UNIVERSIDADE ESTADUAL DE CAMPINAS
FACULDADE DE ODONTOLOGIA DE PIRACICABA

BRENDO VINICIUS RODRIGUES LOURÊDO

EPIDEMIOLOGIA E SOBREVIDA DE PACIENTES COM CARCINOMA ESPINOCELULAR DE LÁBIO, CAVIDADE ORAL E OROFARINGE EM UMA POPULAÇÃO DO SUDESTE BRASILEIRO

EPIDEMIOLOGY AND SURVIVAL OF PATIENTS WITH LIP, ORAL CAVITY, AND OROPHARYNGEAL SQUAMOUS CELL CARCINOMA IN A SOUTHEAST BRAZILIAN POPULATION

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

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Orientador: Prof. Dr. Pablo Agustin Vargas

Coorientadora: Dra. Maria Paula Curado

Este trabalho corresponde à versão final da dissertação defendida pelo aluno Brendo Vinicius Rodrigues Lourêdo, e orientada pelo Prof. Dr. Pablo Agustin Vargas.

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“Não adianta se entregar aos sonhos se
você se esquece de viver”

J. K. Rowling

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Dedico este trabalho à minha pequena e amada irmã

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RESUMO

O câncer de cabeça e pescoço é um problema crescente de saúde pública, afetando homens e mulheres ao redor do planeta. Os carcinomas espinocelular (CECs) de lábio, cavidade oral e orofaringe são os principais e mais prevalentes representantes desse grupo. Apesar de compartilharem semelhanças entre si, a exposição crônica à radiação solar é o principal carcinógeno do CEC de lábio, tabaco e álcool do CEC de cavidade oral e o papilomavirus humano do CEC de orofaringe. O objetivo deste estudo foi descrever o perfil epidemiológico e a sobrevida dos pacientes com CEC de lábio, cavidade oral e orofaringe no estado de São Paulo. Os dados clinicopatológicos de todos os pacientes com CEC de lábio (ICD-O-3: C00), cavidade oral (C02-06) e orofaringe (C01 e C08-10) foram obtidos dos registros hospitalares de câncer da Fundação Oncocentro do Estado de São Paulo entre os anos de 2010 e 2015. Taxas de sobrevida e outras análises foram realizadas através do programa SPSS. Dos 368.116 casos de câncer, 12.099 pacientes foram diagnosticados com CEC de lábio, cavidade oral e orofaringe. Houve uma maior prevalência de pacientes do sexo masculino, especialmente nos casos de orofaringe (82,3%). A média de idade foi maior para os casos de lábio (65±13,5 anos) comparado aos outros sítios (cavidade oral: 60,3±12,1 anos; orofaringe: 58,6±10 anos). O nível de escolaridade foi baixo para a maioria dos pacientes em todos os três sítios estudados (≤ 8 anos de estudo), com a maior taxa observada para as lesões de lábio (87,9%). Cerca de 90,6% de todos os pacientes obtiveram o diagnóstico através do sistema único de saúde (SUS). A maioria dos pacientes com CEC de cavidade oral (71,8%) e de orofaringe (86,3%) apresentaram doença em estágio avançado, enquanto 83,3% dos pacientes com CEC de lábio foram diagnosticados com tumor em estágios iniciais (I-II). Excisão cirúrgica foi o principal tratamento para CEC de lábio (72%) e cavidade oral (23.5%) e a combinação de radioterapia e quimioterapia para CEC de orofaringe (40.2%). A sobrevida global em 5 anos para CEC de lábio, cavidade oral e orofaringe foi de 66,3%, 30,9% e 22,6%, respectivamente. A análise multivariada revelou que o período de diagnóstico e o diagnóstico através do SUS foram preditores independentes de sobrevida apenas para os pacientes com CEC de orofaringe, a idade acima de 60 anos para CEC de lábio e cavidade oral e o sexo masculino e tempo entre diagnóstico e tratamento superior a 60 dias para os casos de cavidade oral e orofaringe. O estágio clínico foi preditor independente para as três localizações e os diferentes tipos de tratamento variaram entre as topografias. Portanto, concluiu-se que esses tumores ocorrem mais em homens acima dos 60 anos de idade, com baixa instrução e doença em estágio avançado nos casos de cavidade oral e orofaringe. Os preditores de sobrevida variaram de acordo com a topografia analisada e as taxas de sobrevida foram melhores para os pacientes com CEC de lábio.

Palavras-chave: Carcinoma de Células Escamosas; Lábio; Cavidade oral; Orofaringe; Análise de Sobrevida.

ABSTRACT

Head and neck cancer is a growing public health problem affecting men and women around the world. Lip, oral cavity, and oropharyngeal squamous cell carcinoma (SCC) are the main and most prevalent types of this group. Despite sharing similarities, chronic exposure to solar radiation is the main carcinogen for lip SCC, tobacco and alcohol consumption for oral cavity SCC, and human papillomavirus for oropharyngeal SCC. This study aimed to describe the epidemiological profile and survival of patients with lip, oral cavity, and oropharyngeal SCC in the state of São Paulo. The clinicopathological data of all patients with lip (ICD-O-3: C00), oral cavity (C02-06), and oropharyngeal (C01 and C08-10) SCC were obtained from the hospital cancer registries of the Fundação Oncocentro do Estado de São Paulo between 2010 and 2015. Survival rates and other analyzes were performed through the SPSS software. Of the 368,116 cancer cases, 12,099 patients were diagnosed with lip, oral cavity, and oropharyngeal SCC. There was a higher prevalence of male patients, especially in oropharyngeal cases (82.3%). The mean age was higher for lip cases (65±13.5 years) compared to other sites (oral cavity: 60.3±12.1 years; oropharynx: 58.6±10 years). Schooling level was low for most patients of all three sites studied (≤ 8 years of study), with the highest rate observed for lip lesions (87.9%). About 90.6% of all patients were diagnosed through the Sistema Único de Saúde (SUS). Most patients with the oral cavity (71.8%) and oropharyngeal (86.3%) SCC had the advanced-stage disease, while 83.3% of patients with lip SCC were diagnosed with early-stage (I -II) tumor. Surgical excision was the main treatment for lip (72%) and oral cavity (23.5%) SCC, and the combination of radiotherapy and chemotherapy for oropharyngeal (40.2%) SCC. The 5-year overall survival rates for lip, oral cavity, and oropharyngeal SCC were 66.3%, 30.9%, and 22.6%, respectively. The multivariate analysis revealed that the period of diagnosis and diagnosis by SUS were independent predictors of survival only for patients with oropharyngeal SCC, age over 60 years for lip and oral cavity SCC, and male sex and time between diagnosis and treatment more than 60 days for cases of oral cavity and oropharynx. The clinical stage was an independent predictor for the three sites and the different types of treatment varied between the sites. Therefore, it was concluded that these tumors occur more often in men over 60 years of age, with low education and advanced-stage disease in cases of oral cavity and oropharynx. Survival predictors varied according to the topography analyzed, and survival rates presented better results for patients with lip SCC.

Keywords: squamous cell carcinoma; lip; oral cavity; oropharynx; survival analysis.

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1 INTRODUÇÃO

1.1 Epidemiologia do carcinoma espinocelular de lábio, cavidade oral e orofaringe

O projeto GLOBOCAN da Agência Internacional para Pesquisa do Câncer (IARC) é um banco de dados que reúne informações sobre a incidência e mortalidade de 36 tipos de cânceres em 185 países (Ferlay et al. 2020). De acordo com a última edição publicada em 2021, estimou-se cerca de 19,3 milhões de novos casos e 10 milhões de mortes no mundo em 2020 (Sung et al. 2021). Além disso, no ano de 2019, a Organização Mundial da Saúde estimou que o câncer foi a primeira ou segunda principal causa de morte antes dos 70 anos em mais da metade dos países analisados (World Health Organization 2020).

Desse total, estima-se que cerca de 377,713 novos casos ocorram em lábio e cavidade oral, sendo apontado como um dos tipos de câncer mais prevalentes, estando entre os dez principais em vários países do mundo e sendo responsável por 177,757 mortes anualmente (Sung et al. 2021). Quanto ao câncer de orofaringe, estima-se a ocorrência de 98,412 novos casos e 48,143 mortes e quando analisados em conjunto com o câncer de lábio e cavidade oral, essas duas localizações compreendem a oitava posição no top 10 dos mais prevalentes, correspondendo a 2.5% de todos os casos (Warnakulasuriya and Greenspan 2020).

Variações regionais consideráveis são observadas na incidência desses cânceres. O câncer de lábio, por exemplo, ocorre com maior frequência em países desenvolvidos como Austrália, Espanha, Grécia, Ucrânia e partes do Canadá (Diz et al. 2017; Warnakulasuriya and Greenspan 2020). Por outro lado, estima-se que aproximadamente dois terços dos casos de câncer de cavidade oral ocorram em países de baixa renda e em desenvolvimento, principalmente nos países do sul da Ásia (Índia, Sri Lanka e Paquistão) que compreendem cerca de metade dos casos no mundo. Partes da Europa Ocidental (por exemplo, Portugal e França), Leste europeu (por exemplo, Hungria, Eslováquia e Eslovênia) e partes das Américas Central (Porto Rico) e do Sul (por exemplo, Brasil e Uruguai) são outras regiões que apresentam altas taxas de incidência para o câncer de cavidade oral (Han et al. 2016; Warnakulasuriya and Greenspan 2020).

O câncer de orofaringe tem sido alvo de maior interesse nas últimas décadas devido à tendência de aumento de novos casos, principalmente de tumores relacionados ao papilomavírus humano (HPV) (Chaturvedi et al. 2013). Essa tendência é observada principalmente em países desenvolvidos da Europa (França, por exemplo), América do Norte

e Austrália (Diz et al. 2017; Warnakulasuriya and Greenspan 2020). A revisão sistemática mais recente sobre o assunto (Mariz et al. 2020) descreve que Nova Zelândia, Suécia e Dinamarca apresentam as maiores proporções de CEC de orofaringe HPV+ do mundo (61.7-74.5%), enquanto que as menores foram encontradas no Brasil (11.1%).

O carcinoma espinocelular (CEC) corresponde por até 90% dos tumores malignos diagnosticados em cavidade oral e orofaringe e de acordo com Curado et al. (2016) a incidência desses tumores na América do Sul entre os anos de 1998 e 2007 mostrou que as maiores taxas foram encontradas no Brasil, até três vezes maior quando comparadas aos países vizinhos. O Instituto Nacional do Câncer (INCA) estimou que cerca de 15,190 novos casos de cânceres de lábio, cavidade oral e orofaringe tenham ocorrido no Brasil no ano de 2020, ocupando a quinta e décima terceira posições entre todos os cânceres em homens e mulheres, respectivamente (INCA 2019).

1.2 Características clínicas e demográficas do CEC de lábio, cavidade oral e orofaringe

Classicamente, os CECs de lábio, cavidade oral e orofaringe sempre mostraram uma alta incidência em homens comparado a mulheres. Essa proporção já esteve em 7:1, mas, atualmente essa relação já se mostra de 2:1 na maioria dos países. Isso se deve, em grande parte à adoção de hábitos historicamente associados ao comportamento masculino, por parte das mulheres, principalmente tabagismo e consumo de álcool (Warnakulasuriya and Greenspan 2020). Contudo, os CECs de lábio e orofaringe continuam mostrando alta prevalência em homens com proporção masculino-feminino de 4.6:1 e 6:1, respectivamente (Han et al. 2016; Schnelle et al. 2017; Kowalski et al. 2020). E curiosamente, essas duas localizações estão associadas a fatores de risco distintos (radiação ultravioleta para o lábio e HPV para a orofaringe) do CEC de cavidade oral (Moore et al. 1999; Gillison et al. 2019).

A incidência do CEC de lábio e cavidade oral aumenta com a idade e a maioria dos casos acomete pacientes acima dos 50 anos (Warnakulasuriya and Greenspan 2020). Em diversos países, incluindo o Canadá (Lubpairee et al. 2019), Uruguai (Oliveira et al. 2015), Estados Unidos (Han et al. 2016), Japão (Fukumoto et al. 2020), México (Hernández-Guerrero et al. 2013), entre outros, a média de idade ao diagnóstico está acima dos 60 anos. Por outro lado, a incidência de CEC de orofaringe aumentou muito em indivíduos mais jovens (inferior a 60 anos), afetados principalmente pelos tumores HPV+ (Chaturvedi et al. 2013; Mariz et al. 2020). Estudos da Austrália (Elwood et al. 2014) e Estados Unidos da América (Dahlstrom et al. 2015),

por exemplo, mostraram média de idade em torno de 55 anos para pacientes afetados por CEC de orofaringe.

A definição dos limites da cavidade oral varia entre os estudos. Alguns autores incluem lábios nas análises, enquanto outros não (Oliveira et al. 2015). A prevalência do CEC de lábio apresenta substanciais diferenças regionais. No Brasil, essa malignidade representou 10% de todos os carcinomas orais (Souza et al. 2011). Nos Estados Unidos, a prevalência relatada foi de aproximadamente 30% (Han et al. 2016), enquanto na Austrália, foi de 49% de todos os cânceres orais (Abreu et al. 2009).

Quanto a localização, a literatura reconhece o lábio inferior como o principal sítio acometido em pacientes diagnosticados com CEC de lábio (Abreu et al. 2009; Casal et al. 2010; Maruccia et al. 2012; Han et al. 2016), pois o lábio superior é naturalmente mais protegido da exposição prolongada à radiação solar (Luna-Ortiz et al. 2004). Dos tumores intraorais, a grande maioria dos estudos de diferentes países como Brasil (Moro et al. 2018), Canadá (Lubpairee et al. 2019), África (Asio et al. 2018), Uruguai (Oliveira et al. 2015), China (Bai et al. 2020) e França (Jéhannin-Ligier et al. 2017) descrevem a parte móvel da língua como o sitio mais afetado pelo CEC intraoral. Contudo, em países do sul e sudeste asiáticos como Índia (Tandon et al. 2017; Abdulla et al. 2018), Siri Lanka (Jayasooriya et al. 2016) e outros dessas regiões (Shrestha et al. 2020), a mucosa bucal/jugal é o sítio mais comumente afetado por esses tumores, tradicionalmente associados ao hábito cultural dessas populações de mastigar tabaco e seus derivados como o reconhecido sachê de Betel. Na orofaringe, o CEC HPV+ apresenta forte predileção pela base de língua e tonsilas (Fakhry et al. 2014; Dahlstrom et al. 2015), enquanto que o CEC HPV-, envolve mais comumente o palato mole (El-Naggar et al. 2017).

Por ser uma região de fácil acesso e visibilidade, a grande maioria dos CECs de lábio são detectados e diagnosticados ainda nos estágios iniciais da doença (estágios I e II do estadiamento TNM da *American Joint Committee on Cancer* - AJCC) (American Joint Committee on Cancer 2017; Moro et al. 2018). No estudo de Han et al, 78.5% e 12% dos casos foram diagnosticados ainda em estágios clínicos I e II, respectivamente (Han et al. 2016). No Brasil, esses valores são menores – 67.3% no estágio I e 16.6% no estágio II (Biasoli et al. 2016). Contudo, o mesmo nem sempre se reproduz para os tumores da cavidade oral e orofaringe. Pra os casos intraorais, tanto em países considerados desenvolvidos como França (Jéhannin-Ligier et al. 2017), Alemanha (Listl et al. 2013) e Japão (Fukumoto et al. 2020) quanto em países em desenvolvimento da África (Asio et al. 2018) e América Latina, como

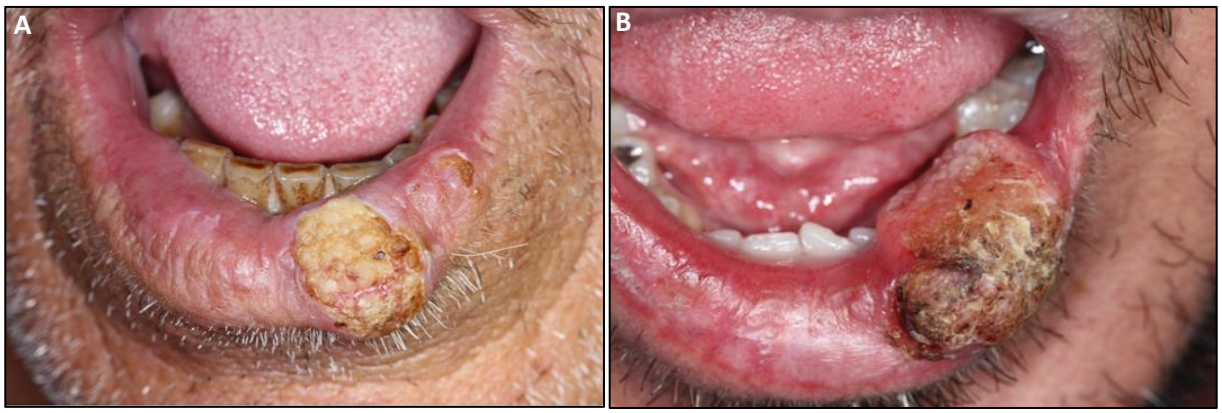
Brasil (Curado et al. 2016) e Uruguai (Oliveira et al. 2015), a maioria dos casos são diagnosticados em estágios avançados (estágios III e IV). Mas alguns países como Canadá (Lubpairee et al. 2019) e China (Bai et al. 2020), esses tumores são diagnosticados mais precocemente. Independente do país de origem, cerca de 80% dos CECs de orofaringe são diagnosticados em estágios avançados da doença (Dahlstrom et al. 2015; Curado et al. 2016; Kowalski et al. 2020; Schroeder et al. 2020).

Os sinais e sintomas iniciais comuns do CEC de lábio são ulceração, formação de crosta e dor. Nos estágios avançados apresentam-se como extensas lesões ulcerativas e/ou infiltrativas (**figura 1**) (Moore et al. 1999). O CEC de cavidade oral possui múltiplas formas de apresentação. A manifestação clínica mais comum em estágios iniciais da doença é a presença de uma lesão eritroleucoplásica (**figuras 2A**). Por outro lado, lesão nodular, ulceração, e fixação dos tecidos adjacentes associada a dor são apresentações clássicas da doença em estágio avançado (**figura 2B**) (Warnakulasuriya and Greenspan 2020).

O CEC de orofaringe frequentemente se apresenta em um estágio mais avançado que o CEC de lábio e cavidade oral devido à sua capacidade de crescer sem ser detectado e sua propensão para metástases. Devido a isso, as queixas principais mais comuns são a presença de uma massa cervical (doença metastática) para os tumores HPV-positivos e dor de garganta e disfagia para os tumores HPV-negativos (Chi et al. 2015). Clinicamente, o CEC de orofaringe se desenvolve com mais frequência nas tonsilas e na base da língua, frequentemente apresentando-se como um nódulo ulcerado, irregular, com alteração eritematosa da mucosa (**figura 3**).

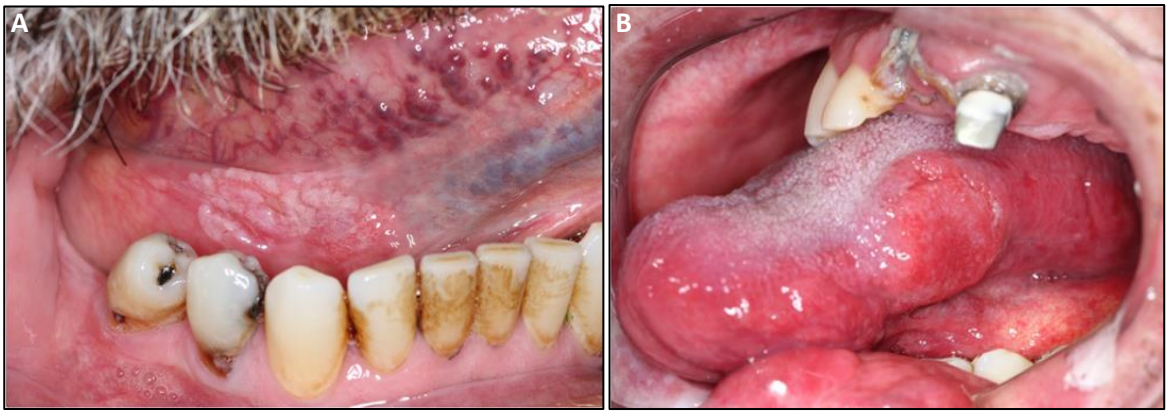
A classificação mais recente da AJCC publicada em 2016 – oitava edição, apresentou mudanças significantes para o estadiamento do CEC de cavidade oral e orofaringe. A atualização mais significativa foi a criação de um algoritmo de estadiamento separado para câncer de orofaringe associado ao HPV de alto risco, distinguindo-o do câncer de orofaringe associado à tabaco e etilismo crônico. Isso aconteceu, pois já é reconhecido que os tumores HPV positivos são altamente responsivos ao tratamento e apresentam um melhor prognóstico. A superexpressão da proteína p-16 (≥75%) é considerada um indicador robusto para a carcinogênese mediada pelo HPV, sendo, portanto, uma fator prognóstico independente de sobrevida para o câncer de orofaringe associado ao HPV e indicado para todos os tumores dessa localização (Lydiatt et al. 2017). Outras alterações importantes foram realizadas nas categorias do tamanho do tumor e envolvimento noral.

Figura 1. Paciente apresentando lesão nodular com superfície crostosa e endurecida à palpação em lábio inferior esquerdo com 2 meses de evolução **(A).** Paciente com nódulo exofítico, acastanhado, com bordas irregulares e limites mal definidos, endurecido à palpação, com área ulcerada em mucosa labial esquerda com evolução de 24 meses **(B).**



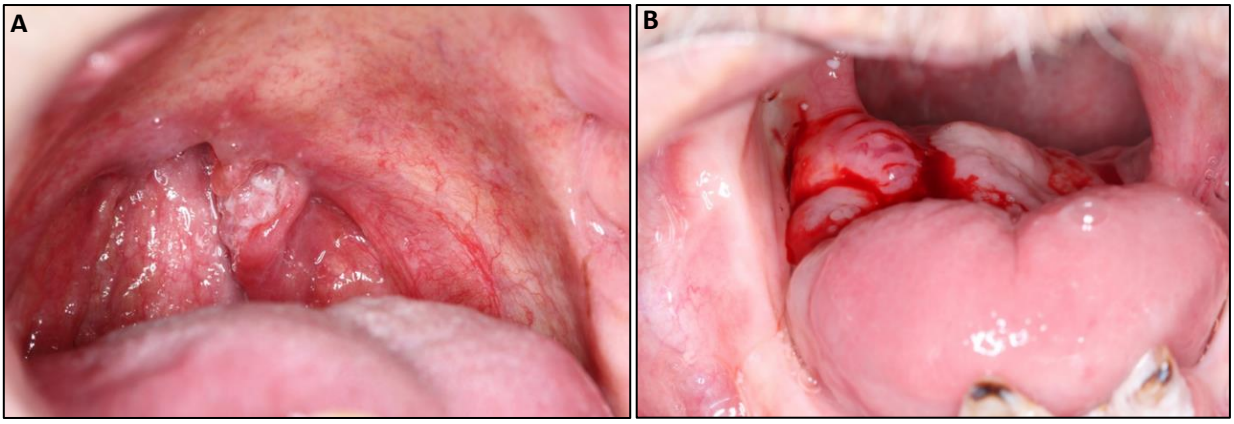
Fonte: Orocentro FOP/UNICAMP.

Figura 2. Paciente apresentando placa eritroleucoplásica em borda lateral direita de língua com cerca de 12 meses de evolução **(A).** Paciente com lesão ulcerada infiltrativa, de bordas irregulares, consistência firme à palpação e sintomatologia dolorosa em borda lateral de língua com evolução de 8 meses **(B).**



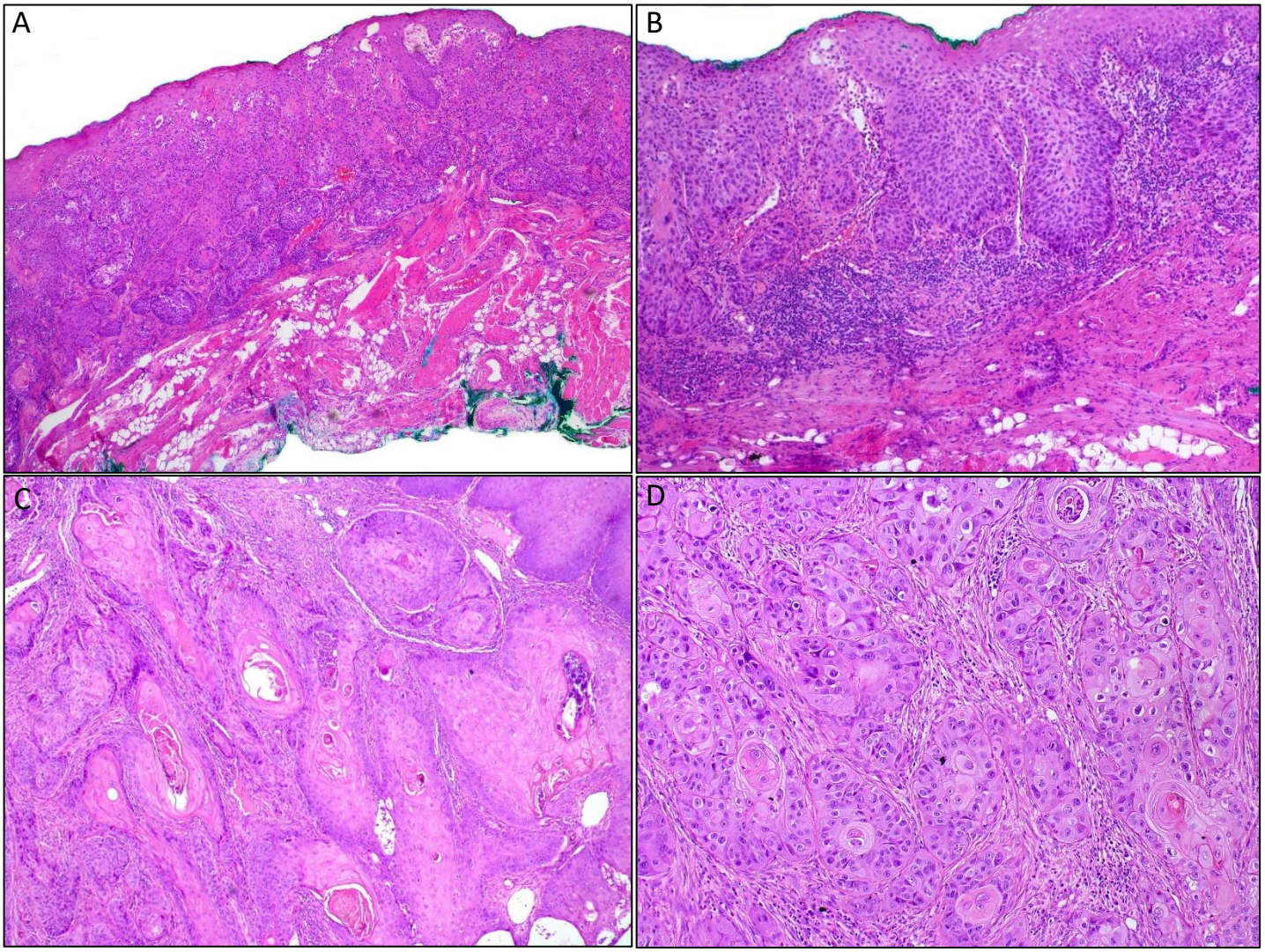
Fonte: Orocentro FOP/UNICAMP.

Figura 3. Paciente apresentando lesão ulcerada com bordas elevadas em pilar amigdaliano esquerdo com 1 mês de evolução **(A).** Paciente com lesão nodular extensa, de consistência firme e infiltrativa em base de língua com evolução de 6 meses. Os dois terços anteriores da língua estavam endurecidos e sem movimentos.



Fonte: Orocentro FOP/UNICAMP.

Figura 4. Fotomicrografias do carcinoma espinocelular de cavidade oral. Ninhos e cordões de células neoplásicas proliferando a partir do epitélio de superfície displásico **(A)**. Imagem em maior aumento evidenciando a proliferação das células tumorais se destacando do epitélio de superfície em direção ao tecido conjuntivo subjacente inflamado **(B)**. Ninhos de células tumorais bem diferenciadas com formação abundante de pérolas de ceratina **(C).** Em maior aumento, observa-se intenso pleomorfismo celular com nucléolos evidentes e figuras de mitoses atípicas, permeados por um estroma escasso e celularizado **(D)**.



Fonte: Laboratório de Patologia Oral da FOP/UNICAMP.

1.3 Tratamento e sobrevida do CEC de lábio, cavidade oral e orofaringe

Os carcinomas de lábio, por serem detectados geralmente em uma fase mais precoce, são tratados apenas por excisão cirúrgica com bom prognóstico. A sobrevida global em 5 anos para pacientes com CEC de lábio gira em torno de 85% (Warnakulasuriya and Greenspan 2020). Contudo, diferenças regionais e socioeconômicas também interferem nas taxas de sobrevida dessa doença, até mesmo entre países economicamente desenvolvidos como Alemanha (Listl et al. 2013) e Estados Unidos (Han et al. 2016), onde a sobrevida relatada foi de 86.5% e 69%, respectivamente. No CEC de cavidade oral, os determinantes prognósticos adversos e doença em estágio avançado, geralmente estabelece a necessidade de radioterapia e/ou quimioterapia adjuvante ao tratamento cirúrgico (Warnakulasuriya and Greenspan 2020).

Apesar dos avanços tecnológicos nas modalidades de tratamento e diagnóstico nas últimas décadas, as taxas de sobrevida continuam baixas para o CEC de cavidade oral (Rao et al. 2013). Alguns países como Japão (85.8%) (Fukumoto et al. 2020) e Itália (76.8%) (Arduino et al. 2008) apresentam resultados bem acima da média encontrada na maior parte dos outros países. Contudo, a grande maioria reporta taxas de sobrevida em 5 anos em torno dos 50%, como é o caso do Uruguai (58.5%) (Oliveira et al. 2015), China (54.5%) (Wang et al. 2013), Brasil (51%) (Kowalski et al. 2020), Estados Unidos da América (49%) (Farhood et al. 2019) e África (20.7%) (Asio et al. 2018).

A maioria dos carcinomas de orofaringe são tratados por terapia combinada de cirurgia, radioterapia e/ou quimioterapia, pois muitos desses casos são diagnosticados em estágios avançados da doença, necessitando, portanto, de tratamentos mais complexos quando possível (Kowalski et al. 2020). Isso resulta, claro, em taxas de sobrevida ainda mais baixas que o CEC de cavidade oral. Contudo, a literatura já reconhece que os pacientes com CEC de orofaringe positivos para HPV apresentam melhor prognóstico e melhores taxas de sobrevida em 5 anos em comparação aos casos HPV- nos Estados Unidos (72.7% vs 50.1%) (Schroeder et al. 2020), na França (80% vs 40%) (Mirghani et al. 2019) e na América do Sul (75.6% vs 44.6%) (Abrahão et al. 2020). O estudo de Fakhry e colaboradores descreve o status do HPV como um preditor forte e independente de sobrevida, pois estimou que a positividade do HPV nesses tumores reduziu em 52% as chances de óbito (Fakhry et al. 2014).

A seguir apresentaremos os resultados da nossa Dissertação na forma de artigo científico.

2 ARTIGO: Epidemiology and survival outcomes of the lip, oral cavity, and oropharyngeal squamous cell carcinoma in a southeast Brazilian population

Artigo submetido ao periódico internacional *Oral Oncology* (Anexo 3)

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ABSTRACT

Objectives: The epidemiological and clinical profile and survival outcomes of lip, oral cavity, and oropharyngeal squamous cell carcinoma (SCC) was studied in São Paulo State, Brazil. **Patients and methods:** The clinicopathological data of patients with lip, oral cavity, and oropharyngeal SCC were obtained from hospital cancer registries of the *Fundação Oncocentro de São Paulo*, Brazil (2010–2015). Survival rates and other analyses were performed using SPSS software. **Results:** The data from 12,099 patients were obtained. A clear male predominance was observed, particularly for patients with oropharyngeal SCC (88.3%). The average age of patients was higher for lip cases (65 ± 13.5 years) compared to other sites. The schooling level was low for most patients, especially in lip cases (87.9%). Most of the patients with oral cavity (71.8%) and oropharyngeal SCC (86.3%) had advanced-stage (III–IV) disease. However, the majority of lip cases (83.3%) were at an early stage (I–II). Surgical excision was the main treatment for lip (72%) and oral cavity SCC (23.5%), and chemoradiotherapy was the main treatment for oropharyngeal SCC (40.2%). The 5-year overall survival (OS) for patients with lip, oral cavity, and oropharyngeal SCC were 66.3, 30.9, and 22.6%, respectively. Multivariate analysis revealed that the determinants of OS were different for lip, oral cavity, and oropharyngeal SCC, except for those at the clinical stage, which was an independent predictor for all sites. **Conclusion:** OS-independent determinants varied according to the affected site. Oral cavity and oropharyngeal SCC presented worse survival rates than those for lip SCC.

Keywords: squamous cell carcinoma of head and neck; lip neoplasms; mouth neoplasms; oropharyngeal neoplasms; survival analysis.

INTRODUCTION

Oral cancer, including lip cancer, is one of the most common cancers around the world, falling within the top ten cancers in several countries, with an estimated 377,713 new cases in 2020. When analysed together with the oropharynx, these two locations comprise approximately 476,125 new cases, accounting for 2.5% of all cancer cases and 225,900 deaths (177,757 deaths for oral cancer and 48,143 deaths for oropharyngeal cancer) [1,2].

In 2020, the estimated age-standardised rates of lip and oral cavity cancers were 6.0 and 2.3 per 100,000 in men and women, respectively, whereas for oropharyngeal cancer, they were 1.8 and 0.4 per 100,000 in men and women, respectively [1]. Most patients diagnosed with oral cavity and oropharyngeal cancers report a previous history of smoking and alcohol consumption, which are well recognised risk factors [3]. Additionally, human papillomavirus (HPV) infection has been associated with the development of a distinct subset of head and neck squamous cell carcinomas (SCC), particularly in the oropharynx [4], and ultraviolet radiation from sunlight exposure for lip SCC [1].

The incidence of oral cavity and oropharyngeal SCC in South America is not homogenous, and the highest rates are seen in Brazil, particularly for males, and are up to three-times higher than in other South American countries [5]. The *Fundação Oncocentro de São Paulo* (FOSP) is a Brazilian public database that collects data from all hospitals that perform cancer treatment in São Paulo State, and it is updated every three months. The epidemiological and clinical profile and survival outcomes of the lip, oral cavity, and oropharyngeal SCC were assessed in the São Paulo State, Brazil, from a FOSP database (2010–2015).

PATIENTS AND METHODS

Sample

This is a retrospective cross-sectional study using secondary data. Data of patients with histopathological diagnosis of primary lip (International Classification of Diseases for Oncology [ICD-O-03]: C00), oral cavity (ICD-O-3: C02, C03, C04, C05 [except C05.1 and C05.2] and C06), and oropharyngeal (ICD-O-3: C01, C05.1, C05.2, C09, and C10) cancers in São Paulo State were obtained from hospital cancer registries (HCRs) in the FOSP database from January 2010 to December 2015 (available at: http://www.fosp.saude.sp.gov.br/publicacoes/downloadarquivos, accessed 15 January 2021). The morphological codes (8051/3, 8052/3, 8070/3, 8071/3, 8072/3, 8073/3, 8074/3, 8075/3, 8076/3, 8078/3, 8082/3, 8083/3, and 8084/3) [6] used for lip, oral cavity, and oropharyngeal SCC were considered for analysis.

Data collect

São Paulo State has 17 Heath Regional Departments (HRDs): São Paulo, Araçatuba, Araraquara, Baixada Santista, Barretos, Bauru, Campinas, Franca, Marília, Piracicaba, Presidente Prudente, Registro, Ribeirão Preto, São João da Boa Vista, São José do Rio Preto, Sorocaba, and Taubaté. The following variables were collected: HRD, period of diagnosis, gender, age group, schooling level, primary tumour site, previous diagnosis and treatment, type of diagnosis, clinical stage (TNM: I-II and III-IV) [7,8], time between diagnosis and treatment, cancer treatment, and patients' status (alive or died).

Statistical analysis

The qualitative and quantitative data were presented descriptively, and missing values were excluded from the analysis, with only valid percentages being considered. An association analysis between demographic and clinicopathological variables with tumour site was performed using the Chi-square test. All lip, oral cavity, and oropharyngeal SCC cases that

reported the patients' follow-up and status were included for survival analysis. The Kaplan-Meier method was used to estimate survival rates, and the difference between survival curves was investigated by using the Log-Rank univariate test. The univariate Cox proportional hazard regression model was employed to identify potential prognostic factors. A multivariate Cox regression model was created using all variables that achieved a p-value ≤ 0.20. Data analyses were performed with SPSS software version 22.0 (IBM Corporation, Armonk, NY, USA), and a p-value ≤ 0.05 was considered statistically significant.

The present study assessed information from a Brazilian public database (FOSP), with no risk of patient data disclosure; thus, ethical approval was not required (Resolution 510/16 of the Brazilian National Health Council).

RESULTS

The data collected from 76 HCRs of the São Paulo State found a total of 368,116 cancer cases in the period between 2010 and 2015. Of these, 12,099 patients were diagnosed with lip, oral cavity, and oropharyngeal SCC (**Figure 5**). Figure 6 shows the distribution of all cases according to the 17 HRDs in São Paulo State. The demographic and clinicopathological features of the 12,099 cases of lip, oral cavity, and oropharyngeal SCC are summarised in **Table 1**.

Lip SCC

About 73.3% (n = 732) of 998 patients with lip SCC were male, with a male-to-female ratio of 2.8:1. Regarding schooling level, most individuals (87.9%; n = 717) had less than or equal to 8 years of formal education. The patients' ages ranged from 22 to 104 years old, with a mean age at diagnosis of 65.0 ± 13.5 years, mainly affecting patients over 60 years (61.8%; n = 616).

The most common site-affected subsite was the lower lip (79.4%; n = 793), followed by lip, not otherwise specified (NOS; 9.5%; n = 95) and upper lip (7.5%; n = 75; Supplemental Table 1). Most patients presented early-stage tumours (I–II) at diagnosis (83.3%; n = 810).

For most patients, the treatment was performed 60 days after diagnosis (69.5%; n = 423), with surgery being the main treatment modality (72.0%; n = 718), followed by radiotherapy (RT) alone (7.1%; n = 71), and a combination of surgery and RT (7%; n = 69). Approximately 5.1% (n = 51) of cases did not receive any active treatment, and the main reason was not specified (2.8%; n = 29).

Data from 789 (78.8%) individuals with lip SCC with a median follow-up time of 52 months were available (range: 1–122 months). Survival analysis from the Kaplan-Meier method estimated that the 5-year overall survival (OS) for lip SCC was 66.3% (**Figure 7**). Based on the log-rank test (**Table 2**), there was a significant increase in the OS for patients diagnosed in more recent years (58.7% in 2010–2012 to 72.7% in 2013–2015; $p < 0.0001$).

Oral cavity SCC

Among 5,398 individuals with oral cavity SCC (OSCC), 77.4% (n = 4,179) were male, with a male-to-female ratio of 3.4:1. The patients' ages ranged from 11 to 100 years old, with a mean age of 60.3 ± 12.1 years. The most affected age group were patients over 60 years old (46.2%; n = 2,496). For schooling level, 81.0% (n = 3,195) of patients had less than or equal to 8 years of formal education.

The mobile tongue comprised 42.5% (n = 2,298) of cases, followed by the floor of the mouth (22.2%; n = 1,200), mouth NOS (10.9%; n = 590), retromolar trigone (7.9%; n = 429), and hard palate (7.1%; n = 383; **Supplemental Table 1**). At diagnosis, 71.8% (n = 3,743) of patients were diagnosed with stages III/IV.

Approximately 60.9% (n = 2,605) of patients received treatment in the period of more than 60 days after diagnosis. Proportionally, surgery alone was the main treatment employed, being used in 23.5% (n = 1,270) of cases, followed by chemoradiotherapy (CT; 19.3%; n = 1,040), and a combination of surgery, RT, and CT (15.4%; n = 833). About 7.9% (n = 423) of individuals did not receive any treatment, and the main described reasons were that the patient died of disease before commencing treatment (3.1%; n = 172) or had advanced untreatable disease (1.8%; n = 98).

Of those evaluated, 4,759 (88.2%%) had a median follow-up time of 19 months (range: 1–122 months). The OS rate for OSCC was 30.9% in the 5 years after diagnosis (**Figure 7**). However, an improvement was observed in the overall survival for patients diagnosed in the more recent years of study (25.1% in 2010–2012 to 35.8% in 2013–2015; $p < 0.0001$; Table 2).

Oropharyngeal SCC

Of the 5,703 patients with oropharyngeal SCC (OPSCC), 88.3% (n = 5,035) were male, with a male-to-female ratio of 7.5:1. The patients' ages ranged from 20 to 99 years old, with a mean age of 58.6 ± 10 years at diagnosis, with the most cases occurring in the sixth decade of life (40.6%; n = 2,317). Based on schooling level, 81.5% (n = 3,349) of patients had less than or equal to 8 years of formal education.

Most cases did not report the exact location of the tumour (oropharynx, NOS; 30.5%; n = 1,741; Supplemental Table 1). The base of the tongue (30%; n = 1,711), tonsils (18.7%; n = 1,067), soft palate (11.4%; n = 650), and lateral oropharyngeal wall (3.2%; n = 180) were the most affected sites of the oropharynx. Most of the tumours (86.3%) were at an advanced clinical stage (III–IV).

In most cases, the treatment was performed 60 days after diagnosis (54%; n = 2,506), and chemoradiotherapy was the main treatment (40.2%; n = 2,290), followed by a combination

of surgery, RT, and CT (11.4%; n = 649), and RT alone (10.2%; n = 579). Approximately 10% (n = 572) of individuals did not receive any active treatment, and the main reasons reported were that the patient died of disease before commencing treatment 4.4% (n = 258) or had an advanced untreatable tumour 2.6% (n = 149).

For survival analysis, 5,114 (89.7%) patients with a median follow-up time of 15 months were considered (range: 1–120 months). Five-year OS for OPSCC was 22.6% (**Figure 7**), with a slight increase observed from 2013 to 2015, compared with the period of 2010 to 2012 (27.7% vs 20.2%, respectively; $p < 0.0001$; **Table 2**).

The results showed a significant association between all demographical and clinicopathological variables, except period of diagnosis and tumour site (Table 1). The proportion of patients lost to follow-up was 21.2, 11.8, and 10.3% for lip SCC, OSCC, and OPSCC, respectively.

For lip SCC, the multivariate analysis model (**Table 4**) revealed that patients aged over 60 years (hazard ratio (HR): 2.45; 95% CI, 1.33–4.52), advanced-stage disease (HR: 1.97; 95% CI, 1.32–2.95), patients treated by chemoradiation (HR: 4.56; 95% CI, 2.15–9.67), and other treatments such as RT alone, CT alone, and other combinations (HR: 2.90; 95% CI, 2.06–4.08) were associated with a higher mortality hazard. For patients with OSCC, mortality hazards were significantly higher among male patients (HR: 1.20; 95% CI, 1.05–1.38), in those over 60 years old (1.25; 95% CI, 1.09–1.45), with time between diagnosis and treatment over 60 days (HR: 1.27; 95% CI, 1.14–1.41), in those with advanced-stage tumours (HR: 2.19; 95% CI, 1.88–2.55), and in patients treated by chemoradiation (HR: 1.62; 95% CI, 1.37–1.91) and other treatments (HR: 2.21; 95% CI, 1.88–2.61).

In OPSCC (**Table 4**), an increase in mortality hazard was observed for patients diagnosed between 2010–2012 (HR: 1.13; 95% CI, 1.01–1.26), in male individuals (HR: 1.45;

95% CI, 1.23–1.71), those with diagnosis from SUS (HR: 2.45; 95% CI, 1.66–3.62), those with time between diagnosis and treatment over 60 days (HR: 1.19; 95% CI, 1.08–1.31), those with advanced stage cancer (HR: 2.51; 95% CI, 2.09–3.00), and patients treated by other treatments (HR: 1.42; 95% CI, 1.15–1.75).

DISCUSSION

Lip, oral cavity, and oropharyngeal cancers represent a major health problem in the global scenario, and together, comprise the eighth most common malignancy worldwide [2]. Brazil has the highest incidence of oral cavity and oropharyngeal cancer in South America, and over 90% of cases are represented by the SCC [5].

Data retrieved from the FOSP showed that lip SCC, OSCC, and OPSCC accounted for 8.3 (n = 998), 44.6 (n = 5,398), and 47.1% (n = 5,705) of the cases evaluated, respectively, in 2010–2015. Among them, there was marked male predominance at the three sites, especially in the oropharynx, in accordance with the available literature [3,9–14].

Lip SCC and OSCC mainly occurred in older people. The average age at the time of diagnosis was approximately 65 ± 13.5 years and 60.3 ± 12.1 years in the present study, respectively, which corroborates previous studies performed in Italy [14], Mexico [15], and the United States (US) [16] for lip SCC and Brazil [11], Japan [17], and Australia [18] for OSCC. In contrast, the mean age at diagnosis was lowest for OPSCC (58.6 ± 10 years), with the prevalence peaking in the sixth decade of life. Similar findings were reported by other studies [10,19], in which the average age was lower compared to lip SCC and OSCC, mainly in the cases of HPV-driven OPSCC, where the mean age was usually less than 60 years [20,21]. However, the FOSP database did not report the HPV status in the recorded OPSCC cases.

Oral cancer is related to socioeconomic status and deprivation, with the highest incidence rates occurring in the most disadvantaged population groups [2]. Moro et al. [3],

Oliveira et al. [22], and Asio et al. [23] reported a marked association between lip SCC/OSCC/OPSCC and the low schooling level of patients. Similarly, 81.9% of all patients in the present study had up to 8 years of formal education. Nevertheless, studies from developed countries, such as the US [20] and Australia [12], reported higher educational levels in these patients.

The definition of the limits of the oral cavity varies between studies. Some authors include lips [3,15,23], whereas others do not [11,22]. Due to this controversy, the lip and oral cavity were classified as different sites in this study. Lip SCC accounted for approximately one-third of OSCC cases [16]. When lip SCC was exclusively analysed, previous studies reported that the lower lip was the most commonly affected site [14,16,24], similar to our findings. In the oral cavity, according to previous reports [3,9,15,23] and our results, the tongue (excluding the base of the tongue) was the most commonly affected subsite. However, in India and surrounding countries, the most frequent subsite of OSCC was the buccal mucosa, as a repercussion of the habit of chewing tobacco [25]. However, Elwood et al. [19] and Dahlstrom et al. [20] reported that the most common subsite for OPSCC were tonsils, which is in contrast with the present study, where the base of the tongue was the most common subsite.

In general, the lip region is more accessible, facilitating early cancer detection and diagnosis [3]. Previous studies performed in the US [16] and Serbia [24] reported that most lip SCC cases were in the early stage (I–II) at diagnosis, with few patients presenting regional and distant metastasis. In contrast, Fukumoto et al. [17], Oliveira et al. [22], and Listl et al. [26] described that the diagnosis of OSCC was usually delayed, allowing for local extension and regional metastasis; consequently, most cases were advanced-stage disease (III–IV). Schroeder et al. [21] and Kowalski et al. [11] observed that more than 70% of OPSCC patients were at stages III–IV. In agreement, these observations were consistent with our findings for the three sites.

Due to the early stages at the time of diagnosis, surgical resection with wide local excision was the main choice of treatment for lip SCC [16,24]. Likewise, in our sample, 72% of lip SCC cases were treated with surgery alone. Although most cases were in the advanced stage, surgery alone was the most frequently employed treatment for OSCC cases in our sample, which corroborates previous reports [11,17,27]. Nevertheless, in the studies performed by Asio et al. [23] and Oliveira et al. [22], RT alone was the most used treatment in OSCC cases. The oropharynx is not easy to access, and OPSCC usually presents as an advanced disease. Chemoradiotherapy was the main choice of treatment, being employed in approximately 40.2% of our cases, and confirming previous reports from Brazil [11] and another from the United Kingdom [21].

It is important to emphasise that lip SCC exhibited a better survival curve in our study, with a 5-year OS rate of 66.3%, which agreed with reports in the US [16] and Germany [26] that showed 5-year OS rates of 69.9 and 86.5%, respectively. Although advances in cancer treatments have occurred in recent decades, OSCC and OPSCC are still considered cancers with poor prognosis, presenting lower survival rates when compared to lip SCC. The SEER database analysis by Farhood et al. [28] demonstrated an OS rate of 49% at 5 years after the initial diagnosis for OSCC. A study conducted in Northeast China [29] found that the 5-year OS rate was slightly better than the report from the US, at 54.5%. The worst outcomes were reported in southern Taiwan [30] and Uganda [23], in which the 5-year OS rates were 36.1 and 20.7%, respectively. Similarly, a 5-year OS rate of 30.9% for OSCC was observed in the current study.

Tumours located in the oropharynx present worse survival rates, especially in HPV-negative cases [3]. OPSCC showed a lower 5-year OS (22.6%) between the three sites analysed in the sample. Similarly, Kowalski et al. [11] and Miller et al. [31] reported 5-year OS of 45 and 29.6%, respectively. A study conducted by Fakhry et al. [32] concluded that when compared to p16-negative OPSCC patients, p16-positive OPSCC patients had an estimated

52% reduction in risk of death being associated with better OS rates [21]. Similarly, Abrahão et al. [33] found that 3-year OS rates were 44.6% and 75.6% for p16-negative OPSCC and p16-positive OPSCC, respectively, and concluded that HPV status was an important prognosis predictor of OS (HR: 3.35; 95% CI, 1.33–8.45).

Male sex was an independent predictor of OS in the multivariate analysis for OSCC (HR: 1.20; 95% CI, 1.05–1.38) and OPSCC (HR: 1.45; 95% CI, 1.23–1.71). These findings were consistent with a study that collected data from four countries in South America, in which male patients with OPSCC (HR: 1.84; 95% CI, 1.08–3.14) [33] presented higher mortality rates than females. Nevertheless, Farhood et al. [28] (HR: 0.98; 95% CI, 0.93–1.04) and Kowalski et al. [11] (HR: 1.14; 95% CI, 0.86–1.51) did not observe an increase in mortality hazard for male patients with OSCC. In contrast, this study showed that the increasing age for patients with lip SCC (> 60 years—HR: 2.45; 95% CI, 1.33–4.52) and OSCC (> 60 years—HR: 1.25; 95% CI, 1.09–1.45) was associated with low OS rates, which corroborates the findings by Han et al. [16] (HR, 1.07; 95% CI, 1.07–1.08) for lip SCC and Abrahão et al. [33] (HR: 1.82; 95% CI, 1.18–2.78) for OSCC. Individuals diagnosed with lip SCC (HR: 1.97; 95% CI, 1.32–2.95), OSCC (HR: 2.19; 95% CI, 1.88–2.55), and OPSCC (HR: 2.51; 95% CI, 2.09–3.00) with advanced-stage (stages III–IV) tumours were more likely to die than patients with early-stage disease, which was an important independent determinant of OS, corroborating the findings reported in earlier studies [9,11,16,23,28]. The meta-analysis performed by Seoane et al. [34] reported that diagnostic delay was moderately related to mortality hazard for patients with head and neck cancer.

Pathology laboratories provide cancer diagnostic services and key prognostic factors that guide patient treatment decisions [35]. In Brazil, the university oral pathology laboratories performed an important role in oral cancer diagnosis and the national public health system (SUS) [36]. In our study, patients with OPSCC diagnosed by public laboratories/hospitals

(SUS) presented higher mortality rates (HR: 2.45; 95% CI, 1.66–3.62). Furthermore, the delay between diagnosis and the start of treatment at over 60 days was associated with a low mortality hazard for OSCC (HR: 1.27; 95% CI, 1.14–1.41) and OPSCC (HD: 1.19; 95% CI, 1.08–1.31) patients. In Australia [18], the median time between diagnosis and treatment was 30 days for OSCC, and in Brazil, the median time was up to 3-times higher [37], which was similar to our findings (75 days). Finally, according to Felippu et al. [37], this delay was associated with factors such as the low intellectual and social status of most patients, as well as the shortcomings of the public health care system.

Patients treated with surgery alone presented higher survival rates compared to patients treated with combinations of RT and CT. Fukumoto et al. [17], Bai et al. [9], and Farhood et al. [28] found similar results. However, the treatment must be done carefully, as advanced-stage disease usually requires more complex treatments with the use of RT and/or CT. Furthermore, the protocols used and the patient's collaboration can also influence the choice of treatment.

CONCLUSION

Based on this robust analysis of 12,099 cases of lip SCC, OSCC, and OPSCC derived from the FOSP database, this report highlights a marked male predominance, mainly affecting patients over 60 years old and with less than or equal to 8 years of education, presenting as an advanced-stage (stages III–IV) disease. The independent prognostic factors varied according to tumour site in multivariate analysis, except for tumour stage, which was a significant determinant of survival for all three sites. In addition, OSCC and OPSCC presented worse 5-year OS rates, whereas lip SCC had a high OS rate. However, an improvement in OS was observed for patients diagnosed in the more recent years of study (2013–2015).

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Table 1. Demographical and clinicopathological features of 12,099 patients with lip, oral cavity, and oropharyngeal squamous cell carcinoma diagnosed in São Paulo State, 2010–2015.

Characteristics	Lip	Oral cavity	Oropharynx	All sites	p^a
	No. (%)	No. (%)	No. (%)	No. (%)	
Total	998 (8.3)	5,398 (44.6)	5,703 (47.1)	12,099 (100.0)	
Period of diagnosis					0.887
2010-2012	480 (48.1)	2,591 (48.0)	2,763 (48.4)	5,834 (48.2)	
2013-2015	518 (51.9)	2,807 (52.0)	2,940 (51.6)	6,265 (51.8)	
Gender					**<0.0001**
Male	732 (73.3)	4,179 (77.4)	5,035 (88.3)	9,946 (82.2)	
Female	266 (26.7)	1,219 (22.6)	668 (11.7)	2,153 (17.8)	
Schooling level					**<0.0001**
≤ 8 years	717 (87.9)	3,195 (81.0)	3,349 (81.5)	7,261 (81.9)	
> 8 years	99 (12.1)	749 (19.0)	758 (18.5)	1,606 (18.1)	
Age group (years)					**<0.0001**
Mean (±SD)	65.0 (±13.5)	60.3 (±12.1)	58.6 (±10)	59.9 (±11.4)	
≤ 50	141 (14.1)	1,080 (20.0)	1,158 (20.4)	2,379 (19.7)	
51-60	241 (24.1)	1,822 (33.8)	2,317 (40.6)	4,380 (36.2)	
> 60	616 (61.8)	2,496 (46.2)	2,228 (39.0)	5,340 (44.1)	
Previous diagnosis and treatment					**<0.0001**
No diagnosis and without treatment	601 (60.2)	2,453 (45.4)	2,855 (50.1)	5,909 (48.8)	
With diagnosis and without treatment	397 (39.8)	2,945 (54.6)	2,848 (49.1)	6,190 (51.2)	
Type of diagnosis					**<0.0001**
Health insurance	38 (5.0)	359 (8.7)	274 (6.4)	671 (7.3)	
Public (SUS)	716 (93.2)	3,685 (89.1)	3,893 (91.6)	8,294 (90.6)	
Private	14 (1.8)	94 (2.2)	82 (2.0)	190 (2.1)	
Clinical stage					**<0.0001**
I-II	810 (83.3)	1,468 (28.2)	760 (13.7)	3,038 (25.9)	
III-IV	162 (16.7)	3,743 (71.8)	4,781 (86.3)	8,686 (74.1)	
Time between diagnosis and treatment					**<0.0001**
Median (days)	90	75	65	70	
≤ 60 days	186 (30.5)	1,673 (39.1)	2,134 (46.0)	3,993 (41.9)	
> 60 days	423 (69.5)	2,605 (60.9)	2,506 (54.0)	5,534 (58.1)	
Cancer treatment					**<0.0001**
Surgery alone	718 (72.0)	1,270 (23.5)	393 (6.9)	2,381 (19.7)	
Surgery + RT	69 (7.0)	769 (14.2)	260 (4.5)	1,098 (9.1)	
Surgery + RT + CT	25 (2.5)	833 (15.4)	649 (11.4)	1,507 (12.5)	
RT + CT	17 (1.6)	1,040 (19.3)	2,290 (40.2)	3,347 (27.7)	
Others[b]	118 (11.8)	1,063 (19.7)	1,539 (27.0)	2,720 (22.5)	
No treatment	51 (5.1)	423 (7.9)	572 (10.0)	1,046 (8.5)	
Patient's status at last follow-up					**<0.0001**
Alive with disease	22 (2.8)	211 (4.5)	209 (4.2)	442 (4.2)	
Alive, NOS	454 (57.8)	1,119 (23.5)	806 (15.7)	2,379 (22.3)	
Died of Disease	107 (13.6)	2,705 (56.8)	3,363 (65.7)	6,175 (57.9)	
Died of the other causes, NOS	203 (25.8)	724 (15.2)	736 (14.4)	1,663 (15.6)	

Abbreviations CT: chemotherapy; NOS: not otherwise specified; RT: radiotherapy; SD: standard deviation; SUS: Brazilian national health system.

Missing data schooling level: 3,232 cases (26.7%); type of diagnosis: 2,944 cases (24.3%); clinical stage: 375 cases (3.1%); time between diagnosis and treatment: 2,572 cases (21.3%); patient's status at last follow-up: 1,440 cases (11.9%).

[a]Comparison between the three topographies (lip, oral cavity, and oropharynx) and the clinicopathological variables.

[b]Radiotherapy alone: 1,067 cases (39.2%); Chemotherapy alone: 726 cases (26.7%); Surgery + Chemotherapy: 235 cases (8.7%); other combinations, not specified: 692 cases (25.4%).

Table 2. Survival probabilities after 5 years in patients with lip, oral cavity, and oropharyngeal squamous cell carcinoma diagnosed in São Paulo State, 2010–2015.

Variables	Lip (n=786)			Oral cavity (n=4,759)			Oropharynx (n=5,114)			p-value
	Deaths/Total	5-year survival (%)	Estimative (95% CI)	Deaths/Total	5-year survival (%)	Estimative (95% CI)	Deaths/Total	5-year survival (%)	Estimative (95% CI)	
Overall	310/786	66.3	80.2 (76.5-83.8)	3,429/4,759	30.9	43.1 (41.7-44.4)	4,099/5,114	22.6	33.4 (32.2-34.6)	**<0.0001**
Period										**<0.0001**
2010-2012	188/361	58.7	75.6 (70.8-80.5)	1,761/2,197	25.1	40.0 (38.2-41.9)	2,029/2,418	20.2	30.2 (28.7-31.7)	
2013-2015	122/425	72.7	65.5 (62.5-68.4)	1,668/2,562	35.8	37.9 (36.5-39.3)	1,976/2,696	27.7	30.9 (29.7-32.1)	
Gender										**<0.0001**
Male	222/575	66.8	81.6 (77.4-85.7)	2,773/3,725	28.7	41.0 (39.5-42.5)	3,696/4,529	21.2	31.9 (30.8-33.1)	
Female	88/211	64.9	78.1 (71.6-84.5)	656/1,034	38.7	50.8 (47.6-54.0)	403/585	32.8	44.2 (40.2-48.3)	
Age group										
≤ 50 years	18/103	84.5	98.4 (91.5-105.4)	643/926	33.4	46.6 (43.5-49.8)	795/1019	23.7	35.6 (33.0-38.2)	**<0.0001**
51-60 years	49/182	78.6	89.9 (83.7-96.0)	1,144/1,626	32.7	45.4 (43.1-47.8)	1,650/2,096	24.1	35.4 (33.5-37.2)	
> 60 years	243/501	58.1	71.2 (66.8-75.6)	1,642/2,207	28.5	39.5 (37.5-41.4)	1,654/1,999	20.3	29.8 (28.1-31.4)	
Schooling level										**<0.0001**
≤ 8 years	229/579	67.0	81.1 (77.0-485.1)	2,151/2,898	29.0	42.3 (40.6-44.0)	2,538/3,078	20.8	32.2 (30.8-33.6)	
> 8years	23/75	73.3	86.1 (76.4-95.9)	393/623	39.6	51.5 (47.6-55.5)	432/613	31.8	42.4 (38.8-46.0)	
Diagnosis type										**<0.0001**
Health insurance	5/23	78.3	82.7 (62.3-103.1)	132/259	51.7	49.7 (43.8-55.6)	96/201	54.7	55.3 (47.4-63.1)	
Public (SUS)	200/583	69.3	83.4 (79.2-87.5)	2,343/3,343	32.2	44.8 (43.1-46.5)	2,801/3,583	24.1	35.0 (33.6-36.4)	
Private	4/10	60.0	69.7 (49.6-89.8)	17/57	73.7	75.6 (62.3-88.8)	16/34	52.9	41.6 (28.6-54.7)	
Time between diagnosis and treatment										**<0.0001**
≤ 60 days	57/137	56.9	70.7 (62.6-78.7)	1,100/1,461	28.1	39.5 (37.2-41.9)	1,544/1,908	21.9	32.8 (31.0-34.6)	
> 60 days	121/336	68.8	83.4 (78.0-88.8)	1,624/2,355	34.0	47.4 (45.5-49.4)	1,775/2,292	25.4	37.2 (35.5-38.9)	
Clinical stage										**<0.0001**
0-II	209/635	72.4	87.1 (83.2-90.9)	580/1,186	56.0	69.5 (66.5-72.4)	386/637	45.7	56.1 (52.4-59.8)	
III-IV	90/136	40.4	50.8 (43.1-58.5)	2,731/3,417	22.3	34.4 (32.9-35.8)	3,594/4,339	19.4	30.3 (29.1-31.4)	

Treatment										**<0.0001**
Surgery	176/573	75.2	89.3 (85.3-93.3)	534/1,032	51.8	64.6 (61.3-67.9)	209/333	42.6	48.2 (43.1-53.4)	
Surgery+RT	25/56	60.7	76.4 (64.8-88-0)	370/663	49.2	63.0 (59.1-66.8)	139/228	43.9	55.9 (49.9-61.9)	
Surgery+RT+CT	13/24	42.3	58.0 (42.9-73.1)	527/750	33.9	48.6 (45.3-51.9)	412/582	33.3	47.2 (43.8-50.7)	
RT+CT	11/14	28.6	31.5 (15.8-47.2)	807/969	18.2	30.6 (28.4-32.9)	1,630/2,062	23.5	36.2 (34.5-38.0)	
Others[a]	60/85	36.5	48.7 (40.1-57.3)	835/966	15.9	26.0 (23.9-28.2)	1,223/1,414	15.8	25.1 (23.2-26.9)	
No treatment	25/34	29.4	31.3 (21.2-41.4)	356/379	6.6	10.6 (8.2-13.0)	486/495	2.0	6.2 (5.1-7.2)	

Abbreviations CI: confidence interval; CT: chemotherapy; RT: radiotherapy; SUS: Brazilian national health system.

[a]Radiotherapy alone: 976 cases (9.1%); chemotherapy alone: 682 cases (6.4%); surgery + chemotherapy: 213 cases (1.9%); other combinations: 594 cases (5.6%).

Table 3. Relationship of demographics and clinicopathological variables to the hazard of death for patients with lip, oral cavity, and oropharyngeal squamous cell carcinoma diagnosed in São Paulo State, 2010–2015—univariate Cox regression.

Variables	Lip (n=786)		Oral cavity (n=4,759)		Oropharynx (n=5,114)	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Period						
2010-2012	1.39 (1.10-1.77)	**0.006**	1.16 (1.08-1.24)	**<0.0001**	1.19 (1.12-1.26)	**<.0001**
2013-2015	Reference		Reference		Reference	
Gender						
Male	1.07 (0.83-1.37)	0.607	1.26 (1.15-1.37)	**<0.0001**	1.33 (1.20-1.48)	**<0.0001**
Female	Reference		Reference		Reference	
Age group						
≤ 50 years	Reference		Reference		Reference	
51-60 years	1.59 (0.93-2.73)	**0.0092**	0.99 (0.91-1.10)	0.992	1.00 (0.92-1.09)	0.925
> 60 years	3.42 (2.12-5.51)	**<0.0001**	1.18 (1.08-1.29)	**<0.0001**	1.16 (1.06-1.26)	**0.001**
Schooling level						
≤ 8 years	1.34 (0.87-2.06)	0.179	1.28 (1.15-1.43)	**<0.0001**	1.33 (1.20-1.47)	**<0.0001**
> 8 years	Reference		Reference		Reference	
Diagnosis type						
Health insurance	Reference		Reference		Reference	
Public (SUS)	1.34 (0.55-3.26)	0.518	1.42 (1.19-1.70)	**<0.0001**	2.07 (1.69-2.54)	**<0.0001**
Private	1.29 (0.35-4.81)	0.704	0.52 (0.31-0.86)	**0.010**	1.23 (0.72-2.08)	0.449
Time between diagnosis and treatment						
≤ 60 days	1.45 (1.08-1.96)	**0.014**	1.23 (1.14-1.33)	**<0.0001**	1.18 (1.10-1.26)	**<0.0001**
> 60 days	Reference		Reference		Reference	
Clinical stage						
0-II	Reference		Reference		Reference	
III-IV	3.01 (2.35-3.85)	**<0.0001**	2.56 (2.34-2.81)	**<0.0001**	2.07 (1.86-2.30)	**<0.0001**
Treatment						
Surgery	Reference		Reference		Reference	
Surgery + RT	1.54 (1.02-2.35)	**0.042**	1.02 (0.89-1.16)	0.801	0.79 (0.64-0.98)	**0.031**
Surgery + RT + CT	2.27 (1.29-4.00)	**0.004**	1.42 (1.26-1.61)	**<0.0001**	0.96 (0.83-1.15)	0.765
RT + CT	5.65 (3.06-10.43)	**<0.0001**	2.31 (2.07-2.58)	**<0.0001**	1.35 (1.17-1.56)	**<0.0001**
Others[a]	3.28 (2.45-4.41)	**<0.0001**	2.84 (2.54-3.16)	**<0.0001**	1.79 (1.86-2.51)	**<0.0001**
No treatment	5.32 (3.49-8.12)	**<0.0001**	7.73 (6.75-8.86)	**<0.0001**	7.46 (6.32-8.79)	**<0.0001**

Abbreviations CI: confidence interval; CT: chemotherapy; HR: hazard ratio; RT: radiotherapy; SUS: Brazilian national health system.

[a]Radiotherapy alone: 976 cases (9.1%); chemotherapy alone: 682 cases (6.4%); surgery + chemotherapy: 213 cases (1.9%); other combinations: 594 cases (5.6%).

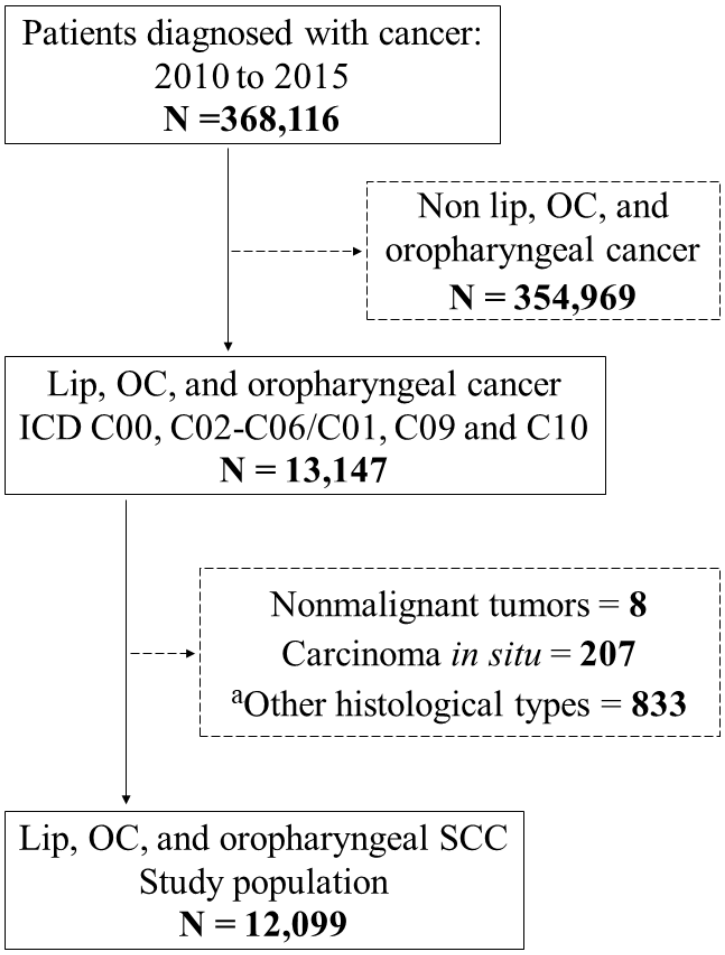
Table 4. Relationship of demographics and clinicopathological variables to the hazard of death for patients with lip, oral cavity, and oropharyngeal squamous cell carcinoma diagnosed in São Paulo State, 2010–2015—multivariate Cox regression model created using all variables that achieved a *p*-value < 0.20 in univariate Cox regression analysis.

Variables	Lip (n=786)		Oral cavity (n=4,759)		Oropharynx (n=5,114)	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Period						
2010-2012	1.04 (1.20-2.67)	0.822	1.09 (0.97-1.22)	0.148	1.13 (1.01-1.26)	**0.034**
2013-2015	Reference		Reference		Reference	
Gender						
Male	-	-	1.20 (1.05-1.38)	**0.010**	1.45 (1.23-1.71)	**<0.0001**
Female	-	-	Reference		Reference	
Age group						
≤ 50 years	Reference		Reference		Reference	
51-60 years	1.02 (0.50-2.08)	0.958	0.99 (0.86-1.15)	0.925	0.85 (0.75-0.97)	**0.019**
> 60 years	2.45 (1.33-4.52)	**0.004**	1.25 (1.09-1.45)	**0.002**	1.04 (0.90-1.19)	0.617
Schooling level						
≤ 8 years	1.06 (0.63-1.80)	0.823	1.04 (0.90-1.21)	0.596	1.07 (0.94-1.23)	0.304
> 8 years	Reference		Reference		Reference	
Diagnosis type						
Health insurance	-	-	Reference		Reference	
Public (SUS)	-	-	1.02 (0.76-1.37)	0.893	2.45 (1.66-3.62)	**<0.0001**
Private	-	-	0.85 (0.36-1.99)	0.703	1.39 (0.53-3.61)	0.502
Time between diagnosis and treatment						
≤ 60 days	1.37 (0.98-1.91)	0.069	Reference		Reference	
> 60 days	Reference		1.27 (1.14-1.41)	**<0.0001**	1.19 (1.08-1.31)	**0.001**
Clinical stage						
0-II	Reference		Reference		Reference	
III-IV	1.97 (1.32-2.95)	**0.001**	2.19 (1.88-2.55)	**<0.0001**	2.51 (2.09-3.00)	**<0.0001**
Treatment						
Surgery	Reference		Reference		Reference	
Surgery+ RT	1.00 (0.60-1.65)	0.996	0.83 (0.69-1.00)	.053	0.59 (0.44-0.80)	**0.001**
Surgery + RT + CT	1.93 (0.98-3.79)	0.057	1.05 (0.88-1.26)	.572	0.65 (0.51-0.83)	**<0.0001**
RT + CT	4.56 (2.15-9.67)	**<0.0001**	1.62 (1.37-1.91)	**<0.0001**	0.86 (0.70-1.06)	0.168
Others[a]	2.90 (2.06-4.08)	**<0.0001**	2.21 (1.88-2.61)	**<0.0001**	1.42 (1.15-1.75)	**0.001**
No treatment	4.28 (2.49-7.35)	**<0.0001**	6.18 (5.01-7.64)	**<0.0001**	6.21 (4.87-7.94)	**<0.0001**

Abbreviations CI: confidence interval; CT: chemotherapy; HR: hazard ratio; RT: radiotherapy; SUS: Brazilian national health system.

[a]Radiotherapy alone: 976 cases (9.1%); chemotherapy alone: 682 cases (6.4%); surgery + chemotherapy: 213 cases (1.9%); other combinations: 594 cases (5.6%).

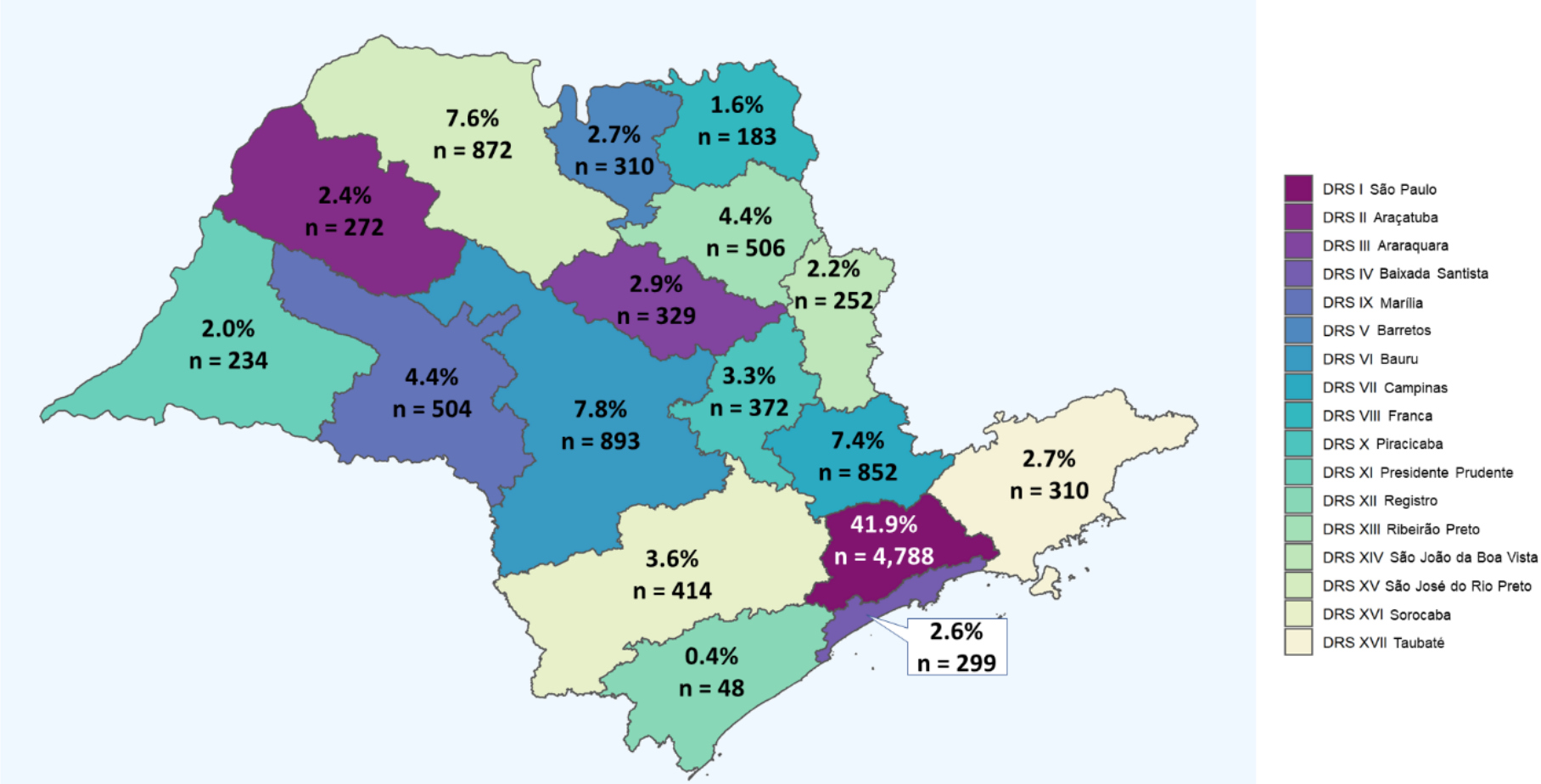
Figure 5. Flow diagram of selection of study sample.



[a]Salivary gland cancer (480 cases); Lymphomas (230 cases); Sarcoma (47 cases); Neuroendocrine tumour (15 cases); Malignant tumour, not otherwise specified (33 cases); other malignant tumours (28 cases).

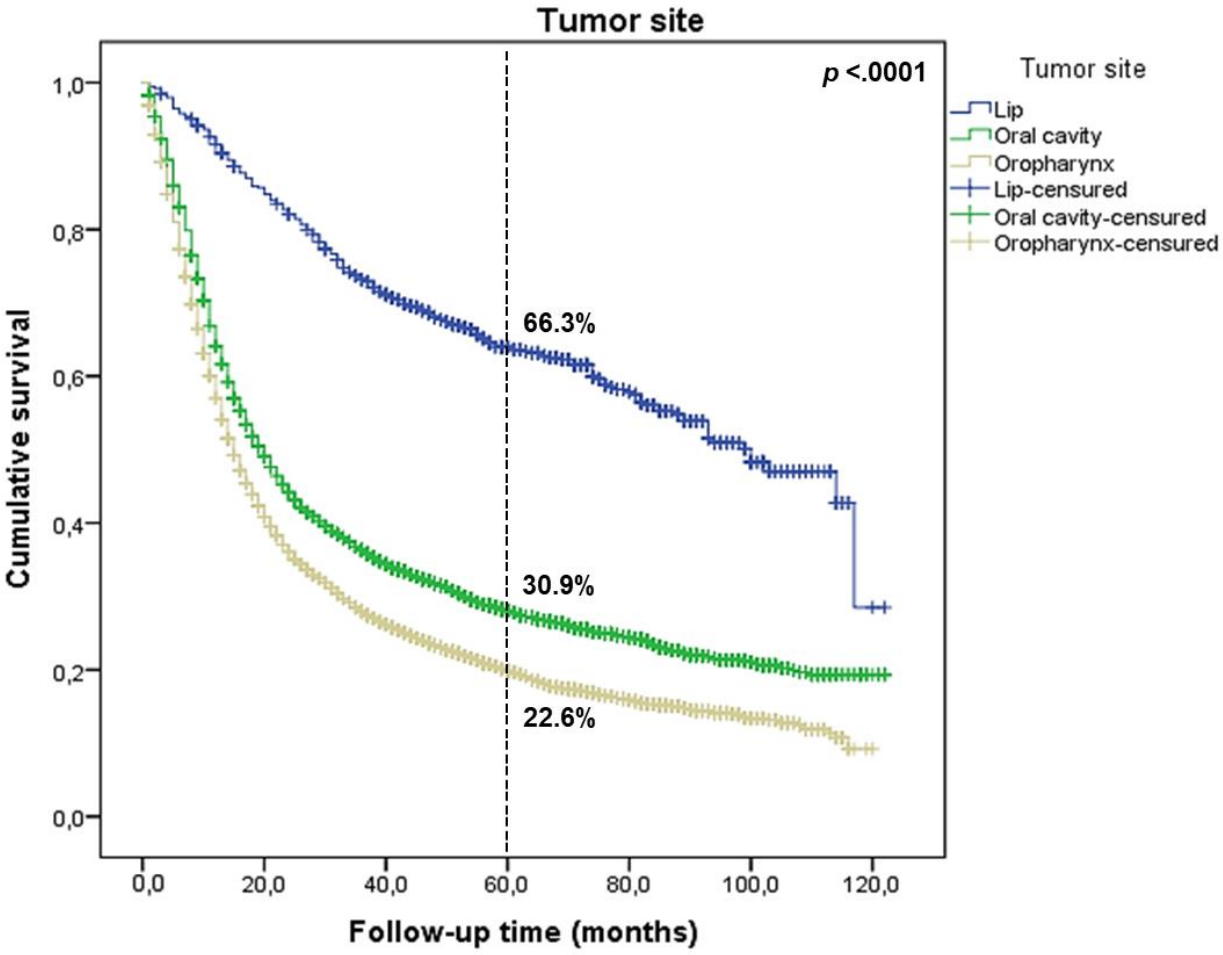
Abbreviations ICD: International classification of diseases; OC: Oral cavity; SCC: Squamous cell carcinoma.

Figure 6. Distribution of lip, oral cavity, and oropharyngeal squamous cell carcinoma diagnosed between 2010 and 2015 according to 17 Heath Regional Departments of São Paulo State.



Missing data n=660 cases (5.5%)

Figure 7. Five-year overall survival of 10,659 patients with lip, oral cavity, and oropharyngeal squamous cell carcinoma diagnosed in São Paulo State, 2010–2015, by tumour site.



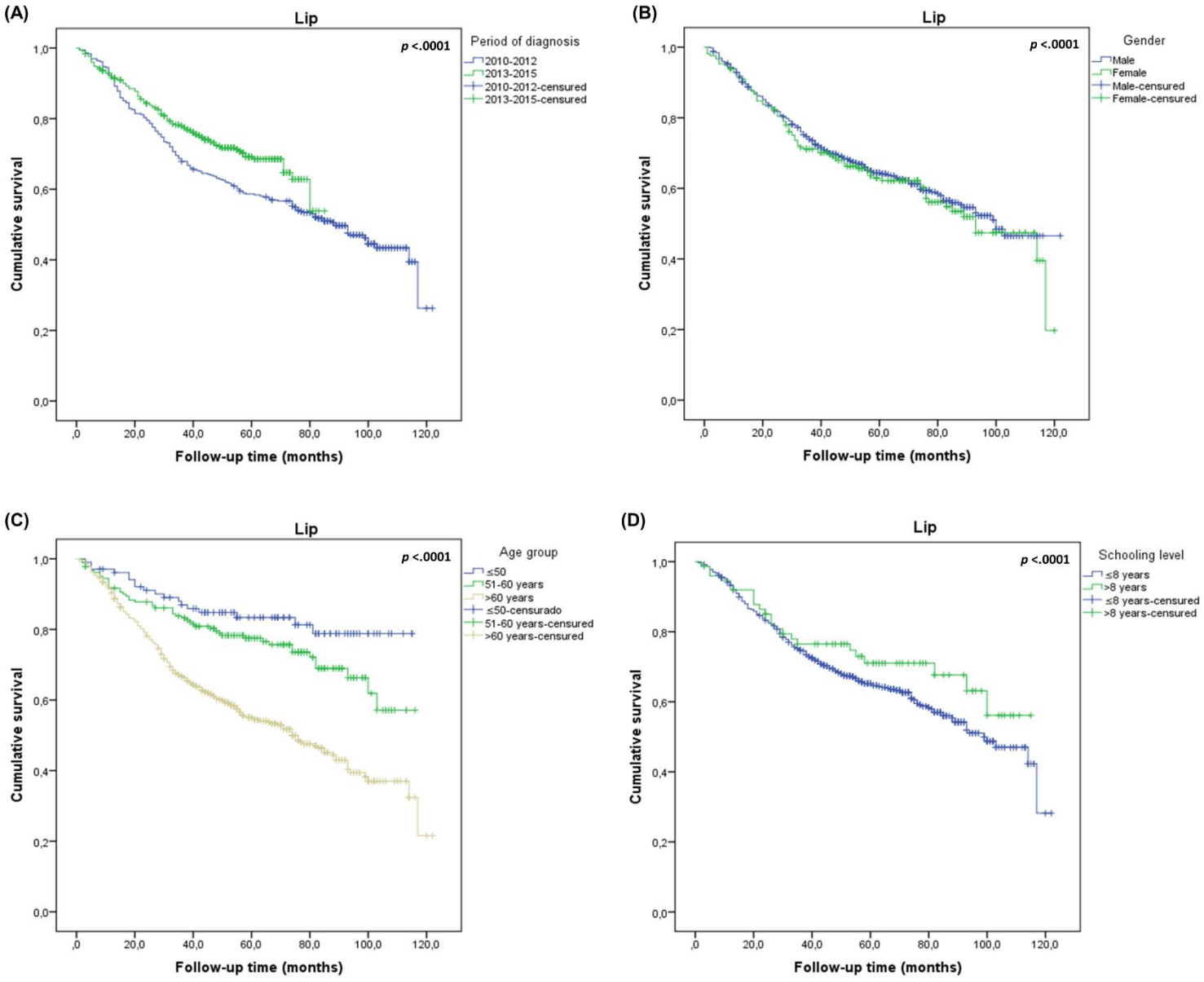
Material Suplementar do artigo

Supplemental table 1. Distribution of 12,099 patients diagnosed with lip, oral cavity, and oropharyngeal squamous cell carcinoma according to subsite tumor.

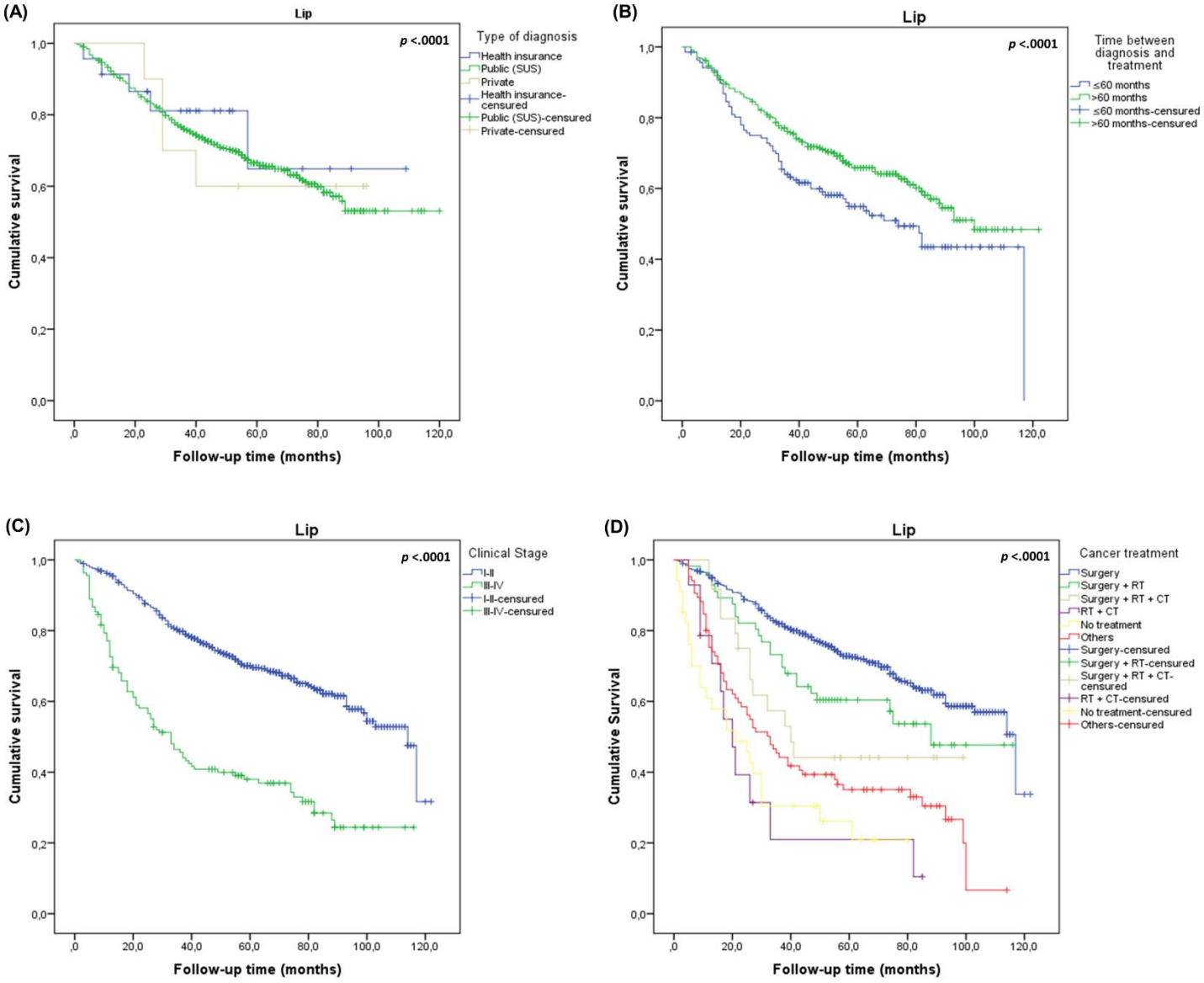
Lips		**Oral Cavity**		**Oropharynx**	
Site	**N (%)**	**Site**	**N (%)**	**Site**	**N (%)**
Upper lip	75 (7.5)	Oral tongue	2,298 (42.5)	Base of tongue	1,711 (30.0)
Lower lip	793 (79.4)	Floor of the mouth	1,200 (22.2)	Tonsil	1,067 (18.7)
Commissure	35 (3.6)	Retromolar trigone	429 (7.9)	Soft palate	650 (11.4)
Lip, NOS	95 (9.5)	Hard palate	383 (7.1)	Lateral wall	180 (3.2)
		Gum	300 (5.6)	Vallecula	116 (2.0)
		Buccal mucosa	198 (3.8)	Uvula	99 (1.7)
		Mouth, NOS	590 (10.9)	Posterior wall	76 (1.3)
				Anterior face of epiglottis	63 (1.2)
				Oropharynx, NOS	1,741 (30.5)
Total	998 (100)	**Total**	5,398 (100)	**Total**	5,703 (100)

Abbreviations NOS: not otherwise specified.

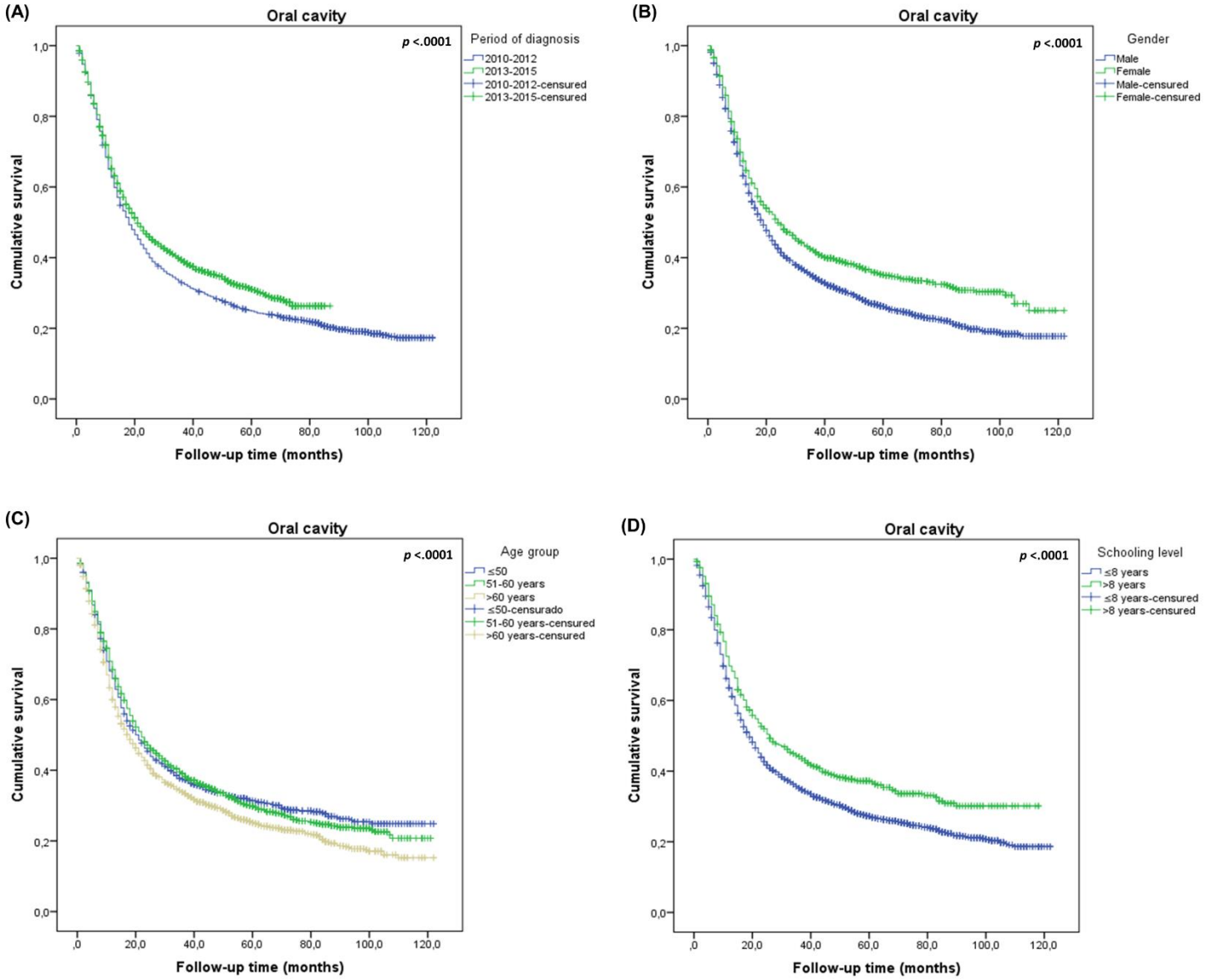
Supplemental figure 1. Kaplan-Meier survival curves of patients with **LIP SQUAMOUS CELL CARCINOMA** diagnosed at São Paulo State, 2010-2015, by period of diagnosis (A), gender (B), age group (C), and schooling level (D).



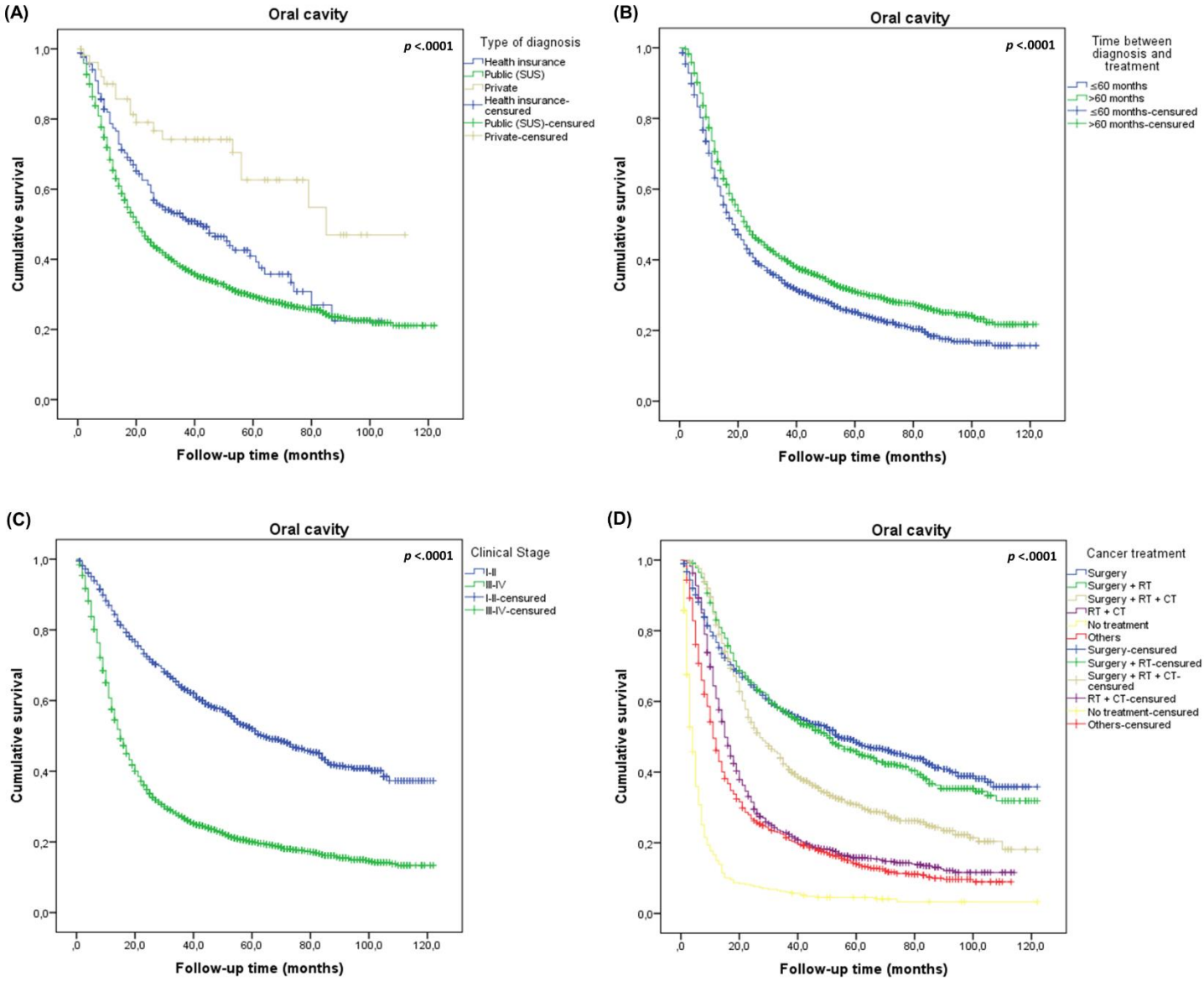
Supplemental figure 2. Kaplan-Meier survival curves of patients with **LIP SQUAMOUS CELL CARCINOMA** diagnosed at São Paulo State, 2010-2015, by diagnosis type (A), clinical stage (B), time between diagnosis and treatment (C), and treatment (D).



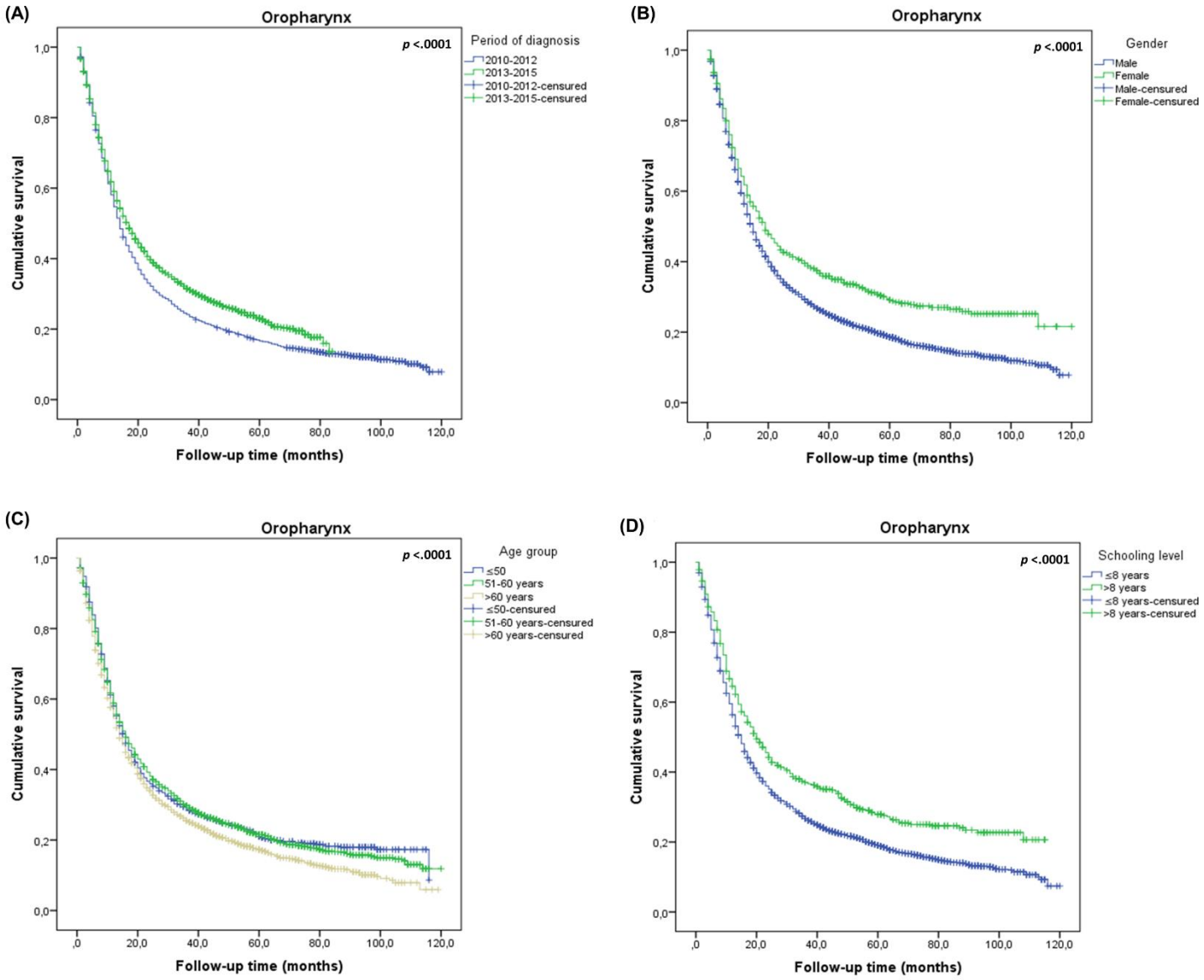
Supplemental figure 3. Kaplan-Meier survival curves of patients with **ORAL CAVITY SQUAMOUS CELL CARCINOMA** diagnosed at São Paulo State, 2010-2015, by period of diagnosis (A), gender (B), age group (C), and schooling level (D).



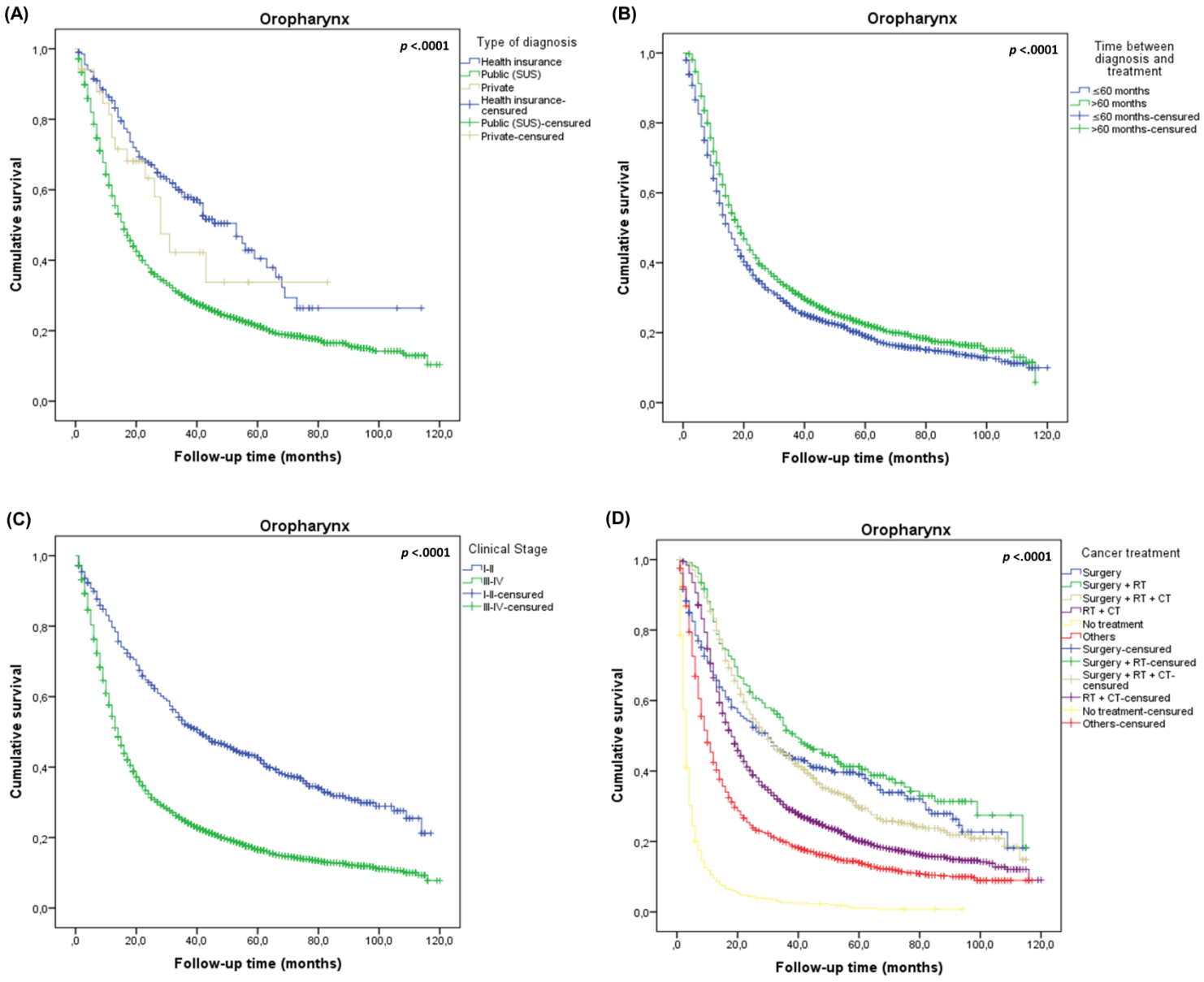
Supplemental figure 4. Kaplan-Meier survival curves of patients with **ORAL CAVITY SQUAMOUS CELL CARCINOMA** diagnosed at São Paulo State, 2010-2015, by diagnosis type (A), clinical stage (B), time between diagnosis and treatment (C), and treatment (D).



Supplemental figure 5. Kaplan-Meier survival curves of patients with **OROPHARYNGEAL SQUAMOUS CELL CARCINOMA** diagnosed at São Paulo State, 2010-2015, by period of diagnosis (A), gender (B), age group (C), and schooling level (D).



Supplemental figure 6. Kaplan-Meier survival curves of patients with **OROPHARYNGEAL SQUAMOUS CELL CARCINOMA** diagnosed at São Paulo State, 2010-2015, by diagnosis type (A), clinical stage (B), time between diagnosis and treatment (C), and treatment (D).



3 CONCLUSÃO

- Os CECs de lábio, cavidade oral e orofaringe tratados no estado de São Paulo entre os anos de 2010 e 2015 acometeram preferencialmente pacientes do sexo masculino acima dos 60 anos de idade e com baixa escolaridade;
- Mais de 90% dos pacientes obtiveram o diagnóstico de câncer através do sistema único de saúde (SUS);
- A maioria dos pacientes com CEC de lábio apresentaram tumor em estágio inicial (estágios I e II). Por outro lado, a maioria dos pacientes com CEC de cavidade oral e orofaringe apresentaram doença em estágio avançado (estágios III e IV) no momento do diagnóstico;
- A excisão cirúrgica foi o principal tratamento para os casos de CEC de lábio e cavidade oral, e a combinação de radioterapia e quimioterapia para os casos de orofaringe;
- As maiores taxas de sobrevida foram observadas nos pacientes com CEC de lábio e as menores nos pacientes com CEC de orofaringe. Contudo, notou-se uma melhora na sobrevida global dos pacientes diagnosticados nos anos mais recentes do estudo (2013-2015);
- O período do diagnóstico e o diagnóstico através do SUS foram preditores independentes de sobrevida apenas para os pacientes com CEC de orofaringe, a idade acima de 60 anos para CEC de lábio e cavidade oral e o sexo masculino e o tempo entre diagnóstico e tratamento superior a 60 dias para os casos de cavidade oral e orofaringe. O estágio clínico foi preditor independente para as três localizações e os diferentes tipos de tratamento variaram entre as topografias;

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ANEXOS

ANEXO 1 – Dispensa de aprovação no Comitê de Ética em Pesquisa

GOVERNO DO ESTADO
DE SÃO PAULO

FUNDAÇÃO ONCOCENTRO DE SÃO PAULO
Secretaria de Estado da Saúde
REGISTRO HOSPITALAR DE CÂNCER

FOSP

DECLARAÇÃO

A quem interessar possa, declaramos para os devidos fins, que as bases de dados disponibilizadas no site oficial da Fundação Oncocentro de São Paulo (FOSP) - http://www.fosp.saude.sp.gov.br - são de domínio público, não nominais. Assim, podem ser utilizadas por estudantes, pesquisadores e demais interessados, dispensando aprovação por parte de Comitês de Ética em Pesquisa na realização de projetos, artigos ou outros estudos.

São Paulo, 03 de Junho 2019.

Diretora Adjunta de
Informações e Epidemiologia

Stela Peres
Diretora
Dir. Adj. de Inf. e Epidemiologia
Fundação Oncocentro de São Paulo

Diretora Técnica

Diane Dedie Cohen
Diretora Técnico Científica
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R. Oscar Freire, 2396 ▪ São Paulo – SP ▪ CEP 05409-012 ▪ F: (11) 3797-1836 / 3797-1837
http://fosp.saude.sp.gov.br ▪ rhc@fosp.saude.sp.gov.br

ANEXO 2 – Relatório de verificação e prevenção de plágio

Dissertação Brendo

RELATÓRIO DE ORIGINALIDADE

13%	9%	9%	2%
ÍNDICE DE SEMELHANÇA	FONTES DA INTERNET	PUBLICAÇÕES	DOCUMENTOS DOS ALUNOS

FONTES PRIMÁRIAS

1	Brendo Vinícius Rodrigues Louredo, Alan Roger Santos - Silva, Pablo Agustin Vargas, Márcio Ajudarte Lopes et al. "Clinicopathological analysis and survival outcomes of primary salivary gland tumors in pediatric patients: a systematic review", Journal of Oral Pathology & Medicine, 2020 Publicação	1%
2	worldwidescience.org Fonte da Internet	1%
3	www.science.gov Fonte da Internet	1%
4	link.springer.com Fonte da Internet	1%
5	Carla Isabelly Rodrigues-Fernandes, Maria Eduarda Pérez-de-Oliveira, Lady Paola Aristizabal Arboleda, Felipe Paiva Fonseca et al. "Clinicopathological analysis of oral Burkitt's lymphoma in pediatric patients: A	<1%

ANEXO 3 – Comprovante de submissão do artigo

Oral Oncology

Epidemiology and survival outcomes of lip, oral cavity, and oropharyngeal squamous cell carcinoma in a southeast Brazilian population

--Manuscript Draft--

Manuscript Number:	
Article Type:	Original Research Article
Section/Category:	Epidemiology and Public Health Research
Keywords:	squamous cell carcinoma of head and neck; lip neoplasms; mouth neoplasms; oropharyngeal neoplasms; survival analysis
Corresponding Author:	Pablo Agustin Vargas, DDS, PhD Dental School - UNICAMP Piracicaba, BRAZIL
First Author:	Brendo Vinícius Rodrigues Louredo, DDS
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	Márcio Ajudarte Lopes, DDS, PhD
	Luiz Paulo Kowalski, MD, PhD
	Pablo Agustin Vargas, DDS, PhD
Abstract:	Objectives The epidemiological and clinical profile and survival outcomes of lip, oral cavity, and oropharyngeal squamous cell carcinoma (SCC) was studied in São Paulo State, Brazil. Patients and methods The clinicopathological data of patients with lip, oral cavity, and oropharyngeal SCC were obtained from hospital cancer registries of the Fundação Oncocentro de São Paulo, Brazil (2010–2015). Survival rates and other analyses were performed using SPSS software. Results The data from 12,099 patients were obtained. A clear male predominance was observed, particularly for patients with oropharyngeal SCC (88.3%). The average age of patients was higher for lip cases (65 ± 13.5 years) compared to other sites. The schooling level was low for most patients, especially in lip cases (87.9%). Most of the patients with oral cavity (71.8%) and oropharyngeal SCC (86.3%) had advanced-stage (III–IV) disease. However, the majority of lip cases (83.3%) were at an early stage (I–II). Surgical excision was the main treatment for lip (72%) and oral cavity SCC (23.5%), and chemoradiotherapy was the main treatment for oropharyngeal SCC (40.2%). The 5-year overall survival (OS) for patients with lip, oral cavity, and oropharyngeal SCC were 66.3, 30.9, and 22.6%, respectively. Multivariate analysis revealed that the determinants of OS were different for lip, oral cavity, and oropharyngeal SCC, except for those at the clinical stage, which was an independent predictor for all sites. Conclusion OS-independent determinants varied according to the affected site. Oral cavity and oropharyngeal SCC presented worse survival rates than those for lip SCC.