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Review Article

Tumour budding as a risk factor for lymph node metastases in cutaneous squamous cell carcinoma: a systematic review and meta-analysis

Pedro Gil-Pallares[1,2] Maria Eugenia Gil-Pallares[3] Alba Navarro-Bielsa[4,5] Olalla Figueroa-Silva[1] Laura Taboada-Paz[1] and José Manuel Suárez-Peñaranda[2,6]

[1]Department of Dermatology, Complejo Hospitalario Universitario de Ferrol, Ferrol, Spain
[2]Universidad de Santiago de Compostela, Santiago de Compostela, Spain
[3]Eidgenössische Technische Hochschule Zürich, Zürich, Switzerland
[4]Department of Dermatology, Miguel Servet University Hospital, Zaragoza, Spain
[5]Universidad de Zaragoza, Zaragoza, Spain
[6]Department of Pathology, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain

Correspondence: Alba Navarro-Bielsa. Email: albanavarrobielsa@hotmail.com

P.G.-P. and M.E.G.-P. share first authorship.

Abstract

Background Current staging systems have limitations in stratifying high-risk cutaneous squamous cell carcinoma (cSCC). Tumour budding (TB) has emerged as a potential prognostic factor in various cancers.

Objectives To evaluate the prognostic significance of TB in predicting lymph node metastases (NM) in cSCC.

Methods A comprehensive search of the PubMed, Web of Science, Embase and Cochrane databases was conducted. Studies investigating the association of TB using a 5-bud cutoff and NM in cSCC were included. A meta-analysis was performed using odds ratios (OR) to evaluate the association between TB and NM.

Results Six retrospective studies comprising 793 patients with cSCC were included. The random-effects analysis showed a significant association between high TB (≥ 5 buds) and NM (OR = 13.29, 95% confidence interval 5.55–31.86).

Discussion TB is a promising histopathological feature for predicting NM in cSCC. The results show a strong association between high TB and NM, supporting its utility as a risk factor for NM in cSCC. Its inclusion in clinical practice and cSCC staging might be helpful in the stratification of patients with high-risk cases and to guide optimal management strategies for each patient. However, further investigation is needed to determine standardized reporting guidelines for TB in cSCC.

Cutaneous squamous cell carcinoma (cSCC) is the second most common cutaneous cancer after basal cell carcinoma. The reported mortality is relatively low (about 2%), and lymph node metastases (NM) occur in around 5% of patients, worsening the prognosis.[1] However, because of its high incidence, the death rate is similar to that of other cancers, such as melanoma or leukaemia.[2]

Current staging systems[3] and their modifications by other groups[4] are limited and do not adequately identify all patients where there is a poor prognosis. Several research groups have investigated additional features[1,5] that could help to accurately stratify patients with high-risk cases and to select optimal individualized treatment strategies.

In recent years, clinical or histopathological features with prognostic value in cSCC that could be implemented in clinical practice have been studied.[1,6–8] One of these is tumour budding (TB), which represents an invasion pattern in which isolated or small clusters of tumour cells are thought to acquire mesenchymal characteristics, allowing them to separate from the tumour mass and infiltrate the surrounding tissue.[9]

TB is an established prognostic factor for NM and is associated with poor prognosis in tumours such as colorectal cancer[10] or oral SCC.[11,12] It is being studied with promising results in other cancers, such as lung[13] and cervical[14] carcinomas as well as in cSCC.[1,7] However, although most authors use a TB assessment method similar to that utilized for colorectal cancer,[15] there is still no formal consensus on recommendations for TB reporting, and it is not currently included in the cSCC staging systems.[3,4,16]

With this systematic review and a meta-analysis, we aimed to provide a comprehensive evaluation of the current evidence on the prognostic significance of TB in predicting NM in cSCC and, therefore, high-risk cSCC.

Methods

This review was performed according to the PRISMA guidelines (see Tables S1 and S2 in Supporting Information), the protocol is explained here (but has not been previously

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published in PROSPERO). GRADE was not used, as our aim was to synthesize the available data.

Search strategy and selection

The PubMed, Web of Science, Embase and Cochrane databases were systematically searched by two reviewers (P.G.-P. and J.M.S.-P.) for English or Spanish language articles on the prognostic role of TB in patients with cSCC to 1 October 2023. The following keywords were used: tumour budding AND squamous cell carcinoma AND (cutaneous OR skin). The article titles and abstracts were screened for articles providing information on the prognostic role of TB in patients with cSCC. References from the eligible studies were also searched for related articles.

We included prospective or retrospective studies with histologically confirmed invasive cSCC, in which the association of TB and NM was studied with either reported or extractable data. Articles including cSCC with metastases detected both at the time of the diagnosis and during follow-up were included.

Similar to what has been reported in other tumours,[12,13] and according to the International Tumour Budding Consensus Conference (ITBCC),[15] buds were defined as groups of <5 tumour cells either at the invasive front or intratumoral (Figure 1), and high budding as the presence of ≥ 5 buds at a hotspot in the selected area. Only studies that met these criteria or in which these data could be extracted were included.

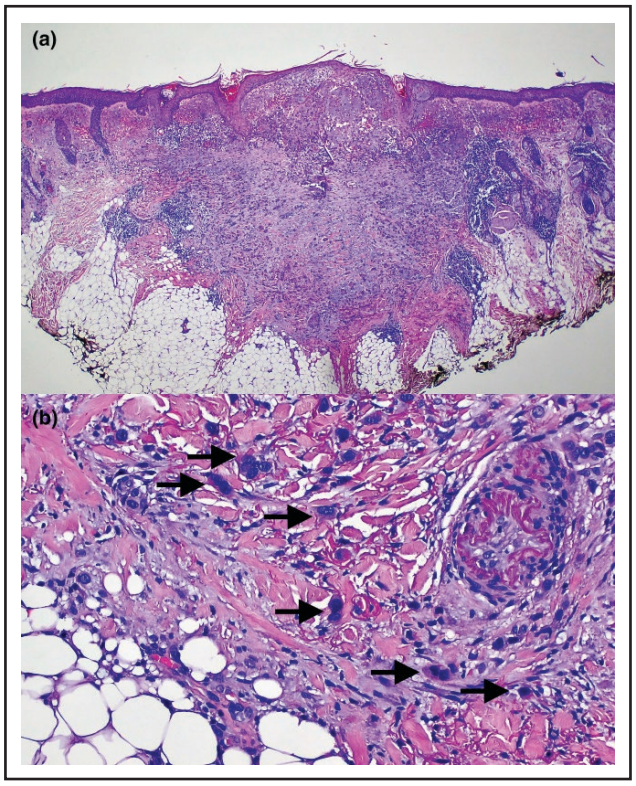

Figure 1 (a) Example of cutaneous squamous cell carcinoma [haematoxylin and eosin (H&E) ×20] showing tumour budding (TB) in the deep infiltrating margin. (b) At ×200, TB number (some of them marked with arrows) can be easily evaluated (H&E). Figure courtesy of Dr Maria Blanco-Bellas.

Studies without specific data for cSCC, noncomparative studies, letters or posters were excluded.

Data extraction

Two reviewers (P.G.-P. and J.M.S.-P.) independently performed data extraction from the six studies finally included. Data were extracted from the text or tables, and the authors were contacted if relevant data were missing.

Statistical analysis

The odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the risk of TB in NM. *P*-values <0.05 were considered statistically significant. Given the limited number of studies and foreseeable heterogeneity, a random-effects meta-analysis model was performed. Heterogeneity was evaluated using Cochran's *Q*-test and I^2 test, and the presence or absence of outliers was examined through the Galbraith plot. Sensitivity analysis was performed using the leave-one-out method to evaluate the influence of individual studies. Fixed-effects analyses were conducted to determine the robustness of the results. Publication bias was assessed with a funnel plot, the rank correlation test of funnel plot asymmetry with continuity correction, Macaskill's linear regression test of funnel plot asymmetry, and the trim-and-fill method. The Newcastle–Ottawa Scale (NOS) was used to assess the risk of bias in the included studies. The analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study selection and characteristics

Of the 117 articles initially screened, 13 were found eligible. However, only six articles could be included because two used a different method to assess TB,[9,17] specific data for cSCC could not be extracted from one article, which also included oral SCC,[6] and four were either noncomparative letters or poster abstracts (Figure 2). The search for eligible studies in references yielded no additional articles.

All the selected articles were retrospective studies, and 793 patients were included. Extracted data can be found in Table 1. Two of the six studies were conducted in Spain, two in Japan, one in the USA and one in Chile. The estimated mean follow-up period for the nonmetastatic groups was 3 years, during which no metastases were observed.

Three studies restricted the inclusion of cSCC to those thicker than 0.5 mm,[1] thicker than 2 mm,[18] and smaller than 4 cm in size,[19] respectively. Two studies excluded patients who were immunosuppressed,[19,20] whereas two included them.[18,21] One of the articles included only cSCC located in the head and neck,[18] whereas the others also included extremities and the trunk. However, two articles excluded cSCC in the oral mucosa or genitalia,[7,19] one excluded periorbital tumours[1] and one excluded cSCC of the eyelid.[19] One study excluded micrometastases found in sentinel lymph node biopsy,[19] one study excluded people who received adjuvant therapy[18] and one study excluded people who

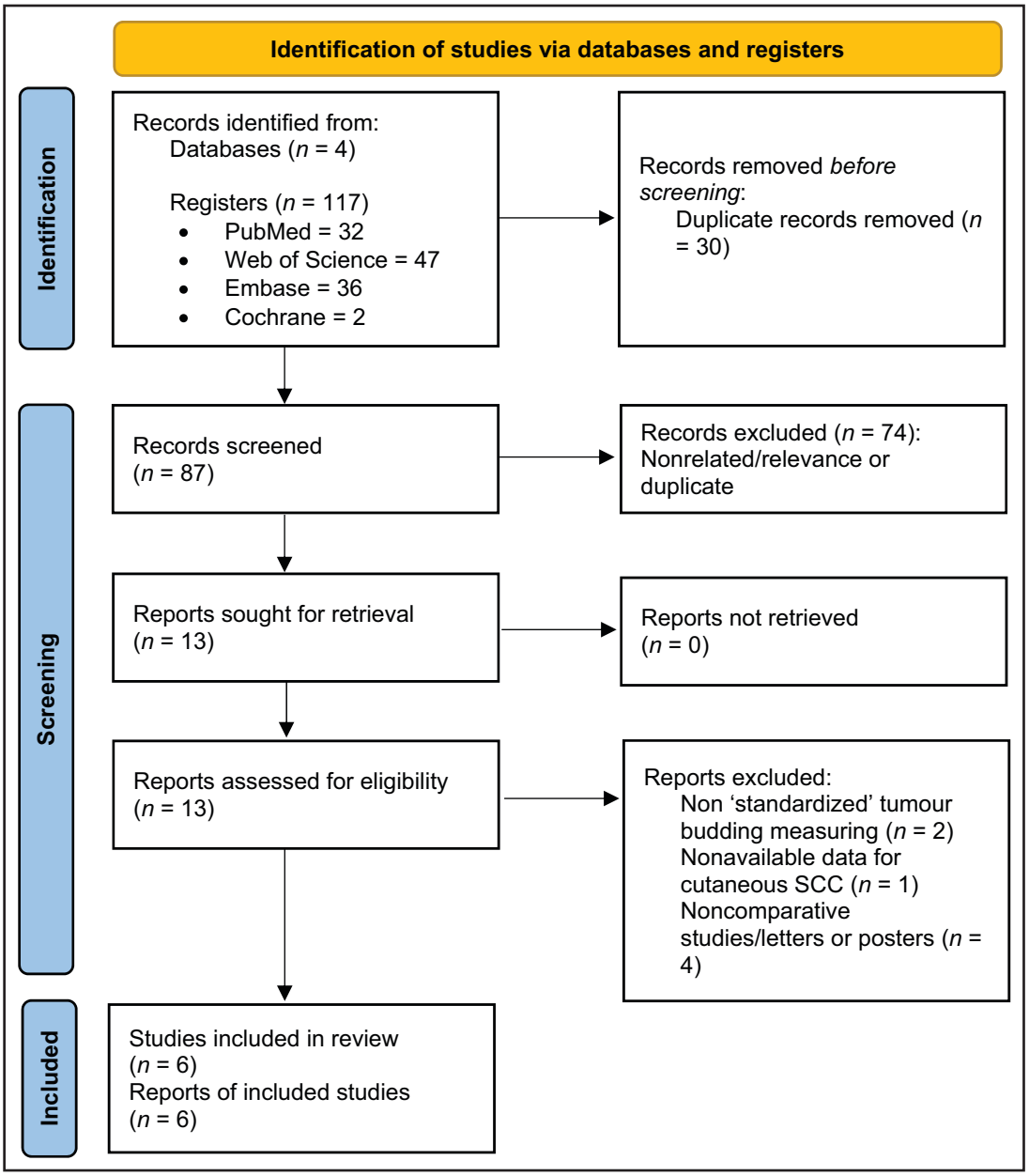

Figure 2 PRISMA 2020 flow diagram for new systematic reviews. SCC, squamous cell carcinoma.

Table 1 Summary of the included studies that examined the association of tumour budding and lymph node metastases (NM) of cutaneous squamous cell carcinoma (cSCC)

				Extracted data, *n*					
				High budding (≥ 5 buds)			Low budding (< 5 buds)		
Study	Country	cSCC, *n*	Follow-up of cSCC with no NM (years)	cSCC with NM	cSCC with no NM	Total	cSCC with NM	cSCC with no NM	Total
Fujimoto[20] (2016)	Japan	159 (15 with NM)	Median 1	14	37	51	1	107	108
González-Guerrero[18] (2017)	Spain	98 (49 with NM)	Minimum 4	20	0	20	29	49	78
Hernández-Ruiz[21] (2019)	Spain	102 (50 with NM)	Minimum 5	34	18	52	16	34	50
Fujimoto[19] (2019)	Japan	48 (24 with NM)	Minimum 3	20	9	29	4	15	19
Farah[1] (2022)	USA	230 (31 with NM)	Minimum 2	14	53	67	3	160	163
Heredia[7] (2023)	Chile	156 (9 with NM)	N/S	7	14	21	2	133	135

N/S, not specified.

received neoadjuvant therapy,[20] whereas the rest did not specify if these groups were included or excluded (Table 2).

All studies had a low risk of bias (scores of 8–9) on the NOS scale (Table S3; see Supporting Information).

Tumour budding assessment

All selected studies defined buds as foci of < 5 tumour cells at the invasive front and one assessed them both intratumorally and at the invasive front.[19] A magnification of × 200 was used in four studies,[1,7,19,20] and the other two used a × 400 magnification power.[18,21] The presence of ≥ 5 buds was considered high or positive budding by five studies,[1,7,18,20,21] and two followed the ITBCC[15] grading.[7,19]

Meta-analysis

The meta-analysis for NM included all the selected studies ($n = 6$). The random-effects analysis for NM comparing high vs. low TB showed higher OR for NM with high TB (OR = 13.29, 95% CI 5.55–31.86, $P < 0.001$) (Figure 3). Although heterogeneity was moderate with the I^2 test (52%), Cochran's Q-test was not statistically significant, and the absence of outliers in the Galbraith plot indicates a consistent and homogeneous distribution of effect estimates across the included studies (Figure S1; see Supporting Information). In addition, the leave-one-out analysis did not show excessive influence of any specific study (Figure 4), and in all possibilities, the OR for NM with high TB remained > 11.04 (lowest bound of all CI of 4.41). Fixed-effects analysis showed similar results with a shorter CI (OR = 10.96, 95% CI 6.49–18.49, $P < 0.001$), absence of outliers in the Galbraith plot and similar leave-one-out analysis outcomes (Figures S2–S4; see Supporting Information).

Although the funnel plot (Figure S5; see Supporting Information) exhibited certain asymmetry, both the rank correlation test of funnel plot asymmetry with continuity correction ($z = 1.13$, $P = 0.26$) and Macaskill's linear regression test of funnel plot asymmetry ($t = 1.00$, degrees of freedom = 4, $P = 0.38$) did not find evidence of publication bias. Furthermore, the adjusted OR after applying the trim-and-fill method (Figure S6; see Supporting Information) remained statistically significant and showed no changes in the direction of the effect (adjusted OR = 9.60, 95% CI = 4.34–21.24), reaffirming the lack of evidence of publication bias.

Discussion

cSCC is the second most common cancer worldwide, and although its metastatic rate is low, precise staging systems to stratify its risk are lacking. The availability of new therapeutic options, such as immune checkpoint inhibitors,[22–24] and the necessity to identify patients who could benefit most from sentinel lymph node biopsy[25–27] make this need even more pressing. A recent study, which included a large dataset of metastatic and nonmetastatic cSCC, compared the ability of four staging systems to predict cSCC behaviour, concluding that further improvement and refining of current cSCC staging is essential.[16] Although the Brigham and Women's Hospital staging system showed the highest overall discriminative ability and highest specificity, positive predictive value and C-index, the 8th edition of the American Joint Committee on Cancer system performed

Table 2 Main differences in patient selection criteria and tumour budding assessment among the included studies

	Inclusion/exclusion criteria						Tumour budding assessment	
Study	**Location**	**Size/ thickness included**	**Recurrence/ positive margins**	**Micrometastases in SLNB**	**Immunosuppression**	**Adjuvant/ neoadjuvant therapy**	**Magnification**	**Location of buds**
Fujimoto[20] (2016)	Head and neck, extremities and trunk	N/S	N/S	N/S	Excluded	Excluded neoadjuvant	× 200	Invasive front
González-Guerrero[18] (2017)	Head and neck	Thickness > 2 mm	Excluded recurrences	N/S	Included	Excluded adjuvant	× 400	Invasive front
Hernández-Ruiz[21] (2019)	Head and neck, extremities and trunk	N/S	Recurrences not excluded	N/S	Included	N/S	× 400	Invasive front
Fujimoto[19] (2019)	Excluded eyelid, nonhair-bearing lip and genitalia	Size < 4 cm	N/S	Excluded	Excluded	N/S	× 200	Invasive front or intratumoral
Farah[1] (2022)	Excluded periorbital tumours	Thickness > 0.5 mm	Excluded recurrences and excisions with positive margins	N/S	N/S	N/S	× 200	Invasive front
Heredia[7] (2023)	Excluded genitalia and oral mucosa	N/S	Excluded excisions with positive margins	N/S	N/S	N/S	× 200	Invasive front

N/S, not specified; SLNB, Sentinel lymph node biopsy.

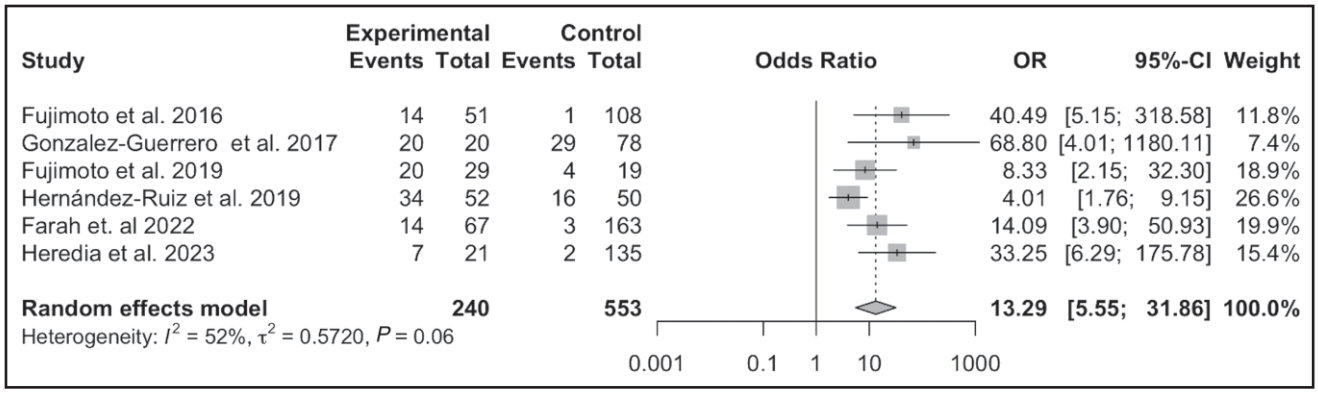

Figure 3 Forest plot. The random-effects analysis shows a significant OR for high tumour budding and lymph node metastases of cutaneous squamous cell carcinoma. CI, confidence interval; OR, odds ratio.

best in terms of negative predictive value. In this context, the study of the prognostic value of some new histopathological features of cSCC, such as TB, has shown promising results, revealing it as an independent risk factor for NM,[7,18,20] and also showing association with myxoid stroma, another independent factor for NM in some cohorts.[21] The same as in other tumours, this could indicate that TB is a step towards metastasis.[12] The present systematic review and meta-analysis, which comprises six retrospective studies including a total of 793 patients, showed a strong association between high TB and NM, suggesting that TB could be a valuable prognostic factor that could improve the accuracy of cSCC staging.

Criteria for TB assessment in cSCC have yet to be defined, which may explain some variability between studies. The ITBCC[15] recommendations (buds counting in one field of 0.785 mm^2 at a hotspot) were originally described for colorectal cancer. All studies included in this meta-analysis evaluated TB in one field. However, research in other cancers, such as lung cancer, has shown that buds counting in 10 fields at a hotspot could have higher interobserver reproducibility.[13] With regard to magnification, four studies used ×200 magnification,[1,7,19,20] of which only one[7] followed the ITBCC recommended field area, whereas two[19,20] considered a 1.23 mm^2 area. The other two studies used ×400 magnification.[18,21] This would be expected to result in a smaller field, potentially leading to false negatives. Nevertheless, all the studies found similar results, which could mean that buds counting in a ×400 field at a hotspot might give similar results to conducting the count at ×200 with a 5-bud cutoff, possibly making it easier to identify them. Likewise, all studies evaluated TB at a hotspot at the invasive front, except for one study that also included intratumoral TB.[19] However, the lack of difference in the results suggests that both locations could be valid, as in colorectal cancer.[15]

The 5-bud cutoff as a definition of high budding has been widely used in various tumours, including cSCC, although with different names (positive TB,[7,20,21] high TB[1,18] or TB grade ≥ 2[7,19]). The ITBCC[15] proposed a grading classification (0–4 buds, low; 5–9, intermediate; ≥ 10, high). However, the two studies that followed this classification found the same results as the rest of the articles: the presence of ≥ 5 buds (TB grade ≥ 2) was associated with an increased risk of NM in cSCC.[7,19] Alternative methods have been proposed, such as the mean number of buds in five adjacent high-power fields (× 250) at a hotspot that was used by two excluded articles.[9,17] The presented results suggest that the 5-bud threshold for the definition of high TB allows a good prediction of NM. However, further studies are warranted to establish standardized criteria for reporting TB in cSCC, similar to what has been done in other tumours.[15]

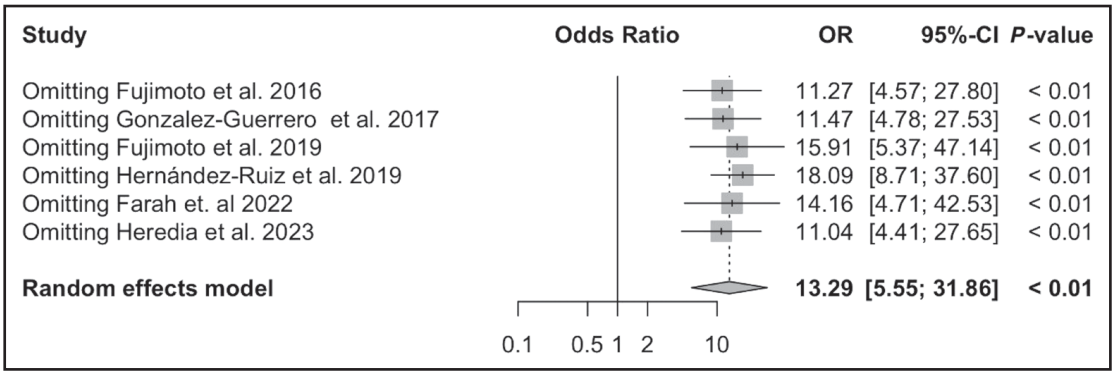

Figure 4 Leave-one-out analysis (random effects). None of the studies showed excessive influence, and significance was maintained in all cases. CI, confidence interval; OR, odds ratio.

The present meta-analysis has some limitations. The small number of studies made a comprehensive assessment of heterogeneity difficult and led us to use a random-effects model to account for potential variability. Nevertheless, fixed-effects analysis showed consistent results.

Considering articles with certain differences in the inclusion criteria was another limitation. Some studies involved patients who were immunosuppressed,[18,21] but they did not find higher NM in the immunosuppressed group.[18] Similarly, one study only included head and neck tumours,[18] three studies restricted the size of the included tumours[1,18,19] and three excluded micrometastases,[19] use of adjuvant[18] and neoadjuvant[20] therapies, respectively, whereas the rest of the studies did not specify these inclusion or exclusion criteria. Although more studies are needed to confirm the results in each specific subgroup, the consistent results of the random-effects and leave-one-out analyses indicate a robust relationship despite certain variations in inclusion criteria.

Moreover, because it was not possible to extract comparable data on the main prognostic factors for cSCC from all the included studies, a multivariate meta-analysis or a subgroup analysis could not be conducted. Nevertheless, it would be important to consider standardized data reporting on various prognostic factors, facilitating further data comparison and analysis.

Although concern regarding publication bias could arise because of all papers reporting an OR > 1 and the asymmetry shown in the funnel plot, the conducted tests (rank correlation test of funnel plot asymmetry with continuity correction, Macaskill's linear regression test of funnel plot asymmetry and trim-and-fill method) did not show evidence of publication bias, which reinforces the likelihood that the observed effect is real. Finally, the reliance on retrospective studies alone represents another limitation of this study.

Nonetheless, the meta-analysis shows a strong association between NM and high TB, with a pooled TB OR of 13.29 (95% CI 5.55–31.86, $P < 0.001$), supporting TB's importance in cSCC prognosis. These results could fill a gap in the current literature, providing valuable information for the management of cSCC. Therefore, TB is a simple, cheap and reproducible[7] histopathological feature that does not require specific equipment for its identification, which could help identify the best candidates for sentinel lymph node biopsy or adjuvant therapies, among other options.

In conclusion, our meta-analysis supports TB as a robust and promising risk factor for NM in cSCC. Although further validation studies are needed to consolidate the role of TB in the management of cSCC, the consistent findings across sensitivity analyses reinforce the importance of incorporating TB assessment into clinical practice, which could improve risk stratification and offer individualized strategies for patients with cSCC.

Learning points

- Current staging systems for cutaneous squamous cell carcinoma (cSCC) do not accurately stratify those with high-risk cSCC.
- High tumour budding, defined as ≥ 5 buds, has a strong association with lymph node metastases in cSCC.
- Inclusion of tumour budding in staging systems could help to individualize cSCC management.

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Conflicts of interest

The authors declare no conflicts of interest.

Data availability

Data available within the article or its supplementary materials.

Ethics statement

Ethical approval: Not applicable. Informed consent: The patients signed informed consent for the publication of recognizable photographs.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

References

1 Farah M, Milton DR, Gross ND *et al.* Histopathologic features predictive of metastasis and survival in 230 patients with cutaneous squamous cell carcinoma of the head and neck and non-head and neck locations: a single-center retrospective study. *J Eur Acad Dermatol Venereol* 2022; **36**:1246–55.
2 Tokez S, Wakkee M, Kan W *et al.* Cumulative incidence and disease-specific survival of metastatic cutaneous squamous cell carcinoma: a nationwide cancer registry study. *J Am Acad Dermatol* 2022; **86**:331–8.
3 Ruiz ES, Karia PS, Besaw R, Schmults CD. Performance of the American Joint Committee on Cancer Staging Manual, 8th Edition vs the Brigham and Women's Hospital Tumor Classification System for Cutaneous Squamous Cell Carcinoma. *JAMA Dermatol* 2019; **155**:819–25.
4 Puebla-Tornero L, Corchete-Sánchez LA, Conde-Ferreirós A *et al.* Performance of Salamanca refinement of the T3-AJCC8 versus the Brigham and Women's Hospital and Tübingen alternative staging systems for high-risk cutaneous squamous cell carcinoma. *J Am Acad Dermatol* 2021; **84**:938–45.
5 Jowkar F, Sari Aslani F, Pourian B, Nozari F. Evaluation of peritumoral inflammatory infiltration and its relationship with different prognostic factors in cutaneous squamous cell carcinoma. *J Cutan Pathol* 2023; **50**:66–71.
6 Caruntu A, Moraru L, Lupu M *et al.* Assessment of histological features in squamous cell carcinoma involving head and neck skin and mucosa. *J Clin Med* 2021; **10**:2343.
7 Heredia L, Vargas-Mora P, Jahr C *et al.* Tumour budding in cutaneous squamous cell carcinoma: a novel prognosis risk factor. *Australas J Dermatol* 2023; **64**:e340–7.
8 Marti-Marti I, Podlipnik S, Cañueto J *et al.* Prognostic factors for satellitosis or in-transit metastasis in cutaneous squamous cell carcinoma: a multicentric cohort study. *J Am Acad Dermatol* 2023; **89**:119–27.

9 Karayannopoulou G, Euvrard S, Kanitakis J. Tumour budding correlates with aggressiveness of cutaneous squamous-cell carcinoma. *Anticancer Res* 2016; **36**:4781–6.
10 Basile D, Broudin C, Emile JF *et al.* Tumor budding is an independent prognostic factor in stage III colon cancer patients: a post-hoc analysis of the IDEA-France phase III trial (PRODIGE-GERCOR). *Ann Oncol* 2022; **33**:628–37.
11 Bjerkli IH, Laurvik H, Nginamau ES *et al.* Tumor budding score predicts lymph node status in oral tongue squamous cell carcinoma and should be included in the pathology report. *PLOS ONE* 2020; **15**:e0239783.
12 Almangush A, Pirinen M, Heikkinen I *et al.* Tumour budding in oral squamous cell carcinoma: a meta-analysis. *Br J Cancer* 2018; **118**:577–86.
13 Wankhede D, Hofman P, Grover S. Prognostic impact of tumour budding in squamous cell carcinoma of the lung: a systematic review and meta-analysis. *Histopathology* 2023; **82**:521–30.
14 Park JY, Chong GO, Park JY *et al.* Tumor budding in cervical cancer as a prognostic factor and its possible role as an additional intermediate-risk factor. *Gynecol Oncol* 2020; **159**:157–63.
15 Lugli A, Kirsch R, Ajioka Y *et al.* Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. *Mod Pathol* 2017; **30**:1299–311.
16 Venables ZC, Tokez S, Hollestein LM *et al.* Validation of four cutaneous squamous cell carcinoma staging systems using nationwide data. *Br J Dermatol* 2022; **186**:835–42.
17 Karayannopoulou G, Panteris E, Kanitakis J. Tumour budding is an independent predictive factor of cutaneous squamous-cell carcinoma aggressiveness. *Anticancer Res* 2020; **40**:2695–9.
18 González-Guerrero M, Martínez-Camblor P, Vivanco B *et al.* The adverse prognostic effect of tumor budding on the evolution of cutaneous head and neck squamous cell carcinoma. *J Am Acad Dermatol* 2017; **76**:1139–45.
19 Fujimoto M, Yamamoto Y, Takai T *et al.* Tumor budding is an objective high-risk factor associated with metastasis and poor clinical prognosis in cutaneous squamous cell carcinoma sized <4 cm. *Am J Surg Pathol* 2019; **43**:975–83.
20 Fujimoto M, Yamamoto Y, Matsuzaki I *et al.* Tumor budding is an independent risk factor for lymph node metastasis in cutaneous squamous cell carcinoma: a single center retrospective study: tumor budding in skin squamous cell carcinoma. *J Cutan Pathol* 2016; **43**:766–71.
21 Hernández-Ruiz E, Hernández-Muñoz I, Masferrer E *et al.* A myxoid fibrotic reaction pattern is associated with metastatic risk in cutaneous squamous cell carcinoma. *Acta Derm Venereol* 2019; **99**:89–94.
22 Koch Hein EC, Vilbert M, Hirsch I *et al.* Immune checkpoint inhibitors in advanced cutaneous squamous cell carcinoma: real-world experience from a canadian comprehensive cancer centre. *Cancers* 2023; **15**:4312.
23 García-Foncillas J, Tejera-Vaquerizo A, Sanmartín O *et al.* Update on management recommendations for advanced cutaneous squamous cell carcinoma. *Cancers* 2022; **14**:629.
24 McLean LS, Lim AM, Bressel M *et al.* Immune checkpoint inhibitor therapy for advanced cutaneous squamous cell carcinoma in Australia: a retrospective real world cohort study. *Med J Aust* 2024; **220**:80–90.
25 Costantino A, Canali L, Festa BM *et al.* Sentinel lymph node biopsy in high-risk cutaneous squamous cell carcinoma of the head and neck: Systematic review and meta-analysis. *Head Neck* 2022; **44**:2288–300.
26 Keohane SG, Botting J, Budny PG *et al.* British Association of Dermatologists guidelines for the management of people with cutaneous squamous cell carcinoma 2020. *Br J Dermatol* 2021; **184**:401–14.
27 Baljer BC, Hill SR, Coughlan D *et al.* Time for consensus on "high-risk" – sentinel lymph node biopsy for cutaneous squamous cell carcinoma: an international survey of skin cancer specialists and a literature update. *J Plast Reconstr Aesthetic Surg* 2023; **76**:62–4.

CPD questions

Learning objective

To gain up-to-date knowledge of the usefulness of tumour budding in the prognosis of cutaneous squamous cell carcinoma (cSCC).

Question 1

Which of the following statements about cSCC staging systems is correct?

(a) Both the Brigham and Women's Hospital and the 8th edition of the American Joint Committee on Cancer staging systems accurately stratify high-risk cases of cSCC.
(b) The Brigham and Women's Hospital and the 8th edition of the American Joint Committee on Cancer (AJCC) staging systems showed similar overall discriminative ability and highest specificity, positive predictive value, C-index and negative predictive value in all studies.
(c) The 8th edition of the AJCC is the only staging system available for cSCC.
(d) Tumour budding is not included in current cSCC staging systems.
(e) The statements (a), (b) and (d) are correct.

Question 2

Which of the following statements about tumour budding is *not* correct?

(a) It represents an invasion pattern in which isolated or small clusters of tumour cells separate from the tumour mass and infiltrate the surrounding tissue.
(b) Tumour cells are thought to acquire mesenchymal characteristics.
(c) Tumour budding is associated with poor prognosis in colorectal cancer and oral SCC.
(d) Tumour budding utility has only been studied for cSCC.
(e) The statements (a), (b) and (c) are all correct.

Question 3

Which of the following statements is correct?

(a) According to the International Tumour Budding Consensus Conference 2016 (ITBCC), buds are defined as groups of <5 tumour cells either at the invasive front or intratumoral.
(b) According to the ITBCC recommendations, the presence of ≥ 2 buds is considered high budding.
(c) According to the ITBCC, tumour budding is assessed by counting the number of buds at a hotspot in the selected area.

(d) All published studies of tumour budding in cSCC used the ITBCC recommended field area for tumour budding assessment.
(e) The statements (a) and (c) are correct.

Question 4

Which of the following statements is correct?

(a) According to the meta-analysis results, a 5-bud cut-off for defining high budding could allow a good prediction of cSCC prognosis.
(b) In some studies, tumour budding showed association with other independent factors for lymph node metastasis in cSCC, such as myxoid stroma.
(c) In the presented meta-analysis, tumour budding shows as a strong prognostic factor of lymph node metastases in cSCC.
(d) Tumour budding is being studied in other tumours, such as lung or cervical carcinomas, with promising results.
(e) All statements (a) to (d) are correct.

Question 5

Which of the following statements is *not* correct?

(a) More studies are needed to establish standardized criteria for reporting tumour budding in cSCC.
(b) The inclusion of tumour budding in cSCC staging systems could improve risk stratification.
(c) Tumour budding assessment requires specific equipment.
(d) Tumour budding could help individualize cSCC management.
(e) The statements (a) and (d) are true.