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LIGIA AKIKO NINOKATA MIYAHARA

CARCINOMA EPIDERMOIDE DE BOCA: ANÁLISE DE SOBREVIDA, FATORES PROGNÓSTICOS E EFETIVIDADE DE UMA ESTRATÉGIA DE ENFRENTAMENTO CONTRA O CÂNCER ORAL

ORAL SQUAMOUS CELL CARCINOMA: ANALYSIS OF SURVIVAL, PROGNOSTIC FACTORS AND EFFECTIVENESS OF A COPING STRATEGY AGAINST ORAL CANCER

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

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Orientador: Prof. Dr. Hélder Antônio Rebelo Pontes

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RESUMO

O Carcinoma epidermoide é a neoplasia maligna mais comum de boca, representando mais de 90% dos casos diagnosticados neste sítio anatômico. Muitos casos de carcinoma epidermoide de boca (CEB) podem ser precedidos ou estão associados a desordens orais potencialmente malignas (DOPM), especialmente as leucoplasias orais (LO). Considerando a importância do câncer oral para a saúde pública, este trabalho teve como proposta avaliar uma estratégia de enfrentamento quanto à melhora na sobrevida de pacientes acometidos por CEB. Em 2012, um projeto foi criado para capacitar dentistas da atenção primária em saúde e equipes odontológicas da atenção secundária para a identificação de DOPM e CEB, especialmente aqueles em estágios iniciais. Posteriormente, os dados clinicopatológicos e as taxas de sobrevida antes e após a implantação do projeto foram comparados. Um total de 360 pacientes foi incluído no presente estudo (86 LO e 274 CEB). Um aumento nos diagnósticos de LO de baixo risco foi observado após o projeto. Em relação à análise de CEB, foi observado um aumento de carcinomas in situ e em T1-2, assim como em N0, resultando em uma maior quantidade de casos diagnosticados em estágios precoces (0 e I-II). A análise de sobrevida evidenciou uma melhora significativa na sobrevida dos pacientes após a realização do projeto, com uma taxa de sobrevida em cinco anos de 14,8% pré-projeto e 38,4% na análise pós-projeto ($p < 0.0001$). Em conclusão, os resultados deste trabalho demonstram que políticas de saúde que facilitem o acesso dos pacientes ao diagnóstico precoce, levando em consideração as realidades regionais, são ferramentas essenciais para melhorar a sobrevida associada ao CEB.

Palavras-chave: câncer oral; leucoplasia oral; epidemiologia, sobrevida, política pública.

ABSTRACT

Oral squamous cell carcinoma (OSCC) is the most common malignant neoplasm of the mouth, representing more than 90% of the cases diagnosed in this anatomical site. Many cases of OSCC can be preceded or are associated with oral potentially malignant disorders (OPMD), especially oral leukoplakia (OL). Considering the importance of oral cancer for public health, this study aimed to evaluate a coping strategy regarding the improvement in survival rates of patients diagnosed with OSCC. In 2012, a project was created to empower dentists of primary health care and dental teams of secondary care to identify OPMD and OSCC, especially those in early stages. Subsequently, the clinicopathological data and the survival rate before and after the implementation of the project were compared. A total of 360 patients were included in the present study (86 LO and 274 OSCC). An increase in low-risk LO diagnoses were observed after the project. Regarding the OSCC analysis, an increase was observed in Tis and T1-2, as well as N0, resulting in a greater number of cases diagnosed in early stages (0 and I-II). The survival analysis showed a significant improvement in patient's survival after the project, with a 5-year survival rate of 14.8% pre-project and 38.4% in the post-project analysis (p-value < 0.0001). In conclusion, the results of this study demonstrate that health policies that facilitate access of patients to early diagnosis, taking into account regional realities, are essential tools to improve the survival associated with OSCC.

Key Words: oral cancer; oral leukoplakia; epidemiology; survival; public policy.

SUMÁRIO

1 INTRODUÇÃO

Neoplasias malignas orais representam grandes desafios enfrentados pela saúde pública global, devido aos múltiplos comprometimentos da saúde e da qualidade de vida dos pacientes afetados por essas patologias, além de suas altas incidências. As funções fisiológicas, a aparência cosmética e o bem-estar psicológico podem ser comprometidos durante o diagnóstico, tratamento e sobrevida desses pacientes (Valdez & Brennan, 2018). Mundialmente, o câncer oral é a sexta neoplasia maligna mais frequente e mais de 90% das lesões são diagnosticadas como Carcinoma Epidermoide de Boca (CEB) (Warnakulasuriya, 2009; Kumar M. *et al*. 2016). No mundo, a incidência anual estimada para o CEB é de aproximadamente 350.000 casos, com uma taxa de mortalidade de cerca de 170.000 (Bray *et al.,* 2018). Para o Brasil, estimam-se 11.180 casos novos de câncer da cavidade oral em homens e 4.010 em mulheres para cada ano do triênio 2020-2022. Esses valores correspondem a um risco estimado de 10,69 casos novos a cada 100 mil homens, ocupando a quinta posição; e de 3,71 para cada 100 mil mulheres, sendo a décima terceira mais frequente entre todos os cânceres (INCA, 2019).

Uma maior exposição a fatores de risco, como o consumo de tabaco e álcool - fatores mais comumente associados ao CEB - pode ser a causa de uma maior prevalência observada em homens, embora um aumento em mulheres seja observado, o que pode estar relacionado a mudanças nos hábitos nesse gênero (Tota *et al*., 2017; Capote-Moreno *et al*., 2020). Adicionalmente, já está bem estabelecido na literatura o papel do papilomavírus humano (HPV), especialmente os subtipos 16 e 18, na etiologia do CEB nas regiões de orofaringe, base de língua e tonsilas (Hübbers & Akgül, 2015; Yete *et al*., 2018). Os componentes presentes nos diversos tipos de tabaco estão associados a mutações carcinogênicas e o álcool no organismo causa a produção de espécies reativas de oxigênio e acetaldeído, podendo levar danos ao DNA, além de aumentar a permeabilidade da mucosa oral e poder atuar como solvente para os produtos do tabaco; ou seja, quando associado ao tabagismo, o consumo de álcool agrava o potencial dos efeitos carcinogênicos (Mello *et al*, 2019). Entretanto, nas últimas décadas, nota-se uma mudança no perfil clínico clássico do CEB. A incidência da doença tem aumentado em pacientes jovens e mulheres, mesmo na ausência de fatores de risco (Gholizadeh *et al*., 2016; Yosefof *et al*., 2020).

A maioria, se não todos os CEBs, são precedidos por alterações clinicamente visíveis da mucosa oral (van der Waal, 2019). Dentre as Desordens Orais Potencialmente Malignas (DOPMs) que apresentam risco de malignização, a mais comumente encontrada na

prática clínica é a Leucoplasia Oral (LO), a qual é definida como "uma placa predominantemente branca de risco questionável tendo excluído (outras) doenças conhecidas ou desordens que não apresentam risco aumentado de câncer" (Warnakulasuriya, 2007). O diagnóstico precoce de DOPM pode ser útil na prevenção do CEB e, consequentemente, na redução da mortalidade e morbidade relacionadas (Kumar *et al*., 2019).

As localizações anatômicas mais comuns de acometimento do CEB são a língua (ventre e borda lateral, 40% dos casos), seguido pelo assoalho de boca (30% dos casos) (Rivera, 2015; Bagan *et al*., 2010). CEB nessas localizações apresentam piores prognósticos (Abdo *et al*., 2007). Embora a dor seja o principal sintoma, esta geralmente surge apenas quando as lesões atingem um tamanho notável, sendo o momento em que o paciente procura por atendimento profissional. Assim, CEBs precoces muitas vezes passam despercebidos porque são assintomáticos (Bagan *et al*., 2010).

O tratamento desta doença frequentemente incorpora abordagens multimodais. Novas opções de tratamentos vêm surgindo nas últimas décadas. Maiores ressecções cirúrgicas e reconstruções primárias dos defeitos melhoraram com o uso de retalhos livres microvasculares, fornecendo melhores resultados estéticos e qualidade de vida para o paciente. Novas modalidades de radiação e protocolos de quimioterapia tentam melhorar a sobrevida. Recentemente, a imunoterapia foi introduzida para o tratamento de CEBs recorrentes e tumores metastáticos, melhorando o sistema imunológico contra células tumorais (Capote-Moreno *et al*., 2020).

No entanto, apesar dos avanços nas estratégias de diagnóstico e tratamento, não houve melhora na sobrevida dos pacientes e a taxa de sobrevida em cinco anos ainda é baixa (Lindemann *et al*, 2018), variando em torno de 30 a 50% (Pontes *et al*. 2015), visto que muitos destes tumores recebem diagnósticos tardios, em estadiamentos avançados da doença. Se detectado em um estágio inicial, o CEB tem uma taxa de sobrevida de até 80% em comparação com a detecção em estágios posteriores (T3-T4), quando uma taxa de 20 a 30% está presente (Dumache, 2017). Sendo assim, o diagnóstico precoce e a redução dos fatores de riscos constituem estratégias importantes para um melhor prognóstico da doença. Em países em desenvolvimento e localidades menos urbanizadas, a efetividade dessas estratégias é reduzida, principalmente pela dificuldade de acesso a centros de referência em diagnóstico e pela carência de um treinamento das equipes profissionais de unidades de saúde locais para o diagnóstico precoce nas regiões mais afastadas.

Mundialmente, sabe-se que há uma grande variação geográfica na incidência do câncer oral (Warnakulasuriya, 2009; Curado *et al*., 2016, Gupta *et al*., 2016). As taxas de

prevalência, características clínicas de pacientes e fatores etiológicos diferem de acordo com a localização geográfica mesmo entre regiões do mesmo país (INCA, 2019; Kumar *et al*., 2019). Isso pode ser devido a diferenças regionais, como hábitos comuns e outros fatores culturais que podem potencialmente afetar a prevalência dessas neoplasias (Mello *et al*., 2019). Assim, o levantamento das características clínicas e histológicas das lesões, bem como o perfil dos pacientes acometidos, torna-se importante nesse contexto. Estudos de acompanhamento a longo prazo são necessários para melhor compreender o padrão da doença (Kumar *et al*., 2019), e estudos epidemiológicos são igualmente essenciais para monitorar situações de saúde, a fim de criar estratégias de prevenção e tratamento.

O Brasil é um país de dimensões continentais e fortes diferenças regionais por abrigar uma população de comportamentos, crenças e atitudes de modo bem diversificado (INCA, 2018). O Estado do Pará é o segundo maior estado brasileiro em extensão territorial, sendo formado por 144 municípios. A região Norte difere-se de muitas maneiras de outras regiões do Brasil, como em seu grande número de rios que são utilizados como as principais rotas de transporte (Pontes *et al*., 2011). Em razão de tal extensão, dificulta-se o acesso da população aos serviços de saúde, atrasa-se o diagnóstico e, consequentemente, o tratamento, influenciando na sobrevida desses pacientes e prejudicando também a obtenção de dados referentes à população em questão.

Pontes *et al*., em 2011, publicaram a primeira análise de CEB de língua e soalho de boca para correlacionar a taxa de sobrevida de pacientes com fatores prognósticos clínicos independentes na região amazônica. Em 2012, foi realizado um projeto, em parceria com a Secretaria de Saúde Pública do Estado do Pará (SESPA), através dos 13 Centros Regionais de Saúde (CRS). CRS são Unidades Administrativas da SESPA distribuídas em todo o território paraense visando à descentralização de serviços e redução das barreiras geográficas para melhor atender o cidadão. Eles foram instituídos para fornecer à população orientações/acesso mais rápido à rede estadual de saúde. Este projeto visava capacitar um grupo de cirurgiões-dentistas de todas as Regionais de Saúde do Estado do Pará para identificar e realizar biópsias de DOPMs e lesões malignas de boca, uma vez que os profissionais da atenção primária têm um papel fundamental no diagnóstico precoce e acompanhamento a longo prazo de pacientes em risco. A proposta objetivava essencialmente diminuir os altos índices de pacientes que chegam à capital (Belém) com cânceres de boca em estágios avançados, e, consequentemente, aumentar a sobrevida e diminuir os custos do tratamento dos pacientes acometidos por CEB no Estado do Pará.

Nesta linha de pensamento, considerando a importância do câncer oral para a saúde pública, este trabalho teve como proposta avaliar uma estratégia de enfrentamento quanto à melhora na sobrevida de pacientes acometidos por CEB. A pesquisa descreveu as características clinicopatológicas de casos diagnosticados como LO e CEB, bem como as taxas de sobrevida antes e após a implantação do projeto no Estado do Pará. Neste sentido, o presente trabalho torna-se relevante, uma vez que estudos desta natureza são ferramentas importantes para o planejamento, gerenciamento e acompanhamento de situações de saúde, tomada de decisões e desenvolvimento de ações, com o propósito de gerar intervenções mais adequadas e oportunas frente às necessidades da população (INCA,2019).

2 ARTIGO

Artigo submetido ao periódico Community Dentistry and Oral Epidemiology (Anexo 3).

PUBLIC POLICY FOR ORAL CANCER: A SUCCESSFUL STRATEGY IN A STATE OF BRAZILIAN AMAZON REGION.

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ABSTRACT

Objective: To evaluate a coping strategy regarding the improvement in survival rates of patients diagnosed with oral squamous cell carcinoma (OSCC) in a Brazilian Amazon region state and to compare the clinicopathologic data of oral leukoplakia (OL) and OSCC previous and post the public policy.

Methods: Date of subjects with histologically confirmed OL and OSCC of tongue and floor of the mouth were retrieved from João de Barros Barreto University Hospital medical records. A project was created in 2012 to empower dentists of primary and secondary-care dental teams of all regional health departments of the state to identify potentially malignant disorders and OSCC in early stages. The cases were evaluated and compared in two periods: before the project implementation (from 2007 to 2012) and after its implementation (from 2013 to 2019).

Results: A total of 360 patients were included in the present study, including 86 patients with OL and 274 patients with OSCC. An increase of OL with low risk grade of dysplasia was observed in the post-project period. Regarding the OSCC analysis, it was observed an increase in the number of in situ OSSC and T1-2, as well as N0 lymph node metastasis and AJCC-stage 0 and I-II. Survival analysis evidenced a significant increase in the patient's survival, and showed a 5-year survival rate of 14.8% previous to the project and 38.4% in the post-project analysis (p-value: < 0.0001).

Conclusion: Early detection is key to improving survival associated with OSCC. The creation of a health public policy that facilitate patients' access to early diagnosis, taking into account regional realities, is an essential tool to minimize morbidity and increase survival rates.

INTRODUCTION

Oral cancer is the sixth most common malignant neoplasm worldwide and oral squamous cell carcinoma (OSCC) represents more than 90% of neoplasm in this anatomical site[1,2,3]. Despite advances in the treatment strategies and in the knowledge about the biological features of lesions, it remains a lethal and deforming disease, resulting in severe morbidity, limited quality of life and short survival[4,5].

There is a large geographical variation in oral cancer incidence around the world. Worldwide there are 350,000–400,000 new cases diagnosed every year[6,7]. The prevalence rates, clinical characteristics of patients and lesions, and aetiological factors differ according to geographic location[1,8,9] and even between regions of the same country[10,11]. Brazil has the highest incidence of OSCC among South American countries[8,12], which is attributed to cultural habits such as the consumption of tobacco and alcohol, the two most widely known risk factors, especially when synergistically consumed[13].

In the north of Brazil, where the Amazon region is located, oral cavity cancer is the sixth most frequent cancer (3.80/100 thousand) in men, and the twelfth (1.69/100 thousand) in women[14]. The Amazon region differs in many ways from other regions of Brazil, such as in its huge number of rivers that are used as the main routes of transportation. Pará is an Amazon state which presents a large territorial expanse, being larger than many countries in Europe. In addition, the state still has several social problems, which make it harder for a large part of the population to access public health services, especially for the residents of inner cities[15]. Additionally, this state presents about half of all the registered cases of OSCC in the north region, with 220 cases expected in 2020[14]. Furthermore, delayed diagnosis accounts for the high mortality and morbidity found in this Brazilian region[15].

Our team of researchers published a study in 2011 analysing the survival rate of patients with OSCC in the Amazon region. In this paper, the authors showed that the overall 5-year survival rate found was markedly low[15]. Taking into account that strategies with real impact on health policies must emphasize early diagnosis, and that appropriate knowledge on the clinical appearance of oral cancer and oral potentially malignant disorders (OPMD), as well as understanding its management, are prerequisites for dentists to provide correct mouth examinations, in 2012 the same group of researchers devised a project to empower dentists of primary and secondary-care dental teams with the aim of improving survival rates of patients

with OSCC in this Brazilian state. Seven years of project have been completed and the results obtained are encouraging.

The aim of this study was to compare the clinicopathologic data and overall survival rates of patients diagnosed with oral leukoplakia (OL) and OSCC in an Amazon region state previous and post a public policy for oral cancer, in order to verify the effectiveness of the creation of a protection network against oral cancer.

METHODOLOGY

This work has been approved by the ethical committee of the João de Barros Barreto University Hospital under approval number 4.238.444.

Project description

This project was carried out with the support of the Foundation for Research Support of the State of Pará (FAPESPA). The project aimed to train a group of dentists from all of the Regional Health Departments (RHDs) of the state to identify, especially in the early stages, and to perform biopsies on potentially malignant and malignant lesions of the oral cavity. RHDs are administrative units of the Health Secretary of Pará distributed throughout the state territory. The distribution of the 13 RHDs is illustrated in Figure 1. In the first phase of the project, two professors with training in oral diagnostics, from the Federal University of Pará, went to the host cities of the 13 RHDs to give lectures on the clinical and imaging aspects of OPMD and OSCC, as well as teaching the dentists biopsy techniques. Subsequently, two dentists from each RHD underwent practical training at the Diagnostic Service in Oral Pathology, João de Barros Barreto University Hospital (HUJBB), in Belém/Pará on biopsy techniques. These professionals have become a reference in their regions for the management of oral lesions. The proposal was fundamentally aimed at reducing the high rates of patients who arrived at the capital state (Belém) with advance-stage oral cancers. In addition, the project sought to map the regions with the highest incidence of malignant oral lesions in the State of Pará, so that prevention measures could be intensified in these micro-regions. The biopsies performed, after training, by all the general dentists should be sent to the Diagnostic Service in Oral Pathology HUJBB, where the histopathological diagnosis should be made. Only where surgical access to perform the biopsy is difficult, or the patient presents with debilitating illness, or for any other reason conditions are not ideal for the biopsy to be

performed, patients are referred directly to the Diagnostic Service in Oral Pathology at HUJBB.

Registry selection

The study was conducted from January 2007 to December 2019. The cases of OL and OSCC located on the tongue or floor of the mouth were evaluated and compared in two periods: before the project implementation (from 2007 to 2012) and after its implementation (from 2013 to 2019). Subjects with histologically confirmed OL and OSCC were retrieved from HUJBB medical records. The survival time of each case was determined by the time difference between the date of diagnosis and the date of death, the date of last follow-up, or the closing date of follow-up (60 months).

Inclusion criteria were primary OL and OSCC in the tongue or floor of the mouth, presenting complete medical records with confirmed histopathological diagnoses. Cases in which it was not possible to confirm the final diagnosis and those in which it was not possible to evaluate the registry files were considered as exclusion criteria. Patients who died of other causes and patients with no segment were also excluded from the study. We assumed that a patient was lost to follow-up when could not be tracked by any source of information in the last 24 months of the study completion.

Histological sections (5 μm) of all samples were stained routinely with haematoxylin and eosin (H&E) and analysed under light microscopy. Two experienced pathologist and expert in the area without prior knowledge of the clinical data assessed the stained sections to confirm the diagnosis and classify the histological grades.

Monitoring strategies for OL

All OLs of the study were localized on the tongue or floor of the mouth due to the increased risk to become a malignant lesion. It was considered patient's sex, age (≤45 and >45 years old), site, smoking and alcoholism habits, clinical subtype (homogeneous and non-homogeneous) and grade of dysplasia (low risk – no epithelial dysplasia or mild dysplasia, and high risk – moderate or severe dysplasia). We classify the malignant transformation risk as being lower or higher risk. The patient with OL considered to have a higher risk of malignant transformation should be reviewed every 3 months, while the patients with lower risk should be followed every 6 months.

Monitoring strategy for OSCC

All cases of OSCC were localized in the floor of the mouth and tongue.

It was considered patient's sex, age (≤45 and >45 years old), site, smoking and alcoholism habits, tumour size (T in situ, T1–2 and T3–4), lymph node metastasis (N0 and N1-2-3), distant metastasis (yes or no), AJCC stage (0, I–II and III–IV), treatment and recurrence. The 2018 American Joint Committee of Cancer (AJCC) Stage System was used to classify the lesions into categories[16,17].

Statistical analysis

The means and percentages are presented as descriptive statistics. Overall survival rates were estimated by a Kaplan–Meier analysis and logrank test was performed to evaluate the significance of survival comparison. A P-value < 0.05 was considered statistically significant. Data was analysed using the Statistical Package for Social Sciences software for Windows, version 23.0 (SPSS Inc, Chicago, Illinois).

RESULTS

Oral leukoplakia pre- and post-project

The summary of clinicopathological factors is evidenced in Table 1.

A total of 14 patients were diagnosed with OL pre-project achievement. Female patients were more affected than males, with a male: female ratio of 1:1.3, and patients older than 45 years old were most affected (10 patients; 71.4%). The tongue was affected in 92.8% of cases (13 patients) and floor of the mouth in 7.2% of cases (one case). Smoking habit was observed in 21.4% (three patients), while alcoholism was observed in none of the patients. Clinically, the lesions were mainly non-homogeneous (13 cases; 92.8%) and high-risk grade of dysplasia (13 cases; 92.8%). Malignant transformation was observed in one patient (7.2%).

Post-project evaluation showed 72 patients affected by OL. Female patients were more affected than male, with a male: female ratio of 1:2.8, and patients older than 45 years old were most commonly seen (50 cases; 69.4%). The tongue was the most commonly affected site (64 patients; 88.9%), followed by floor of the mouth (eight cases; 11.1%). Smoking habit was detected in 16.7% (12 cases) and alcoholism in 20.8% (15 cases). Clinical subtype analysis evidenced that non-homogeneous lesions (65 cases; 90.3%) and low-risk grade of

dysplasia (47 cases; 65.3%) were most commonly seen. Malignant transformation was observed in six patients (8.3%).

OSCC pre- and post-project

Clinicopathological factors are summarized in Table 2.

A total of 149 patients were diagnosed with OSCC pre-project achievement. Male patients were significantly more affected than women, with a male: female ratio of 2.8:1, and patients older than 45 years old were most affected (128 patients; 85.9%). Smoking habit was observed in 65.8% (98 patients) and alcoholism in 47.7% (71 patients) of the studied cases. Tongue lesions were presented in 63.8% (95 cases) and floor of the mouth in 36.2% (54 cases) of patients. Tumour size T3–4 was significantly increased and was observed in 106 patients (71.1%), followed by T1–2, which was seen in 43 patients (28.9%). Lymph node metastasis N-1-2-3 was evidenced in 80 patients (53.7%), while no lymph node metastasis was observed in 69 patients (46.3%). Distant metastasis was diagnosed in two patients (1.4%). Advanced disease stage III–IV (Figure 2A/B) was recognized in 123 cases (82.6%), while disease stage I–II was seen in 26 cases (17.4%). Patients were treated with radical surgery in 26 cases (17.5%) and no treatment was employed in 33 cases (22.1%). In addition, recurrence was detected in 11 patients (7.4%).

Post-project analysis evidenced 125 patients affected by OSCC. Regarding sex, male patients were more affected than female, with a male: female ratio of 2.2:1, and patients older than 45 years old were most affected (113 patients; 90.4%). Smoking habit was observed in 64% (80 patients) and alcoholism in 50.4% (63 patients) of the studied patients. Tongue lesions were mostly presented in 71.2% (89 cases) and floor of the mouth in 28.8% (36 cases) of patients. Tumour size T3–4 represented 56.8% (71 patients) and T1–2 were seen in 39.2% (49 patients) of samples. Lymph node metastasis N1-2-3 was observed in 41 cases (32.8%), but not in 84 patients (67.2%). Distant metastasis was not presented in any of the analysed patients. Disease stage III–IV was observed in 81 cases (64.8%), disease stage I–II was seen in 39 cases (31.2%) and *in situ* OSCC (Figure 2C/D) was shown in five cases (4%). Patients were treated with radical surgery in 19 cases (15.2%) and no treatment was employed in 31 cases (24.8%). Recurrence was observed in four patients (3.2%).

Survival analysis of OSCC pre- and post-project

The general overall survival evidenced that the post-project curve showed a higher survival index, which demonstrates a better patients' prognosis after the project (p-value: < 0.0001). The 5-year survival rate in the post-project period was 38.4%, in contrast to a rate of only 14.8% in the previous period (Figure 3).

DISCUSSION

In Brazil, the public health system is free of charge and available to all citizens; it is considered the biggest programme of social inclusion in the world (SUS – Unified Health System). SUS was incorporated into the 1988 Brazilian Constitution based on the principle of equity and universality[18]. Beginning in 2004, the public oral health network of Brazil requires that patients with a suspect oral malignant lesion must be referred by the primary dental care to the Dental Specialty Centres (DSCs), where the final diagnosis is performed, after a biopsy. Subsequently, the patient is referred to a health establishment qualified as a High Complexity Assistance Unit in Oncology (Unacon) or a High Complexity Assistance Centre in Oncology (Cacon). Unacons and Cacons must offer specialized and comprehensive assistance to cancer patients, working on diagnosis, staging and treatment.

It was expected that the implementation of DSCs in Brazil, in 2004, would provide an increased number of oral cancer diagnoses; however, regional disparities had not been taken into account. There are a little over 1000 DSCs in Brazil, but only 36 in Pará State, with 8 localized in the capital, Belém. Add to these conditions two more important factors: first, it is extremely difficult, in many cases, to contact the patient to inform them of the date of their dental appointment in the DSC or in the cancer reference hospital, since a considerable number of patients live in locations that are connected by rivers, without access to a telephone signal or post office. Second, there are currently only 16 active experts in oral medicine in Pará State[19]. This might partly explain the delay in the scheduling of appointments and the more advanced stage of the disease found at diagnosis time. In this sense, the literature supports the view that advance-stage oral cancer is closely related to the chronology of OSCC growth[20].

From the point of the view of public health, the strategies that provide early diagnosis of OSCC are the most important to improve survival and decrease morbidity[21,22]. The difference in the mortality rates of OSCC described in Brazil places emphasis on the need to consider the regional disparities in the evaluation approaches proposed[23]. For example, a great

part of the population of the interior of Pará State shows poor socio-economic conditions, a factor associated with a worse patient survival rate[24,25]. In this context, many inhabitants of the Amazon region, particularly those known as 'river dwellers' or '*caboclos*', live at the margins of an optimal health service. This unfavourable condition is due to the poor health infrastructure and the difficulty in accessing these localities. These shortcomings help to understand why the majority of patients with OSCC were diagnosed in late staging[15].

The main reason for the poor survival rate reported in the Pará State pre-project was the delay in the diagnosis[15]. The diagnostic delay reported was intrinsically attributed to the health professional in cases of misdiagnosis or wrong and late referrals. In a similar fashion, the delay concerning the specialized consultation contributed to delaying the diagnosis, due to the delay in performing the biopsy. The training in oral diagnostics provided to the general dentists of all the RHDs resulted in a significant decrease in misdiagnosis, contributing to a decrease in the gaps in professional training. Likewise, the learning opportunity on biopsy techniques provided conditions whereby the biopsies were performed in the same microregion where the patients lived. Thus, the project pursued the permanent optimization of oral health services in primary- and secondary-health care, which must be accessible to all the population[26]. After the diagnosis of malignant neoplasia, the patient would be referred to a cancer reference hospital for treatment. This decision aimed to facilitate patient access to diagnosis, since the patient can be referred for a biopsy at the same time as the initial consultation.

OPMD have greater potential for malignant transformation than other oral lesions, with the majority of OSCC developing from of OPMD. Another important question encompassed by the project was the monitoring of these disorders, an action that was previously absent. The importance of follow-up visits was emphasized. It is hoped that the introduction of this protocol will help identify higher-risk patients, as well as enabling the detection of early lesions during surveillance. There is a gap in the knowledge surrounding the management of OPMD. Surgical removal does not rule out the risk of malignant transformation because of field cancerization. For this reason, it is vital to have follow-up protocols for these patients.

In relation to the prognostic relevance associated with care delay, we consider two factors: the first is the time that elapses from the first symptoms until the final diagnosis, and the second is related to the onset of treatment. The project intervened in a significant way only

in the delay of performing the diagnosis. Nowadays, significant improvement in the survival rate of patients with OSCC in Pará State is dependent on an improvement in the tertiary health care, with the need to increase the number of specialists to treat the patients and also the number of hospital beds, putting an end to the waiting list for treatment. It is important to emphasize the fact that little over half of patients who develop OSCC survive beyond 5 years, even in countries with adequate health-care systems[21].

Our results pointed to better survival after the project's implementation, a larger number in OL diagnostics and more tumours diagnosed in earlier stages. A wider reflection should be addressed to the oral cancer referral system in the Amazonian region. A well-structured primary- and secondary-care dental team in this region could favour the access of unassisted populations, contributing to a decrease in the mortality associated with OSCC.

We are conscious that the project did not embrace the primary prevention for oral cavity cancers. We believe that changing behaviour or lifestyle, which means efforts to discourage tobacco use and alcohol abuse, is a longer process[27], although necessary. The survival rate found in the pre-project period required changing the paradigm to shorter time intervals and the resources available were scarce. That is why we intervened on secondary prevention: OPMD detection and early diagnosis of OSCC. There is a complex chain of factors that affect the survival rate of oral cancer that need to be evaluated together. A limitation of our analysis is that some variables that interfere with the delayed diagnosis of OSCC were not investigated, such as socio-demographic parameters, patients' educational level and socio-economic[7].

In conclusion, oral cancer remains a health problem in Brazil. Early detection is key to improve survival associated with OSCC. The creation of a public health policy to minimize diagnostic delays of OSCC is a complex issue that needs to consider geographical and cultural aspects to obtain the expected results, which are minimizing the morbidity and improving survival rates. On this point, we are all agreed with Gómez et al.[7] (2010):

> *Strategies to diminish overall diagnostic delay must include political measures that assure a reduction in the time needed to see a healthcare professional, particularly to underserved populations. The design of a simple, clear, fail-safe referral scheme for those suspected with cancer may diminish greatly the length of the diagnosis delay.*

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TABLES

Table 1: Clinicopathological factors of oral leukoplakia pre- and post-project

Table 2: Clinicopathological factors of oral squamous cell carcinoma pre- and post-project

FIGURE LEGENDS

Figure 1: Map evidencing the 13 Regional Health Departments. Public Health Secretariat of the State of Pará (SESPA)

Figure 2: Clinical appearance (A) and microscopic analysis (B) of OSCC in advanced staging in the pre-project period. Clinical appearance (C) and microscopic analysis (D) of in situ carcinoma in the post-project period

Figure 3: General overall survival analysis of OSCC pre and post-project

Table 1: Clinicopathological factors of oral leukoplakia pre and post-project.

	Pre-project (N = 14)		Post-project (N = 72)	
Variables	N	%	N	%
Sex				
Male	6	42.8	19	26.4
Female	8	57.2	53	73.6
Age				
≤ 45	3	21.4	20	27.8
> 45	10	71.4	50	69.4
NR	1	7.2	2	2.8
Site				
Tongue	13	92.8	64	88.9
Floor of the mouth	1	7.2	8	11.1
Smoking				
Yes	3	21.4	12	16.7
No	9	64.2	24	33.3
Unknown	2	14.4	36	50
Alcoholism				
Yes	0	0	15	20.8
No	10	71.4	21	29.2
Unknown	4	28.6	36	50
Clinical subtype				
Homogenous	1	7.2	7	9.7
Non-homogenous	13	92.8	65	90.3
Grade of dysplasia (Binary system)				
Low Risk	1	7.2	47	65.3
High Risk	13	92.8	24	33.3
ISC	0	0	1	1.4
Malignant transformation				
Yes	1	7.2	6	8.3
No	13	92.8	66	91.7

Table 2: Clinicopathological factors of oral squamous cell carcinoma pre and post-project.

	Pre-project (N = 149)		Post-project (N = 125)	
Variables	N	%	N	%
Sex				
Male	110	73.8	87	69.6
Female	39	26.2	38	30.4
Age				
≤ 45	20	13.4	11	8.8
> 45	128	85.9	113	90.4
NR	1	0.7	1	0.8
Site				
Tongue	95	63.8	89	71.2
Floor of the mouth	54	36.2	36	28.8
Smoking				
Yes	98	65.8	80	64
No	16	10.7	44	35.2
Unknown	35	23.5	1	0.8
Alcoholism				
Yes	71	47.7	63	50.4
No	41	27.5	59	47.2
Unknown	37	24.8	3	2.4
T-stage				
Tis	0	0	5	4
T1-2	43	28.9	49	39.2
T3-4	106	71.1	71	56.8
N-stage				
N0	69	46.3	84	67.2
N1-2-3	80	53.7	41	32.8
M-stage				
Yes	2	1.4	0	0
No	147	98.6	125	100
AJCC-stage				
0	0	0	5	4
I-II	26	17.4	39	31.2
III-IV	123	82.6	81	64.8
Treatment				
Surgery alone	26	17.5	19	15.2
Others	90	60.4	75	60
None	33	22.1	31	24.8
Recurrence				
Yes	11	7.4	4	3.2
No	90	60.4	89	71.2
Unknown	48	32.2	32	25.6

Figure 1: Map evidencing the 13 Regional Health Departments. Public Health Secretariat of the State of Pará (SESPA)

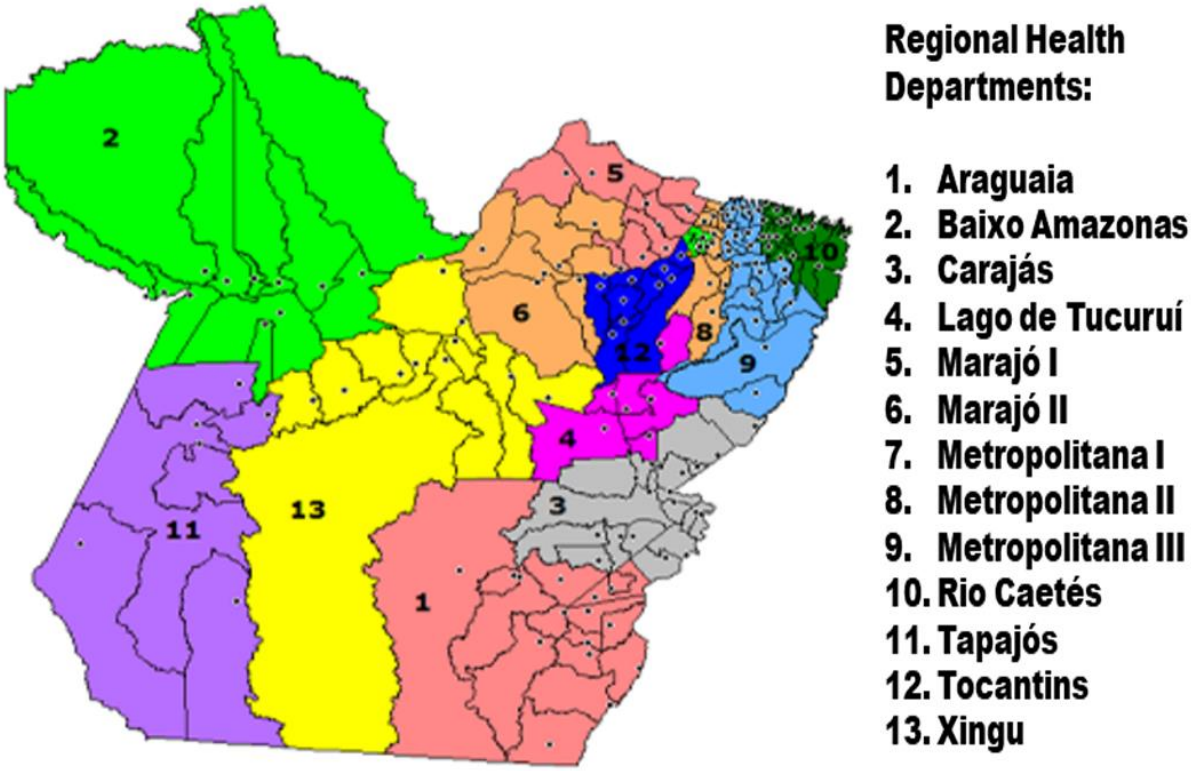


Figure 2: Clinical appearance (A) and microscopic analysis (B) of OSCC in advanced staging in the pre-project period. Clinical appearance (C) and microscopic analysis (D) of in situ carcinoma in the post-project period

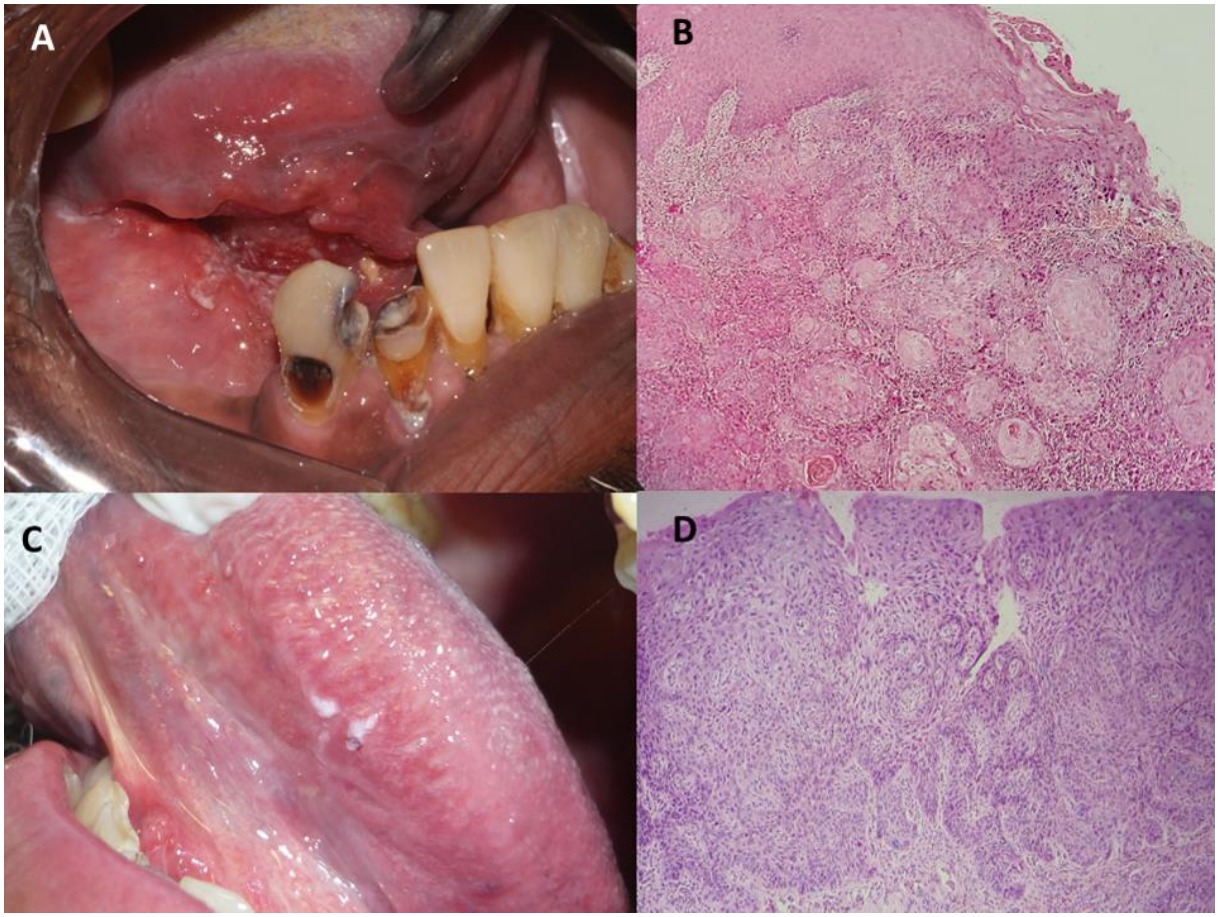
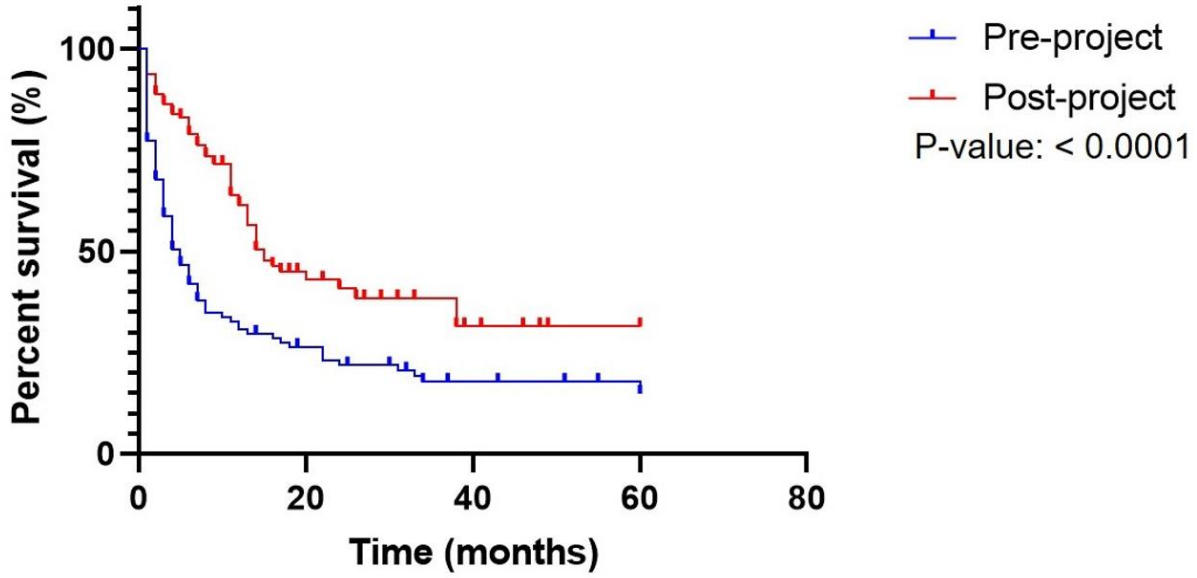


Figure 3: General overall survival analysis of OSCC pre and post-project



3 CONCLUSÃO

Houve melhora na sobrevida dos pacientes afetados por CEB no período pós-projeto.

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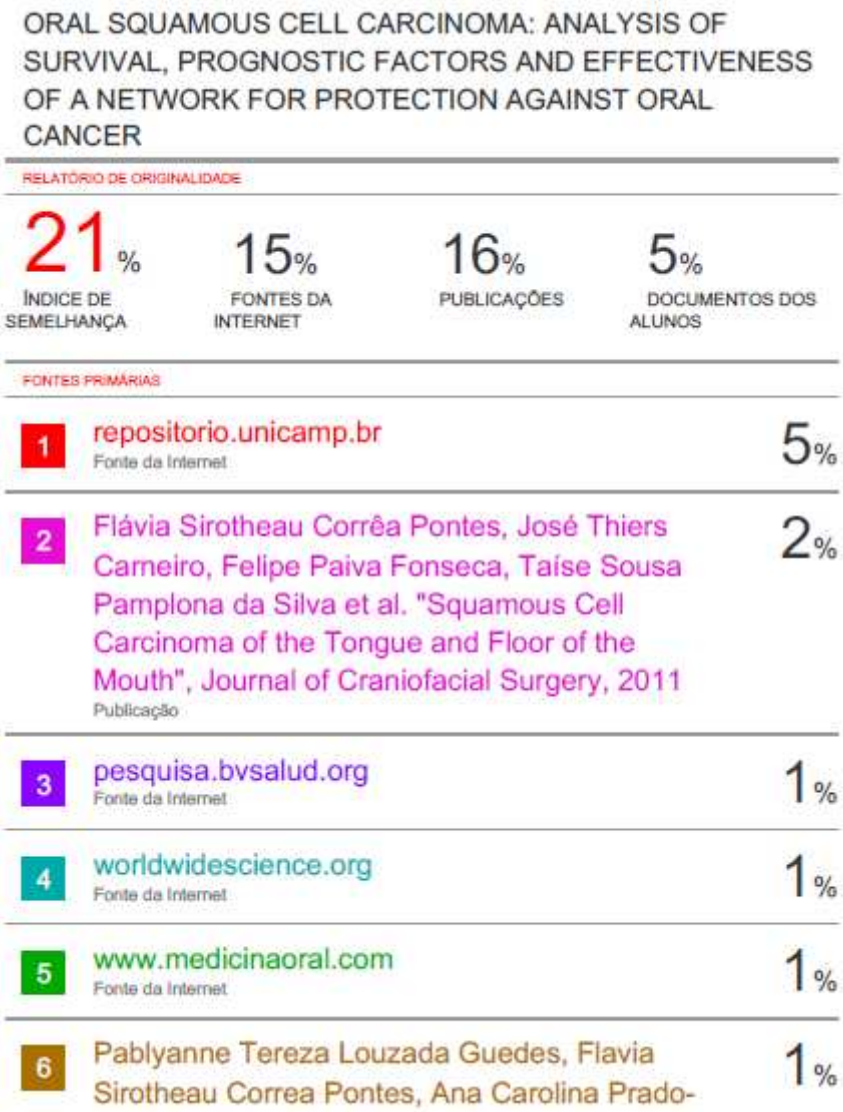
ANEXOS

Anexo 1 – Relatório de verificação de originalidade e prevenção de plágio



ORAL SQUAMOUS CELL CARCINOMA: ANALYSIS OF SURVIVAL, PROGNOSTIC FACTORS AND EFFECTIVENESS OF A NETWORK FOR PROTECTION AGAINST ORAL CANCER

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Anexo 2 – Certificado do Comité de Ética em Pesquisa

UFPA - HOSPITAL UNIVERSITÁRIO JOÃO DE BARROS BARRETO DA UNIVERSIDADE FEDERAL DO PARÁ

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: CARCINOMA EPIDERMÓIDE EM LÍNGUA E SOALHO DE BOCA: AVALIAÇÃO DOS FATORES INFLUENCIADORES DA SOBREVIDA NO ESTADO DO PARÁ

Pesquisador: HÉLDER ANTÔNIO REBELO PONTES

Área Temática:

Versão: 2

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Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.238.444

Anexo 3 - Certificado de submissão ao periódico

Submission Confirmation

Print

Thank you for your submission

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Title
PUBLIC POLICY FOR ORAL CANCER: A SUCCESSFUL STRATEGY IN A STATE OF BRAZILIAN AMAZON REGION

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