Development and Evolution of a Diagnostic and Oral Pathology Service in a Southeast Brazilian State

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Desenvolvimento e Evolução de um Serviço de Diagnóstico e de Patologia Bucal em um Estado do Sudeste Brasileiro Desarrollo y Evolución de un Servicio de Diagnóstico y Patología Oral en un Estado del Sudeste Brasileño

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ABSTRACT

Introduction: Oral squamous cell carcinoma (OSCC) is one of the most frequent cancers whose main causes are preventable because oral cavity is easily accessible for examination. OSCC involves many steps from the diagnosis until treatment which can result in late diagnosis and worst prognosis. **Objective**: Development and evolution of a Stomatology and Oral Pathology Service at the Federal University of Alfenas addressing early diagnosis and management of oral lesions. **Method**: Retrospective study developed with the files from 1998 to 2019. Data from all the cases diagnosed as oral malignancies were collected and the demographical, clinical, and microscope diagnosis were included. **Results**: 270 (84.64%) OSCC were found among 8,952 histopathological diagnoses. The patients age ranged from 24 to 94 years (mean 59.7±13.1 years), and more frequent in the sixth (32.3%) and seventh (26%) decades of life. Men were 2.5 times more affected than women. Most of patients were Caucasian (74.8%), and users of tobacco and alcohol. Over the years, there was an increase in the number of cases diagnosed and expansion of the area covered by the Service. **Conclusion**: The Dental Clinic (Stomatology) and Oral Pathology Laboratory has been playing an important role for the establishment and improvement of the healthcare system to the local population, mainly in rural areas.

Key words: mouth neoplasms/diagnosis; carcinoma, squamous cell; early diagnosis; health services.

RESUMO

Introdução: O carcinoma de células escamosas (CEC) de boca está entre os cânceres mais frequentes. Suas principais causas são evitáveis, pois a cavidade oral é uma área de fácil acesso para exame. No entanto, desde o estabelecimento do diagnóstico até o tratamento final dos pacientes, o CEC envolve muitas etapas e pode resultar em diagnóstico tardio e, portanto, em pior prognóstico para os pacientes. Objetivo: Apresentar o desenvolvimento e a evolução de um Serviço de Estomatologia e Patologia Oral da Universidade Federal de Alfenas, que tem como foco o diagnóstico precoce e o tratamento de lesões bucais. Método: Estudo retrospectivo com os prontuários de 1998 a 2019. Foram coletados dados de todos os casos diagnosticados como malignidades orais e incluídos os diagnósticos demográficos, clínicos e microscópicos. Resultados: Entre 8.952 diagnósticos histopatológicos realizados, 270 (84,64%) eram CCE. A idade dos pacientes variou de 24 a 94 anos (média 59,7±13,1 anos), sendo mais frequente na sexta (32,3%) e sétima (26%) décadas de vida. Os homens foram 2,5 vezes mais afetados do que as mulheres. A maioria dos pacientes era branca (74,8%) e o uso de tabaco e álcool, frequente. Ao longo dos anos, houve um aumento do número de casos diagnosticados, bem como uma ampliação da área de cobertura do Serviço. Conclusão: O Serviço de Estomatologia e Patologia Oral tem desempenhado um papel importante na implantação e melhoria do sistema de saúde da população local, principalmente nas Regiões interioranas e em áreas rurais.

Palavras-chave: neoplasias bucais/diagnóstico; carcinoma de células escamosas; diagnóstico precoce; serviços de saúde.

RESUMEN

Introducción: El carcinoma de células escamosas (CCE) de boca se encuentra entre los cánceres más frecuentes. Sus principales causas se pueden prevenir ya que la cavidad bucal es un área de fácil acceso para su examen. Sin embargo, desde el establecimiento del diagnóstico hasta el tratamiento final de los pacientes, la CEC implica muchos pasos y puede resultar en un diagnóstico tardío y, por lo tanto, un peor pronóstico para los pacientes. Objetivo: Presentar el desarrollo y evolución de un Servicio de Estomatología y Patología Bucal de la Universidad Federal de Alfenas que se enfoca en el diagnóstico y tratamiento precoz de las lesiones bucales. Método: Estudio retrospectivo con historias clínicas de 1998 a 2019. Se recolectaron datos de todos los casos diagnosticados como neoplasias bucales, incluyendo diagnósticos demográficos, clínicos y microscópicos. Resultados: De los 8.952 diagnósticos histopatológicos realizados, 270 (84,64%) fueron CCE. La edad de los pacientes osciló entre 24 y 94 años (media 59,7±13,1 años), siendo más frecuente en la sexta (32,3%) y séptima (26%) décadas de la vida. Los hombres se vieron 2,5 veces más afectados que las mujeres. La mayoría de los pacientes eran de raza blanca (74,8%) y el consumo de tabaco y alcohol era frecuente. A lo largo de los años, ha habido un aumento en el número de casos diagnosticados, así como una expansión del área de cobertura del Servicio. **Conclusión**: El Servicio de Estomatología y Patología Bucal ha jugado un papel importante en la implementación y mejora del sistema de salud para la población local, especialmente en las Regiones del interior y áreas rurales.

Palabras clave: neoplasias de la boca/diagnóstico; carcinoma de células escamosas; diagnóstico precoz; servicios de salud.

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INTRODUCTION

In Brazil, oral squamous cell carcinoma (OSCC) is predominant in males between 50 and 60 years old, mainly in the lateral and ventral tongue and floor of the mouth¹⁻⁷. Tobacco and alcohol use and low life standards are the main risk factors^{2,4,6-9}. The country's high mortality rates are explained by the diagnosis usually at more advanced stages which hampers appropriate treatment, making cure more unlikely^{1,2,4,6-10}. The low level of education has also been associated with increased oral cancer incidence, particularly in advanced cases^{5,7,9}.

The state of Minas Gerais (MG) belongs to the Brazilian Southeast region, it has the highest incidence of oral cancer in the country^{8,10}. According to the estimates of the National Cancer Institute José Alencar Gomes da Silva (INCA)¹¹ for 2020, 1,620 new cases of oral malignant neoplasm are anticipated for the state, the incidence for males is 9.21-11.17 cases per 100,000 inhabitants, and 2.01-2.69 for females.

The Bayesian model-based evaluation of death rate in MG to find more accurate data on oral and oropharynx cancer mortality identified accumulation of cases in the North, Central, and South regions of the state. The crude rate showed that *Alfenas*, a southern city of MG, presented 0.01-10.12 deaths per 100,000 inhabitants, and the Spatial Empirical Bayesian rate showed 5.57-36.85 deaths per 100,000 inhabitants¹².

Oral cancer studies developed in *Belo Horizonte*, the state's capital, concluded that typically the population at risk for oral cancer is found in the poorest social classes. There was higher prevalence in males (4 to 5:1) with mean age around 60 years, tobacco and alcohol users, mostly at the tongue and floor of the mouth at advanced stages^{1,13} with prolonged time of evolution¹.

More recently, a social-spatial analysis of a public hospital at *Belo Horizonte*, concluded that individual economic status and geographical area of residence are important factors related to the disparities in the prevalence of oral cancer¹³. The population was interviewed about what level of knowledge they had about oral cancer, revealing that dentists are important sources of information, providing guidance on prevention and drawing attention to the etiology of the disease¹⁴.

Along the years, the Brazilian public health system has been improving and has become more accessible in less developed areas far from the capital. Therefore, the aim of this study is to present the evolution of the Dental Clinic (Stomatology) and Oral Pathology Service along its 22 years of existence at the Federal University of *Alfenas*, MG, Brazil and its significant contribution for the local community, mostly for patients with oral cancer.

METHOD

A retrospective study developed with the files of the Oral Pathology Laboratory of the Federal University of *Alfenas* (Unifal), from 1998 to 2019. Data from all the cases diagnosed as oral malignancies were collected and included: demographical (age, gender, race, tobacco and alcohol use, city of origin), clinical (anatomic site and aspect of the lesion), and microscopic diagnosis. In addition, the cases were divided in two periods (1998-2006 and 2007-2019) to evaluate the development of the Service and compared with a previous study developed by the group¹⁵.

Hematoxylin-eosin-stained slides were used to review all the cases. Diagnosis included oral squamous cell carcinoma, verrucous carcinoma, malignant salivary gland neoplasia and others. An optical microscope (AxioLab - Carl Zeiss, Göttingen, Germany) with the objective N-Achroplan 40X/0,65, with final 400X was utilized for morphological analyzes. Two blind experienced reviewers developed two independent analyses. OSCC cases included in this study were classified according to El-Naggar et al. ¹⁶ as Grade I or well differentiated, Grade II or moderately differentiated and Grade III or poorly differentiated.

All data collected were analyzed statistically with STATA version 16.0 (StataCorp LP, College Station, Texas)¹⁷. Distribution of frequencies was used to describe categorical variables (number of cases and relative percentage), and measures of central tendency (mean and median) and variability (minimum, maximum and standard deviation) for numerical variables. To compare the groups with two categories ("Year") for age, Student's T-Test was applied; for categorical variables, the chi-square test was used for comparison between the groups, and when the expected frequency was <5, Fisher Exact Test was used. The verification of normality of the data was developed with Shapiro-Wilk test. Significance level was set at 5% (p≤0.05).

The Institutional Review Board of Unifal (CAAE: 24091519.6.0000.5142) approved the study.

RESULTS

Among 8,952 histopathological diagnoses from January/1998 to December/2019 at the Oral Pathology Laboratory – Federal University of *Alfenas*, 319 cases (3.56%) were of oral malignant neoplasia. Among these cases, 270 (84.64%) were oral squamous cell carcinoma (OSCC), 21 (6.58%) were malignant salivary gland neoplasia, 19 (5.96%) verrucous carcinoma, 6 (1.88%) sarcomas, 2 (0.63%) lymphomas, and one (0.31%)

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melanoma. The other 8,633 cases comprise inflammatory and infectious diseases and non-malignant neoplasms.

Considering the increasing number of patients with oral cancer diagnosed at the Federal University of *Alfenas*, the patient profile was also evaluated for better understanding of the role this Public Health Service plays in the community. The distribution of OSCC cases according to the year of diagnosis showed that 2017 had the highest number (27 cases), followed by 2013 and 2019 (25 cases each). The analysis of the frequency of cases during the interval 1998-2006, when the first study of the Service was developed¹⁵, versus 2007-2019, showed high increase in the mean number of cases of OSCC per year from 4.7 cases/year to 17.5 cases/year, respectively (Table 1).

The age of the patients ranged from 24 to 94 years (mean 59.7 ± 13.1 years) (Table 1), and more frequent on the sixth (32.3%) and seventh (26%) decades of life. Men were 2.5 times more affected than women. Most patients were Caucasian (74.8%), and users of tobacco and alcohol. The predominant locations of the tumor were tongue (32.2%), floor of the mouth (24.4%) and gingiva/alveolar ridge (19.4%); clinically, most of the lesions presented as ulcers (Table 1).

The biopsies forwarded by the dentists of the community off-University failed to present data about the patients' habits such as tobacco and alcohol use, and location of the lesion, hampering the analysis of these variables (Table 1).

Along the years, different descriptive terms for OSCC could be identified (Table 1), therefore a complete review of all the cases and reclassifications according to El-Naggar et al. ¹⁶ was developed to eliminate bias of histopathological diagnosis. It revealed that the sample consisted of 116 cases (43.0%) of Grade I or well differentiated SCC, 145 (53.7%) of Grade II or moderately differentiated SCC, and only 9 (3.3%) of Grade III or poorly differentiated SCC (Table 2).

In order to evaluate the evolution of the patient profile diagnosed at the Oral Pathology Laboratory of Unifal, they were categorized as before and after 2006 (Tables 3 and 4). The demographical profile of the patients did not change. However, there was a tendency towards the change of the frequency of tumor anatomic location from gingiva/alveolar ridge to tongue and floor of the mouth. In addition, it seems that the off-University dentists have improved their clinical description of the lesions sampled for histopathologic analysis; for example, the general descriptive term "ulcer/ulceration" have been more specifically termed "infiltrative ulcer" (Table 3). The histopathological diagnoses changed significantly because earlier they did not specify the degree of OSCC differentiation (Table 3).

Table 1. Distribution of the patients according to demographical and clinical variables (N=270)

Variable	Category	Frequency (%)/ Measures
	1998 – 2006	42 (15.6)
Year	2007 - 2019	228 (84.4)
	N	254
	Variation	24 – 94
Age (years)	Median	59
	Mean (Standard deviation)	59.7 (13.1)
	Male	193 (71.5)
Gender	Female	77 (28.5)
	Caucasian	166 (74.8)
Race	Non-Caucasian	29 (13.1)
	Black	27 (12.2)
Tobacco use	No	3 (4.8)
(N=63)	Yes	60 (95.2)
Alcohol use	No	4 (8.9)
(N=45)	Yes	41 (91.1)
	Lower lip	31 (12.0)
	Tongue	83 (32.2)
Location (N=258)	Floor of the mouth	63 (24.4)
	Gingiva/Alveolar ridge	50 (19.4)
	Palate	26 (10.1)
	Buccal mucosa	5 (1.9)
	Superficial ulcer	13 (5.5)
	Infiltrative ulcer	78 (32.9)
Clinical aspect	Vegetative ulcer	15 (6.3)
of the lesion	Nodule	14 (5.9)
(N=237)	Leukoplakia	24 (10.1)
	Erythroplakia	17 (7.2)
	Ulcer/Ulceration	76 (32.1)
Histopathological diagnosis (N=270)	SCC in situ/ invasive	30 (11.1)
	SCC well differentiated	33 (12.2)
	SCC moderately differentiated	93 (34.4)
Captions: SCC = Squamous	SCC cell carcinoma.	114 (42.2)

Table 2. Distribution of the patients according to clinical and pathological variables (N=270)

Variable	Category	Frequency (%)
	SCC Grade I	116 (43.0)
Classification ¹⁶	SCC Grade II	145 (53.7)
	SCC Grade III	9 (3.3)
	Alfenas	108 (45.2)
	Passos	5 (2.1)
CDC (NI_220)	Pouso Alegre	40 (16.7)
SRS (N=239)	Varginha	68 (28.4)
	Other SRS*	14 (5.9)
	Other State	4 (1.7)

Captions: SCC = Squamous cell carcinoma; SRS = Health regional superintendence.

Over the years, the number of cases diagnosed increased as well as the Service' coverage area, in terms of the origin of the patients. To better understand this scenario, the patients were classified according to the State Health Regional Superintendence (SRS).

Until 2006 the patients were predominantly from SRS Varginha (52.9%) and SRS Alfenas (29.4%), and none of the cases from other Brazilian States. From 2007, there is a clear inversion of this profile by means of SRS Alfenas having 47.8% and SRS Varginha 24.4% of the cases, as well as an expansion of the covered area with patients residing in other SRS of the State (SRS Passos, Pouso Alegre, Varginha, Divinópolis, Itabira, Manhuaçu, Sete Lagoas, and Ubâ) and São Paulo State (4 cases) (Table 4). The distribution of the cases during these two periods can be observed in Figure

Table 3. Distribution of demographical and clinical variables according to the year (N=270)

Variable	Category/ Measures				
		Measure/Fi			
	N	40	214		
Age (years)	Variation	31 – 85	24 – 94	0.832	
, igo (/ caro)	Median	56.5	59.5	0.002	
	Mean (Standard deviation)	59.3 (14.2)	59.8 (12.9)		
Gender	Male	27 (64.3)	166 (72.8)	0.261*	
Gender	Female	15 (35.7)	62 (27.2)	0.201	
	Caucasian	21 (61.8)	145 (77.1)		
Race (N=222)	Non-Caucasian	8 (23.5)	21 (11.2)	0.106*	
	Black	5 (14.7)	22 (11.7)		
T-h (NI42)	No	0 (0.0)	3 (5.7)	>0.05**	
Tobacco use (N=63)	Yes	10 (100.0)	50 (94.3)		
Alcohol use (N=45)	No	0 (0.0)	4 (10.3)	. 0.05**	
	Yes	6 (100.0)	35 (89.7)	>0.05**	
	Lower lip	5 (12.8)	26 (11.9)		
	Tongue	8 (20.5)	75 (34.2)		
L	Floor of the mouth	5 (12.8)	58 (26.5)	N 14	
Location (N=258)	Gingiva/Alveolar ridge	12 (30.8)	38 (17.4)	NA	
	Palate	6 (15.4)	20 (9.1)		
	Buccal mucosa	3 (7.7)	2 (0.9)		
	Superficial ulcer	1 (2.9)	12 (5.9)		
Clinical aspect of the lesion (N=237)	Infiltrative ulcer	6 (17.7)	72 (35.5)		
	Vegetative ulcer	3 (8.8)	12 (5.9)		
	Nodule	0 (0.0)	14 (6.9)	NA	
	Leukoplakia	3 (8.8)	21 (10.3)		
	Erythroplakia	3 (8.8)	14 (6.9)		
	Ulcer/Ulceration	18 (52.9)	58 (28.6)		
Histopathological diagnosis (N=270)	SCC in situ/invasive	4 (9.5)	26 (11.4)		
	SCC well differentiated	19 (45.2)	14 (6.1)		
	SCC moderately differentiated	15 (35.7)	78 (34.2)	<0.001*	
	scc	4 (9.5)	110 (48.3)		

Captions: SCC = Squamous cell carcinoma; NA = statistically not available.

^(*) Divinópolis, Itabira, Manhuaçu, Sete Lagoas, and Ubá.

^(#) p-value by Student's T test.

 $^{(\}sp{*})$ p-value by chi-square frequency test.

^(**) p-value by Fisher's exact test.

1, showing the increasing number of regional cases and a clear expansion of the cases in the State.

When cases only from MG are analyzed comparing the two periods, it can be observed that in 1998-2006,

70.6% of the cases were not from SRS *Alfenas* despite the location of the Service, and today this SRS represents 48.8% of the cases. This significant change (p=0.036) shows the importance of the Service for the local population (Table 4).

Table 4. Distribution of clinical and pathological variables according to the Year (N = 270)

Variable	Category/ Measures	YEAR 1998-2006 2007-2019 Measure/Frequency (%)		p-value#
	SCC Grade I	21 (50.0)	95 (41.7)	
Classification ¹⁶	SCC Grade II	19 (45.2)	126(55.3)	NA
	SCC Grade III	2 (4.8)	7 (3.1)	
SRS (N=239)	Alfenas	10 (29.4)	98 (47.8)	
	Passos	0 (0.0)	5 (2.4)	
	Pouso Alegre	3 (8.8)	37 (18.0)	NIA
	Varginha	18 (52.9)	50 (24.4)	NA
	Other SRS*	3 (8.8)	11 (5.4)	
	Other State	0 (0.0)	4 (2.0)	
SRS-MG	Alfenas	10 (29.4)	98 (48.8)	0.024
	Other SRS**	24 (70.6)	103 (51.2)	0.036

Captions: NA = statistically not available; SRS = Health regional superintendence.

^(**) Passos, Pouso Alegre, Varginha, Divinópolis, Itabira, Manhuaçu, Sete Lagoas, and Ubá.

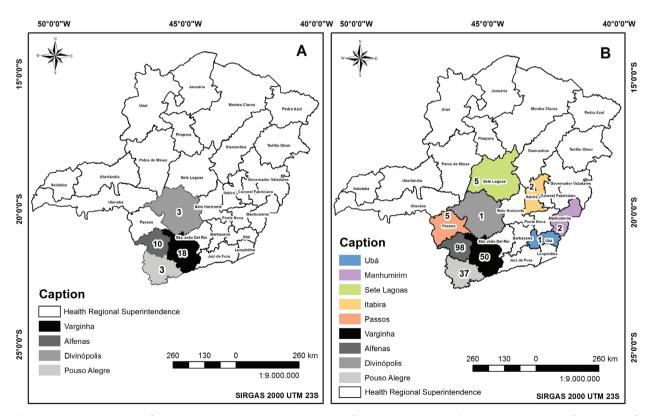


Figure 1. Representation of the Health Regional Superintendence of Minas Gerais State¹⁸ and the distribution of the cases of OSCC from the Oral Pathology Laboratory - Unifal during the periods A) 1998-2006 and B) 2007-2019

^(#) p-value by chi-square frequency test.

^(*) Divinópolis, Itabira, Manhuaçu, Sete Lagoas, and Ubá.

DISCUSSION

The National Health System (SUS) was created in 1990 and it is a public health system with universal access for the population. It is based on decentralization, creating health regions with integrated health planning by means of regional management boards under the supervision of health state secretariats in partnership with municipal authorities¹⁹. Thereby, MG is divided into 18 Health Regional Superintendence (SRS) and 10 Health Regional Management (GRS)¹⁸. The present Service belongs to SRS *Alfenas*.

Primary health care is the main access to SUS, providing primary (control of risk factors) and secondary prevention (early detection) for oral and oropharyngeal cancer. The increasing number of dentists in primary care resulted in early detection of oral cancer, easily screened at clinical examination where suspicious lesions are able to be identified visually²⁰. However, the access to specialists remains a major bottleneck resulting in unmet demands, queues, long waiting times, and diagnoses^{2,19} delays.

Through this system, the final diagnosis of oral and oropharyngeal cancer is to be performed on the Specialized Dental Care (SDC) centers. When the primary care dentist detects a potentially malignant oral lesion, the Oral Health Team is expected to refer the patient to a SDC, where a biopsy will be run and later to a hospital for cancer treatment, if needed²⁰.

In this scenario, the Dental Clinic (Stomatology) at the Dental School and the Oral Pathology Laboratory of the Unifal plays an important role on oral cancer diagnosis for the local community whose main economic activity is agriculture. In addition, this region is 350km far from the State's capital. Once the patients receive a cancer diagnosis at the Service, they can proceed to the nearest SUS healthcare system available for subsequent treatment.

The first study to evaluate the present Service included the OSCC cases reported in the period of 1998-2006¹⁵; there were no significant differences in demographical, clinical, and histopathological data between the first and the current period of 2007-2019 (Tables 3 and 4), and the patient profile is compatible with other previous Brazilian studies (Table 1) – male, around 60 years of age, tobacco and/or alcohol user, advanced tumors in the tongue or floor of the mouth¹⁻⁷. Nevertheless, the data analysis was flawed because many off-University dentists forwarded the biopsies without data of the patient's use of tobacco and alcohol and location of the lesion.

However, it stands out the increase of the number of OSCC cases diagnosed from 1.64% (1998-2006) to 3.56% (2007-2019) of all cases received at the Oral Pathology Laboratory. These data show the evolution from

4.7 to 17.5 cases/year, probably reflecting an increased demand for consultation to the local population, which calls for professional qualification to improve the diagnosis of oral cancer. It is possible to infer that these results do not necessarily mean that the incidence of oral cancer has increased, but a higher number of patients was evaluated at the Service instead. On the other hand, the predominance of Grade II tumors (Table 2) remains through the whole period evaluated, which may indicate the need for improvement of the process of early diagnosis (Table 4).

Today, the tumor is more prevalent at the tongue and floor of the mouth instead of gingiva/alveolar ridge and palate, a clear tendency in its location. In addition, the quality of the description of the clinical aspect of the lesion has changed over the years: instead of ulcer/ulceration, there is significant presence of more specific descriptions such as infiltrative, superficial, or vegetative ulcer (Table 4). This change can be attributed to dentists' improved skills for diagnostic process.

A study identified that approximately 12 years of education is a predictor protective factor for oral cancer, while risk factors were past or present use of alcohol, tobacco and previous diagnosis of cancer^{4,14}. The delay in the process of oral cancer diagnosis may be associated with many factors involving the patients, the health system, and professionals. The lack of information and patients fear, in addition to several asymptomatic lesions are concerning^{2,21}. Programs that aim to create strategies for awareness and education regarding risk factors such as tobacco and alcohol use, self-examination and symptoms of oral cancer are important tools as well^{1,5,7-9,13,14,21,22}.

However, the existence of a healthcare system itself does not guarantee the diagnosis of oral cancer¹³ because health professionals need to be trained to identify potentially malignant lesions and cancer^{2,13,14,21}. In addition, the medical consultation scheduling, the public transportation system, cultural and financial issues may cause delay². Moreover, the information from geospatial analysis could be useful for policymakers in the implementation of place-specific control and preventive policies focused to high-risk populations¹³.

Therefore, the responsibility of a University as an Educational Institution for the community goes beyond its geographical localization. The Service has improved along its 22 years of existence with significant achievements as:

1) The number of local patients consulted increased significantly in this period and today, it represents almost half of the cases:

2) The staff of the Dental Clinic (Stomatology) increased, and a substantial number of biopsies were performed, and the Oral Pathology Laboratory received more biopsies from off-University dentists;

- 3) Dental students at the Federal University of *Alfenas* were extensively trained to detect and manage oral premalignant lesions during these past few years, which may possibly explain the increasing number of patients from SRS's other than *Alfenas*' (many undergraduate and graduate students start their practice on nearby towns). Moreover, the use of mobile phone applications and cameras ensure easy exchange of information among former and current students and the University staff;
- 4) Oral Medicine Professors offer training as continuing education for local health professionals;
- 5) The recent creation of an Institute of Oncology in the city of *Alfenas* strengthened the bond between the University and the regional population, possibly ensuring the early access to diagnosis and treatment of oral cancer.

CONCLUSION

In conclusion, the evolution of the Dental Clinic (Stomatology) and Oral Pathology Laboratory at the Federal University of *Alfenas* reinforces the importance of offering specialized dental services in underserved regions through training and continuing education for local health professionals as well as improvement of the care network for early diagnosis and treatment of oral cancer.

CONTRIBUTIONS

Laura Cruz-Mamani contributed for the study design, methodology, original draft; Alessandro Antônio Costa Pereira, João Adolfo Costa Hanemann contributed for the study design; Marta Miyazawa contributed for the methodology, writing, review and editing; Denismar Alves Nogueira contributed for the methodology; Felipe Fornias Sperandio contributed for the methodology; João Adolfo Costa Hanemann for funding acquisition and supervision. All reviewed, read and approved the final version to be published.

CONFLICTS OF INTEREST

There is no conflict of interest to declare.

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