UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE
PIRACICABA

JOHN LENNON SILVA CUNHA

ESTUDO COLABORATIVO INTERNACIONAL DE TUMORES DE GLÂNDULAS SALIVARES: UMA ANÁLISE CLINICOPATOLÓGICA E IMUNOHISTOQUÍMICA

INTERNATIONAL COLLABORATIVE STUDY OF SALIVARY GLAND TUMORS:
A CLINICOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL ANALYSIS

Piracicaba

2021

JOHN LENNON SILVA CUNHA

ESTUDO COLABORATIVO INTERNACIONAL DE TUMORES DE GLÂNDULAS SALIVARES: UMA ANÁLISE CLINICOPATOLÓGICA E IMUNOHISTOQUÍMICA

INTERNATIONAL COLLABORATIVE STUDY OF SALIVARY GLAND TUMORS: A CLINICOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL ANALYSIS

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. Oslei Paes de Almeida
Coorientador: Prof. Dr. Ciro Dantas Soares

ESTE EXEMPLAR CORRESPONDE À VERSÃO FINAL DA DISSERTAÇÃO DEFENDIDA PELO ALUNO JOHN LENNON SILVA CUNHA E ORIENTADA PELO PROF. DR. OSLEI PAES DE ALMEIDA.

Piracicaba

2021

Ficha catalográfica
Universidade Estadual de Campinas
Biblioteca da Faculdade de Odontologia de Piracicaba
Marilene Girello - CRB 8/6159

C914e

Cunha, John Lennon Silva, 1991-
Estudo colaborativo internacional de tumores de glândulas salivares : uma análise clinicopatológica e imunohistoquímica / John Lennon Silva Cunha. – Piracicaba, SP : [s.n.], 2021.

Orientador: Oslei Paes de Almeida.
Coorientador: Ciro Dantas Soares.
Dissertação (mestrado) – Universidade Estadual de Campinas, Faculdade de Odontologia de Piracicaba.

1. Epidemiologia. 2. Neoplasias das glândulas salivares. I. Almeida, Oslei Paes de, 1948-. II. Soares, Ciro Dantas, 1990-. III. Universidade Estadual de Campinas. Faculdade de Odontologia de Piracicaba. IV. Título.

Informações para Biblioteca Digital

Título em outro idioma: International collaborative study of salivary gland tumors : a clinicopathological and immunohistochemical analysis
Palavras-chave em inglês:
Epidemiology
Salivary gland neoplasms
Área de concentração: Patologia
Titulação: Mestre em Estomatopatologia
Banca examinadora:
Ciro Dantas Soares [Coorientador]
Bruno Augusto Benevenuto de Andrade
Jacks Jorge Junior
Data de defesa: 24-02-2021
Programa de Pós-Graduação: Estomatopatologia

Identificação e informações acadêmicas do(a) aluno(a)
- ORCID do autor: https://orcid.org/0000-0002-0679-8485
- Currículo Lattes do autor: http://lattes.cnpq.br/4810420348125574

UNIVERSIDADE ESTADUAL DE CAMPINAS
Faculdade de Odontologia de Piracicaba

A Comissão Julgadora dos trabalhos de Defesa de Dissertação de Mestrado, em sessão pública realizada em 24 de fevereiro de 2021, considerou o candidato JOHN LENNON SILVA CUNHA aprovado.

PROF. DR. CIRO DANTAS SOARES

PROF. DR. BRUNO AUGUSTO BENEVENUTO DE ANDRADE

PROF. DR. JACKS JORGE JUNIOR

A Ata da defesa, assinada pelos membros da Comissão Examinadora, consta no SIGA/Sistema de Fluxo de Dissertação/Tese e na Secretaria do Programa da Unidade.

AGRADECIMENTOS

À Universidade Estadual de Campinas, na pessoa do Magnífico Reitor, Prof. Dr. Marcelo Knobel.

À Faculdade de Odontologia de Piracicaba, na pessoa de seu Diretor, Prof. Dr. Francisco Haiter Neto e seu Diretor Associado, Prof. Dr. Flávio Henrique Baggio Aguiar.

À Profa. Dra. Karina Gonzales Silvério Ruiz, Coordenadora Geral da Pós-Graduação da Faculdade de Odontologia de Piracicaba.

Ao Coordenador do Programa de Pós-Graduação em Estomatopatologia, Prof. Dr. Pablo Agustin Vargas.

O presente trabalho foi realizado com apoio da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Código de Financiamento 001. Agradecemos todo apoio financeiro da instituição citada.

AGRADECIMENTOS ESPECIAIS

Primeiramente agradeço a Deus por estar comigo em todos os momentos, sempre me guiando e iluminando minhas decisões, me confortando nas horas difíceis e me fortalecendo para continuar seguindo sempre em frente.

Quero agradecer também aos meus pais, em especial a minha mamãe, meu porto seguro, que é minha maior professora e exemplo na vida, pelo extraordinário exemplo de amor, luta, dedicação e determinação. Obrigado por me ensinar a persistir, a desdobrar, a não pautar as minhas decisões por conquistas materiais e por me preparar para ser do tamanho dos sonhos que tenho. Obrigado por se manter presente em todos os momentos. Se hoje estou aqui é porque você acreditou em mim e caminhou ao meu lado, mesmo estando a milhares de quilômetros de distância. Te amo!

A minha irmã, meus avós e familiares por todo cuidado, atenção, e por estarem sempre torcendo por mim, estivessem perto ou longe. Que permaneçamos sempre unidos, protegendo e fortalecendo uns aos outros. Amo vocês!

Aos meu orientador, Prof. Oslei Paes de Almeida por ter me concedido a honra de aprender patologia, uma das minhas maiores paixões, com um grande ser humano como você e em um centro como a FOP. Ao Ciro Dantas Soares pela compreensão, parceria e toda preocupação e responsabilidade em fazer desse percurso o mais tranquilo possível. Serei sempre muito grato por todas as oportunidades que vocês me proporcionaram até aqui.

Aproveito também para agradecer a todos os professores do programa de pós-graduação em Estomatopatologia em especial ao Prof. Alan Roger, Prof. Márcio Lopes, Prof. Jacks e Prof. Pablo Vargas.

Não poderia deixar de agradecer ao Prof. Bruno Benevenuto, que por diversos momentos acompanhou de perto minha trajetória no mestrado e se tornou um grande amigo do qual admiro muito. Obrigado por ter me dado a oportunidade e a honra de aprender tanto com você. Gostaria de estender os meus mais sinceros agradecimentos a toda equipe da UFRJ (Mário Romañach, Aline Abrahão, e Michelle Agostini) pela parceria durante o mestrado e por fazerem um trabalho tão bonito no Rio de Janeiro e servirem de inspiração para todos. Obrigado por tudo!

Aos meus amigos de sempre, por se fazerem presentes na minha vida mesmo estando a quilômetros de distância. Obrigado pelo companheirismo, amizade, e por todo carinho e confiança que vocês depositam em mim todos os dias. Rose Nely, Saygo, Bruna, Ivan, Júlia, Matheus, Emerson, Ademir, André e Samuca, amo vocês! Obrigado por tudo!

Ao meus dois maiores mestres e referência na docência e na vida, Ricardo Albuquerque e Sílvia Sousa, pela dedicação, paciência, confiança e, principalmente, por todos os ensinamentos ao longo desses anos. Sou muito grato por ter vocês na minha vida, e de poder me inspirar diariamente no ser humano que vocês são. Obrigado por transformar a minha maneira de ver o mundo e por torcerem tanto por mim. É alguém como vocês que quero me tornar.

Por fim, gostaria de agradecer a todos os colegas de pós-graduação que compartilharam comigo tantos bons momentos. Em especial, a Celeste Sanchez Romero, pela parceria na vida acadêmica, por ter me recebido tão bem no início dessa minha nova jornada aqui em Piracicaba e por todos os valiosos conselhos.

RESUMO

Os tumores de glândulas salivares (TGS) correspondem a um grupo heterogêneo de lesões com comportamentos biológicos variáveis. O presente estudo teve como objetivo determinar a distribuição e os achados demográficos dos TGS em quatro centros de patologia da Região Nordeste do Brasil (Aracaju, Sergipe) e um centro de patologia bucal no México. Todos os casos foram revisados morfologicamente e dados clínicos foram coletados. Adicionalmente, foi realizado um estudo clínico-patológico e imunohistoquímico de 39 novos casos de carcinomas ex-adenomas pleomórficos (CEXAP) acometendo as glândulas salivares menores. Um total de 588 casos de TGS foram diagnosticados entre 2006 e 2016 nos quatro serviços de patologia no estado de Sergipe (Brasil) e 164 casos em um centro de patologia oral no México (2000-2019). No Brasil, 470 (79,9%) tumores foram benignos e 118 (20,1%) malignos. A maioria dos pacientes eram do sexo feminino (n=328, 55,8%). As glândulas salivares maiores foram mais acometidas do que as glândulas salivares menores (69,5% vs. 30,5%). O adenoma pleomórfico (n=419, 71,3%) e o carcinoma mucoepidermóide (n=29, 4,9%) foram os tumores benignos e malignos mais frequentes, respectivamente. Além disso, os tumores benignos e malignos ocorreram com maior frequência na glândula parótida (n= 300, 51%, p <0,05). No México, a maioria dos tumores também foram benignos (n=110, 67,1%) e acometiam principalmente pacientes do sexo feminino (n=100, 61,0%). Contudo, as glândulas salivares menores foram mais acometidas do que as glândulas salivares maiores (68,9% vs. 25,6%). O palato (n=67, 40,9%) foi o sítio anatômico mais comum, seguido pela glândula parótida (n=37, 22,6%), lábios (n=16, 9,8%) e mucosa jugal (n=14, 8,5%). O adenoma pleomórfico (n = 88; 80,0%) e o carcinoma mucoepidermóide (n=16, 29,6%) também foram os tumores benignos e malignos mais frequentes, respectivamente. Adicionalmente, 39 casos de CXPA foram coletados de 6 centros de patologia Latino-americanos. Destes, 22 (56,4%) eram mulheres e 17 (43,6%) homens, com idades variando de 19 a 81 anos (média de 45 anos). A maioria dos tumores acometeu o palato (n=24, 61,5%), seguido pela mucosa jugal (n=9, 23,1%). Histologicamente, o carcinoma mioepitelial foi o subtipo mais comum (n=13, 33,3%), seguido por adenocarcinoma sem outra especificação (n=10, 25,6%). Além disso, foram revisados 561 casos de adenomas pleomórficos de glândulas salivares menores. Após reavaliação microscópica e estudos imunohistoquímicos, 10 casos (1,7%) foram reclassificados como CEXAP em estágios iniciais, representando 25,6% dos casos de CXPA relatados. Alto índice proliferativo celular evidenciado por meio da marcação nuclear do Ki-67 e expressão de p53 foram úteis na identificação das áreas malignas. Os presentes dados confirmam que o adenoma pleomórfico e o carcinoma mucoepidermóide são os TGS benignos e malignos mais comuns. Contudo, é importante considerar que as diferenças nos subtipos de tumor podem ser influenciadas pelo tipo de centro onde os estudos foram conduzidos (patologia bucal vs. médica). Adenomas pleomórficos das glândulas salivares menores devem ser analisados morfologicamente com cautela. Em casos duvidosos, a avaliação do índice proliferativo celular e da expressão de p53 é recomendada para diferenciar CEXAPs de adenomas pleomórficos, principalmente CEXAPs em estágios iniciais.

Palavras-chaves: Epidemiologia. Neoplasias de glândulas salivares. Patologia de cabeça e pescoço.

ABSTRACT

Salivary gland tumors (SGT) correspond to a heterogeneous group of lesions with variable biological behaviors. The present study aimed to determine the distribution and demographic findings of SGT in four pathology centers in the Northeast region of Brazil (Aracaju, Sergipe) and one oral pathology center in Mexico. All cases were morphologically reviewed, and clinical data were collected. Additionally, a clinical-pathological and immunohistochemical study of 39 new cases of carcinomas ex-pleomorphic adenomas (CXPA) affecting the minor salivary glands was performed. A total of 588 cases of SGT were diagnosed between 2006 and 2016 in the four pathology services in the state of Sergipe (Brazil) and 164 cases in an oral pathology center in Mexico (2000-2019). In Brazil, 470 (79.9%) tumors were benign and 118 (20.1%) malignant. Most patients were female (n = 328, 55.8%). The major salivary glands were affected more than the minor salivary glands (69.5% vs. 30.5%). Pleomorphic adenoma (n = 419, 71.3%) and mucoepidermoid carcinoma (n = 29, 4.9%) were the most frequent benign and malignant tumors, respectively. In addition, benign and malignant tumors occurred more frequently in the parotid gland (n = 300.51%, p <0.05). Similarly, in Mexico, most tumors were also benign (n = 110, 67.1%) and affected mainly female patients (n = 100, 61.0%). However, the minor salivary glands were more affected than the major salivary glands (68.9% vs. 25.6%). The palate (n = 67, 40.9%) was the most affected anatomical site, followed by the parotid gland (n = 37, 22.6%), lips (n = 16, 9.8%) and buccal mucosa (n = 14, 8.5%). Pleomorphic adenoma (n = 88; 80.0%) and mucoepidermoid carcinoma (n = 16, 29.6%) were also the most frequent benign and malignant tumors, respectively. Additionally, 39 cases of CXPA were collected from six Latin American Pathology centers. Of these, 22 (56.4%) were women, and 17 (43.6%) were men, ranging in age from 19 to 81 years (mean: 45 years). Most tumors affected the palate (n = 24, 61.5%), followed by the buccal mucosa (n = 9, 23.1%). Histologically, myoepithelial carcinoma was the most common subtype (n = 13, 33.3%), followed by adenocarcinoma not otherwise specified (n = 10, 25.6%). In addition, 561 cases of pleomorphic adenomas of minor salivary glands were reviewed. After microscopic reassessment and immunohistochemical studies, ten (1.7%) were reclassified as early CXPAs, representing 25.6% of the cases of CXPAs reported. High Ki-67 proliferative index and expression of p53 were useful in the identification of malignant areas. The present data confirm that pleomorphic adenoma and mucoepidermoid carcinoma are the most common benign and malignant SGT. However, it is important to consider that differences in tumor subtypes may be influenced by the type of center where the studies were conducted (medical or dental service). Pleomorphic adenomas of the minor salivary glands should be analyzed morphologically with caution. In doubtful cases, the Ki-67 labeling index and p53 expression evaluation are recommended to differentiate CXPA from pleomorphic adenomas, especially in incipient cases.

Key-words: Epidemiology. Salivary gland tumors. Head and neck pathology.

SUMÁRIO

1 INTRODUÇÃO

Uma variedade de neoplasias pode se desenvolver nas glândulas salivares (Reinheimer et al., 2019). Recentemente, a Organização Mundial da Saúde (OMS) publicou algumas mudanças na classificação dos tumores de glândulas salivares (TGS), reconhecendo 31 neoplasias epiteliais primárias (El Naggar et al., 2017). No entanto, apesar desse grande número de subtipos histológicos, esses tumores são raros e representam cerca de 3 a 6% de todos os tumores na região de cabeça e pescoço, com uma incidência global estimada de 0,4 a 13,5 por 100.000 pessoas anualmente (Cunha et al., 2020a; da Silva et al., 2018; El Naggar et al., 2017; Tian et al., 2010). Considerando a ampla variedade histológica e diferentes comportamentos biológicos, conhecer as características clínicas e patológicas e perfil de incidência desses tumores são essenciais para estabelecer uma abordagem terapêutica e prognóstico adequados (Cunha et al., 2020; da Silva et al., 2018).

Estudos epidemiológicos realizados em diferentes partes do mundo (Cunha et al., 2020a; Cunha et al., 2020b; da Silva et al., 2018; Gao et al., 2017; Vasconcelos et al., 2016; Bittar et al., 2015; Wang et al., 2015; Wang et al., 2012; Fonseca et al., 2012; Mejía-Velázquez et al., 2012; Reinheimer et al., 2012; Li et al., 2008; Ito et al., 2005; Vargas et al., 2002) mostraram variações geográficas na frequência e incidência desses tumores, além de discrepâncias entre os aspectos clínico-patológicos, principalmente quanto à localização anatômica e subtipos histológicos mais comuns (Cunha et al., 2020a; Cunha et al., 2020b; da Silva et al., 2018; Wang et al., 2015; Fonseca et al., 2012). No entanto, poucas informações foram publicadas na literatura sobre a epidemiologia dos TGS no nordeste brasileiro, particularmente no estado de Sergipe. Dentre os países latino-americanos, o Brasil e o México são os mais populosos, no entanto, estudos epidemiológicos de TGS no México são escassos (Mejía-Velázquez et al., 2012). Até onde sabemos, este é o primeiro estudo abordando a epidemiologia e características clínicas dos tumores de glândulas salivares realizados no estado de Sergipe (Cunha et al., 2020a) e o segundo estudo clínico patológico realizado no México (Cunha et al., 2020b; Mejía-Velázquez et al., 2012).

Dentre os tumores benignos de glândula salivar, o adenoma pleomórfico (AP) é a neoplasia mais comum da cavidade oral e responsável por aproximadamente 80% dos tumores dessa região (Cunha et al., 2020a; Cunha et al., 2020b). Apesar de sua natureza benigna, a transformação maligna em um carcinoma ex-adenoma pleomórfico (CEXAP), um tumor raro e agressivo, pode ocorrer e varia entre 3,3 e 13% de todos os casos (Lopes et al., 2017;

Vasconcelos et al., 2016; El Nagar et al., 2017). A maioria dos CEXAPs ocorre nas glândulas salivares maiores, especialmente na glândula parótida e submandibular, e o envolvimento das glândulas salivares menores da cavidade oral é raro (El Nagar et al., 2017).

Morfologicamente, o diagnóstico diferencial do CEXAP é amplo e inclui AP, tumores metastáticos mistos, adenocarcinomas salivares de alto grau e outras neoplasias malignas das glândulas salivares (El Nagar et al., 2017). Além disso, em alguns casos os APs podem representar um desafio para o manejo clínico e diagnóstico, principalmente por causa da grande diversidade de características morfológicas e sua tendência à recorrência local (Lopes et al., 2017; Pérez-de-Oliveira et al., 2019). Embora histologicamente, a maioria dos CEXAPs mostrem claramente áreas de transição entre o componente benigno do AP e o carcinomatoso (Pérez-de-Oliveira et al., 2019), esse achado pode não ser evidente, especialmente em pequenas biópsias incisionais e casos incipientes, e os CEXAPs podem ser frequentemente diagnosticados erroneamente como APs. Nestes casos, a análise imunoistoquímica pode ser útil na identificação do componente maligno e estabelecimento do correto diagnóstico (Scarini et al., 2019). O uso de diversos marcadores imunohistoquímicos foram propostos como métodos auxiliares para identificar o componente maligno em CEXAPs, como HER2/neu, p53, receptor de andrógeno, BCL-2, FASN e Ki-67 (Mariano et al., 2015; Sedassari et al., 2015; Freitas et al., 2005; Di Palma, 2013; Días et al., 2018).

Embora o perfil clínico e epidemiológico dos CEXAPs acometendo as glândulas salivares maiores esteja bem estabelecido na literatura (Mariano et al., 2013), as características clínico-patológicas de CEXAPs das glândulas salivares menores não são totalmente compreendidas devido à sua raridade e grande variedade morfológica.

Assim, o objetivo da presente dissertação foi descrever os aspectos clínicos e demográficos dos TGS diagnosticados em um serviço privado de patologia oral na Cidade do México e em 4 centros de patologia no Nordeste do Brasil (Aracaju, Sergipe) e comparar os achados com dados epidemiológicos de diferentes localizações geográficas obtidos por meio de uma revisão da literatura. Adicionalmente, foi realizado um estudo com o objetivo de relatar as características clínico-patológicas e imunohistoquímicas de 39 novos casos de CEXAPs acometendo as glândulas salivares menores, uma das maiores séries reportadas na literatura.

2 ARTIGOS

2.1 Artigo:

EPIDEMIOLOGIC ANALYSIS OF SALIVARY GLAND TUMORS OVER A 10-YEARS PERIOD DIAGNOSED IN A NORTHEAST BRAZILIAN POPULATION

Artigo publicado no periódico *Medicina Oral Patologia Oral y Cirugia Bucal*

DOI: 10.4317/medoral.23532 (Anexo 2)

John Lennon Silva Cunha[1], Ana Carolina Penha Coimbra[2], João Vitor Rocha Silva[3], Amanda Feitoza da Silva[3], Ilmara Silva do Nascimento[3], Maria Eliane de Andrade[4], Clauberto Rodrigues de Oliveira[4], Oslei Paes de Almeida[5], Ciro Dantas Soares[6], Sílvia Ferreira de Sousa[7], Ricardo Luiz Cavalcanti de Albuquerque-Júnior[8]

[1] DDS, MSc student, Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, SP, Brazil.
[2] MD, Department of Medicine, Federal University of Sergipe (UFS), Aracaju, Sergipe, Brazil.
[3]Department of Dentistry, Tiradentes University (UNIT), Aracaju, Sergipe, Brazil.
[4]PhD student, Laboratory of Morphology and Experimental Pathology, Institute of Technology and Research, Tiradentes University (UNIT), Aracaju, Sergipe, Brazil.
[5]DDS, PhD, Professor, Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, SP, Brazil.
[6]DDS, PhD student, Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, SP, Brazil.
[7]DDS, PhD, Professor, Department of Dentistry, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Minas Gerais, Brazil.
[8]DDS, PhD, Professor, Department of Dentistry, Tiradentes University (UNIT), Aracaju, Sergipe, Brazil.

Corresponding author:

Ricardo Luiz Cavalcanti de Albuquerque Júnior

Laboratory of Morphology and Experimental Pathology, Institute of Technology and Research, Tiradentes University, Av. Murilo Dantas, 300, Farolândia, Aracaju, SE 49032-490, Brazil.

E-mail: ricardo.patologia@uol.com.br.

Abstract

Background: Salivary gland tumors (SGT) correspond to a heterogeneous group of lesions with variable biological behavior. The present study aimed to determine the distribution and demographic findings of salivary gland neoplasms in a northeast Brazilian population.

Material and methods: A retrospective descriptive cross-sectional study was performed. A total of 588 cases of SGT were diagnosed between 2006 and 2016 of 4 pathology services in the state of Sergipe, Brazil. All cases were reviewed, and data such as sex, age, anatomical location, and histopathological diagnosis were collected.

Results: A total of 470 (79.9%) tumors were benign and 118 (20.1%) were malignant. The majority of the patients were females (n=328, 55.8%) with an overall female:male ratio of 1.2:1. The major salivary glands were affected more than the minor glands (69.5% vs. 30.5%). Pleomorphic adenoma (n=419, 71.3%) and mucoepidermoid carcinoma (n=29, 4.9%) were the most frequent benign and malignant tumors, respectively. In addition, both benign and malignant tumors occurred more frequently in the parotid gland (n=300, 51%, $p<0.05$).

Conclusions: The epidemiologic profile and clinical characteristics of SGT were similar to those described in other countries and other regions of Brazil. Epidemiological studies of SGT help to understand their clinical and pathological features and are essential to establish the proper management and prognosis.

Key-words: Salivary gland; tumors; epidemiology; head and neck pathology.

1. INTRODUCTION

Salivary gland tumors (SGT) are uncommon lesions that present a wide variation in relation to the clinical, histological, and biological aspects (1,2). In addition, these lesions often represent a diagnostic challenge for the pathologist due to the overlapping of morphological findings (2,3).

SGT account for about 3 to 6% of all tumors in the head and neck region, with an annual estimated global incidence ranging from 0.4 to 13.5 cases per 100,000 individuals (2,4). Although several studies evaluate the frequency and incidence of these tumors in Brazil (1,2,5-10) and other countries of the world (11-16), the epidemiological data of these lesions is not well established because there is a wide variation in the incidence and prevalence of these

tumors across countries, indicating a geographic variation in the frequency of these neoplasms (2,9).

Thus, the objective of the present study was to describe the demographic and clinical aspects of salivary gland neoplasms diagnosed in four reference pathology centers in the state of Sergipe (Aracaju, Brazil), and to compare the findings with epidemiological data from different geographic locations.

2. MATERIAL AND METHODS

Study design and ethical aspects

In this study, the files of four surgical pathology centers in Aracaju, Sergipe State, Brazil were retrospectively reviewed: Laboratory of Surgical Pathology of the University Hospital of the Federal University of Sergipe (HU-UFS), Oral Pathology Service of the Tiradentes University (UNIT), and two private general pathology services. During a 10-year period, between January 2006 and December 2016, 588 cases of salivary gland neoplasms were retrieved from these archives. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of the Tiradentes University (Protocol nº 3.238.266).

Sample

All cases of salivary gland tumors were retrieved, and data such as gender, age, anatomical location, and histopathological diagnosis were obtained from clinical records and analyzed. The lesions were classified into benign and malignant tumors in accordance with the current WHO classification of the head and neck tumors (17). Microscopical slides of all cases were examined by two independent pathologists with more than 25 years of experience. Immunohistochemical and histochemical analyses were performed when routine staining (hematoxylin-eosin) was not sufficient to establish the final diagnosis.

Analysis

Descriptive and quantitative data analysis was performed using the Statistical Package for the Social Sciences for Windows 20.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were expressed as mean, median and standard deviation values. Categorical variables were expressed as absolute number of cases and percentage values. Person's chi-square test and Fisher's exact test were used to evaluate association between biological behavior (malignant vs

benign tumors) and clinical and demographic characteristics, adopting a *p*-value of ≤ 0.05 and a 95% confidence interval.

3. RESULTS

In a 10-year period (2006-2016), there were 588 salivary gland neoplasms diagnosed at the 4 pathology reference centers in Aracaju, Sergipe State, Brazil. Of the total of 588 cases of salivary gland neoplasms, 470 (79.9%) were benign and 118 (20.1%) malignant neoplasms with a benign:malignant ratio of 3.9:1, distributed among 7 benign and 10 malignant histologic subtypes (Table 1).

The majority of patients were female (n = 328, 55.8%) with an overall female:male ratio of 1.2:1 (Table 1). Most tumors occurred in the patients between the third and seventh decades of life, with a mean age of 57.9 years (range 2-106 years). The distribution of each salivary gland neoplasm, according to the age of patients, is showed in Table 2.

Regarding the anatomical site, 69.5% of the tumors occurred in the major salivary glands (n = 363, 69.5%) while only 30.5% affected the minor salivary glands. The parotid gland was the most commonly affected, with a frequency of 51% (n = 300), followed by the palate (n = 101, 17.2%), submandibular gland (n = 63, 10.7%), lips (n = 33, 5.6%), buccal mucosa (n = 22, 3.7%), and floor of the mouth (n = 1, 0.2%). There were 66 cases with unspecified anatomic location (11.2%), and none tumor affected the sublingual gland (Figure 2). Both benign and malignant neoplasms predominated in the parotid gland, followed by the palate and submandibular gland, respectively (Table 3).

Among the benign salivary gland tumors, pleomorphic adenoma (PA) was most frequent (n = 419; 89.1%) followed by Warthin's tumor (n = 30, 6.4%), canalicular adenoma (n = 6, 1.3%) and myoepithelioma (n = 6, 1.3%) (Table 1). These tumors were diagnosed mainly between the fourth and fifth decades of life (Figure 1); however, the age ranged from 2 to 92 years, with an average age of 55.7 years (SD ± 7.4) (Table 2). Most cases occurred in the parotid gland (n=248, 52.8%) and female patients (n = 275; 58.5%), with a female:male ratio of 1.4:1 (275 female and 195 male). Regarding the malignancies, mucoepidermoid carcinoma was the most frequent malignant tumor (n = 29, 24.6%), followed by adenocarcinomas not otherwise specified (n = 24, 20.3%), and adenoid cystic carcinoma (n = 21, 17.8%) (Table 1). The age ranged from 11 to 106 years, with a mean age of 59.4 years (SD ± 11.1) (Table 2). Most cases also occurred in the parotid gland (n = 52, 44.1 %) and male (n = 65; 55.1%), with a female:male ratio of 0.8:1.0 (53 female and 65 male) (Table 3).

When the behavior of the tumors (malignant vs benign tumors) was evaluated, the parotid was the most affected gland mainly by benign tumors ($p < 0.05$). Also, the benign salivary gland tumors were more common in female patients ($p < 0.05$); results were statistically significant (Table 4).

4. DISCUSSION

In the last two decades (1999-2019) several studies performed worldwide have been published on the epidemiology of salivary gland neoplasms, as shown in figure 3. According to the WHO (2017), overall, female patients are slightly more affected by salivary gland neoplasms than male patients (17). However, some variations can be found when analyzing specific tumor subtypes (2,9,17,18). In the present study, the female-to-male ratio was 1.2:1, which is in agreement with most studies (19,20), including Brazilian reports (2,6,8,9). In addition, benign neoplasms presented a male-to-female ratio of 1:1.4, while malignant neoplasms demonstrated a male-to-female ratio of 1:0.8, indicating that benign tumors were more common in female patients, whereas malignancies were slightly more common in males. These data are in accordance with several previous studies (2,9). However, a previous study performed in Mexico showed that female patients were more affected by malignant neoplasms than male patients (21).

In the present study, most tumors were benign (79.9%), data similar to other studies where these tumors correspond to about 51.5 to 86.4% of all salivary gland neoplasms (2,5-9,13). However, some studies conducted on the African (22,23) and Asian continents (24,25) have shown a higher incidence of malignancies, and suggest geographic variation in the frequency of these tumors.

Regarding the benign neoplasms, pleomorphic adenoma was the most common tumor in this study, accounting for 89.1% of all benign neoplasms followed by Warthin's Tumor (6.4%). In fact, pleomorphic adenoma is the most common benign neoplasm in all previously published studies (1,2,4,5-16,18-30), and Warthin's Tumor was the second benign tumor more frequent (1,5,6,8-10). However, some studies have shown basal cell adenoma (2,26) or myoepithelioma (23,24,27-30) as the second most common benign tumors.

On the other hand, Silva *et al.* (2) performed a retrospective multicentric study in Brazil and observed that basal cell adenoma and cystadenoma were the second and third most common neoplasms, respectively, different from most studies published in Brazil that shows the Whartin's Tumor as the second most common benign neoplasm (1,5,6,8-10). These results

suggest that multi-institucional studies can better characterize the heterogeneity of tumors in large territories, such as Brazil, for example, and contribute to the comprehension of epidemiological differences in the population (2). Also, the fact that this study was performed in oral pathology services may explain this apparent difference. The Warthin's Tumor is a neoplasm that affects almost exclusively the parotid gland, and some studies show that most cases from surgical pathology centers affect the major salivary glands, particularly the parotid gland, whereas tumors of the minor salivary glands represent the majority of cases diagnosed in oral pathology services (9). In addition, some other benign tumors, such as oncocytomas, were diagnosed in our study (n = 2, 0.3%). However, these tumors are very rare and are usually observed only in large sample studies (2).

The most common malignant tumor was the mucoepidermoid carcinoma, accounting for 24.6% of the cases, followed by adenocarcinomas not otherwise specified (AcNOS), which represented 20.3%, and cystic adenoid carcinoma (17.8%), that corroborate with previous studies (12-15,19,24-26,29,30). On the other hand, other studies indicate cystic adenoid carcinoma as the most frequent malignant tumor (1,4,7,8,11,21-23,28). In general, the four most frequent malignant tumors are mucoepidermoid carcinoma, cystic adenoid carcinoma, acinar cell carcinoma, and AcNOS.

The morphological diagnosis of salivary gland tumors is challenging due to a large number of histological subtypes, overlapping of morphological findings, and different classifications (2,3). The diagnosis of polymorphous adenocarcinoma, in particular, can be difficult, especially in pathology centers without an experienced pathologist in oral and maxillofacial lesions, since this tumor shares some morphological characteristics with several other tumors (2). In our study, 13 cases of polymorphous adenocarcinomas were diagnosed, of which 8 affected minor intraoral salivary glands, 3 affected parotid glands, and 3 cases with unspecified anatomical sites. This strong predilection for polymorphic adenocarcinoma by minor salivary glands, especially in the palate region, is well established in the literature (17). Furthermore, until the last WHO classification, polymorphous adenocarcinoma was called "low-grade polymorphous adenocarcinoma", because in most cases, it exhibits indolent behavior. However, approximately 10% to 33% of patients develop local recurrences, 9% to 15% have nodal metastases, and some cases are extremely aggressive, with imprecise clinical behavior (2). Considering the variation in the biological behavior of these lesions, the new classification proposed by the WHO for salivary gland neoplasms abandoned the term "low grade" and renamed these tumors only as polymorphous adenocarcinoma (2,17). The purpose of this modification is to avoid possible

terminological confusion and to facilitate the choice of treatment, especially for the most unusual cases (2,17). In addition, in our study, some other malignant tumors were very rare, such as salivary duct carcinomas (n=3, 0.5%) and myoepithelial carcinomas (n=1, 0.2%). Although these entities are well recognized, they are also rarely reported in studies with small samples (2).

Regarding the anatomical location, most of the SG tumors of this study were diagnosed in the parotid gland, followed by the minor salivary glands of the palate and submandibular gland. In general, this result was also reported by other studies (1,4,9,11,14,15,19,20,23,26). However, some studies have shown that malignant neoplasms preferentially affect the minor intraoral salivary glands (1,2,9).

In summary, although several studies evaluate the frequency and incidence of salivary gland neoplasms, continuous studies that report the incidence and characteristics of these lesions are essential to keep physicians and surgeons up to date, especially when the classification of these tumors undergoes some change (2).

5. CONCLUSIONS

The results of this study were similar to those found by several other authors in Brazil and worldwide. The pleomorphic adenoma was the most common benign tumor, and the mucoepidermoid carcinoma the most frequent malignant tumor in the salivary glands. In addition, both benign and malignant tumors occurred more frequently in the parotid gland.

Acknowledgments: This work was supported by the Brazilian National Council for Scientific and Technological Development (CNPq) and Coordination for the Improvement of Higher Education Personnel (CAPES).

Conflicts of interest: No conflicts of interest declared concerning the publication of this article.

Funding: None.

References

1. Vasconcelos AC, Nör F, Meurer L, Salvadori G, Souza LB, Vargas PA, et al. Clinicopathological analysis of salivary gland tumors over a 15-year period. Braz Oral 2016:30:e2.

2. da Silva LP, Serpa MS, Viveiros SK, Sena DAC, de Carvalho Pinho RF, de Abreu Guimarães LD, et al. Salivary gland tumors in a Brazilian population: A 20-year retrospective and multicentric study of 2292 cases. J Craniomaxillofac Surg. 2018:46:2227-33.

3. Rooper LM. Challenges in Minor Salivary Gland Biopsies: A Practical Approach to Problematic Histologic Patterns. Head Neck Pathol. 2019:13:476-84.

4. Tian Z, Li L, Wang L, Hu Y, Li J. Salivary gland neoplasms in oral and maxillofacial regions: a 23-year retrospective study of 6982 cases in an eastern Chinese population. Int J Oral Maxillofac Surg. 2010:39:235-42.

5. Vargas PA, Gerhard R, Araújo Filho VJ, de Castro IV. Salivary gland tumors in a Brazilian population: a retrospective study of 124 cases. Rev Hosp Clin Fac Med Sao Paulo. 2002:57:271-76.

6. Ito FA, Ito K, Vargas PA, de Almeida OP, Lopes MA. Salivary gland tumors in a Brazilian population: a retrospective study of 496 cases. Int J Oral Maxillofac Surg. 2005:34:533-36.

7. Lima SS, Soares AF, Amorim RFB, Freitas RA. Epidemiologic profile of salivary gland neoplasms: analysis of 245 cases. Ver Bras Otorrinolaringol. 2005:71:335-40.

8. de Oliveira FA, Duarte EC, Taveira CT, Máximo AA, de Aquino EC, Alencar Rde C, et al. Salivary gland tumor: a review of 599 cases in a Brazilian population. Head Neck Pathol. 2009:3:271-5.

9. Fonseca FP, Carvalho M de V, de Almeida OP, Rangel AL, Takizawa MC, Bueno AG, et al. Clinicopathologic analysis of 493 cases of salivary gland tumors in a Southern Brazilian population. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012:114:230-39.

10. Bittar RF, Ferraro HP, Moraes Gonçalves FT, Couto da Cunha MG, Biamino ER. Neoplasms of the salivary glands: analysis of 727 histopathological reports in a single institution. Otolaryngol Pol. 2015:69:28-33.

11. Bello IO, Salo T, Dayan D, Tervahauta E, Almangoush A, Schnaiderman-Shapiro A, et al. Epithelial salivary gland tumors in two distant geographical locations, Finland (Helsinki and Oulu) and Israel (Tel Aviv): a 10-year retrospective comparative study of 2,218 cases. Head Neck Pathol. 2012:6:224-31.

12. Wang YL, Zhu YX, Chen TZ, Wang Y, Sun GH, Zhang L, et al. Clinicopathologic study of 1176 salivary gland tumors in a Chinese population: experience of one cancer center 1997-2007. Acta Otolaryngol. 2012:132:879-86.

13. Bradley PJ, McGurk M. Incidence of salivary gland neoplasms in a defined UK population. Br J Oral Maxillofac Surg. 2013:51:399-03.

14. Wang XD, Meng LJ, Hou TT, Huang SH. Tumours of the salivary glands in northeastern China: a retrospective study of 2508 patients. Br J Oral Maxillofac Surg. 2015:53:132-37.

15. Gao M, Hao Y, Huang MX, Ma DQ, Chen Y, Luo HY, et al. Salivary gland tumours in a northern Chinese population: a 50-year retrospective study of 7190 cases. Int J Oral Maxillofac Surg. 2017:46:343-49.

16. Campolo González A, Ramírez Skinner H, Vargas Díaz A, León Ramírez A, Goñi Espildora I, Solar González A. Epithelial tumors of salivary glands. Review of 286 pathology reports. Rev Med Chil. 2018:146:1159-66.

17. Seethala RR, Stenman G. Update from the 4th Edition of the World Health Organization Classification of Head and Neck Tumours: Tumors of the Salivary Gland. Head Neck Pathol. 2017;11:55-67.

18. Noel L, Medford S, Islam S, Muddeen A, Greaves W, Juman S. Epidemiology of salivary gland tumours in an Eastern Caribbean nation: A retrospective study. Ann Med Surg (Lond). 2018:8:148-51.

19. Li LJ, Li Y, Wen YM, Liu H, Zhao HW. Clinical analysis of salivary gland tumor cases in West China in past 50 years. Oral Oncol. 2008:44:187-92.

20. Araya J, Martinez R, Niklander S, Marshall M, Esguep A. Incidence and prevalence of salivary gland tumours in Valparaiso, Chile. Med Oral Patol Oral Cir Bucal. 2015:20:e532–39.

21. Mejía-Velázquez CP, Durán-Padilla MA, Gómez-Apo E, Quezada-Rivera D, Gaitán-Cepeda LA. Tumors of the salivary gland in Mexicans. A retrospective study of 360 cases. Med Oral Patol Oral Cir Bucal. 2012:17:e183–89.

22. Fomete B, Adebayo ET, Ononiwu CN. Management of salivary gland tumors in a Nigerian tertiary institution. Ann Afr Med. 2015:14:148-54.

23. Lawal AO, Adisa AO, Kolude B, Adeyemi BF, Olajide MA. A review of 413 salivary gland tumours in the head and neck region. J Clin Exp Dent. 2013:5:e218–22.

24. Taghavi N, Sargolzaei S, Mashhadiabbas F, Akbarzadeh A, Kardouni P. Salivary Gland Tumors: A 15- year Report from Iran. Turk Patoloji Derg. 2016:32:35-9.

25. Tilakaratne WM, Jayasooriya PR, Tennakoon TM, Saku T. Epithelial salivary tumors in Sri Lanka: a retrospective study of 713 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009:108:90-8.

26. Jones AV, Craig GT, Speight PM, Franklin CD. The range and demographics of salivary gland tumours diagnosed in a UK population. Oral Oncol. 2008:44:407-17.

27. Otoh EC, Johnson NW, Olasoji H, Danfillo IS, Adeleke OA. Salivary gland neoplasms in Maiduguri, north-eastern Nigeria. Oral Dis. 2005:11:386-91.

28. Vuhahula EA. Salivary gland tumors in Uganda: clinical pathological study. Afr Health Sci. 2004:4:15–23.

39. Torabinia N, Khalesi S. Clinicopathological study of 229 cases of salivary gland tumors in Isfahan population. Dent Res J (Isfahan). 2014:11:559-63.

30. Saghravanian N, Ghazi N, Saba M. Clinicopathologic evaluation of salivary gland neoplasms: a 38-year retrospective study in Iran. Ann Diagn Pathol. 2013:17:522-25.

Table 1. Histologic and gender distribution of 588 benign and malignant neoplasms of salivary glands.

					Sex			
		n=588	%[a]	%[b]	Male		Female	
					n	%	n	%
Benign tumors	Pleomorphic adenoma	419	71.3	89.1	162	27.6	257	43.7
	Warthin's Tumor	30	5.1	6.4	22	3.7	8	1.4
	Canalicular adenoma	6	1.0	1.3	4	0.7	2	0.3
	Myoepithelioma	6	1.0	1.3	2	0.3	4	0.7
	Basal cell adenoma	4	0.7	0.9	2	0.3	2	0.3
	Cystadenoma	3	0.5	0.6	1	0.2	2	0.3
	Oncocytoma	2	0.3	0.4	2	0.3	0	0.0
	Total	**470**	**79.9**	**100**	**195**	**33.2**	**275**	**46.8**
Malignant tumors	Mucoepidermoid carcinoma	29	4.9	24.6	14	2.4	15	2.6
	Adenocarcinoma NOS	24	4.1	20.3	17	2.9	7	1.2
	Adenoid cystic carcinoma	21	3.6	17.8	10	1.7	11	1.9
	Polymorphous adenocarcinoma	13	2.2	11.0	5	0.9	8	1.4
	Carcinoma ex-PA	10	1.7	8.5	8	1.4	2	0.3
	Acinic cell carcinoma	9	1.5	7.6	5	0.9	4	0.7
	Epithelial-myoepithelial carcinoma	6	1.0	5.1	3	0.5	3	0.5
	Salivary duct carcinoma	3	0.5	2.5	2	0.3	1	0.2
	Squamous cell carcinoma	2	0.3	1.7	1	0.2	1	0.2
	Myoepithelial carcinoma	1	0.2	0.8	0	0.0	1	0.2
	Total	**118**	**20.1**	**100**	**65**	**11.0**	**53**	**9.0**

[a]Percent in relation to the total number of cases; [b]Percent of the sample in relation to the group of benign or malignant tumors;

Table 2. Age group distribution (decade of life) of benign and malignant salivary gland tumors.

				Age groups					Total	
		Age range	Mean age[a]	0-20	21-40	41-60	>61	NS	n	%
Benign neoplasms	Pleomorphic adenoma	02-92	43.5	35	160	137	74	13	419	71.3
	Warthin's Tumor	33-81	58.8	0	2	19	9	0	30	5.1
	Canalicular adenoma	53-78	67.8	0	0	1	5	0	6	1.0
	Myoepithelioma	27-72	51.5	0	1	3	2	0	6	1.0
	Basal cell adenoma	48-61	57.0	0	0	3	1	0	4	0.7
	Cystadenoma	48-61	57.0	0	0	2	1	0	3	0.5
	Oncocytoma	51-57	54.0	0	0	2	0	0	2	0.3
Malignant neoplasms	Mucoepidermoid carcinoma	11-106	47.0	4	7	10	8	0	29	4.9
	Adenocarcinoma NOS	26-88	57.6	0	4	10	10	0	24	4.1
	Adenoid cystic carcinoma	29-82	57.1	0	3	8	10	0	21	3.6
	Polymorphous adenocarcinoma	37-78	58.2	0	1	5	7	0	13	2.2
	Carcinoma ex-PA	38-77	60.4	0	1	3	6	0	10	1.7
	Acinic cell carcinoma	20-69	47.8	1	1	6	1	0	9	1.5
	Epithelial-myoepithelial carcinoma	59-100	78.2	0	0	2	4	0	6	1.0
	Salivary duct carcinoma	52-74	60.3	0	0	2	1	0	3	0.5
	Squamous cell carcinoma	74-83	78.5	0	0	0	2	0	2	0.3
	Myoepithelial carcinoma	49	49.0	0	0	1	0	0	1	0.2

NS: not specified; [a]years.

Table 3. Distribution of the 588 salivary gland tumors according to the location (major and minor salivary glands).

		Major salivary glands			Minor salivary glands						**Total**	
		Parotid	Submandibular	Sublingual	Palate	Lips	Cheek mucosa	Tongue	Floor of the mouth	NS	n	%
Benign tumors	Pleomorphic adenoma	215	54	0	56	26	18	1	0	49	419	71.3
	Warthin's Tumor	25	2	0	0	0	0	0	0	3	30	5.1
	Canalicular adenoma	0	0	0	1	4	1	0	0	0	6	1.0
	Myoepithelioma	1	0	0	4	0	0	0	0	1	6	1.0
	Basal cell adenoma	4	0	0	0	0	0	0	0	0	4	0.7
	Cystadenoma	1	0	0	1	0	0	0	1	0	3	0.5
	Oncocytoma	2	0	0	0	0	0	0	0	0	2	0.3
	Total	**248**	**56**	**0**	**62**	**30**	**19**	**1**	**1**	**53**	**470**	**79.9**
	%	52.8	11.9	0	13.2	6.4	4	0.2	0.2	11.3	100	
Malignant tumors	Mucoepidermoid carcinoma	8	1	0	16	0	0	1	0	3	29	4.9
	Adenocarcinoma NOS	17	2	0	2	0	1	0	0	2	24	4.1
	Adenoid cystic carcinoma	6	3	0	9	0	0	0	0	3	21	3.6
	Polymorphous adenocarcinoma	3	0	0	4	3	1	0	0	2	13	2.2
	Carcinoma ex-PA	3	0	0	6	0	0	0	0	1	10	1.7
	Acinic cell carcinoma	5	0	0	1	0	1	0	0	2	9	1.5
	Epithelial-myoepithelial carcinoma	5	1	0	0	0	0	0	0	0	6	1.0
	Salivary duct carcinoma	2	0	0	1	0	0	0	0	0	3	0.5
	Squamous cell carcinoma	2	0	0	0	0	0	0	0	0	2	0.3
	Myoepithelial carcinoma	1	0	0	0	0	0	0	0	0	1	0.2
	Total	**52**	**7**	**0**	**39**	**3**	**3**	**1**	**0**	**13**	**118**	**20.1**
	%	44.1	5.9	0	33.1	2.5	2.5	0.8	0	11	100	

NS: not specified.

Table 4. Anatomic site, gender, and age group distribution of benign and malignant salivary gland tumors.

		Benign		Malignant		Total		*P* value
		n	%	n	%	n	%	
Anatomic site	Parotid	248	82.7	52	17.3	300	51.0	0.0021[a]
	Submandibular	56	88.9	7	11.1	63	10.7	
	Minor salivary glands	113	71.1	46	28.9	159	27.0	
	NI	53	80.3	13	19.7	66	11.2	
Gender	Female	275	83.8	53	16.2	328	55.8	0.0094[b]
	Male	195	75.0	65	25	260	44.2	
Age	19 ≤	35	87.5	5	12.5	40	6.8	0.2278[b]
	≥20	422	78.9	113	21.1	535	91.0	
	NI	13	100	0	0	13	2.2	

NI: Not informed; %: Percentage; [a]: Pearson's Chi-square test; [b]: Fisher's exact test.

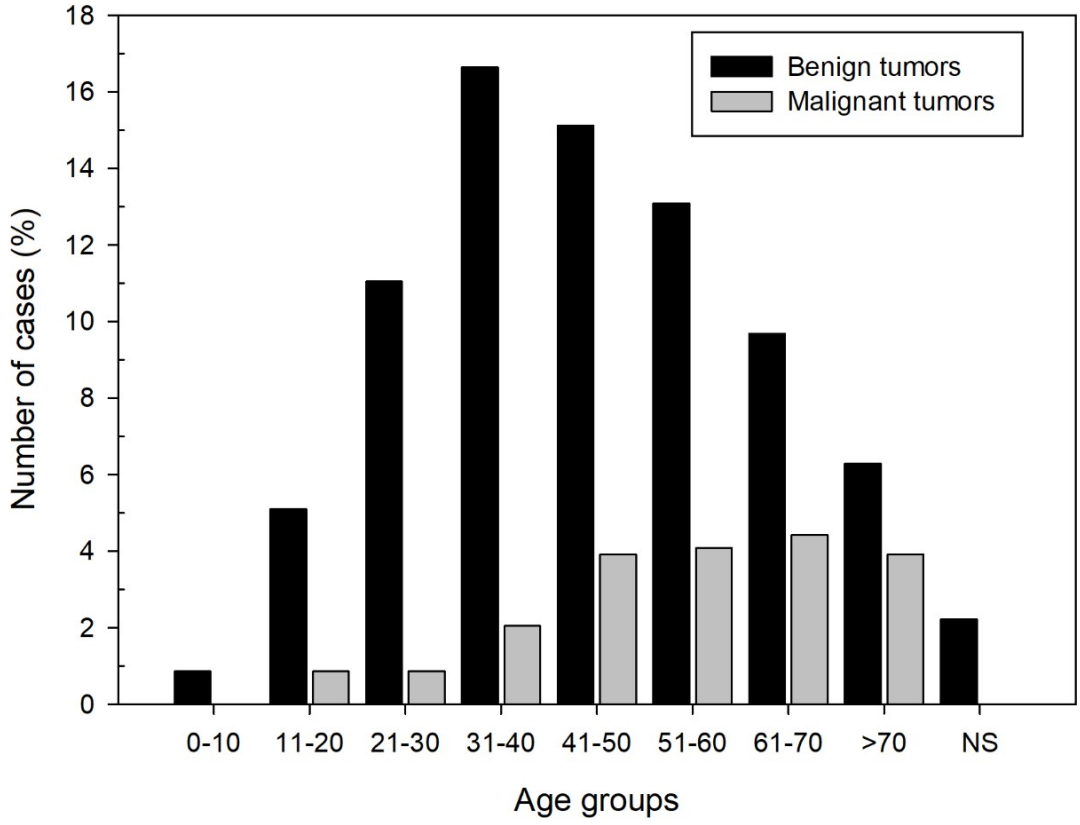


Figure 1. Distribution of 588 salivary gland tumors according to the age group (decade of life).

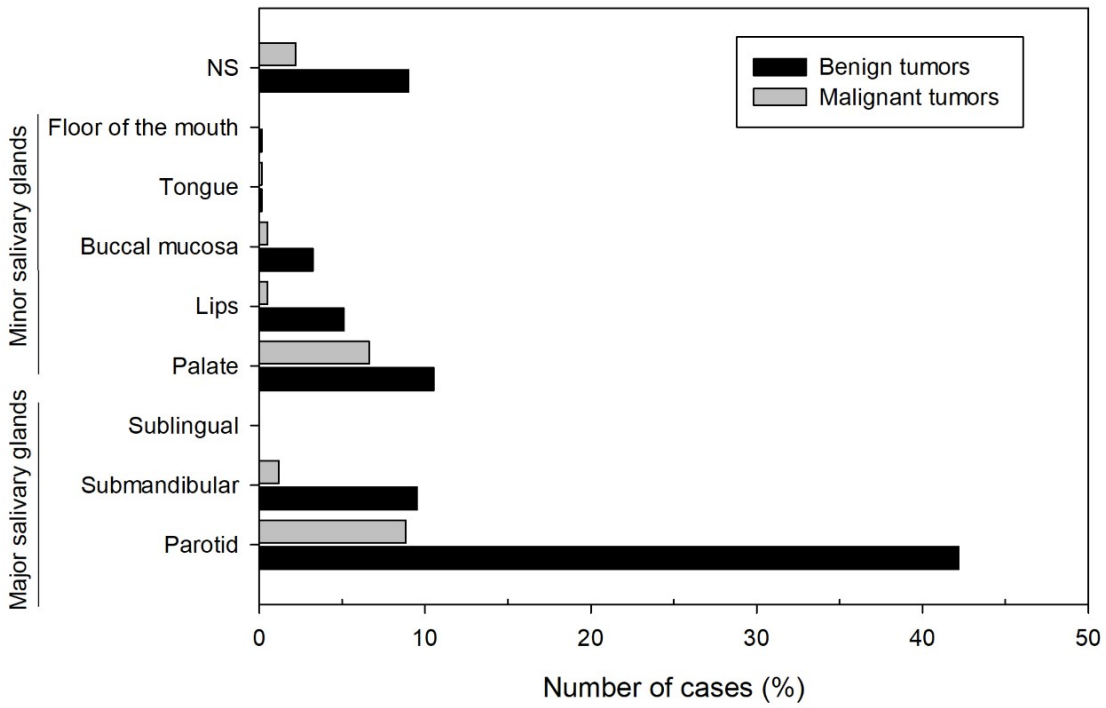


Figure 2. Distribution of 588 salivary gland tumors according to the primary site of involvement. NS, not specified.

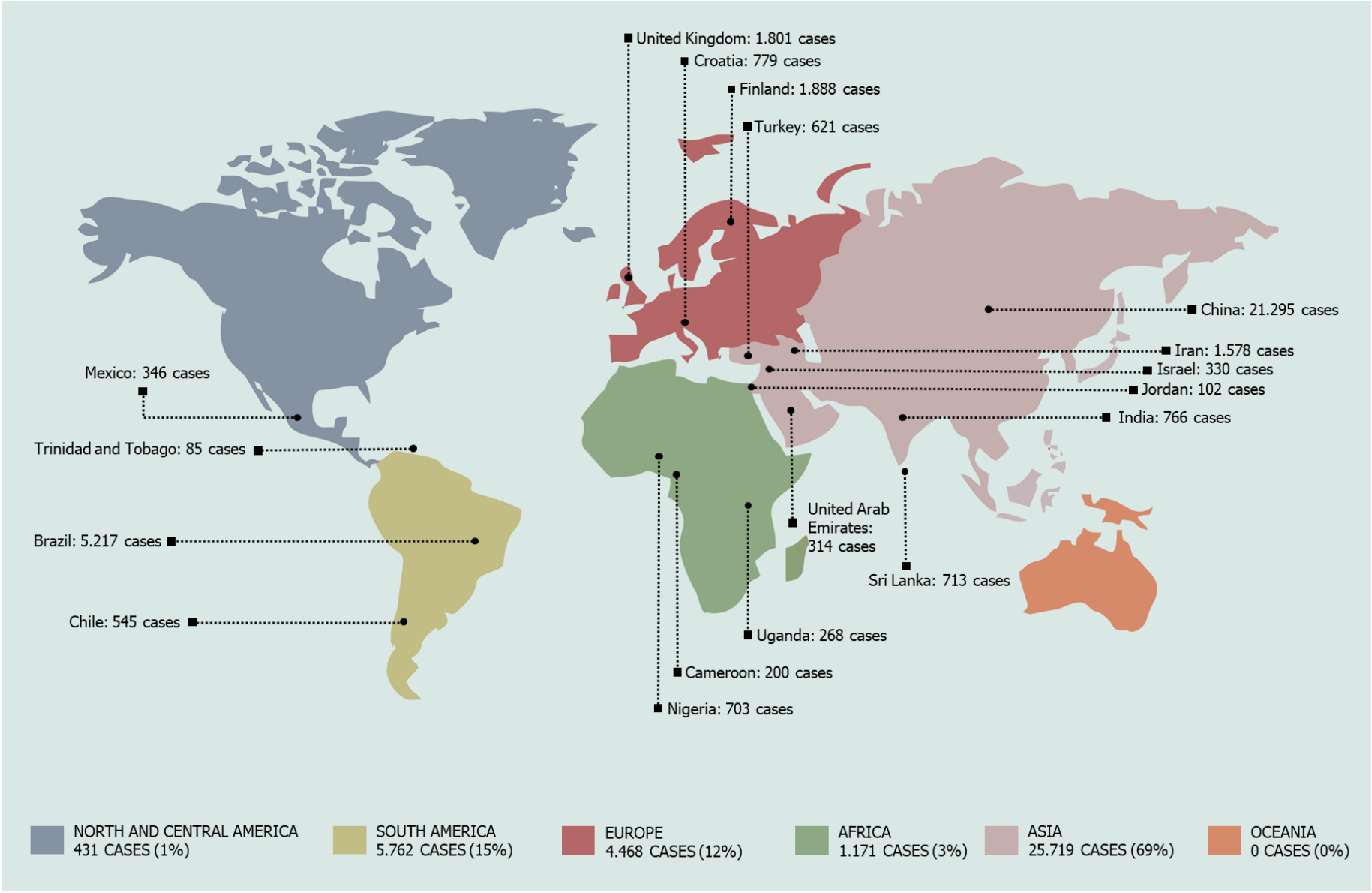


Figure 3. World distribution of 37.205 cases of SGT reported in the literature in the last 20 years (1999-2019).

2.2 Artigo:

SALIVARY GLAND TUMORS: A RETROSPECTIVE STUDY OF 164 CASES FROM A SINGLE PRIVATE PRACTICE SERVICE IN MEXICO AND LITERATURE REVIEW

Artigo publicado no periódico *Head and Neck Pathology*

DOI: 10.1007/s12105-020-01231-2 (Anexo 3)

John Lennon Silva Cunha[a], Juan Carlos Hernandez-Guerrero[b], Oslei Paes de Almeida[a], Ciro Dantas Soares[a], Adalberto Mosqueda-Taylor[c]

[a] Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, SP, Brazil.
[b] Facultad de Odontología, Laboratory of Immunology, Universidad Nacional Autónoma de México (UNAM), México City, México
[c] Facultad de Odontología, Universidad Autónoma Metropolitana Xochimilco (UAM), México City, México.

***Corresponding Author:**

Ciro Dantas Soares

Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), Av. Limeira 901, P.O. Box. 52, Piracicaba, São Paulo 1314-903, Brazil.

E-mail: ciro.dss@gmail.com.

Abstract

Salivary gland tumors (SGT) represent an uncommon heterogeneous group of tumors with complex clinical and pathological characteristics. The prevalence of these lesions varies between studies but has been estimated between 3 and 6% of all tumors in the head and neck region. The present study aimed to evaluate the distribution and demographic findings of salivary gland tumors diagnosed in an oral pathology service in Mexico. A

retrospective descriptive cross-sectional study was performed. A total of 164 cases of SGT from a private oral pathology service were diagnosed between 2000 and 2019 in Mexico City. All cases were reviewed histologically, and demographic data and histopathological diagnoses were collected. A total of 110 (67.1%) tumors were benign, and 54 (32.9%) were malignant. The majority of patients were female (n = 100, 61.0%) with an overall female:male ratio of 1.6:1. The minor salivary glands were affected more than the major salivary glands (68.9% vs. 25.6%). The palate (n = 67, 40.9%) was the most commonly affected site, followed by the parotid gland (n = 37, 22.6%), lips (n = 16, 9.8%), and buccal mucosa (n = 14, 8.5%). Pleomorphic adenoma (n = 88; 80.0%) and mucoepidermoid carcinoma (n = 16, 29.6%) were the most frequent benign and malignant tumors, respectively. The general features of SGT from the studied Mexican population shared some similarities and differences compared to previously reported series from various parts of the world.

1. Introduction

The salivary glands are exocrine glands that produce secretions contributing to the lubrication, digestion, and protection of the upper aerodigestive tract [1]. They can be divided into major (parotid, submandibular, sublingual) and minor salivary glands [2]. Due to its complex histology, a variety of primary tumors can develop in these structures independently of the anatomical site [1,2]. Also, the morphological diagnosis of these lesions is frequently challenging due to many histological subtypes, overlapping of morphological findings, and different classifications [2-4].

Although several epidemiological studies across the world have evaluated the frequency and incidence of these tumors [2,3,5-16], geographic variations have been observed in this group of lesions, particularly in relation to anatomical location and histological subtypes [2,3,8]. In addition, there are only a few studies about the incidence in the Mexican population, despite its large geographical size and population [14].

Thus, the objective of the present study was to describe the clinical and demographic aspects of salivary gland tumors (SGT) diagnosed in a private oral pathology service in Mexico City and to compare the findings with epidemiological data from different geographic locations obtained through the review of the literature.

2. Material and Methods

2.1 Study design and sample

In this study, the files of a private oral pathology service in Mexico were retrospectively reviewed during a 20-year period (between January 2000 and December 2019). All cases of SGT were retrieved, and data such as gender, age, anatomical location, and histopathological diagnosis were obtained from clinical records and analyzed. The lesions were reviewed histologically and were reclassified into benign and malignant tumors in accordance with the current WHO Classification of Head and Neck Tumours [17]. Microscopical slides of all cases were reexamined by two independent pathologists with more than 20 years of experience. Immunohistochemical, molecular, cytogenetic, and histochemical studies were performed during the reassessment of cases when routine staining (hematoxylin-eosin) was not sufficient to establish the final diagnosis.

2.2 Analysis

Descriptive and quantitative data analysis was performed using the Statistical Package for the Social Sciences for Windows 20.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were expressed as mean, median, and standard deviation values. Categorical variables were expressed as absolute number of cases and percentage values.

3. Results

The Private Oral Pathology Service received 11,017 surgical specimens between 2000–2019, of which 164 were diagnosed as SGT (1.48%). Of these, 110 (67.1%) were benign, and 54 (32.9%) malignant neoplasms with a benign:malignant ratio of 2.3:1, distributed among seven benign and ten malignant histologic subtypes (Table 1).

The majority of patients were female (n = 100, 61.0%) with an overall female:male ratio of 1.5:1 (Table 1). Most tumors occurred in patients between the fourth and sixth decades of life, with a mean age of 47.9 years (range 04–91 years). Table 2 shows the distribution of each salivary gland neoplasm, according to the age of patients.

Regarding the anatomical site, 68.9% of the tumors occurred in the minor salivary glands (n = 113), while only 25.6% affected the major salivary glands (n = 42). The palate was the most commonly affected site, with a frequency of 40.9% (n = 67), followed by the parotid gland (n = 37, 22.6%), lips (n = 16, 9.8%), buccal mucosa (n = 14, 8.5%), and submandibular gland (n = 5, 3.0%). There were 9 cases with unspecified anatomic

location (5.5%), and none affected the sublingual gland. Both benign and malignant tumors predominated in the soft and hard palate, followed by the parotid gland (Table 3).

Among the benign salivary gland tumors, pleomorphic adenoma (PA) was the most frequent (n = 88; 80.0%), followed by myoepithelioma (n = 13, 11.8%), and Warthin's Tumor (n = 3, 2.7%) (Table 1). Most tumors were diagnosed in the fourth and fifth decades of life (Fig. 1); however, the age ranged from 4 to 89 years, with an average of 47.1 years (SD ± 18.9). Most cases occurred in the palate (n = 45, 40.9%) and female patients (n = 63; 57.3%), with a female:male ratio of 1.3:1 (63 female and 47 male).

Regarding the malignancies (n = 54), mucoepidermoid carcinoma was the most frequent malignant tumor (n = 16, 29.6%), followed by polymorphous adenocarcinoma (n = 10, 18.5%), and adenoid cystic carcinoma (n = 8, 14.8%) (Table 1). The age ranged from 14 to 91 years, with a mean of 49.0 years (SD ± 17.3) (Table 2). Most cases also occurred in the minor salivary glands of the palate (n = 22, 40.7%) and female patients (n = 37; 68.5%), with a female:male ratio of 2.2:1 (37 female and 17 male) (Tables 1 and 3).

Immunohistochemical reactions (IHC) were used in 6 cases (3.7%). In 4 of the cases, IHC was used to determine the proliferative index; in only 2 of the cases, it aimed to identify cells and structures in order to facilitate the diagnosis. After reevaluation of morphology, immunohistochemical, molecular, and cytogenetic studies, six cases (3.7%) were reclassified. Of these, four benign tumors (2.4%) were reclassified as malignant neoplasms, and two malignant tumors (1.2%) reclassified according to the morphological subtype. Four cases of PA were reclassified as carcinoma ex-pleomorphic adenomas. One case of adenocarcinoma NOS as clear cell hyalinizing carcinoma. Also, one case of ACC and two of polymorphous adenocarcinomas were compatible as cribriform adenocarcinoma of minor salivary glands (CAMSG), a variant of polymorphous adenocarcinoma. However, cases compatible with CAMSG were maintained as polymorphous adenocarcinomas based on the current WHO Classification of Head and Neck Tumors [17].

4. Discussion

In the last 20 years, the histological classification of salivary gland tumors has been modified twice, in 2005 and 2017, and several studies have been published on the incidence and characteristics of SGT worldwide [2-5,18-23,30]. However, the relative

frequency and distribution of salivary gland neoplasms remain topics of discussion in the scientific literature. In the present study, the sample represented about 1.48% of all lesions diagnosed in the referred oral pathology service. Studies conducted in other oral pathology services reveal that SGT accounts for about 0.08% to 2.6% of all diagnosed lesions [2,16], which are data similar to our results, and variations in frequency depend on the referral sources and type of diagnostic services (private, public, hospital-based, etc).

Overall, according to the WHO Histological Classification of Head and Neck Tumors (2017), female patients are slightly more affected by SGT than male patients [17]. However, when analyzing specific tumor subtypes, some variations can be found [2,3,8,15]. In the present study, the female-to-male ratio was 2.3:1, which is in agreement with most studies [13,19], including Mexican reports [14].

In this study, most tumors were benign (67.1%), data similar to other studies where these tumors correspond to about 64.7 to 80.0% of all salivary gland neoplasms [11,15]. However, some studies have shown a higher incidence of malignancies [20-23] and suggest geographic variation in the frequency of these tumors. In addition, benign neoplasms presented a female-to-male ratio of 1.3:1, while malignant neoplasms demonstrated a female-to-female ratio of 2.2:1, indicating that both benign and malignant tumors were more common in female patients. These data are in accordance with a previous study performed in Mexico that also showed that female patients were more affected by malignant neoplasms than male patients [14]. However, unlike our results, other studies show that men are mainly affected by malignant salivary gland tumors, but no explanation has been offered for this data [3,8].

Regarding the benign neoplasms, PA was the most common tumor in this study, accounting for 80.0% of all benign neoplasms, followed by myoepithelioma (11.8%). In fact, PA is the most common benign neoplasm [2,3,5-16,18-20]. However, in contrast to our results, most studies have shown Warthin's Tumor [3,5-13,18] and basal cell adenoma [2,10-13,15,19,22] as the second or third most common benign tumor, respectively. The fact that the present study was carried out in an oral pathology service may explain this apparent difference. Warthin's tumor is a benign neoplasm that affects almost exclusively the parotid gland, and some studies show that most cases of surgical pathology centers affect the major salivary glands, especially the parotid gland. In contrast, tumors of the minor salivary glands represent the majority of the cases diagnosed in oral pathology

services [3, 8]. These findings suggest that studies involving the participation of several centers can better characterize the heterogeneity of these tumors and contribute to a better understanding of the epidemiological differences in the population [3]. In addition, some other benign tumors were very rare, such cystadenoma (n = 2, 1.8%) and sialadenoma papilliferum (n = 1, 0.9%), in accordance with previous studies [12,13].

Regarding malignancies, the most common Tumor was MEC, accounting for 29.6% of the cases, similar to previous studies [2,3,6-13,16,19]. However, other series found ACC as the most frequent malignant tumor [14,18,20,21], including Brazilian reports, where ACC corresponded to approximately 58.3% of all malignant neoplasms of the salivary glands [5]. In the current study, the second most common malignant tumor was polymorphous adenocarcinoma, accounting for 18.5% of all malignant neoplasms. Interestingly, only one of the previously published studies shows polymorphous adenocarcinoma among the three most common malignancies [2]. In general, the most frequent malignant tumors are mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, and adenocarcinoma not otherwise specified [2,3]. In addition, other malignant tumors such as salivary duct carcinomas (n = 1, 1.9%) and myoepithelial carcinoma (n = 1, 1.9%) were rare. Although these neoplasms are well recognized, they are also rarely reported in studies with small samples [2,3]. This difference may be explained perhaps due to lack of uniform histomorphological criteria for diagnosis, different classifications, and time of experience and familiarity of pathologists with these lesions.

In addition, it is essential to be aware of the recent changes in terminology of SGTs, as some primary malignant epithelial SGTs were included in the current WHO classification (2017), such as secretory carcinoma, intraductal carcinoma, and poorly differentiated carcinoma [17]. Also, polymorphous low-grade adenocarcinoma (PLGA) is now termed polymorphous adenocarcinoma [3,17] because of the variable biological behavior of this neoplasm. The purpose of this modification, in particular, is to facilitate the choice of treatment and to avoid possible terminological confusion, especially in the most unusual cases [2,3,17]. In the present study, we reevaluated the morphologic diagnosis of all tumors according to the latest WHO classification (2017) [17], and six cases (3.7%) were reclassified based on morphological characteristics and immunohistochemical and molecular studies.

Four cases of PA were reclassified as carcinoma ex-pleomorphic adenomas and one case of adenocarcinoma NOS as clear cell hyalinizing carcinoma after reevaluation of morphology and immunohistochemistry analysis. Also, one case of ACC and two of polymorphous adenocarcinomas were compatible as cribriform adenocarcinoma of minor salivary glands (CAMSG). The first description of this tumor was done by Michal et al. (1999) under the term cribriform adenocarcinoma of the tongue (CAT) [24]. Later, it was renamed by Skalova et al. as "cribriform adenocarcinoma of minor salivary gland origin" in a series of 23 new cases because they affected other minor salivary glands, including those of the palate, retromolar region, tonsils, and upper lip [25].

Currently, CAMSG is a provisional entity without a clear statement as to whether it represents a genuine entity or is merely a possible variant of polymorphous adenocarcinoma [17,26]. However, it is essential to emphasize that although some cases of CAMSG have an indolent clinical course such as polymorphous adenocarcinoma, it presents a higher probability to metastasize to cervical lymph nodes [17]. Although polymorphous adenocarcinoma shares some histologic similarities with CAMSG, polymorphous adenocarcinoma has more diverse histology and the characteristic ground glass nuclei [17,25]. Moreover, recent molecular studies indicate that rearrangements of PRKD1-3, including ARID1A-PRKD1 and DDX3X-PRKD1 gene fusions, are seen in about 80% of cases of CAMSG, as also observed in our cases, and in less than 10% of cases with classic morphology of polymorphous adenocarcinoma [27]. In contrast, PRKD1 E710D mutations are largely restricted to classic polymorphous adenocarcinoma, with only about 10% of CAMSG showing a mutation [28, 29].

Like previous authors [24-26], we agree that CAMSG is a distinct tumor entity that differs from polymorphous adenocarcinoma by location (most often arising on the posterior region of the tongue), histological architecture, and biological behavior, with frequent metastases at the time of presentation of the primary tumor [25,26]; however, the counterpoints to these arguments are that the findings in the literature are still scarce, there is some morphological and genotypic overlap between these lesions, and despite the regional aggressiveness, it has not been established differences in survival rates [17]. For these reasons, despite the extensive debate, the decision of the WHO was to maintain a more conservative and unifying approach and leave the CAMSG as a variant of polymorphous adenocarcinoma for this edition. This is also consistent with the fact that

both polymorphous adenocarcinoma and CAMSG are driven by genes of the same family, which possibly indicates that are variants of the same spectrum [17].

The classification of SGT is dynamic, and with the recent advances in immunohistochemistry and application of in situ fluorescence hybridization for molecular cytogenetic analysis, specific and refined changes continue to occur [30]. Thus, continuous epidemiological studies of SGT are essential because they help to improve understanding of their clinical and pathological characteristics and are essential to keep physicians and surgeons up to date, especially when the classification of these tumors undergoes some change [2,3].

Regarding the anatomical location, most of the SGT of this study were diagnosed in the minor salivary glands of the palate (Figs. 2, 3). Similarly, this result was also reported by other studies [22,23]. Nonetheless, some studies have shown that SGT preferentially affects the parotid gland [2,3,5-16,18-21]. This difference maybe can be explained by the fact that most surgical specimens sent for an oral pathology service are incisional biopsies or relatively small surgical specimens managed by oral and maxillofacial surgeons, while larger lesions from major salivary glands tend to be treated in hospitals that also perform the histopathological diagnosis [8]. In the present study, benign tumors were greater in number than malignant tumors in all decades of life in both major and minor salivary glands. However, no benign or malignant tumor occurred in the sublingual gland, perhaps because these tumors have a low prevalence in the sublingual glands, as shown by some studies [12, 16]. On the other hand, when these lesions occur in this region, 70–90% of the tumors are malignant [16].

In summary, the data from the present study suggest slight variations in the relative frequency and distribution of SGT among populations in Mexico and other regions of the world. Further research is needed to clarify whether such differences derive from the peculiar characteristics of the populations analyzed or the particularities of the service in which the study was conducted. Also, despite the rarity in which SGTs are encountered in the practice of medicine and dentistry, it is essential that physicians and dentists be informed about salivary gland function, abnormalities, and the diseases that can affect these glands, contributing to early diagnosis and effective treatment of these lesions and cancer prevention.

Funding

No funding sources to disclose.

Compliance with Ethical Standards

Conflict of interest

No conflicts of interest to disclose.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of the School of Dentistry of Piracicaba (Protocol nº 20726819.6.0000.5418).

Acknowledgments

This work was supported by the Coordination for the Improvement of Higher Education Personnel (CAPES).

References

1. Ogle OE. Salivary Gland Diseases. Dent Clin North Am. 2020;64(1):87–104. doi:10.1016/j.cden.2019.08.007
2. da Silva LP, Serpa MS, Viveiros SK, Sena DAC, de Carvalho Pinho RF, de Abreu Guimarães LD, et al. Salivary gland tumors in a Brazilian population: A 20-year retrospective and multicentric study of 2292 cases. J Craniomaxillofac Surg. 2018 Dec;46(12):2227-2233. doi: 10.1016/j.jcms.2018.09.028.
3. Cunha JLS, Coimbra AC, Silva JV, IS Nascimento, CR Oliveira, ME Andrade, et al. Epidemiologic analysis of salivary gland tumors over a 10-years period diagnosed in a northeast Brazilian population. Med Oral Patol Oral Cir Bucal. 2020;25(4):e516-e522. doi: 10.4317/medoral.23532.
4. Rooper LM. Challenges in Minor Salivary Gland Biopsies: A Practical Approach to Problematic Histologic Patterns. Head Neck Pathol. 2019 Mar 18. doi: 10.1007/s12105-019-01010-8.
5. Vasconcelos AC, Nör F, Meurer L, Salvadori G, Souza LB, Vargas PA, et al. Clinicopathological analysis of salivary gland tumors over a 15-year period. Braz Oral Res 30:pii:S1806-83242016000100208. 2016.

6. Vargas PA, Gerhard R, Araújo Filho VJ, de Castro IV. Salivary gland tumors in a Brazilian population: a retrospective study of 124 cases. Rev Hosp Clin Fac Med Sao Paulo. 2002 Nov-Dec;57(6):271-6.
7. Ito FA, Ito K, Vargas PA, de Almeida OP, Lopes MA. Salivary gland tumors in a Brazilian population: a retrospective study of 496 cases. Int J Oral Maxillofac Surg. 2005 Jul;34(5):533-6. doi: 10.1016/j.ijom.2005.02.005
8. Fonseca FP, Carvalho M de V, de Almeida OP, Rangel AL, Takizawa MC, Bueno AG, et al. Clinicopathologic analysis of 493 cases of salivary gland tumors in a Southern Brazilian population. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012 Aug;114(2):230-9. doi: 10.1016/j.oooo.2012.04.008.
9. Bittar RF, Ferraro HP, Moraes Gonçalves FT. Couto da Cunha MG. Biamino ER. Neoplasms of the salivary glands: analysis of 727 histopathological reports in a single institution. Otolaryngol Pol. 2015;69(4):28-33. doi: 10.5604/00306657.1163578.
10. Wang YL, Zhu YX, Chen TZ, Wang Y, Sun GH, Zhang L, et al. Clinicopathologic study of 1176 salivary gland tumors in a Chinese population: experience of one cancer center 1997-2007. Acta Otolaryngol. 2012 Aug;132(8):879-86. doi: 10.3109/00016489.2012.662715.
11. Gao M, Hao Y, Huang MX, Ma DQ, Chen Y, Luo HY, et al. Salivary gland tumours in a northern Chinese population: a 50-year retrospective study of 7190 cases. Int J Oral Maxillofac Surg. 2017 Mar;46(3):343-349. doi: 10.1016/j.ijom.2016.09.021.
12. Wang XD, Meng LJ, Hou TT, Huang SH. Tumours of the salivary glands in northeastern China: a retrospective study of 2508 patients. Br J Oral Maxillofac Surg. 2015 Feb;53(2):132-7. doi: 10.1016/j.bjoms.2014.10.008.
13. Li LJ, Li Y, Wen YM, Liu H, Zhao HW. Clinical analysis of salivary gland tumor cases in West China in past 50 years. Oral Oncol. 2008 Feb;44(2):187-92. doi: 10.1016/j.oraloncology.2007.01.016.
14. Mejía-Velázquez CP, Durán-Padilla MA, Gómez-Apo E, Quezada-Rivera D, Gaitán-Cepeda LA. Tumors of the salivary gland in Mexicans. A retrospective study of 360 cases. Med Oral Patol Oral Cir Bucal. 2012;17(2):e183–e189. Published 2012 Mar 1. doi:10.4317/medoral.17434
15. Sentani K, Ogawa I, Ozasa K, Sadakane A, Utada M, Tsuya T, Kajihara H, Yonehara S, Takeshima Y, Yasui W. Characteristics of 5015 Salivary Gland

Neoplasms Registered in the Hiroshima Tumor Tissue Registry over a Period of 39 Years. J Clin Med. 2019 Apr 26;8(5):566. doi: 10.3390/jcm8050566.

16. Reinheimer A, Vieira DS, Cordeiro MM, Rivero ER. Retrospective study of 124 cases of salivary gland tumors and literature review. J Clin Exp Dent. 2019;11(11):e1025–e1032. doi:10.4317/jced.55685
17. Seethala RR, Stenman G. Update from the 4th Edition of the World Health Organization Classification of Head and Neck Tumours: Tumors of the Salivary Gland. Head Neck Pathol. 2017 Mar;11(1):55-67. doi: 10.1007/s12105-017-0795-0. Epub 2017 Feb 28.
18. de Oliveira FA, Duarte EC, Taveira CT, Máximo AA, de Aquino EC, Alencar Rde C, et al. Salivary gland tumor: a review of 599 cases in a Brazilian population. Head Neck Pathol. 2009 Dec;3(4):271-5. doi: 10.1007/s12105-009-0139-9.
19. Araya J, Martinez R, Niklander S, Marshall M, Esguep A. Incidence and prevalence of salivary gland tumours in Valparaiso. Chile. Med Oral Patol Oral Cir Bucal. 2015;20(5):e532–e539. doi:10.4317/medoral.20337
20. Fomete B, Adebayo ET. Ononiwu CN. Management of salivary gland tumors in a Nigerian tertiary institution. Ann Afr Med. 2015 Jul-Sep;14(3):148-54. doi: 10.4103/1596-3519.152071.
21. Lawal AO, Adisa AO, Kolude B, Adeyemi BF, Olajide MA. A review of 413 salivary gland tumours in the head and neck region. J Clin Exp Dent. 2013;5(5):e218–e222. doi:10.4317/jced.51143
22. Bussari S, Shedam TM, Debta P, Shaikh NA, Yeli NR, Jeergal PA, et al. A Retrospective Clinicopathological Study of Salivary Gland Tumors with Particular Reference to Histological Types. Site. Age. and Sex Distribution. J Int Oral Health. 2016;8:1082 1088.
23. Tilakaratne WM, Jayasooriya PR, Tennakoon TM, Saku T. Epithelial salivary tumors in Sri Lanka: a retrospective study of 713 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 108:90 98. 2009.
24. Michal M, Skálová A, Simpson RHW, Raslan WF, Curik R, Leivo I, et al. Cribriform adenocarcinoma of the tongue: a hitherto unrecognized type of adenocarcinoma characteristically occurring in the tongue. Histopathology. 1999;35:495–501. doi: 10.1046/j.1365-2559.1999.00792.x
25. Skalova A, Sima R, Kaspirkova-Nemcova J, Simpson RH, Elmberger G, Leivo I, et al. Cribriform adenocarcinoma of minor salivary gland origin principally

affecting the tongue: characterization of new entity. Am J Surg Pathol. 2011 Aug;35(8):1168-76. doi: 10.1097/PAS.0b013e31821e1f54.

26. Michal M, Kacerovska D, Kazakov DV. Cribriform adenocarcinoma of the tongue and minor salivary glands: a review. Head Neck Pathol. 2013 Jul;7 Suppl 1(Suppl 1):S3-11. doi: 10.1007/s12105-013-0457-9.
27. Weinreb I, Zhang L, Tirunagari LM, Sung YS, Chen CL, Perez-Ordonez B, et al. Novel PRKD gene rearrangements and variant fusions in cribriform adenocarcinoma of salivary gland origin. Genes Chromosomes Cancer. 2014;53(10):845–856. doi: 10.1002/gcc.22195. (A)
28. Weinreb I, Piscuoglio S, Martelotto LG, Waggott D, Ng CK, Perez-Ordonez B, et al. Hotspot activating PRKD1 somatic mutations in polymorphous low-grade adenocarcinomas of the salivary glands. Nat Genet. 2014;46(11):1166–1169. doi: 10.1038/ng.3096. (B)
29. Weinreb I, Chiosea SI, Seethala RR, Reis-Filho JS, Weigelt B, Piscuoglio S, et al. Genotypic and phenotypic comparison of polymorphous and cribriform adenocarcinomas of salivary gland. Mod Pathol. 2015;28(S2):333.
30. Mahomed Y, Meer S. Primary Epithelial Minor Salivary Gland Tumors in South Africa: A 20-Year Review. Head Neck Pathol. 2020 Sep;14(3):715-723. doi: 10.1007/s12105-019-01111-4.

Table 1. Histologic and gender distribution of 164 salivary gland tumors.

					Sex		
		n=164	%[a]	%[b]	Male		Female	
					n	%	n	%
Benign tumors	Pleomorphic adenoma	88	80.0	53.7	35	21.3	53	32.3
	Myoepithelioma	13	11.8	7.9	7	4.3	6	3.7
	Warthin's Tumor	3	2.7	1.8	2	1.2	1	0.6
	Canalicular adenoma	2	1.8	1.2	1	0.6	1	0.6
	Cystadenoma	2	1.8	1.2	2	1.2	0	0.0
	Basal cell adenoma	1	0.9	0.6	0	0.0	1	0.6
	Sialadenoma papilliferum	1	0.9	0.6	0	0.0	1	0.6
	Total	**110**	**100**	**67.1**	**47**	**28.7**	**63**	**38.4**
Malignant tumors	Mucoepidermoid carcinoma	16	29.6	9.8	3	1.8	13	7.9
	Polymorphous adenocarcinoma	10	18.5	6.1	0	0.0	10	6.1
	Adenoid cystic carcinoma	8	14.8	4.9	2	1.2	6	3.7
	Acinic cell carcinoma	7	13.0	4.3	6	3.7	1	0.6
	Carcinoma ex-pleomorphic adenoma	5	9.3	3.0	2	1.2	3	1.8
	Clear cell hyalinizing carcinoma	3	5.6	1.8	2	1.2	1	0.6
	Epithelial-myoepithelial carcinoma	2	3.7	1.2	0	0.0	2	1.2
	Adenocarcinoma NOS	1	1.9	0.6	0	0.0	1	0.6
	Salivary duct carcinoma	1	1.9	0.6	1	0.6	0	0.0
	Myoepithelial carcinoma	1	1.9	0.6	1	0.6	0	0.0
	Total	**54**	**100**	**32.9**	**17**	**10.3**	**37**	**22.6**

[a]Percent in the group (benign or malignant); [b] Percent in relation to the total number of cases;

Table 2. Age group distribution (decade of life) of salivary gland tumors

				Age groups									Total	
		Age range	Mean age[a]	0-10	11-20	21-30	31-40	41-50	51-60	61-70	>70	NS	n	%
Benign tumors	Pleomorphic adenoma	13-85	44.7	0	6	11	18	14	22	7	5	5	88	53.7
	Myoepithelioma	04-77	45.3	1	1	1	2	1	0	4	1	2	13	7.9
	Warthin's Tumor	54-82	65	0	0	0	0	0	2	0	1	0	3	1.8
	Canalicular adenoma	69-78	73.5	0	0	0	0	0	0	1	1	0	2	1.2
	Cystadenoma	82-89	85.5	0	0	0	0	0	0	0	2	0	2	1.2
	Basal cell adenoma	-	73	0	0	0	0	0	0	0	1	0	1	0.6
	Sialadenoma papilliferum	-	55	0	0	0	0	0	1	0	0	0	1	0.6
	Total	**13-89**	**47.1**	**1**	**7**	**12**	**20**	**15**	**25**	**12**	**11**	**7**	**110**	**67.1**
Malignant tumors	Mucoepidermoid carcinoma	14-91	42.4	0	1	3	3	5	2	0	1	1	16	9.8
	Polymorphous adenocarcinoma	26-76	57.2	0	0	1	0	2	3	2	2	0	10	6.1
	Adenoid cystic carcinoma	29-63	49.2	0	0	1	1	1	4	1	0	0	8	4.9
	Acinic cell carcinoma	29-68	49.7	0	0	1	1	1	1	2	0	1	7	4.3
	Carcinoma ex-pleomorphic adenoma	25-78	50	0	0	2	0	0	1	1	1	0	5	3.0
	Clear cell hyalinizing carcinoma	21-69	50	0	0	1	0	0	1	1	0	0	3	1.8
	Epithelial-myoepithelial carcinoma	32-85	58.5	0	0	0	1	0	0	0	1	0	2	1.2
	Adenocarcinoma NOS	-	40	0	0	0	1	0	0	0	0	0	1	0.6
	Salivary duct carcinoma	-	55	0	0	0	0	0	1	0	0	0	1	0.6
	Myoepithelial carcinoma	-	37	0	0	0	1	0	0	0	0	0	1	0.6
	Total	**14-91**	**49.0**	**0**	**1**	**9**	**8**	**9**	**13**	**7**	**5**	**2**	**54**	**32.9**

NS: not specified; [a]Years;

Table 3. Distribution of the 164 salivary gland tumors according to the location (major and minor salivary glands).

		Major salivary glands		**Minor salivary glands**									**Total**	
		Parotid	Submandibular	Palate	Lips	Buccal mucosa	Tongue	Floor of the mouth	Retromolar	IO	Maxillary sinus	NS	**n**	**%**
Benign tumors	Pleomorphic adenoma	27	3	35	9	8	1	0	0	0	0	5	88	53.7
	Myoepithelioma	0	0	9	2	1	0	1	0	0	0	0	13	7.9
	Warthin's Tumor	2	0	0	1	0	0	0	0	0	0	0	3	1.8
	Canalicular adenoma	0	0	0	2	0	0	0	0	0	0	0	2	1.2
	Cystadenoma	0	0	0	0	1	0	0	0	1	0	0	2	1.2
	Basal cell adenoma	0	0	0	0	0	0	0	0	0	1	0	1	0.6
	Sialadenoma papilliferum	0	0	1	0	0	0	0	0	0	0	0	1	0.6
	Total	**29**	**3**	**45**	**14**	**10**	**1**	**1**	**0**	**1**	**1**	**5**	**110**	67.1
Malignant tumors	Mucoepidermoid carcinoma	2	0	9	0	1	0	0	2	1	0	1	16	9.8
	Polymorphous adenocarcinoma	0	0	6	0	1	0	1	1	1	0	0	10	6.1
	Adenoid cystic carcinoma	0	2	1	0	1	1	0	1	1	1	0	8	4.9
	Acinic cell carcinoma	3	0	0	1	0	0	0	1	0	0	2	7	4.3
	Carcinoma ex-pleomorphic adenoma	3	0	1	0	1	0	0	0	0	0	0	5	3.0
	Clear cell hyalinizing carcinoma	0	0	1	1	0	0	0	0	0	0	1	3	1.8
	Epithelial-myoepithelial carcinoma	0	0	1	0	0	0	0	0	1	0	0	2	1.2
	Adenocarcinoma NOS	0	0	1	0	0	0	0	0	0	0	0	1	0.6
	Salivary duct carcinoma	0	0	1	0	0	0	0	0	0	0	0	1	0.6
	Myoepithelial carcinoma	0	0	1	0	0	0	0	0	0	0	0	1	0.6
	Total	**8**	**2**	**22**	**2**	**4**	**1**	**1**	**5**	**4**	**1**	**4**	**54**	**32.9**

NS: not specified; IO: intraosseous.

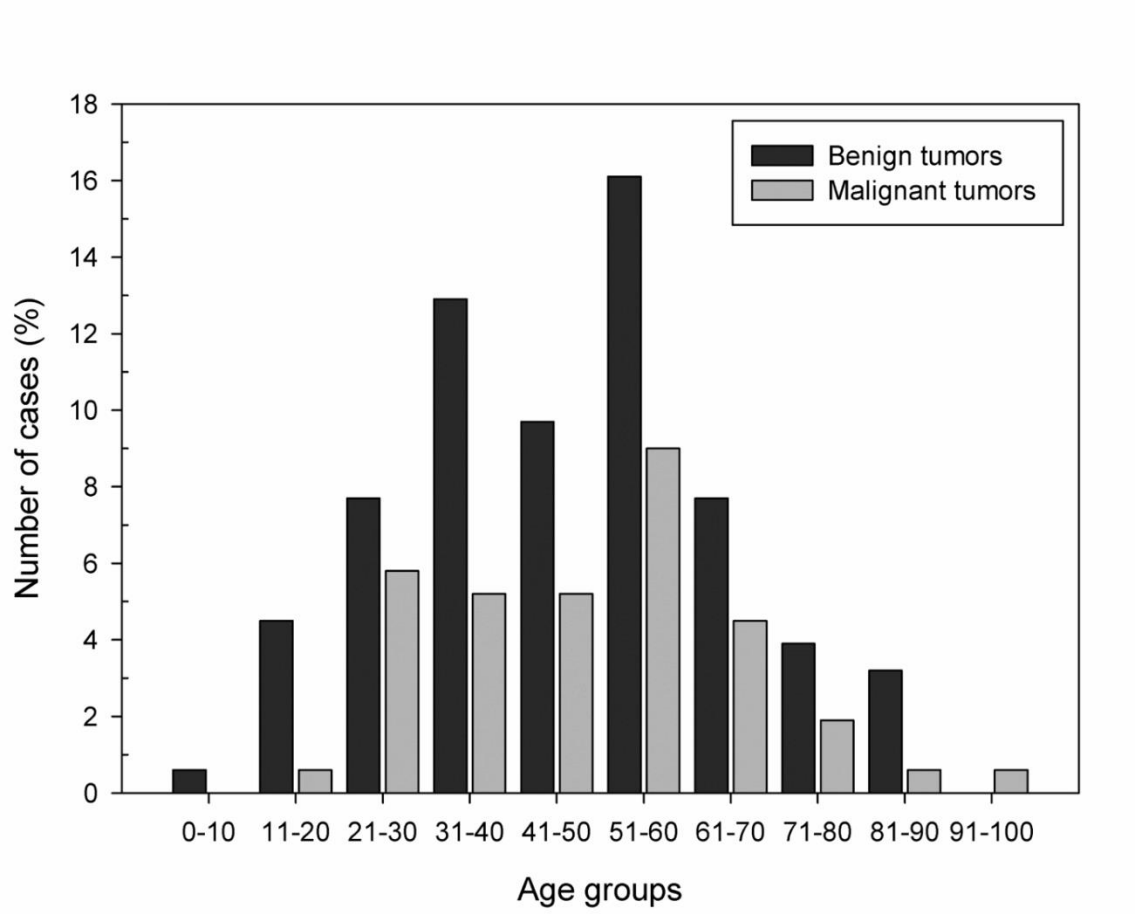


Figure 1. Distribution of 164 salivary gland tumors according to the age group (decade of life).

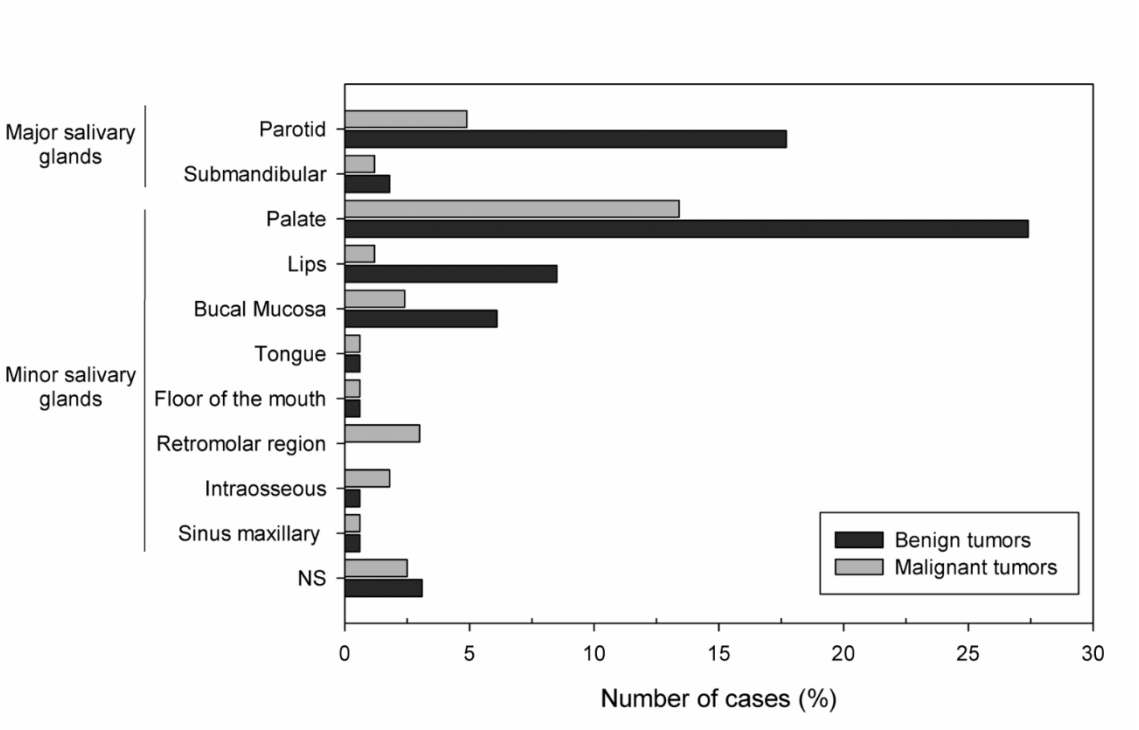


Figure 2. Distribution of 164 salivary gland tumors according to the primary site of involvement. NS, not specified.

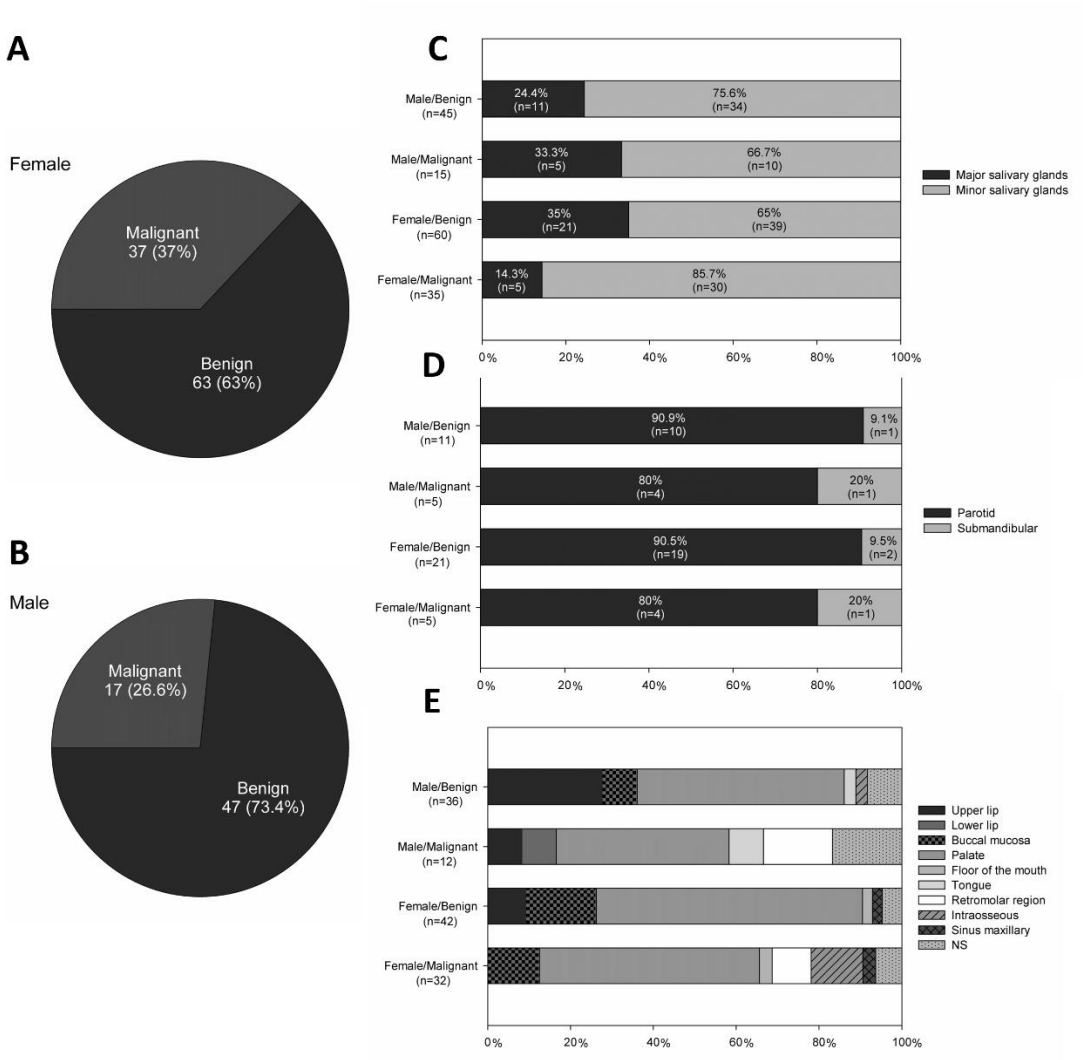


Figure 3. A and B. Distribution of benign and malignant salivary gland tumors by sex; C, D, and E. Distribution of benign and malignant salivary gland tumors by location (major vs. minor salivary glands). NS, not specified.

2.3 Artigo:

CARCINOMA EX PLEOMORPHIC ADENOMA OF MINOR SALIVARY GLANDS: A LATIN-AMERICAN COLLABORATIVE STUDY OF 39 CASES

Short Title: Carcinoma Ex-Pleomorphic Adenoma of Minor Salivary Glands

John Lennon Silva Cunha[1], Alicia Rumayor Pinã[2], Maria Goretti Freire de Carvalho[3], Ricardo Luiz Cavalcanti de Albuquerque Júnior[4], Ana Carolina Penha Coimbra[5], Juan Carlos Hernandez-Guerrero[6], Oslei Paes de Almeida[1], Adalberto Mosqueda-Taylor[7], Roman Carlos[8], Ciro Dantas Soares[1,3]

[1]Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, Brazil

[2]Facultad de Odontología, Universidad Autónoma de Coahuila (UAdeC), Saltillo, Coahuila, México

[3]Private Pathology Service, Laboratório de Citopatologia, Natal, Brazil

[4]Laboratory of Morphology and Experimental Pathology, Institute of Technology and Research, Tiradentes University (UNIT), Aracaju, SE, Brazil

[5]Department of Medicine, Federal University of Sergipe (UFS), Aracaju, SE, Brazil

[6] Facultad de Odontología, Laboratory of Immunology, Universidad Nacional Autónoma de México (UNAM), México City, México

[7]Facultad de Odontología, Universidad Autónoma Metropolitana Xochimilco (UAM), México City, México

[8]Pathology Division, Centro Clınico de Cabeza y Cuello/Hospital Herrera Llerandi, Guatemala City, Guatemala

Corresponding Author:

Ciro Dantas Soares

Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), Av. Limeira 901, P.O. Box. 52, Piracicaba, São Paulo 1314-903, Brazil. **E-mail:** ciro.dss@gmail.com. Phone number: +55 19 2106-5315/2106-5200

Abstract

Background: Carcinoma ex pleomorphic adenoma (CXPA) involving the minor salivary glands is rare. Detection of the carcinomatous component in incisional biopsy samples is difficult and can be a challenge, especially in incipient cases and small biopsy samples. This study aimed to characterize and describe the clinicopathologic features of a series of intraoral CXPA and reassess 561 cases of pleomorphic adenomas (PA) affecting the minor salivary glands with emphasis on the detection of the carcinomatous component.

Methods: A retrospective descriptive cross-sectional study was carried out. Records of all cases of CXPA and 561 pleomorphic adenomas (PAs) of the minor salivary glands were retrieved from six Latin-American pathology services. Clinicopathologic data were collected from medical records. Morphological and immunohistochemical (CK-7, CK-14, α-SMA, calponin, p63, p53, and Ki67) analyses were performed.

Results: A total of 39 cases of CXPAs were collected. Twenty-two (56.4%) were from women and 17 (43.6%) from men, ranging in age from 19 to 81 years (mean: 45.9 years). Most tumors affected the palate (n = 24, 61.5%), followed by the buccal mucosa (n = 9, 23.1%). The most common morphologic subtype was myoepithelial carcinoma (n = 13, 33.3%) followed by adenocarcinoma not otherwise specified (n = 10, 25.6%). We also reviewed 561 PAs of minor salivary glands; after microscopic reevaluation and immunohistochemical studies, ten (1.7%) were reclassified as early CXPA, representing 25.6% of the CXPA cases reported herein. High cellular proliferative index (calculated by Ki67 expression) and p53 expression were useful in the identification of the malignant areas.

Conclusions: Although CXPA may have similar clinical and pathologic features as PA, tumours of minor salivary glands must be analyzed with caution. Assessing cellular proliferative index and p53 expression is recommended to differentiate CXPA of PA, particularly in identifying incipient cases.

Keywords: carcinoma ex-pleomorphic adenoma; pleomorphic adenoma; minor salivary glands; histopathological subtypes.

1. INTRODUCTION

Pleomorphic adenoma (PA) is the most common benign salivary gland (SG) tumour of the oral cavity, representing approximately 80% of the SG tumours in this region.[1,2] Despite its benign nature, malignant transformation into a carcinoma ex pleomorphic adenoma (CXPA), a rare and aggressive tumour, can occur and varies between 3.3 and 13% of all cases.[3-5] Most CXPAs occur in major salivary glands such as the parotid and submandibular gland, and involvement of the minor salivary glands of the oral cavity is rare.[5] The carcinogenic alterations are well-recognized as a multistep process that culminate in the malignant transformation resulting from mutations in oncogenes and loss of expression of tumour suppressor genes.[6,7] Morphologically, the differential diagnosis is broad and includes benign pleomorphic adenomas, metastatic mixed tumours, high-grade salivary adenocarcinomas, and other salivary gland malignancies.[4]

In addition, sometimes PAs can represent a challenge for clinical management and diagnosis, mainly because of a great diversity of morphologic features and growth patterns and its tendency to recurrence.[5,8] Although histologically, most CXPAs clearly show the transition of benign PA into carcinoma,[8] this finding may not be evident, especially in small incisional biopsies and incipient cases may be often misdiagnosed as APs. In these cases, the immunohistochemistry analysis can help establish the correct diagnosis and identification of the malignant component.[9] The use of several immunohistochemical markers has been proposed as an auxiliary method to identify the malignant component in CXPAs, such as HER2/neu, p53, androgen receptor, BCL-2, FASN, and Ki-67.[9-13]

Although the clinical and epidemiological profile of CXPA affecting the major salivary glands is well established in the literature,[9,14-16] the clinicopathologic features of CXPA of minor salivary glands are not fully understood given their relative rarity and histological variety. Thus, in the present study, we report the clinicopathological and immunohistochemical features of 39 new cases of CXPA affecting the minor salivary glands and describe the immunohistochemical characteristics of these rare tumours. In addition, we reviewed 561 PAs in order to identify possible additional incipient cases of CXPA. To the best of our knowledge, this study represents the first Latin-American series with the largest sample of intraoral CXPAs to date.

2. MATERIAL AND METHODS

In the current study, all cases of CXPA and 561 PAs were retrieved from the archives of six oral and maxillofacial pathology services in Brazil, Guatemala, and Mexico. All cases

were subjected to a detailed histopathologic analysis for confirmation of morphologic diagnosis. PAs with more than 5% of the total area of the tumour with morphologic atypia or presenting evidence of extracapsular invasion were submitted to immunohistochemical study.

Formalin-fixed, paraffin-embedded specimens were obtained, and 5-µm histologic sections were stained with hematoxylin-eosin to confirm the histopathologic diagnosis. Disagreements between pathologists were resolved through discussion and consensus between them. Clinical and demographic data, treatment performed, recurrence, and follow-up period were obtained from clinical records (when available).

All cases of CXPA were included and classified according to the extent of invasion beyond the PA capsule as (1) intracapsular carcinoma (contained by the capsule); and (2) frankly invasive CXPA (more than 10% of the tumours were malignant and there was an evident invasion of the adjacent structures). The transformed phenotype was also evaluated based on the diagnostic criteria described by the current edition of the World Health Organization.[4] The malignant areas of CXPA were also classified according to the proliferated cell type (luminal and/or myoepithelial). Finally, the presence or absence of lymphatic, vascular, and perineural invasion, and the presence or absence of compromised lymph nodes (when removed), were analyzed.

Immunohistochemical staining was performed in 3-µm tissue sections in silanized slides using standard protocols for the following antibodies: Cytokeratin 7 (clone OV-TL 12/30, dilution 1:300, Dako), Cytokeratin 14 (clone LL 002, dilution 1:200, Novocastra), α-smooth muscle actin (α-SMA) (clone 1A4, dilution 1:400, Dako), Calponin (clone CALP, dilution 1:600, Dako), p63 (clone 4A4, dilution 1:300, Dako), p53 (clone, dilution 1:300, Dako) and Ki-67 (clone MIB1, dilution 1:100, Dako). The expression of p53 and the high cellular proliferative index (evidenced by Ki-67 nuclear expression), were used as complementary tools to define the malignant area. Internal positive controls and negative controls were considered in all reactions.

The study was approved by the Ethical Committee of the School of Dentistry of Piracicaba (No. 20726819.6.0000.5418).

3. RESULTS

In the present study, a total of 29 cases of CXPA of the minor salivary glands and 10 misdiagnosed as PAs were retrospectively analyzed. A total of 561 pleomorphic adenomas

were reevaluated, of which ten were reclassified as CXPA based on morphological and immunohistochemical findings, corresponding to about 1.7% of the total PAs analyzed. Extracapsular invasion, increased mitotic activity, cellular pleomorphism, areas of necrosis and hyalinization, a high cellular proliferative index, and diffuse expression of p53 were used parameters to identify malignant transformation. The areas of reminiscent PA were also represented by a densely hyalinizing stroma with entrapped ductal structures (**Fig. 1A**). The Ki67-index was low or absent in these areas, mean 0-1% (**Fig. 1B**). In contrast, the Ki67-index varied from 5% to 60% in the malignant component (**Fig. 1D**).

Table 1 summarizes the clinical and morphologic features of these 39 cases. The patients comprised 22 females (56.4%) and 17 males (43.6%), with a mean age of 45.9±16.5 years (ranging from 19 to 81 years) and a 1.3:1 female-to-male ratio. Individuals in the fourth and fifth decades of life were most affected (n = 9, 23.1%, and n = 8, 20.5%, respectively). The palate was the most affected site (n = 24; 61.5%), followed by the buccal mucosa (n = 9; 23.1%). Other locations included lips (n = 4; 10.3%) and floor of the mouth (n = 2; 5.1%). Symptom information was available for 12 cases. Of these, most patients were asymptomatic (n = 8, 66.7%), but pain was mentioned in four cases (33.3%). Evolution time of lesions varied from 4 to 24 months (mean: 9.1 ± 5.6 months). Most tumours occurred in primary PAs (n = 36; 92.3%), and only two cases (7.7%) developed in the recurrent PA.

Microscopically, most tumours appeared without a capsule with an invasion of adjacent structures (salivary glands, adipose tissue, muscle). A combination of hypercellularized areas with chondromyxoid stroma was observed, and it was possible to detect in low power (**Fig. 2**). The benign areas' stroma was composed of myoepithelial cells and double-layered ducts, commonly seen in PA. In **Fig. 2**, an epithelial-myoepithelial carcinoma is illustrated, demonstrating the conventional double-layered structures, with the luminal cells showing squamous differentiation.

The most common histologic subtype was myoepithelial carcinoma (n = 13, 33.3%) (**Fig. 3**), followed by adenocarcinoma not otherwise specified (AdNOS) (n = 10, 25.6%), and salivary duct carcinoma (n = 6, 15.4%). The first one was composed of spindle-shaped, clear, and plasmacytoid cells associated with a variable amount of hyalinized tissue. Tumour cells of the malignant component were positive for α-SMA, calponin, and P63. The cellular proliferative index in benign areas was lower than 1%, whereas in the malignant component varying from 15-50%. High-grade myoepithelial carcinomas were also detected in our

sample (**Fig. 4**). Similarly, these tumours showed a myoepithelial morphology with an increased number of mitosis, nuclear and cellular atypia, necrosis, and invasion of the vessels and nerves. Salivary duct carcinoma (SDC) was the third most common subtype (n = 6; 15.4%), represented by tumour cells arranged in a ductal pattern of different sizes. Early lesions showed small ducts with preservation of the myoepithelial cells (intraductal phase), whereas invasive SDC had rounded cystic and solid tumour lobules of variable size.

Eighteen cases (46.2%) had extracapsular invasion, whereas 21 cases (53.84%) were diagnosed in the intracapsular phase. Vascular and neural invasion were rare, being present in 5 (12.8%) and 2 (5.1%) cases, respectively.

Treatment information was available for ten patients, and all cases were treated by surgical resection. Of these, two cases underwent neck dissection, and one was diagnosed with regional metastasis. Follow-up information was available in 25 patients, ranging from 2 to 49 months (mean 17.1 months). During the follow-up period, 18 patients (72.0%) were alive without signs of recurrence, nodal and distant metastasis; three patients (12.0%) died by the advanced tumour with distant metastasis (lung, brain, and another site without specification), and four died of causes unrelated to the tumour (16.0%). **Table 2** provides the clinicopathological characteristics of each case individually.

4. DISCUSSION

CXPA is a malignant tumour originating from primary or recurrent benign PA representing 1.7-3% of all SG tumours and about 8.5-9.3% of SG malignancies.[1,2] The incidence of CXPA is low; however, there has been observed an increased incidence of these tumours, especially in the last decade.[18] This finding may result from greater recognition of CXPA as a specific diagnostic entity by pathologists specialized in SG tumours. For the correct diagnosis, it is essential to identify co-existent or pre-existing PA.[6,7,18] Although histologically, most CXPAs clearly show the transition of benign PA into carcinoma[8] in small incisional biopsies and incipient cases, this finding may not be evident, and these tumours are often misdiagnosed as PAs. Indeed, some CXPAs cases are challenging to diagnose due to their morphologic similarity with PA, and often the two elements (benign and malignant) are intermixed.[12]

In the present study, we reviewed a large sample of PAs of minor salivary glands (mSG) histologically and encountered a relatively high percentage of tumours that comprise early CXPA. Pathologists should be aware of detecting the early alterations that suggest a

malignant transformation in PAs, including invasion to the adjacent tissues, presence of cellular pleomorphism, hyalinization, necrosis, and frequent mitotic figures.[8,9] Thus, it is essential to highlight the importance of a thorough review of all PA histologic characteristics. In doubtful cases, a small immunohistochemical panel, including p53 and Ki-67, should be used to distinguish these tumours. These observations are in accordance with previous studies that show that the Ki-67 immunoexpression and other markers, such as HER2/neu, p53, androgen receptor, and BCL-2 are overexpressed in CXPAs compared with PAs, suggesting these molecules may play a role in the malignant transformation of PA and may serve as specific markers to distinguish CXPA from PA.[9-12] In addition, fatty acid synthase and Ki-67 immunoexpression in combination have also been shown to be useful for identifying malignant components in CXPAs.[13] Thus, PAs must be carefully analyzed for the presence of atypical histopathological features, especially necrosis, and prominent hyalinization, since studies have associated the presence of these findings with a greater risk of malignant transformation.[5,8,9] In this study, an increase in mitotic activity, cellular pleomorphism, prominent hyalinization, and areas of necrosis was observed, reinforcing that such atypical characteristics are not expected in most PAs and should raise the suspicion of possible carcinomatous transformation.

Several genetic alterations underlie the pathogenesis of CXPA, including mutations in the p53 gene;[19] loss of copy number of the genes CD44, RASSF1, and TP73;[20] fusions involving the gene PLAG1 (CTNNB1-PLAG1);[21] and gain of HER2 and EGFR gene copy numbers.[22] The variety of genetic alterations support the heterogeneity of the CXPA and suggest that the events occur as a multistep carcinogenic process and are closely related to PA.

The great majority of CXPA occurs in major salivary glands (mainly in the parotid). Some series have reported an index of approximately 20% in the minor salivary glands.[23] In the present study, intraoral tumours occur mainly in the palate, followed by buccal mucosa and lips. Interestingly, these areas are the most affected by PA.[2] Also, the clinical presentation is very similar.[1,2] Mariz et al. (2019) have attempted to determine clinical parameters that distinguish between benign and malignant palatal salivary gland tumours.[24] The presence of pain and colour alteration were considered consistent predictors of malignancy.[24] Although pain has been reported in some of our cases (**Table 2**), we could not analyze the symptoms and clinical features of most cases.

Overall, microscopically, CXPAs are categorized as early lesions with no evident invasion and frankly invasive tumours. The first ones make the diagnosis a potential histological dilemma once the malignant areas may be scarce and focal.[9,25] These concepts in the face of the mSGs are challenging once PA of this region may be partially encapsulated. Regarding this point, we suggest that mSG tumours are usually more challenging to determine the malignization based only on morphologic features, and immunohistochemical studies must be performed to establish the diagnosis in doubtful cases.

In the present series, we identified that the main histologic subtypes of CXPA were myoepithelial carcinomas followed by adenocarcinomas, not otherwise specified. Only a minor group was suggestive of high-grade malignancy. Previous studies have demonstrated similar findings in CXPA of major salivary gland tumours.[6,26] Curiously, there was an amount of evidence that the myoepithelial carcinoma subtype increases the risk of recurrence in CXPA in major salivary gland tumours.[27] However, in the present study, in the mSG the tumours tend to have an indolent course with no recurrence episodes.

The best treatment for these tumours has not been established yet.[28] The majority of the studies suggest a wide surgical excision, similar to the current cases, with or no adjuvant therapies.[6,26,29] Thus, it is reasonable to control the disease with surgery; and complementary radiotherapy can be useful in cases with compromised margins. Nevertheless, future studies will clarify these aspects regarding the best therapeutic approaches for these tumours.

With respect to the clinical behaviour, in our series, we observed that most tumours tend to be locally aggressive. However, a low mortality rate (n = 3, 12.0%) was observed in our study, similar to previous reports.[6] However, follow-up data for approximately one-third of cases was not available. Although we have reported a relatively large sample, it is difficult to determine these tumours' behaviour. Considering the rarity of CXPA in the intraoral sites, prospective studies are suggested to determine the clinical and molecular features that can help identify predictive signs and develop targeted therapies.

In conclusion, we have reported 39 new cases of CXPA, rare tumours of the minor salivary glands; they usually arise in the palate. Different histological variants were encountered, being the myoepithelial subtype and adNOS the most common. Immunohistochemical studies are essential to determine the malignant nature of the tumour and classify the morphologic subtype (biphasic - composed of ductal and myoepithelial cells; or monophasic). The cellular proliferative index and p53 expression are useful in the

identification of the malignant areas. Although these tumours seem to present an indolent clinical course, additional studies are needed to clarify their biological potential. The current evidence indicates that these lesions should be completely removed by surgical excision once they can be locally invasive and recur. Despite the rarity of these lesions, physicians and dentists must know about the diversity of CXPA, thus contributing to the early diagnosis and effective treatment of these tumours.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Ethical approval for this study was obtained from Institutional Review Board (No. 20726819.6.0000.5418).

Funding

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001. The author John Lennon Silva Cunha received a MSc scholarship by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES)

References

1. Cunha JL, Coimbra AC, Silva JV, et al. Epidemiologic analysis of salivary gland tumors over a 10-years period diagnosed in a northeast Brazilian population. Med Oral Patol Oral Cir Bucal. 2020;25(4):e516-e522.
2. Cunha JLS, Hernandez-Guerrero JC, de Almeida OP, Soares CD, Mosqueda-Taylor A. Salivary Gland Tumors: A Retrospective Study of 164 Cases from a Single Private Practice Service in Mexico and Literature Review. Head Neck Pathol. 2020 Oct 12. doi: 10.1007/s12105-020-01231-2. Epub ahead of print.
3. Andreasen S, Therkildsen MH, Bjørndal K, Homøe P. Pleomorphic adenoma of the parotid gland 1985-2010: A Danish nationwide study of incidence, recurrence rate, and malignant transformation. Head Neck. 2016 Apr;38 Suppl 1:E1364-9.

4. El-Naggar, AK, Chan, JKC, Grandis, JR, Takata, T, Slootweg, PJ. World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours. 4th ed. Lyon, France: International Agency for Research on Cancer; 2017.
5. Lopes MLDS, Barroso KMA, Henriques ÁCG, Dos Santos JN, Martins MD, de Souza LB. Pleomorphic adenomas of the salivary glands: retrospective multicentric study of 130 cases with emphasis on histopathological features. Eur Arch Otorhinolaryngol. 2017 Jan;274(1):543-551.
6. Mariano FV, Noronha AL, Gondak RO, Altemani AM, de Almeida OP, Kowalski LP. Carcinoma ex pleomorphic adenoma in a Brazilian population: clinico-pathological analysis of 38 cases. Int J Oral Maxillofac Surg. 2013 Jun;42(6):685-92.
7. Scarini JF, Rosa LF, Souza RAL, et al. Gene and immunohistochemical expression of HIF-1α, GLUT-1, FASN, and adipophilin in carcinoma ex pleomorphic adenoma development. Oral Dis. 2020 Mar 16. doi: 10.1111/odi.13332. Epub ahead of print.
8. Pérez-de-Oliveira ME, Leonel ACLDS, de Castro JFL, Carvalho EJA, Vargas PA, Perez DEDC. Histopathological Findings of Intraoral Pleomorphic Adenomas: A Retrospective Study of a Case Series. Int J Surg Pathol. 2019 Oct;27(7):729-735.
9. Di Palma S. Carcinoma ex pleomorphic adenoma, with particular emphasis on early lesions. Head Neck Pathol. 2013;7 Suppl 1(Suppl 1):S68-S76.
10. Mariano FV, Costa AF, Gondak RO, et al. Cellular Proliferation Index between Carcinoma Ex-Pleomorphic Adenoma and Pleomorphic Adenoma. Braz Dent J. 2015;26(4):416-421.
11. Sedassari BT, Dos Santos HT, Mariano FV, da Silva Lascane NA, Altemani A, Sousa S. Carcinoma ex pleomorphic adenoma of minor salivary glands with major epithelial-myoepithelial component: clinicopathologic and immunohistochemical study of 3 cases. Ann Diagn Pathol. 2015;19(3):164-168.
12. Freitas LL, Araújo VC, Martins MT, Chone C, Crespo A, Altemani A. Biomarker analysis in carcinoma ex pleomorphic adenoma at an early phase of carcinomatous transformation. Int J Surg Pathol. 2005;13:337-342.
13. Díaz KP, Gondak R, Martins LL, et al. Fatty acid synthase and Ki-67 immunoexpression can be useful for the identification of malignant component in carcinoma ex-pleomorphic adenoma. J Oral Pathol Med. 2019 Mar;48(3):232-238.
14. Lewis JE, Olsen KD, Sebo TJ. Carcinoma ex pleomorphic adenoma: pathologic analysis of 73 cases. Hum Pathol. 2001 Jun;32(6):596-604.

15. Zbären P, Zbären S, Caversaccio MD, Stauffer E. Carcinoma ex pleomorphic adenoma: diagnostic difficulty and outcome. Otolaryngol Head Neck Surg. 2008 May;138(5):601-5.
16. Katabi N, Gomez D, Klimstra DS, Carlson DL, Lee N, Ghossein R. Prognostic factors of recurrence in salivary carcinoma ex pleomorphic adenoma, with emphasis on the carcinoma histologic subtype: a clinicopathologic study of 43 cases. Hum Pathol. 2010 Jul;41(7):927-34.
17. Olsen KD, Lewis JE. Carcinoma ex pleomorphic adenoma: a clinicopathologic review. Head Neck. 2001;11:705–712.
18. Okano K, Ishida M, Sandoh K, Fujisawa T, Iwai H, Tsuta K. Cytological features of carcinoma ex pleomorphic adenoma of the salivary glands: A diagnostic challenge. Diagn Cytopathol. 2020 Feb;48(2):149-153.
19. Gedlicka C, Item CB, Wögerbauer M, et al. transformation of pleomorphic adenoma to carcinoma ex pleomorphic adenoma of the parotid gland is independent of p53 mutations. J Surg Oncol. 2010;101(2):127-130.
20. Mariano FV, Rincon D, Gondak RO, et al. Carcinoma ex-pleomorphic adenoma of upper lip showing copy number loss of tumor suppressor genes. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;116(1):69-74.
21. Asahina M, Saito T, Hayashi T, Fukumura Y, Mitani K, Yao T. Clinicopathological effect of PLAG1 fusion genes in pleomorphic adenoma and carcinoma ex pleomorphic adenoma with special emphasis on histological features. Histopathology. 2019 Feb;74(3):514-525.
22. Nishijima T, Yamamoto H, Nakano T, et al. Dual gain of HER2 and EGFR gene copy numbers impacts the prognosis of carcinoma ex pleomorphic adenoma. Hum Pathol. 2015;46(11):1730-1743.
23. Gupta A, Koochakzadeh S, Neskey DM, Nguyen SA, Lentsch EJ. Carcinoma ex pleomorphic adenoma: A review of incidence, demographics, risk factors, and survival. Am J Otolaryngol. 2019;40(6):102279.
24. Mariz BALA, do Socorro Queiroz Feio P, Roza ALOC, et al. Clinical predictors of malignancy in palatal salivary gland tumors. Oral Dis. 2019;25(8):1919-1924.
25. Griffith CC, Thompson LD, Assaad A, et al. Salivary duct carcinoma and the concept of early carcinoma ex pleomorphic adenoma. Histopathology. 2014;65(6):854-860.

26. Ye P, Gao Y, Mao C, Guo CB, Yu GY, Peng X. Carcinoma Ex Pleomorphic Adenoma: Is It a High-Grade Malignancy? J Oral Maxillofac Surg. 2016 Oct;74(10):2093-104.
27. Katabi N, Gomez D, Klimstra DS, Carlson DL, Lee N, Ghossein R. Prognostic factors of recurrence in salivary carcinoma ex pleomorphic adenoma, with emphasis on the carcinoma histologic subtype: a clinicopathologic study of 43 cases. Hum Pathol. 2010;41(7):927-934.
28. Seok J, Hyun SJ, Jeong WJ, Ahn SH, Kim H, Jung YH. The Difference in the Clinical Features Between Carcinoma ex Pleomorphic Adenoma and Pleomorphic Adenoma. Ear Nose Throat J. 2019;98(8):504-509.
29. Chooback N, Shen Y, Jones M, et al. Carcinoma ex pleomorphic adenoma: case report and options for systemic therapy. Curr Oncol. 2017;24(3):e251-e254.

Table 1. Clinicopathological features of patients with carcinoma ex pleomorphic adenoma of minor salivary glands

Variables	n (%)
Sex	
Female	22 (56.4)
Male	17 (43.6)
F:M	1.3:1
Age (years)	
0-9	0 (0.0)
10-19	1 (2.6)
20-29	6 (15.4)
30-39	9 (23.1)
40-49	8 (20.5)
50-59	5 (12.8)
60-69	6 (15.4)
70-79	3 (7.7)
80-89	1 (2.6)
Mean ± SD	45.9 ± 16.5
Range	19-81
Anatomic location	
Palate	24 (61.5)
Buccal mucosa	9 (23.1)
Upper lip	3 (7.7)
Lower lip	1 (2.6)
Floor of the mouth	2 (5.1)
Size (cm)	
≤ 2	6 (60.0)
2 > 4	3 (30.0)
≥ 4	1 (10.0)
Mean ± SD	2.07 ± 0.96
Range	01-04
Duration (months)	
Mean	9.1 ± 5.6
Range	4-24
No information	28
Symptoms	
Asymptomatic	8 (66.7)
Pain	4 (33.3)
No information	27
Disease history	
Primary	36 (94.7)
Recurrent PA	2 (5.3)
No information	1
Microscopic characteristics of CXPA	
Capsular invasion	
Intracapsular	21 (53.8)
Frankly invasive	18 (46.2)
Histological type/subtype	
Luminal	

Adenocarcinoma not otherwise specified	10 (25.6)
Salivary duct carcinoma	6 (15.4)
Clear cell carcinoma	4 (10.3)
Epidermoid carcinoma	2 (5.1)
Adenoid cystic carcinoma	1 (2.6)
Myoepithelial	
Myoepithelial carcinoma	13 (33.3)
Epithelial-myoepithelial carcinoma	3 (7.7)
Other features	
Vascular invasion	5 (12.8)
Neural invasion	2 (5.1)
Follow-up (months)	
Mean ± SD	17.1±11.8
Range	02-49
No information	14
Clinical status	
Alive without disease	18 (72.0)
Died of other causes	4 (16.0)
Died of disease	3 (12.0)
No information	14

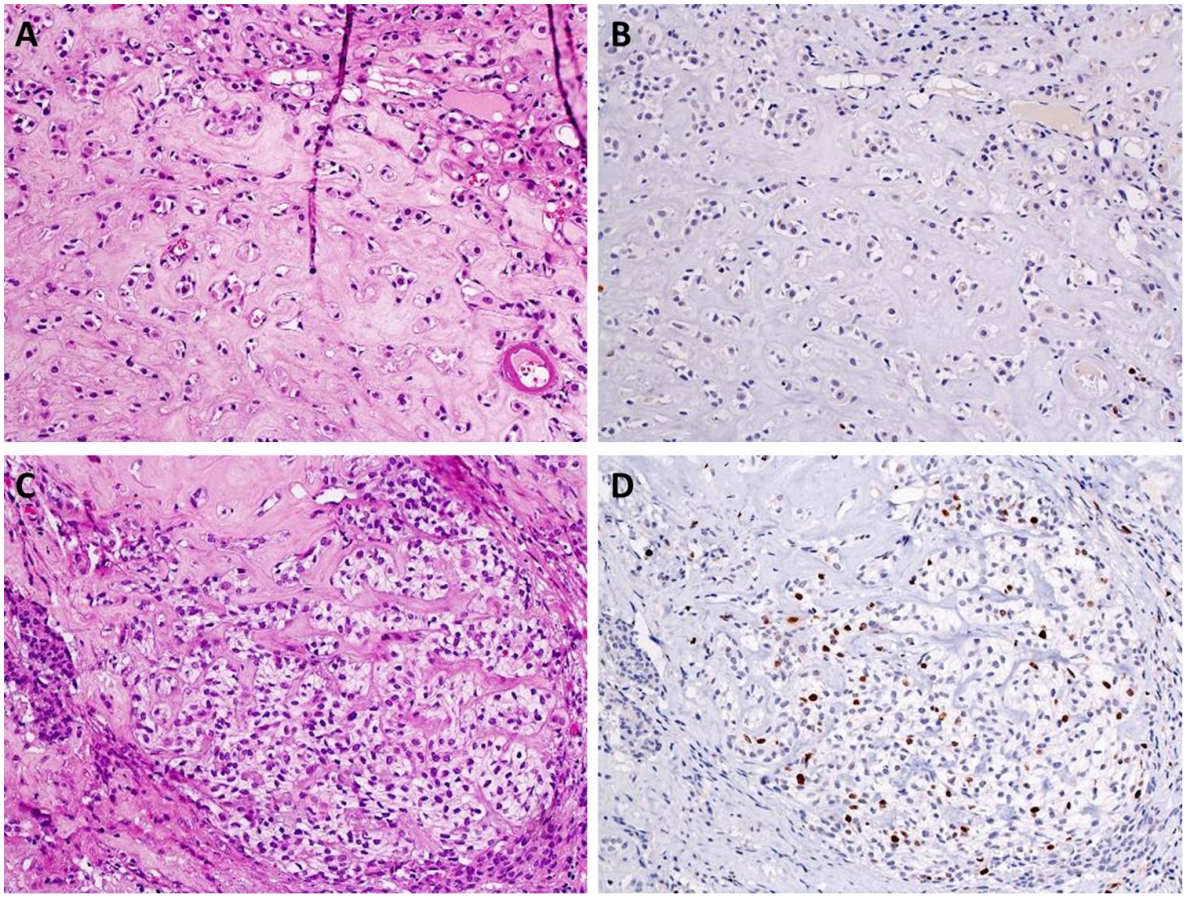


Figure 1. Clear cell carcinoma ex pleomorphic adenoma. (A) Areas reminiscent of residual pleomorphic adenoma presenting a hyalinized stroma with entrapped ductal structures (H&E, 200×). (B) The Ki67-expression in these areas was less than 1% (IHC, 200×). (C) In the malignant component, sheets, and nests of tumour cells with cytoplasmic and nuclear atypia were arranged in a multilobular architecture with invasion in the adjacent areas. (H&E, 200×). (D) The cellular proliferative index assessed by Ki67 expression was higher than the benign component (IHC, 200×).

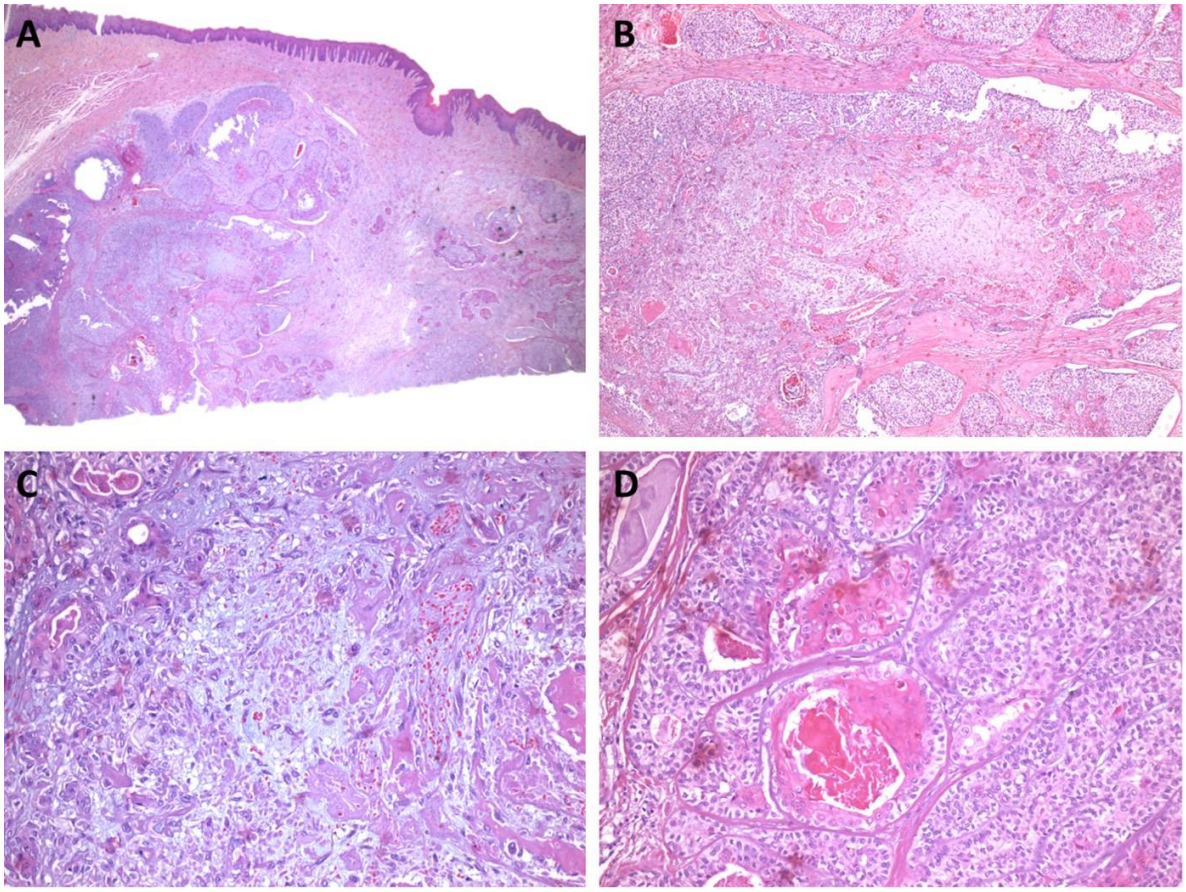


Figure 2. Extracapsular epithelial-myoepithelial carcinoma ex pleomorphic adenoma. (A) Note non-encapsulated lesion and tumour cells invading adjacent structures (H&E, 25×). (B) The tumour presents a biphasic architecture composed of hypercellularized areas and areas with a clear appearance that represents the benign component (H&E, 50×). (C) Areas with myxoid stroma, myoepithelial cells, and dispersed ductal structures characterizing the PA benign component (H&E, 200×). (D) In the malignant component, the ducts are formed by luminal epithelial cells with irregular shape and showing squamous differentiation; the abluminal cells had a clear cytoplasm distributed in a multilobulated architecture separated by hyaline septa (H&E, 200×).

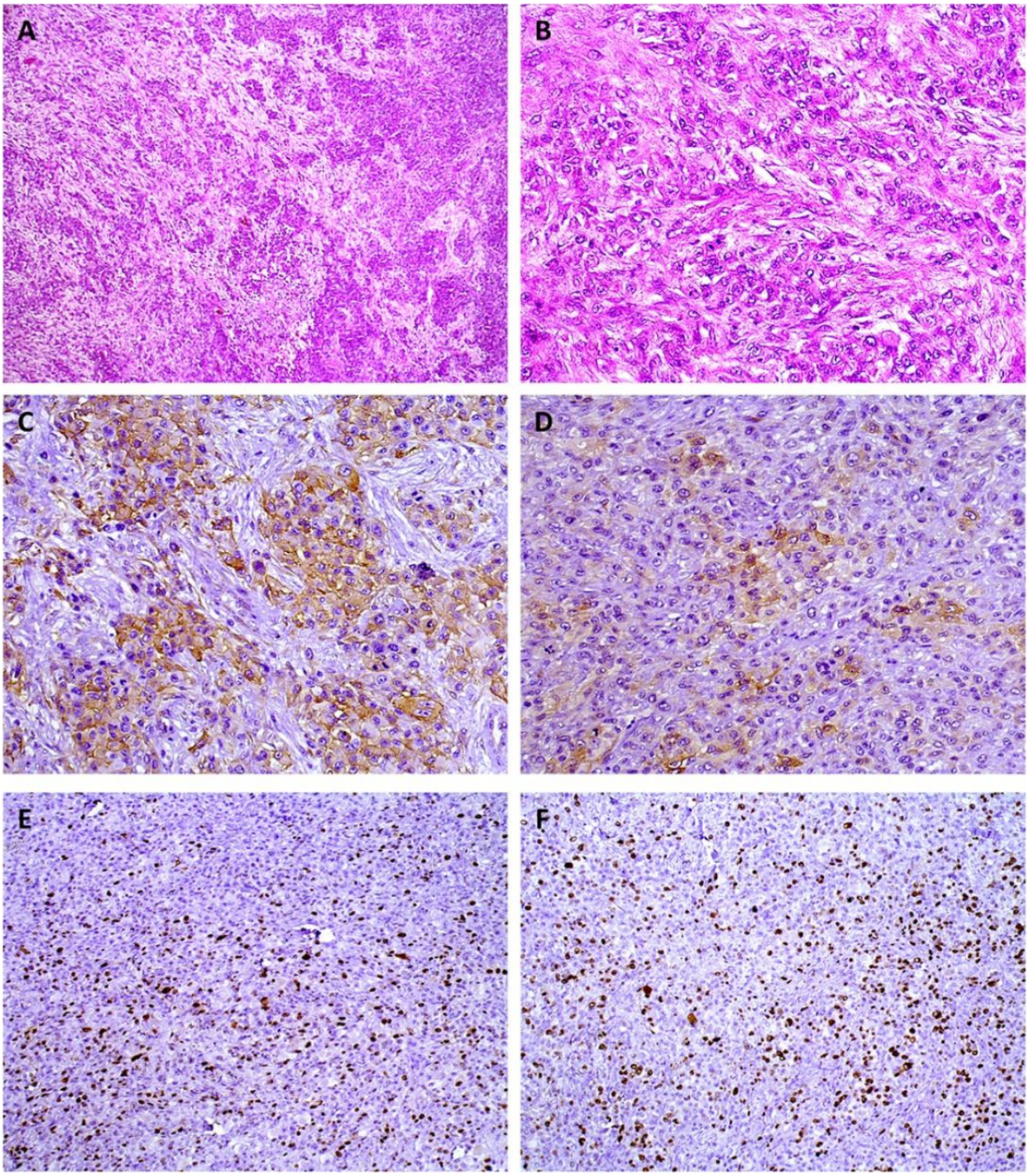


Figure 3. Invasive myoepithelial carcinoma ex pleomorphic adenoma. (A) Variable architecture, showing hypo/hypercellularized areas (H&E, 50×). (B) Myoepithelial cells with a plasmacytoid and fusiform aspect showing atypia and pleomorphism (H&E, 200×). Intense and diffuse expression of α-SMA (C) and calponin (D) in the tumour cells. (E) High cellular proliferative index (based on Ki67 immunoexpression). (F) Strong nuclear p53 immunopositivity cells of the malignant areas. (IHC, C-D 200×, E-F 100×).

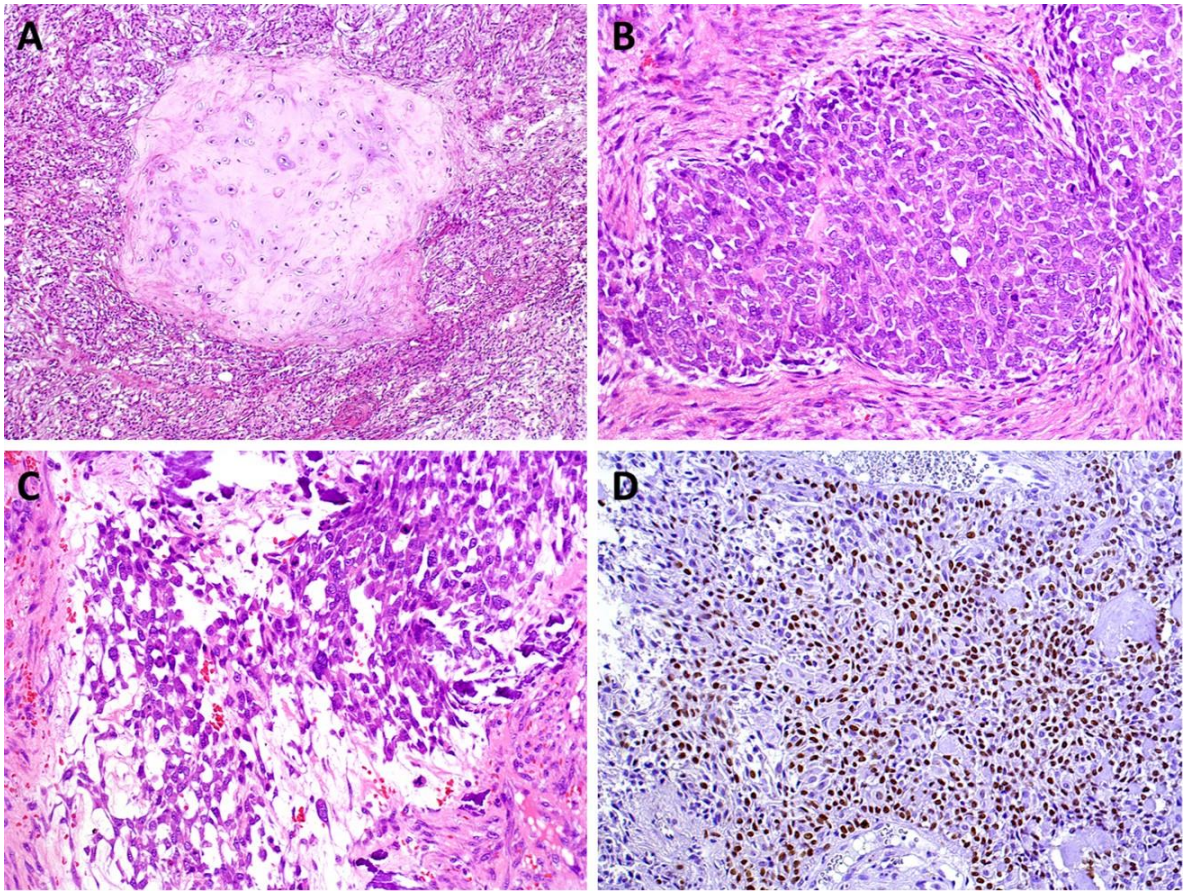


Figure 4. High-grade carcinoma ex pleomorphic adenoma, myoepithelial subtype. (A) The benign component demonstrated chondroid differentiation (H&E, 100×). (B) Myoepithelial cells displayed in solid arrangement intercepted by fibrous septa with marked pleomorphism and frequent mitosis (H&E, 200×). (C) Spindle-shaped myoepithelial cells in a myxoid stroma. Note that the cells have marked pleomorphism and mitotic figures (H&E, 200×). (D) Strong nuclear p63 immunopositivity in the myoepithelial cells of the malignant component (IHC, 200×).

Table 2. Clinicopathologic information of CXPA cases.

Case	Age	Sex	Localization	Duration (months)	Size (cm)	Symptoms	Histological subtype	Type	Vascular invasion	Neural invasion	Disease history	Treatment	Metastasis	Follow-up time (mo)	Clinical status
1	51	F	Palate	NA	NA	NA	Myoepithelial carcinoma	EC	Absent	Absent	Primary PA	NA	No	49	DOC
2	22	F	Upper lip	NA	NA	NA	Myoepithelial carcinoma	IC	Absent	Absent	Primary PA	NA	No	5	AWD
3	27	F	Palate	NA	NA	NA	Myoepithelial carcinoma	IC	Absent	Absent	Primary PA	NA	No	2	AWD
4	31	F	Palate	NA	NA	NA	Myoepithelial carcinoma	IC	Absent	Absent	Primary PA	NA	No	NA	NA
5	58	F	Floor of the mouth	NA	NA	NA	Myoepithelial carcinoma	IC	Absent	Absent	Primary PA	NA	No	3	AWD
6	39	F	Palate	NA	NA	NA	Myoepithelial carcinoma	IC	Absent	Absent	Recurrente PA	NA	No	21	AWD
7	41	F	Buccal mucosa	NA	NA	NA	Salivary duct carcinoma	IC	Absent	Absent	Recurrente PA	NA	No	NA	NA
8	59	F	Palate	NA	NA	NA	Salivary duct carcinoma	EC	Absent	Absent	Primary PA	NA	No	20	AWD
9	37	F	Palate	NA	NA	NA	Salivary duct carcinoma	IC	Absent	Absent	Primary PA	NA	No	6	AWD
10	19	F	Buccal mucosa	NA	NA	NA	Clear cell carcinoma, NOS	IC	Absent	Absent	Primary PA	NA	No	NA	NA
11	81	F	Buccal mucosa	NA	NA	NA	Clear cell carcinoma, NOS	EC	Absent	Absent	Primary PA	NA	No	11	DOC
12	63	F	Palate	NA	NA	NA	Epithelial-myoepithelial carcinoma	IC	Absent	Absent	Primary PA	NA	No	NA	NA
13	46	F	Palate	NA	NA	NA	Epithelial-myoepithelial carcinoma	EC	Absent	Absent	Primary PA	NA	No	NA	NA
14	20	F	Palate	NA	NA	NA	AdNOS	IC	Absent	Absent	Primary PA	NA	No	NA	NA
15	39	F	Buccal mucosa	NA	NA	NA	AdNOS	EC	Present	Absent	Primary PA	NA	DM (brain)	19	DOD
16	27	F	Upper lip	NA	NA	NA	AdNOS	EC	Absent	Absent	Primary PA	NA	No	6	AWD
17	41	F	Buccal mucosa	NA	NA	NA	AdNOS	IC	Absent	Absent	Primary PA	NA	No	17	AWD
18	63	F	Palate	NA	NA	NA	AdNOS	IC	Absent	Absent	Primary PA	NA	No	13	AWD
19	44	M	Palate	NA	NA	NA	Myoepithelial carcinoma	EC	Present	Absent	Primary PA	NA	No	13	AWD
20	22	M	Buccal mucosa	NA	NA	NA	Myoepithelial carcinoma	IC	Absent	Absent	Primary PA	NA	No	NA	NA
21	35	M	Lower lip	NA	NA	NA	Salivary duct carcinoma	IC	Absent	Absent	Primary PA	NA	No	NA	NA
22	49	M	Palate	NA	NA	NA	Epidermoid carcinoma	IC	Absent	Absent	Primary PA	NA	No	NA	NA

23	33	M	Palate	NA	NA	NA	Epidermoid carcinoma	EC	Present	Present	Primary PA	NA	No	NA	NA
24	34	M	Palate	NA	NA	NA	Adenoid cystic carcinoma	EC	Present	Present	Primary PA	NA	No	NA	NA
25	55	M	Palate	NA	NA	NA	AdNOS	IC	Absent	Absent	Primary PA	NA	No	31	AWD
26	58	M	Palate	NA	NA	NA	AdNOS	IC	Absent	Absent	Primary PA	NA	No	NA	NA
27	38	F	Buccal mucosa	13	2	Pain	Clear cell carcinoma, NOS	IC	Absent	Absent	Primary PA	Surgery	No	27	AWD
28	77	M	Floor of the mouth	7	1,5	Asymptomatic	Clear cell carcinoma, NOS	EC	Absent	Absent	Primary PA	Surgery	DM (lung and brain)	8	DOD
29	48	M	Palate	9	2	Asymptomatic	Myoepithelial carcinoma	EC	Absent	Absent	Primary PA	Surgery	No	36	AWD
30	59	M	Palate	24	1.2	Asymptomatic	Myoepithelial carcinoma	EC	Absent	Absent	Primary PA	Surgery	No	13	AWD
31	43	F	Palate	8	NA	Asymptomatic	Myoepithelial carcinoma	IC	Absent	Absent	Primary PA	Surgery, neck dissection, negative lymph nodes	No	21	AWD
32	63	M	Palate	4	1	Asymptomatic	Myoepithelial carcinoma	EC	Absent	Absent	Primary PA	Surgery	No	19	DOC
33	71	M	Palate	NA	NA	NA	Myoepithelial carcinoma	EC	Absent	Absent	Primary PA	Surgery	DM (site without specification)	11	DOD
34	67	F	Upper lip	6	NA	Asymptomatic	Salivary duct carcinoma	IC	Absent	Absent	Primary PA	NA	No	NA	NA
35	47	M	Buccal mucosa	NA	3	Pain	AdNOS	EC	Absent	Absent	Primary PA	Surgery	No	4	AWD
36	52	M	Palate	11	2.5	Asymptomatic	Salivary duct carcinoma	EC	Absent	Absent	Primary PA	Surgery, neck dissection,positive lymph nodes	RM	13	AWD
37	30	M	Palate	6	4	Pain	AdNOS	EC	Absent	Absent	NA	NA	No	NA	NA
38	73	M	Palate	9	2.5	Pain	Epithelial-myoepithelial carcinoma	IC	Absent	Absent	Primary PA	Surgery	No	24	DOC
39	29	F	Buccal mucosa	4	1	Asymptomatic	AdNOS	EC	Present	Absent	Primary PA	Surgery	No	36	AWD

F, female; M, male; AdNOS, adenocarcinoma not otherwise specified; FI, frankly invasive; IC, intracapsular; AWD, alive without disease; DOC, died of other causes; DOD, died of disease; P, present; A, absent; NA, not available.

2.4 Artigo:

SIALOLIPOMAS OF MINOR SALIVARY GLANDS: A MULTI-INSTITUTIONAL STUDY AND LITERATURE REVIEW

Artigo publicado no periódico *Journal of oral pathology and medicine*

DOI: 10.1111/jop.13124 (Anexo 4)

Short title: Sialolipomas of minor salivary glands

John Lennon Silva Cunha[1], Sílvia Ferreira de Sousa[2], Carolina Peres Mota[2], João Vitor Rocha Silva[3], Israel Leal Cavalcante[4], Erasmo Bernardo Marinho[4], Ciro Dantas Soares[1], Ricardo Luiz Cavalcanti de Albuquerque-Júnior[3], Roberta Barroso Cavalcante[4], Aline Corrêa Abrahão[5], Michelle Agostini[5], Mario José Romañach[5], Bruno Augusto Benevenuto de Andrade[5], Pablo Agustin Vargas[1], Oslei Paes de Almeida[1]

[1]Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, SP, Brazil.

[2]Department of Oral Surgery and Pathology, School of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil

[3]Laboratory of Morphology and Experimental Pathology, Institute of Technology and Research, Tiradentes University (UNIT), Aracaju, SE, Brazil.

[4]Oral Pathology, School of Dentistry, University of Fortaleza (UNIFOR), Fortaleza, CE, Brazil.

[5]Department of Oral Diagnosis and Pathology, School of Dentistry, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil

Corresponding Author:

John Lennon Silva Cunha

Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), Av. Limeira 901, P.O. Box. 52, Piracicaba, São Paulo 1314-903, Brazil.

E-mail: lennonrrr@live.com.

Acknowledgments

This work was supported by the Coordination for the Improvement of Higher Education Personnel (CAPES).

Abstract

Background: Sialolipoma is a rare histological variant of lipoma commonly misdiagnosed and composed of a proliferation of mature adipocytes with secondary entrapment of normal salivary gland tissue. The purpose of the present study is to report the clinicopathologic and immunohistochemical features of 10 new cases of sialolipomas in conjunction with a review of the literature.

Methods: A retrospective descriptive cross-sectional study was performed. A total of 54,190 biopsy records of oral and maxillofacial lesions from four oral and maxillofacial pathology services in Brazil were analysed. All cases of lipomas were reviewed, and clinical, demographic, and histopathological data were collected of all cases compatible with sialolipomas. In addition, immunohistochemistry stains (AE1/AE3, CK7, 34βE12, S-100, HHF35, α-SMA, and Ki-67) and a literature review based on a search of three electronic databases (PubMed, Web of Science, and Scopus) were performed.

Results: Among all lipomas reviewed, there were 10 cases of sialolipomas. The series comprised of 7 females (70.0%) and 3 males (30.0%), with a mean age of 46.1 ± 21.5 years (range: 11–71 years) and a 2.3:1 female-to-male ratio. The lower lip (n = 3, 30.0%), and tongue (n = 2, 20.0%), were the most common locations, presenting clinically as a nodule of slow growth and normal colour. Conservative surgical excision was the treatment in all cases. No recurrence was observed.

Conclusion: Sialolipomas are a rare histological variant of lipoma, affecting the salivary glands, mainly in the parotid gland and palate of female adults. Pathologists must recognise sialolipomas to avoid misdiagnoses with other lipomatous tumours that can affect salivary glands.

Keywords: sialolipoma; histopathology; salivary gland; diagnosis

INTRODUCTION

Sialolipoma is a distinct histological variant of lipoma first described by Nagao et al. in 2001[1], mentioned in the WHO classification of 2005, and included as a separate entity only in the current WHO Classification of Head and Neck Tumours of 2017.[2] Sialolipoma appears characteristically as a well-circumscribed mass with a fibrous

capsule, composed of neoplastic mature fat tissue and non-neoplastic salivary gland elements.[1,3]

Although some reports have been published in the literature,[1,3–28] sialolipoma remains poorly characterised, and several salivary gland conditions or tumours with lipomatous components might be confused with this lesion,[21] such as conventional lipoma, lipoadenoma, lipomatosis, and pleomorphic adenoma with extensive lipometaplasia.[1,2,10,18,22,23] In addition, recently, some clinical and histopathological differences have been proposed between sialolipomas affecting the major and minor salivary glands, such as sex predilection, size, and histological changes such as marked periductal fibrosis, observed mainly in cases involving the minor salivary glands.[3,23]

Herein, we report the clinicopathological and immunohistochemical characteristics of 10 new cases of sialolipomas affecting the minor salivary glands in a multi-institutional study from Brazil, the largest series reported in the literature. In addition, we also reviewed the literature to analyse if there are other demographical differences between patients with sialolipomas affecting the minor and major salivary glands in order to provide a basis for a better understanding of this unusual oral lesion.

MATERIALS AND METHODS

Multi-institutional retrospective-study

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of the School of Dentistry of Piracicaba (No. 20726819.6.0000.5418).

A total of 54,190 histopathological records of oral and maxillofacial biopsies were analysed in a retrospective study, and all cases of lipomas (n = 402, 0.7%) were recovered. The records were retrieved from the archives of four Brazilian oral and maxillofacial pathology services (Table 1). Five-micrometer hematoxylin and eosin-stained sections were obtained from each case, and all oral pathologists included in the study re-evaluated the histological features of the lesions. Only well-circumscribed tumours composed of mature adipocytes and containing islands of normal glandular tissue within the tumour, compatible with the diagnostic criteria described by Nagal et al. (2001),[1] were included. Disagreements between the examiners were solved upon discussion and reaching a

consensus between them. Patients' age, sex, symptoms, anatomical location, size, treatment performed, recurrence, and follow-up period were obtained from clinical records and evaluated. The proportion of adipose tissue of the tumour was measured by estimating more than ten randomly selected fields (10 × 10 magnification).[1]

For immunohistochemical characterisation of the sialolipomas immunohistochemistry reactions were performed in 3-μm tissue sections in silanised slides, using standard protocols for the following antibodies: pan-Cytokeratin (clone AE1/AE3, dilution 1:400), Cytokeratin 7 (clone AA 1, dilution 1:10000), Cytokeratin 34βE12 (monoclonal, dilution 1:50), epithelial membrane antigen (monoclonal, dilution 1:100), S-100 protein (polyclonal, dilution 1:10000), α-SMA (clone h-CD, dilution 1:400), muscle-actin-specific (clone HHF35, dilution 1:800), and Ki-67 (clone MIB1, dilution 1:100). All antibodies were obtained from Dako (Glostrup, Denmark). Internal positive controls and negative controls were considered in all reactions.

Literature review

An electronic search, using the keyword "sialolipoma", without time restrictions was carried out in February 2020, accessing the following electronic databases: PubMed/MEDLINE, Scopus, and Web of Science. Inclusion criteria comprised case reports, case series, or retrospective studies of patients with sialolipomas published in Portuguese, English, or Spanish languages, with sufficient clinical data and histopathological characteristics for a definitive diagnosis. After removing duplicates, the selection of studies was carried out in two steps. Titles/abstracts that met the eligibility criteria were included. If a title/abstract provided insufficient information for a decision on inclusion or exclusion, the full text was obtained and evaluated. The following information was extracted from each selected study (when available): year of publication, the number of cases, patients' sociodemographic data, clinical features, duration of the lesion, treatment performed, and follow-up period. Information on histopathological and immunohistochemical features was also extracted.

Analysis

Descriptive and quantitative data analyses were performed using the Statistical Package for the Social Sciences for Windows 20.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were expressed as mean, median, and standard deviation values. Categorical variables were expressed as the absolute number of cases and percentage

values. Chi-square test and Fisher's exact test were used to evaluate the association between clinical and demographic characteristics, adopting a p-value of ≤ 0.05 and 95% confidence interval. The Student's t-test was used to compare the means between two groups (minor vs. major salivary glands sialolipomas). The data from the present study were added to the literature review so that an appropriate comparison could be made.

RESULTS

Clinicopathologic and immunohistochemistry features

In the present study, ten cases of sialolipomas were found among 402 cases of lipomas in our series. The incidence of lipoma and sialolipoma was 0.7% and 0.02%, respectively, from a total of 54,190 diagnostics. Table 1 summarises the clinical features of these 10 cases. The patients comprised seven women (70.0%) and three men (30.0%), with a mean age of 46.1 ± 21.5 years (range 11 to 71 years) and 2.3:1 female-to-male ratio. The lower lip was the most affected site (3 cases; 33.3%), followed by the tongue (2 cases, 22.2%). Other locations included palate, buccal mucosa, the floor of the mouth, and retromolar region. There was one case with an unspecified intraoral anatomical location.

Clinically, all cases presented as a submucosal, well-circumscribed nodule, soft to firm in consistency. In seven cases (70.0%), the oral mucosa that covers the lesion presented normal colour. In two cases, it was reddish, and in only one case, the nodule showed a yellowish colour. Lesion size ranged from 0.5 to 4.0 cm, with a mean of 1.6 cm. All the patients were asymptomatic, and time of evolution at the time of diagnosis varied from 6 months to 2 years (mean: 12.5 ± 8.1 months). The clinical diagnosis included mainly reaction lesions such as fibrous hyperplasia, ranula, and benign tumours, including lipoma and pleomorphic adenoma. No patients reported a previous history of diabetes mellitus or chronic alcoholism. All tumours were excised through excisional biopsy or by conservative surgical excision. Outcome information was available for 3 patients (30.0%) with clinical follow-up ranging from 8 to 22 months, and a mean of 14 months. At follow-up, no evidence of tumour recurrence was observed.

On gross examination, the lesions were described as well-circumscribed with smooth or irregular surface, soft to firm in consistency, and uniform yellowish colour with bluish or brownish areas and greasy cut surface (Figures 1A,B, and 2B).

Microscopically, all tumours were well-circumscribed, partly encapsulated by thin fibrous tissue (Figure 1C) and composed of mature neoplastic adipose tissue containing islands of normal salivary gland tissue (Figure 2C,D). The epithelial islets consisted uniformly of normal ductal and acinar units of the salivary gland parenchyma, without atypia (Figure 2E,F). In addition, the glandular component was often distributed throughout the tumour and, occasionally, tended to be located on the periphery of the lesion but within the tumour. Adipocytes exhibited typical morphology, with no evidence of atypical cells or mitotic figures (Figures 1D and 2C–F), and were organised in a diffuse arrangement, sometimes slightly nodular (Figure 3B). The proportion of adipose tissue varied from 60% to over 90%. Additionally, atrophy of the glandular component, duct dilatation (Figure 1D,E), periductal fibrosis (Figure 1E), nerve bundles (Figure 3C), mild to moderate lymphocyte infiltration (Figure 3D), and enlarged congested vessels were also seen. The presence of oncocytic metaplasia or myxoid areas were not observed.

Immunohistochemically, the duct and acinar cells in all the tumours were positive for pan-cytokeratin AE1/AE3 (Figure 4A), cytokeratin 7 (Figures 1F and 4B), and epithelial membrane antigen (EMA). High molecular weight cytokeratin 34βE12 was expressed in ductal cells (Figure 4C), but not in acinar cells. Positive cells for S-100 protein, specific muscle actin (HHF-35), and smooth muscle actin (α-SMA), suggesting myoepithelial cells, were observed surrounding the acini and intercalated ducts (Figure 4D). In addition, acinar and adipose cells were positive for S-100 protein (Figure 4 E,F). The cell proliferation index assessed by immunostaining for Ki67 was lower than 1% in all cases.

Literature review

A total of 48 publications reporting 75 cases of sialolipomas were selected through electronic search. Of these, three misdiagnosed cases before 2001 and seven included in surveys of lipomas were identified by a histopathological description and/or figures reported. Table 2 provides an overview of the summary data of sialolipomas reported in the literature and compares these data with the 10 new sialolipomas diagnosed in the present study. Overall, from 75 sialolipomas, 39 (56.5%) cases occurred in females and 30 (43.5%) in males (female-to-male ratio: 1.3:1), and in six cases, the patient's gender was missing. The mean age of the affected individuals was 47.3 ± 23.7 years (range: 0–84 years). Regarding the anatomical site, 58.7% of the sialolipomas occurred in the major salivary glands (n = 44), while 41.3% affected the minor salivary glands (n = 31).

In sialolipomas of the major salivary glands, the patient age ranged from 0 (newborn) to 77 years, with an average of 40.9 years, and occurred mainly in the fifth decade of life (n =13, 29.5%). Twenty-three (52.3%) cases occurred in males and 21 (47.7%) in females (male-to-female ratio: 1.1:1). Regarding the anatomical location, the vast majority involved the parotid gland (n = 36, 81.8%), followed by the submandibular gland (n = 8, 18.2%). No tumour affected the sublingual gland. The size of the tumours ranged from 0.8 to 9.0 cm (largest diameter), with an average of 4.4 cm (SD ± 2.0), and most sized more than 2.0 cm in diameter (38 cases, 88.4%). The time of evolution of the lesions varied from a few weeks to 15 years, and five were congenital ones. Total or superficial parotidectomy or surgical excision were the treatment of choice. The follow-up period ranged from 1 to 120 months, with a mean of 27.0 months, and only one case exhibited recurrence due to incomplete resection.

Regarding the cases of sialolipomas affecting the minor salivary gland, the patient age ranged from 6 months to 84 years, with an average of 58.1 years, and occurred mainly in patients in the seventh decade of life (n = 12, 46.2%). Eighteen (72.0%) cases occurred in females and 7 (28.0%) in males (female-to-male ratio: 2.5:1). Regarding the anatomical distribution, the palate (n = 9, 29.0%) was the most commonly involved site, followed by the buccal mucosa (n = 7, 22.6%), and floor of the mouth (n = 5, 16.1%). Other anatomic sites included tongue, retromolar region, and lips. The size of the tumours ranged from 0.5 to 5.0 cm (largest diameter), with an average of 1.8 cm (SD ± 1.0). The time of evolution of the lesions varied from 1 to 10 years. Conservative surgical excision was carried out in all cases, and despite the lack of follow-up data in some cases, no recurrence or malignant transformation was reported. The follow-up period ranged from 1 to 36 months, with a mean of 14.7 months.

All cases showed similar morphological features and were characterised as well-circumscribed lesions, often exhibiting a thin fibrous tissue capsule and composed of mature adipose tissue and entrapped normal salivary gland within the lipomatous component. The proportion of adipose component varied from 40% to over 90%. Additional pathological findings included atrophy of the salivary glandular components, lymphoid infiltration, duct dilatation, periductal fibrosis, peripheral nerve involvement, oncocytic changes, sebaceous and/or squamous metaplasia, myxoid change in adipose tissue, mild to moderate mononuclear inflammatory infiltrate, and enlarged congested vessels.

When sex and site of the lesions (major vs. minor salivary glands) were evaluated, we observed a significant association (p = 0.0409; Fisher's exact test) between being female and having lesions on the minor salivary glands. The major salivary gland sialolipomas had larger size averages compared to lesions affecting the minor salivary glands (p = 0.0074, Student's t-test). In addition, the average age of patients with sialolipomas involving major salivary was statistically lower (40.9 ± 24.4) when compared to that of patients with sialolipomas of minor salivary glands (54.8 ± 19.7) (p <0.0001; Student's t-test).

DISCUSSION

The term *sialolipoma* was first introduced in 2001 by Nagao et al., to describe tumours characterised by well-delimitated proliferation of mature adipose tissue with secondary involvement of the salivary gland parenchyma.[1] Since then, 75 well-documented cases of sialolipomas reported in the literature and 10 new cases in the current series are described involving major and minor salivary glands,[1,3–28] highlighting the rarity of this lesion. To the best of our knowledge, this study is the first multi-institutional retrospective study with the largest sample of sialolipomas. Thus, the results of our study summarised the findings of 85 sialolipomas, being 41 (48.3%) of minor and 44 (51.7%) of major salivary glands.

Our results, in conjunction with previous reports, show that sialolipomas occur at any age, ranging from newborns to the elderly (mean age 47.1 years). Although previous studies have reported male predominance,[1,12,23] the review of published cases, including the current series, revealed a female preponderance (58.2%), with a female-to-male ratio of 1.3:1. Also, differences were observed in the age distribution between sialolipomas of the minor and major salivary glands (Table 2). Sialolipomas involving major salivary glands affected mainly adults, with an average age of approximately 40 years, with no predilection for gender (1:1). In contrast, sialolipomas of minor salivary glands usually affected older patients, with peak prevalence in the seventh decade of life (46.2%), a mean age of 58.1 years, and showed a clear female predilection (2.5:1).

Regarding the anatomical site, the palate was the most affected minor salivary glands, with a frequency of 11.9% (n = 10), followed by the buccal mucosa (n = 8, 9.5%). On the other hand, the lips (33.3%) and tongue (22.2%) were the main sites in the present study. However, any location of the oral cavity that contains salivary glands may be

affected. Occurrence in the retromolar region and lips (**Figures 1 and 2**), as observed in our series, are excessively rare, with only a few well-documented cases published in the literature (**Table 2**).[18,23]

Clinically, sialolipomas presented as a well-circumscribed asymptomatic swelling of slow growth,[1,18,23] measuring about 0.6 to 9.0 cm (mean 3.3 cm). Minor salivary gland sialolipomas tended to be smaller, with mean greatest dimension 1.8 cm (p <0.05; Student's t-test), compared with major salivary gland sialolipomas (mean size 4.4 cm), despite having a longer evolution time (most were present for more than one year). The time of evolution of the lesion was quite variable, ranging from months to 11 years[1,3,10,18] and some reports of congenital sialolipomas have been reported.[6,10,20,24]

The clinical differential diagnosis is influenced mainly by the location of the lesion.[15] Most intraoral tumours are clinically diagnosed as reactive lesions and benign tumours, such as fibrous hyperplasia, ranula, lipoma, pleomorphic adenoma,[1,7,12,18] similar to the present series. In the major salivary glands, clinical features often suggest salivary gland neoplasms or lipomas[18] and imaging exams may be helpful during the clinical investigation to guide the diagnosis and treatment.[15,22] The ultrasonography (USG) typically shows heterogeneous hypoechoic lesions, with echogenicity similar to that of fat tissue.[15] Furthermore, magnetic resonance imaging (MRI) is more advantageous because they provide accurate information about the location and size of the tumour, facilitating surgical planning.[15] However, imaging exams do not distinguish between conventional lipomas and sialolipomas, and the definitive diagnosis can only be confirmed by histopathological analysis.[22]

Histologically, sialolipomas are well-circumscribed lesions, often exhibiting a very thin fibrous capsule, and characterised by the presence of mature neoplastic adipose tissue and islands of salivary gland tissue entrapped within the lipomatous component.[1,3,9,18,23] Differences in the proportion of glandular and adipose components have been observed according to the type of salivary gland affected (major versus minor).[1,23] In the major salivary glands, adipose tissue corresponds to 50% to over 90% of the tumour component.[1,21] In contrast, those located in the minor salivary glands, adipose tissue is responsible for about 40% to 80% of the lesion content.[18,23] In general, these findings are similar to those observed in the present study.

On the other hand, the glandular component consists of epithelial islands of variable size, sparsely distributed throughout the tumour, showing salivary glandular

parenchyma with normal morphological appearance.[1,3,18,21,23] Occasionally, these epithelial islands are found on the periphery of the tumour. Others histologic features include atrophy of the glandular component, duct dilation, periductal fibrosis, mild to moderate lymphocyte infiltration, myxoid change in adipose tissue, enlarged congested vessels, and squamous and/or oncocytic metaplasia in ductal cells.[3,18,21,23]

The pathogenesis of sialolipoma remains uncertain,[1] although some theories have been proposed.[1,13,17] The first theory proposes that the development of this lesion is associated with dysfunctions of the salivary glands.[17] These dysfunctions could lead to a change in the morphological architecture of the salivary glands, characterised microscopically by the replacement of normal tissue of the salivary gland by mature adipose tissue mixed with atrophic salivary glandular elements and chronic alterations of ductal epithelial cells, such as oncocytic/squamous metaplasia, periductal fibrosis, and lymphocytic inflammatory infiltrate.[17] Other characteristics that support this theory include the long duration of the disease and the absence of recurrence.[17] In the present series, periductal fibrosis with mild to moderate mononuclear inflammatory infiltrate and focal lymphoid aggregates, as well as acinar atrophy was observed. Therefore, at least in part, dysfunctions of the salivary glands may be the possible pathogenic mechanism.

Another theory proposes that sialolipomas represent a type of adenoma with a mature adipose component;[1] however, unlike adenomas, sialolipomas have indolent clinical behaviour, absence of recurrence, lack of cell atypia, and low cell proliferation rate (Ki-67),[1,17] as shown in the present study. Another unlikely proposition[17] considers a hamartomatous nature.[6,10,13,20] Hamartomas are defined as a tumour-like nodule that consists of normal tissue arranged in a disorganised manner, different from what is often observed in sialolipomas.[17] However, rare cases showing a disorganised proliferation of vascular and nervous structures in the tumour stroma have been described.[13]

Finally, the possibility of sialolipomas representing a histological variant of the conventional lipoma with elements of the salivary gland trapped in the stroma has been suggested and widely accepted.[1] Both tumours develop mainly in females between the 4th and 6th decades of life, present clinically as asymptomatic soft tissue swelling or nodule, and recurrence is infrequent;[30] besides, the immunohistochemistry results revealed that both the duct and acinar cells in the sialolipomas was positive for pan-cytokeratin AE1/AE3, CK7, and EMA. High molecular weight cytokeratin 34βE12 was expressed in ductal cells, but not in acinar cells. Positive cells for HHF-35, α-SMA, and S-100 protein

were observed surrounding the acini and intercalated ducts, suggesting myoepithelial cells. The cell proliferation index assessed by immunostaining for Ki67 was lower than 1% in all cases, indicating low cell-proliferative activity in the glandular and adipose component of the tumour. In addition, adipose cells were positive for S-100 protein. These features of the present study were in line with previous studies[1,5] and revealed that the glandular component within the tumours expressed normal cell phenotypes, preserving the typical structural organisation of the salivary glandular epithelium. Thus, the salivary gland tissue is most likely not to be part of the neoplastic process[1] and had become entrapped during the adipocytic proliferation. However, this neoplastic nature cannot be ruled out, and molecular investigations may help to elucidate the nature of this tissue.[1,8]

Several conditions of the salivary gland or tumours with lipomatous components can be confused with sialolipomas due to the great overlap of morphological findings, such as conventional lipoma, lipoadenoma, pleomorphic adenoma with extensive lipometaplasia, and various functional, metabolic or atrophic changes (lipomatosis).[1,18] Therefore, careful analysis of the general architecture and cellular constituents of these lesions is essential to avoid misdiagnosis. Lipomatosis occurs due to the deposition of non-neoplastic adipose tissue throughout the parenchyma of the salivary gland, resulting in a diffuse increase of the affected gland.[1,18] Although the pathophysiology of this condition remains uncertain, lipomatosis has often been associated with several conditions such as diabetes mellitus, liver cirrhosis, chronic alcoholism, hormonal disorders, and malnutrition.[1,7,8,11,12,18,19] In this study, patients did not report any of these conditions. Also, the presence of a fibrous capsule, as observed in most cases, helps to distinguish sialolipomas from lipomatosis.[1,3,7,8,11,12,18,19] It is worthwhile to emphasise that with advancing age, acinar atrophy accompanied by increased adipose tissue may occur.[1] However, in our cases, the proportion of adipose tissue in the tumour was higher than that of non-tumour salivary gland tissue, regardless of age. Lipoadenoma is characterised by a mixture of ducts containing eosinophilic proteinaceous material and adipose tissue but, in contrast to sialolipomas, are deprived of typical acinar structures.[1,8] Such findings were not observed in our cases. In addition, immunohistochemical studies have shown the presence of myoepithelial and acinar cells in our cases. Pleomorphic adenomas, on the other hand, are composed of ducts and sheets or strands of dark-staining epithelial cells intermingled with the fibrous and myxoid element.[1,18,28]

Regarding the treatment of sialolipomas, most of the lesions located in the parotid gland have been treated by total or superficial parotidectomy.[1,15,26] Conservative surgical excision has been used in sialolipomas of the minor salivary glands,[3,18,23] similar to the present study. Despite the lack of follow-up data in some cases, only one recurrence has been reported so far.[29]

In summary, despite its rarity, sialolipomas should be considered in the differential diagnosis of soft tissue lesions located in the oral cavity and major salivary glands, principally in the parotid. Pathologists and clinicians must recognise sialolipomas in order to avoid misdiagnosis with common lipomatous tumours affecting the salivary glands and provide adequate management through conservative surgical excision.

CONFLICT OF INTEREST

The authors declared no potential conflict of interest with respect to the research, authorship, and publication of this article.

FUNDING

None.

5. REFERENCES

1. Nagao T, Sugano I, Ishida Y, *et al*. Sialolipoma: A report of seven cases of a new variant of salivary gland lipoma. *Histopathology*. 2001;38:30-6.

2. Seethala RR, Stenman G. Update from the 4th Edition of the World Health Organization Classification of Head and Neck Tumours: Tumors of the Salivary Gland. *Head Neck Pathol*. 2017;11(1):55-67.

3. Okada H, Yokoyama M, Hara M, Akimoto Y, Kaneda T, Yamamoto H. Sialolipoma of the palate: a rare case and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2009;108(4):571-6.

4. Fregnani ER, Pires FR, Falzoni R, Lopes MA, Vargas PA. Lipomas of the oral cavity: clinical findings, histological classification and proliferative activity of 46 cases. *Int J Oral Maxillofac Surg*. 2003;32:49–53.

5. Lin YJ, Lin LM, Chen YK, *et al*. Sialolipoma of the floor of the mouth: a case report. *Kaohsiung J Med Sci*. 2004;20(8):410-4.

6. Hornigold R, Morgan PR, Pearce A, Gleeson MJ. Congenital sialolipoma of the parotid gland first reported case and review of the literature. *Int J Pediatr Otorhinolaryngol*. 2005;69(3):429-434.

7. Sakai T, Iida S, Kishino M. Sialolipoma of the hard palate. *J Oral Pathol Med*. 2006;35:376–378.

8. Michaelidis IG, Stefanopoulos PK, Sambaziotis D, Zahos MA, Papadimitriou GA. Sialolipoma of the parotid gland. *J Craniomaxillofac Surg*. 2006;34(1):43-6.

9. Kadivar M, Shahzadi SZ, Javadi M. Sialolipoma of the parotid gland with diffuse sebaceous differentiation in a female child. *Pediatr Dev Pathol*. 2007;10(2):138-41.

10. Bansal B, Ramavat AS, Gupta S, *et al*. Congenital sialolipoma of parotid gland: a report of rare and recently described entity with review of literature. *Pediatr Dev Pathol*. 2007;10(3):244-6.

11. Ponniah I, Lavanya N, SureshKumar P. Island of salivary gland in adipose tissue: a report of three cases. *J Oral Pathol Med*. 2007;36(9):558-562.

12. Ramer N, Lumerman HS, Ramer Y. Sialolipoma: report of two cases and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;104(6):809-13.

13. Parente P, Longobardi G, Bigotti G. Hamartomatous sialolipoma of the submandibular gland: case report. *Br J Oral Maxillofac Surg*. 2008;46(7):599-600.

14. Doğan S, Can IH, Unlü I, Süngü N, Gönültaş MA, Samim EE. Sialolipoma of the parotid gland. *J Craniofac Surg*. 2009;20(3):847-8.

15. Jang YW, Kim SG, Pai H, Park JW, Lee YC, Rotaru H. Sialolipoma: case report and review of 27 cases. *Oral Maxillofac Surg*. 2009;13(2):109-13.

16. Juliasse LE, Nonaka CF, Pinto LP, Freitas Rde A, Miguel MC. Lipomas of the oral cavity: clinical and histopathologic study of 41 cases in a Brazilian population. *Eur Arch Otorhinolaryngol*. 2010;267(3):459-65.

17. Akrish S, Leiser Y, Shamira D, Peled M. Sialolipoma of the salivary gland: two new cases, literature review, and histogenetic hypothesis. *J Oral Maxillofac Surg*. 2011;69(5):1380-4.

18. Nonaka CF, Pereira KM, de Andrade Santos PP, de Almeida Freitas R, da Costa Miguel MC. Sialolipoma of minor salivary glands. *Ann Diagn Pathol*. 2011;15(1):6-11.

19. Sato K, Gotoh C, Uchida H, *et al*. Sialolipoma of the submandibular gland in a child. *J Pediatr Surg*. 2011;46(2):408-10.

20. Kidambi T, Been MJ, Maddalozzo J. Congenital sialolipoma of the parotid gland: presentation, diagnosis, and management. *Am J Otolaryngol.* 2012;33(2):279-81.

21. Agaimy A, Ihrler S, Märkl B, *et al*. Lipomatous salivary gland tumors: a series of 31 cases spanning their morphologic spectrum with emphasis on sialolipoma and oncocytic lipoadenoma. *Am J Surg Pathol*. 2013;37(1):128-37.

22. Ahn D, Park TI, Park J, Heo SJ. Oncocytic sialolipoma of the submandibular gland. *Clin Exp Otorhinolaryngol*. 2014;7(2):149-52.

23. Leyva-Huerta E, Quezada Rivera D, Tenorio Rocha F, Tapia JL, Portilla Robertson J, Gaitán Cepeda LA. Sialolipoma of minor salivary glands: presentation of five cases and review of the literature with an epidemiological analyze. *Indian J Otolaryngol Head Neck Surg*. 2015;67(Suppl 1):105-9.

24. Mazlumoglu MR, Altas E, Oner F, Ucuncu H, Calik M. Congenital Sialolipoma in an Infant. *J Craniofac Surg*. 2015;26(8):e696-7.

25. O'Rourke C, Khan H, Wallis F, Fenton JE. Lipomas of the submandibular space: case report of a sialolipoma and review of diagnostic investigations available. *J Oral Maxillofac Surg*. 2015;73(1):99-105.

26. Ruangritchankul K, Connor S, Oakley R. Oncocytic Sialolipoma of Parotid Gland: Case Report and Literature Review. *Head Neck Pathol*. 2019;13(4):548-553.

27. Shrikrishna BH, Patel VI, Stephan R, Mazhar MS. Sialolipoma of Parotid Gland a Rare Histological Presentation. *Indian J Otolaryngol Head Neck Surg*. 2019;71(Suppl 1):805-808.

28. de Moraes M, de Matos FR, de Carvalho CP, de Medeiros AM, de Souza LB. Sialolipoma in minor salivary gland: case report and review of the literature. Head Neck Pathol. 2010;4(3):249-252.

29. Lee PH, Chen JJ, Tsou YA. A recurrent sialolipoma of the parotid gland: A case report. *Oncol Lett*. 2014;7(6):1981-1983.

30. Perez-Sayáns M, Blanco-Carrión A, Oliveira-Alves MG, et al. Multicentre retrospective study of 97 cases of intraoral lipoma. J Oral Pathol Med. 2019;48(6):499-504.

Table 1 Source and clinicopathological data of the 10 new cases of sialolipoma of minor salivary glands.

Center	Case	Sex	Age (years)	Location	Size (cm)	Duration (months)	Clinical appearence	Color	Treatment	Follow-Up	Fatty tissue (%)
FOP/UNICAMP[a]	1	F	48	Lower lip	1.0	8	Nodule	Normochromic	Excision	NI	60
FO/UFRJ[b]	2	F	51	Retromolar region	NI	NI	Nodule	Normochromic	Excision	NI	70
	3	F	68	Lower lip	1.0	12	Nodule	Normochromic	Excision	NI	>90
UNIFOR[c]	4	F	31	Hard palate	0.5	NI	Nodule	Reddish	Excision	NI	60
	5	F	74	Buccal mucosa	1.0	NI	Nodule	Normochromic	Excision	NI	80
	6	M	71	NI	NI	NI	Nodule	Normochromic	Excision	NI	60
	7	M	11	Floor of the mouth	4.0	NI	Nodule	Normochromic	Excision	NED at 1 year 10 months	60
	8	F	20	Tongue (dorsum)	3.0	NI	Nodule	Reddish	Excision	NI	60
UNIT[d]	9	M	51	Tongue (lateral margin)	1.5	24	Nodule	Yellow	Excision	NED at 1 year	80
	10	F	36	Lower lip	1.0	6	Nodule	Normochromic	Excision	NED at 8 months	60

Legend: NI, not informed; M, male; F, female; NED, no evidence of disease. [a]School of Dentistry of Piracicaba, University of Campinas (South-East region); [b]Department of Oral Diagnosis and Pathology, School of Dentistry, Federal University of Rio de Janeiro (South-East region); [c] School of Dentistry, University of Fortaleza (North-East region); [d]School of Dentistry, Tiradentes University (North-East region).

Table 2. Clinical and demographic features of 85 cases of sialolipomas reviewed (including the 75 cases reported in the literature and the 10 reported in the present series)

	Literature review		Present series	Total	
	Major SG (n=44)	Minor SG (n=31)	(n=10)	(n=85)	
Variables	**n, %**	**n, %**	**n, %**	**n, %**	***p* value**
Age (years)					
0-9	8 (18.2)	1 (3.8)	0 (0.0)	9 (11.3)	
10-19	3 (6.8)	0 (0.0)	1 (10.0)	4 (5.0)	
20-29	1 (2.3)	1 (3.8)	1 (10.0)	3 (3.8)	
30-39	3 (6.8)	3 (11.5)	2 (20.0)	8 (10.0)	
40-49	13 (29.5)	1 (3.8)	1 (10.0)	15 (18.8)	
50-59	4 (9.1)	2 (7.7)	2 (20.0)	8 (10.0)	
60-69	7 (15.9)	12 (46.2)	1 (10.0)	20 (25.0)	
>70	5 (11.4)	6 (23.1)	2 (20.0)	13 (16.3)	
NS	0	5	0	5	
Mean	40.9 (±24.4)	58.1 (±18.3)	46.1 (±21.5)	47.1 (±23.3)	0.0074[†]
Sex					
Female	21 (47.7)	18 (72.0)	7 (70.0)	46 (58.2)	
Male	23 (52.3)	7 (28.0)	3 (30.0)	33 (41.8)	0.0409[‡]
NS	0	6	0	6	
Location					
Parotid	36 (81.8)			36 (42.9)	
Submandibular	8 (18.2)			8 (9.5)	
Palate		9 (29.0)	1 (11.1)	10 (11.9)	
Buccal mucosa		7 (22.6)	1 (11.1)	8 (9.5)	
Floor of the mouth		5 (16.1)	1 (11.1)	6 (7.1)	
Tongue		4 (12.9)	2 (22.2)	6 (7.1)	
Lip		2 (6.5)	3 (33.3)	5 (6.0)	
Retromolar area		3 (9.7)	1 (11.1)	4 (4.8)	
Alveolar ridge		1 (3.2)	0 (0.0)	1 (1.2)	
NS		0	1	1	
Duration of complaints					
<6 months	16 (50.0)	1 (9.1)	1 (25.0)	18 (38.3)	
7-12 months	4 (12.5)	2 (18.2)	2 (50.0)	8 (17.0)	
13-24 months	1 (3.1)	0 (0.0)	1 (25.0)	2 (4.3)	
25-60 months	6 (18.8)	4 (36.4)	0 (0.0)	10 (21.3)	
>60 months	5 (15.6)	4 (36.4)	0 (0.0)	9 (19.1)	
NS	14	20	6	40	

Clinical appearence					
Painless nodule	12 (27.3)	10 (32.3)	10 (100.0)	32 (37.6)	
Painful nodule	1 (2.3)	1 (3.2)	0 (0.0)	2 (2.4)	
Swelling/nodule[§]	31 (70.4)	20 (64.5)	0	51 (60.0)	
Tumor size (cm)					
Up to 2.0 cm	5 (11.6)	17 (77.3)	6 (75.0)	30 (40.0)	
> 2.0	38 (88.4)	5 (22.7)	2 (25.0)	45 (60.0)	
NS	1	9	2	12	
Mean	4.4 (±2.0)	1.8 (±1.0)	1.6 (±1.2)	3.3 (±2.1)	<0.0001[†]
Treatment					
Superficial parotidectomy	24 (63.2)			24 (33.8)	
Total parotidectomy	5 (13.2)			5 (7.0)	
Surgical excision	9 (23.6)	23 (100.0)	10 (100.0)	42 (59.2)	
NS	6	8		14	

Legend: SG, salivary glands; NS, not specified; *n* number of cases; *(%)* relative frequency; *(±)* standard deviation; *p* statistical significance ($p<0.05$, and 95% confidence interval); *NS* not specified; [†]Student's t-test; [‡]Fisher's exact test. [§]Information on absence or presence of pain not provided. The general average age of patients with sialolipomas in minor salivary glands was 54.8±19.7 (present series and literature review).

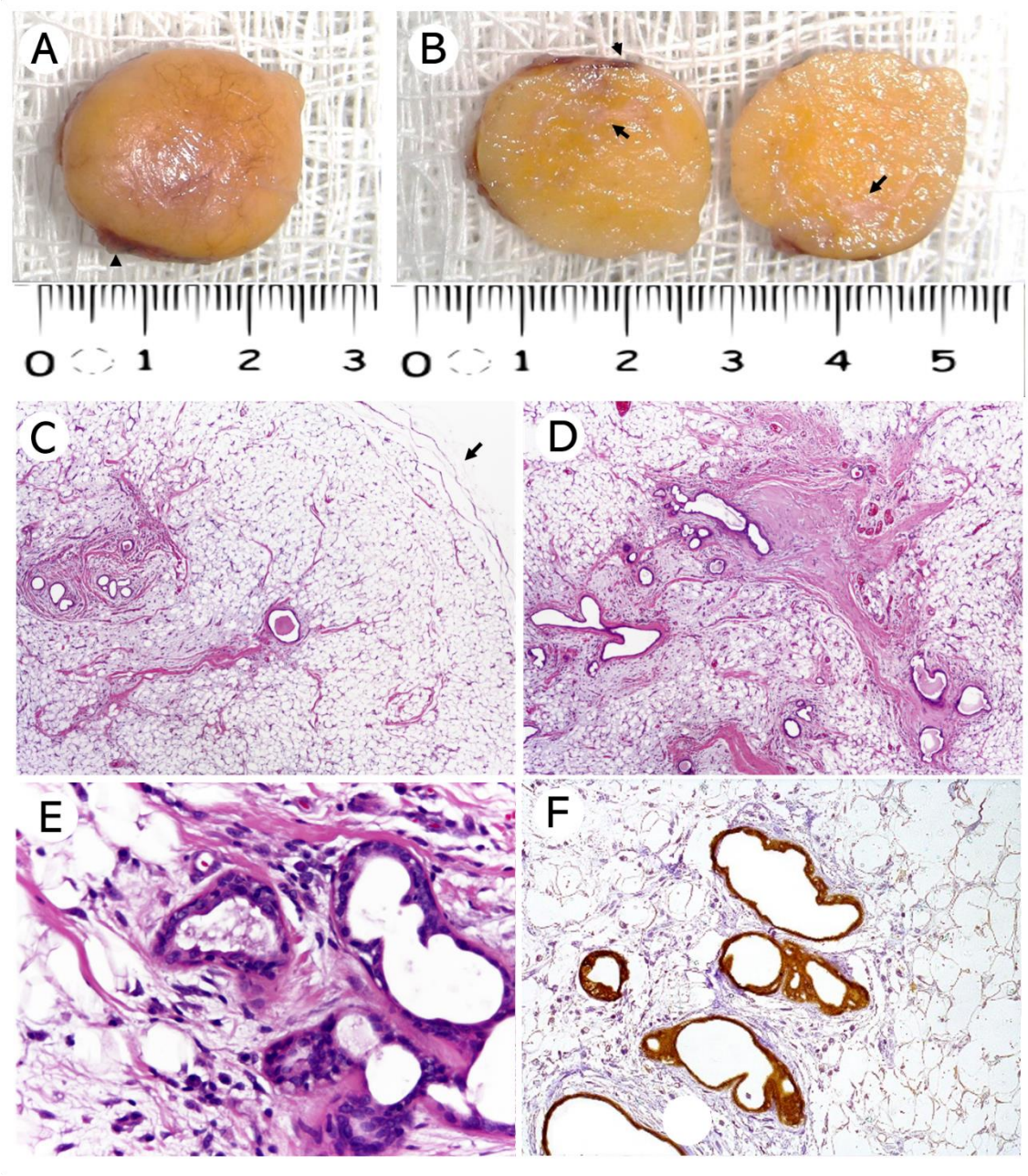


Figure 1. Macroscopic and microscopic aspect of sialolipoma of minor salivary glands (case 3). **A** and **B**) The gross specimen showed a well-circumscribed, soft, and yellowish nodule with a well-demarcated light-pink coloured, nodular component (arrowheads) surrounded by fat tissue and ill-defined brown lesions (arrows) scattered peripherally in the tumour. Histological examination identified these structures as salivary glandular tissue. **C**) The tumour was encapsulated by a thin fibrous capsule (arrow), and most of the lesion consisted of mature adipocytes. **D and E**) Detail of markedly dilated ducts with basophilic amorphous material compatible with mucin surrounded by significant fibrosis (hematoxylin and eosin stain, original magnification C ×40, D ×100, E ×400, F ×200). **F**)

Ductal cells showing positive immunohistochemical staining for cytokeratin 7 (IHQ, original magnification ×200).

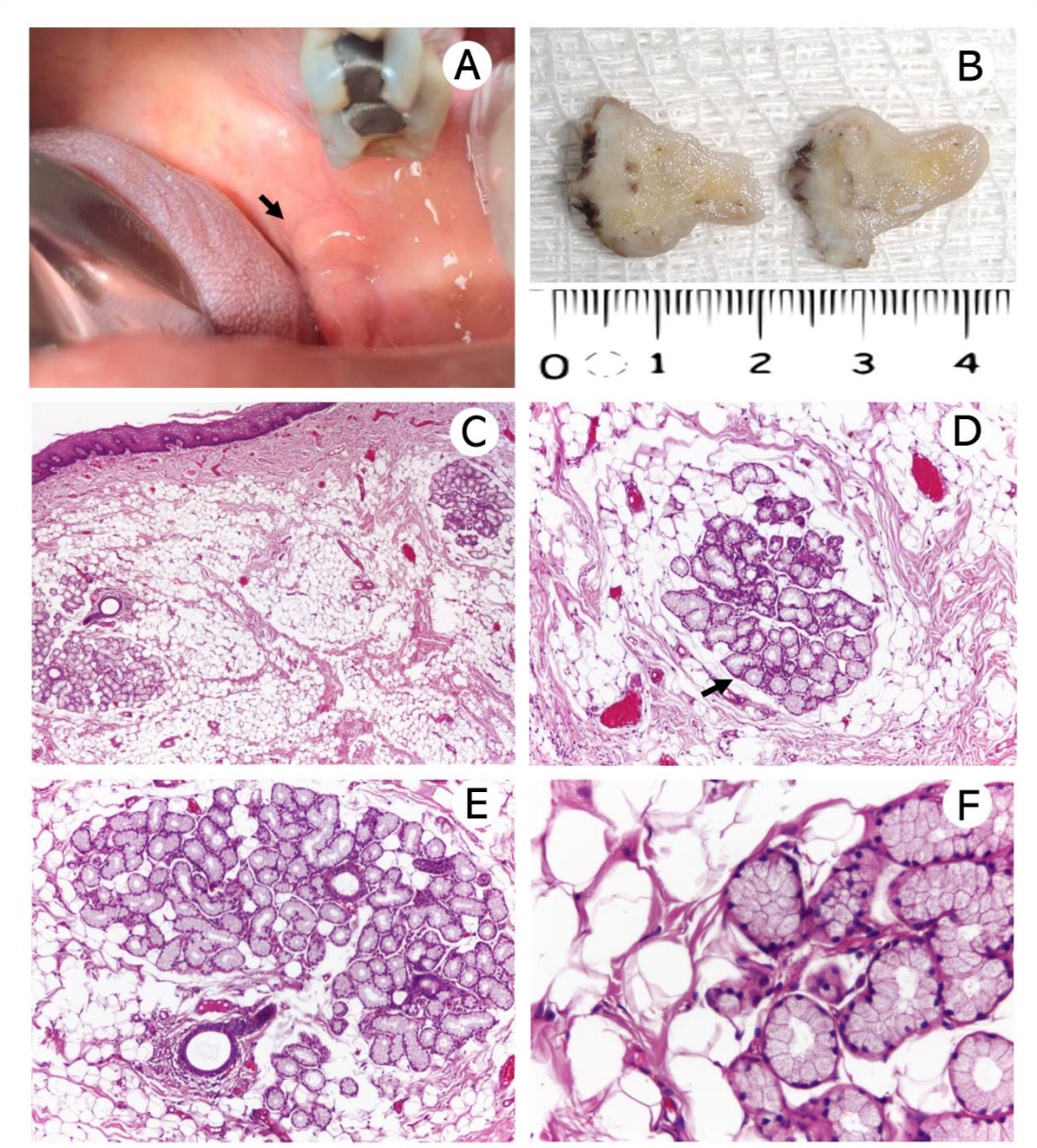


Figure 2. The clinical and microscopic aspect of sialolipoma of minor salivary glands (case 2). **A**) Clinical aspect of the lesion showing a small nodule in the retromolar region covered by normal coloured mucosa. **B**) Macroscopic aspect of surgical specimen displaying typical yellowish colour due to fat predominance. **C**) The tumour consists of salivary gland tissue and adipose elements. Note that the lesion has apparently abundant adipose elements compared with the salivary gland tissue (hematoxylin and eosin stain, original magnification ×40). **D–F**) Detail of mature adipocytes and seromucous acinus of normal aspect (hematoxylin-eosin stain, original magnification D ×100, E ×200, F ×400).

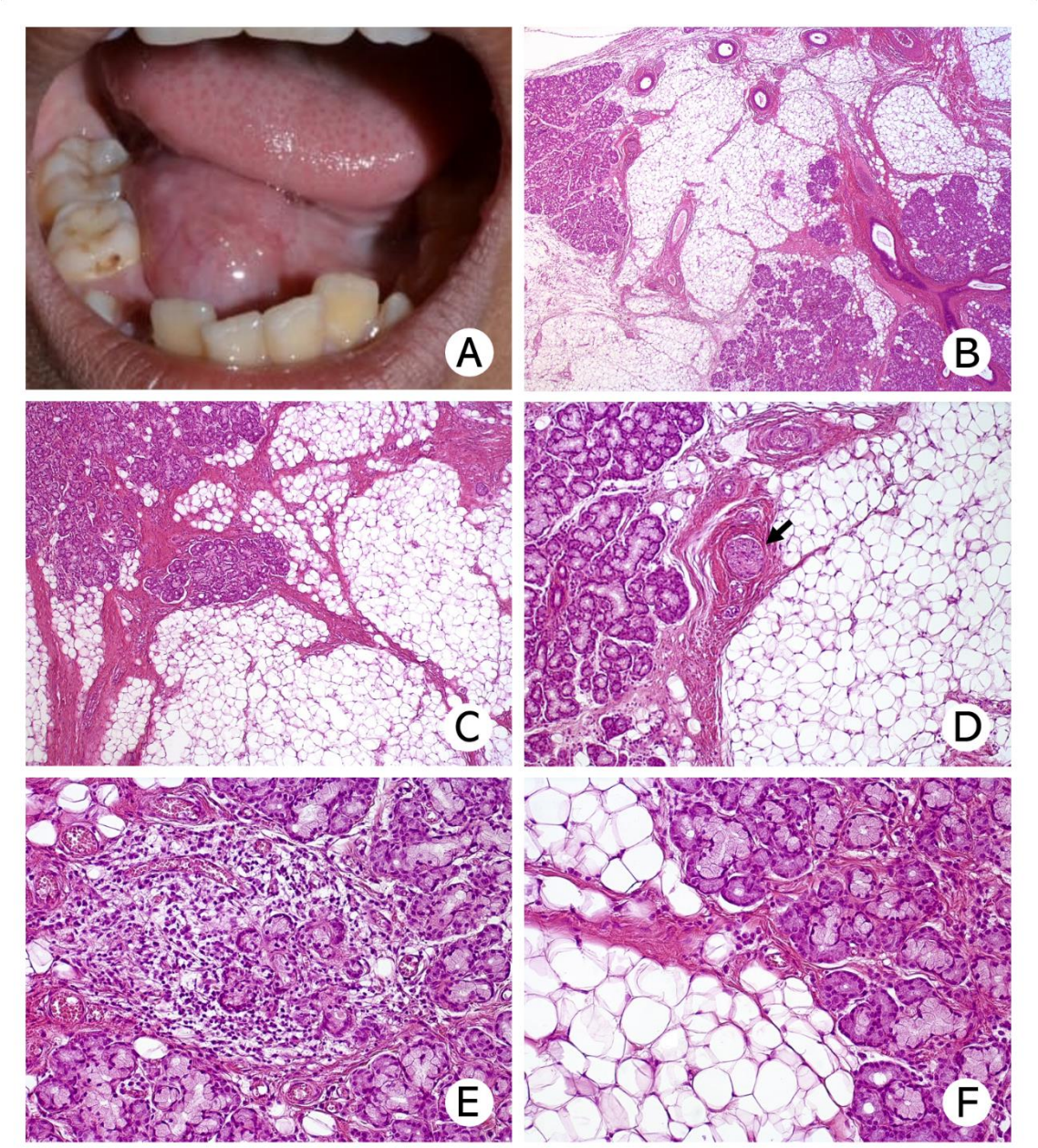


Figure 3. The clinical and microscopic aspect of sialolipoma of minor salivary glands (case 7). **A**) Intraoral view showing swelling in the floor of the mouth covered by normal-coloured mucosa. **B** and **C**) Photomicrograph of well-circumscribed, lobulated lesion composed primarily of mature adipose tissue with some salivary gland elements (hematoxylin-eosin stain, original magnification **B** ×40, **C** ×100). **D**) Mature adipose tissue encircling salivary acini and nerve bundle (black arrow) **E**) Gland parenchyma surrounded by a mild mononuclear inflammatory cell infiltrate and acinar atrophy (hematoxylin-eosin stain, original magnification ×200). **F**) Detail of neoplastic adipocytes and seromucous acinus of normal aspect (hematoxylin-eosin stain, original magnification ×200).

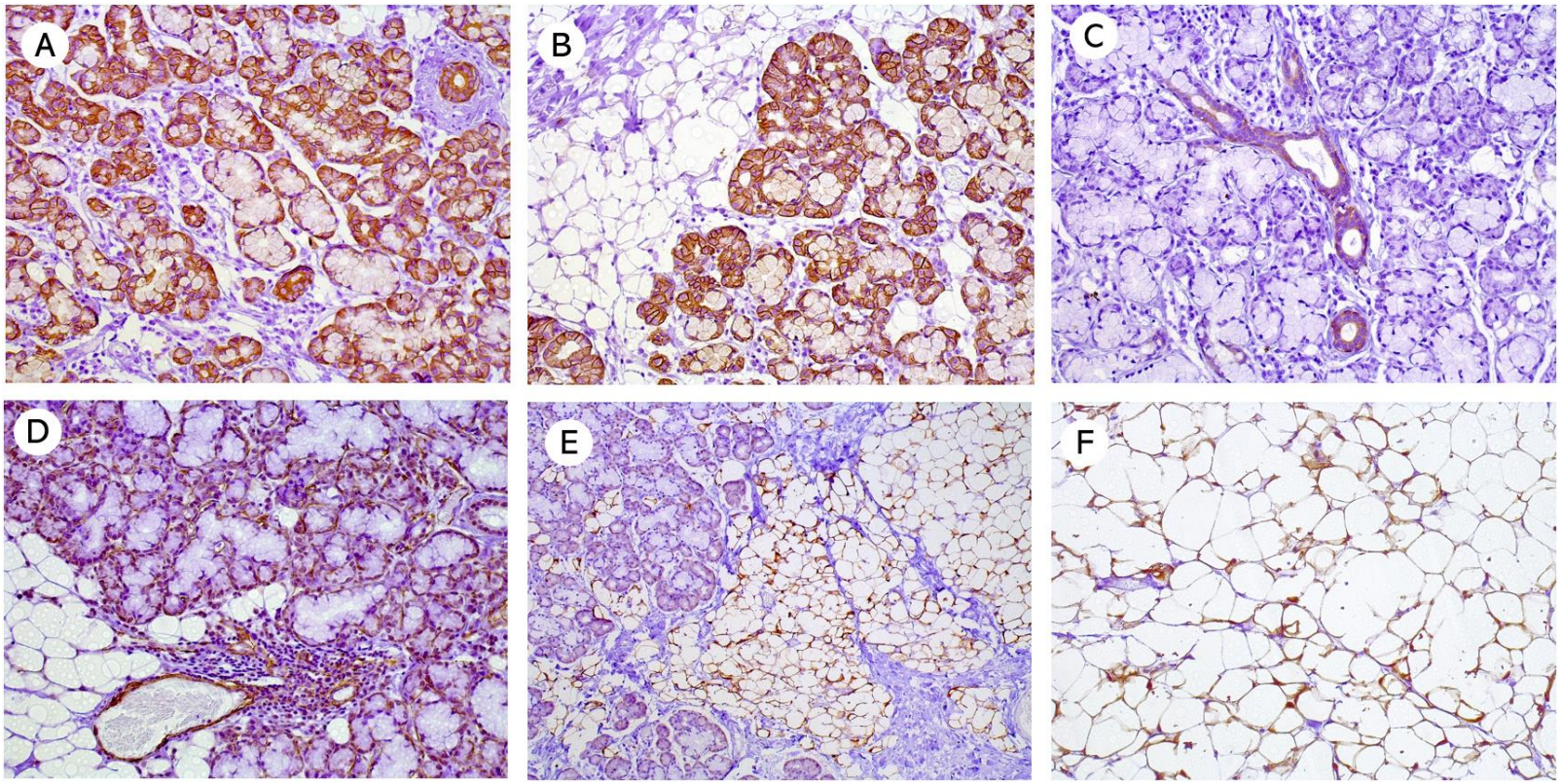


Figure 4. Immunohistochemical features of sialolipoma of minor salivary glands (case 7). Ductal and acinar cells positive for pan-cytokeratin AE1/AE3 **A**) and cytokeratin 7, **B**) (LSAB, original magnification A ×40, B ×100). **C**) Ductal cells showing cytoplasmic staining for high molecular weight cytokeratin 34βE12. Note negativity in acinar cells (LSAB, original magnification A ×40, B ×100). **D**) Myoepithelial cells were positive for smooth muscle actin (α-SMA) surrounding the acini and intercalated ducts. **E and F**) Acinar and adipose cells positive for S-100 protein (LSAB, original magnification A ×40, B ×100).

3 DISCUSSÃO

Como os aspectos mais relevantes de cada artigo já foram previamente abordados, nessa seção serão discutidos apenas os resultados principais de cada capítulo, além de uma breve discussão e as principais conclusões desses estudos.

Nos capítulos 1 e 2 determinamos o perfil clinicopatológico dos pacientes com neoplasias de glândulas salivares em 4 centros de referência no nordeste brasileiro (Aracaju, Sergipe) e no México (Cunha et al., 2020a; Cunha et al., 2020b). Embora os resultados tenham sido semelhantes àqueles previamente reportados na literatura (da Silva et al., 2018; Gao et al., 2017; Vasconcelos et al., 2016; Bittar et al., 2015; Wang et al., 2015; Wang et al., 2012; Fonseca et al., 2012; Mejía-Velázquez et al., 2012; Reinheimer et al., 2012; Li et al., 2008; Ito et al., 2005; Vargas et al., 2002),algumas diferenças foram observadas entre os países, particularmente com relação a localização anatômica mais acometida pelas lesões. No México, 68,9% dos tumores ocorreram nas glândulas salivares menores (n = 113), enquanto apenas 25,6% acometeram as glândulas salivares maiores (n = 42). O palato foi o local mais acometido (n = 67, 40,9%), seguido da glândula parótida (n = 37, 22,6%) (Cunha et al., 2020b). Em contraste com os resultados Brasileiros em que as glândulas salivares maiores foram mais acometidas do que as glândulas menores (69,5% x 30,5%) (Cunha et al., 2020a). Esta diferença pode ser explicada pelo fato de que os resultados do México são provenientes de um serviço de patologia oral, ao contrário dos resultados brasileiros que incluem tumores diagnosticados em dois centros de patologia médica, com um volume de biópsias maiores. Além disso, a maioria dos espécimes cirúrgicos enviados para serviços de patologia oral são provenientes de biópsias incisionais ou espécimes cirúrgicos relativamente pequenos tratados por cirurgiões bucomaxilofaciais, enquanto lesões mais extensas acometendo glândulas salivares maiores tendem a ser tratadas em hospitais ou centros que também realizam o diagnóstico histopatológico. Em relação às neoplasias malignas, o carcinoma mucoepidermóide foi o tumor maligno mais frequente em ambos os centros (Cunha et al., 2020a; Cunha et al., 2020b). De fato, diversos estudos apontam o carcinoma mucoepidermóide como a neoplasia maligna mais comum (da Silva et al., 2018; Gao et al., 2017; Bittar et al., 2015; Wang et al., 2015; Wang et al., 2012; Fonseca et al., 2012; Ito et al., 2005; Vargas et al., 2002). A segunda neoplasia maligna mais comum variou entre os centros. No Brasil o Adenocarcinoma SOE foi o segundo subtipo mais comum (Cunha et al., 2020a), e no México foi o adenocarcinoma polimorfo (n = 10, 18,5%)

(Cunha et al., 2020b). Contudo, em ambos os centros o adenocarcinoma polimorfo apresentou uma forte predileção pelo pelas glândulas salivares menores, principalmente na região do palato. Assim, essa aparente diferença também pode ser explicada, em partes, às diferenças no tipo de centro onde os estudos foram conduzidos (patologia oral x médica).

O terceiro capítulo trata de um estudo clinicopatológico e imunohistoquímico latino-americano de CEXAPs envolvendo glândulas salivares menores. Além da raridade em sítios intraorais, a detecção do componente carcinomatoso em amostras de biópsia incisional pode ser desafiadora no exame morfológico, especialmente em casos incipientes e amostras de biópsias incisionais pequenas. Por essa razão, nós caracterizamos e descrevemos as características clínico-patológicas de uma série de 39 CEXAP intraorais e reavaliamos 561 casos de APs de glândulas salivares menores com ênfase na detecção de alterações morfológicas que sugerissem uma possível transformação malina em CEXAP. A maioria dos tumores ocorreu em mulheres (56,4%), com média de idade de 45,9 ± 16,5 anos (variando de 19 a 81 anos) e em palato (n = 24, 61,5%). O subtipo morfológico mais comum foi o carcinoma mioepitelial (n = 13, 33,3%), seguido pelo adenocarcinoma sem outra especificação (n = 6, 15,4%). Curiosamente, após a reavaliação microscópica e estudos imunohistoquímicos de 561 AP de glândulas salivares menores, dez (1,7%) foram reclassificados como CEXPAs em estágios iniciais, representando 25,6% dos casos de CEXPAs relatados no estudo. Alto índice proliferativo celular (calculado pela expressão nuclear de Ki67) e expressão de p53 foram úteis na identificação das áreas malignas, o que sugere que esses marcadores podem ser utilizados para identificar possíveis áreas de transformação carcinomatosa em APs e, assim, auxiliar na diferenciar no diagnóstico em fases iniciais do CEXAP. Esse fato reforça a importância do patologista oral, com treinamento diagnóstico em tumores de GS na detecção precoce de tumores malignos, que terão uma abordagem diferente.

No capítulo 4, nós apresentamos as características clínico-patológicas e imunohistoquímicas de 10 novos casos de sialolipomas em conjunto com uma revisão da literatura. O sialolipoma é uma variante histológica rara do lipoma composta por uma proliferação de adipócitos maduros associada com de tecido normal da glândula salivar. Essas lesões são mais comuns em glândula parótida e glândulas salivares menores do palato de mulheres adultas, sendo comumente subdiagnosticadas. Os patologistas devem

reconhecer os sialolipomas para evitar confusão com outros tumores lipomatosos que podem afetar as glândulas salivares.

4 CONCLUSÃO

- O perfil epidemiológico e as características clínicas das neoplasias de glândulas salivares foram semelhantes aos descritos em outros países e outras regiões do Brasil e as diferenças encontradas refletem as particularidades de cada serviço onde os estudos foram desenvolvidos (centros de patologia bucal x centros de patologia médica).
- Os carcinomas ex-adenoma pleomórficos são tumores malignos raros em sítios intraorais, geralmente acometendo o palato de mulheres adultas. Diferentes variantes histológicas foram encontradas, sendo o subtipo mioepitelial e adenocarcinoma SOE os mais comuns.
- O índice proliferativo celular evidenciado por meio da imunoexpressão nuclear do Ki-67 e a expressão de p53 são úteis na identificação de áreas malignas em casos com suspeita de malignidade, no entanto a análise morfológica cuidadosa ainda é um fator essencial para diagnóstico de CEXPA.
- Embora os carcinomas ex-adenoma pleomórficos das glândulas salivares menores pareçam apresentar curso clínico indolente, estudos adicionais são necessários para esclarecer seu potencial biológico. As evidências atuais indicam que essas lesões devem ser completamente removidas por excisão cirúrgica, uma vez que podem ser localmente invasivas e recorrentes.
- O sialolipoma é uma variante histológica rara do lipoma comumente diagnosticados incorretamente, sendo mais comuns em glândula parótida e glândulas salivares menores do palato de mulheres adultas. O reconhecimento dessa variante, por parte dos patologistas, é essencial para evitar confusão com outros tumores lipomatosos que podem acometer as glândulas salivares.

REFERÊNCIAS[*]

Bittar RF, Ferraro HP, Moraes Gonçalves FT, Couto da Cunha MG, Biamino ER. Neoplasms of the salivary glands: analysis of 727 histopathological reports in a single institution. Otolaryngol Pol. 2015:69:28-33.

Cunha JL, Coimbra AC, Silva JV, Nascimento IS, Andrade ME, Oliveira CR, et al. Epidemiologic analysis of salivary gland tumors over a 10-years period diagnosed in a northeast Brazilian population. Med Oral Patol Oral Cir Bucal. 2020 Jul 1;25(4):e516-e522. (a)

Cunha JLS, Hernandez-Guerrero JC, de Almeida OP, Soares CD, Mosqueda-Taylor A. Salivary Gland Tumors: A Retrospective Study of 164 Cases from a Single Private Practice Service in Mexico and Literature Review. Head Neck Pathol. 2020 Oct 12. doi: 10.1007/s12105-020-01231-2. Epub ahead of print. (b)

da Silva LP, Serpa MS, Viveiros SK, Sena DAC, de Carvalho Pinho RF, de Abreu Guimarães LD, et al. Salivary gland tumors in a Brazilian population: A 20-year retrospective and multicentric study of 2292 cases. J Craniomaxillofac Surg. 2018:46:2227-33.

Di Palma S. Carcinoma ex pleomorphic adenoma, with particular emphasis on early lesions. Head Neck Pathol. 2013;7 Suppl 1(Suppl 1):S68-S76.

Díaz KP, Gondak R, Martins LL, de Almeida OP, León JE, Mariano FV, et al. Fatty acid synthase and Ki-67 immunoexpression can be useful for the identification of malignant component in carcinoma ex-pleomorphic adenoma. J Oral Pathol Med. 2019 Mar;48(3):232-238.

El-Naggar, AK, Chan, JKC, Grandis, JR, Takata, T, Slootweg, PJ. World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours. 4th ed. Lyon, France: International Agency for Research on Cancer; 2017.

[*] De acordo com as normas da UNICAMP/FOP, baseadas na padronização do International Committee of Medical Journal Editors - Vancouver Group. Abreviatura dos periódicos em conformidade com o PubMed.

Fonseca FP, Carvalho M de V, de Almeida OP, Rangel AL, Takizawa MC, Bueno AG, et al. Clinicopathologic analysis of 493 cases of salivary gland tumors in a Southern Brazilian population. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012:114:230-39.

Freitas LL, Araújo VC, Martins MT, Chone C, Crespo A, Altemani A. Biomarker analysis in carcinoma ex pleomorphic adenoma at an early phase of carcinomatous transformation. Int J Surg Pathol. 2005;13:337-342.

Gao M, Hao Y, Huang MX, Ma DQ, Chen Y, Luo HY, et al. Salivary gland tumours in a northern Chinese population: a 50-year retrospective study of 7190 cases. Int J Oral Maxillofac Surg. 2017:46:343-49.

Ito FA, Ito K, Vargas PA, de Almeida OP, Lopes MA. Salivary gland tumors in a Brazilian population: a retrospective study of 496 cases. Int J Oral Maxillofac Surg. 2005 Jul;34(5):533-6. doi: 10.1016/j.ijom.2005.02.005

Li LJ, Li Y, Wen YM, Liu H, Zhao HW. Clinical analysis of salivary gland tumor cases in West China in past 50 years. Oral Oncol. 2008 Feb;44(2):187-92. doi: 10.1016/j.oraloncology.2007.01.016.

Lopes MLDS, Barroso KMA, Henriques ÁCG, Dos Santos JN, Martins MD, de Souza LB. Pleomorphic adenomas of the salivary glands: retrospective multicentric study of 130 cases with emphasis on histopathological features. Eur Arch Otorhinolaryngol. 2017 Jan;274(1):543-551.

Mariano FV, Costa AF, Gondak RO, Martins AS, Del Negro A, Tincani ÁJ, et al. Cellular Proliferation Index between Carcinoma Ex-Pleomorphic Adenoma and Pleomorphic Adenoma. Braz Dent J. 2015;26(4):416-421.

Mariano FV, Noronha AL, Gondak RO, Altemani AM, de Almeida OP, Kowalski LP. Carcinoma ex pleomorphic adenoma in a Brazilian population: clinico-pathological analysis of 38 cases. Int J Oral Maxillofac Surg. 2013 Jun;42(6):685-92.

Mejía-Velázquez CP, Durán-Padilla MA, Gómez-Apo E, Quezada-Rivera D, Gaitán-Cepeda LA. Tumors of the salivary gland in Mexicans. A retrospective study of 360 cases. Med Oral Patol Oral Cir Bucal. 2012:17:e183–89.

Pérez-de-Oliveira ME, Leonel ACLDS, de Castro JFL, Carvalho EJA, Vargas PA, Perez DEDC. Histopathological Findings of Intraoral Pleomorphic Adenomas: A Retrospective Study of a Case Series. Int J Surg Pathol. 2019 Oct;27(7):729-735.

Reinheimer A, Vieira DS, Cordeiro MM, Rivero ER. Retrospective study of 124 cases of salivary gland tumors and literature review. J Clin Exp Dent. 2019;11(11):e1025–e1032. doi:10.4317/jced.55685

Scarini JF, Rosa LF, Souza RAL, Egal ESA, Tincani AJ, Martins AS, et al. Gene and immunohistochemical expression of HIF-1α, GLUT-1, FASN, and adipophilin in carcinoma ex pleomorphic adenoma development. Oral Dis. 2020 Mar 16. doi: 10.1111/odi.13332. Epub ahead of print.

Sedassari BT, Dos Santos HT, Mariano FV, da Silva Lascane NA, Altemani A, Sousa S. Carcinoma ex pleomorphic adenoma of minor salivary glands with major epithelial-myoepithelial component: clinicopathologic and immunohistochemical study of 3 cases. Ann Diagn Pathol. 2015;19(3):164-168.

Tian Z, Li L, Wang L, Hu Y, Li J. Salivary gland neoplasms in oral and maxillofacial regions: a 23-year retrospective study of 6982 cases in an eastern Chinese population. Int J Oral Maxillofac Surg. 2010:39:235-42.

Vargas PA, Gerhard R, Araújo Filho VJ, de Castro IV. Salivary gland tumors in a Brazilian population: a retrospective study of 124 cases. Rev Hosp Clin Fac Med Sao Paulo. 2002:57:271-76.

Vasconcelos AC, Nör F, Meurer L, Salvadori G, Souza LB, Vargas PA, et al. Clinicopathological analysis of salivary gland tumors over a 15-year period. Braz Oral 2016:30:e2.

Wang XD, Meng LJ, Hou TT, Huang SH. Tumours of the salivary glands in northeastern China: a retrospective study of 2508 patients. Br J Oral Maxillofac Surg. 2015:53:132-37.

Wang YL, Zhu YX, Chen TZ, Wang Y, Sun GH, Zhang L, et al. Clinicopathologic study of 1176 salivary gland tumors in a Chinese population: experience of one cancer center 1997-2007. Acta Otolaryngol. 2012:132:879-86.

ANEXOS

Anexo 1: Certificado do Comitê de Ética em Pesquisa

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

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: ESTUDO CLINICOPATOLÓGICO E IMUNOHISTOQUÍMICO DE MARCADORES RELACIONADOS AO METABOLISMO GLICOLÍTICO E LIPÍDICO EM NEOPLASIAS BENIGNAS E MALIGNAS DE GLÂNDULAS SALIVARES

Pesquisador: JOHN LENNON SILVA CUNHA

Área Temática:

Versão: 4

CAAE: 20726819.6.0000.5418

Instituição Proponente: Faculdade de Odontologia de Piracicaba - Unicamp

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.427.473

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 dos dados e arquivos da última versão apresentada.

Trata-se de SOLICITAÇÃO DE EMENDA (E1) AO PROTOCOLO originalmente aprovado em 25/11/2019 para ajuste no título do protocolo. A descrição detalhada da solicitação está ao final do parecer. O texto do parecer foi ajustado conforme a documentação apresentada na solicitação.

Anexo 2: Página inicial do artigo 1

Journal section: Oral Medicine and Pathology
Publication Types: Research

doi:10.4317/medoral.23532

Epidemiologic analysis of salivary gland tumors over a 10-years period diagnosed in a northeast Brazilian population

John Lennon Silva Cunha [1], Ana Carolina Penha Coimbra [2], João Vitor Rocha Silva [3], Ilmara Silva do Nascimento [3], Maria Eliane de Andrade [4], Clauberto Rodrigues de Oliveira [4], Oslei Paes de Almeida [5], Ciro Dantas Soares [6], Silvia Ferreira de Sousa [7], Ricardo Luiz Cavalcanti de Albuquerque-Júnior [8]

[1] DDS, MSc student. Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), SP, Brazil
[2] MD. Department of Medicine, Federal University of Sergipe (UFS), Aracaju, Brazil
[3] Department of Dentistry, Tiradentes University (UNIT), Aracaju, Sergipe, Brazil
[4] PhD student. Laboratory of Morphology and Experimental Pathology, Institute of Technology and Research, Tiradentes University (UNIT), Aracaju, Sergipe, Brazil
[5] DDS, PhD, Professor. Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), SP, Brazil
[6] DDS, PhD student. Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), SP, Brazil
[7] DDS, PhD, Professor. Department of Oral Surgery and Pathology, School of Dentistry, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil
[8] DDS, PhD, Professor. Department of Dentistry, Tiradentes University (UNIT), Aracaju, Sergipe, Brazil

Correspondence:
Laboratory of Morphology and Experimental Pathology
Institute of Technology and Research, Tiradentes University
Av. Murilo Dantas, 300, Farolândia, Aracaju, SE 49032-490, Brazil
ricardo.patologia@uol.com.br

Received: 26/10/2019
Accepted: 24/02/2020

Cunha JLS, Coimbra ACP, Silva JVR, Nascimento ISd, Andrade MEd, Oliveira CRd, *et al.* Epidemiologic analysis of salivary gland tumors over a 10-years period diagnosed in a northeast Brazilian population. Med Oral Patol Oral Cir Bucal. 2020 Jul 1;25 (4):e516-22.

Article Number: 23532 *http://www.medicinaoral.com/*
© Medicina Oral S. L. C.I.F. B 96689336 - pISSN 1698-4447 - eISSN 1698-6946
eMail: medicina@medicinaoral.com
Indexed in:
Science Citation Index Expanded
Journal Citation Reports
Index Medicus, MEDLINE, PubMed
Scopus, Embase and Excerpta
Index Médicus Español

Abstract

Background: Salivary gland tumors (SGT) correspond to a heterogeneous group of lesions with variable biological behavior. The present study aimed to determine the distribution and demographic findings of salivary gland neoplasms in a northeast Brazilian population.

Material and Methods: A retrospective descriptive cross-sectional study was performed. A total of 588 cases of SGT were diagnosed between 2006 and 2016 of 4 pathology services in the state of Sergipe, Brazil. All cases were reviewed, and data such as sex, age, anatomical location, and histopathological diagnosis were collected.

Results: A total of 470 (79.9%) tumors were benign and 118 (20.1%) were malignant. The majority of the patients were females (n=328, 55.8%) with an overall female:male ratio of 1.2:1. The major salivary glands were affected

Anexo 3: Página inicial do artigo 2

Head and Neck Pathology
https://doi.org/10.1007/s12105-020-01231-2

ORIGINAL PAPER

Salivary Gland Tumors: A Retrospective Study of 164 Cases from a Single Private Practice Service in Mexico and Literature Review

John Lennon Silva Cunha[1] · Juan Carlos Hernandez-Guerrero[2] · Oslei Paes de Almeida[1] · Ciro Dantas Soares[1] · Adalberto Mosqueda-Taylor[3]

Received: 23 July 2020 / Accepted: 1 October 2020

Abstract

Salivary gland tumors (SGT) represent an uncommon heterogeneous group of tumors with complex clinical and pathological characteristics. The prevalence of these lesions varies between studies but has been estimated between 3 and 6% of all tumors in the head and neck region. The present study aimed to evaluate the distribution and demographic findings of salivary gland tumors diagnosed in an oral pathology service in Mexico. A retrospective descriptive cross-sectional study was performed. A total of 164 cases of SGT from a private oral pathology service were diagnosed between 2000 and 2019 in Mexico City. All cases were reviewed histologically, and demographic data and histopathological diagnoses were collected. A total of 110 (67.1%) tumors were benign, and 54 (32.9%) were malignant. The majority of patients were female (n = 100, 61.0%) with an overall female:male ratio of 1.6:1. The minor salivary glands were affected more than the major salivary glands (68.9% vs. 25.6%). The palate (n = 67, 40.9%) was the most commonly affected site, followed by the parotid gland (n = 37, 22.6%), lips (n = 16, 9.8%), and buccal mucosa (n = 14, 8.5%). Pleomorphic adenoma (n = 88; 80.0%) and mucoepidermoid carcinoma (n = 16, 29.6%) were the most frequent benign and malignant tumors, respectively. The general features of SGT from the studied Mexican population shared some similarities and differences compared to previously reported series from various parts of the world.

Keywords Salivary gland · Tumors · Epidemiology · Head and neck pathology

Introduction

The salivary glands are exocrine glands that produce secretions contributing to the lubrication, digestion, and protection of the upper aerodigestive tract [1]. They can be divided into major (parotid, submandibular, sublingual) and minor salivary glands [2]. Due to its complex histology, a variety of primary tumors can develop in these structures independently of the anatomical site [1, 2]. Also, the morphological diagnosis of these lesions is frequently challenging due to many histological subtypes, overlapping of morphological findings, and different classifications [2–4].

Although several epidemiological studies across the world have evaluated the frequency and incidence of these tumors [2, 3, 5–16], geographic variations have been observed in this group of lesions, particularly in relation to anatomical location and histological subtypes [2, 3, 8]. In addition, there are only a few studies about the incidence in the Mexican population, despite its large geographical size and population [14].

Thus, the objective of the present study was to describe the clinical and demographic aspects of salivary gland tumors (SGT) diagnosed in a private oral pathology service in Mexico City and to compare the findings with epidemiological data from different geographic locations obtained through the review of the literature.

✉ Ciro Dantas Soares
ciro.dss@gmail.com

[1] Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), Av. Limeira 901, P.O. Box. 52, Piracicaba, São Paulo 1314-903, Brazil

[2] Facultad de Odontología, Laboratory of Immunology, Universidad Nacional Autónoma de México (UNAM), México City, México

[3] Facultad de Odontología, Universidad Autónoma Metropolitana Xochimilco (UAM), México City, México

Published online: 12 October 2020

Anexo 4: Página inicial do artigo 4

Received: 30 June 2020 | Revised: 19 September 2020 | Accepted: 13 October 2020
DOI: 10.1111/jop.13124

ORIGINAL ARTICLE

Journal of Oral Pathology & Medicine WILEY

Sialolipomas of minor salivary glands: A multi-institutional study and literature review

John Lennon Silva Cunha[1] | Sílvia Ferreira de Sousa[2] | Carolina Peres Mota[2] | João Vitor Rocha Silva[3] | Israel Leal Cavalcante[4] | Erasmo Bernardo Marinho[5] | Ciro Dantas Soares[1] | Ricardo Luiz Cavalcanti de Albuquerque-Júnior[3] | Roberta Barroso Cavalcante[4] | Aline Corrêa Abrahão[6] | Michelle Agostini[6] | Mario José Romañach[6] | Bruno Augusto Benevenuto de Andrade[6] | Pablo Agustin Vargas[1] | Oslei Paes de Almeida[1]

[1]Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, Brazil
[2]Department of Oral Surgery and Pathology, School of Dentistry, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil
[3]Laboratory of Morphology and Experimental Pathology, Institute of Technology and Research, Tiradentes University (UNIT), Aracaju, Brazil
[4]Oral Pathology, School of Dentistry, University of Fortaleza (UNIFOR), Fortaleza, Brazil
[5]Department of Dental Clinic, Division of Oral Pathology, Faculty of Pharmacy, Dentistry and Nursing, Federal University of Ceara (UFC), Fortaleza, Brazil
[6]Department of Oral Diagnosis and Pathology, School of Dentistry, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, Brazil

Correspondence
John Lennon Silva Cunha, Oral Pathology Section, Department of Oral Diagnosis, Piracicaba Dental School, University of Campinas (UNICAMP), Av. Limeira 901, P.O. Box. 52, Piracicaba, São Paulo 1314-903, Brazil.
Email: lennonrm@live.com

Abstract

Background: Sialolipoma is a rare histological variant of lipoma commonly misdiagnosed and composed of a proliferation of mature adipocytes with secondary entrapment of normal salivary gland tissue. The purpose of the present study is to report the clinicopathologic and immunohistochemical features of 10 new cases of sialolipomas in conjunction with a review of the literature.

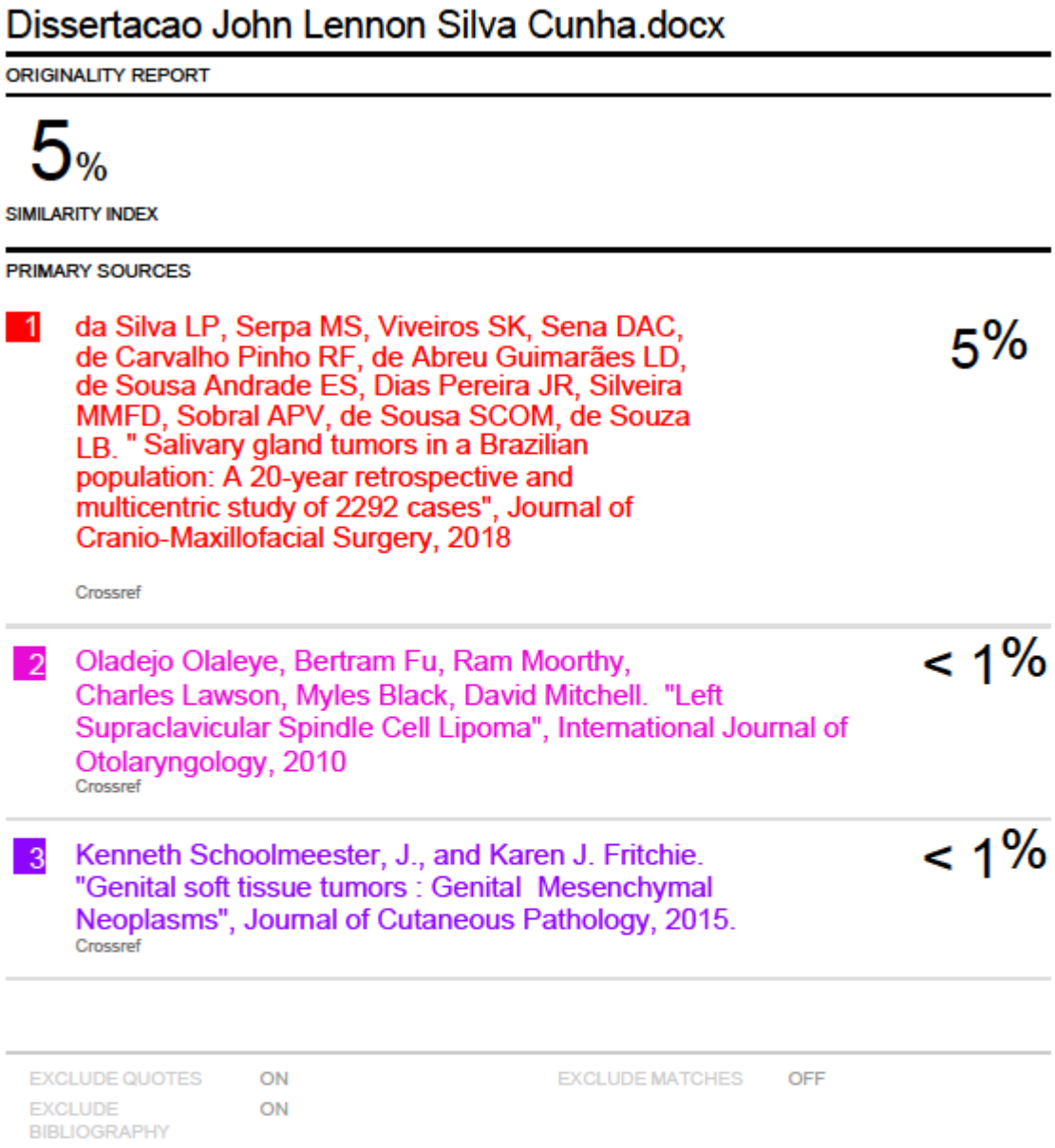
Methods: A retrospective descriptive cross-sectional study was performed. A total of 54,190 biopsy records of oral and maxillofacial lesions from four oral and maxillofacial pathology services in Brazil were analysed. All cases of lipomas were reviewed, and clinical, demographic and histopathological data were collected of all cases compatible with sialolipomas. In addition, immunohistochemistry stains (AE1/AE3, CK7, 34βE12, S-100, HHF35, α-SMA and Ki-67) and a literature review based on a search of three electronic databases (PubMed, Web of Science and Scopus) were performed.

Results: Among all lipomas reviewed, there were 10 cases of sialolipomas. The series comprised of 7 females (70.0%) and 3 males (30.0%), with a mean age of 46.1 ± 21.5 years (range: 11-71 years) and a 2.3:1 female-to-male ratio. The lower lip ($n = 3$, 30.0%) and tongue ($n = 2$, 20.0%) were the most common locations, presenting clinically as a nodule of slow growth and normal colour. Conservative surgical excision was the treatment in all cases. No recurrence was observed.

Conclusion: Sialolipomas are a rare histological variant of lipoma, affecting the salivary glands, mainly in the parotid gland and palate of female adults. Pathologists must recognise sialolipomas to avoid misdiagnoses with other lipomatous tumours that can affect salivary glands.

KEYWORDS
diagnosis, histopathology, salivary gland, sialolipoma

Anexo 5: Relatório de verificação de originalidade e prevenção de plágio



Dissertacao John Lennon Silva Cunha.docx

ORIGINALITY REPORT

5%

SIMILARITY INDEX

PRIMARY SOURCES

1	da Silva LP, Serpa MS, Viveiros SK, Sena DAC, de Carvalho Pinho RF, de Abreu Guimarães LD, de Sousa Andrade ES, Dias Pereira JR, Silveira MMFD, Sobral APV, de Sousa SCOM, de Souza LB. " Salivary gland tumors in a Brazilian population: A 20-year retrospective and multicentric study of 2292 cases", Journal of Cranio-Maxillofacial Surgery, 2018 Crossref	5%
2	Oladejo Olaleye, Bertram Fu, Ram Moorthy, Charles Lawson, Myles Black, David Mitchell. "Left Supraclavicular Spindle Cell Lipoma", International Journal of Otolaryngology, 2010 Crossref	< 1%
3	Kenneth Schoolmeester, J., and Karen J. Fritchie. "Genital soft tissue tumors : Genital Mesenchymal Neoplasms", Journal of Cutaneous Pathology, 2015. Crossref	< 1%

EXCLUDE QUOTES	ON	EXCLUDE MATCHES	OFF
EXCLUDE BIBLIOGRAPHY	ON		