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Depth of Invasion and Lymph Node Metastasis in Oral Cancer: A Systematic Review and Meta-Analysis

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Introduction

Head and neck cancer continues to rank among the top 10 most common cancers worldwide, with oral squamous cell carcinoma (OSCC) accounting for approximately 90 % of cases. Depth of invasion (DOI) of OSCC is the most important predictor for lymph node metastases (LMN) in early stage OSCC (T1-T2), such that in 2018, the American Joint Committee on Cancer (AJCC) guidelines were updated to include DOI in the T staging category of OSCC. In spite of the importance of DOI as a prognostic indicator for LNM, its utilization in clinical management is discrepant due to inconsistencies in definitions, cut-off values for different treatment methods, and varying use of subsite classification.

Aims

The aim of this study was to determine the relationship between depth of invasion (DOI) and rate of lymph node metastasis (LNM) in oral cavity squamous cell carcinoma (OSCC) via a systematic review of the literature and a meta-analysis of the data.

Methods

-The Preferred Reporting Systems for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed for this systematic review
-A search of PubMed, CINAHL, Embase, and Cochrane Library databases was completed in November 2024. Search terms included, but were not limited to, squamous cell carcinoma, oral cancer, mouth, tongue, and palatal cancer and neoplasm, depth of invasion, and lymph node metastasis
-Case series, prospective and retrospective cohort studies were included. Records were imported to Covidence. To be included, studies require 2 of the 3 reviewers to agree and conflicts were resolved by the senior author (C.A.B.)
-Using MATLAB, Random-effects meta-analyses were performed to estimate the pooled prevalence of the primary outcome (lymph node metastasis) with 95% confidence intervals (CIs) at each millimeter DOI from 1mm-5mm
-Using the Methodological Index for Non-Randomized Studies (MINORS) criteria, two authors (S.M.S and C.H.) independently performed a bias assessment for each included study

Results

-A total of 6117 references were initially obtained. A total of 16 references were included in the final analysis
-All studies were non-comparative with a mean MINORS score of 9.9 (3 poor quality and 12 moderate quality)
-Articles were published between the years of 1997 and 2024 and were all retrospective in nature. Patient data was gathered from as early as 1974 to as late as 2023
-Random effects meta-analysis resulted in estimates for lymph node metastasis rate at each level of DOI (per mm) as follows: 12.4% at 1-1.9mm [95% confidence interval (CI): 7.3%-17.5%], 14.8% at 2-2.9mm [95% CI: 7.3%-17.5%], 18.3% at 3-3.9mm [95% CI: 13.4%-23.1%], and 28.4% at 4-4.9mm [95% CI: 22.5% - 34.2%].
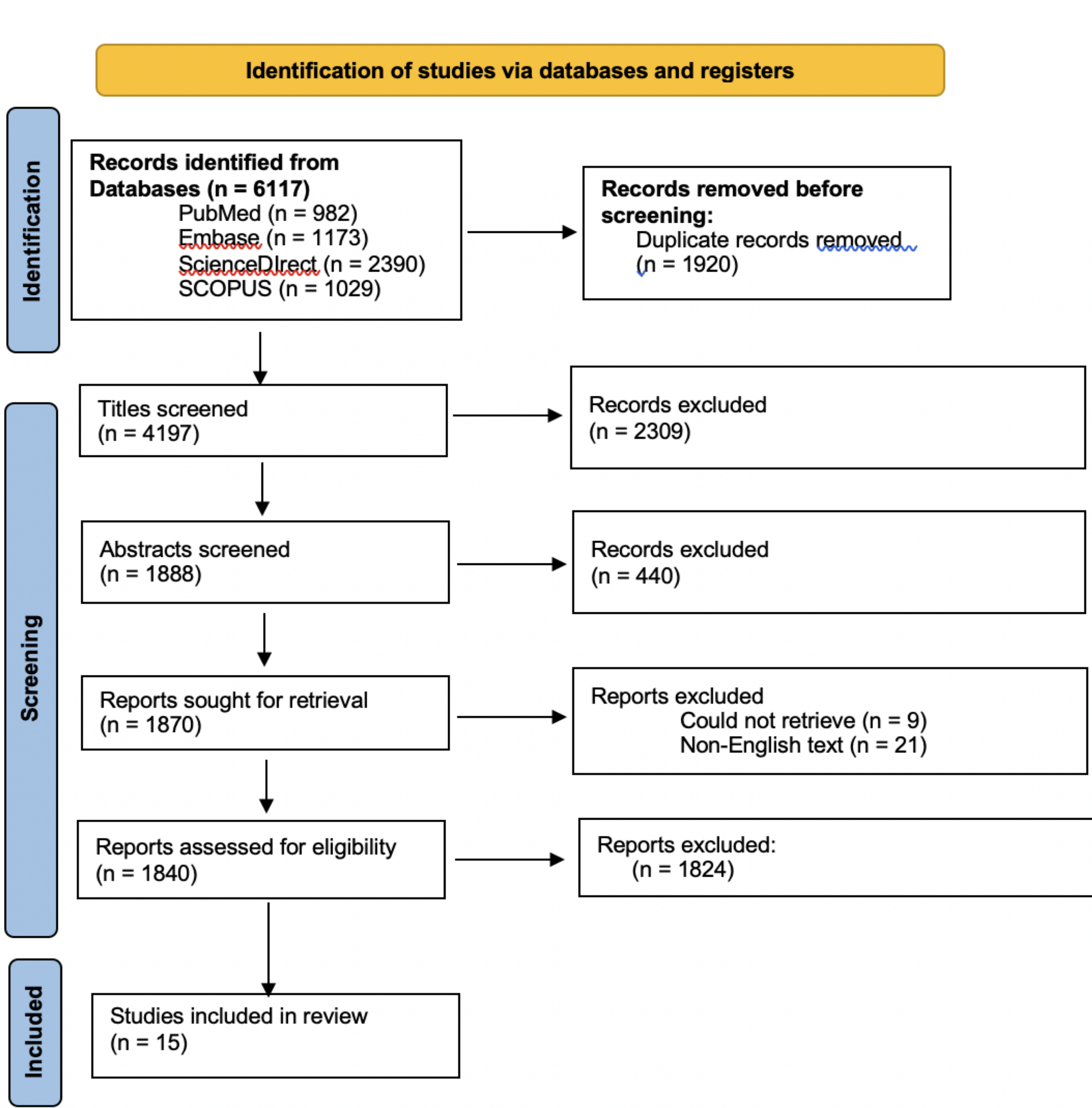

Figure 1: PRISMA Diagram

Supplemental Table 1: MINORS scores

TABLE 1

DOI	Prevalence Range (%)	Pooled Prevalence (%)	95% Confidence Interval
0-.9mm	0% - 14.29%	4.2%	-0.04% – 12.2%
1-1.9mm	0% - 18.18%	12.4%	7.3% - 17.5%
2-2.9mm	0% - 23.33%	14.8%	10.1% - 19.6%
3-3.9mm	8.33% - 85.71%	18.3%	13.4% - 23.1%
4-4.9mm	14.29% - 100%	28.4%	22.5% - 34.2%

Table 1: Prevalence of LMN at DOI by mm

Discussion

-DOI, which is the measurement of tumor depth from the basement membrane to the deepest point of invasion of the primary tumor, is another metric within the T stage that is often used in OSCC
-The relevance of DOI in OSCC prognosis led to the AJCC including it in their 8th edition as a marker for lymph node metastasis in early-stage oral tongue OSCC
-The upstaging of OSCC since the release of the 8th edition AJCC has led to more adequate management of previously under-staged and under-treated cancer
-Based on the results of this study, END could be beneficial at a DOI as low as 2mm. Rates of LMN averaged 14.8 at >2mm with a 95% confidence interval that includes 15%, a baseline LMN rate that can be used when deciding to pursue END
-The average rate did not exceed 20%, the widely accepted LMN rate for END, until a DOI of >4mm was reached, which is comparable with the current guidelines of clinical decision making with DOI between 2-4mm and END with DOI above 4mm (NCCN).
- Limitations: retrospective design and is therefore subject to inherent bias, studies were not always consistent and clear in their definition and parameters of DOI, did not evaluate DOI by tumor location, which some studies have also found to impact the decision-making process for END and could be a valuable direction for future systematic reviews and meta-analyses to investigate

Conclusion

-DOI is an important predictor of LNM and can be used as a marker for determining the need for END
-END should be performed in patients with DOI with 4+ DOI as there is ~28% rate of LMN
-END can be considered as low as 2mm as there is ~15% rate of LNM

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