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**FREQUÊNCIA DE CARCINOMA EPIDERMOIDE ORAL EM PACIENTES
JOVENS EM SERVIÇOS DE REFERÊNCIA AO REDOR DO MUNDO**

**Faculdade de Odontologia
Universidade Federal de Minas Gerais
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Dissertação apresentada ao Colegiado de Pós-Graduação em Odontologia da Faculdade de Odontologia da Universidade Federal de Minas Gerais, como requisito parcial a obtenção do grau de Mestre em Odontologia – Área de concentração em Estomatologia

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Coorientador: Prof. Dr. Ricardo Alves Mesquita

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FOLHA DE APROVAÇÃO

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RAFAEL FERREIRA E COSTA

Dissertação submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em Odontologia, como requisito para obtenção do grau de Mestre, área de concentração Estomatologia.

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“Existem muitas hipóteses em ciência que estão erradas. Isso é perfeitamente aceitável, eles são a abertura para achar as que estão certas.”

Carl Sagan

RESUMO

O carcinoma epidermoide oral é uma neoplasia maligna com origem no epitélio de revestimento da boca que responde por aproximadamente 95% das neoplasias malignas que acometem esta região anatômica, sendo, portanto, o câncer de boca mais comum. O carcinoma epidermoide oral é mais frequente em pessoas com mais de 45 anos de idade, sendo pouco comum em indivíduos jovens; entretanto, ao longo das últimas décadas alguns estudos desenvolvidos principalmente nos EUA e nos países nórdicos da Europa demonstraram haver um possível aumento na incidência do carcinoma epidermoide de língua no grupo de pacientes mais jovens (em geral < 40 anos de idade), em especial entre as mulheres brancas que nunca estiveram expostas aos fatores de risco mais bem conhecidos para o desenvolvimento da doença. Entretanto, uma possível explicação para esta mudança de perfil epidemiológico permanece inexistente. Portanto, este trabalho tem como objetivo analisar a frequência do carcinoma epidermoide oral em pacientes jovens (≤ 40 anos) em serviços de referência em diagnóstico e/ou tratamento de câncer oral ao redor do mundo. Para isto, no período de janeiro/1998 a dezembro/2018, foram coletados dos arquivos de serviços localizados no Brasil, Argentina, México, Reino Unido, Espanha, África do Sul, Índia e China, os dados demográficos referentes aos pacientes afetados por carcinoma epidermoide oral, incluindo informações sobre sexo, idade, localização e ano de diagnóstico de todos os casos de carcinoma epidermoide oral, além de informações sobre diferenciação microscópica e exposição à fatores de risco para o grupo de pacientes jovens. Foram coletadas informações de 10.727 casos de carcinoma epidermoide oral, sendo que 626 casos (5.8%) afetaram pacientes jovens. Neste grupo, os homens permaneceram como os mais afetados, com uma média de idade de 33,4 anos. A língua/assoalho bucal foi a região mais afetada, com exceção da Índia onde o fundo de vestibulo esteve mais acometido. A maioria dos casos são diagnosticados como neoplasias bem ou moderadamente diferenciadas (71,9%). Apenas 16,2% dos pacientes jovens relataram nunca estar expostos a fatores de risco como álcool e tabaco. Não foi observada uma tendência de aumento na frequência de casos em pacientes jovens em nenhum serviço investigado; contudo, observou-se uma tendência de diminuição no Brasil e na China, o que se repetiu quando a amostra geral foi avaliada. Assim, concluímos que pacientes jovens com menos de 40 anos de idade nunca expostos a fatores de risco para o carcinoma epidermoide oral representa um grupo incomum de pacientes e nossos resultados não corroboram os achados da literatura de aumento na incidência da doença nesta população.

Palavras-chave: Câncer de boca. Carcinoma epidermoide. Jovens. Incidência.

ABSTRACT

Frequency of oral squamous cell carcinoma affecting young patients in referral centers around the world

Oral squamous cell carcinoma is a malignant neoplasm originating from the lining epithelium of the mouth, which accounts for approximately 95% of malignant neoplasms that affect this anatomical region, being, therefore, the most common oral cancer. As with other malignancies, its incidence increases with the patient's age and oral squamous cell carcinoma thus becomes more frequent in people over 45 years of age, being uncommon in young individuals; however, over the past few decades some studies developed mainly in the USA and in the Nordic countries of Europe have shown a possible tendency to increase the incidence of oral squamous cell carcinoma in the younger group of patients (generally <40 years of age), especially among white women who have never been exposed to the most well-known risk factors for the development of the disease. Indeed, a possible explanation for this change in the epidemiological profile remains non-existent. Therefore, this study aims to analyze the frequency of oral squamous cell carcinoma in young patients (<40 years old) in reference services in the diagnosis and / or treatment of oral diseases around the world. For this purpose, from January / 1998 to December / 2018, demographic data referring to patients affected by carcinoma were collected from the service files located in Brazil, Argentina, Mexico, United Kingdom, Spain, South Africa, India and China. oral epidermoid, including information on sex, age, location and year of diagnosis of all cases of oral squamous cell carcinoma, as well as information on microscopic differentiation and exposure to risk factors for the group of young patients. Information was collected on 10,727 cases of oral squamous cell carcinoma, with 626 cases (5.8%) affecting young patients. Among young people, men remained the most affected, with an average age of 33.4 years. The tongue / floor was the most affected region, with the exception of India, where the bottom of the vestibule was most affected. Most cases are diagnosed as well or moderately different neoplasms (71.9%). Only 16.2% of young patients reported never being exposed to risk factors such as alcohol and tobacco. We did not observe an increasing trend in the frequency of cases in young patients in any investigated service, however, we observed a decreasing trend in Brazil and China, which was repeated when the general sample was evaluated. Thus, we conclude that young patients under 40 years of age never exposed to risk factors for oral squamous cell carcinoma represent an unusual group of patients and our results do not corroborate the findings described in the USA and Nordic countries of an increase in the incidence of the disease in this population.

Keywords: Oral cancer. Squamous cell carcinoma. Youth. Incidence.

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1 CONSIDERAÇÕES INICIAIS

No Brasil o câncer de boca representa o quinto tipo de câncer mais comum em homens e o 12º em mulheres, excetuando os tipos de câncer de pele não melanoma. Em todo o mundo, representa o oitavo câncer mais prevalente (BRAY; FERLAY; SOERJOMATARAM *et al.*, 2018; DOS SANTOS COSTA; BRENNAN; GOMEZ *et al.*, 2018; INCA, 2019). De acordo com dados do Instituto Nacional do Câncer (INCA) foram estimados para o ano de 2020, 15.190 novos casos de câncer oral, sendo 11.180 para o sexo masculino e 4.010 para o sexo feminino. Isso significa uma incidência estimada de 10,7 novos casos para cada 100 mil homens e 3,71 para cada 100 mil mulheres.

O carcinoma epidermoide oral é uma neoplasia maligna que se origina do epitélio de revestimento da mucosa oral e é responsável por cerca de 95% dos tumores malignos de boca (DOS SANTOS COSTA; BRENNAN; GOMEZ *et al.*, 2018). Países do sudeste asiático como Índia, Paquistão, Sri Lanka e Taiwan representam as regiões geográficas com maior incidência de carcinoma epidermoide oral no mundo, devido à sua forte relação com hábitos socioculturais como o uso de sachê de Betel nas suas mais variadas apresentações comerciais, fazendo com que o câncer de boca na Índia e Sri Lanka seja o tipo de câncer mais comum entre os homens (BRAY; FERLAY; SOERJOMATARAM *et al.*, 2018). Nos países ocidentais, os principais fatores de risco para o carcinoma epidermoide oral são o uso de tabaco e ingestão de álcool, cujo consumo simultâneo eleva significativamente o risco de desenvolvimento desta neoplasia maligna agressiva.

O carcinoma epidermoide oral afeta mais predominantemente o sexo masculino em todas as regiões do planeta onde este grupo possui uma maior exposição aos fatores de risco, com uma relação homem-mulher aproximada de 3:1. A língua (borda lateral e ventre) e o assoalho de boca são os sítio intraorais mais comuns para o carcinoma epidermoide oral, sendo que 41% a 44% dos casos afetam a língua e 16% a 21% o assoalho de boca (GERVÁSIO; DUTRA; TARTAGLIA *et al.*, 2001; KOMOLMALAI; CHUACHAMSAI; TANTIWIPIWIN *et al.*, 2015). Há uma significativa mudança nestes dados em países do centro-sul da Ásia, onde o hábito de mascar betel leva à um aumento no índice de carcinoma epidermoide em gengiva

e mucosa jugal (KOMOLMALAI; CHUACHAMSAI; TANTIWIPIWIN *et al.*, 2015; LIU; GAO; LIANG; *et al.*, 2016; MOHIDEEN; KRITHIKA; JEDDY *et al.*, 2019).

A incidência do carcinoma epidermoide oral aumenta com a progressão da idade, especialmente entre os homens. Portanto, sua incidência é maior em pacientes nas sextas e sétimas décadas de vida, usualmente seguindo um longo histórico de exposição aos fatores de risco supracitados (DOS SANTOS COSTA; BRENNAN; GOMEZ *et al.*, 2018; INCA 2019; KAMINAGAKURA; VILLA; ANDREOLI; SOBRINHO *et al.*, 2012; MARTIN-GRANIZO; RODRIGUEZ-CAMPO; GONZALEZ, 1997).

Apesar de avanços nas diferentes técnicas cirúrgicas e nas modalidades de radioterapia observadas ao longo dos últimos anos, o prognóstico dos pacientes acometidos pelo carcinoma epidermoide oral permanece pobre, com sobrevida relativa em torno de 66% após cinco anos de acompanhamento (CHANDRA; SINGH; SEBASTIAN, *et al.*, 2013; HOWLADER; NOONE; KRAPCHO *et al.*, 2020). Além disso, esquemas quimioterapêuticos atualmente disponíveis não parecem elevar este índice de sobrevivência de forma significativa (ADELSTEIN; LI; ADAMS *et al.*, 2003). Segundo o INCA e uma série de estudos clínicos internacionais, o estadiamento clínico dos pacientes baseado no sistema TNM para classificação de tumores malignos da região de cabeça e pescoço, permanece como sendo a principal ferramenta de estratificação de risco de óbito para os pacientes acometidos pelo carcinoma epidermoide oral, uma vez que indivíduos classificados nos estágios mais avançados, III e IV, apresentam uma taxa de sobrevivência significativamente menor do que aqueles em estágios mais precoces. Entretanto, a busca por novos determinantes prognósticos permanece de grande importância para melhor conduzir o manejo clínico dos pacientes.

Um ponto de intenso debate ao longo dos últimos anos no que diz respeito ao carcinoma epidermoide oral é uma possível mudança nas curvas de incidência desta neoplasia dentro do grupo de pacientes jovens. Alguns estudos conduzidos principalmente por grupos americanos e europeus dos países nórdicos/escandinavos tem demonstrado desde a década de 1970 que a ocorrência do câncer de boca entre pacientes com menos de 40 ou 45 anos de idade, com especial destaque para as mulheres brancas afetadas pelo câncer de língua e sem histórico de exposição a fatores de risco conhecidos, vem aumentando significativamente (ANNERTZ; ANDERSON; BIÖRKLUND *et al.*, 2002; ANNERTZ; ANDERSON; PALMÉR *et al.*, 2012; MULLER; PAN; LI *et al.*, 2008; PATEL; CARPENTER; TYREE *et al.*, 2011).

Além desta possível alteração representar um importante achado epidemiológico, ela também leva à discussão quanto a existência de um possível fator etiológico desconhecido que possa justificar este aumento na taxa de ocorrência de câncer de boca em pessoas mais jovens. Muitos fatores já foram investigados, com especial atenção à possível participação do papiloma vírus humano (HPV); entretanto, os resultados disponíveis até o momento não foram capazes de atribuir um papel etiológico a este vírus (ADDURI; KOTAPALLI; GUPTA *et al.*, 2014; BRÄGELMANN; DAGOGO-JACK; DINALI *et al.*, 2013; BRAY; FERLAY; SOERJOMATARAM *et al.*, 2018).

Vale ressaltar, porém, que a discussão quanto ao aumento da incidência do carcinoma epidermoide oral em pacientes jovens baseia-se fundamentalmente em resultados obtidos em poucas regiões geográficas, utilizando tanto dados de base populacional como oriundos de instituições de referência no diagnóstico e tratamento destes pacientes (ANNERTZ; ANDERSON; BIÖRKLUND *et al.*, 2002; ANNERTZ; ANDERSON; PALMÉR *et al.*, 2012; CAMPBELL; NETTERVILLE; SINARD *et al.*, 2018; MULLER; PAN; LI *et al.*, 2008; PATEL; CARPENTER; TYREE *et al.*, 2011; SHIBOSKI; SCHIMIDT; JORDAN 2004; TOTA; ANDERSON; COFFEY *et al.*, 2017; VAN-MONSJOU; LOPEZ-YURDA; HAUPTMANN, 2013). Portanto, uma vez que a etiopatogênese desta neoplasia está fortemente associada com fatores socioculturais e ambientais, torna-se de grande importância a validação destes achados epidemiológicos em outras regiões do planeta a fim de não somente verificar o real aumento nas taxas de carcinoma epidermoide oral em pacientes jovens, mas também como uma tentativa inicial de elucidação de possíveis fatores etiológicos que estejam contribuindo com esta mudança epidemiológica.

2 OBJETIVOS

2.1 Objetivo geral

Determinar o número de casos de carcinoma epidermoide oral em pacientes jovens (≤ 40 anos de idade) em serviços de referência no diagnóstico e/ou tratamento de câncer oral em diversas regiões do mundo.

2.2 Objetivos específicos

- Determinar o percentual de pacientes jovens (≤ 40 anos de idade) afetados por carcinoma epidermoide oral na amostra coletada;
- Determinar a frequência do carcinoma epidermoide oral em pacientes jovens a cada quinquênio ao longo dos últimos 20 anos;
- Investigar qual a região anatômica mais acometida pelo carcinoma epidermoide oral em pacientes jovens;
- Investigar qual o sexo mais acometido pelo carcinoma epidermoide oral em pacientes jovens;
- Investigar a frequência de pacientes jovens afetados pelo carcinoma epidermoide oral que relataram estar expostos a algum fator de risco conhecido, como o uso de tabaco e álcool;
- Determinar o grau de diferenciação histológica dos casos de carcinoma epidermoide oral em pacientes jovens.

3 METODOLOGIA EXPANDIDA

Todos os casos diagnosticados como carcinoma epidermoide oral no período de janeiro de 1998 a dezembro de 2018 foram recuperados retrospectivamente dos arquivos dos serviços de diagnóstico e/ou tratamento das seguintes instituições: Universidade Federal de Minas Gerais (Belo Horizonte / Brasil), *Manipal Academy of Higher Education* (Manipal / Índia) , *University of Pretoria* (Pretória / África do Sul), *University of Sheffield* (Sheffield / Reino Unido), *Universidad Nacional de Córdoba* (Córdoba / Argentina), *Universidad Autónoma Metropolitana - Xochimilco* (Cidade do México / México), *Universidad del País Vasco* (Bilbal / Espanha) e *University of Hong Kong* (Hong Kong / China).

Dados demográficos referentes à idade, sexo, localização do tumor e o ano do diagnóstico foram coletados para todos os pacientes afetados por carcinoma epidermoide oral. Além disso, apenas para os pacientes jovens, definidos como aqueles com 40 anos de idade ou menos, ainda foram obtidas informações sobre o grau de diferenciação microscópica do tumor de acordo com as diretrizes da Organização Mundial da Saúde e sobre a exposição destes pacientes a fatores de risco conhecidos para o desenvolvimento da neoplasia, como uso de tabaco, álcool e betel. Estas informações infelizmente não estiveram disponíveis para todos os pacientes e não puderam ser disponibilizadas para a amostra obtida da *University of Hong Kong*.

Todos os casos que afetavam a orofaringe e os lábios foram excluídos devido à sua associação etiológica conhecida com a infecção por HPV e exposição aos raios ultravioletas, respectivamente. Todos os casos diagnosticados microscopicamente como carcinoma cuniculatum, carcinoma papilar, carcinoma verrucoso, carcinoma de células fusiformes, carcinoma acantolítico, carcinoma adenoescamoso e carcinoma basaloides; casos com informações indisponíveis sobre o local anatômico afetado e aqueles sem informações sobre a idade dos pacientes também foram removidos da análise. Por fim, sempre que possível, foram excluídos os casos de carcinoma epidermoide oral que afetavam pacientes diagnosticados com qualquer síndrome ou condição sistêmica sabidamente predisponente ao desenvolvimento da neoplasia.

Comparações foram feitas entre pacientes jovens e aqueles com mais de 40 anos de idade para avaliar possíveis diferenças entre essas duas populações quanto

a distribuição de sexo e ao local mais afetado (língua + assoalho da boca vs. mucosa bucal + crista alveolar + gengiva + trígono retromolar vs. palato vs. cavidade oral, SOE). Além disso, também foram feitas comparações entre os dados coletados de acordo com o período em que os casos foram diagnosticados usando a seguinte sequência: 1998–2003, 2004–2009, 2010–2014 e 2015–2018, para detectar possíveis variações e tendências ao longo dos anos. Os dados referentes à diferenciação microscópica e exposição à fatores de risco, por terem sido coletados apenas para o grupo de pacientes jovens, foram analisados apenas de forma descritiva. Os testes qui-quadrado e exato de Fisher foram usados para analisar possíveis associações entre variáveis categóricas e possíveis alterações no número de casos ao longo do tempo. Todas as análises foram realizadas usando o pacote estatístico SPSS versão 22.0 e um resultado significativo foi obtido quando o valor de p foi $\leq 0,05$.

Este estudo seguiu os princípios estabelecidos pela Declaração de Helsinque sobre pesquisa em seres humanos e obteve a aprovação do Comitê de Ética da Universidade Federal de Minas Gerais (CAAE # 91158918.0.0000.5149) (ANEXO A).

4 ARTIGO

Os resultados deste trabalho foram escritos em língua inglesa na forma de artigo científico que, entretanto, ainda não foi submetido para publicação em periódico internacional porque aguarda o recebimento de dados adicionais da *University of Toronto* (Canadá) e da *University of Parma* (Itália). Este atraso é consequência direta da pandemia causada pelo novo Coronavírus. A solicitação de permissão de defesa sem o comprovante de submissão do artigo científico junto ao Colegiado do Programa de Pós-Graduação em Odontologia da UFMG encontra-se no ANEXO B desta dissertação.

FREQUENCY OF ORAL SQUAMOUS CELL CARCINOMA AFFECTING YOUNG PATIENTS IN REFERRAL CENTERS AROUND THE WORLD

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Abstract

Background: Oral squamous cell carcinoma (OSCC) commonly affects older patients; however, several studies mostly developed in America and Nordic countries have documented an increase in the incidence among younger patients, especially white females not exposed to known risk habits. Therefore, it is important to determine if this trend is also present in other regions. **Methods:** The pathology files of oral cancer referral diagnostic and therapeutic institutions from different parts of the globe were searched and all OSCC cases diagnosed from 1998 to 2018 were retrieved. Data regarding diagnosis date, sex, age and tumor location of all cases, and the microscopic grade and exposure to risk habits of cases diagnosed in young patients were obtained. The percentage of cases affecting young patients (≤ 40 years) was investigated yearly and every five years. Chi-square test was used to determine any increasing trend. **Results:** A total of 10,727 OSCC cases were identified, and 626 cases affected young patients (5.8%). Manipal (India) showed the highest incidence of cases in young patients (13.2%). Males were the most affected in both age groups and the tongue/floor of the mouth were the most affected sites. OSCC in young individuals are usually well/moderately differentiated and only 51 out of 5,535 cases (0.9%) were young patients not associated with any risk habit. There was no increasing trend in any of the institutions and in the period investigated ($p > 0.05$), but it was observed a decreasing trend in Hong Kong ($p < 0.001$) and in the whole sample ($p < 0.001$). **Conclusion:** There was no increasing incidence of OSCC in young patients from the institutions investigated, but a general decrease in the number of cases. Moreover, white females not exposed to any known risk factor still represents an uncommon group of patients affected by OSCC.

Keywords: Oral squamous cell carcinoma, oral cancer, young patients, incidence.

Introduction

Oral cancer represents the 18th most common malignancy worldwide with 354,864 new cases estimated for 2018, which represents approximately 2% of all human cancers in this period. In addition to this high frequency, oral cancer is also associated with a high mortality rate, with 177,384 new deaths being estimated as consequence of this disease (1.9% of all cancer related deaths) (Bray et al., 2018).

Although oral cancer represents an important health problem worldwide, its importance is even more relevant in specific geographic regions where the incidence of this neoplasm ranks top human cancers, mostly because of local cultural habits associated with the use of oral carcinogenic agents. In South America, Brazil's got the highest incidence of oral cancer (Curado et al., 2016), with 14,700 new cases being estimated by the Brazilian National Institute of Cancer for 2018/2019, representing the fifth most common cancer in males (INCA, 2019). Meanwhile, oral cancer is one of the most common human cancers in India, Pakistan, Taiwan and Sri-Lanka due to the strong association with tobacco use and betel quid chewing since early in life.

Oral squamous cell carcinoma (OSCC) is the most common malignant neoplasm of the oral cavity, accounting for 90% of all oral cancer notifications (Scully *et al.*, 2009; Rodrigues et al., 2012; Morais *et al.*, 2017). It usually affects the tongue and the floor of the mouth, frequently manifesting as an advanced-stage disease, which negatively impact the patients' survival rates. Although an uncountable number of biomarkers have been investigated regarding their prognostic potential, clinical staging remains the most important prognostic determinant for these individuals, and it is the main clinicopathological feature used to determine therapeutic approaches. More recently, as an attempt to optimize this staging system, microscopic parameters including tumor grade, nerve and vessel involvement, infiltrative growth pattern profile and some other histological findings have gained more importance (Rodrigues et al., 2012). Nevertheless, despite these known prognostic characteristics of OSCC

and the improvements in some surgical and radiotherapy methodologies, the survival rates of patients remain poor and more recent studies have pointed towards an overall survival achieving approximately 50% after 5 years of follow-up.

OSCC more frequently affects patients older than 50 years, with a predominance for males due to their stronger linkage with risk habits (Curado et al., 2016). However, some studies have demonstrated a higher incidence of cases affecting younger patients (Patel et al., 2011; Annertz et al., 2012). Although some of these individuals have been exposed to tobacco earlier in life simulating the biological context of the more common older population, a specific group of young individuals, usually white women, has not reported the use of any known risk habit (Castro Junior et al., 2016). The molecular basis of OSCC in young patients still needs to be fully characterized and only few differences have been described between both age populations to date (Santos-Costa et al., 2018). Moreover, during many years cases diagnosed in patients younger than 40 years were considered to be significantly more aggressive, but more recent studies demonstrated that there seems to be no such difference between older and younger individuals (Campbell et al., 2018).

During the last decade, our group has investigated the clinicopathological and some molecular aspects of oral cancer in young patients to better understand the pathogenesis of OSCC in this important clinical scenario (Ribeiro et al., 2009; Fonseca et al., 2014; Miranda Galvis et al., 2018; Santos-Costa et al., 2018). However, we would like to determine if the increasing trend in the incidence of OSCC in young patients previously reported mainly in USA and European Nordic countries would also be taking place in other parts of the world. Therefore, counting with the collaboration of several colleagues representing referral international institutions for oral cancer diagnosis and management, we analysed the distribution of OSCC affecting patients younger than 40 years-old during the last 20 years.

Material and methods

All cases diagnosed as OSCC during a 20-years period from 1998 to 2018 were retrospectively retrieved from the files of the oral pathology services of the *Universidade Federal de Minas Gerais* (Belo Horizonte/Brazil), Manipal Academy of Higher Education (Manipal/India), University of Pretoria (Pretoria/South Africa), University of Sheffield (Sheffield/UK), *Universidad Nacional de Córdoba* (Córdoba/Argentina), *Universidad Autónoma Metropolitana - Xochimilco* (Mexico City/Mexico), University of Basque Country (Bilbao/Spain) and the University of Hong Kong (Hong Kong/China). Demographic data regarding age, sex and tumor location and the date of diagnoses were collected from the pathology reports for all OSCC cases, whereas data on the microscopic tumor grade according to the World Health Organization guidelines and the exposure to known risk factors for OSCC development like tobacco use, alcohol intake and betel quid chewing, were collected from pathology reports only for the young patients group.

Patients were categorized as younger individuals when 40-years-old or less. All cases affecting oropharynx and the lips were excluded given their known etiological association with HPV infection and sunray exposure, respectively. Always that possible, all cases microscopically diagnosed as carcinoma cuniculatum, papillary, verrucous, spindle, acantholytic, adenosquamous and basaloid squamous cell carcinomas, those with unavailable information regarding the affected site and the patients' age were also removed from the analysis. Finally, known OSCC cases affecting patients diagnosed with any syndrome or predisposing systemic condition were also excluded.

Comparisons were made between younger patients and those older than 40 years old to find out if there is difference between these two age cohorts regarding sex and affected site (tongue + floor of the mouth vs buccal mucosa + alveolar ridge + gingiva + retromolar trigone vs palate vs oral cavity, NOS). In addition, comparisons were also made between data collected according to the period in which cases were diagnosed using the following sequence: 1998–

2003, 2004–2009, 2010–2014, and 2015–2018, to detect possible variations and trends across the years. Pearson Chi-square test and Fisher exact test were used to analyze categorical variables, while two sample t-tests are used to analyze continuous variables. All analyses were performed using the SPSS version 22.0 statistical package and a significant result was obtained when p -value was ≤ 0.05 .

This study followed the principles established by the Helsinki Declaration on human research and obtained the approval of the Ethical Committee of the *Universidade Federal de Minas Gerais* (CAAE# 91158918.0.0000.5149).

Results

The distribution of OSCC affecting young patients registered in the files of each institution investigated in this series is described in **Table 1**. Taken together, all five services diagnosed 10,727 cases of OSCC, and 626 cases affected patients ≤ 40 years of age, representing 5.8% of this sample. There were 6,567 cases affecting males (61.2%), the most affected sites were the tongue and the floor of the mouth (60.6%), although the Buccal mucosa/alveolar ridge/Gingiva/Retromolar region was the most affected in Manipal/India (63.7%), and the mean age of this large sample of OSCC achieved 62 years-old (range of 5 – 100 years-old). Regarding only the young patients, males also outnumbered females (M:F ratio of 1.3:1.0), the mean age at diagnosis was 33.4 years-old (range 5 to 40 years) and the tongue and the floor of the mouth were the most affected sites (73.2%), although buccal mucosa/alveolar ridge/Gingiva/Retromolar regions were again the most affected in Manipal/India (57.1%). Most of the cases diagnosed in young patients was classified as well to moderately differentiated tumors (31.8% and 40.1%, respectively), whereas only 18.2% of the cases were diagnosed as poorly differentiated. Data concerning the exposure of young patients to known risk habits showed that 32.5% of the patients were exposed to tobacco, 14% to alcohol

consumption and 43% to any risk habits, including other types of tobacco use like the use of massa pan, betel quid, and toombak, especially in Manipal/India, whereas 16.2% of the young patients reported not have been exposed to risk habits.

Regarding the variation in the frequency of young patients affected by OSCC through the 20-years period investigated, the results obtained are detailed illustrated for each service and for the whole population in **Figure 1**. Arbitrarily aggregating data for every five years, we could not demonstrate any statistically significant increase in the number of young patients affected by OSCC in any of the services investigated neither in the general population ($p > 0.05$), on the contrary, there was a significant decrease in the number of cases when we compared 2003/2008 to 2009/2013 periods in Belo Horizonte/Brazil ($p < 0.05$), from 2003/2008 to 2014/2018 ($p < 0.001$) and from 2009/2013 to 2014/2018 ($p < 0.001$) in Hong Kong/China, and from 2003/2008 to 2014/2018 in the whole population evaluated ($p < 0.01$). Investigating only the group of patients comprised by young female patients never exposed to any known risk habits, we found 8 cases in Brazil, 9 in India, 5 in UK, 0 in Mexico, 0 in Argentina, 7 in South Africa (6 white females and 1 black female) and 1 in Spain. Unfortunately, this data was not available for Hong Kong patients.

Discussion

Oral cancer is an important health problem worldwide and its development is strongly associated with sociocultural habits, which leads to a significant variability of its incidence among many parts of the globe (Curado et al., 2016). Although epidemiological studies have shown a decrease in its incidence followed by an evident rise in the number of HPV-positive oropharyngeal cancer in North America during the last decades (Berman et al., 2017; Farquhar et al., 2018), oral cancer remains the most common human malignancy in South and Southeastern Asiatic countries (Abdulla et al., 2018). OSCC usually affects patients with more

than 50 years-old; however, a series of studies revealed an increase in the number of cases affecting younger individuals, especially white females never exposed to known risk habits (Farquhar et al., 2018). Nevertheless, although these studies were conducted in respectful institutions and used large scale populational databases, they are restricted to only few countries. Therefore, by accessing the files of referral centers worldwide we attempted to determine if this increasing trend was also true for other regions; however, we failed to observe any significant rise in the number of young patients diagnosed with OSCC during the last two decades.

Most of the references currently available that indicates an increase in the incidence of OSCC in young patients were developed in America using the SEER database. Davies et al. (1984) showed a significant increase in the number of cases affecting young patients, which was corroborated by Shiboski et al. (2005) that demonstrated increasing trends for white females younger than 40 years old. These results were further confirmed by Patel et al. (2011) and Tota et al. (2017) using updated versions of the SEER database. Simultaneously, a populational-based study published by Annertz et al. (2002) that was later updated by the same group (Annertz et al., 2012) also documented an increase in the incidence of young patients affected by OSCC in European Nordic countries. These populational-based results were also observed in institutional-based studies (Shemen et al., 1984; Schantz et al., 1988; Muller et al., 2008).

Although these studies are well designed to investigate the incidence of OSCC in young patients and represent the basis of our current knowledge on this subject, they are limited to specific geographic regions and contain important methodological limitations associated with the characteristics of the databases used by these authors. The SEER-based studies have important time overlaps and do not cover the whole American territory; in all studies lip cancer, a disease known to be associated with sunray exposure, is also included in the samples and might

account for some of the cases in this young age group; microscopic confirmation is not performed in the populational studies and some OSCC subtypes that have different clinical features and biological behavior might have also been added to the analyses and, finally, few studies investigated the association of OSCC with known risk factors.

Given the results reported by these previous studies demonstrating an increase in the incidence of young patients affected by OSCC, there is an important need to validate these observations in other regions of the globe. In this study we used institutional databases to investigate if there would be a changing trend in the last twenty years as described by Muller et al. (2008). Although institutional data is less representative than populational-based studies, the centers included in this series are important references for the diagnosis and management of oral cancer in these regions and could potentially demonstrate any increase in the number of OSCC in young patients. Moreover, using institutional data allowed us to overcome some of the above-described limitations of the populational-based studies, including the microscopic confirmation, the exclusion of lip cancers, the exclusion of known cases associated with predisposal syndromes, and the possibility of analyzing the use of risk factors by the patients, although this data was not available for all cases. However, our findings must also be validated in populational studies in each of these countries, since as long as we do not understand the biological basis of the development of oral cancer in young patients not exposed to known risk factors, there might be unknown environmental factors predisposing the onset of OSCC in this clinical scenario, which might be true only for specific geographic regions, what is partially true for the oropharyngeal cancer associated with HPV infection that is more frequent in developed countries (Berman et al., 2017).

In the present survey we observed only 30 OSCC cases in young females reported not to be exposed to known risk factors. Although we failed to demonstrate an increase in the frequency of oral cancer in young patients in the services investigated, it is very clear for us

that there really is this special group of patients that develops OSCC earlier in life, not associated with known risk factors that needs to be more detailed studied. At the meantime, we also observed that most of the young patients diagnosed with OSCC were exposed to some type and degree of risk factors, possibly very early in life, which makes them ordinary oral cancer patients since the period of exposure might have achieved similar time observed for older patients, as demonstrated by Xu et al. (2019) in China. Also, in line with this rationale, Chang et al. (2019) recently demonstrated that earlier age at starting tobacco smoking led to increased head and neck cancer risks, which are largely due to longer duration and higher cumulative tobacco exposures and Choi et al., (2019) did not find significant difference between young and old groups according to tobacco and alcohol exposure. On the other hand, Farquhar et al. (2018) demonstrated that younger patients (< 45 years) were significantly more likely to abstain from tobacco (51% vs 39%) than older ones. Moreover, Patel et al. (2011) claimed that the decrease in the use of cigarette in USA demonstrated by other populational studies and recently reported by the WHO (WHO, 2019), would suggest a lack of association between tobacco use and the increase of OSCC among young patients, whilst Toporcov et al. (2015) showed that attributable fractions for smoking and drinking were lower in young when compared with older adults, although the authors also described positive associations between HNC and duration or pack-years of smoking and drinking were similar across age groups.

The highest number of young patients observed in our study originated from the University of Manipal in India (84 cases). Most of these patients reported to use at least one known risk factor for oral cancer, which is an expected result given the well-known sociocultural habits of chewing and/or smoking different forms of tobacco (Abdulla et al., 2018). As demonstrated here, in India only a minority of patients were reported not to be associated with any kind of tobacco exposure. The use of other products different from cigarette in India also seems to impact clinical presentation if the alveolar ridge/vestibule/gingiva/trigone

location was the most affected only in India (Abdulla et al., 2018), possibly because these are the sites most exposed to the hazard effects of tobacco in this population, whereas the floor of the mouth/tongue represented the most affected sites in all other geographic regions (Pontes et al., 2011). Because the tongue and the floor of the mouth were frequently affected simultaneously by advanced stage OSCC and they are associated with the same etiological factors and similar clinical behavior, for statistical purposes we evaluated these two locations together, as well as the buccal mucosa, gingiva, alveolar ridge and retromolar trigone. This observation is also important to discuss the notion previously stated that the oral cancer affecting young white females would predominantly develop in the oral tongue. Since SEER and other populational databases do not allow us to be detailed discriminate oral tongue from floor of the mouth, specifically using oral tongue as the main affected site in the young white females might not be reliable, and the use of the term oral cancer could be more appropriate.

Distinguishing oral cancer from lip cancer from oropharyngeal cancer affecting both young and older patients is very important because they are associated with different etiological factors, exhibit different clinical behavior, and are treated with different therapeutic schemes; however, many studies do not separate these patients, and this might cause inconsistent results. After observing the increase in the incidence of oropharyngeal cancer in developed countries, HPV infection was determined as a new etiological agent (Berman et al., 2017); therefore, it has been speculated if this virus would also be important and responsible for the development of OSCC in young patients. Although Kaminagakura et al. (2012) observed an evidence to support this theory, this could not be reproduced by many other studies, suggesting that HPV might not be the etiological agent for OSCC in young patients not exposed to known risk factors (Harris et al., 2010; Harris et al., 2011; Santos-Costa et al., 2018; Campbell et al., 2018).

Regarding the microscopic differentiation of oral cancer in young patients, we observed that the great majority of the cases were classified as well to moderate differentiated tumors, as

previously described (Müller et al., 2008). Unfortunately, since we did not have this information for all OSCC affecting older patients, we could not determine if well differentiated tumors were more common in young individuals. Interestingly, we also had several cases described as showing microinvasion of the connective tissue, suggesting that these cases would be in early clinical stages. We have also excluded less common microscopic subtypes of OSCC because some of them might be associated with specific clinicopathological features like adenosquamous carcinoma whose origin is still debatable (Fonseca et al., 2012) and verrucous carcinoma that present distinct clinical presentation and behavior (Peng et al., 2016).

In addition to the high variability present in literature concerning the most appropriate cut-off value to categorize patients as either young or older individuals, the molecular basis, and the prognostic significance of OSCC affecting young patients are also very debatable. We have recently conducted a comprehensive literature review (Santos-Costa et al., 2018) to integrate the available data regarding the molecular alterations described in OSCC of young patients and we observed that to date there has not been any significant molecular difference if compared to their older counterpart, what is in accordance with the conclusions obtained by Campbell et al. (2018). However, an important drawback of most of the studies that attempted to investigate the molecular basis of oral cancer in young patients is the lack of uniformity in the design of their control and study groups, if investigations must focus on a subgroup of patients that accounts for white females never exposed to risk factors (Castro Junior et al., 2016); therefore, future contributions must be concerned in appropriately separate the clinicopathological groups.

This recommendation is also true to determine the prognostic significance of oral cancer in young patients. Although initial observations pointed towards a more aggressive clinical behavior in these patients (Son et al., 1985; Sarkaria et al., 1994), following studies failed to observe any significant difference (Pitman et al., 2000) and more recent studies have shown a

better prognosis for young patients (Pontes et al., 2011). The absence of comorbidities might account for some of these recent results and the use of more conservative therapeutic approaches in the past could also be responsible for worse outcomes in young patients. However, once again, categorizing young patients according to the presence of risk factors exposure might be more reliable to identify any important difference.

Although predisposing syndromes and medical condition associated with a significantly higher risk of developing oral cancer are uncommon, they must be considered in studies dealing with young patients, since some cases affecting children and adolescents might be explained by the presence of these diseases like Fanconi anemia, Peutz-Jaeger syndrome, and others. In this study we attempted to exclude these cases always that possible. Another relevant scenario is the possible association of oral cancer and AIDS, which has been more commonly described in recent years (Lucas et al., 2015; Yoshimura, 2017; Thrift et al., 2018; Méndez-Martínez et al., 2020). In our sample there were 5 young patients diagnosed with oral cancer and AIDS in the sample retrieved from Pretoria (South Africa). However, any etiological importance of AIDS for OSCC development remains unknown.

In conclusion, using data retrieved from different referral oral diagnostic centers around the globe covering the last 20 years, we did not observe a trend towards an increase of the incidence of OSCC in patients younger than 40 years-old or more specifically in young white females never exposed to known risk factors, but this result must be validated using populational databases. This validation is important given that a higher number of publications dealing with young patients and OSCC might lead clinicians and pathologists to be more aware of this clinical scenario, which may cause a false perception that a significantly higher number of young patients not exposed to risk habits is being diagnosed and because local unknown environmental factors might cause a higher incidence of OSCC in young patients in specific geographic regions.

Referencies

1. Annertz K, Anderson H, Biorklund A, Möller T, Kantola S, Mork J, et al. Incidence and survival of squamous cell carcinoma of the tongue in scandinavia, with special reference to young adults. *Int J Cancer*. 2002; 101: 95-99.
2. Annertz K, Anderson H, Palmér K, Wennerberg J. The increase in incidence of cancer of the tongue in the Nordic countries continues into the twenty-first century. *Acta Oto-Laryngol*. 2012; 132: 552-557.
3. Curado MP, Johnson NW, Kerr AR, Silva DRM, Lanfranchi H, Pereira DL, et al. Oral and oropharynx cancer in South America: Incidence, mortality trends and gaps in public databases as presented to the Global Oral Cancer Forum. *Transl Res Oral Oncol*. 2016; 1: 1-7.
4. Davies S, Severson R. Increasing incidence of cancer of the tongue in the United States among young adults. *Lancet*. 1987; 17: 910-911.
5. Kaminagakura E, Villa LL, Andreoli MA, Sobrinho JS, Vartanian JG, Soares FA, et al. High-risk human papillomavirus in oral squamous cell carcinoma of young patients. *Int J Cancer*. 2012; 130: 1726-1732.
6. Méndez-Martínez R, Maldonado-Frías S, Vázquez-Vega S, Caro-Vega Y, Rendón-Maldonado JG, Guido-Jiménez M, et al. High prevalent human papillomavirus infections of the oral cavity of asymptomatic HIV-positive men. *BMC Infec Dis*. 2020; 20: 27.
7. Müller S, Pan Y, Li R, Chi AC. Changing trends in oral squamous cell carcinoma with particular reference to young patients: 1971-2006. The Emory University experience. *Head Neck Pathol*. 2008; 2: 60-66.

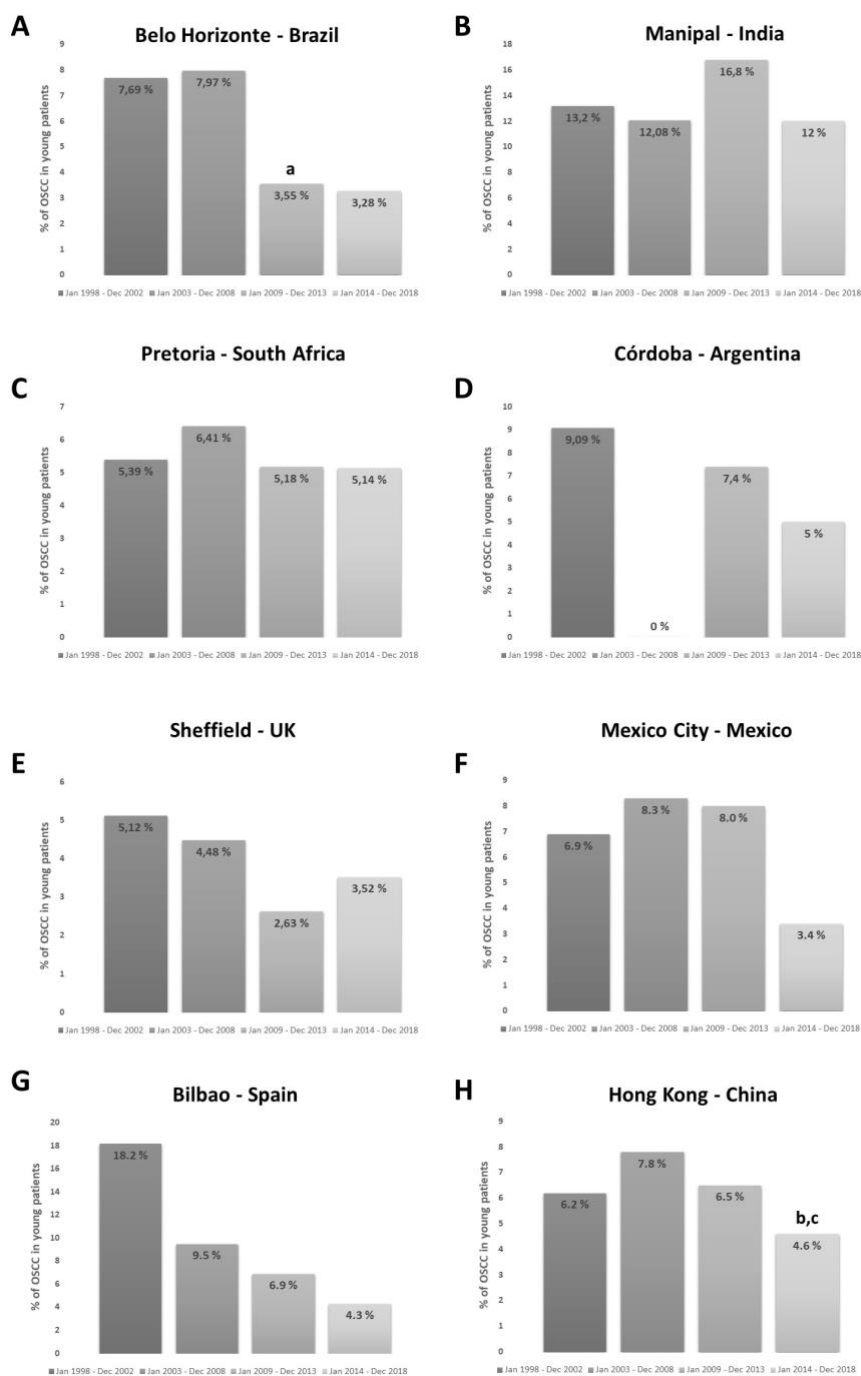
8. Patel SC, Carpenter WR, Tyree S, Couch ME, Weissler M, Hackman T, et al. Increasing Incidence of Oral Tongue Squamous Cell Carcinoma in Young White Women, Age 18 to 44 Years. *J Clin Oncol*. 2011; 29: 1488-1494.
9. Schantz SP, Byers RM, Goepfert H. Tobacco and cancer of the tongue in young adults. *J Am Med Assoc*. 1988; 259: 1943-1944.
10. Shemen LJ, Klotz J, Schottenfeld D, Strong EW. Increase in tongue cancer in young men. *J Am Med Assoc*. 1984; 252: 1857.
11. Shiboski CH, Schmidt BL, Jordan RCK. Tongue and Tonsil Carcinoma. Increasing Trends in the U.S. Population Ages 20–44 Years. *Cancer* 2005; 103: 1843–9.
12. Tota JE, Anderson WF, Coffey C, Califano J, Cozen W, Ferris RL, et al. Rising incidence of oral tongue cancer among white men and women in the United States, 1973–2012. *Oral Oncol*. 2017; 67: 146-152.
13. World Health Organization. WHO launches new report on global tobacco use trends. Number of males using tobacco globally on the decline, showing that government-led control efforts work to save lives, protect health, beat tobacco. Available at: <https://www.who.int/news-room/detail/19-12-2019-who-launches-new-report-on-global-tobacco-use-trends>. Accessed in: 14.01.2020.
14. Dos Santos Costa SF, Brennan PA, Gomez RS, Fregnani ER, Santos-Silva AR, Martins MD, et al. Molecular basis of oral squamous cell carcinoma in young patients: Is it any different from older patients? *J Oral Pathol Med*. 2018; 47: 541-546.
15. Campbell BR, Netterville JL, Sinard RJ, Mannion K, Rohde SL, Langerman A, et al. Early onset oral tongue cancer in the United States: A literature review. *Oral Oncol*. 2018; 87: 1-7.
16. Son YH, Kapp DS. Oral cavity and oropharyngeal cancer in a younger population. Review of literature and experience at Yale. *Cancer* 1985; 55: 441–444.

17. Sarkaria JN, Harari PM. Oral tongue cancer in young adults less than 40 years of age: rationale for aggressive therapy. *Head Neck*. 1994; 16: 107–111.
18. Pontes FS, Carneiro JT Jr, Fonseca FP, da Silva TS, Pontes HA, Pinto Ddos S Jr. Squamous cell carcinoma of the tongue and floor of the mouth: analysis of survival rate and independent prognostic factors in the Amazon region. *J Craniofac Surg* 2011;22: 925-930.
19. Pitman KT, Johnson JT, Wagner RL, Myers EN. Cancer of the tongue in patients less than forty. *Head Neck* 2000; 22: 297–302.
20. Rodrigues PC, Miguel MCC, Bagordakis E, Fonseca FP, Aquino SN, Santos-Silva AR, et al. Clinicopathological prognostic factors of oral tongue squamous cell carcinoma: a retrospective study of 202 cases. *Int. J. Oral Maxillofac. Surg*. 2014; 43: 795–801.
21. Harris SL, Kimple RJ, Hayes DN, Couch ME, Rosenman JG. Never-smokers, never-drinkers: unique clinical subgroup of young patients with head and neck squamous cell cancers. *Head Neck*. 2010; 32: 499–503.
22. Harris SL, Thorne LB, Seaman WT, Hayes DN, Couch ME, Kimple RJ. Association of p16(INK4a) overexpression with improved outcomes in young patients with squamous cell cancers of the oral tongue. *Head Neck*. 2011; 33: 1622–1627.
23. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018; 68: 394-424.
24. Scully C, Bagan JV. Oral squamous cell carcinoma: overview of current understanding of aetiopathogenesis and clinical implications. *Oral Dis*. 2009; 15: 388-399.
25. De Morais EF, et al. Prognostic factors of oral squamous cell carcinoma in young patients: a systematic review. *J Oral Maxillofac Surg*. 2017; 75: 1555-1566.

26. Abdulla R, Adyanthaya S, Kini P, Mohanty V, D'Souza N, Subbannayya Y. Clinicopathological analysis of oral squamous cell carcinoma among the younger age group in coastal Karnataka, India: A retrospective study. *J Oral Maxillofac Pathol* 2018; 22: 180-187.
27. Chang CP, Chang SC, Chuang SC, Berthiller J, Ferro G, Matsuo K, et al. Age at start of using tobacco on the risk of head and neck cancer: Pooled analysis in the International Head and Neck Cancer Epidemiology Consortium (INHANCE). *Cancer Epidemiol.* 2019; 63: 101615.
28. de Castro Junior G, dos Santos-Silva AR, Aparecida de Azevedo Koik e Folgueira M, Toporcov T. Tongue cancer in the Young. *Curr Opin Oncol* 2016; 28: 193-194.
29. Farquhar DR, Tanner AM, Masood MM, Patel SR, Hackman TG, Olshan AF, et al. Oral tongue carcinoma among young patients: An analysis of risk factors and survival. *Oral Oncol.* 2018; 84: 7-11.
30. Toporcov TN, Znaor A, Zhang ZF, Yu GP, Winn DN, Wei Q, et al. Risk factors for head and neck cancer in young adults: a pooled analysis in the INHANCE consortium. *Int J Epidemiol.* 2015; 44: 169-185.
31. Miranda Galvis M., et al. Different patterns of expression of cell cycle control and local invasion-related proteins in oral squamous cell carcinoma affecting young patients. *J Oral Pathol Med.* 2018; 47: 32-39.
32. Ribeiro ACP., et al. Clinical and histopathological analysis of oral squamous cell carcinoma in young people: a descriptive study in Brazilians. *Brit J Oral Maxillofac Surg.* 2009; 47: 95-98.
33. Fonseca FP, Coletta RD, Azevedo MB, Prado Ribeiro AC, Pires Soubhia AM, Miyahara GI, et al. Stromal myofibroblasts in squamous cell carcinoma of the tongue in young

- patients - a multicenter collaborative study. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2014; 118: 483-489.
34. Choi G, Song JS, Choi SH, Nam SY, Kim SY, Roh JL, et al. Comparison of squamous cell carcinoma of the tongue between young and old patients. *J Pathol Transl Med.* 2019; 53: 369-377.
35. Lucas S, Nelson AN. HIV and the spectrum of human disease. *J Pathol.* 2015; 235: 229-241.
36. Thrift AP, Chiao EY. Are Non-HIV Malignancies Increased in the HIV-Infected Population? *Curr Infec Dis Rep.* 20; 22: 2018.
37. Yoshimura K. Current status of HIV/AIDS in the ART era. *J Infect Chemother.* 2017; 23: 12-16.
38. Fonseca FP, Ramos LM, Vargas PA, de Almeida OP, Lopes MA, Santos-Silva AR. Oral adenosquamous carcinoma: evidence that it arises from the surface mucosal epithelium. *Histopathology.* 2012; 61: 321-323.
39. Peng Q, Wang Y, Quan H, Li Y, Tang Z. Oral verrucous carcinoma: From multifactorial etiology to diverse treatment regimens (Review). *Int J Oncol.* 2016; 49: 59-73.
40. Xu Q, et al. The impact of age on oral squamous cell carcinoma: A longitudinal cohort study of 2,782 patients. *Oral Dis.* 2019; 25: 730-741.

Figure 1. Distribution of OSCC in young patients from 1998 to 2018 in different parts of the world for every five years. **A)** Belo Horizonte (Brazil). **B)** Cordoba (Argentina). **C)** Mexico City (Mexico). **D)** Toronto (Canada). **E)** Pretoria (South Africa). **F)** Sheffield (UK). **G)** Parma (Italy). **H)** Bilbao (Spain). **I)** Hong Kong (China) and **J)** Manipal (India).



a,b,c) Statistically significant difference. *a.* between 2003/2008 and 2009/2013. *b.* between 2003/2008 and 2014/2018. *c.* 2009/2013 and 2014/2018.

Table 1. Distribution and clinicopathological features of oral squamous cell carcinoma affecting patients ≤ 40 years old and > 40 years old in referral oral diagnosis centers from different regions of world (1998 – 2018).

	Belo Horizonte (Brazil)	Cordoba (Argentina)	Mexico City (Mexico)	Toronto (Canada)	Sheffield (UK)	Parma (Italy)	Bilbao (Spain)	Pretoria (South Africa)	Hong Kong (China)	Manipal (India)	Total
No. of OSCC cases	934	170	383		2051		174	1186	5192	637	10727
Sex distribution											
Male	685 (73.3%)	97 (57.1%)	167 (43.6%)		1256 (61.2%)		95 (54.6%)	797 (67.2%)	3033 (58.4%)	437 (68.6%)	6567 (61.2%)
Female	249 (26.7%)	73 (42.9%)	216 (56.4%)		795 (38.8%)		79 (45.4%)	389 (32.8%)	2159 (41.6%)	200 (31.4%)	4160 (38.8%)
Mean age (range) (years)	59.5 (18 – 98)	63.1 (18 – 90)	64.3 (26-96)		65.0 (6 – 95)		64.4 (25 – 95)	59.7 (5 – 99)	64.5 (5 – 100)	55.7 (18 – 86)	62.0 (5 – 100)
Affected site											
Buccal mucosa/alveolar ridge/Gingiva/Retromolar	255 (27.3%)	52 (30.6%)	151 (39.4%)		622 (30.3%)		82 (47.1%)	211 (17.8%)	1215 (23.4%)	406 (63.7%)	2994 (27.9%)
Floor of the mouth/Tongue	614 (65.7%)	98 (57.6%)	202 (52.7%)		1246 (60.8%)		78 (44.8%)	690 (58.2%)	3395 (65.4%)	180 (28.3%)	6503 (60.6%)
Palate	65 (7.0%)	15 (8.8%)	24 (6.2%)		134 (6.5%)		14 (8.1%)	49 (4.1%)	367 (7.1%)	24 (3.8%)	692 (6.5%)
Oral mucosa, NOS	0 (0.0%)	5 (2.9%)	6 (1.5%)		49 (2.4%)		0 (0.0%)	236 (19.9%)	215 (4.1%)	27 (4.2%)	538 (5.0%)
No. of OSCC in patients ≤ 40 years (%)	43 (4.6%)	9 (5.3%)	25 (6.5%)		76 (3.7%)		12 (6.8%)	65 (5.5%)	312 (6.0%)	84 (13.2%)	626 (5.8%)
Sex distribution											
Male	28 (65.1%)	6 (66.6%)	14 (56%)		45 (59.2%)		4 (33.3%)	34 (52.3%)	163 (52.2%)	64 (76.2%)	358 (57.2%)
Female	15 (34.9%)	3 (33.4%)	11 (44%)		31 (40.8%)		8 (66.7%)	31 (47.7%)	149 (47.8%)	20 (23.8%)	268 (42.8%)
Mean age (range)	34 (18 – 40)	30.4 (18 – 40)	34.9 (26-40)		33.5 (6 – 40)		33.2 (25 – 40)	34.0 (5 – 40)	32.7 (5 – 40)	34.6 (18 – 40)	33.4 (5 – 40)
Microscopic differentiation											
Well differentiated	14 (32.6%)	6 (66.7%)	17 (68%)		28 (36.8%)		11 (91.7%)	12 (18.5%)	NA	12 (14.3%)	100 (31.8%)
Moderate differentiated	6 (14.0%)	3 (33.3%)	6 (24%)		38 (50.0%)		1 (8.3%)	15 (23.1%)	NA	57 (67.9%)	126 (40.1%)
Poorly differentiated	4 (9.3%)	0 (0.0%)	2 (8%)		10 (13.2%)		0 (0.0%)	33 (50.8%)	NA	8 (9.5%)	57 (18.2%)
NS	19 (44.2%)	0 (0.0%)	0 (0.0%)		0 (0.0%)		0 (0.0%)	5 (7.7%)	NA	7 (8.3%)	31 (9.9%)
Affected site											
Buccal mucosa/alveolar ridge/Gingiva/Retromolar	11 (25.6%)	4 (44.4%)	4 (16%)		12 (15.8%)		1 (8.3%)	11 (16.9%)	23 (7.4%)	48 (57.1%)	114 (18.2%)
Floor of the mouth/Tongue	28 (65.1%)	5 (55.6%)	20 (80%)		63 (82.9%)		11 (91.7%)	37 (56.9%)	262 (84.0%)	32 (38.1%)	458 (73.2%)
Palate	4 (9.3%)	0 (0.0%)	1 (4%)		1 (1.3%)		0 (0.0%)	4 (6.2%)	18 (5.8%)	1 (1.2%)	29 (4.6%)
Oral mucosa, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)		0 (0.0%)	13 (20.0%)	9 (2.8%)	3 (3.6%)	25 (4.0%)
Tobacco use											
Yes	22 (51.2%)	1 (11.1%)	7 (28%)		11 (14.5%)		7 (58.3%)	13 (20.0%)	NA	41 (48.8%)	102 (32.5%)
No	11 (25.6%)	0 (0.0%)	5 (20%)		16 (21.1%)		3 (25.0%)	7 (10.8%)	NA	43 (51.2%)	85 (27.1%)
NS	10 (23.2%)	8 (88.9%)	13 (52%)		49 (64.4%)		2 (16.7%)	45 (69.2%)	NA	0 (0.0%)	127 (40.4%)
Alcohol use											
Yes	13 (30.2%)	0 (0.0%)	1 (4%)		13 (17.1%)		7 (58.3%)	3 (4.6%)	NA	7 (8.3%)	44 (14.0%)
No	18 (41.9%)	1 (11.1%)	11 (44%)		10 (13.2%)		2 (16.7%)	2 (3.1%)	NA	77 (91.7%)	121 (38.5%)
NS	12 (27.9%)	8 (88.9%)	13 (52%)		53 (69.7%)		3 (25.0%)	60 (92.3%)	NA	0 (0.0%)	149 (47.5%)
Exposure to any risk factor											
Yes	23 (53.6%)	1 (11.1%)	7 (28%)		18 (23.7%)		9 (75.0%)	13 (20.0%)	NA	64 (76.2%)	135 (43.0%)
No	10 (23.2%)	0 (0.0%)	5 (20%)		8 (10.5%)		1 (8.3%)	7 (10.8%)	NA	20 (23.8%)	51 (16.2%)
NS	10 (23.2%)	8 (88.9%)	13 (52%)		50 (65.8%)		2 (16.7%)	45 (69.2%)	NA	0 (0.0%)	128 (40.8%)

NS: not specified. NOS: Not otherwise specified. OSCC: Oral squamous cell carcinoma. NA: Not available.

5 CONSIDERAÇÕES FINAIS

No presente trabalho não foi possível demonstrar um aumento significativo no número de pacientes jovens com 40 anos ou menos de idade afetados pelo carcinoma epidermoide oral nas instituições analisadas. Além disso, observamos uma tendência de diminuição em alguns centros e na amostra geral coletada. Portanto, este trabalho demonstra que mulheres jovens sem histórico de exposição à fatores de risco conhecidos para o desenvolvimento de carcinoma epidermoide oral ainda representa um grupo muito incomum de pacientes.

REFERÊNCIAS

- ADDURI, R. S. R.; KOTAPALLI, V.; GUPTA, N. A. *et al.* P53 nuclear stabilization is associated with FHIT loss and younger age of onset in squamous cell carcinoma of oral tongue. **BMC Clin Pathology**. v.14, n.1, p. 37, 2014.
- ADELSTEIN DJ, L. I. Y.; ADAMS, G. L.; WAGNER, H. J. R.; KISH, J. A. ENSLEY, J. F. *et al.* An Intergroup Phase III Comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. **J Clin Oncol**. v21, n. 1, p. 92-98, 2003.
- ANNERTZ, K.; ANDERSON, H.; BIÖRKLUND, A.; MÖLLER, T.; KANTOLA, S.; MORK, J.; OLSEN, J. H.; WENNERBERG, J. Incidence and Survival of Squamous Cell Carcinoma of the Tongue in Scandinavia, with Special Reference to Young Adults. **Int J Cancer**, v.101, n.1, p.95-99, 2002.
- ANNERTZ, K.; ANDERSON, H.; PALMÉR, K.; WENNERBERG, J. The increase in incidence of cancer of the Tongue in the Nordic countries into the twenty-first century. **Acta Oto-laryngologica**, v.132, n.5 p. 552-557, 2012.
- BRÄGELMANN, J.; DAGOGO-JACK, I.; DINALI, M. E. *et al.* Oral cavity tumors in younger patients show a poor prognosis and do not contain viral RNA. **Oral Oncology**. V.49, n.6, p. 525–533, 2013.
- BRAY, F.; FERLAY, J.; SOERJOMATARAM, I.; SIEGEL, R. L.; TORRE, L.A.; JEMAL, A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. **CA: Cancer J Clin**. v.68, n.6, p. 394-424, 2018.
- CAMPBELL, B.R; NETTERVILLE, J.L; SINARD, R.L; MANNION, K; ROHDE, S.L; LANGERMAN, A; KIM, Y.J; LEWIS-JR, J.S; KUHS, K.A.L. Early onset oral tongue cancer in United States: A literature review. **Oral Oncology**. v.87, p. 1-7, 2018.
- CHANDRA, A.; SINGH, A.; SEBASTIAN, B. T.; AGNIHOTRI, A.; BALI. R.; VERMA, P. K. Oral scamous cell carcinomas in age distinct population: A comparison of p53 immunoexpression. **Journal of Cancer Research and Therapeutics**. v.9, n.4, p. 587-59, 2013.
- DOS-SANTOS-COSTA, S. F.; BRENNAN, P. A.; GOMEZ, R. S.;
- FREGNANI, E. R.; SANTOS-SILVA, A. R.; MARTINS, M. D.; DE-CASTRO-JÚNIOR, G.; RAHIMI, S.; FONSECA, F. P. Molecular basis of oral scamous cell carcinoma in young patients: Is it any different from older patients? **J Oral Pathol Med**. v.47, n. 6, p. 541: 546, Jul 2018.
- GERVÁSIO, O. L. A. S.; DUTRA, R. A.; TARTAGLIA, S. M. A.; VASCONCELOS, W. A.; BARBOSA, A. A.; AGUIAR, M. C. F. Oral squamous cell carcinoma: A

retrospective study of 740 cases in a Brazilian Population. **Braz Dent J.** v.12, n.1, p. 57-61, 2001.

HOWLADER, N.; NOONE, A. M.; KRAPCHO, M.; MILLER, D.; BREST, A.; YU, M., RUHL, J.; TATALOVICH, Z.; MARIOTTO, A.; LEWIS, D. R.; CHEN, H. S.; FEUER, E. J.; CRONIN, K. A. (eds). SEER Cancer Statistics Review, 1975-2017, National Cancer Institute. **Bethesda, MD**, based on November 2019 SEER data submission, posted to the SEER web site, April 2020.

Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação de prevenção e vigilância. Estimativa 2020: Incidência de câncer no Brasil. Rio de Janeiro: INCA, 2019.

KAMINAGAKURA, E.; VILLA, L. L.; ANDREOLI, M. A.; SOBRINHO, J. S.; VARTANIAN, J. G.; SOARES, F. A.; NISHIMOTO, I. N.; ROCHA, R. High-risk human papillomavirus in oral squamous cell carcinoma of young patients. **Int J Cancer.** v.130, n.8, p. 1726-1732, 2012.

KOMOLMALAI, N.; CHUACHAMSAI, S.; TANTIWIPIWIN, S.; DEJSUVAN, S.; BUHNGAMONGKOL, P.; WONGVISED, C.; CHITAPANARUX, I.; IAMAROON, A. Ten-year analysis of oral cancer focusing on young people in northern Thailand. **Journal of Oral Science.** 57, n. 4, p. 327-334, 2015.

LIU, X.; GAO, X. L.; LIANG, X. H.; TANG, Y. L. The etiologic spectrum of head and neck squamous cell carcinoma in young patients. **Oncotarget,** 7, n. 40, p. 66226-66238, 2016.

MARTIN-GRANIZO, R.; RODRIGUEZ-CAMPO, F.; GONZALEZ, F. J. D. Squamous cell carcinoma of the oral cavity in patients younger than 40 years. **Otolaryngol Head Neck Surg.** v.117, n.3, p. 268–275, 1997.

MOHIDEEN, K.; KRITHIKA, C.; JEDDY, N.; BHARATHI, R.; THAYUMANAVAN, B.; SANKARI, S. L. Meta-analysis on risk factors of squamous cell carcinoma of the tongue in young adults. **Journal of Oral and Maxillofacial Pathology: JOMFP** v.23, n. 3, p. 450-457, 2019.

MULLER, S.; PAN, Y.; LI, R.; CHI, A. Changing Trends in Oral Squamous Cell Carcinoma with Particular Reference to Young Patients: 1971–2006. The Emory University Experience. **Head and Neck Pathol.** v.2, n.2, p. 60–66, 2008.

PATEL, S. C.; CARPENTER, R.; TYREE, S.; COUCH, M. E.; WEISSLER, M.; HACKMAN, T.; HAYES, D. N.; SHORES, C.; CHERA, B. M. Increasing Incidence of Oral Tongue Squamous Cell Carcinoma in Young Women, Age 18 to 44 Years. **Journal of Clinical Oncology.** v.29, n.11, p. 1488-1494, 2011.

SHIBOSKI, C. H.; SCHIMIDT, B. L.; JORDAN, R. C. K. Tongue and tonsil carcinoma: Increasing Trends in the U.S. Population Ages 20–44 Years. **American Cancer Society.** v.103, n. 9, p. 1843-1849, 2005.

TOTA, J.; ANDERSON, W. F.; COFFEY, C.; CALIFANO, J.; COZEN, W.; FERRIS, R. L.; JOHN, M. S.; COHEN, E. E. W.; CHATURVEDI, A. K. Rising incidence of oral tongue cancer among white men and women in the United States, 1973–2012. **Oral Oncology**. v.67, p. 146-152, 2017.

VAN-MONSJOU, H. S.; LOPEZ-YURDA, M. I.; HAUPTMANN, M. *et al.* Oral and oropharyngeal squamous cell carcinoma in young patients: the Netherlands Cancer Institute experience. **Head Neck**. v.35, n.1 p. 94-102, 2013.

ANEXO A — Aprovação do Comitê de Ética em Pesquisa – UFMG

UNIVERSIDADE FEDERAL DE
MINAS GERAIS



PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Incidência do carcinoma epidermoide oral em pacientes jovens no serviço de patologia bucomaxilofacial da Faculdade de Odontologia da Universidade Federal de Minas Gerais

Pesquisador: Felipe Paiva Fonseca

Área Temática:

Versão: 1

CAAE: 91158918.0.0000.5149

Instituição Proponente: UNIVERSIDADE FEDERAL DE MINAS GERAIS

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.728.277

Apresentação do Projeto:

O carcinoma epidermoide (CEC) é uma neoplasia maligna, com origem no epitélio de revestimento da boca e é responsável por cerca de 95% das lesões malignas nesta região. O CEC é mais frequente em pacientes entre a quinta e sétima décadas de vida e é raro em pacientes jovens, porém tem havido um aumento da incidência da doença para estes pacientes. Este trabalho tem como objetivo analisar a incidência do CEC oral em pacientes jovens (< 40 anos) diagnosticados no Serviço de Patologia Bucomaxilofacial da Universidade Federal de Minas Gerais (UFMG). Serão recuperadas retrospectivamente das fichas de requisição de exame anatomopatológico arquivadas na Faculdade de Odontologia da UFMG no período de 1954 a 2017 as seguintes variáveis: o número de casos de CEC oral em pacientes jovens, o local mais acometido pelo CEC oral em pacientes jovens; o sexo mais acometido pelo CEC oral em pacientes jovens; e a frequência de tabagistas e etilistas na população de pacientes jovens afetados pelo CEC oral. Os dados coletados serão tabelados no software Microsoft Excel 2010 para posterior análise descritiva e estatística.

Objetivo da Pesquisa:

Hipótese:

O número de casos de CEC oral em pacientes com menos de 40 anos de idade está aumentando no Serviço de Patologia Bucomaxilofacial da Universidade Federal de Minas Gerais.

Endereço: Av. Presidente Antônio Carlos, 6627 2º Ad SI 2005

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UNIVERSIDADE FEDERAL DE
MINAS GERAIS



Continuação do Parecer: 2.728.277

Objetivo Primário:

Determinar o número de casos de CEC oral em pacientes jovens (<40 anos de idade) diagnosticados no Serviço de Patologia Bucomaxilofacial da Faculdade de Odontologia da UFMG.

Avaliação dos Riscos e Benefícios:

De acordo com os pesquisadores:

Riscos:

O único risco desta proposta se refere a manutenção da confidencialidade dos indivíduos envolvidos.

Benefícios:

Não haverá benefícios diretos para os indivíduos envolvidos no estudo.

OBS.: Os benefícios indiretos poderiam ter sido citados.

Comentários e Considerações sobre a Pesquisa:

Pesquisa relevante para as áreas de Patologia Bucal e Estomatologia. Término previsto para 30/04/2020. Pesquisa bem delineada e exequível.

Considerações sobre os Termos de apresentação obrigatória:

Foram apresentados os seguintes documentos:

- Informações Básicas do Projeto;
- Folha de Rosto;
- Parecer aprovado pela câmara departamental;
- Currículo Vitae do pesquisador responsável;
- Solicitação de dispensa do TCLE;
- Projeto Detalhado / Brochura Investigador;
- Declaração de Instituição e Infraestrutura - carta anuência do local da pesquisa (Faculdade de Odontologia da UFMG).

Recomendações:

Recomenda-se a aprovação do projeto de pesquisa.

Conclusões ou Pendências e Lista de Inadequações:

Somos favoráveis à aprovação do projeto "Incidência do carcinoma epidermoide oral em pacientes

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Continuação do Parecer: 2.728.277

jovens no serviço de patologia bucomaxilofacial da Faculdade de Odontologia da Universidade Federal de Minas Gerais" do pesquisador responsável Prof. Dr. Felipe Paiva Fonseca.

Considerações Finais a critério do CEP:

Tendo em vista a legislação vigente (Resolução CNS 466/12), o COEP-UFMG recomenda aos Pesquisadores: comunicar toda e qualquer alteração do projeto e do termo de consentimento via emenda na Plataforma Brasil, informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa (via documental encaminhada em papel), apresentar na forma de notificação relatórios parciais do andamento do mesmo a cada 06 (seis) meses e ao término da pesquisa encaminhar a este Comitê um sumário dos resultados do projeto (relatório final).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1074317.pdf	08/06/2018 16:19:58		Aceito
Folha de Rosto	pagina_de_rosto.pdf	08/06/2018 16:19:17	Felipe Paiva Fonseca	Aceito
Outros	Parecer_camara_departamental.pdf	08/06/2018 16:17:13	Felipe Paiva Fonseca	Aceito
Outros	CV_Felipe_Paiva_Fonseca.pdf	08/06/2018 16:16:08	Felipe Paiva Fonseca	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Solicitacao_dispensa_TCLE.pdf	08/06/2018 16:14:12	Felipe Paiva Fonseca	Aceito
Projeto Detalhado / Brochura Investigador	Projeto.pdf	08/06/2018 16:14:02	Felipe Paiva Fonseca	Aceito
Declaração de Instituição e Infraestrutura	Carta_de_anuencia_local_de_pesquisa.pdf	08/06/2018 16:13:43	Felipe Paiva Fonseca	Aceito
Outros	91158918parecer.pdf	21/06/2018 12:31:08	Vivian Resende	Aceito
Outros	91158918aprovacao.pdf	21/06/2018 12:32:30	Vivian Resende	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Endereço: Av. Presidente Antônio Carlos, 6627 2º Ad SI 2005

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Continuação do Parecer: 2.728.277

Não

BELO HORIZONTE, 21 de Junho de 2018

Assinado por:
Vivian Resende
(Coordenador)

Endereço: Av. Presidente Antônio Carlos, 6627 2º Ad SI 2005

Bairro: Unidade Administrativa II **CEP:** 31.270-901

UF: MG **Município:** BELO HORIZONTE

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ANEXO B - Solicitação de defesa sem submissão do artigo científico junto ao CPGO/UFMG



Universidade Federal de Minas Gerais Faculdade de Odontologia

Av. Antônio Carlos, 6627, Pampulha, Belo Horizonte/MG.
odonto.ufmg.br

Belo Horizonte (MG), 11 de junho de 2020.

Prezada Profa. Dra. Isabela Almeida Pordeus,

(Coordenadora do CPGO/UFMG)

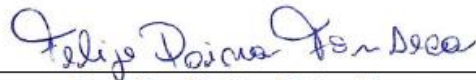
Gostaria de solicitar por meio desta carta uma autorização por parte do Colegiado de Pós-Graduação em Odontologia da UFMG (CPGO/UFMG) para que o aluno Rafael Ferreira e Costa possa defender sua dissertação de mestrado sem realizar a submissão do artigo científico produto desta dissertação.

Justifica-se: O aluno já possui o artigo redigido contando com dados adquiridos de instituições de vários países ao redor do mundo e certamente conseguiríamos uma ótima publicação com a versão atual do artigo. Entretanto, dois dos nossos parceiros de trabalho que nos enviariam seus dados oriundos da University of Toronto (Canadá) e da University of Parma (Itália) solicitaram mais tempo para compartilhar os dados conosco por dificuldades na aquisição causadas pela pandemia do novo coronavírus. Entendemos que seria muito constrangedor e deselegante desconvidá-los

ou submeter o artigo sem a participação de ambos, além de que a inclusão dos dados destas universidades elevaria significativamente a qualidade do nosso artigo.

Portanto, enviamos esta solicitação na expectativa de que o colegiado esteja de acordo.

Atenciosamente,



Prof. Dr. Felipe Paiva Fonseca
Professor Área de Patologia
Faculdade de Odontologia/UFMG
e-Mail: felipefonseca@hotmail.com