Clinical
PRACTICE

Histologic Subtypes of Oral Squamous Cell Carcinoma: Prognostic Relevance

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ABSTRACT

Squamous cell carcinoma (SCC) is the most prevalent malignant neoplasm of the oral cavity. The conventional tumour and several histologic subtypes of SCC present morphologic features and specific behaviour when they occur in the oral mucosa. For example, basaloid SCC is an aggressive tumour and verrucous carcinoma has the lowest invasive and metastatic potential; however, the clinical and biologic course of these oral SCC variants has not been completely established. Furthermore, although numerous clinical and histologic features associated with oral SCC have been identified, none shows unequivocal prognostic significance. The purpose of this article is to review the various subtypes of oral SCC, emphasizing problems in their histologic diagnosis and prognosis.

Cancer is an important public health problem in many parts of the world, and oral cancer is among the 10 most common cancers worldwide.[1] According to the International Agency for Research on Cancer of the World Health Organization (IARC–WHO), cancer rates are expected to increase at an alarming rate: from 10 million new cases globally in 2000 to 15 million in 2020.[2]

In the oral cavity, squamous cell carcinoma (SCC) is the most prevalent malignant neoplasm. Despite the ready accessibility of the oral cavity to direct examination, these malignancies are often still not detected until a late stage and, as a result, the survival rate for oral cancer has remained essentially unchanged over the past 3 decades.[3] In recent years, numerous prognostic factors associated with oral SCC have been identified,[4–12] some of them

inherent to the patient and others associated with the genetic profile of the malignant epithelial cells, which reflect tumour aggressiveness. However, none of the molecular markers associated with the genetic alterations described for oral SCC have shown unequivocal prognostic or predictive significance.[11,12]

The value of histologic classification of conventional oral SCC (well, moderately or poorly differentiated) is controversial, and most authors now recognize that microscopic classification alone is poorly correlated with outcome and response to treatment.[4,11,13] Furthermore, the prognostic value of identifying histologic subtypes of oral SCC (**Fig. 1**), which show characteristic morphology and specific behaviour, has not been clearly established.[14] The main clinicopathologic features
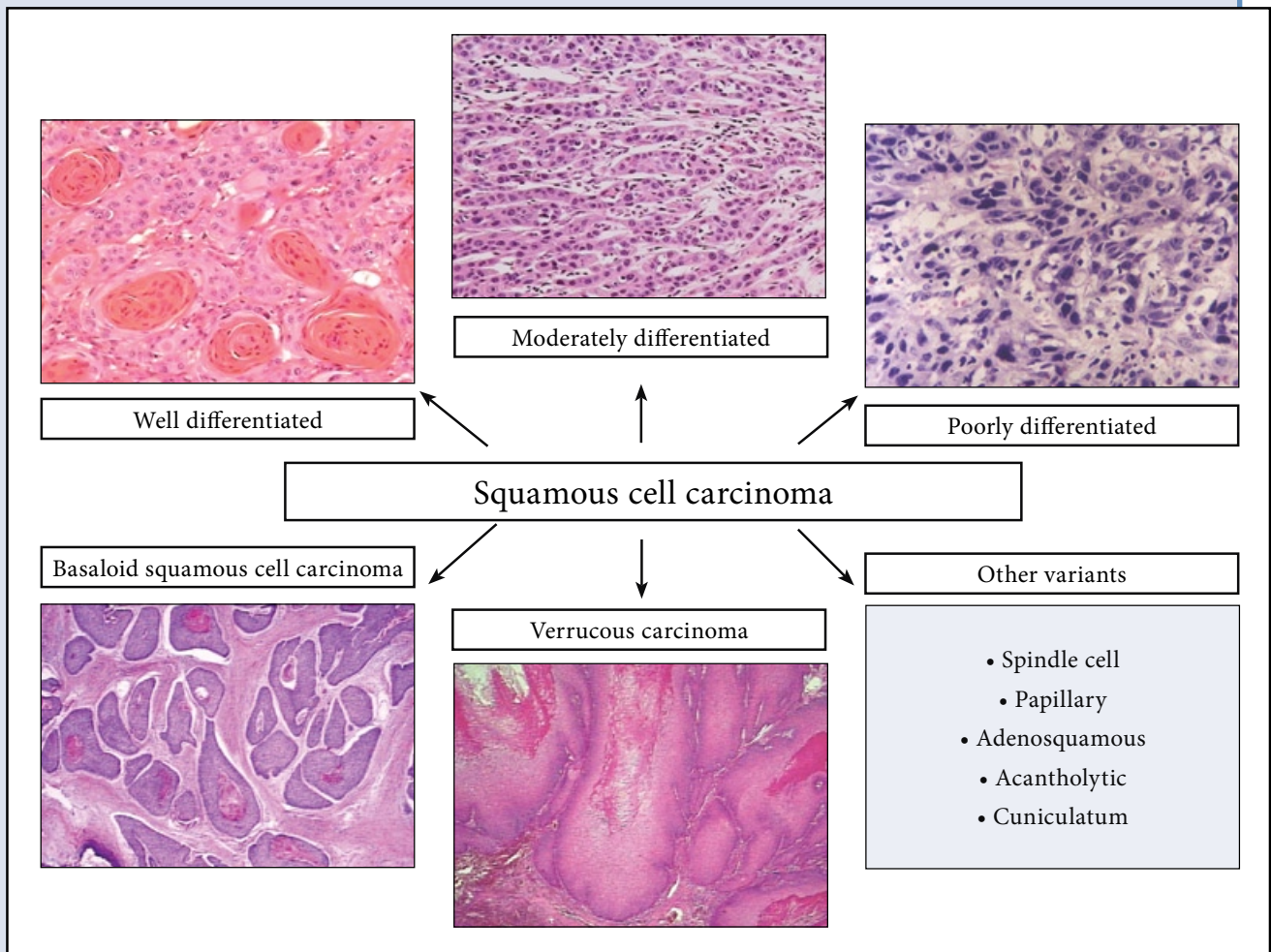
Figure 1: Histologic subtypes of oral squamous cell carcinoma.

of and prognosis associated with the most frequent subtypes of oral SCC are summarized in **Table 1**.

This review includes a brief overview of the histologic subtypes of oral SCC, emphasizing the importance of microscopic diagnosis of these variants, which has important clinical implications for the prognosis of the tumour.

Conventional Squamous Cell Carcinoma

Conventional squamous cell carcinoma (CSSC) is the most frequent neoplasm arising from the oral epithelium (**Fig. 2**) and the risk factors associated with its occurrence, such as tobacco and heavy alcohol consumption, are well established.[1,15,16]

Despite the continuing evolution of diagnostic and therapeutic methods used in oncology, clinical and histopathologic factors with prognostic value for oral CSSC

that might aid in more precise selection of patients for various treatment strategies remain inconclusive.[17]

A wide range of tumour features, including size and site, histologic malignant grade, perineural spread at the invasive front, lymphovascular invasion and tumour thickness, have been described as major risk factors that adversely affect the prognosis for patients with oral SCC. Some of these factors involve a series of genetic alterations, which occur in proto-oncogenes and in tumour suppressor genes and reflect the tumour's aggressiveness as well as the risk of metastasis.[15,18] Abnormalities in the p53 gene, frequently identified by genetic markers,[12,15,16,19] are likely one of the early events in the development of oral SCC.

The presence of 2 or more positive regional nodes, extracapsular extension of nodal disease and positive margin resection[15] have also been correlated with poor

Table 1 Comparison of clinicopathologic features and prognosis of conventional squamous cell carcinoma (CSCC), verrucous carcinoma (VC) and basaloid squamous cell carcinoma (BSCC)

	Histologic subtypes of oral cancer		
	CSCC	**VC**	**BSCC**
Clinical features	Ulcerated appearance	Cauliflower-like appearance	Ulcerated appearance
Preferential sites	Tongue Floor of the mouth	Buccal mucosa Hard palate	Base of the tongue Floor of the mouth
Histopathologic features	Variable degree of keratinization, pleomorphism and mitotic activity	Intense keratinization, compressive pattern and minimal atypia	Basaloid pattern in intimate association with a squamous component
Metastatic potential	High	Absent	High (similar to poorly differentiated CSCC)
Prognosis	Poor	Excellent	Poor (similar to poorly differentiated CSCC)

prognosis. Although the quality of treatment is of paramount importance, most analyses of prognostic factors have failed to show any relation between treatment and survival rate.[16] Furthermore, due to the limited prognostic value of conventional clinical tumour–nodal–metastasis (TNM) staging and histopathologic grading in oral cancer, many patients are still over- or under-treated, resulting in significant personal and socioeconomic impact.[5] Intriguingly, 2 well-established histologic predictive factors — tumour thickness and extracapsular spread of nodal metastases — have not become part of routine TNM classification.[11]

According to Pindborg and others,[4] oral SCCs are classified microscopically based on a method which takes into account a subjective assessment of the degree of keratinization, cellular and nuclear pleomorphism and mitotic activity. The grades are well differentiated (grade 1), moderately differentiated (grade 2) and poorly differentiated (grade 3). Well and moderately differentiated tumours can be grouped together as low grade and poorly differentiated and undifferentiated tumours as high grade.

Generally, histologic grading of malignancy has limited impact on survival rate due to the subjective nature of the assessment of various features; the fact that the small biopsies from these neoplasms may show considerable histologic heterogeneity; poor tissue preservation; reliance on tumour cell structure rather than functional characteristics; and evaluation of tumour cell features in isolation from those of the surrounding supporting tissues and cells.[4,6,9]

Furthermore, the growth of the malignant tumour is frequently accompanied by a dense inflammatory infiltrate. A still-unanswered question is whether these cells are involved in promoting progression of tumours or in their destruction. The protective role of inflammatory cells in the development of tumours has been demonstrated in a series of studies.[18] Our own experience[7] has confirmed that cells such as eosinophils may play a protective role against tumour progression. In our experience, intense tumour-associated tissue eosinophilia obtained by morphometric analysis was an independent favourable prognostic factor for 125 patients submitted to surgical treatment for clinical stage II and III primary SCC located within the oral cavity.

According to Woolgar[11] the identification of accurate prognosticators in oral SCC has been hampered by the relatively small number of cases of the disease, especially in any one treatment centre; by the heterogeneity of clinical features, such as the extent of the disease at presentation; and, in particular, by the lack of standard clinical, management and laboratory protocols combined with inconsistent recording and reporting of data. We agree with this author's suggestion that more efficient research and development would occur with less reliance on subjective interpretation and the wider use of standardized databases, automated techniques, quantitative data and the ability to exchange information.

Verrucous Carcinoma

The lesser aggressiveness of verrucous carcinoma (VC) reinforces its classification as a well-differentiated variant of oral SCC with an excellent prognosis and indolent clinical behaviour.[20–30]

Although the mucous membranes of the head and neck are the most common sites of VC development, especially the oral cavity and larynx, this tumour may also be found on other cutaneous surfaces including the anorectal region, external genitals and skin of the extremities, particularly the sole of the foot.[23,30,31]

Some investigators have described "hybrid" lesions, seen when tumours present the dominant microscopic features of VC, but also contain small areas of tumour invasion, which are common in conventional SCCs.[14,36] However, others consider that the presence of tumour invasion demands a histopathologic diagnosis of SCC, because this indicator will dictate clinical treatment.

Although adequate surgical excision remains the treatment of choice for the oral VC,[24,28,31,37] chemotherapy, alone or in combination with radiotherapy,[25,31,37,38] has also been employed as initial treatment. Radiation therapy alone has been contraindicated due to the possibility of anaplastic transformation from oral VC to more aggressive SCC.[31,38]

The local recurrence of oral VC has been reported frequently.[21,22,31,33,38] Our own retrospective study[39] of 3,500 primary oral well-differentiated SCCs surgically excised between 1980 and 2002, in which 20 oral VCs were identified and treated by excision surgery, showed 38.5% local recurrence rate. The tumours occurred mainly in men older than 60; the sites of most common occurrence were the lower lip and the hard palate. Regional recurrence and distant metastasis were not verified in our sample of oral VCs and all cases presented free surgical margins. Based on these results, we suggest that, although it is rare and is associated with an excellent prognosis, VC has an intrinsic potential for local recurrence that should be considered when planning surgery.

Figure 2: Conventional squamous cell carcinoma in the floor of the mouth.
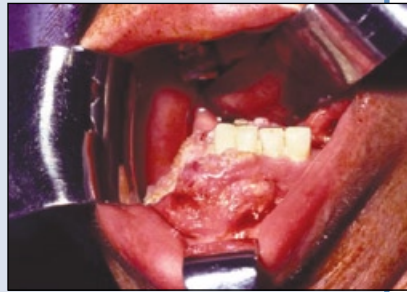

Figure 3: Clinical presentation of verrucous carcinoma arising from gingiva.

Since Ackerman's[20] original description, there have been ongoing discussions regarding the etiology of oral VC. The pathogenesis of this neoplasm has been associated with benign verrucous lesions[22,31] and tobacco carcinogenic factors, especially those related to tobacco chewing.[21,24,28–31] However, there are also reports of patients who developed oral VC without a history of smoking.[23,26,32] A probable relation between oral VC and human papillomavirus has also been suggested. A more acceptable hypothesis is that opportunist viral activity associated with chronic tobacco and alcohol consumption may be involved in the pathogenesis of this neoplasm.[33–35]

Clinically, VC in the oral cavity is characterized by a cauliflower-like exophytic growth with a cleft, warty, whitish-to-gray surface which may have erythematous areas[4,20–24,26,28,29] (**Fig. 3**). Despite being curable in the early stages, this neoplasia can become locally invasive if it is not treated correctly.[20,23,24,31]

Microscopically, VC is a predominantly exophytic growth of well-differentiated stratified squamous epithelium with deep bulbous rete ridges that exhibit little or no cytologic atypia and deep surface invaginations filled with parakeratin or orthokeratin (**Fig. 1**). The lesion's margins show a compressive growth pattern and local destruction of connective tissue can occur in advance of the deep epithelial ("pushing") border. Despite exaggerated rete pegs, the associated basement membrane appears intact.[4,14,22,23] In the most advanced stages, bone, salivary glands, muscles and cartilage involvement can be seen. However, distant metastasis[24] and regional lymph node involvement, which occur in conventional SCC, are rare.[4,14]

The establishment of a clinical or histopathologic diagnosis of VC in the oral cavity may be difficult.[23] It depends heavily on close collaboration between clinician and pathologist and the availability of a sufficiently large biopsy specimen.[26,27,31,36]

Basaloid Squamous Cell Carcinoma

Basaloid squamous cell carcinoma (BSCC) is a rare and aggressive variant of SCC that was first identified as a separate histopathologic entity by Wain and others.[40] This tumour has a predilection for the head and neck region and occurs mainly in the larynx, hypopharynx, oropharynx, epiglottis and at the base of the tongue.[4,41]

Cadier and others[42] first reported it in the oral cavity, and isolated lesions have been described in the palate,[43,44] floor of the mouth[45] and tuberosity area of the maxilla.[46] BSCC is most prevalent among men who are in the sixth or seventh decade of life and have a history of heavy smoking and alcohol abuse. Clinically, the tumour appears as an ulcerated, exophytic, firm mass.[12,40,47,48]

Microscopically, BSCC can have lobular, cord-like, cribriform, tubular, glandular-like or nest patterns, focally connected to the surface epithelium.[49] Cells at the periphery of the lobules are often palisaded, with hyperchromatic nuclei and scant cytoplasm. The central areas of the lobules are characterized by cystic spaces,

sometimes containing material resembling mucin, which stains with periodic acid-Schiff, and displaying comedonecrosis (**Fig. 1**). The distinctive histologic feature of this neoplasm is its appearance as an SCC in intimate relation with a basaloid component.[4,12,40]

It is difficult to establish a diagnosis of BSCC in the head and neck region confidently when only a small specimen is available for biopsy.[50] The lack of a representative sample containing a basaloid component associated (or not) with a squamous component or the lack of continuity with the epithelium of the oral mucosa could lead to diagnosis of poorly differentiated SCC or salivary gland tumours, particularly adenoid cystic carcinoma.[47,51–53] Therefore, when a diagnosis of poorly differentiated SCC is established by incisional biopsy, the possibility of a BSCC should not be excluded, especially when the lesion is located in the oropharynx or base of the tongue.

The clinical course and prognosis of BSCC have been considered worse than for conventional SCC based on its aggressive biological behaviour characterized by early local or regional recurrences and distant metastasis, as well as lower reported survival rates.[41,46,49–52] However, few studies have compared the clinical course and biological behaviour of oral BSCC and SCC[50,51,54] and sample sizes are too small to be representative or allow the establishment of a prognosis.

In a review of BSCCs affecting only the oral cavity, Sampaio-Goes and others[12,48] compared 17 BSCCs with well, moderately and poorly differentiated SCCs, matched by stage and site, in terms of clinical and biologic course, outcome, treatment and prognosis. The authors concluded that the clinical and biological course of BSCC is similar to that of SCC when clinical stage and site are matched. Thus, they suggest that patients with these malignant neoplasms undergo the same therapeutic protocols as for SCC.

Other Histologic Variants of Squamous Cell Carcinoma

Several subtypes of oral SCC, including spindle-cell carcinoma, papillary SCC, adenosquamous carcinoma, acantholytic SCC and carcinoma cuniculatum, were considered in the classification adopted by the IARC–WHO.[14] Most described cases of these malignant neoplasms have been in the larynx and hypopharynx.

Due to the small number of reported cases of these histologic subtypes in the oral cavity,[11,39] information about their prognosis and clinical–biological behaviour has not been established.[4,14]

Conclusion

Although SCC is the most frequent malignant neoplasm of the oral cavity, its clinical and biological course and the prognosis associated with its histologic variants have not been completely established, probably due to the low frequency of these subtypes in the oral cavity. In addition, many histologic variants of SCC are misdiagnosed, either because the biopsy sample is not adequately representative or because of the difficulty of establishing a diagnosis based on histopathologic features with routine hematoxylin-eosin staining. Multiple biopsies from various areas of the lesion should be obtained to ensure correct diagnosis of the subtypes.

Microscopic identification of the various histologic subtypes of SCC should be emphasized among pathologists to contribute to consistent knowledge of clinical and biological tumour behaviour in the oral cavity and result in more accurate treatment protocols. ❖

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