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Comparative study of two histopathological classifications for oral squamous cell carcinoma

Estudo comparativo de duas classificações histopatológicas para carcinoma de células escamosas bucal

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ABSTRACT

Introduction: Squamous cell carcinoma (SCC) is the most common tumor among all cancers in the oral cavity. Despite advances, the prognosis of this neoplasm remains a challenge for professionals. Faced with this situation, several studies try to associate the histopathological analysis with prognosis, so that therapeutic planning becomes more accurate. **Objectives:** This research aimed to conduct an epidemiological study of oral SCC and classify them histopathological assessment according to the World Health Organization (WHO) and the Budding and Depth of Invasion (BD) model. A retrospective research was conducted. **Methodology:** Data from medical records filed at UOPECCAN Hospital between 2009 and 2015 were analyzed. The sample consisted of 57 patients. Epidemiological data were collected and the blocks were rescued and cut for histopathological analysis. Associations were performed using the chi-square test with a significance level of 5% ($p = 0.05$) by the GraphPad Prism program. The two histopathological analyzes were correlated using Spearman's statistical test. **Results:** After analyzing the samples, we found a higher prevalence of oral SCC in male smokers aged above 40 years. There was no correlation between the BD and WHO methods. The WHO classification was significantly associated with age ($p = 0.03$), and follow-up care ($p = 0.05$). However, the BD model associated lymph node involvement ($p = 0.005$) and clinical staging ($p = 0.005$). **Conclusion:** The BD classification was more objective for histopathological analysis and may be an important tool for analyzing patient prognosis, assisting in the treatment decision.

Key words: squamous cell carcinoma; prognosis; neoplasm staging.

RESUMO

Introdução: *O carcinoma de células escamosas (CCE) é o tumor mais frequente entre todos os cânceres localizados na cavidade bucal. Apesar dos avanços, o prognóstico dessa neoplasia ainda é um desafio para os cirurgiões. Diante dessa situação, vários estudos tentam associar a análise histopatológica ao prognóstico, a fim de que os planejamentos terapêuticos se tornem mais precisos.* ***Objetivos:*** *Esta pesquisa teve como objetivo realizar o estudo epidemiológico dos CCEs e classificá-los histopatologicamente conforme a Organização Mundial da Saúde (OMS) e o modelo "Budding and Depth of Invasion" (BD). Um estudo retrospectivo foi realizado.* ***Metodologia:*** *Foram analisados dados dos prontuários arquivados no Hospital UOPECCAN entre 2009 e 2015. A amostra foi composta por 57 pacientes. Os dados epidemiológicos foram coletados e os blocos resgatados e cortados para análise histopatológica. As associações foram realizadas por meio do teste qui-quadrado, com nível de significância de 5% (*p *= 0,05) pelo programa GraphPad Prism. As duas análises histopatológicas foram correlacionadas por meio do teste estatístico de Spearman.* ***Resultados:*** *Após análise das amostras, verificamos mais prevalência de CCE nos pacientes fumantes do sexo masculino com idade superior a 40 anos. Não houve correlação entre os métodos BD e OMS. A classificação da OMS apresentou associação significante com a idade (*p *= 0,03) e a sequência de tratamento (*p *= 0,05). Já o modelo BD associou comprometimento linfonodal*

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(p = 0,005) e estadiamento clínico (p = 0,005). ***Conclusão:*** *A classificação BD foi mais objetiva para a análise histopatológica e pode ser uma importante ferramenta para análise do prognóstico do paciente, auxiliando na decisão do tratamento.*

Unitermos: *carcinoma de células escamosas; prognóstico; estadiamento de neoplasias.*

RESUMEN

Introducción: *El carcinoma de células escamosas (CCE), denominado además carcinoma epidermoide, es el tumor más común entre todos los cánceres de la cavidad oral. A pesar de los avances, el pronóstico de esta neoplasia sigue siendo un desafío para los cirujanos/profesionales/clínicos. Ante esta situación, varios estudios intentan asociar el análisis histopatológico con el pronóstico, para que la planificación terapéutica sea más precisa.* ***Objetivos:*** *Esta investigación tuvo como objetivo realizar un estudio epidemiológico del CCE oral y clasificarlo histopatológicamente de acuerdo con la Organización Mundial de la Salud (OMS) y el modelo Budding and Depth of Invasion (BD). Se realizó una investigación retrospectiva.* ***Metodología:*** *Se analizaron los datos de las historias clínicas archivadas en el Hospital UOPECCAN entre 2009 y 2015. La muestra estuvo formada por 57 pacientes. Se recolectaron datos epidemiológicos y los bloques fueron rescatados y cortados para análisis histopatológico. Las asociaciones se realizaron mediante la prueba de chi-cuadrado con un nivel de significancia del 5% (p = 0.05) por el programa GraphPad Prism. Los dos análisis histopatológicos se correlacionaron mediante la prueba estadística de Spearman.* ***Resultados:*** *Tras analizar las muestras, encontramos una mayor prevalencia de CCE oral en varones fumadores mayores de 40 años. No hubo correlación entre los métodos BD y OMS. La clasificación de la OMS se asoció significativamente con la edad (p = 0,03) y seguimiento del del tratamiento (p = 0,05). Sin embargo, el modelo de BD asoció la afectación de los ganglios linfáticos (p = 0,005) y la estadificación clínica (p = 0,005).* ***Conclusión:*** *La clasificación BD fue más objetiva para el análisis histopatológico y puede ser una herramienta importante para analizar el pronóstico del paciente, asistiendo en la decisión del tratamiento.*

Palabras clave: *carcinoma de células escamosas; pronóstico; estadificación de neoplasias.*

INTRODUCTION

Squamous cell carcinoma (SCC) is the most common malignant neoplasm of the oral cavity, representing 95% of oral cancers[1]. Its incidence varies according to age, gender, habits, occupation, ethnic groups, and geographic location. There are also some areas of the oral cavity that are generally more affected, such as the lower lip, the tongue, and the floor of the mouth[2].

Several factors seem to be involved in the etiology of this disease, however, the discussion of these issues is not yet conclusive; only alcohol and tobacco have proven evidence[3].

The prognosis of SCC is still a challenge for surgeons, despite the progress in diagnosis and treatment in recent decades[1]. One of the main parameters used for therapy and prognosis planning is the TNM system standardized by the American Joint Committee on Cancer (AJCC) called clinical staging, which allows measuring tumor size (T), lymph node involvement (N), and distant metastases (M)[4]. Recently, to improve and strengthen the prognosis, the eighth edition of the AJCC proposed modifications to this system, including the addition of two pathological factors: tumor depth of invasion and extranodal extension[1]. Thus, the main role of histopathological analysis is to complement the TNM system and provide the surgeon with important information for the most appropriate therapy[5].

For years, researchers have proposed several histopathological malignancy grading systems (HMGS) whose objective is to provide subsidies that enable the interpretation of the aggressiveness of the neoplasm. Among them, we can mention those proposed by Broders in 1920, which gave rise to the World Health Organization (WHO) system[6], Anneroth *et al*. in 1987[7], Bryne *et al*. in 1992[8], Brandwein-Gensler *et al*. in 2005[9], and Almangush *et al*. in 2015[5].

The most recent classification byAlmangush *et al*. (2015)[5], known as the Budding and Depth of Invasion (BD) classification, is based on the depth of invasion and the nests of tumor cells in the tumor front. Basically, researchers have shown that individual cells or small groups of cells indicate a poor prognosis due to their invasiveness. In addition, recent studies demonstrate that TNM staging combined with the BD histologic grading model can help with therapeutic planning[10, 11].

The purpose of this study was to conduct an epidemiological survey of SCC cases and make the histopathological classification according to the WHO (current standard histopathological classification) and the BD classification, in addition to analyzing the association of these classifications with demographic data and the TNM system.

METHODOLOGY

The study was approved by the Research Ethics Committee of the State University of West Paraná and by the Cascavel Cancer Hospital [União Oeste Paranaense de Estudos e Combate ao Câncer (UOPECCAN)] – CEP CCAE: 49204715.1.0000.0107.

Sample, inclusion and exclusion criteria

The sample consisted of 57 patients diagnosed with SCC treated at the Cancer Hospital of Cascavel at UOPECCAN between 2009 and 2015. Patients, who underwent total tumor resection surgery, associated or not with postoperative chemotherapy and/or radiotherapy were included. Exclusion criteria included patients with lip SCC (because its etiology is different from that of intraoral SCC), cases where only incisional biopsy was available, and patients who underwent chemotherapy and/or radiotherapy prior to total tumor resection surgery.

Data collection

The information collected were: patient identification and hospital registration number; gender; age of cancer detection; color; smoking or drinking habits; site and size of the lesion; lymph node involvement; metastasis at diagnosis; clinical staging; treatment performed; tumor complaint time; surgical margins; relapses; second primary tumor; and the patient's current state. After data collection, contact with the patients was made by telephone call to request the submission of the Free, Prior and Informed Consent (FPIC), which was signed and sent back by mail to the researchers.

Histopathologic analysis

The respective tumor blocks were sent to the laboratories in the city of Cascavel [Laboratório Anaton Instituto de Anatomia Patológica e Citopatologia S/C Ltda and Laboratório de Anatomia Patológica e Citologia (APC)]. The next step was the of histology slides preparation stained with the hematoxylin and eosin (HE) technique.

With the slides finished, the histopathologic analysis was performed with an Olympus ×71 microscope with the aid of Olympus DP Controler 3.2.1.276 measurement and image capture software, simultaneously by two researchers (SCI and LBC); only the report number was available at the time of histopathologic analysis. The analysis was performed using the WHO model and the BD model. The WHO model is based on the proliferation and differentiation of tumor cells, and cases are classified as well-differentiated (grade 1), moderately differentiated (grade 2), and poorly differentiated (grade 3)[6]. The BD classification is based on tumor cell nests (B) and depth of invasion (D). The cutoff point for counting the tumor cell nests and the depth of invasion was established at five nests and 4 mm, respectively. Depth of invasion was analyzed at 4× magnification, and tumor cell nests at 20× magnification. The results of the analysis of histopathology patterns were classified into three groups[5]:

- score 0 (low risk) – < 4 mm, and tumor cell nests < 5 in the invasive tumor front;
- score 1 (intermediate risk) – the tumor must have one of the following characteristics: a) < 4 mm, and ≥ 5 nests; or b) ≥ 4 mm, and < 5 nests;
- score 2 (high risk) – ≥ 4 mm, and ≥ 5 nests.

Statistical analysis

Chi-square-based association tests with a significance level of 5% ($p = 0.05$) were performed using the GraphPad Prism software. The two histopathologic analyzes were correlated using the Spearman's statistical test.

RESULTS

The epidemiological and histopathological data of the 57 patients are shown in **Table 1**. The analysis of the correlation between the WHO and BD classifications was performed by the Spearman's correlation test with a result of 0.22, showing a weak correlation between them.

Budding and depth of invasion

Table 2 demonstrates the statistical analysis using the chi-square between epidemiological data and histopathologic classifications. Importantly, patients who did not report smoking or drinking habits were not considered in this analysis, as well as those who were classified as "loss to follow-up" in the patient's current state. This test showed significance between the WHO classification with age ($p = 0.03$) and treatment sequencing ($p = 0.05$), while the BD model associated lymph node involvement ($p = 0,005$) and clinical staging ($p = 0.005$).

TABLE 1 – Epidemiological data and histopathological classification (n = 57)

Parameter	*n*	%
Gender		
Male	46	80.7
Female	11	19.3
Age		
≤ 40	4	7.02
> 40	53	92.98
Smoking habit		
No	11	19.3
Yes or ex-smoker	43	75.44
No reported	3	5.26
Drinking habit		
No	35	61.4
Yes or ex-drinker	19	33.33
No reported	3	5.26
Site		
Tongue and/or tongue and another region	28	49.12
Floor of the mouth and/or floor of the mouth and other region	13	22.81
Tongue and floor of the mouth	7	12.28
Palate	1	1.75
Retromolar region	1	1.75
Other	7	12.28
T		
T1	13	22.81
T2	24	42.11
T3	10	17.54
T4	10	17.54
N		
N0	35	61.4
N+	22	38.6
Metastasis		
M0	50	87.72
Mx	7	12.28
Clinical staging		
I	8	14.04
II	16	28.07
III	14	24.56
IV	19	33.33
Treatment		
Surgery	26	45.61
Surgery + RT	14	24.56
Surgery + RT + CTX	17	29.82
Margins		
Committed	1	1.75
Free	56	98.25
Color		
Yellow	1	1.75
White	37	64.91
Black	2	3.51
Brown	16	28.07
No reported	1	1.75
Tumor complaint time		
Less than 1 month	4	7.02
1 to 3 months	18	31.58
4 to 6 months	14	24.56
7 months to 1 year	10	17.54
More than 1 year	2	3.51
No reported	9	15.79
Recurrence		
No	40	70.18
Local	5	8.77
Distant	3	5.26
Lymph node	2	3.51
Local and distant	3	5.26
Local and lymph node	2	3.51
Distant and lymph node	2	3.51
Second primary cancer		
Yes	5	8.77
No	52	91.23
Patient's current state		
Alive without disease	31	54.39
Alive with disease	15	26.32
Death by disease	6	10.53
Death during treatment	4	7.02
Loss to follow-up	1	1.75
WHO		
Well differentiated	31	54.39
Moderately differentiated	16	28.07
Poorly differentiated	10	17.54
BD		
0	14	24.56
1	26	45.61
2	17	29.82

RT: radiotherapy; CTX: chemotherapy; WHO: World Health Organization; BD: Budding and Depth of Invasion.

TABLE 2 – Correlation between variables and BD and WHO classification (n = 57)

Parameter	WHO				BD			
	Well differentiated	Moderately differentiated	Poorly differentiated		0	1	2	
	n%	*n*%	*n*%	*p*	*n*%	*n*%	*n*%	*p*
Gender								
Male	24	12	10		12	23	11	
Female	7	4	0	0.09	2	3	6	0.15
Age								
≤ 40	0	2	2		1	3	0	
> 40	31	14	8	0.03	13	23	17	0.2
Smoking habit								
No	5	4	2		3	3	5	
Yes or ex-smoker	24	11	8		10	22	11	
No reported	2	1	0	0.78	1	1	1	0.63

Cont. →

→ *Cont.*

Drinking habit								
No	19	11	5		7	16	12	
Yes or ex-drinker	10	4	5		6	9	4	
No reported	2	1	0	0.62	1	1	1	0.79
Site								
Tongue and/or tongue and other region	10		5		6	15	7	
Floor of the mouth and/or floor of the mouth and other region	8		1	4	2	6	5	
Tongue and floor of the mouth	5	2	0		2	2	3	
Palate	0	0	1		1	0	0	
Retromolar region	0	1	0		0	1	0	
Other	5	2	0	0.08	3	2	2	0.61
T								
T1	9	3	1		5	6	2	
T2	13	6	5		8	8	8	
T3	3	5	2		1	6	3	
T4	6	2	2	0.56	0	6	4	0.09
N								
N0	18	11	6		13	15	7	
N+	13	5	4	0.99	1	11	10	0.005
Metastasis								
M0	28	12	10		12	22	16	
Mx	3	4	0	0.57	2	4	1	0.98
Clinical staging								
I	4	3	1		4	3	1	
II	10	4	2		7	6	3	
III	7	4	3		3	8	3	
IV	10	5	4	0.97	0	9	10	0.005
Treatment								
Surgery	17	7	2		11	11	4	
Surgery + RT	8	5	1		0	8	6	
Surgery + RT + CTX	6	4	7	0.05	3	7	7	0.07
Margins								
Committed	1	0	0		0	1	0	
Free	30	16	10	0.87	14	25	17	0.81
Tumor complaint time								
Less than 1 month	1	2	1		0	2	2	
1 to 6 months	19	9	4		9	14	9	
6 months to 1 year	5	2	3		3	6	1	
More than 1 year	1	1	0		1	0	1	
No reported	5	2	2	0.82	1	4	4	0.35
Recurrence								
No	23	9	8		10	18	12	
Local	5	0	0		2	1	2	
Distant	0	2	1		0	2	1	
Lymph node	1	1	0		1	0	1	
Lymph node and distant	1	2	0		0	3	0	
Local and lymph node	1	1	0		1	1	0	
Distant and lymph node	0	1	1	0.24	0	1	1	0.64
Second primary cancer								
Yes	3	2	0		2	3	0	
No	28	14	10	0.34	12	23	17	0.14
Patient's current state								
Alive without disease	14	11	6		10	12	9	
Alive with disease	9	2	4		3	7	5	
Death by disease	4	2	0		1	3	2	
Death during treatment	3	1	0		0	3	1	
Loss to follow-up	1	0	0	0.61	0	1	0	0.81

$p \leq 0.05$; *WHO: World Health Organization; BD: Budding and Depth of Invasion RT: radiotherapy; CTX: chemotherapy.*

DISCUSSION

According to epidemiological data, the population of Cascavel with SCC treated from 2009 to 2015 at the UOPECCAN Hospital presented the same epidemiologic profile found in the literature[2, 12-14], that is, male smoker aged above 40 years. In our research, the majority (92.98%) of patients were aged above 40 years, which is consistent, since SCC is a disease that significantly increases its prevalence over the years (especially above the age of 40 years)[14].

In addition to tobacco, alcohol is also reported as a carcinogen. Studies show that neoplasms in the oral cavity can occur due to some habits, such as drinking and/or smoking; the scenario is more aggravating when the patient has both habits[2, 13, 15]. Fron the individuals who participated in the survey, 75.44% used tobacco and 33.33% had the drinking habit. All people who consumed alcohol used tobacco concomitant.

The SCC location is also a significant issue. Although this neoplasm can occur anywhere in the oral cavity, some areas are more commonly affected than others; for example, the lower lip, the tongue, and the floor of the mouth[2, 13, 16]. The site with the highest incidence in this study was the tongue (49.12%) – associated or not with a region other than the floor of the mouth –, followed by the floor of the mouth (22.81%) – associated or not with another region other than the tongue – and concomitant the tongue and the floor of the mouth (12.28%). It is important to report that patients with lip SCC are not part of the sample, as the etiology of this neoplasm is related to sun exposure, as well as its biological behavior and its more favorable prognosis[17].

Despite the theoretical ease of finding lesions in early stages, the absence of symptoms at this stage leads the patient to neglect it. Most SCC lesions do not heal within three weeks and are painless[4, 13]. An important fact is that most of the patients in this study sought professional assistance from one to three months after the onset of the lesions (31.51%). According to van der Waal (2013)[18], the average delay in seeking medical care is three to five weeks; the longer the patient takes to seek treatment, the worse their clinical staging and, consequently, their prognosis. Most patients were diagnosed at clinical stage IV (33.33%). The stage at which oral cancer is diagnosed has a significant effect on overall survival and on the increase in treatment-related morbidities[19], besides hindering treatment success[20].

As for the correlation between the histopathologic classifications, they showed a weak relationship (Spearman correlation = 0.22). A survey conducted in 2015 analyzed the same classifications and demonstrated the existence of a weak correlation between these systems (Spearman correlation = 0.09)[10]. In practice, the WHO model and the BD model are analyzed with different standards. A single tumor section that showed a good prognosis (well-differentiated) in one classification (WHO), for example, had a poor prognosis (grade 2) when analyzed in the other classification model (BD). Furthermore, when performing the statistical analysis, the WHO classification showed a significant association with the treatment follow-up ($p = 0.05$). This data is coherent, since the WHO is the current standard model of histopathologic classification and, together with the TNM system, it helps in deciding patient's prognosis and treatment[13].

Our study also showed an association between the WHO classification and age ($p = 0.03$). We believe that this result is due to the fact that age increases the chances of comorbidities, which leads to a worse prognosis for the disease. However, the literature still does not show associations between age, sex, and SCC prognosis[21]. Therefore, we suggest that further investigations should be carried out between WHO classification and patients age.

The BD classification was associated with lymph node involvement ($p = 0.005$) and clinical staging ($p = 0.005$). Such information is relevant since a study that evaluated histologic grading methods for lip SCC demonstrated that TNM staging combined with the BD model may help in therapeutic planning[11], thus avoiding inappropriate treatment for patients. Our research also suggests that the BD classification can be used as a basis for determining treatment, but further studies are needed to confirm this fact.

It has been well established for decades that the presence of lymph node involvement is an important prognostic factor in early-stage[24] head and neck cancer[22-24]. A study by Almangush *et al*. (2018), using the BD classification with preoperative biopsies and the corresponding postoperative tongue SCC specimens from 100 patients, showed a statistically significant relationship between the pre- and postoperative BD scores, thus suggesting that this classification may be used from biopsies for treatment planning[25]. Thus, based on the data found in our research, we suggest that the BD classification can provide important information regarding patient's prognosis, besides being a more objective classification with well-defined parameters.

CONCLUSION

This research presents results that reveal the prevalence of SCC in male smokers aged above 40 years in the population surveyed. The most affected area of the oral cavity was the tongue. We

observed that the BD and WHO histopathologic analysis methods did not correlate with each other. The WHO model showed an association with the follow-up care, which is significant since it is the universal standard model for SCC histopathologic classification. The BD model, on the other hand, associated two recognized prognostic factors: lymph node involvement and clinical staging. This classification method was considered the easiest to perform by researchers due to its more objective standards.

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