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REVIEW ARTICLE

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Tumor depth of invasion and prognosis of early-stage oral squamous cell carcinoma: A meta-analysis

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Abstract

Objectives: To assess the prognosis for early-stage oral squamous cell carcinoma according to tumor depth of invasion (DOI).

Methods: This study was logged in the PROSPERO database under protocol # CRD42017059976. The search was conducted in six electronic databases up to May 2019. Fixed-effects meta-analysis was performed for the calculation of the *odds ratio* (OR) and respective 95% CI. Primary outcomes were lymph node metastasis, recurrence, and survival. Heterogeneity was calculated by the I^2 test. The certainty of evidence was assessed by Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

Results: Twenty-seven studies were included (19 in the meta-analysis) with 2,404 patients with a mean of 60 years of age. High tumor DOI is associated with a greater chance of presenting lymph node metastasis, regardless of the cutoff point for DOI (13 meta-analysis; OR 1.69–53.08), recurrence (five meta-analysis; OR 1.22–3.83), and lower chance of survival (1 meta-analysis; OR 0.49). The certainty of evidence varied from very low to low.

Conclusions: Tumor DOI is a good prognosticator for early-stage OSCC. The findings of the current meta-analysis highlight the clinical relevance of DOI and corroborate its incorporation for staging OSCC.

KEYWORDS

lymph node, meta-analysis, oral cancer, prognosis, squamous cell carcinoma

1 | INTRODUCTION

Squamous cell carcinoma represents 90% of the malignancies of the oral cavity, affecting mainly men who are smokers and who consume alcohol. Oral squamous cell carcinoma (OSCC) presents high mortality rates, especially in patients with a late diagnosis (Bray et al., 2018). Several factors influence the prognosis of patients with OSCC, which may be related to the tumor, the applied treatment, or the patient (Scully & Bagan, 2009; Woolgar & Hall, 2009). The presence of lymph node metastasis is considered to be the most adverse prognostic factor in OSCC (de Bree et al., 2009; Lundqvist, Stenlund, Laurell, & Nylander, 2012; Woolgar & Hall, 2009).

The recommended treatment for OSCC patients diagnosed with stage I and II tumors is usually extensive surgical excision of the tumor, with or without elective neck dissection (de Bree et al., 2009; Ganly et al., 2013). It is important to note that patients with early-stage tumors (T1 and T2) may present occult lymph node metastasis, which can go undetected upon clinical examination, thus affecting

the survival rate of these patients (de Bree et al., 2009; Woolgar & Hall, 2009). Consequently, researchers have been searching for histopathological parameters that influence patient survival, tumor recurrence, and metastasis, which can help to determine treatment approaches in these patients.

There was evidence of depth of invasion (DOI) as a useful guide for elective neck dissection of OSCC in the 1980s (Crissman, Gluckman, Whiteley, & Quenelle, 1980; Mohit-Tabatabai, Sobel, Rush, & Mashberg, 1986; Spiro et al., 1986; Thompson, 1986). Since then, many studies have been conducted, and in 2014, the *International Consortium for Outcome Research in Head and Neck Cancer* recommended the incorporation of DOI in oral cancer staging, since this feature had an impact on disease-related survival and the overall survival of patients (Ebrahimi et al., 2014). This multicenter retrospective elaborated and compared the performance (prognostic stratification and discrimination) of five models for staging OSCC, which incorporated optimal DOI cutoff points identified by the authors. All clinical stages were included (most comprehended stage IV), and overall survival and disease-specific survival were the outcomes evaluated (Ebrahimi et al., 2014). Finally, in 2017, DOI was included in the eighth edition of the American Joint Cancer Committee (AJCC) staging manual for OSCC, following the cutoff values suggested by Ebrahimi et al. (AJCC, 2017; Lydiatt et al., 2017).

This systematic review aims to meta-analyze the patients surgically treated for early-stage oral squamous cell carcinoma (patients—"P") for the occurrence of lymph node metastasis (N+), tumor recurrence, and survival (outcome—"O"), according to several tumor DOI cutoffs (from 2 mm to 10 mm) (exposition—"E," comparison—"C"). In the current study, the definition of DOI used was the measure from the closest adjacent normal mucosal surface to the deepest point of tumor invasion. This is the first meta-analysis evaluating tumor DOI for the occurrence of lymph node metastasis, recurrence, and survival, focusing on early-stage OSCC. The results presented here intend to highlight the clinical relevance of tumor DOI for the prognosis of oral cancer patients, specifically those in the early stages (T1T2N0M0) of the disease.

2 | MATERIALS AND METHODS

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (the PRISMA statement) (Moher, Liberati, Tetzlaff, Altman, & Group, 2009). This study was logged in the PROSPERO database under protocol # CRD42017059976.

2.1 | Eligibility criteria

The PECO question was as follows: Patients surgically treated for early-stage (T1T2N0M0) oral squamous cell carcinoma (OSCC) and with low DOI have a better clinical outcome than patients with high tumor DOI [Population: patients surgically treated for with early-stage OSCC; Exposure: high tumor DOI; Comparison: low tumor DOI; Outcome: lymph node metastasis, tumor recurrence, survival]. The cutoff value used to classify DOI into low or high DOI was the one reported by the authors of each included study (*e.g.*, for low DOI ≤4 mm, high DOI would be >4 mm).

2.2 | Inclusion criteria

Observational studies that evaluated the association between the tumor DOI and clinical outcome (lymph node metastasis [occult or late], tumor recurrence [local or loco-regional], survival [overall, disease-specific, or disease-free]) of patients surgically treated for early-stage OSCC are included. The data need to have been submitted to statistical analysis comparing tumor DOI and any of the clinical outcomes.

2.3 | Exclusion criteria

Studies evaluating T3 and/or T4 tumors (stages III and/or IV), oropharyngeal and lip vermilion cancer, intraosseous lesions, secondary tumors, pretreated patients for oral cancer, patients who underwent radiotherapy/chemotherapy prior to surgical resection, tumor DOI measured by any imagining modality, OSCC of non-conventional histological subtypes and not performed in human subjects, case reports, letters to the editor, expert opinions, narrative reviews, literature reviews, and systematic reviews were all excluded from the present study. Moreover, studies for which the DOI was not measured from the closest adjacent normal mucosal surface to the deepest point of tumor invasion were excluded, as were those not clearly reporting the DOI definition used.

2.4 | Information sources

An electronic search was performed, with no restrictions regarding publication dates, in four electronic databases: MEDLINE through PubMed, Scopus, Web of Science, and the Cochrane Library. Gray literature was searched for in "Clinical Trials" and in the "National Institute for Health and Care Excellence" (NICE) platforms. Only studies in English were included. Searches were performed up to May 2019. A manual search was conducted in the list of references of the included studies. Reference Manager software, version 12, was used to identify duplicate articles and organize the abstracts.

2.5 | Search strategies

The following search strategy was used in PubMed, the Cochrane Library, the Web of Science, and Scopus: ((oral squamous cell carcinoma OR mouth neoplasms [mesh] OR mouth neoplasm* OR oral carcinoma OR tongue neoplasms [mesh] OR tongue neoplasm*) AND (depth of invasion OR invasive depth OR tumor thickness OR tumor thick) AND (survival [mesh] OR survival OR recurrence [mesh] OR node metastasis OR lymph node metastasis OR relapse OR outcome OR prognosis [mesh] OR prognosis OR prognostic OR mortality

[mesh] OR death [mesh] OR death OR treatment outcome [mesh] OR treatment outcome*)).

For the search in the "Clinical Trials," the keywords oral squamous cell carcinoma, mouth neoplasms, mouth neoplasm, oral carcinoma, tongue neoplasm, and tongue neoplasms were used, together with tumor thickness or depth of invasion. For the NICE platform, the keywords were oral squamous cell carcinoma, mouth neoplasms, mouth neoplasm, oral carcinoma, tongue neoplasm, tongue neoplasms.

Both "tumor thickness" and "depth of invasion" were used in search, because many studies use them as synonyms, but only studies that accomplished with the DOI definition described above were included in the current systematic review.

2.6 | Study selection

All studies were selected and read by two independent trained reviewers (P.C.C. and M.C.F.A.). The first selection of articles was based on the title and abstract. All studies were read, and any discrepancies in eligibility were reconciled by the two researchers re-reviewing the abstract until they reached a consensus. The selected abstracts were included for full-text reading and re-selection, considering the inclusion and exclusion criteria by the same two independent reviewers. In this second phase, the researchers also resolved disagreements by discussion.

2.7 | Data collection process and data items

Two reviewers (P.C.C. and A.M.L.S.) extracted the data independently, collecting information regarding author, year of publication, country of origin of authors and of the sample, sample size, tumor site, age, sex, adjuvant radiotherapy, how many years of data collection, cutoff point for DOI, follow-up period, number of events for lymph node metastasis, tumor recurrence, and survival.

2.8 | Risk of bias

The TRIPOD Checklist (Collins, Reitsma, Altman, & Moons, 2015): Prediction Model Development and Validation was used by the same two researchers separately to assess the risk of bias in the individual studies. Disagreements were solved by consensus. The methods and results of the articles were evaluated regarding the data source, participants, outcome, predictors, missing data, statistical analysis and methods, model development, specification, and performance.

2.9 | Synthesis of results

2.9.1 | Meta-analysis

A descriptive analysis of the study characteristics was done using SPSS (IMB Statistics for Windows version 22.0, IBM Corp). Data of percentage of 5-year survival (overall survival, disease-specific survival, and disease-free survival) were abstracted. The mean percentage of 5-year survival was calculated for each continent, based on the origin of the sample: North America (USA and Canada), South America (Brazil), Asia (India, Pakistan, China, and Taiwan), and Europe (Switzerland, UK, Finland, and Ireland). Japan was analyzed separately from other Asian countries, because it has a very high human development index (HDI; 0.909), contrary to the other Asian countries that have high (0.799–0.700) and medium HDI (0.0699–0.566) (http://hdr.undp.org/en/composite/HDI).

Review Manager (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for meta-analysis for primary outcomes: lymph node metastasis, tumor recurrence, and survival. The number of events and total sample for each DOI cutoff point was extracted, according to the author's descriptions, in order to calculate the *odds ratio* (OR) and 95% CI. Heterogeneity was tested by the I^2 test, and a fixed-effects meta-analysis was used for not important (I^2 = 0%–40%) to moderate (I^2 = 30–60) heterogeneity when p-value was non-significant ($p > .05$) (Higgins, 2015). Cutoff point comparisons were extracted according to the authors' description and are detailed in Table 1.

Data were abstracted according to the findings reported in prior articles, and only those articles from which data could be extracted were included in the meta-analysis.

2.9.2 | Certainty of evidence through GRADE approach

The GRADE approach was applied (Guyatt et al., 2008) to rate the certainty of evidence per each outcome and per each DOI cutoff point comparison. Observational studies start with a low certainty of evidence (Atkins et al., 2004). The certainty of evidence was rated down in one or two levels if there was a problem of risk of bias, inconsistency, indirectness, imprecision, or publication bias. Moreover, to compensate the initial low certainty of evidence of observational studies, three additional criteria that could raise the rate of the certainty of evidence were evaluated: large effect, dose-response gradient, and plausible confounders (Atkins et al., 2004).

3 | RESULTS

The PRISMA flow diagram is shown in Figure 1. The list of fully read articles that were excluded is available in Appendix S1. Twenty-seven observational retrospective studies were included (19 included in the meta-analysis) (Appendix S2, Appendix S3), enrolling 2,404 patients, mostly men (1,516), with a mean of 60 years of age. Not all studies reported all three outcomes.

Appendix S4 shows the study's main characteristics: the majority were from Asia (48%), were published after 2010 (63%), received funding from government or university grant (89%), and report nothing regarding conflict of interest (63%).

TABLE 1 Summary of findings (SoF) table showing the certainty of evidence of the studies reporting association of tumor DOI and lymph node metastasis, tumor recurrence, or survival

Certainty assessment							No. of patients		Effect			
No.of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High DOI	Low DOI	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance[i]
Lymph node metastasis for >2 mm versus ≤2 mm												
1	observational studies	serious[a]	not serious[1, i]	not serious	Serious[2, c]	very strong association[3, d]	14/38 (36.8%)	1/19 (5.3%)	OR 10.50 (1.26–87.37)	316 more per 1.000 (from 13 more to 777 more)	⊕⊕◯◯ LOW	2
Lymph node metastasis for 2.2-7 mm versus 0.5-2.2 mm												
1	observational studies	serious[a]	not serious[1, b]	serious[e]	Serious[2, c]	very strong association[3, d]	7/11 (63.6%)	1/16 (6.3%)	OR 26.25 (2.46–280.20)	574 more per 1.000 (from 78 more to 887 more)	⊕◯◯◯ VERY LOW	2
Lymph node metastasis for <3.3 mm versus ≥3.3mm												
1	observational studies	serious[a]	not serious[b]	serious[f]	Serious[2, c]	very strong association[3, d]	14/40 (35.0%)	2/57 (3.5%)	OR 14.81 (3.13–70.00)	315 more per 1.000 (from 67 more to 683 more)	⊕◯◯◯ VERY LOW	2
Lymph node metastasis for ≥4 versus <4 mm												
6	observational studies	serious[a]	not serious[1, g]	serious[f]	Serious[2, c]	very strong association[3, d]	67/134 (50.0%)	14/151 (9.3%)	OR 10.16 (5.05–20.46)	417 more per 1.000 (from 248 more to 584 more)	⊕◯◯◯ VERY LOW	2
Lymph node metastasis for ≤4 mm versus >4 mm												
1	observational studies	serious[a]	not serious[1, b]	serious[f]	Serious[2, c]	strong association[3, d]	48/110 (43.6%)	9/58 (15.5%)	OR 4.22 (1.89–9.42)	281 more per 1.000 (from 103 more to 479 more)	⊕◯◯◯ VERY LOW	2
Lymph node metastasis for <5 mm versus ≥5 mm												
1	observational studies	serious[a]	not serious[1, b]	not serious	Serious[2, c]	strong association[3, d]	10/30 (33.3%)	2/18 (11.1%)	OR 4.00 (0.76–20.92)	222 more per 1.000 (from 24 fewer to 612 more)	⊕◯◯◯ VERY LOW	2
Lymph node metastasis for ≤5 mm versus >5 mm												
5	observational studies	serious[a]	not serious[1, g]	not serious	Serious[2, c]	strong association[3, d]	105/221 (47.5%)	39/177 (22.0%)	OR 2.86 (1.96–4.17)	227 more per 1.000 (from 136 more to 321 more)	⊕◯◯◯ VERY LOW	2
Lymph node Metastasis for ≤7 mm versus >7 mm												
1	observational studies	serious[a]	not serious[1, b]	serious[h]	Serious[2, c]	very strong association[3, d]	25/49 (51.0%)	0/25 (0.0%)	OR 53.08 (3.06 to 920.65)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕◯◯◯ VERY LOW	2
Lymph node metastasis for ≤10mm versus >10 mm												
1	observational studies	serious[a]	not serious[1, b]	serious[h]	Serious[2, c]	strong association[3, d]	17/32 (53.1%)	44/147 (29.9%)	OR 2.65 (1.22–5.78)	232 more per 1.000 (from 43 more to 412 more)	⊕◯◯◯ VERY LOW	2
Lymph node metastasis for ≤5 mm versus 6–10 mm												
1	observational studies	serious[a]	not serious[1, b]	serious[h]	Serious[2, c]	none	29/84 (34.5%)	15/63 (23.8%)	OR 1.69 (0.81–3.51)	108 more per 1.000 (from 36 fewer to 285 more)	⊕◯◯◯ VERY LOW	2

(Continues)

TABLE 1 (Continued)

Certainty assessment							No. of patients		Effect			
No.of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High DOI	Low DOI	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance[i]
Lymph node metastasis for ≤5 mm versus >10 mm												
1	observational studies	serious[a]	not serious[1, b]	serious[h]	serious[2, c]	strong association[d]	17/32 (53.1%)	15/63 (23.8%)	OR 3.63 (1.47–8.96)	293 more per 1.000 (from 77 more to 499 more)	⊕◯◯◯ VERY LOW	2
Lymph node metastasis for 6–10 mm versus >10mm												
1	observational studies	serious[a]	not serious[1, b]	serious[h]	serious[2, c]	strong association[3, d]	17/32 (53.1%)	29/84 (34.5%)	OR 2.15 (0.94–4.92)	186 more per 1.000 (from 14 fewer to 377 more)	⊕◯◯◯ VERY LOW	2
Lymph node Metastasis for <2 mm versus ≥2 mm												
1	observational studies	serious[a]	not serious[1, b]	serious[h]	serious[2, c]	very strong association[d]	18/42 (42.9%)	2/23 (8.7%)	OR 7.88 (1.63–38.00)	342 more per 1.000 (from 47 more to 697 more)	⊕◯◯◯ VERY LOW	
Recurrence for ≤5 mm versus >5 mm												
2	observational studies	serious[a]	not serious[1, g]	serious[h]	serious[2, c]	none	76/256 (29.7%)	28/166 (16.9%)	OR 1.94 (1.18–3.19)	114 more per 1.000 (from 24 more to 224 more)	⊕◯◯◯ VERY LOW	3
Recurrence for >10 mm versus ≤10 mm												
2	observational studies	serious[a]	not serious[1, b]	serious[h]	serious[2, c]	strong association[3, d]	16/46 (34.8%)	32/200 (16.0%)	OR 3.07 (1.46–6.44)	209 more per 1.000 (from 58 more to 391 more)	⊕◯◯◯ VERY LOW	3
Recurrence for ≤5 mm versus 6–10 mm												
2	observational studies	serious[a]	not serious[1, g]	serious[h]	serious[2, c]	none	17/100 (17.0%)	12/100 (12.0%)	OR 1.22 (0.54–2.74)	23 more per 1.000 (from 51 fewer to 152 more)	⊕◯◯◯ VERY LOW	3
Recurrence for ≤5 mm versus >10 mm												
2	observational studies	serious[a]	not serious[1, b]	serious[h]	serious[2, c]	strong association[3, d]	16/46 (34.8%)	12/100 (12.0%)	OR 3.83 (1.60–9.14)	223 more per 1.000 (from 59 more to 435 more)	⊕◯◯◯ VERY LOW	3
Recurrence for 6–10 mm versus >10 mm												
2	observational studies	serious[a]	not serious[1, b]	serious[h]	serious[2, c]	strong association[3, d]	16/46 (34.8%)	17/100 (17.0%)	OR 3.14 (1.37–7.23)	221 more per 1.000 (from 49 more to 427 more)	⊕◯◯◯ VERY LOW	3
Survival for ≤5 mm versus >5 mm												
1	observational studies	serious[a]	not serious[1, b]	not serious	serious[2, c]	strong association[3, d]	18/23 (78.3%)	22/25 (88.0%)	OR 0.49 (0.10 to 2.34)	98 fewer per 1.000 (from 457 fewer to 65 more)	⊕◯◯◯ VERY LOW	1

Abbreviations: CI, confidence interval; OR, odds ratio.

Explanations:

[a]Rated down due to some problem with high risk of bias.

[b]There is no problem of inconsistency when it is only one study.

[c]There is problem of imprecision because the number of events is less than 300 according to OIS (optimal information size).

[d]Large effect if OR >2–5 or OR = 0.5–02; and very large effect if OR >5 or OR <0.2.

[e]The evidence is based from a population that was not treated by radiotherapy, limiting the applicability to all populations.

[f]The evidence is based from populations with tumors on tongue and not treated by radiotherapy, limiting the applicability to other populations.

[g]There is no problem of inconsistency: Effect estimates are similar, overlap of 95%CI, low I^2, and non-significant p-value for heterogeneity.

[h]The evidence is based from populations with tumors on tongue, limiting the applicability to other populations

[i]Importance: 1 = survival; 2 = metastasis; 3 = recurrence.

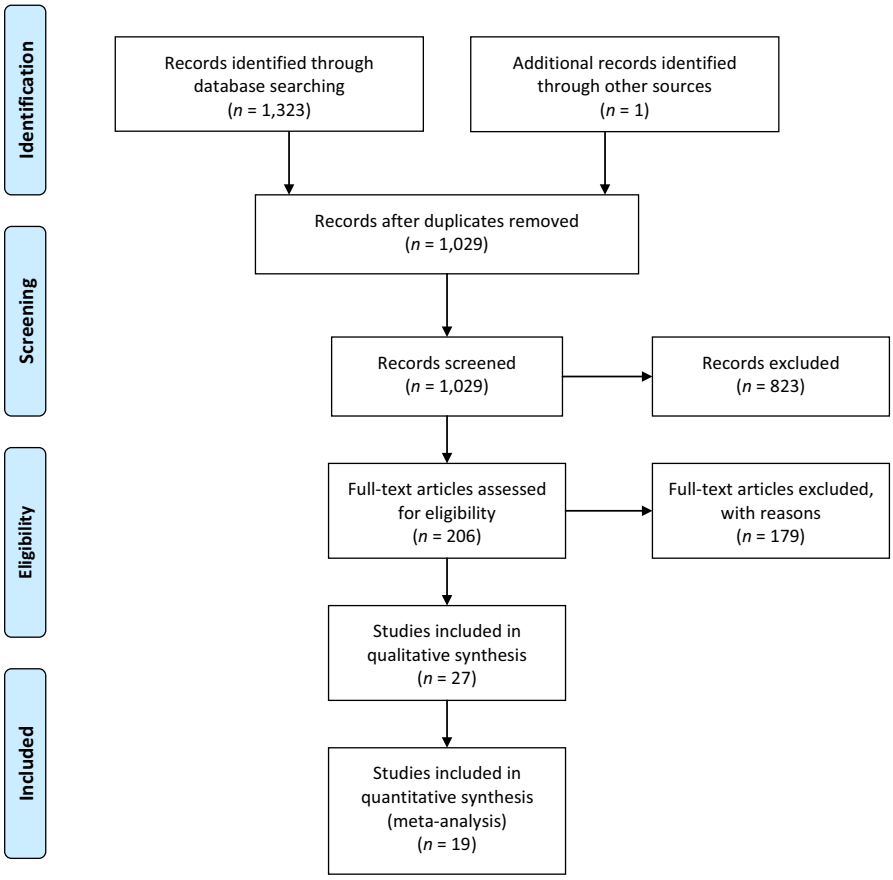

FIGURE 1 PRISMA flow diagram for the identification and selection of eligible studies. Source: Moher and colleagues (Moher et al., 2009)

Appendix S5 shows the mean percentage of 5-year survival for each continent: overall survival ranged from 72.2% (South America) to 90% (Asia); disease-specific survival ranged from 83.4% (Japan) to 85.6% (North America); and disease-free survival varied from 61% (Asia) to 79% (North America).

3.1 | Outcome: Lymph node metastasis (N+)

Either occult or late lymph node metastasis was considered altogether (17 studies, 13 forest plots—Appendix S6). We evaluated how different cutoffs for tumor DOI would impact on the occurrence of N+: >2 mm versus ≤2 mm; ≥2 mm versus <2 mm; 2.2–7 mm versus 0.5–2.2 mm; ≥3 mm versus <3 mm; ≥4 mm versus <4 mm; >4 mm versus ≤4 mm; ≥5 mm versus <5 mm; >5 mm versus ≤5 mm; >7 mm versus ≤7 mm; >10 mm versus ≤10 mm; 6–10 mm versus ≤5 mm; >10 mm versus ≤5 mm; >10 mm versus 6–10 mm. The results show that high tumor DOI is associated with a greater chance of presenting a lymph node metastasis, with *odds ratio* ranging from 1.69 to 53.08 for all 13 meta-analyses (Appendix S6), with low to very low certainty of evidence (Table 1).

3.2 | Outcome: Tumor recurrence

Both local and any recurrence were considered together (two studies, five forest plots— Appendix S7). We evaluated how different cutoffs for tumor DOI would impact on the occurrence of recurrence: >5 mm versus ≤5 mm; >10 mm versus ≤10 mm; 6–10 mm versus ≤5 mm; >10 mm versus ≤5 mm; >10 mm versus 6–10 mm. Tumors with high DOI had chance of presenting tumor recurrence with the *odds ratio* ranging from 1.22 to 3.83 for all five meta-analyses (Appendix S7), with very low certainty of evidence (Table 1).

3.3 | Outcome: Survival

Survival (overall) was calculated for tumor DOI ≤5 mm and >5 mm only, since only one study reported the absolute number of deaths for each DOI cutoff. The result shows that patients with DOI >5 mm had less chance of survival (*odds ratio* = 0.49; 0.10–2.34) (Appendix S8), with very low certainty of evidence (Table 1).

3.4 | Certainty of evidence and risk of bias

Reasons for rating down the certainty of evidence were risk of bias, indirectness, and imprecision.

Overall, the studies showed a good quality of reported data, although we rated down risk of bias, as the studies did not: report actions for the blind assessment of the outcome (59%), describe how the missing data were handled (96%), and report performance measures (with CIs) for the prediction model (41%). Appendix S9 and Appendix S10 show the summary of the evaluation for the risk of bias.

There were *odds ratios* with large and very large effects for the majority of comparisons, which rated up the certainty of evidence by one or two levels (Table 1).

4 | DISCUSSION

This meta-analysis revealed that patients surgically treated for early-stage OSCC presenting high tumor DOI were more likely to present lymph node metastasis, whether occult or late, had a higher probability of experiencing a tumor recurrence, and had less chance of survival, although with very low certainty of evidence. Regardless of DOI, the 5-year overall and disease-free survival differed between continents; however, similar disease-specific survival was observed.

The subject of the adverse effect of tumor DOI in lymph node metastasis, recurrence, and survival for oral cancer patients has been explored since the first report published in 1980 (Crissman et al., 1980). The meta-analysis published in 2009 by Huang et al. (Huang, Hwang, Lockwood, Goldstein, & O'Sullivan, 2009) indicated DOI as a strong predictor for lymph node metastasis in OSCC (all "T" stages) and suggested an optimal cutoff value of 4 mm for DOI classification. It is important to note that we demonstrated that many studies on this issue were published after 2010 and were therefore not included in the previous meta-analysis (Huang et al., 2009).

The multicenter retrospective study by *The International Consortium for Outcome Research in Head and Neck Cancer* suggested the incorporation of DOI in TNM staging (Ebrahimi et al., 2014). Later, the AJCC incorporated DOI into OSCC staging in its 8th edition guidelines (AJCC, 2017; Lydiatt et al., 2017). Some studies have already evaluated the performance of such a change, pointing out that the implementation of DOI in OSCC staging improves patient risk discrimination and enables more precise counseling of patients who were previously all considered to be at a low risk of disease progression (Amit et al., 2019; Lee et al., 2019). The results of the current research reinforce the clinical relevance of DOI for OSCC in early-stage tumors. Tumor DOI was indicative of higher chances of occult or late lymph node metastasis, tumor recurrence, and lower survival, as pointed above. All these outcomes have important implications for patient treatment and prognosis, highlighting the relevance of DOI evaluation when staging OSCC.

It is known that lymph node metastasis is a major single prognosis indicator for OSCC (de Bree et al., 2009; Lundqvist et al., 2012; Woolgar & Hall, 2009). For those patients with an early-stage disease, the management of the neck is still a matter of debate, and around 20% of all patients will carry an occult neck metastasis (Hanai, Asakage, Kiyota, Homma, & Hayashi, 2019). Performing elective neck dissection, despite conferring microscopic assurance of the neck's status, carries with it a series of major morbidity. By contrast, the "watchful waiting" approach may favor the regional and distant dissemination of the disease (de Bree et al., 2009; Huang et al., 2009; Pentenero, Gandolfo, & Carrozzo, 2005).

The current meta-analysis evidenced an association of high tumor DOI with a greater chance of presenting a lymph node metastasis, whether occult or late. However, the reported *odds ratio* varied from 1.69 to 53.08. It should be mentioned that the cutoff values for tumor DOI have varied largely among studies. Thus, future studies should follow the definition of DOI and the cutoff values predefined by AJCC for OSCC, *that is*, ≤5 mm, >5 mm and ≤10 mm, >10 mm (AJCC, 2017; Lydiatt et al., 2017). From the available studies, the only one adopting these cutoff values (Faisal et al., 2018) reported *odds ratio* of 1.69 (≤5 mm vs. >5 mm and ≤10 mm), 2.15 (>5 mm and ≤10 mm vs. >10 mm), and 3.63 (≤5 mm vs. >10 mm) for occult lymph node metastasis. Interestingly, one recent study opens a new avenue toward the usefulness of machine learning algorithms in the prediction of occult lymph node metastasis in early-stage OSCC (Bur et al., 2019). In this study, the machine learning algorithms outperformed DOI in predicting occult lymph node metastasis, with higher sensitivity and specificity (Bur et al., 2019).

The management of recurrent tumors is usually a clinical challenge, mainly because of their limitations to surgical re-intervention (fibrosis, trismus, and organ dysfunction) or re-irradiation (Marur & Forastiere, 2016). Results on recurrences were limited to two studies, which have indicated *odds ratio* of 1.22–3.83 for tumors with high DOI. Therefore, it seems that tumor DOI may help to guide clinicians to identify those patients prone to develop recurrences, although the certainty of evidence is still very low.

Depth of invasion also seemed to be inversely associated with the survival of patients with early-stage OSCC (*odds ratio* = 0.49); nevertheless, few definite conclusions can be drawn, as only one study was recorded. Finally, the differences in the overall and disease-free survival rates found worldwide should reflect distinct health assessment and assistance quality in countries with discrepant HDI, and survival can be underreported by medical records.

Radiotherapy is a pivotal adjuvant therapy for OSCC. Some patients of the studies included in the current meta-analysis were submitted to adjuvant radiotherapy for diverse clinical indications. This might have interfered in the estimates; thus, it has been taken into account in the certainty of evidence evaluation (see below). It is important to note that, as mentioned by Ganly et al., the tumor DOI is not yet a criterion for radiation therapy for patients with cN0 (Ganly et al., 2013). Accordingly, a recent multicenter study showed that DOI alone should not be indicative for postoperative radiotherapy in early-stage OSCC in the absence of other adverse features (Ebrahimi et al., 2019).

The certainty of evidence varied from very low to low. Not reporting missing data was a main problem in almost all the studies, followed by blinding, and not reporting performance measures and prediction models. Moreover, problems were identified due to indirectness, for which we have considered if the evidence from the studies included in the respective comparison could be applied to the PECO question (Guyatt, Oxman, Kunz, Woodcock, et al., 2011). Two main issues were attributed to rating down indirectness in the current study: Some studies only evaluated tongue tumors and some did not include patients who have received adjuvant radiotherapy. In both cases, the applicability of the evidence to other populations (tumors of other oral sites and patients receiving adjuvant

radiotherapy) is limited. Moreover, we dealt with large 95% CIs by rating down for imprecision (Guyatt, Oxman, Kunz, Brozek, et al., 2011). Large 95% CI is also a result of the limited number of events according to optimal information size (OIS) (Guyatt, Oxman, Kunz, Brozek, et al., 2011). Limited number of events could be a problem of underreporting events based on data collection from medical records. Effect estimates were large (when OR >2–5 or from 0.5 to 0.2) or very large (when OR >5 or <0.2) (Guyatt, Oxman, Sultan, et al., 2011). This demonstrates that high tumor DOI effectively has a role in prognosing early-stage OSCC.

As a limitation, only studies published in English were included; therefore, some language bias might be expected. By contrast, the present research attempted to find unpublished studies by searching in Clinical Trials.

In conclusion, the current meta-analysis shows that tumor DOI is a good prognosticator for early-stage OSCC, with tumors with high DOI presenting a higher probability of presenting lymph node metastasis, recurrence, and lower survival. Very low certainty of evidence was identified. These findings highlight the clinical relevance of DOI and corroborate its incorporation for staging OSCC.

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CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

Caldeira PC participated in the study design and concepts, data acquisition and interpretation, manuscript preparation, editing and reviewing. Soto AML participated in data acquisition and interpretation, manuscript preparation and editing. Aguiar MCF participated in the study concepts, data acquisition, manuscript editing and reviewing. Martins participated in the study design and concepts, data interpretation, statistical analysis, manuscript editing and reviewing.

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SUPPORTING INFORMATION

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