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-Paz1 and José Manuel Suárez-Peñaranda 2,6

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

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

https://orcid.org/0000-0001-8469-1942 (Pedro Gil-Pallares)
https://orcid.org/0000-0003-1171-6007 (Alba Navarro-Bielsa)

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

Teaser Text
Current staging systems do not accurately stratify high-risk cutaneous squamous cell carcinoma (cSCC). The present systematic review and meta-analysis showed a strong association between tumour budding in cSCC and lymph node metastasis and therefore, worse prognosis. Our results suggest that incorporating tumour budding in clinical practice could help identify people with high-risk cases of cSCC and individualize management.

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 leukemia.2

Current staging systems3 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 therefore have investigated additional features1,5 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 are being 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 cancer10 or oral SCC.11,12 It is being studied with promising results in other cancers such as lung13 and cervical14 carcinomas and also in cSCC.1,7 However, although most authors use a TB assessment method similar to that utilized for colorectal cancer15 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 Table S1 and S2 in the Supporting Information), and the protocol explained in the Methods section (not previously published in PROSPERO). GRADE was not used since 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.
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 for 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 I2 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. 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 cases 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 tumours1 and one cSCC of the eyelid.19 One study excluded micrometastases found in sentinel lymph node biopsy,19 one excluded individuals who received adjuvant therapy18 and one individuals who received neoadjuvant therapy20, while 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 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 ITBCC15 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 I2 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 confidence interval (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 (Supporting information, Figure 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 (new OR = 9.60, 95% CI = 4.34–21.24), reassessing 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 biopsy25–27 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 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 nodal metastases ,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 previous step to metastasis.12 The present systematic review and meta-analysis, which comprises six retrospective studies including a total of 793 cases, 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 ITBCC15 recommendations (buds counting in one field of 0.785 mm2 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, have shown that buds counting in 10 fields at a hotspot could have an extended prognostic effect with higher interobserver reproducibility.13 With regard to magnification, four studies used × 200 magnification,1,7,19,20 of which only one7 followed the ITBCC recommended field area, whereas two19,20 considered a 1.23 mm2 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 TB1,18 or TB grade ≥ 27,19). The ITBCC15 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

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 immunosuppressed18,21 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 tumours1,18,19 and three excluded micrometastases,19 use of adjuvant18 and neoadjuvant20 therapies, respectively, while 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, a simple, cheap and reproducible7 histopathological feature , could help to 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. Not applicable.

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, Herranz J, Ferrer-Rosende P. 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.

Figure legends

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. Figure courtesy of Dr Maria Blanco-Bellas.

Figure 2 PRISMA 2020 flow diagram for new systematic reviews.

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

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.

Study	Inclusion/exclusion criteria						Tumor budding assessment		
	Location	Size / thickness	Recurrence/ Positive	Micrometastasis in SLNB[1]	Inmunosuppresion	Adjunvant/ neoadj	Magnification	Location of buds	Number of fields
Fujimoto et	Head and neck,	N/S[2]	N/S[2]	N/S[2]	Excluded	Excluded	200x	Invasive front	One field at a hotspot
Gonzalez-Guerre	Head and neck	Thickness > 2 mm	Excluded recurrences	N/S[2]	Included	Excluded adjuva	400x	Invasive front	One field at a hotspot Highest count
Hernández-Ruiz et	Head and neck, extremities	N/S[2]	Not excluded recurrenc	N/S[2]	Included	N/S[2]	400x	Invasive front	One field at a hotspot Highest count
Fujimoto et al.	Excluded eyelid, non-hair bearing	Size < 4cm	N/S[2]	Excluded	Excluded	N/S[2]	200x	Invasive front or intratum	One field at a hotspot
Farah et al. 2022	Excluded periorbital tumors	Thickness > 0.5 mm	Excluded recurrences and excisions	N/S[2]	N/S[2]	N/S[2]	200x	Invasive front	One field at a hotspot
Heredia et al. 2023	Excluded genitalia and oral mucosa	N/S[2]	Excluded excisions with	N/S[2]	N/S[2]	N/S[2]	200x	Invasive front	One field at a hotspot

Table 2. Main differences in patient selection criteria and tumor budding assessment among the included studies
[1] Sentinel lymph node biopsy
[2] Not specified

Study	Inclusion/exclusion criteria						Tumor budding assessment		
	Location	Size / thickness	Recurrence/ Positive	Micrometastasis in SLNB[1]	Inmunosuppresion	Adjunvant/ neoadj	Magnification	Location of buds	Number of fields
Fujimoto et	Head and neck,	N/S[2]	N/S[2]	N/S[2]	Excluded	Excluded	200x	Invasive front	One field at a hotspot
Gonzalez-Guerre	Head and neck	Thickness > 2 mm	Excluded recurrences	N/S[2]	Included	Excluded adjuva	400x	Invasive front	One field at a hotspot Highest count
Hernández-Ruiz et	Head and neck, extremities	N/S[2]	Not excluded recurrenc	N/S[2]	Included	N/S[2]	400x	Invasive front	One field at a hotspot Highest count
Fujimoto et al.	Excluded eyelid, non-hair bearing	Size < 4cm	N/S[2]	Excluded	Excluded	N/S[2]	200x	Invasive front or intratum	One field at a hotspot
Farah et al. 2022	Excluded periorbital tumors	Thickness > 0.5 mm	Excluded recurrences and excisions	N/S[2]	N/S[2]	N/S[2]	200x	Invasive front	One field at a hotspot
Herediа et al. 2023	Excluded genitalia and oral mucosa	N/S[2]	Excluded excisions with	N/S[2]	N/S[2]	N/S[2]	200x	Invasive front	One field at a hotspot

CPD questions
Learning objective
To gain up-to-date knowledge of the usefulness of tumor budding in the prognosis of cutaneous squamous cell carcinoma.
Question 1[
Which of the following statements about cutaneous squamous cell carcinoma (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 cutaneous squamous cell carcinoma.
(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 cutaneous squamous cell carcinoma.
(d) Tumour budding is not included in current cutaneous squamous cell carcinoma staging systems.
(e) All statements are correct (a) to (d).

Answer 1
Which of the following statements about cutaneous squamous cell carcinoma (cSCC) staging systems is correct?
(a) Incorrect. Current staging systems are limited and do not adequately identify all patients where there is a poor prognosis.
(b) Incorrect. A recent study by Venables et al. showed that the Brigham and Women's Hospital staging system had the highest overall discriminative ability and specificity, positive predictive value and c-index. The 8th edition of the AJCC system performed best in terms of negative predictive value.
(c) Incorrect. Other cutaneous squamous cell carcinoma stratification systems such as Brigham and Women's Hospital, staging system is also used in clinical practice.
(d) Correct. Current cutaneous squamous cell carcinoma staging systems do not consider tumour budding.
(e) Incorrect. Statements in options (a) to (d) are not all correct; only (d).

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 squamous cell carcinoma.
(d) Tumour budding utility has only been studied for cutaneous squamous cell carcinoma.
(e) The statements (a), (b), and (c) are all correct.

Answer 2
Which of the following statements about tumour budding is not correct?
(a) Incorrect. Tumour budding represents an invasion pattern in which the cells are believed to lose adhesion between them, separate from the tumour mass, and infiltrate the surrounding tissues.
(b) Incorrect. In tumour budding, the cells potentially undergo epithelial–mesenchymal transition, losing cell adhesion.
(c) Incorrect. Tumour budding is an established prognostic factor for lymph node metastases and is associated with poor prognosis in colorectal cancer and oral squamous cell carcinoma.
(d) Correct. Tumour budding demonstrated its utility in colorectal cancer and oral squamous cell carcinoma and is being studied in other tumours, such as lung or cervical carcinomas.
(e) Incorrect. (a), (b), and (c) are all true.

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 cutaneous squamous cell carcinoma follow the ITBCC recommendations for reporting tumour budding in colorectal cancer.
(e) The statements (a) and (c) are correct.

Answer 3
Which of the following statements is correct?
(a) Incorrect. Although the sentence is correct according to the ITBCC recommendations for reporting tumour budding, this is not the only correct answer.
(b) Incorrect. The ITBCC proposed a grading classification: 0–4 buds: low, 5–9: intermediate, ≥ 10: high.
(c) Incorrect. Although the sentence is correct according to the ITBCC recommendations for reporting tumour budding, this is not the only correct answer.
(d) Incorrect. Only the study by Heredia et al. followed all the ITBCC recommendations, including the recommended field area for tumour budding asessment.
(e) Correct. (a) and (c) are both correct.

Question 4
Which of the following statements is correct?
(a) According to the meta-analysis results, a 5-bud cutoff 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.

Answer 4
Which of the following statements is correct?
(a) Incorrect. Although the results using a 5-bud cutoff for defining high budding showed a strong association between high budding and lymph node metastases, this is not the only correct answer.
(b) Incorrect. Although Hernánez-Ruiz et al. found that tumour budding was associated with myxoid stroma, which was an independent factor for lymph node metastasis in cSCC in their study, this is not the only correct answer.
(c) Incorrect. Although the random effects analysis showed a significant association between high budding and lymph node metastases (odds ratio = 13.29, 95% confidence interval 5.55–31.86), this is not the only correct answer.
(d) Incorrect. Although tumour budding has shown promising results as a prognostic factor for lung and cervical cancer, this is not the only correct answer.
(e) Correct. (a), (b), (c), and (d) are all 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 cutaneous squamous cell carcinoma.
(b) The inclusion of tumour budding in cutaneous squamous cell carcinoma staging systems could improve risk stratification.
(c) Tumour budding assessment requires specific equipment.
(d) Tumour budding assessment showed good reproducibility.
(e) Tumour budding could help individualize cSCC management.

Answer 5
Which of the following statements is not correct?

(a) Incorrect. There are certain differences in tumour budding assessment methods among the articles, which, in the case of two of the excluded articles made extraction of comparable data impossible. Standardized criteria for reporting criteria would facilitate tumour budding interpretation and analysis of the results of future studies.
(b) Incorrect. The meta-analysis results show a strong association between high budding and lymph node metastases, which could complement current cSCC staging systems.
(c) Correct. Tumour budding is assessed using the standard equipment employed in routine histopathological examinations without requiring any additional tools.
(d) Incorrect. González-Gerrero et al., among other authors, demonstrated good reproducibility in intra- and interobserver agreement studies for tumour budding assessment.
(e) Incorrect. Authors like Fujimoto et al. even suggest that [UdMO43] tumour budding could be useful for selecting patient's cases that would benefit from sentinel lymph node biopsy.