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Tumor budding is a prognostic marker for overall survival and not for lymph node metastasis in Oral Squamous Cell Carcinoma – Systematic Review Update and Meta-Analysis

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ABSTRACT

Objective: Tumor budding (TB) has shown promising results as a prognostic marker in several cancers such as colorectal carcinoma, breast carcinoma etc. It has been co-related to aggressiveness of the tumor and can also predict the metastasis to the lymph nodes. This systematic review evaluates the prognostic potential of TB in predicting lymph node metastasis (LNM) in OSCC.

Data sources: Systematic search was carried out in the electronic data-bases i.e. PubMed, Cochrane and Google scholar for original studies related to TB in OSCC. The assessment of risk bias was done using QUIPS tool. Meta-analysis was done using STATA software.

Results: A total of 25 articles were included. A significant association was noted for overall survival and prognosis but not for TB LNM in OSCC. Meta-analysis revealed a pooled estimate i.e odds ratio of 2.10 (CI - 0.00 - 4.20) for TB and LNM while for overall survival, it was 2.29 (CI-1.81–2.76).

Conclusion: Tumor budding though is strongly associated with LNM in OSCC did not show significant relationship in this systematic review but demonstrated a higher correlation with overall survival. It highlights that TB is an important parameter for prognosis of oral cancer but its potential in prediction of LNM needs further validation.

1. Introduction

Around 90 % malignancies of the oral cavity comprise of Oral squamous cell carcinoma making it the sixth common cancer globally. In India, it has been categorized as the third most frequent malignancy and has reached alarming trends due to the widespread prevalence of tobacco and areca nut habits.[1,2]

The prognosis is usually unpredictable as the clinical progression is typically aggressive characterized by loco-regional relapses with more than 60 % of the cases having cervical lymph node metastasis (LNM) at presentation.[3] OSCC with cervical LNM have been reported to demonstrate marked reduction in survival (almost 50 %) and are associated with greater incidence of distant metastasis, making it the central factor to envisage the clinical outcome in these patients. Currently, TNM staging system remains the established approach for ascertaining the prognosis and to decide on management modalities[3] However, the uncertainty of being dependent on TNM alone has been confirmed by reports that suggest that early-stage tumors i.e., T1 and T2 tumors can also present with LNM and aggressive behavior leading to mortality.[3,4]

Various clinical indicators and pathologic variables that could suggest tumor aggressiveness have been investigated so as to recognize patients with enhanced risk of developing LNM and furthermore be subjected to elective neck dissections or other personalized interventions as is suitable. Several other histological markers that have been known to have prognostic impact include tumor differentiation, thickness of the tumor, pattern of invasion, depth of invasion, lymphovascular emboli, perineural invasion, regional lymph node metastasis, extracapsular spread in the lymph nodes and which are evaluated customarily and indicated in the histopathology reports.[3,4] Additionally, considerable molecular studies do exist of biomarkers that can predict the prognostic outcomes in OSCC, however majority of them have not shown conclusive findings and there is ambiguity and unsatisfactory

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evidence concerning their use in routine practice.[3] So the pursuit for a more reliable and consistent prognostic parameter is still tangible. One such important prognostic parameter widely described in several cancers but has been most thoroughly investigated in colorectal carcinomas is tumor budding. Tumor budding (TB) is evident histopathologically and signifies scattered invasion composed of individual single cells or tumor cells in clusters (of around 5 cells) seen predominantly located at invasive edge dispersed within the stroma for variable distance.[5]

It was originally described as "sprouting" by Imai et al. in the 1950's but the earliest detailed description is credited to Gabbert et al. who identified these isolated tumor cells and clusters at the invasive front in colorectal cancers.[6,7] Tumor budding is an important refinement in pattern of invasion and is a morphological feature that represents an aggressive invasive phenotype characterized by local invasion due to loss of cell-to-cell adhesion. TB is strongly linked with epithelial-mesenchymal transition (EMT) which is an important biologic process characterized by conversion of a highly polarized epithelial cell into a motile mesenchymal cell which is a hallmark for invasion and subsequent metastasis[8,9] Consequently, it has been related to aggressive behavior of the tumor and has shown a definitive correlation with poor prognosis.

Tumor budding has been related to tumor aggressiveness, presence of LNM as well as distant metastasis, increased chances of recurrence and reduced overall survival in various cancers especially in colorectal, anal, pancreatic, lung, esophageal cancers etc.[5–7], Tumor budding has been evaluated in several studies in OSCC with numerous studies evaluating this parameter in tongue squamous cell carcinoma[5–21]

Studies have shown that tumor budding is a powerful prognosticator for lymph node metastasis (LNM). Tumor budding has shown a strong correlation with LNM and in multivariate analysis, it has been reported to be an independent predictor which means that TB counts can be used to assess the risk of LNM.[10,11,21] In a recent meta-analysis by Almangush A et al.,[11] it was evidenced that high tumor budding intensity of more than 5 buds significantly correlated with decreased disease-free survival as well as overall survival. Additionally, tumor budding has shown a strong correlation with tumor grade, tumor size, clinical stage, depth of invasion etc.[9,11,21]

The clinical implication of tumor budding is the relatively simple way of its detection using routine H&E sections making it cost effective not necessitating use of molecular based procedures, nevertheless use of pan cytokeratin immunohistochemistry certainly assists its identification.[11] This systematic review evaluates all the studies that correlate tumor budding with LNM and overall survival in OSCC so as to assess the prognostic potential of this histopathologic parameter.

2. Materials and methods

Design: The search was performed as per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta- Analyses and Cochrane handbook of Systematic reviews guidelines. QUIPS checklist was used for quality assessment.

Search Strategy: Systematic searches for original researches and case series were conducted in PubMed, Cochrane library, SCOPUS, Google Scholar databases using variations of the following keywords: "*Oral cancer, Oral squamous cell carcinoma, Prognosis, Lymph node metastasis and Tumor budding*". The search was restricted for articles in English language only. No unpublished studies were sought. The full text articles chosen as per the predefined criteria were assessed further for data extraction.

Article Selection: The applicability of the individual studies included in the review was evaluated independently by two reviewers (GSP and PVA: Initials of the authors) in two stages i.e. screening of titles and abstracts followed by screening of the complete articles. The title screening followed by abstract screening stage included articles that mentioned "tumor budding", "prognosis" and "oral squamous cell carcinoma". The second stage included screening of the full text articles using the preset inclusion and exclusion criteria i.e. Inclusion criteria: Original studies on tumor budding with lymph node metastasis, Descriptive studies, evaluation of lymph node metastasis, patients with OSCC exhibiting tumor budding histologically, Studies in English literature, Full text articles. Exclusion criteria: Systematic reviews, Review articles, Individual Case reports, Conference abstracts/Editorials/Commentaries/Animal studies, Studies published in other languages, no mention about lymph node metastasis. Additionally, Bibliography review of the included articles was also done. Any uncertainty regarding any study to be eligible for inclusion, the problem was resolved by the third person acknowledged in the study. Fig. 1 represents the PRISMA flowchart used in this study. PubMed and Cochrane revealed 20 records using the data search strategy previously mentioned; while Google scholar retrieved 6610 articles and 12 articles were identified in SCOPUS. Thus, the total numbers of articles found for the present systematic review were 6642. After screening through the titles, around 6597 articles were excluded because they were not linked to the objectives of the systematic review. The remaining 45 articles were then screened for duplicates. 15 articles of the 45 screened were found to be duplicates and were excluded, and thus finally 30 articles remained which were then screened for their abstracts as next stage. Following this, 5 articles were excluded out of the 30 studies for various reasons including; review article (01), systematic review (01) and studies with no lymph node metastasis correlation (03). Finally, 25 articles were selected for reviewing full text and for data synthesis in the present systematic review (Table 1). 20 articles in which measure of outcome was given were included for meta-analysis (9 for LNM and 11 for Survival) (Table 2).

Quality Assessment: The risk of bias assessment for each article was done by two authors (GSP and PVA) independently using a quality assessment checklist for prognostic factor studies i.e. the modified QUIPS tool (Quality in Prognostic Factor Studies).

Data Extraction: Two authors (GSP and PVA) reviewed the 25 articles included in the review. The following data was collected including; Author name (first), publication year, population studied, sample size, age and gender of the population, site of the oral squamous cell carcinoma, prevalence of tumor budding reported, evaluation method, statistical analysis performed, outcome measure used for lymph node metastasis, other prognostic factors and their outcome measure, Interpretation of the prognostic value and discussion was considered.

Statistical Analysis: Meta-analysis was done using Statistical software STATA version 16.0. Meta-analysis was conducted using the Random effects model. Forest plots were constructed to depict the effect size and the weight for each study, and to obtain the pooled analysis with 95 % confidence intervals. No subgroup analysis was planned.

3. Results

Study Characteristics: In this review, overall, 25 articles were included for the assessment. Table 1 gives the summary of the study parameters from various studies included in this review. 4175 OSCC patients was the sample size of the 25 studies included and individual studies had sample ranging from 23 to 337 patients. The population included in the various ranged through 9 countries, four studies each were in China and Japan respectively, 3 in India, 2 each in Denmark, Finland, Germany and 1 each in Iran, Taiwan and Korea.

The age range of the patients included ranged from 15 to 100 years,[5–40] in majority of the studies males were affected more than females, except few studies which showed female predominance.[10,22,30,35] The location of OSCC included in most studies were predominantly related to tongue[5,10,15,17,20,22–26,28,35] followed by other site such as buccal mucosa, floor of mouth, lip, palate etc.[27–40] Only one study each considered certain unusual sites such as mandibular gingiva[32] and gingivo-buccal complex in particular.[30]

The tumor budding evaluation was done predominantly in post-operative tissue specimens and only two studies were conducted on pre-operative biopsies and frozen sections.[17,26] The mode of evaluation

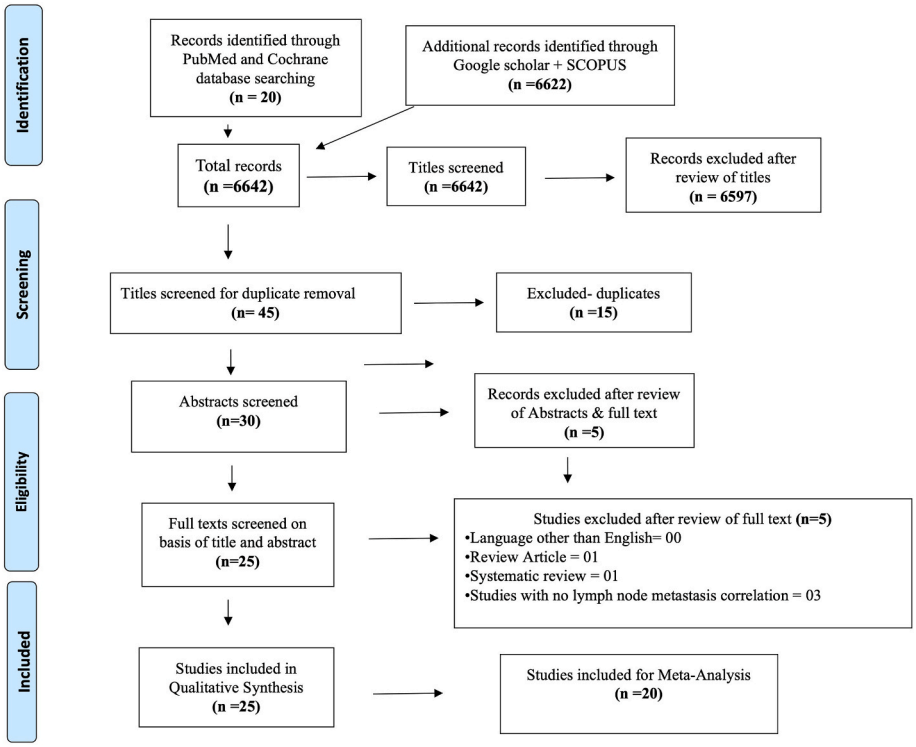

Fig. 1. PRISMA flowchart used in this systematic review and meta-analysis.

of tumor budding in all studies was manual, except in one study, it was digitally evaluated.[10] The evaluation was done on routine hematoxylin and eosin (H & E) section along with cytokeratin IHC in most of studies, however few studies did it only on H & E stained sections alone with the field of evaluation at 20X magnification in most of the studies.[21,23,24,27,30,31,34,36–38,40] Tumor budding evaluation method most commonly used was according to Wang et al. i.e., <5 buds is considered as low intensity tumor budding and >5 buds as high intensity tumor budding.[5]

Occurrence of TB in OSCC patients: The prevalence of TB ranged from 53 % to 89 % overall in all the selected studies.[9,16–40] The tumor budding (high Intensity) was seen to be linked with LNM, occult cervical lymph node metastasis, delayed neck metastasis, distant metastasis, depth of invasion, tumor size, cell differentiation, clinical stage, reduced overall survival, decreased disease free survival, poor prognosis and worst patient outcomes according to various studies. All the studies suggested that TB is a important and independent factor for prognosis especially with regards to LNM,[9,16–29,31–40] except one study by Manjula et al. who concluded that this parameter has no role in LNM specifically in gingiva-buccal oral carcinoma.[30]

Quality Assessment: The risk of bias for quality assessment was done using the modified QUIPS tool (Quality in Prognostic Factor Studies) across 5 different domains. All the studies of this systematic review showed low risk of bias in the 'study participation' as well as 'prognostic factor measurement' domains. All included studies showed low risk of bias in this domain, except few studies such as Farhadi et al. (2017),[27] Hong et al. (2018),[28] Mohan et al. (2018),[31] Okuyama et al. (2018),[32] Yamanouchi et al. (2018)[37] showed high risk of bias as the details regarding outcome measures have not be mentioned in the article, whereas Yamada et al.[36] showed moderate risk of bias.[27,28,31,32,36,37] For the domain of 'other prognostic factors', all the studies exhibited low risk of bias. With regards to 'statistical analysis & reporting', all 25 articles displayed low risk of bias as these studies did mention clearly regarding the statistical analysis done. The overall risk of bias of all the 25 articles included in the review was low with few falling in the moderate category, which means that this may not have influence on the conclusion of the systematic review (Fig. 2).

TB and its prognostic value for predicting LNM: A total of 4175 oral OSCC patients were identified for TB evaluation in OSCC and its prognostic potential with regards to LNM. The prevalence of budding reported in selected studies varied from 53 % to 89 %. A total of 9 articles[15,20,21,24–26,29,33,36] were qualified to enter into the forest plot analysis as they mentioned the outcome measure i.e. odds ratio for high grade tumor budding for predicting the risk of LNM in patients with OSCC. The effect size or the estimate in the individual studies ranged from as low as 1.28 to as high as 31.00 at 95 % confidence interval. Meta-analysis of these studies revealed a pooled estimate i.e. odds ratio of 2.10 at 95 % confidence interval ranging from 0.00 (LL) and 4.20 (UL). Though, the pooled odds ratio was 2.10, the confidence interval crossed 1.00, it suggests that the existing studies did not show significant prognostic relationship between tumor budding and lymph node metastasis. The heterogeneity was detected with I^2 value of 0 %($p \leq 0.01$).(Fig. 3).

Prognostic value of TB in evaluating overall survival: An additional meta-analysis with regards to the role of TB as a predictor for overall survival was also undertaken, as 11 articles[5,10,17,20,22,23,34,35,38–40] had also mentioned the Hazard ratio outcome measure. The effect size in the individual studies ranged from 1.60 to 5.58 at 95 % confidence interval. Meta-analysis of these studies revealed a pooled estimate i.e. hazard ratio of 2.29 at 95 % confidence interval ranging from 1.81 (LL) and 2.76 (UL).This suggest that higher tumor budding has a significant relationship with decreased overall survival in OSCC. The heterogeneity was detected with I^2 value of 49.69 % ($p \leq 0.01$).(Fig. 4).

4. Discussion

Tumor budding is evident histopathologically and signifies scattered invasion composed of individual single cells or tumor cells in clusters (of around 5 cells) seen predominantly located at invasive edge dispersed within the stroma for variable distance.[5]Tumor budding is an important refinement in pattern of invasion and is a morphological feature that represents an aggressive invasive phenotype characterized by local

Table 1
Study characteristics of studies included for the systematic review.

Sl. No	Author Name and Year	Sample size	Population	Site	Age	TB Assessment Method	TB prevalence	Outcome	HR (95 % CI)	OR (95 % CI)
1	Angadi et al., 2015	75	India	Buccal mucosa-35, tongue-14, gingivobuccalsucus, alveolus, retromolartrigone, lip, palate	20–90	According to Shinto et al. & Ueno et al. <10 tumor buds low intensity & >10 tumor buds high intensity	89.3 %	Aggressive behaviour, lymph node metastasis	NA	OR 6.79 CI 2.28–20.18
2	Xie et al. (2014)	195	China	Tongue	21–83	According to Wang et al. <5 tumor buds low intensity & >5 tumor buds high intensity	85.60 %	Lymph node metastasis, local relapse & worse pattern of invasion	HR 5.582 CI 1.23–25.38	NA
3.	Wang et al. (2011)	230	China	Tongue	NA	According to Wang et al. <5 tumor buds low ntensity & >5 tumor buds high intensity	71.70 %	Lymph node metastasis & reduced overall survival	HR 3.029–3.350 CI 1.535–5.977	NA
4	Yu et al. (2019)	246	China	Tongue	20–87	According to Wang et al. <5 tumor buds low ntensity & >5 tumor buds high intensity	24.8 % (high)	Lymph node metastasis & recurrence	HR 3.921 CI 2.210–6.056	NA
5	Jensen et al. (2015)	224	Denmark	Tongue 105 Floor of mouth 94	NA	According to Wang et al. <5 tumor buds low ntensity & >5 tumor buds high intensity	NA	Lymph node metastasis, reduced overall survival & disease free survival & prognosis	NA	NA
6	Arora et al. (2017)	336	India	Buccal mucosa, tongue, retromolartrigone, floor of the mouth, mandibular gingiva, lip	54.5	According to Wang et al. <5 tumor buds low ntensity & >5 tumor buds high intensity	NA	Lymph node metastasis & prognosis	NA	OR 1.17 CI 0.50–2.73
7	Seki et al. (2016)	209	Japan	Tongue & floor of mouth	23–90	According to Seki et al. <3 low, intermedtaite 3 or 4 & high >5	NA	Lymph node metastasis & prognosis	NA	OR 1.17 CI 0.50–2.73
8	Shimizu et al. (2018)	91	Japan	NA	33–88	According to ITBCC 2016 low intensity <5 buds/ field, intermediate intensity >5-<10 & high intensity tumor bud >10 buds/field	NA	Regional lymph node metastasis, 5-years disease free survival & prognosis	HR 3.05 CI 0.29–5.30	NA
9	Pedersen et al. (2017)	253	Denmark	Floor of mouth & tongue	30–95	Lower tertile, intermediate tertile & upper tertile	NA	Occult lymph node metastasis & overall survival	HR 4.0 CI 1.9–8.4	NA
10	Seki et al. (2015)	107	Japan	Tongue & floor of mouth	23–90	According to Ueno et al. <3 tumor buds low intensity & >3 tumor buds high intensity	NA	Lymph node metastasis	NA	OR 31.0 CI 2.6–331.8
11	Ebhihara et al. (2019)	64	Japan	Tongue	22–89	A/C to Watanabe et al. TBG grade grade1 (0–4 buddings), grade 2 (5–9 buddings), grade 3 (>10 buddings)	67 %/11 %/22 %	Lymph node metastasis, overall survival, disease specific survival & mean survival range	NA	OR 9.55 CI 1.80–50.8
12	Farhadi et al. (2017)	90	Iran	NA	22–88	A/C to Almangush et al. <3 buds low intensity & >3	33 %/67 %	Lymph node metastasis & prognosis	NA	NA

(*continued on next page*)

Table 1 (*continued*)

Sl. No	Author Name and Year	Sample size	Population	Site	Age	TB Assessment Method	TB prevalence	Outcome	HR (95 % CI)	OR (95 % CI)
						buds high intensity				
13	Hong et al. (2018)	56	Korea	NA	20–70	A/C to Teramoto et al. <3 buds negative & >3 buds positive	NA	Lymph node metastasis & prognosis	NA	NA
14	Hori et al. (2017)	48	Japan	Tongue	34–87	Low grade 4 0r less & high grade 5 or more	NA	Lymph node metastasis		RR 24.07 CI 2.27–254.89
15	Manjula et al. (2014)	33	India	Gingivo-buccalcomples	26–84	A/C to Hayers et al. low intensity 0–10 foci & high intensity 0.10 foci	36.5 %/63.6 %	Lymph node metastasis & prognosis	HR 1.32 CI 0.59–2.95	NA
16	Mohan et al. (2019)	60	India	Buccal mucosa 23, tongue 21, lower alvelous 5, lower gingiva 3, floor of the mouth 2, upper alvelous 1	20–75	According to Wang et al. <5 tumor buds low intensity & >5 tumor buds high intensity	NA	Lymph node metastasis & prognosis	NA	NA
17	Okuyama et al. (2018)	25	Japan	Mandibular gingiva	60–93	According to Wang et al. <5 tumor buds low intensity & >5 tumor buds high intensity	NA	LNM & prognosis	NA	NA
18	Sakata et al. (2017)	97	Japan	Tongue	27–93	According to Wang et al. <5 tumor buds low intensity & >5 tumor buds high intensity	33 %/64 %	Occult neck metastasis & prognosis	NA	OR 9.014 CI 1.563–89.075
19	Xie et al. (2016)	100	China	Tongue	53.6	NA	89 %	Prognosis	HR 2.228 CI 0.991–5.008	NA
20	Xie et al. (2019)	255	China	Tongue	19–83	A/C to Brandwien Gensler et al. low budding 0–4 (Bd1), intermediate budding 5–9 (Bd2), high budding >10 (Bd3)	86.28 %	LNM & prognosis	NA	NA
21	Yamada et al. (2017)	260	Germany	Tongue 111, lower gingiva 32, upper gingiva 26, oral floor 23, buccal mucosa 20, primary intra-osseous 3	28–96	According to Ueno et al. <3 tumor buds low intensity & >3 tumor buds high intensity	NA	Cervical LNM	NA	OR 2.824
22	Yamanouchi et al. (2018)	23	Japan	Tongue	22–100	A/C to JSCCR guidelines tumor budding grade 1 0–4 buds, grade 2 5–9 buds & grade 3 > 10 buds	High BD-34.8 %	LNM & prognosis	NA	NA
23	Ho et al. (2019)	200	Taiwan	Tongue 91, mouth floor 8, buccal mucosa 47, gingiva 33, lip 13, retromolar 6, palate 2	28–94	According to Wang et al. <5 tumor buds low intensity & >5 tumor buds high intensity	53 %	LNM & prognosis	HR 6.387 CI 1.889–21.594	NA
24	Zhang et al. (2019)	80	China	NA	35–55	A/C to Almangush et al. <3 buds low intensity & >3 buds high intensity	48.75 %/51.25 %	Prognosis	HR 4.347 CI 1.126–16.776	NA
25	Yamakawa et al. (2018)	337	Japan	Tongue	15–92	Low grade tumor bud no buds, intermediate grade 1–4 buds & high grade >5 buds	NA	Delayed neck metastasis	HR 2.22 CI 1.15–4.30	NA

Footnotes: NA: Not available OR: Odds Ratio HR: Hazar Ratio CI: Confidence Interval TB: Tumor Budding LNM: Lymph node metastasis.

Table 2
List of articles included in meta-analysis.

Sl. No	Author	Year
1	Angadi et al.	2015
2	Arora et al.	2017
3	Seki et al.	2015
4	Seki et al.	2016
5	Ebhihara et al.	2019
6	Hori et al.	2017
7	Manjula et al.	2014
8	Sakata et al.	2017
9	Yamada et al.	2017
10	Xie et al.	2014
11	Wang et al.	2011
12	Yu et al.	2019
13	Jensen et al.	2015
14	Shimizu et al.	2016
15	Pedersen et al.	2017
16	Xie et al.	2016
17	Zhang et al.	2019
18	Ho et al.	2019
19	Yamakawa et al.	2018
20	Xie et al.	2019

invasion due to loss of cell-to-cell adhesion. Consequently, it has been related to aggressive behavior of the tumor and has shown a definitive correlation with poor prognosis. It could represent a histo-morphological indicator of tumor invasion and metastasis. This has contributed to its popularity as it is relatively simple to use and can be assessed on routinely used Hematoxylin and eosin (H&E) stained section and does not mandate use of any other additional expensive techniques or equipment's.[6,7,8]

Tumor budding has shown a strong correlation with LNM and in multivariate analysis, it has emerged as an independent predictor, which means that tumor bud counts should be used to evaluate the possibility of LNM.[8,11,21,25,] Further higher budding intensity has been associated with LNM even in early stage and node negative OSCC($T_{1,2}N_0$ M_0) as well as overall survival.[10,11,17] However so far, tumor budding is not been officially inducted in OSCC pathologic staging nor is it an official component in pathologic grading nor it being assessed routinely by pathologists. The results of our review demonstrate though TB has been suggested to have the immense potential as an adverse prognostic indicator, however this meta-analysis failed to establishes that a significant association of tumor budding with augmented risk of LNM in OSCC but categorically established its association with decreased overall survival thus emphasizing the importance of inclusion of tumor budding in OSCC staging imperative in the future.

In our review in OSCC, the most accepted and widely used method is that proposed by Wang et al., in 2011.[5] This was also corroborated by Almangush et al. in their systematic review, who said that a cut off of 5 buds is widely accepted for OSCC.[11] Thus, this method could be standardized for evaluation of tumor budding in OSCC in any prospective trials. Most studies identified tumor budding using routine histopathologic methods (H&E, light microscopy) making it a cost-effective addition to the existing staging practices. Tumor bud identification may be enhanced using cytokeratin immunohistochemistry especially in situations with excessive peritumoral infiltrate or in identification of single cell budding. However, the IJCC Recommendations for tumor budding appraisal in colorectal carcinoma endorses use of H&E-stained sections underscoring its adaptability to routine use and worldwide utility.[29]

Pooled data discussion: Many prognostic markers have been studied including grade of the tumor, tumor thickness, type of invasion, depth of invasion, presence of lymphovascular emboli, perineural spread, etc. for lymph node metastasis in OSCC. Though, these parameters are all considered to have a negative prognostic marker for LNM and overall

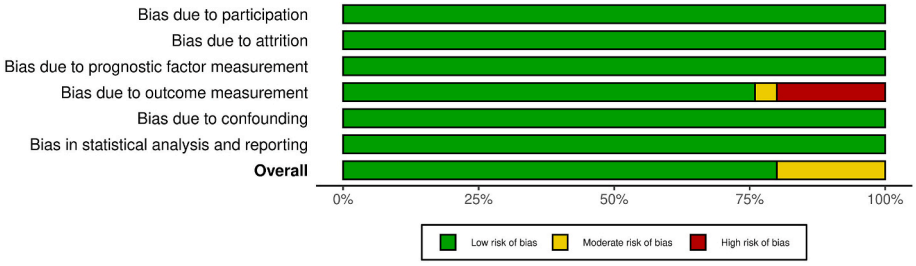

Fig. 2. QUIPS Tool for assessment of risk bias of all included studies.

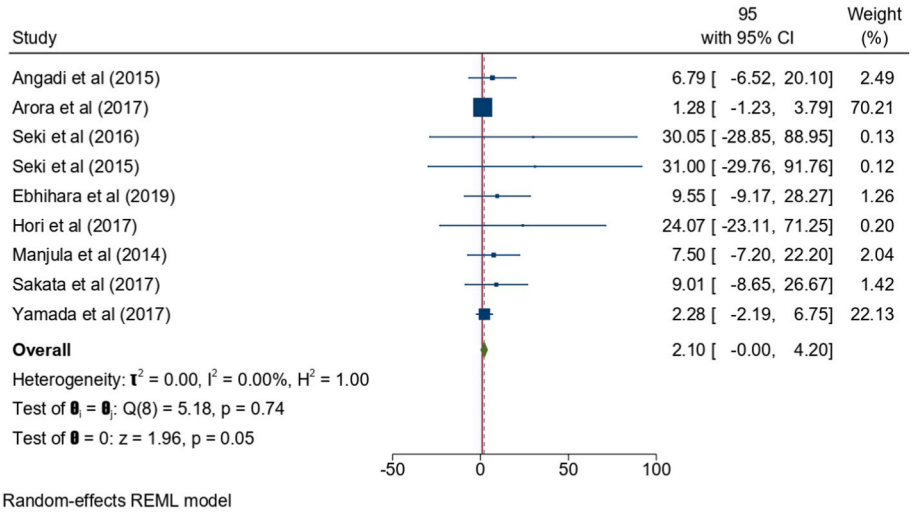

Fig. 3. Forest plot for prognostic significance of tumor budding for lymph node metastasis.

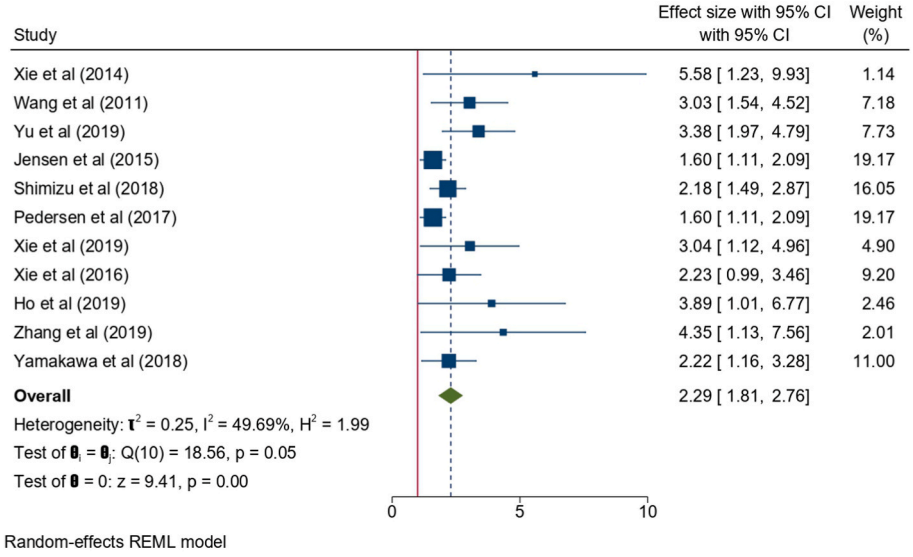

Fig. 4. Forest plot for prognostic significance of tumor budding for overall survival.

survival in OSCC, many have not shown a pooled ratios of >2 on systematic reviews.[9,11] The pooled estimate in this meta-analysis of tumor budding showed i.e. odds ratio of 2.10 for lymph node metastasis (CI 0.00–4.20) suggesting a poor correlation of tumor budding with LNM but showed significant correlation for reduced survival in patients with high grade tumor budding with a hazard ratio of 2.29(CI-1.81–2.76). These results support its insertion into OSCC pathologic staging as an indicator of aggressive disease phenotype but reiterates the earlier systematic reviews that suggested that it is a good predictor of LNM.

4.1. Strengths of the systematic review

The articles included in the systematic review and meta-analysis were recent articles as compared to the earlier published systematic review, and thus provides updated information with studies from most parts of the world. A wide-ranging database search and analytical approach was used to evaluate the role of tumor budding in the prognosis of oral cancer. Most studies included were of valid quality as per the QUIPS assessment tool and study was conducted as per PRISMA Checklist.

4.2. Limitation of the systematic review

The data extraction was affected by the varied methodology used by different authors, a higher tendency of articles reporting tumor budding mainly in the tongue squamous cell carcinoma a qualitative assessment of heterogeneity between studies. Further, when doing the metanalysis the OR for TB/LNM was based almost entirely on two studies (Arora 2015 and Yamada 2017 comprised 92.3 % of the result).

4.3. Clinical implication of this meta-analysis

- This updated systematic review and meta-analysis offers additional support for the assumption that Tumour budding is associated with poor prognosis in OSCC.
- Tumour budding did not show significance in predicting the LNM mandating in-depth study and more comprehensive clinical investigations with large sample sizes. This will foster additional evidence essential to benchmark and validate the use of tumour budding in the clinical settings.
- Tumour budding evaluation in OSCC can be used as a predictor of poor overall survival, and may be incorporated in OSCC staging so as to aid in deciding on the management strategies on individual basis.
- Even though, the different methods of tumour budding assessment did show similar results, a standard assessment method needs to be adopted by large consensus meetings.

5. Conclusions

Tumor budding has the potential to identify the aggressiveness of the tumour and predict poor overall survival but this meta-analysis failed to establishes that a significant association of tumor budding with augmented risk of LNM in OSCC.

The review recommends that this easy to assess parameter could be incorporated in OSCC staging as well as endorse the routine assessment of this prognostic parameter by oral pathologists in histopathology reporting of oral squamous cell carcinoma so as to aid in deciding on the management strategies on individual basis.

Author statement

The conceptualization, investigation, validation, analysis, writing and review, supervision and project administration was done by Dr. Punnya Angadi, The methodology, validation, investigation, analysis, collection of resources, draft was done by Dr Gouri P.

Patient consent not applicable

No patients were included in the study-since it is a sytematic review.

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Declaration of competing interest

The authors declare no conflict of interest.

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