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Histopathological grading systems and their relationship with clinical parameters in lower lip squamous cell carcinoma

H. B. de P. Santos[a], A. L. do Ó Silva[a], L. H. de A. Cavalcante[b], P. M. Alves[b], G. P. Godoy[b], C. F. W. Nonaka[b,]
[a]School of Dentistry, State University of Paraíba, Campina Grande, PB, Brazil; [b]Postgraduate Program in Dentistry, State University of Paraíba, Campina Grande, PB, Brazil

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Abstract. The objective of this study was to evaluate the histopathological grade of malignancy in a series of lower lip squamous cell carcinomas (LLSCCs) using three histopathological grading systems (invasive front grading system, World Health Organization (WHO) grading system, and histological risk assessment), and to correlate this with clinical parameters (tumour size/extent, regional lymph node metastasis, and clinical stage). Haematoxylin–eosin-stained histological sections obtained from 59 cases of LLSCC were analyzed by light microscopy. Grading of the invasive tumour front showed a significant association between low grade of malignancy and the absence of regional lymph node metastasis ($P = 0.030$) and initial clinical stage ($P = 0.043$). No significant associations were observed between the clinical parameters analyzed and the WHO system ($P > 0.05$). Using the risk assessment, a highly significant association was observed between the risk score and regional lymph node metastasis ($P = 0.004$) and clinical stage ($P = 0.002$). In addition, the lymphocytic infiltrate was significantly associated with regional lymph node metastasis ($P = 0.017$) and clinical stage ($P = 0.040$). The results of the present study suggest that, among the histopathological grading systems evaluated, the histological risk assessment is the best option to predict the biological behaviour of LLSCCs.

Keywords: Lip; Squamous cell carcinoma; Histopathological grading systems; Histopathology.

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Introduction

Squamous cell carcinoma is a malignant tumour that arises from the stratified squamous epithelium and can affect both the oral cavity and lip vermilion. This tumour is the most common malignancy of the lower lip.[1,2] The prognosis of patients with lower lip squamous cell carcinoma (LLSCC) is good when the disease is diagnosed at an early stage, with 5-year survival rates ranging from 80% to 90%.[3,4] Although cervical lymph node metastases are identified in only 6.6–26.5% of cases,[3,5,6] only 25–50% of these patients are still alive after 5 years, indicating a poor prognosis.[4–7]

The clinical staging system of tumours (TNM), which evaluates the extent of the primary tumour (T) and the presence of regional lymph node metastases (N) and distant metastases (M), is the international standard to classify malignant tumours into stages and to estimate the clinical response to therapy and patient survival.[8–10] However, some cases of squamous cell carcinoma progress to local recurrence and metastatic dissemination

even when they are diagnosed at an early stage and treated correctly, eventually leading to the patient's death. This observation has led to the search for other prognostic factors to complement the TNM system.[10–13]

Several histopathological grading systems for malignancy have been developed for oral squamous cell carcinoma (OSCC) in an attempt to provide additional information that could explain the divergent biological behaviours of tumours with apparently similar clinical characteristics.[10] Among the main histopathological grading systems for OSCC are those proposed by Bryne et al.,[14] also known as the 'invasive front grading system', and the World Health Organization (WHO).[15] Although the results of investigations evaluating the usefulness of these histopathological grading systems are conflicting,[9–12,16–20] recent studies have highlighted the potential of the 'histological risk assessment' model developed by Brandwein-Gensler et al.[21] to indicate the presence of lymph node metastasis and to predict local recurrence and overall survival of patients with OSCCs.[10,13,20,22,23] Despite these important findings, to the best of our knowledge, there have been no studies investigating the possible use of the histopathological grading system developed by Brandwein-Gensler et al.[21] to determine the prognosis in LLSCCs (PubMed database).

Therefore, the objective of the present study was to evaluate the histopathological grade of malignancy in a series of LLSCC cases using the invasive front grading system,[14] the WHO grading system,[15] and the histological risk assessment,[21] and to correlate this with clinical parameters. The overall objective was to determine the usefulness of these systems as indicators of the biological behaviour of LLSCCs.

Materials and methods

Specimens

Fifty-nine cases of LLSCC were selected for this study. Only cases of LLSCC derived from surgical resections, with paraffin blocks containing sufficient material for histopathological analysis, were included in the sample. The tumours of patients who had been submitted to radiotherapy or chemotherapy and cases where data regarding patient gender and age, tumour size/extent, presence of regional lymph node metastases and distant metastases, and clinical stage were incomplete were excluded. The parameters listed in the sixth edition of the TNM Classification of Malignant Tumours were used for clinical staging.[8] The study was approved by the institutional research ethics committee.

Table 1. Morphological parameters and their respective scores in the histopathological grading system proposed by Bryne et al.[14].

Morphological parameters	Score
Degree of keratinization	
Highly keratinized (>50% of the cells)	1
Moderately keratinized (20–50% of the cells)	2
Minimal keratinization (5–20% of the cells)	3
No keratinization (0–5% of the cells)	4
Nuclear pleomorphism	
Little pleomorphism (>75% mature cells)	1
Moderately abundant pleomorphism (50–75% mature cells)	2
Abundant pleomorphism (25–50% mature cells)	3
Extreme pleomorphism (0–25% mature cells)	4
Pattern of invasion	
Pushing, well delineated infiltrating borders	1
Infiltrating, solid cords, bands and/or strands	2
Small groups or cords of infiltrating cells ($n > 15$)	3
Marked and widespread cellular dissociation in small groups and/or in single cells ($n < 15$)	4
Inflammatory infiltrate	
Marked	1
Moderate	2
Slight	3
None	4

Histopathological analysis

Five-micrometre thick sections were obtained from paraffin-embedded tissue blocks, deparaffinized, and stained with haematoxylin and eosin. Two previously trained examiners, who were unaware of the clinical data of the cases, analyzed the specimens under a light microscope (Leica DM500; Leica Microsystems Vertrieb GmbH, Wetzlar, Germany) according to the histopathological grading systems proposed by Bryne et al.,[14] the WHO,[15] and Brandwein-Gensler et al.[21] If the examiners disagreed on the histopathological grade of malignancy, the slides were re-examined until consensus was reached.

For the system proposed by Bryne et al.,[14] the histopathological grading of malignancy was performed at the invasive front of the tumour. This histopathological grading system attributes scores of 1–4 to the following parameters: degree of keratinization, nuclear pleomorphism, pattern of invasion, and inflammatory infiltrate (Table 1). Next, the scores are summed to obtain a final score of malignancy for each case. In accordance with Silveira et al.,[19] tumours with a final score ≤ 8 were classified as having a low grade of malignancy and those with a final score ≥ 9 were classified as having a high grade.

Using the histopathological grading system proposed by the WHO,[15] the tumours were analyzed in their entire length and were classified as well-differentiated, moderately differentiated, or poorly differentiated. According to this system, well-differentiated tumours resemble normal squamous epithelium, whereas moderately differentiated tumours exhibit distinct nuclear pleomorphism and mitotic activity, including atypical mitoses, as well as reduced keratinization. In poorly differentiated carcinomas, immature cells predominate, accompanied by numerous typical and atypical mitoses and minimal keratinization.[15]

For the histological risk assessment,[21] the worst pattern of invasion, lymphocytic infiltrate, and perineural invasion were evaluated (Table 2). The first two parameters were analyzed at the tumour–host interface. The scores obtained for each parameter were summed to give a final score of malignancy for each case. Tumours with a final score of 0 were classified as low-risk, those with a final score of 1 or 2 as intermediate-risk, and those with a final score ≥ 3 as high-risk.[21]

Statistical analysis

The clinical and morphological results were analyzed statistically using SPSS v. 17.0 (SPSS Inc., Chicago, IL, USA). The χ^2 test was used to determine possible associations between the histopathological grade of malignancy of the tumour determined by the system proposed by Bryne et al.[14] and clinical parameters (tumour size/extent, regional lymph node metastasis, and clinical stage). Possible associations between single morphological parameters (degree of keratinization, pattern of invasion, nuclear pleomorphism, and inflammatory infiltrate) and