UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

ÉDER GERARDO DOS SANTOS LEITE

NEOPLASIAS GENGIVAIS: UM ESTUDO COLABORATIVO INTERINSTITUCIONAL NO BRASIL

GINGIVAL NEOPLASMS: AN INTERINSTITUTIONAL COLLABORATIVE STUDY IN BRAZIL

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Dissertação apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestre em Estomatopatologia, na Área de Patologia.

Dissertation presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requirements for the degree of Master in Stomatopathology, in Pathology area.

Orientador: Prof. Dr. Danyel Elias da Cruz Perez

Este exemplar corresponde à versão final da dissertação defendida pelo aluno Éder Gerardo dos Santos Leite e orientada pelo Prof. Dr. Danyel Elias da Cruz Perez.

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RESUMO

Introdução: As doenças gengivais não induzidas por placa se apresentam clinicamente de maneira diversa e podem ter etiologia distinta. Por se tratar de um grupo de lesões pouco frequentes, estudos que avaliam a prevalência de neoplasias gengivais são raros e não representativos para a população brasileira. O presente estudo avaliou a prevalência de neoplasias gengivais por meio um levantamento interinstitucional envolvendo seis serviços de Diagnóstico Oral no Brasil. **Metodologia:** Nesse estudo retrospectivo, foram revisados todos os laudos histopatológicos arquivados em seis serviços de Diagnóstico Oral entre 1979 e 2020. Apenas os casos de neoplasias gengivais benignas e malignas foram incluídos no estudo. Dados clínicos e demográficos, diagnóstico clínico e histopatológicos foram coletados das fichas clínicas dos pacientes. Análise estatística descritiva foi realizada e o teste Qui-quadrado foi utilizado para avaliar a associação entre as características clínicas nos grupos estudados. O teste de medianas para amostras independentes e o teste de Mann-Whitney foram utilizados para avaliar a diferença entre idade, tamanho do tumor e tempo de evolução entre as neoplasias benignas e malignas. **Resultados:** De 85.981 lesões bucais diagnosticadas, 839 (0,97%) casos de tumores gengivais foram encontrados. A média de idade foi de 54,85 anos (1-104 anos). Havia 238 (28.3%) tumores benignos e 601 (71.7%) tumores malignos. Os homens foram acometidos por tumores malignos (61.7%) com maior frequência, enquanto a mulheres foram mais acometidas por tumores benignos (56.7%). A lesão fundamental mais comum nos tumores benignos foi um nódulo (47.1%) e os tumores malignos se apresentaram comumente como uma úlcera (39.1%). O tumor benigno mais comum foi o papiloma escamoso (67,6%) e o carcinoma espinocelular (79,3%) a neoplasia maligna mais comum. A análise estatística demonstrou que as neoplasias malignas foram mais comuns em homens ($p<0,001$). O tempo de queixa foi menor em pacientes com neoplasias malignas quando comparados àqueles com tumores benignos ($p<0,001$). A mediana de idade foi maior em indivíduos com câncer em gengiva ($p<0,001$), e tumores benignos foram mais comuns em indivíduos mais jovens ($p<0,001$). Os tumores malignos foram maiores do que os tumores benignos ($p<0,001$) e a biópsia incisional foi o procedimento clínico mais comum para o diagnóstico de neoplasia malignas ($p<0,001$), enquanto a biópsia excisional foi mais comum para tumores

benignos em gengiva (p<0,001). Os tumores benignos e malignos foram mais comuns na gengiva inferior posterior (p=0,005). Houve correlação entre a hipótese clínica e o diagnóstico histopatológico em 66% dos casos, enquanto que a hipótese clínica não foi confirmada pelo exame histopatológico em 27,5% dos casos. **Conclusão:** Neoplasias malignas, sobretudo o carcinoma espinocelular, devem ser consideradas no diagnóstico diferencial de úlceras gengivais únicas. Exames clínicos, radiográficos e histopatológicos detalhados são essenciais para o diagnóstico precoce e preciso das neoplasias gengivais.

Palavras-chave: gengiva; doenças da gengiva; neoplasias gengivais; tumores orais; prevalência

ABSTRACT

Introduction: Non-plaque-induced gingival diseases present clinically differently and may have different etiologies. As it is a group of infrequent lesions, studies that assess the prevalence of gingival neoplasms are rare and not representative of the Brazilian population. The present study evaluated the prevalence of gingival neoplasms through an inter-institutional survey involving six Oral Diagnosis services from all regions of Brazil. **Methodology:** In this retrospective study, all histopathological reports filed in six Oral Diagnosis services between 1979 and 2020 were reviewed. Only cases of benign and malignant gingival neoplasms were included in the study. Clinical and demographic, clinical diagnosis, and histopathological data were collected from the patients' clinical records. Descriptive statistical analysis was performed using IBM SPSS. The chi-square test was used to assess the association between clinical characteristics in the studied groups. The median test for independent samples and the Mann-Whitney test were used to assess the difference between age, tumor size, and time of evolution between the groups. **Results:** Of 85,981 diagnosed oral lesions, 839 (0.97%) cases of gingival tumors were found. The mean age was 54.85 years (range from 1 to 104 years). There were 238 (28.3%) benign tumors and 601 (71.7%) malignant tumors. Men were affected by malignant tumors (61.7%) more frequently, while women were more affected by benign tumors (56.7%). The most common fundamental lesion in benign tumors was a nodule (47.1%) and malignant tumors commonly presented as an ulcer (39.1%). The most common benign tumor in the sample was squamous papilloma (67.6%) and the most common malignant tumor was squamous cell carcinoma (79.3%). Statistical analysis showed that malignant neoplasms were more common in men ($p<0.001$). Complaint time was shoter in the group of malignant tumors than in the group of benign tumors ($p<0.001$). The median age was higher in individuals with gingival cancer ($p<0.001$), and benign tumors were more common in younger individuals ($p<0.001$). Malignant tumors were larger in length than benign tumors ($p<0.001$) and incisional biopsy was the most common clinical procedure for the diagnosis of malignant neoplasms ($p<0.001$), while the excisional biopsy was more common for benign tumors. in gingiva ($p<0.001$). Benign and malignant tumors were more common in the posterior gingiva of the mandible ($p=0.005$). There was a correlation between the clinical hypothesis and the histopathological

diagnosis in 66% of the cases, while the clinical hypothesis was not confirmed by the histopathological examination in 27.5% of the cases. **Conclusion:** Malignant neoplasms, especially squamous cell carcinoma, should be considered in the differential diagnosis of single gingival ulcers. Detailed clinical, radiographic, and histopathological examinations are essential for the early and accurate diagnosis of gingival neoplasms.

Keywords: Gingiva; Gingival Neoplasms; Mouth Neoplasms; Gingival Diseases; Prevalence

Sumário

1 INTRODUÇÃO

A maioria das doenças gengivais é de origem inflamatória e está associada ao acúmulo do biofilme dentário como uma reação do organismo a estes patógenos (Holmstrup, Plemons e Meyle, 2018; Murakami *et al.*, 2018). A Academia Americana de Periodontia (AAP) e a Federação Europeia de Periodontia (FEP) denominam como Doenças Gengivais Não Induzidas por Placa (DGNIP), o grupo de doenças que afetam os tecidos gengivais que não são ocasionadas pela presença do biofilme dentário ou não se resolvem após a remoção dele (Hernández-Ríos *et al.*, 2018; Holmstrup, Plemons e Meyle, 2018). Apesar das DGNIP serem menos comuns do que aquelas induzidas pelo biofilme dentário, estas têm bastante significância para os indivíduos acometidos, pois frequentemente representam neoplasias malignas ou manifestações orais de doenças sistêmicas e, nesses casos, não seriam um problema limitado aos tecidos gengivais (Alblowi e Binmadi, 2018; Hernández-Ríos *et al.*, 2018; Holmstrup, 1999).

As DGNIP podem ser de natureza não neoplásica ou neoplásica, sendo que as lesões neoplásicas são classificadas em benignas ou malignas (Gambino *et al.*, 2017). As manifestações clínicas das DGNIP variam de acordo com sua etiologia. Podem se apresentar como áreas com perda de substância, úlceras e erosões, aumentos de volumes localizados ou difusos apresentando superfície normal ou alterada, a exemplo de tumores, lesões exofíticas e papilíferas. Variações de cor também podem ser observadas, com lesões exibindo colorações que podem ser branco-amareladas, avermelhadas, azuladas/arroxeadas ou acastanhadas/enegrecidas (Gambino *et al.*, 2017; Hirschfeld *et al.*, 2019).

Devido a quantidade de conhecimento científico acumulado nos últimos anos, houve uma melhora na compreensão da patogênese das doenças que afetam os tecidos gengivais. Por esse motivo, uma classificação contemporânea foi proposta no Workshop de 2017 da AAP. Nesta classificação é possível encontrar a etiologia e descrição detalhada das doenças que acometem a gengiva e que não tem relação com o biofilme dentário, são elas: desordens genéticas do

desenvolvimento, infecções específicas de origem bacteriana, fúngica ou viral, lesões e condições inflamatórias ou imunológicas, processos reativos, neoplasias, doenças metabólicas, nutricionais e endócrinas, lesões traumáticas, pigmentações gengivais e outras condições não especificadas (Holmstrup, Plemons e Meyle, 2018). Embora o conhecimento de que neoplasias benignas e malignas podem acometer o tecido gengival não seja novo, o grupo das neoplasias só foi incluído na classificação de 2018(Holmstrup, Plemons e Meyle, 2018; Li *et al.*, 2021). O diagnóstico das DGNIP é estabelecido a partir do exame clínico associado ao exame histopatológico, considerado padrão ouro para diagnóstico dessas alterações(Gambino *et al.*, 2017). Ainda que a nova classificação apresente uma coleção mais abrangente e compreensível das DGNIP, a classificação e distribuição das neoplasias gengivais ainda carece de melhores elucidações. O grupo das neoplasias, por exemplo, não reúne nenhuma neoplasia benigna acometendo os tecidos gengivais. Neste grupo estão descritas apenas as lesões potencialmente malignas da cavidade oral e neoplasias malignas, como o carcinoma espinocelular, leucemias e linfomas, as quais apresentam histogênese distintas. Além disso, não há nenhuma menção sobre a ocorrência de metástases gengivais de tumores malignos de outros sistemas(Holmstrup, Plemons e Meyle, 2018). O conhecimento da prevalência e distribuição dessas lesões nos tecidos gengivais poderia contribuir para alertar clínicos que doenças neoplásicas também acometer a gengiva, resultando em um diagnóstico mais rápido e preciso desses tumores, além de aumentar as chances de cura para essas doenças.

Estudos que avaliaram amostras de biópsias gengivais evidenciaram que as doenças inflamatórias e os processos reacionais são mais frequentes(Alblowi e Binmadi, 2018; Carbone *et al.*, 2012; Gambino *et al.*, 2017; Hernández-Ríos *et al.*, 2018; Manjunatha *et al.*, 2014). Contudo, não há consenso na literatura sobre a prevalência de neoplasias benignas e malignas que acometem o tecido gengival. Isto porque trabalhos que buscaram avaliar a prevalência de neoplasias gengivais apresentam limitações por serem regionais ou por representarem um grupo populacional específico, o que ocasiona uma ampla variedade entre os resultados. No que se refere às neoplasias benignas, é difícil avaliar com precisão a ocorrência

desses tumores em tecido gengival. Muitos trabalhos que se propuseram a avaliar a ocorrência desses tumores apontam divergências na classificação dessas doenças em lesões reacionais ou neoplasias verdadeiras(Gambino *et al.*, 2017; Hernández-Ríos *et al.*, 2018; Holmstrup, Plemons e Meyle, 2018; Li *et al.*, 2021). Portanto, a prevalência de tumores benignos que acometem o tecido gengival não está bem estabelecida. Alguns estudos publicados que tiveram como objetivo avaliar as doenças gengivais biopsiadas em serviços de diagnóstico bucal, demonstraram que entre as neoplasias, tumores benignos são diagnosticados com menor frequência(Gambino *et al.*, 2017; Li *et al.*, 2021). Hernández-Rios et al. avaliaram 1.012 casos de biópsias gengivais e encontraram apenas 65 (6,42%) tumores benignos diagnosticados.

Ao longo dos anos, estudos publicados na literatura têm buscado estabelecer a prevalência, histogênese, tratamento e sobrevida das neoplasias malignas que se desenvolvem em tecido gengival, sejam elas primárias ou metastáticas(Allon *et al.*, 2013; Bagan *et al.*, 2019; Bark *et al.*, 2016; Cady e Catly, 1969; Gomez *et al.*, 2000; Hirshberg *et al.*, 2008; Hou *et al.*, 2019; Kirschnick *et al.*, 2020; Soo *et al.*, 1988; Uchiyama *et al.*, 2009). A gengiva é um local de fácil acesso, caracterizada por ser um tecido mucoso com uma fina camada de epitélio e conjuntivo, que está diretamente apoiada sobre o osso. Assim, a gengiva se configura como um local relativamente incomum para o desenvolvimento de neoplasias malignas(Bark *et al.*, 2016; Cady e Catly, 1969). Avaliar a ocorrência de tumores malignos em gengiva ainda é desafiador. Parte desta dificuldade se deve a tendência em classificar os tumores gengivais dentro do grupo dos cânceres orais e agrupá-los às neoplasias que ocorrem dentro da boca junto a outras topografias da mucosa oral, mesmo sabendo que essas neoplasias podem apresentar características e comportamento biológico distintos(Bark *et al.*, 2016; Nassiri *et al.*, 2019).

O carcinoma espinocelular (CEC) é a neoplasia maligna mais comum da gengiva. Por esta razão, a maioria dos estudos que avaliam neoplasias malignas gengivais se restringem a estudar o tratamento, prognóstico e sobrevida do CEC (Du *et al.*, 2019; Nassiri *et al.*, 2019; Obayemi *et al.*, 2019; Yoshida *et al.*, 2018). A

maioria dos casos é diagnosticada em estádios clínicos avançados, o que limita as opções terapêuticas(Bark *et al.*, 2016). Entretanto, além do CEC, existem outras neoplasias malignas, menos frequentes, que também podem acometer a gengiva, tais como as infiltrações leucêmicas, linfomas, sarcomas e metástases (Gambino *et al.*, 2017; Gomez *et al.*, 2000; Hou *et al.*, 2019; Kirschnick *et al.*, 2020; Sahni *et al.*, 2015; Uchiyama *et al.*, 2009).

Outro fator importante é que neoplasias gengivais podem mimetizar doenças periodontais associadas ao biofilme dentário. Há na literatura diversos casos de neoplasias malignas mimetizando doenças periodontais de origem inflamatória e que foram, por muito tempo, tratadas como tal(Bornstein *et al.*, 2018; Gupta *et al.*, 2014; Kim *et al.*, 2012). As neoplasias gengivais malignas são inicialmente assintomáticas, mas com o tempo, frequentemente, apresentam aumento de volume, ulceração, dor, mobilidade e perda dentária ou desadaptação de próteses (Gomez *et al.*, 2000). Metástases gengivais de tumores primários localizados em outros órgãos e sistemas também podem ocorrer. Estudos têm demonstrado que a gengiva é o tecido mole de maior prevalência de metástases orais, sendo os tumores de pulmão, rins, mama e próstata aqueles que usualmente causam metástases orais com maior frequência(Allon *et al.*, 2013; Kirschnick *et al.*, 2020).

Não há estudos que tenham avaliado a prevalência de neoplasias gengivais na população brasileira. Trabalhos publicados têm demonstrado uma ampla variabilidade de lesões, que acometem indivíduos de todas as idades, cujo tratamento pode ser conservador ou agressivo dependendo da natureza, se benigna ou maligna, e do estadiamento da lesão no momento do diagnóstico nos casos de neoplasias malignas(Bark *et al.*, 2016; Dubner e Heller, 1993; Hernández-Ríos *et al.*, 2018; Nassiri *et al.*, 2019; Vasconcelos Carvalho, De *et al.*, 2011). Considerando que muitas neoplasias gengivais se iniciam com uma aparência clínica que muitas vezes lembram processos periodontais induzidos por biofilme dentário(Bornstein *et al.*, 2018; Gupta *et al.*, 2014; Kim *et al.*, 2012), o cirurgião-dentista desempenha um papel primordial na identificação e diagnóstico precoce dessas doenças. Desse modo, tendo em vista a diversidade histológica das

neoplasias gengivais e os danos que estas representam à saúde da população, o objetivo desse estudo colaborativo interinstitucional será avaliar a prevalência de neoplasias gengivais em uma população brasileira.

2 ARTIGO

Artigo: GINGIVAL NEOPLASMS: A MULTICENTER COLLABORATIVE STUDY OF 839 PATIENTS IN BRAZIL

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Conflict of interest

The authors declare that they have no conflict of interest.

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CLINICAL RELEVANCE

Scientific rationale for study: The dentists, particularly periodontists, have a key role in the early diagnosis and management of gingival neoplasms. However, there are few studies evaluating the prevalence and clinicopathological features of gingival neoplasms. Majority of the studies series have evaluated only malignant tumors and are small case series or single case reports.

Principal findings: Most gingival neoplasms were malignant, which appeared more commonly in men as a single ulcer or a red/purple nodule larger than 3 cm in diameter. In about 15% of malignant neoplasms, the lesions were clinically considered to be reactional or of infectious origin.

Practical implications: Gingival malignant neoplasms may mimic inflammatory or reactive lesions. Persistent gingival single ulcers and nodules should be biopsied, and the histopathological analysis is mandatory for diagnosis.

ABSTRACT

Aim: To evaluate the prevalence and clinicopathological features of a large series of gingival neoplasms in Brazil.

Materials and methods: All gingival benign and malignant neoplasms were retrieved from the records of six Oral Pathology Services in Brazil, during a 41-year period. Clinical and demographic data, clinical diagnosis, and histopathological data were collected from the patients' clinical charts. For statistical analysis, the chi-square, median test of independent samples and the *U* Mann-Whitney tests were used, considering a significance of 5%.

Result: From 85,981 oral lesions, 839 (0.97%) were gingival neoplasms. There were 475 (56.5%) males, with a mean age of 54.8 years. Most cases (71.7%) were malignant neoplasms. Nodules (41.7%) and ulcers (39.1%) were the most common clinical appearance for benign and malignant neoplasms, respectively. Squamous cell carcinoma (56.8%) was the most common gingival neoplasm, followed by squamous cell papilloma (19.1%). In 122 (14.5%) malignant neoplasms, the lesions were clinically considered to be inflammatory or of infectious origin. Malignant neoplasms were more common in older men, appeared with larger size, and with a time of complaint shorter than benign neoplasms ($p<0.001$).

Conclusion: Malignant neoplasms, especially squamous cell carcinoma, should be considered in the differential diagnosis of persistent single gingival ulcers.

Keywords: Gingiva; Gingival Neoplasms; Mouth Neoplasms; Gingival Diseases; Prevalence

INTRODUCTION

Although most gingival diseases are of inflammatory origin, resulting from the inflammatory reaction to the accumulation of dental biofilm, several non-plaque-induced gingival diseases (NPIGD) may occur (Palle Holmstrup et al., 2018; Murakami et al., 2018). The American Academy of Periodontics (AAP) and the European Federation of Periodontics (EFP), at the 2017 World Workshop on Periodontal and Peri-Implant Diseases and Conditions, proposed a classification for the NPIGD based on their etiology. Among the diseases classified as NPIGD, there are malignant neoplasms and oral manifestations of systemic diseases, which have high clinical significance (Alblowi & Binmadi, 2018; Hernández-Ríos et al., 2018; P. Holmstrup, 1999). Other diseases classified as NPIGD are genetic/developmental abnormalities, specific bacterial, fungal and viral infections, inflammatory and immune conditions/lesions, reactive processes, endocrine, nutritional and metabolic diseases, traumatic lesions, and gingival pigmentation(Hernández-Ríos et al., 2018; Palle Holmstrup et al., 2018).

The 2017 World Workshop on Periodontal and Peri-Implant Diseases and Conditions presents a more comprehensive and understandable collection of NPIGD. However, the classification and distribution of gingival neoplasms still needs improvement because their important clinical significance. In the current classification, there is no group that includes benign gingival neoplasms, nor the description of gingival metastases and sarcomas. The gingival malignant neoplasms, primary or metastatic, present particular characteristics. They often mimic inflammatory or reactional conditions, and in early stages, they may be misdiagnosed as an inflammatory periodontal condition (Bornstein et al., 2018; Palle Holmstrup et al., 2018; Kim et al., 2012).

The squamous cell carcinoma (SCC) is the most common neoplasm of the gingiva, representing about 10 to 20% of all oral cancers (Bark et al., 2016; Palle Holmstrup et al., 2018). However, in addition to SCC, other neoplasms can affect the gingival tissue, such as benign neoplasms, leukemic infiltrations, lymphomas, and sarcomas (Hernández-Ríos et al., 2018; Li et al., 2021; Uchiyama et al., 2009).

Gingival metastases may also occur. Previous studies have shown that about 50% of the oral soft tissue metastases occur in gingiva (Allon et al., 2013; Kirschnick et al., 2020).

Most studies that assessed the distribution and prevalence of NPIGD included diseases of different etiology, not specifically neoplasms lesions (Gambino et al., 2017; Hernández-Ríos et al., 2018). The dentists, particularly periodontists, has a key role in the early identification and diagnosis of these tumors. Clinicians should keep in mind that neoplasms also occur in the gingiva. Studies evaluating the prevalence and clinicopathological features of gingival neoplasms may be important to warning dentists about these diseases. There are few studies evaluating the prevalence and clinicopathological features of gingival neoplasms. Most series have evaluated only malignant tumors, particularly SCC, or represent small case series or single case reports (Chen et al., 2020; Fitzpatrick et al., 2012, 2013). Thus, the objective of this interinstitutional collaborative study was to evaluate the prevalence and clinicopathological features of a large series of gingival neoplasms in Brazil.

MATERIALS AND METHODS

This study was approved by the Research Ethics Committee of the Piracicaba Dental School, University of Campinas (UNICAMP), Brazil under the protocol 52882621.5.0000.5418, and is in accordance with the Helsinki Declaration.

Gingival benign and malignant neoplasms, with a definitive histopathological diagnosis, were selected from the files of the Oral Pathology Laboratory of the Piracicaba Dental School, University of Campinas (Southeast, Brazil); Oral Pathology Laboratory, Federal University of Pernambuco (Northeast, Brazil); Oral Surgical Pathology Laboratory, Federal University of Bahia (Northeast, Brazil); Oral Pathology Laboratory, School of Dentistry, Federal University of Rio de Janeiro (Southeast, Brazil); Oral Pathology Laboratory, School of Dentistry, Federal University of Rio Grande do Sul (South, Brazil); and Oral Laboratory Pathology, João de Barros Barreto University Hospital, Federal University of Pará (North, Brazil), in the period between 1979 and 2020. Only cases with enough clinical information and histopathological diagnosis were evaluated.

This cross-sectional study followed the STROBE statement. Clinical and demographic data, such as age, sex, ethnicity, location (maxillary, mandibular, posterior, and anterior gingiva), elementary lesion, the color of mucosal surface, time of complaint, tumor size, type of biopsy performed, clinical diagnoses, and histopathological diagnosis were retrieved from the patient's records. All subjects regardless of gender or age, who had sufficiently described clinical data in the charts were included in the study. Non-neoplastic lesions, tumors located on the edentulous alveolar ridge, alveolar mucosa, or floor of the mouth, as well as intraosseous lesions that ruptured cortical bone and involved the gingival tissue, were excluded from the sample. In addition, neoplasms were classified as benign or malignant, primary, metastatic or systemic, according to the WHO Classification of Head and Neck Tumors (El-Naggar et al., 2017).

The data collected were analyzed using the SPSS software (SPSS for windows, version 22, SPSS inc, Chicago, IL, USA). The results were assessed with descriptive statistics, with absolute and relative frequencies distribution. The chi-square (X^2) test was used to analyze the associations between the evaluated variables. To analyze the differences in the medians between age, tumor size, and time of complaint, the median test of independent samples and the *U* Mann-Whitney test were used, considering a significance of 5%. To assess the correlation between clinical and histopathological diagnoses, it was considered that there was an agreement between clinical and histopathological diagnosis in cases in which the final diagnosis was considered in the initial clinical hypothesis. The data were tabulated and expressed in percentages of agreement and non-agreement.

RESULTS

From 85,981 cases of oral lesions diagnosed in the period of study, 839 (0.97%) were gingival neoplasms. There were 475 (56.5%) males and 364 (43.5%) females, with a mean age of 54.8 years (ranging from 1 to 104 years; SD=20.5), being the mean age of 53.9 years (ranging from 4 to 93 years; SD=18.2) for men and 55.9 years (ranging from 1 to 104 years; SD=23.0) for women. In this series, 238 (28.3%) cases were benign tumors and 601 (71.7%) malignant.

Among the benign tumors, the women (56.7%, n=135) were more frequently affected than men (43.3%; n=103). Most cases occurred in patients during the sixth decade of life, totaling 16.0% (n=38) of the patients diagnosed with benign tumors (Table 1). Clinically, the benign tumors mostly appeared as nodules (47.1%; n=112), followed by papules (31.5%; n=75) and exophytic/vegetative lesions (4.6%; n=11). The mean size of lesions was 0.6 cm (ranging from 0.2 cm to 9.0 cm; Q_1-Q_3 =1.20), with a mean time of complaint of 6 months (ranging from 1 to 170 months; Q_1-Q_3 =15.0). The most common location was the mandibular and posterior gingiva, with 140 (58.8%) and 130 (54.6%) cases, respectively. Furthermore, 96 (40.3%) benign tumors exhibited whitish coloration, while 86 (36.1%) showed normal mucosal coloration. In addition, excisional biopsy was the most performed procedure among benign tumors. Other clinical features can be found in Table 2.

Considering the malignant tumors, the men (61.7%; n=371) were more affected than women (38.1%; n=229). Malignant neoplasms were more frequent in older individuals, with the peak of prevalence in people aged 70 years or older (27.4%; n=165). The most common location was the mandibular gingiva (58.6%; n=352), with predilection for the posterior region (54.6%; n=328). The mean time of complaint was 2 months (ranging from 1 to 120 months; Q_1-Q_3=5), with a mean size of 3.0 cm (ranging from 0,2 cm to 10 cm; Q_1-Q_3=3.5) (Table 1). Clinically, most malignant tumors appeared as an ulcer (39.3%, n=236) or nodule (25.5%; n=153). Regarding the color surface, red lesions appeared as the most common (37.3%; n=224), followed by reddish white (17.8%; n=107) and white (11.5%; n=69) lesions. The malignant tumors commonly presented as single lesions (84.5%; n=508), and the incisional biopsy (84.9%; n=510) was the most common clinical procedure for diagnosis (Table 2).

Table 1. Sociodemographic characteristics and location of gingival neoplasms.

Variables	Benign tumors	Malignant tumors	p-value
	n=238 (28.3%)	n=601 (71.7%)	
Gender			
Male	103 (43.3%)	371 (61.7%)	*p*<0.001*
Female	135 (56.7%)	229 (38.1%)	
Not informed	-	1 (0.2%)	
Ethnicity			
White	139 (58.4%)	299 (49.8%)	*p*=0.210
Black	20 (8.4%)	64 (10.6%)	
Brown	25 (10.5%)	81 (13.5%)	
Outros	2 (0.8%)	2 (0.3%)	
Not informed	52 (21.9%)	155 (25.8%)	
Age			
Median	33.00 Q_1-Q_3= 37	60.00 Q_1-Q_3= 21	*p*<0.001*
0-9	23 (9.7%)	1 (0.2%)	
10.19	31 (13.0%)	5 (0.8%)	
20-29	31 (13,0%)	16 (2.7%)	
30-39	33 (13.9%)	39 (6.5%)	
40-49	31 (13.0%)	70 (11.6%)	
50-59	38 (16.0%)	130 (21.6%)	
60-69	30 (12.6%)	159 (26.5%)	
≥70	15 (6.3%)	165 (27.5%)	
Not informed	6 (2.5%)	16 (2,6%)	
Location			
Gingiva, NOS†	18 (7.6%)	60 (10.1%)	*p*=0.378
Maxillary gingiva	80 (33.6%)	188 (31.3%)	
Mandibular gingiva	140 (58.8%)	352 (58.6%)	
Anterior gingiva	59 (24.8%)	85 (14.1%)	*p*=0.005*
Posterior gingiva	130 (54.6%)	328 (54.6%)	
Not informed	49 (20.6)	188 (31.3%)	

*Statistically significant

†NOS – Not otherwise specified

Table 2. Clinical features of gingival tumors.

Variables		Benign tumors	Malignant tumors	p-value
		n=238 (28.3%)	n=601 (71.7%)	
Complaint time (months)	Median	6.00 (Q_1Q_3=15)	2.00 (Q_1-Q_3=5)	*p*<0.001*
Size	Median	0.6 cm (Q_1-Q_3 =1.20)	3.0 cm (Q_1-Q_3=3.5)	*p*<0.001*
Elementary lesion				
	Nodule	112 (47.1%)	153 (25.5%)	*p<0,001*
	Papule	75 (31.5%)	16 (2.7%)	
	Ulcer	1 (0.4%)	236 (39.3%)	
	Exophytic/Vegetative	11 (4.6%)	13 (2.2%)	
	Plaque	3 (1.3%)	32 (5.3%)	
	Verrucous/Papillary	4 (1.7%)	7 (1.2%)	
	Nodule ulcerated	-	29 (4,8)	
	Macule	2 (0.8%)	5 (0.8%)	
	Not informed	30 (12.6%)	110 (18.2%)	
Color of surface				
	Red	26 (10.9%)	224 (37.3%)	*p<0,001*
	White	96 (40.3%)	69 (11.5%)	
	White and red	2 (0.8%)	107 (17.8%)	
	Purple	3 (1.3%)	20 (3.3%)	
	Brown/black	1 (0.4%)	12 (2.0%)	
	Yellow	5 (2.1%)	13 (2.2%)	
	Blue	–	3 (0.5%)	
	Normal in color	86 (36.1%)	19 (3.2%)	
	Not informed	19 (8.1%)	134 (22.2)	
Number				
	Single	217 (91.2%)	508 (84.5%)	*p*=0.116
	Multiple	13 (5.5%)	50 (8.3%)	
	Not informed	8 (3.3%)	43 (7.2%)	
Type of biopsy				
	Incisional	46 (19.3%)	510 (84.9%)	*p*<0.001*
	Excisional	175 (73.5%)	38 (6.3%)	
	Not informed	17 (7.2%)	53 (8.8%)	

**Statistically significant*

The histological types and the number of each diagnosed tumor are described in Table 3. The most frequent benign neoplasm was the squamous cell papilloma (67.8%; n=161), followed by peripheral odontogenic fibroma (7.8%; n=18), neurofibroma (6.7%; n=16), lipoma (5.1%; n=12), and hemangioma (5.1%; n=12). Considering the malignant tumors, the SCC was the most diagnosed neoplasm (79.5%; n=478), followed by Non-Hodgkin lymphomas (4.2%; n=25). In addition, gingival metastases and Kaposi's Sarcoma were diagnosed in 16 cases each (2.7%; n=16). Other gingival malignant neoplasms were also diagnosed, such as verrucous carcinoma (2.2%; n=13), malignant spindle cell neoplasm, not otherwise specified (NOS) (1.7%; n=10), Langerhans cells histiocytosis (1%; n=6), and undifferentiated carcinoma (1%; n=6). Hematolymphoid malignant neoplasms and metastases were also diagnosed (Table 3).

The SCC presented mostly as an ulcerated (56.1%, n=222) and red (49.7%, n=182) lesion, with a size greater than 3 cm in 41% (n=120) of the cases (Fig. 1). The tumor was more frequent in males (62.3%; n=297) than in females (37.7%; n=180), and predominantly in individuals aged 70 years or older (32.5%; n=152). However, 18 cases (3.8%) occurred in patients younger than 40 years of age. Non-Hodgkin lymphomas, on the other hand, appeared more frequently as a nodule (81.0%; n=17) larger than 2 cm (53.3%; n=8), showing a reddish color (34.8%, n= 8). The lymphomas were more common in men (80.8%; n=21) aged over 50 years (46.2%; n=12). Concerning to the metastases, most tumors appeared as a reddish (50.0%; n=5) nodule (83.3%; n=10) in women (56.3%; n=9), aged over 40 years (71.4%; n=10). Based on the frequency of clinical features observed in this series, a drew of main clinical profile of the most prevalent malignant tumors is summarized in Table 4.

There was correlation between the clinical and histopathological diagnoses in 555 (66.0%) cases, but in 231 (27.5%) the clinical diagnosis was not confirmed by histopathological examination. In 55 (6.5%) cases this information was not available. Among the benign tumors, the success rate of the clinical hypothesis was 61.8% (n=147), while the percentage of hypotheses that were not confirmed in the

histopathological examination was 33.2% (n=79). In malignant neoplasms, the correlation between clinical and histopathological diagnosis was 67.6% (n=407), but in 25.2% (n=152) of the cases no correlation was observed. Among the hypotheses listed, reactional lesions, benign and malignant tumors were the most hypothesized diseases. In 122 (14.5%) cases of malignant neoplasms, the lesions were clinically considered to be reactional or of infectious origin.

Statistical analysis revealed that malignant neoplasms were more common in men ($p<0.001$) and the median age was higher in patients with gingiva cancer ($p<0.001$) when compared to the benign tumors, which affected more commonly younger individuals ($p<0.001$). Regarding to the time of duration of the lesions, patients with malignant neoplasms had a lower median time of complaint than those with benign tumors ($p<0.001$). The malignant tumors presented larger size than benign ($p<0.001$), and the incisional biopsy was the most common clinical procedure for diagnosis of malignant neoplasms ($p<0.001$). In contrast, the excisional biopsy was more frequent in benign tumors ($p<0.001$). Furthermore, the cases with clinical diagnoses of malignant lesions were more frequently submitted to incisional biopsy, while hypotheses involving benign lesions were more commonly excised ($p<0.001$). For both malignant and benign neoplasms, the posterior mandibular gingiva was the most common site ($p=0.005$).

Fig. 1

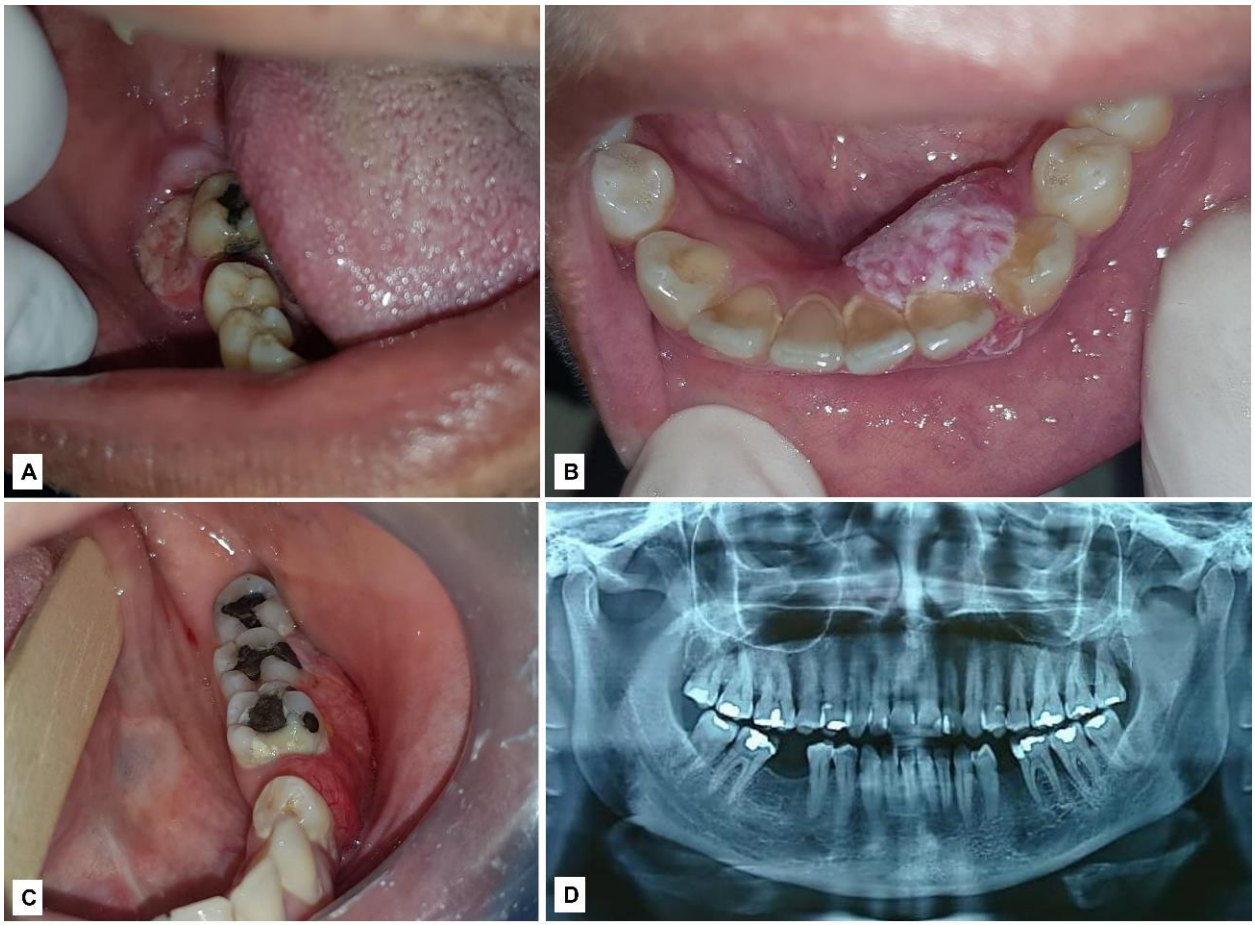

Figure 1 – Different clinical presentation of gingival squamous cell carcinoma. A - A 53-year-old male patient, with an ulcerated lesion with indurated and raised margins in the gingiva of right mandibular second molar. B- A 28-year-old female patient with a reddish-white nodule, with papillary surface, involving the buccal and lingual mandibular anterior gingiva at right. C- A 42-year-old female patient with a reddish swelling in the left posterior mandibular gingiva, appearing with a granular surface and focal areas of telangiectasia. The first molar presented mobility and the patient was under treatment for periodontitis. D - The same patient of patient in C. Panoramic radiograph revealed a mandibular diffuse radiolucency in the region of the left first molar, which caused alveolar bone loss.

Table 3. Benign and malignant neoplasms diagnosed in the sample.

Benign neoplasms	n (%)	Malignant neoplasms	n (%)
Squamous cell papilloma	161 (67.8)	Squamous cell carcinoma	478 (79.5)
Peripheral odontogenic fibroma	18 (7.8)	Non-Hodgkin lymphoma	25 (4.2)
Neurofibroma	16 (6.7)	Metastatic tumors	16 (2.7)
Lipoma	12 (5.1)	Kaposi's sarcoma	16 (2.7)
Hemangioma	12 (5.1)	Verrucous squamous cell carcinoma	13 (2.1)
Schwannoma	4 (1.8)	Malignant spindle cell neoplasm, NOS†	10 (1.6)
Myofibroma	3 (1.3)	Melanoma	7 (1.1)
Verrucous dyskeratoma	2 (0.8)	Undifferentiated carcinoma / Malignant epithelial neoplasm	6 (1.0)
Pleomorphic adenoma	2 (0.8)	Langerhans cell histiocytosis	6 (1.0)
Congenital epulis of the newborn	2 (0.8)	Undifferentiated malignant neoplasm	3 (0.5)
Leiomyoma	2 (0.8)	Carcinoma in situ	2 (0.3)
Peripheral benign neoplasm of odontogenic origin, NOS*	1 (0.4)	Angiosarcoma	2 (0.3)
Fibrous histiocytoma	1 (0.4)	Granulocytic sarcoma	2 (0.3)
Peripheral complex odontoma	1 (0.4)	Large cell malignant neoplasm	2 (0.3)
		Acinic cell carcinoma	2 (0.3)
		Rhabdomyosarcoma	2 (0.3)
		Cuniculatum carcinoma	1 (0.2)
		Basaloid squamous cell carcinoma	1 (0.2)
		Alveolar soft tissue sarcoma	1 (0.2)
		Lymphocytic leukemia	1 (0.2)
		Plexiform histiocytic tumor	1 (0.2)
		Adenocarcinoma, NOS*	1 (0.2)

		Polymorphous adenocarcinoma	1 (0.2)
		Mucoepidermoid carcinoma	1 (0.2)
		Adenoid cystic carcinoma	1 (0.2)
Total	238 (100)	Total	601 (100)

†NOS – Not otherwise specified

DISCUSSION

The gingiva is an easily accessible site, characterized by mucous tissue with a thin layer of epithelium and connective tissue, which is directly supported on the bone. It represents a relatively uncommon site for the development of neoplasms (Bark et al., 2016; Cady & Catly, 1969). In this series, after reviewing 85,981 histopathological reports, we identified 839 cases of gingival neoplasms, which corresponds to 0.97% of all histopathological reports retrieved. To the best of our knowledge, this is the second largest series of gingival neoplasms reported in the English-language literature (Li et al., 2021). In this study, the gingival neoplasms were more common in males, with a mean age of 54.85 years. It is noteworthy to highlight that the higher prevalence in men is associated with the higher prevalence of malignant tumors in this sample, which occurred significantly more in men. On the other hand, benign neoplasms were more common in women.

Several studies were dedicated to survey all gingival biopsies in a specific population, but none reviewed only gingival neoplasms (Carbone et al., 2012; Gambino et al., 2017; Hernández-Ríos et al., 2018; Li et al., 2021). These studies showed that most cases consisted of non-neoplastic lesions. A survey of 788 samples revealed that the clinical appearances that most motivated the gingival biopsies were exophytic lesions and/or swellings (45%), changes in the color of the mucosa (39%) and loss of substance (16%) (Gambino et al., 2017). In the present study, nodules, papules, and exophytic lesions also represented the clinical changes

most biopsied in the benign neoplasms. In malignant tumors, the most frequent elementary lesion was an ulcer. The most common location was the posterior mandibular gingiva for both benign and malignant tumors (Effiom et al., 2008; Fitzpatrick et al., 2012; Li et al., 2021; Torres-Domingo et al., 2008). The tumors also appeared as single lesions. The benign neoplasms were more often submitted to an excisional biopsy, whereas the incisional biopsy was commonly performed in malignant tumors, as it is usually preconized by literature (Avon and Klieb, 2012). Malignant neoplasms were significantly larger than benign tumors. Tumor size influenced the choice of biopsy type. Lesions larger than 3 cm, common in malignant tumors, were more frequently submitted to incisional biopsy (Frydrych et al., 2010; Nassiri et al., 2019). The clinical diagnosis also influenced the choice of the clinical procedure for diagnosis. Incisional and excisional biopsies were more common in malignant and benign neoplasms, respectively, as recommended by literature (Logan & Goss, 2010; Shanti et al., 2020).

The benign neoplasms often showed whitish or normal coloration of the lesion surface, probably because most cases were squamous cell papilloma. Li et al. (2021) also found the squamous cell papilloma as the most common benign tumor occurring on gingiva. This lesion usually appears as a whitish papule or nodule, with papillary and verrucous surface (Andrade et al., 2019; Avon & Klieb, 2012; Yeom et al., 2022). The most prevalent benign tumor in our sample after squamous papilloma was neurofibroma, lipoma, and hemangioma.

The SCC was the most common malignant gingival neoplasm, similar to found in other series (Dhanuthai et al., 2018; Gambino et al., 2017; Hernández-Ríos et al., 2018; Li et al., 2021). In our study, SCC commonly appeared as a gingival ulcerated lesion in men aged over 50 years. Another series found similar clinical features, but in patients with a mean age of 41 years (Effiom et al., 2008). In contrast, Fitzpatrick et al. (2012) reported exophytic and verrucous lesions as the most often clinical presentation for gingival SCC in patients with a lower mean age. Most patients developed a SCC in the mandibular gingiva, similar to our findings (Effiom et al., 2008; Fitzpatrick et al., 2012). Regarding the risk factors, gingival SCC seems

to be less associated with tobacco and alcohol consumption when compared to other oral sites, mainly tongue and floor of the mouth. A survey showed that SCC of oral tongue is 38 times more likely to be diagnosed in smokers when compared to gingival tumors (Barasch et al., 1994). In addition, another study revealed that the percentage of smokers is relatively lower for gingival SCC when compared to SCC of the tongue and floor of the mouth (Schmidt et al., 2004). Another survey found that 52.5% of patients with gingival SCC were non-smokers (Nassiri et al., 2019). In the current series, information on habits and risk factors was not available.

Other malignant tumors can occur in the gingival tissue, such as leukemic infiltrations, lymphomas, sarcomas, Langerhans cell histiocytosis, melanomas, and metastases (Dhanuthai et al., 2018), as observed in the present study. Kaposi's sarcoma (KS) and plasmablastic lymphoma (PBL) are malignant neoplasms that frequently occur in immunocompromised patients, particularly HIV-associated immunosuppression (Yarchoan and Uldrick, 2018). KS is a vascular neoplasm of endothelial origin that affects mucocutaneous tissues, caused by human herpesvirus (HHV-8) infection. Oral manifestations of KS occur in all variants, but it is predominantly seen in HIV-infected individuals (Fatahzadeh & Schwartz, 2013; Pantanowitz et al., 2013). In the present study, four patients had HIV infection at the time of diagnosis of neoplasia. The cases were treated with antiretroviral therapy combined with chemotherapy. The PBL is an uncommon and aggressive form of diffuse large B-cell lymphoma characterized by the proliferation of immunoblasts and plasmablasts, strongly associated with EBV infection. Most cases occur in immunocompromised patients associated with HIV infection (Fonseca et al., 2021; Yarchoan & Uldrick, 2018). PBL was initially described in oral cavity and may be the first sign of HIV-infection (Flaitz et al., 2002; Zizzo et al., 2020). In this series, one patient was identified with HIV-infection after the diagnosis of PBL. Although the emergence of antiretroviral therapy has decreased considerably the incidence of neoplasms linked to AIDS, when faced with these neoplasms, particularly PBL and KS, the possibility of HIV infection should be investigated (Yarchoan and Uldrick, 2018).

Table 4. Main clinical profile of most common gingival malignant tumors diagnosed in the sample.

Malignant neoplasms	N	Most common elementary lesion	Color alteration	Time of complaint	Gender	Age
Squamous cell carcinoma	478	Ulcer	Red lesion	1 month	Male	6th to 8th decades of life
Sarcomas	31	Nodule	Purple lesion	1 month	Male	2nd and 3rd decades of life
Hematolymphoid neoplasms						
Plasmablastic lymphoma	2					
Diffuse CD20 positive large B cell lymphoma	1					
Diffuse large B-cell lymphoma, NOS	2					
Non-Hodgkin's lymphoma	11	Nodule	Purple lesion	1 month	Male	5th and 6th decades of life
Anaplastic large cell lymphoma	2					
Burkitt's Lymphoma	5					
Plasmacytoma	2					
Total	25					
Metastases						
Metastatic carcinoma†	3					
Metastatic neuroendocrine tumor†	3					
Colorectal	4					
Kidney	3	Nodule	Red lesion	1 month	Female	4th and 6th decades of life
Liver	2					
Breast	1					
Total	16					

†The site of primary tumor was not available

Overall, metastasis of malignant tumors to the oral cavity is rare and usually indicates the possibility of disseminated disease linked to a worse prognosis (Allon et al., 2013; Hirshberg et al., 2008). In our study, 16 cases of gingival metastases were described. A recent systematic review revealed that the gingiva is the most common site for oral soft tissue metastases (Kirschnick et al., 2020). Based on the evidence that metastasis is a highly regulated and specific process, some authors hypothesize that some local factors in the gingival tissue, such as chronic inflammation, could favor the attraction of circulating tumor cells to the gingiva (Allon et al., 2013).

In addition, they suggest that there is a significant association between the presence of teeth and the occurrence of gingival metastasis, because 80% of the cases occurred in dentate patients. Only one-third of edentulous patients with oral metastases presented gingival lesions. In these patients, the metastases were located in other sites of the oral cavity, such as the tongue (Allon et al., 2013). For Hirshberget al. (2008), malignant cells can be attracted through the extensive network of capillaries that form the chronic gingival inflammation. This microenvironment, present in chronically inflamed gingiva, can favor the progression of metastatic cells, since in the past, the chronic inflammation has been associated with tumorigenesis processes, such as cell transformation, promotion, survival, proliferation, and invasion, as well as angiogenesis and metastasis (Aggarwal et al., 2006; Hirshberg et al., 2008; Mantovani, 2005).

Regarding the clinical diagnoses listed by the clinicians, lesions of different etiologies were hypothesized. Some non-neoplastic lesions that constitute the differential diagnosis of gingival tumors, such as pyogenic granuloma, peripheral giant cell granuloma, peripheral ossifying fibroma, and infectious diseases, were considered, as observed in other published series (Fitzpatrick et al., 2012; Gambino et al., 2017). In the present study, although 66.0% of the cases had the clinical diagnosis confirmed after histopathological analysis, no correlation between the clinical and microscopic diagnoses was observed in 27.5% of the cases. The differential diagnosis of gingival tumors is challenging because the clinical

presentation often mimic indolent and non-neoplastic lesions (Bornstein et al., 2018; Brooks et al., 2019; Gupta et al., 2014; Kim et al., 2012). Therefore, in cases of persistent lesions that do not heal after plaque removal or after periodontal standard therapy is instituted, the clinician should perform a biopsy and send the specimen for histopathological analysis.

The present study has several strengths, including the second-largest series of gingival neoplasms already reported, which discusses the clinical features and differential diagnosis. However, some limitations need to be considered, mainly because it represents a retrospective study that evaluated lesions located on a limiting site, as the gingival tissue. The gingiva is a scarce tissue when compared to other oral sites. For this reason, although the study had rigorous inclusion criteria, some cases included in this study could be sited on the edentulous alveolar ridge because the location recorded may have been incorrect. On the contrary, cases of gingival neoplasms could have been missed. The tumors tend to grow and invade contiguous anatomical sites, such as floor of the mouth, palate, and the buccal mucous fold. This fact could also lead to an incorrect recording of the exact location of the lesion.

In conclusion, malignant gingival tumors are notably more frequent than benign, and usually appear as an ulcer or a reddish/purple nodule, with large dimensions, and in older individuals. Nevertheless, gingival cancers also occur in young patients, including SCC. Thus, dentists should keep in mind that malignant neoplasms can also occur in gingiva. Malignant neoplasms should be considered in the differential diagnosis of a gingival ulcerated lesion or a red/purple nodule with short-term growth, without evidence of healing. In these cases, an incisional biopsy must be performed to prompt diagnosis and treatment.

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3 CONCLUSÃO

Este estudo demonstrou que neoplasias, apesar de raras, podem acometer o tecido gengival. Em nossa amostra, tumores benignos em gengiva tiveram menor frequência do que os tumores malignos, este resultado sugere que a gengiva é um sítio raro para o desenvolvimento de tumores benignos, sendo o papiloma escamoso o tipo histológico mais comum. Os tumores malignos foram mais frequentes nessa amostra. O carcinoma espinocelular foi o tumor mais comum e apresentou-se tipicamente como uma úlcera única, maior que 3 cm em sua maior extensão, sendo submetida com mais frequência a biópsia incisional. Devido ao fato dos tumores gengivais mimetizarem doenças de outras origens etiológicas que mais frequentemente acometem o tecido gengival, lesões gengivais ulceradas ou nodulares que apresentem alterações de coloração ou superfície, cuja resolução falhe após terapia periodontal convencional e conservadora, devem ser biopsiadas para correto diagnóstico e tratamento da doença.

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ANEXOS

Anexo 1 – Parecer do Comitê de Ética da Faculdade de odontologia de Piracicaba

UNICAMP - FACULDADE DE ODONTOLOGIA DE PIRACICABA DA UNIVERSIDADE DE CAMPINAS - FOP/UNICAMP

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: NEOPLASIAS GENGIVAIS: ESTUDO COLABORATIVO INTERINSTITUCIONAL NO BRASIL

Pesquisador: Êder Gerardo dos Santos Leite

Área Temática:

Versão: 2

CAAE: 52882621.5.0000.5418

Instituição Proponente: Faculdade de Odontologia de Piracicaba - Unicamp

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.096.595

Apresentação do Projeto:

O parecer inicial é elaborado com base na transcrição editada do conteúdo do registro do protocolo na Plataforma Brasil e dos arquivos anexados à Plataforma Brasil. Os pareceres de retorno, emendas e notificações são elaborados a partir do último parecer e dos dados e arquivos da última versão apresentada. A EQUIPE DE PESQUISA citada na capa do projeto de pesquisa inclui, em ordem alfabética, exceto pesquisador responsável, ÉDER GERARDO DOS SANTOS LEITE (Cirurgião - Dentista, Mestrando no PPG em Estomatopatologia da FOP-UNICAMP, Pesquisador responsável), ÁGUIDA CRISTINA GOMES HENRIQUES (Cirurgiã Dentista, Docente da Universidade Federal da Bahia), DANYEL ELIAS DA CRUZ PEREZ (Cirurgião Dentista, Docente da Universidade Federal de Pernambuco e do PPG em Estomatopatologia da FOP-UNICAMP), FÁBIO RAMÔA PIRES (Cirurgião Dentista, Docente da Faculdade de Odontologia da Universidade do Estado do Rio de Janeiro), JEAN NUNES DOS SANTOS (Cirurgião Dentista, Docente da Universidade Federal da Bahia), JUREMA FREIRE LISBOA DE CASTRO (Cirurgiã Dentista, Docente da área de Patologia Oral da Universidade Federal de Pernambuco), MARIO JOSÉ ROMAÑACH GONZALEZ SOBRINHO (Cirurgião Dentista, Docente da Faculdade de Odontologia da Universidade Federal do Rio de Janeiro), PABLO AGUSTIN VARGAS (Cirurgião Dentista, Docente da FOP-UNICAMP), PAULO ROGERIO FERRETI BONAN (Cirurgião Dentista,

		17:40:44	Santos Leite	
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Situação do Parecer:
Aprovado

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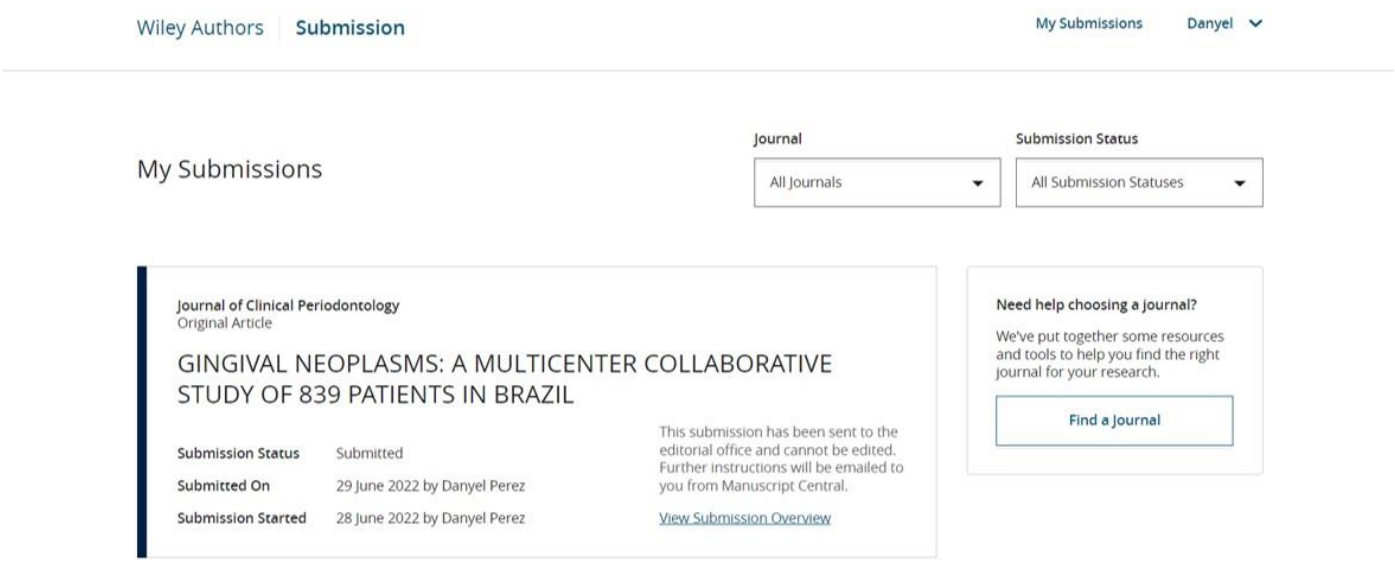
Bairro: Areião **CEP:** 13.414-903
UF: SP **Município:** PIRACICABA
Telefone: (19)2106-5349 **Fax:** (19)2106-5349 **E-mail:** cep@fop.unicamp.br

Não

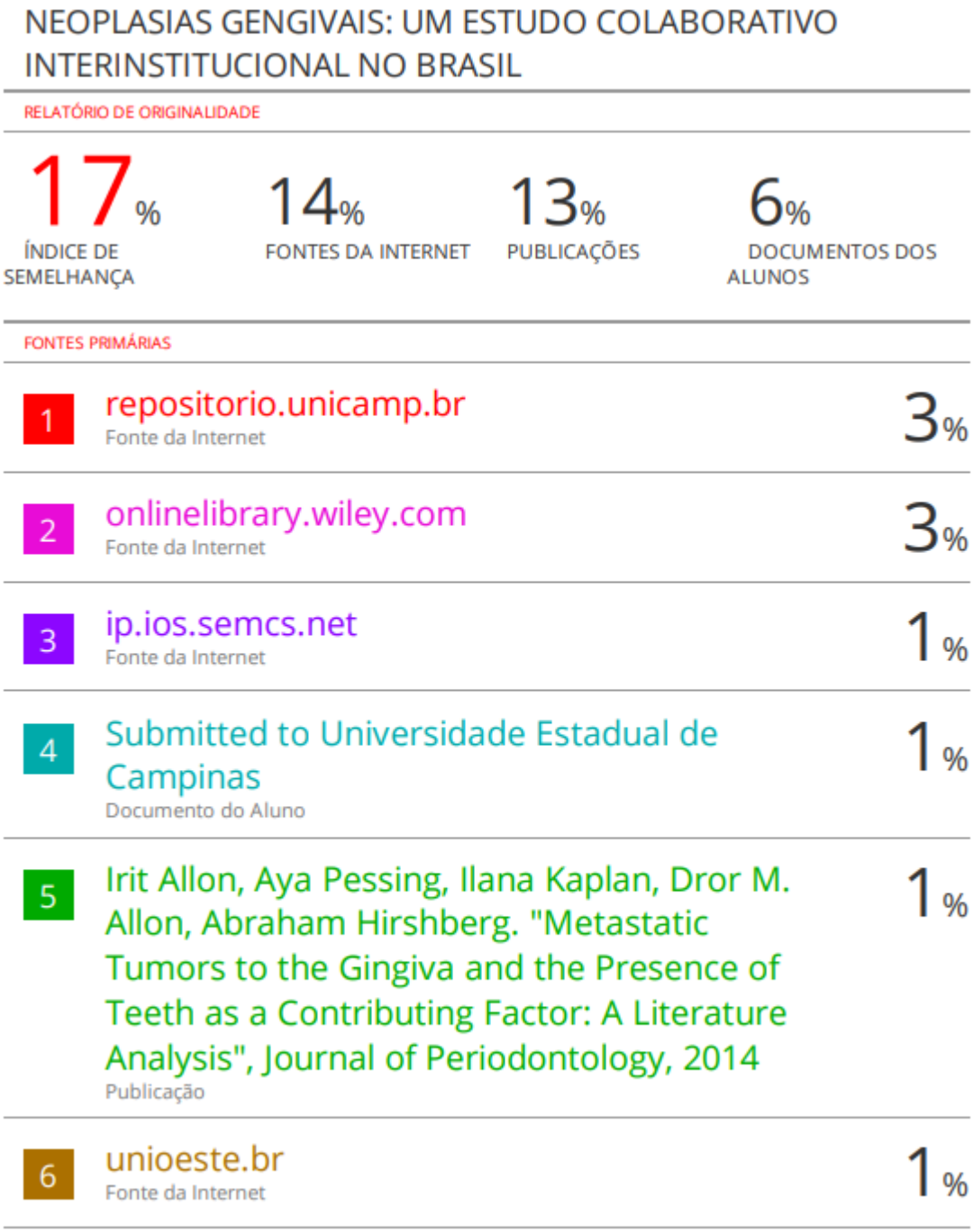
PIRACICABA, 10 de Novembro de 2021

Assinado por:
jacks jorge junior
(Coordenador(a))

Anexo 2 - Comprovante de submissão do artigo no periódico Journal of clinical periodontology.



Anexo 3 – Verificação de originalidade e prevenção de plágio



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