articles will be retrieved and included instead, to avoid duplicate counting. (2) Cases of primary tumor directly invading oral tissues. (3) Non-epithelial malignancies involving or metastasizing to the oral region (lymphoma, leukemia, sarcoma, etc.). (4) Cervical lymph node metastasis without oral tissue involvement. (5) Reviews, conference abstracts, and duplicate publications. (6) Studies in which the primary tumor site or oral metastatic site cannot be confirmed will not be excluded as a whole but will be flagged: they enter the clinical-characteristics analysis only and are excluded from the corresponding survival meta-analyses.

Information sources Electronic databases: PubMed, Embase, Web of Science, and the Cochrane Library for English literature; CNKI, Wanfang Data, and VIP for Chinese literature. Additional sources: VIP for Chinese literature.reference lists of included studies will be hand-searched; corresponding authors will be contacted by email when essential data are missing; full texts that are inaccessible through the institutional subscription will be obtained via interlibrary loan or direct author request. No trial registers or grey literature repositories are planned, because eligible data are expected to come from published case reports and case series.

Main outcome(s) Primary outcomes are: (1) the proportion of each primary tumor type in the spectrum of oral metastatic carcinoma; (2) the proportion of oral metastatic sites (jaw bones versus oral soft tissues, and specific subsites); (3) the sex and age composition of patients; and (4) the 1-year and 2-year survival rates. Proportions and survival rates will be pooled using a generalized linear mixed model (GLMM, binomial distribution with logit link) as single-arm meta-analyses, reported as pooled proportions with 95% confidence intervals and 95% prediction intervals.

Additional outcome(s) Secondary outcomes are: (1) the proportion of patients presenting with an oral lesion as the first manifestation of systemic malignancy (oral-first presentation); (2) the occurrence and distribution of misdiagnosis; (3) clinical warning signs; (4) the distribution of treatment modalities; (5) the completeness of reporting of key variables (primary tumor tracing, survival time, and treatment details); and (6) the methodological quality scores of included studies.

Data management All retrieved records will be imported into EndNote 21 for deduplication. Study selection will be performed independently by two trained reviewers according to the prespecified eligibility criteria, with disagreements resolved by discussion or, if necessary, arbitration by the supervisor. A piloted, finalized data extraction form will be used; two reviewers will extract data independently and cross-check results. Extracted items include publication information (authors, year, country/region, study type, number of cases), patient-level clinical characteristics (sex, age, primary tumor site and histological type, oral metastatic site, timing of metastasis discovery, clinical presentation, misdiagnosis), and treatment and follow-up information (treatment modality, survival status, follow-up duration). To prevent duplicate counting of the same patient across publications, suspected duplicate cases will be verified by matching four elements - age, sex, primary tumor type, and metastatic site - combined with publication date and institutional origin; original authors will be contacted for verification when necessary. Only the most complete single source will be retained for each duplicated case. All extracted data will be managed and analyzed in R (version 4.6.1).

Quality assessment / Risk of bias analysis Because the included evidence consists mainly of case reports and case series, which are observational and expected to be of limited overall quality, the GRADE approach will not be applied. Methodological quality will instead be assessed with the Joanna Briggs Institute (JBI) critical appraisal tools: the JBI checklist for case series for

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studies reporting multiple cases, and the JBI checklist for case reports for single-case publications; when a publication contains both aggregated multi-case data and newly reported cases, the case series checklist will serve as the primary tool. Quality assessment will be performed independently by two reviewers, with disagreements resolved by consensus or third-party adjudication. Based on the appraisal results, studies will be categorized as high, moderate, or low quality, and this classification will feed into sensitivity analyses to examine the robustness of pooled results.

Strategy of data synthesis Study characteristics will first be summarized descriptively in tables. Categorical data (proportions of primary tumor types, metastatic sites, and 1-year/2-year survival rates) will be pooled using a generalized linear mixed model (GLMM with binomial distribution and logit link) in single-arm meta-analyses; the GLMM random-effects structure accommodates the large differences in sample size and the high expected heterogeneity across included studies. For each model, the pooled effect size with 95% confidence interval and 95% prediction interval will be reported. Heterogeneity will be quantified with I-squared: below 50% low, 50%-75% moderate, and above 75% high; when heterogeneity is high, interpretation will rely mainly on prediction intervals, and sources of heterogeneity (differences in primary tumor composition, geographic differences, publication bias) will be explored in the discussion. When at least 10 studies are included in a meta-analysis, publication bias will be assessed with the Egger test. All analyses will be conducted in R 4.6.1, mainly using the metafor package.

Subgroup analysis Prespecified subgroup analyses will be performed to explore heterogeneity and address the prognostic stratification questions: (1) by primary tumor type - lung, breast, kidney, prostate, and digestive system cancers as the main strata, with all other primary tumors combined into an 'other' group; (2) by metastatic site - jaw bone versus oral soft tissue; and (3) by timing of oral metastasis discovery - oral-first presentation, metachronous metastasis after the primary tumor, and synchronous presentation. Subgroup-specific 1-year and 2-year survival rates and clinical-characteristic proportions will be pooled using the same GLMM framework, with 95% confidence intervals and prediction intervals reported for each subgroup.

Sensitivity analysis Sensitivity analyses will be conducted to test the robustness of the pooled results: (1) leave-one-out analysis, excluding one study at a time to evaluate the influence of individual studies on the pooled estimates; (2) restriction to studies rated as high or moderate methodological quality by the JBI appraisal; and (3) exclusion of studies in which the primary tumor site or oral metastatic site could not be confirmed (flagged studies) from the corresponding outcome analyses. Results will be interpreted primarily with reference to the 95% prediction intervals to avoid spurious precision when heterogeneity is high.

Language restriction No language restrictions will be applied. Studies in any language will be included if data are extractable.

Country(ies) involved China (all authors are affiliated with institutions in China).

Other relevant information This protocol is registered prospectively before formal screening begins; pilot preliminary searching and pilot data extraction of seven key articles have been completed to verify the feasibility of the search strategy and the extraction form. The design deliberately differentiates this review from existing systematic reviews in three ways: (1) the pathological scope is strictly restricted to epithelial malignancies (carcinoma), excluding sarcoma, lymphoma, melanoma, and other non-epithelial tumors; (2) the anatomical scope is restricted to the oral cavity proper (oral soft tissues and jaw bones), excluding the facial skin, salivary glands, and orbit; and (3) only original case-collecting studies are included, while aggregated secondary case series are excluded and traceable original sources are retrieved, preventing duplicate counting of the same patient. This is a secondary study based on published literature; it involves no patient privacy or interventions and therefore does not require ethics approval. The literature search will be updated before thesis submission to incorporate the latest publications.

Keywords oral metastatic carcinoma; oral metastasis; mouth neoplasms; jaw; gingiva.

Dissemination plans The findings will be disseminated through: (1) a master's degree thesis entitled 'Clinical characteristics and prognosis of oral metastatic carcinoma: a systematic review and meta-analysis'; (2) a peer-reviewed journal article to be submitted to an SCI-indexed journal (target impact factor 2.0-4.0), with leading Chinese core journals as alternatives; (3) a poster or oral presentation at the annual academic meeting of

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the Oral and Maxillofacial Surgery Committee of the Chinese Stomatological Association or a national head and neck oncology conference; and (4) an anonymized dataset of original case literature (as of October 2026, containing no personal patient information) to support future research. An internal teaching summary of clinical recognition points will be prepared for departmental education only.

Contributions of each author

Author 1 - Ruotong Li.
Email: 3576619147@qq.com

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