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JOAB CABRAL RAMOS

PERFIL EPIDEMIOLÓGICO E IMPLICAÇÕES CLÍNICAS DO CARCINOMA ESPINOCELULAR ORAL ADJACENTE AOS IMPLANTES DENTÁRIOS

EPIDEMIOLOGICAL PROFILE AND CLINICAL IMPLICATIONS OF ORAL SQUAMOUS CELL CARCINOMA ADJACENT TO DENTAL IMPLANTS

PIRACICABA

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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.

Dissertation presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of the requeriments for the degree of Master in Oral Medicine and Oral Pathology, in Pathology area.

Orientador: Prof. Dr. Márcio Ajudarte Lopes

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RESUMO

Os implantes dentários (ID) tiveram grande avanço nas últimas décadas e promoveram grande impacto clínico à reabilitação oral. No entanto, apesar dos benefícios, algumas alterações relacionadas ao ID podem ocorrer como doenças inflamatórias, incluindo mucosite peri-implantar (MPI) e peri-implantite (PI). Tem sido também observados casos de carcinoma espinocelular (CEC) adjacente aos ID. Compreender o perfil clínico e epidemiológico dos pacientes com CEC adjacente aos ID é importante para o manejo clínico adequado. Assim, inicialmente realizamos uma revisão sistemática (RS) da literatura, a fim de avaliar o perfil epidemiológico e clínico desses pacientes. Após um processo de seleção, 33 artigos atenderam aos critérios de elegibilidade. No total, 63 pacientes foram incluídos e as mulheres foram maioria (55,5%). A idade média dos pacientes foi de 66,7 anos. Desordens orais potencialmente malignas (DOPM) foram relatadas em 46% dos pacientes. A DOPM mais comum encontrada nas mulheres foi o líquen plano oral (LPO) (52,6%). A PI foi o diagnóstico clínico inicial em 25,3% dos casos. O segundo estudo analisou retrospectivamente pacientes tratados com CEC adjacente ao ID no AC Camargo Cancer Center entre 2009 e 2020. Trinta e um pacientes preencheram os critérios de elegibilidade e foram incluídos nesta análise. Mulheres foram as mais frequentes (58,1%), a idade média dos pacientes foi de 68,8 anos e 46,9% e 54,9% eram não tabagistas e não etilistas, respectivamente. DOPM foi relatada em 45,2% dos pacientes, afetando principalmente mulheres (78,5%). Leucoplasia (63,7%) seguida de LPO (36,3%) foram as DOPM mais comuns encontradas em mulheres. PI foi o diagnóstico clínico inicial em 16,1% dos CEC adjacentes ao ID. O terceiro estudo foi um relato de uma série de treze pacientes diagnosticados com CEC em torno de ID, 10 mulheres e 3 homens. Em apenas 3 pacientes foi considerada inicialmente a possibilidade de ser uma lesão maligna ou pré-maligna. PI foi o diagnóstico preliminar mais comum, seguido por infecções fúngicas, infecções virais e úlceras traumáticas. O quarto e último capítulo, trata-se de uma carta ao editor alertando sobre dificuldade na diferenciação do LPO da leucoplasia verrucosa proliferativa em fases iniciais em pacientes com CEC adjacente ao ID. De um modo geral, a maioria dos pacientes com CEC adjacente ao ID são mulheres que não tem hábitos de tabagismo e / ou etilismo. É importante enfatizar que esses CECs podem ter características clínicas e radiográficas semelhantes as lesões inflamatórias principalmente MPI e PI, podendo atrasar o diagnóstico e comprometer o prognóstico.

Palavras-chave: Carcinoma de Células Escamosas Oral.Neoplasias Bucais. Implante Dentário. Diagnóstico. Peri-implantite.

ABSTRACT

Dental implants (DI) have made great progress in recent decades and promoted a clinical impact on oral rehabilitation. However, despite the benefits, some changes related to DI can occur such as inflammatory diseases, including peri-implant mucositis (PIM) and peri-implantitis (PI). Cases of squamous cell carcinoma (SCC) adjacent to DIs have also been observed. Understanding the epidemiological and clinical profile of these patients with OSCC adjacent to DI is important for adequate clinical management. Thus, we initially performed a systematic review of the literature in order to assess the epidemiological and clinical profile of patients. After a selection process, 33 articles met the eligibility criteria. In total, 63 patients were included, and women were the majority of cases (55.5%). The mean age of the patients was 66.7 years. Oral potentially malignant disorders (OPMD) were reported in 46% of patients. The most common OPMD found in women was oral lichen planus (OLP) (52.6%). Peri-implantitis was the initial clinical diagnosis in 25.3% of cases. The second study retrospectively analyzed patients treated with OSCC adjacent to the DI at A.C. Camargo Cancer Center between 2009 and 2020. Thirty-one patients met the eligibility criteria and were included for this analysis. Women were the most prevalent (58.1%), the mean age of patients overall was 68.8 years, and 46.9% and 54.9% were non-smokers and non-drinkers, respectively. OPMD was reported in 45.2% of the patients, affecting mainly women (78.5%). Leukoplakia (63.7%) followed by OLP (36.3%) were the most common OPMD found in women. Peri-implantitis was the initial clinical diagnosis in 16.1% of OSCC adjacent to DI. The third study was a report of a series of thirteen patients diagnosed with OSCC around DI, 10 women and 3 men. In only 3 patients, the possibility of being a malignant or premalignant lesion was initially considered. PI was the most common preliminary diagnosis, followed by fungal infection, viral infections and traumatic ulcers. The fourth and last chapter is a letter to the editor warning about a difficulty in differentiating OLP and proliferative verrucous leukoplakia in early stages in patients with SCC adjacent to DI. In general, the majority of patients with SCC adjacent to ID are women who do not have smoking and / or alcohol habits. It is important to emphasize that these SCCs may have clinical and radiographic characteristics similar to inflammatory lesions, mainly PIM and PI, and may delay the diagnosis and compromise the prognosis.

Key Words: Oral Squamous Cell Carcinoma. Mouth Neoplasms. Dental Implant. Diagnosis. Peri-Implantitis.

SUMÁRIO

1 INTRODUÇÃO

Segundo estimativas da Organização Mundial da Saúde (OMS) em 2015, o câncer foi a primeira ou segunda causa de morte antes dos 70 anos em 91 países, e ocupa o terceiro ou quarto lugar em outros 22 países. O câncer da cavidade oral (CCO) é um dos dez mais prevalentes em vários países do mundo com uma incidência de 354.864 novos casos e 177.384 mortes anuais em todo o mundo (Bray et al., 2018). O carcinoma espinocelular (CEC), também conhecido como carcinoma de células escamosas ou carcinoma epidermóide, representa a maioria dos subtipos histológicos e apresenta um prognóstico ruim, com uma taxa de sobrevida de aproximadamente 50% em 5 anos (Siegel et al., 2014; Gupta et al., 2016). Esse tipo de neoplasia é mais prevalente em países de baixa e média rendas e tem maior incidência em homens acima de 50 anos (Siegel et al., 2014; Gupta et al., 2016; Bray et al., 2018).

As variações na incidência ocorrem de acordo com características socioeconômicas e culturais, diferenças nos dados coletados, hábitos de risco, diferenças geográficas, e no nível de desenvolvimento do serviço de saúde (Antunes et al., 2001; Nogueira et al., 2009; Wünsch-Filho, 2009; Souza et al., 2011). No continente Europeu, a mortalidade por CCO vêm diminuindo desde a década de 1970 (Garavello et al., 2010), enquanto na Oceania (Ariyawardana e Johnson, 2013) e em diversos países da América Latina, as taxas de mortalidade vêm aumentando desde a década de 1980, sendo o Brasil o país com a maior mortalidade nessa região (Wünsch-Filho, 2002; Boing et al., 2006; Bray et al., 2018).

No Brasil o CCO vem ocupando papel cada vez mais importante no cenário da saúde pública, segundo o Instituto Nacional de Câncer (INCA), do Ministério da Saúde. Estima-se que, para cada ano do triênio 2020-2022, serão registrados 15.210 novos casos, sendo o quinto mais frequente no sexo masculino e o décimo terceiro no sexo feminino. Esses valores correspondem a um risco estimado de 10.69 casos novos a cada 100 mil homens e 3.71 para cada 100 mil mulheres. Em algumas regiões do país, os índices são alarmantes, como no Sul e Sudeste, com as estimativas das taxas brutas de incidência por 100.000 habitantes atingindo 13.32% e 13.58%, respectivamente (INCA, 2019).

No Brasil, a realidade socioeconômica interfere no quadro da doença, dada a maior incidência em pessoas carentes de baixa renda, desprovidas de recursos e também de informações (Matos e Araujo, 2003). Uma população que não tem hábitos de cuidados gerais e bom nível sócio-econômico-cultural, tende a não perceber as manifestações iniciais do CCO e terá maiores dificuldades para acessar, serviços de saúde (Matos e Araujo, 2003).

Consequentemente, o diagnóstico será tardio impactando na sobrevida e qualidade de vida destas pessoas (Matos e Araujo, 2003).

Tabaco e álcool são considerados os principais fatores de risco para o CEC e têm efeito sinérgico na carcinogênese. A grande maioria dos pacientes com câncer de boca (cerca de 90%) apresenta estes fatores de risco (Petersen, 2009; Bray et al., 2018; Jiang et al., 2019). Em países desenvolvidos, parece que a associação de CEC com consumo de tabaco e bebidas alcoólicas é maior, visto que aproximadamente 75% dos pacientes com CEC têm estes hábitos (Tuyns et al., 1988). Outros fatores também estão relacionados ao maior risco de desenvolvimento de câncer bucal como, o hábito de mascar betel quit, que é mais observado em países asiáticos, principalmente na Índia. Outros determinantes estão ligados a deficiências na ingestão alimentar, por exemplo, frutas e vegetais e consumo de alimentos ricos em nitrosaminas, incluindo peixes salgados (Freedman et al., 2008; IARC 2009; Petti, 2009).

No Reino Unido, Llewellyn et al. (2004), indicaram que muitos pacientes jovens são fumantes e etilistas pesados e, embora o tempo de exposição ainda pareça curto, alguns tiveram mais de 20 anos de tabagismo aos 40 anos de idade. Parece que muitos na faixa etária de 40 a 45 anos têm exposição tradicional a fatores de risco e representam a extremidade final do grupo de pacientes mais comum, enquanto pacientes <40 têm maior probabilidade de não serem fumantes. Nos últimos anos, observa-se um aumento da incidência de CEC de língua em jovens com idades entre 18 – 44 anos, sendo a maior prevalência em mulheres (Kruse et al., 2010). Shiboski et al. (2005), observaram que o carcinoma de língua e base da língua aumentava em mulheres brancas e jovens de 1973 a 2001 nos EUA, e um estudo escandinavo observou um aumento de 5-6x no carcinoma da língua nos menores de 40 anos, em comparação com um aumento de 2x nos pacientes com mais de 40 anos (O'Regan et al., 2006).

Importante enfatizar que vários dos pacientes jovens (abaixo de 40 anos) e mulheres idosas que desenvolveram câncer de boca não apresentam fatores de risco tradicionais como consumo de tabaco e bebidas alcoólicas (O'Regan et al., 2006; Kruse et al., 2010). Sendo assim, alguns outros fatores etiológicos têm sido sugeridos para CEC em pacientes jovens, como predisposição genética, deficiências nutricionais, imunossupressão, infecção por papilomavírus humano de alto risco (Toner e O'Regan, 2009), inflamação crônica (Piemonte et al., 2010) e instabilidade genômica aumentada (Santos-Silva et al., 2011). Foi também sugerido que o contato com materiais odontológicos metálicos como implantes dentários (ID), possam lixiviar íons na saliva e servir como potencial mutagênico no desenvolvimento do CEC (Hafez et al., 2011; Ortiz et al., 2011).

Os ID osseointegrados são atualmente ótima opção para reabilitação de pacientes que perderam dentes. Desempenham um importante papel na odontologia moderna e, particularmente, na reabilitação de idosos desdentados ou na reabilitação de pacientes que foram submetidos à cirurgia para câncer bucal (del Valle et al.,2008; Cuesta-Gil., et al 2009; Javed et al., 2010; Mertens e Steveling, 2011).

As taxas gerais de sucesso na sobrevida dos ID é maior que 90%, a frequência geral de perdas de ID ou complicações graves é baixa (McDermott et al., 2003). No entanto, com o aumento do número total de ID em uso, as potenciais interações entre os ID e o hospedeiro podem alcançar relevância clínica, em particular em conexão com o uso clínico a longo prazo (Moergel et al.,2013). A lixiviação de partículas de titânio (Ti) nos tecidos peri-implantares é bastante comum e pode ocorrer devido a vários fatores, como atrito durante a inserção do implante, corrosão da superfície do implante, atrito na interface implante-pilar, entre outros (Suárez-López et al., 2018). Essas nanopartículas metálicas induzem efeitos inflamatórios devido à sua capacidade imunomoduladora, exercida principalmente em macrófagos, através do aumento de danos ao DNA, estresse oxidativo e carbonilação de proteínas (Lappas, 2015; Noronha et al., 2018). Além disso, os macrófagos são induzidos anormalmente, causando inflamação excessiva e supressão imunológica (Dubey et al., 2015; Huang, 2017). Adicionalmente, as células epiteliais orais podem sofrer danos ao DNA devido a detritos / partículas de Ti, contribuindo para a ruptura da homeostase epitelial e comprometendo potencialmente a barreira epitelial oral (Suárez-López et al., 2017).

A prevalência de CEC adjacente ao ID é de aproximadamente 1,5% (Kaplan et al., 2016). A apresentação clínica dessas lesões nos estágios iniciais pode se assemelhar a uma mucosite peri-implantar (MPI) ou peri-implantite (PI), que são lesões inflamatórias benignas mais comumente encontradas nos pacientes com ID (Bhandari et al., 2016). O CEC adjacente ao ID pode apresentar-se inicialmente como um eritema gengival leve até alterações hiperplásicas granulares e / ou ulceração de tecidos moles, com perda óssea alveolar progressiva (Bhandari et al., 2016). Essas características que se assemelham à lesões inflamatórias benignas dificultam a suspeita clínica inicial (Bhandari et al., 2016).

O prognóstico ruim de pacientes com CEC está diretamente relacionado ao diagnóstico tardio e ao estágio clínico avançado da doença (Forastiere et al., 2001). Infelizmente, nas últimas décadas, não houve melhora nos resultados de sobrevida em pacientes com CEC, enfatizando a necessidade de diagnóstico precoce e melhor compreensão da fisiopatologia dessa doença, a fim de aumentar a sobrevida do paciente, diminuir a morbidade e melhorar a qualidade de vida (Zini et al., 2010).

Portanto, este trabalho teve como objetivo, caracterizar o perfil epidemiológico dos pacientes com CEC em torno de ID, rastreando possíveis fatores de risco envolvidos na carcinogênese, além de avaliar o espectro e as implicações das características clínicas dessa entidade.

2 ARTIGOS

ARTIGO: **Oral Squamous cell carcinoma around dental implants: A systematic review**

CAPÍTULO 1- Artigo submetido ao periódico Critical Reviews in Oncology/Hematology

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ABSTRACT

Objectives: This systematic review aimed to evaluate the epidemiologic profile of oral squamous cell carcinoma (OSCC) around dental implants (DI), and to identify risk factors and possible etiologies related to this disease.

Methods: The systematic review (SR) was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).

Results: After a two-step selection process, 33 articles met the eligibility criteria. In total, the sample consisted of 63 patients, women were the majority of cases (55.5%). The mean age of the patients was 66.7 years. Oral potentially malignant disorders (OPMD) were reported in 46% of patients, of which 65.5% occurred in women. The most common lesion found in women was oral lichen planus (OLP) (52.6%) followed by leukoplakia (31.5%). In 88.8% of OSCC around DI occurred in the mandible, and the most common clinical appearance of the lesions was an exophytic mass (46%). Most of these lesions were initially treated as peri-implantitis. The mean time of installation of DI and the diagnosis of OSCC was 4.5 years.

Conclusions: Most patients with OSCC around to DI were women, non-smokers, non-drinkers and almost half of them had OPMD. It is important to emphasize that these lesions may present clinical and radiographic features that could resemble peri-implantitis, which can lead to delay in the diagnosis and subsequent treatment. OSCC around the DI seems to be into the spectrum of the classic OSCC and should be considered particularly in persistent lesions. Although there is a rationale for DI in the development of the OSCC, this systematic review has failed to prove such a relationship.

Keywords: Dental Implants; Squamous Cell Carcinoma; Delayed diagnosis; Peri-Implantitis, Oral cancer; Systematic Review

INTRODUCTION

Cancer of the oral cavity is one of the most common malignancy among head and neck tumors in the global cancer ranking [1,2]. Oral squamous cell carcinoma (OSCC) represents the majority of histological subtypes and has a poor prognosis [3,4]. This type of cancer is more prevalent in low and middle-income countries and has a higher incidence in men over 50 years of age [1,2,5].

Tobacco and alcohol are considered the main risk factors for oral cancer and have a synergistic effect on carcinogenesis [6,7]. Other etiological factors have also been suggested for the development of OSCC, such as genetic predisposition, nutritional deficiencies, poor oral hygiene, immunosuppression [8], increased genomic instability[9] and chronic inflammation [8,10]. It has also been suggested that contact with metallic dental materials such as dental implants, can leach ions in oral cavity and serve as a mutagenic potential in the development of OSCC [11,12,13]. In recent years, however, there has been an increasing incidence of cancer in young patients with no history of tobacco or alcohol use, mainly in young and white women [8,14,15].

OSCC may be related to a group of potentially malignant conditions may present clinically as leukoplakia or erythroplakia [16,17]. OSSC may also present as mass, granular or verrucous mass, erythema, and/or ulceration of the soft tissues that resemble peri-implantitis (PI) or peri-implant mucositis (PMI) [18].

An increasing number of articles related to OSCC around DI have been published over the years, leaving room for doubt regarding the possible relation of DI and OSCC. Therefore, this systematic review aimed to characterize the epidemiological profile of patients with OSCC around DI, screen for possible risk factors which were involved in carcinogenesis and evaluate the spectrum of clinical characteristics to better understand the misdiagnosis with PI.

METHODS

Protocol and registration

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [19]. The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO).

Study design

This was a SR to characterize the epidemiological profile of patients with OSCC around DI.

Eligibility Criteria

Inclusion criteria

The inclusion criteria for this systematic review were based on the PECOS (population, exposure, comparison, outcome, and study design) approach, which was used to formulate the focused question of the review. It was considered: (P) patients with diagnosis of OSCC around DI; (E) around DI; (C) patients with diagnosis of OSCC without ID; (O) epidemiology and carcinogenesis; (S) case reports, case series and retrospective studies. No language or period restriction was applied.

Exclusion Criteria

Case reports and retrospective studies were excluded in the following circumstances: (1) patients with benign tumors around dental implants, (2) patients with metastasis around implants, (3) malignant neoplasms other than squamous cell carcinoma, (4) squamous cell carcinoma in a patient without dental implant. Reviews, letters to the Editor, personal opinions, book chapters, conferences, abstracts, posters, patents and clinical trials were excluded.

Focused Question

Are patients with OSCC around DI a spectrum of the conventional disease or a distinct clinicopathological entity?

Search Strategy

Studies included in this systematic review were identified using an individual search for each of the following electronic databases: Scopus, PubMed and Embase. An additional gray

literature search was conducted using Google Scholar (**Appendix 1**). The search on database was performed on November 20, 2019. The references cited in the included articles were checked for any potentially relevant studies. An updated search with the same word combinations for each database was performed on March 20, 2020.

All references were managed and duplicates were removed by using Rayyan QCRI (https://rayyan.qcri.org/welcome) [20], a free web, and a mobile app for systematic reviews (Qatar Computing Research Institute, Doha, Qatar).

Study selection

The process of articles selection occurred in two phases. In phase I, titles and abstracts were individually read by two researchers (JCR and ESS). This process was blind and performed using the Rayyan QCRI platform [20]. Articles that did not meet the inclusion criteria were excluded. In phase II, two reviewers (JCR and ESS) read the full text of all screened articles to identify the eligible articles, and all the primary reasons for exclusions were registered for the composition of article selection flow (**Appendix 2**). Disagreements between the two initial evaluators were solved by a third reviewer (AGCN), in order to achieve consensus.

Data extraction

Data were collected independently by two researchers (JCR and ESS) through specific extraction forms, using the Microsoft Office Excel 2016 software (Microsoft Corporation, Redmond, Washington, USA). A third reviewer (AGCN) assessed the accuracy of the information collected. The following information from each study was collected (when available): author, year of publication, country, study design, number of cases, age, gender, risk factors, affected site, the clinical aspect of the lesion, radiographic aspects, the period between implant installation and tumor diagnosis, treatment and follow-up.

Risk of bias

The risk of bias of included studies was evaluated by two reviewers (JCR and ESS) using the Joanna Briggs Institute Critical Appraisal Checklist for Case Reports [21] and Prevalence Studies [22]. Disagreements were resolved by consulting a third author (AGCN).

The risk of bias was categorized as "high" when the study reached up to 49% score "yes"; "moderate" when the study reached 50% to 69% score "yes"; and "low" when the study reached more than 70% score "yes."

Summary Measures

The primary outcome for this systematic review was to characterize the epidemiological profile of patients with OSCC around DI. Secondary outcomes were screening of possible risk factors which may be involved in carcinogenesis of that entity, investigating the spectrum of clinical characteristics and explore the implications resulting from overlapping with PI.

Results

Search and study selection

In phase I, 1,377 articles were found in the 3 databases (PubMed, Scopus and Embase). After duplicate articles were removed, 846 studies remained. A gray literature search was conducted and identified 28 articles, but only 3 articles met the inclusion criteria. Three additional studies were identified using the reference lists, 812 studies were excluded by reading titles and abstracts, thus, a full text review was conducted on the remaining 40 articles retrieved from phase II of study selection. This process led to the exclusion of 7 studies. On search update, 53 new references were found, but only one fulfilled all inclusion criteria. Therefore, 33 studies were included in the qualitative synthesis. A flow diagram of the identification process, inclusion, and exclusion of studies are shown in **Figure 1**.

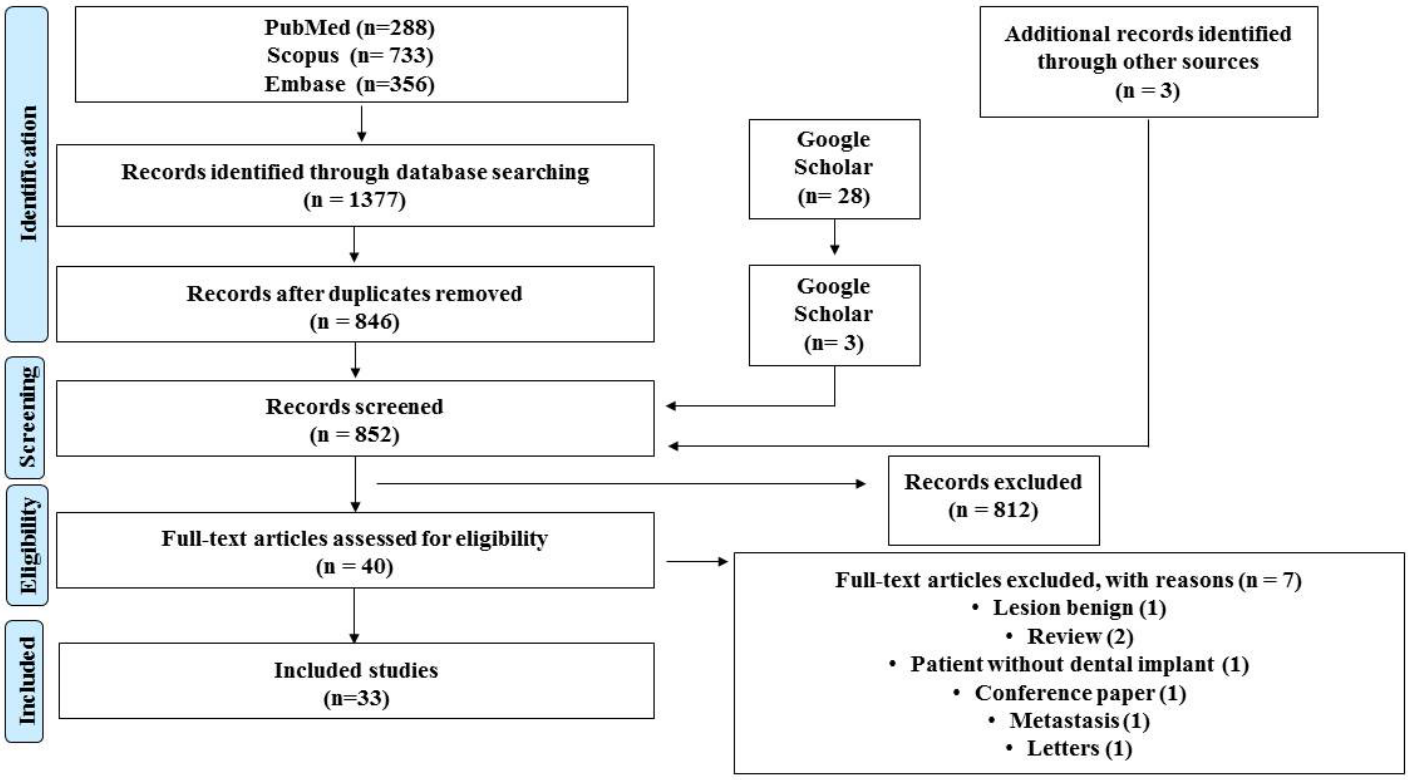

Figure 1. Flow diagram of literature search and selection criteria adapted from PRISMA (Moher et al., 2010).

Study characteristics

Among the 33 included studies, 31 were case report [18,23-52] and 2 retrospective studies [53-54], published between 1983 and 2020 (**Figure 2**). Twenty-three articles presented a single case report [18,23,25,26,30-32,34-40,42-44,46-51], 8 ranged from 2 to 4 cases [24,27-29,33,42,45,52] and 2 retrospective studies presented 5 [54] and 15 [53] cases, respectively. The studies were conducted in twelve countries: United States of America [23-26,39,42,43], Spain [30-32,35,41,48,52], Japan [44,46,47,51], Israel [28,29,45,54], United Kingdom [27,33,34,36], Netherlands [27,33,34,36], Italy [40], France [50], Germany [53], Iran [38], Korea [49] and India [18]. The articles were published in English [18,23-28,30-49,50-54], Spanish [48] and French [29]. The descriptive characteristics of all 33 included studies are summarized in **Table 1**.

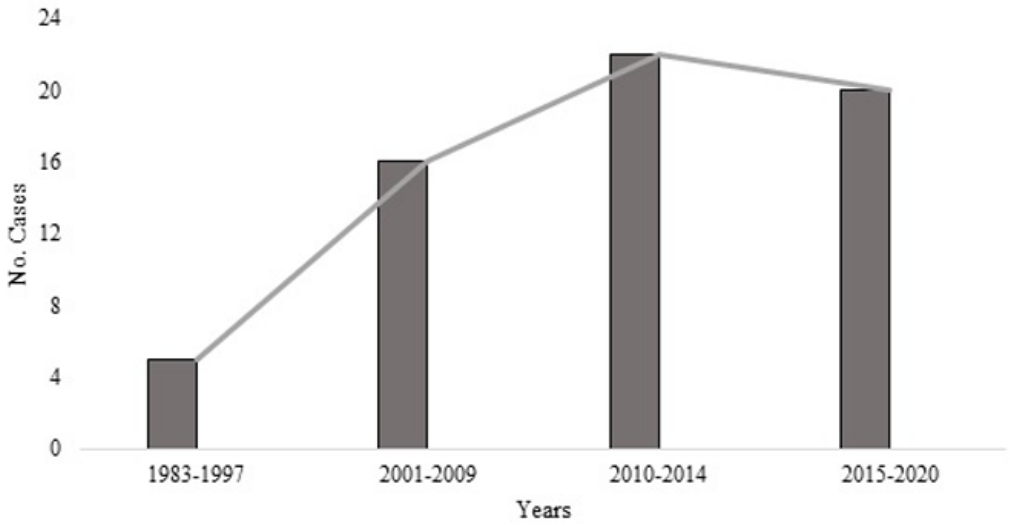

Figure 2. Published articles from cases of OSCC around DI.

Results of individual studies

Sociodemographic data and Risk Behaviors

The total sample was composed of 63 patients, and women were the majority (35 cases, 55%). The age of the patients varied from 42 to 90 years, with an average age of 66.7 years, with men being 1 year older on average (67 vs. 66 years). Thirty-one patients (49.2%) did not have a history of tobacco and alcohol abuse. Ten patients (15.8%) were both smokers and alcohol user and 4 (6.3%) were only smokers. Thirteen patients (20.6%) were former smokers, 6 of them quit smoking <20 years, 2 patients quit smoking ≥20 years and 1 patient the time was not reported. Four patients (6.3%) occasionally consumed alcohol and 12 patients the smoking and alcohol consumption status were unknown.

Clinical Features

OPMD were reported in 29 patients (46%), of which 19 (65.5%) occurred in women (**Figure 3A**). The most common lesion found in women was OLP (10 cases, 52.6%), followed by leukoplakia (6 cases, 31.5%). Among men, OPMD were reported in 10 cases (34.4%) and oral leukoplakia was the most prevalent (6 cases, 60%), followed by OLP (2 cases, 20%) (**Figure 3B**). In 25 patients (39.6%) there was no information about the presence of oral potentially malignant disorders. A previous history of oral cancer was found in 23 patients

(36.5%). In 3 cases (4.7%) were reported a history of cancer in other sites (**Figure 3A)**. The oral hygiene status was reported in 11 cases (17.4%), 5 (45.4%) had poor oral hygiene, 4 (36.3%) had good oral hygiene and 2 (18.1%) had moderate oral hygiene. Fifty-six cases (88.8%) of OSCC around DI were located in the mandibula,7 (7.9%) in the maxilla and only 2 (3.1%) on the lateral border of the tongue in contact with implants installed in the mandible. The most common clinical presentation of OSCC around the implants was an exophytic mass in 29 cases (46%), followed by ulceration (23 cases, 36.5%). There was no report of the clinical aspect of the lesion in 3 patients (4.7%). In 51 patients (80.9%) there was evaluation for peri-implant bone loss through imaging exam and/or clinical probing, of which 44 (86.2%) had a peri-implant bone loss.

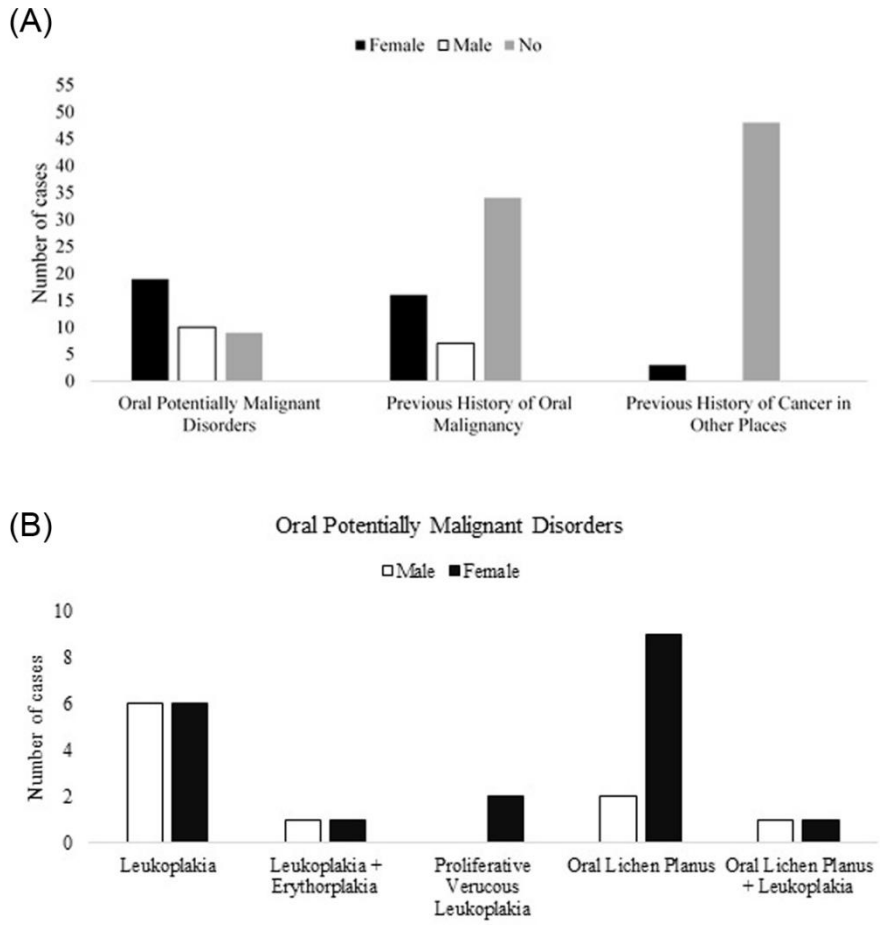

Figure 3. Clinical Features (A) previous history OPMD and malignancy (B) OPMD.

Diagnosis and Outcome

The interval between the installation of DI and diagnosis of OSCC was reported in 49 cases (77.7%) and ranged from 5 months to 15 years, with an average of 4.5 years, (man 4.6 vs. female 4.4 years) (**Figure 4A**). The time of evolution of the lesion observed by the patient or the professional was reported in 17 patients (26.9%), varied from 1 to 12 months, an average of 5.9 months (**Figure 4B**). Men were diagnosed on average 1.9 months earlier than women. PI was the main clinical hypothesis of diagnosis and was reported in 16 patients (25.3%). However, in 27 patients (42.8%) the initial clinical hypothesis of diagnosis was not reported.

In 32 patients (50.7%), exclusive surgery was the main therapeutic option, followed by surgery + radiotherapy (7 patients, 11.1%). Treatment data were not informed in 17 patients (26.9%). Follow-up ranged from 6 to 86 months (average of 24.8 months). The follow-up status was reported in 47 patients (74.6%), and in 37 (78.7%) of them there was no evidence of disease. In 16 patients (25.3%) the follow-up status was not reported.

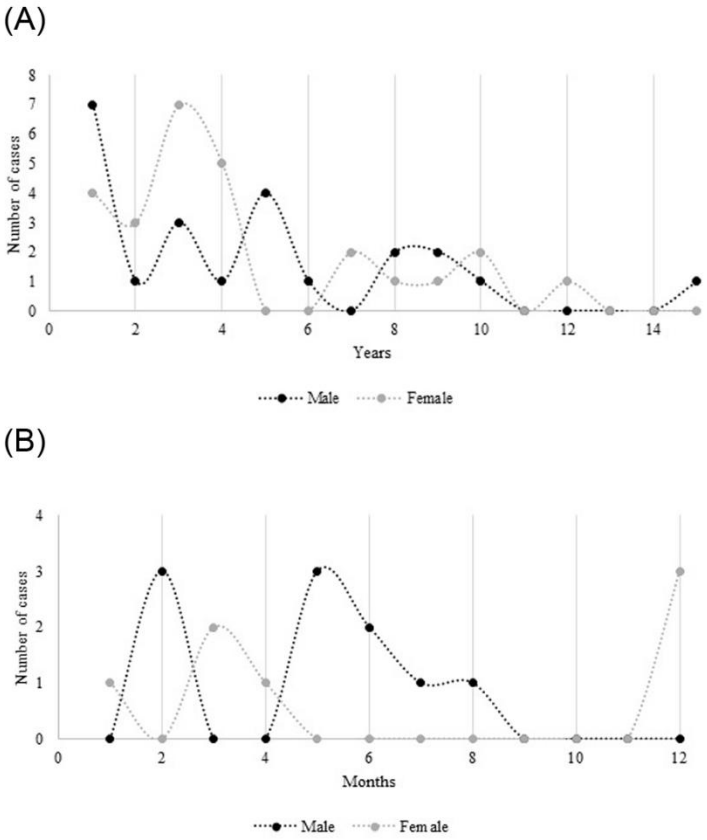

Figure 4. (A) Time until diagnosis after implant installation (B) Time to disease progression.

Risk of bias

The risk of bias was analyzed using two of the JBI's critical appraisal checklist one for Case Reports and the other for Prevalence Studies. In the checklist for case reports, 2 articles had a high risk of bias [27,34], another 7 articles showed a moderate risk of bias [23,24,29,30,39,45,49] and the remaining articles showed a low risk of bias (**Table 2**). Only two studies were analyzed with the tool for prevalence studies and both articles had a moderate risk of bias [27,34] (**Table 3**).

Table 1. Summary of descriptive characteristics of the 33 included studies

Author- Year of Publication- Country- Language	Study Design	Nº of OSCC cases	Gender	Age of cases	Risk factors (tobacco and/or alcohol)	Affected site	Clinical aspect of the lesion	Bone loss	Previous periimplantitis diagnosis	Time until diagnosis after implant installation (years)	Treatment	Follow-up - months (nº patients)
Friedman & Vernon [23] (1983) - USA- English	CR	1	M	65	Yes	Mand	Ulceration	Yes	Yes	0.25	NR	NR
Clapp et al.[24]- (1996) - USA- English	CR	3	M (1) F (2)	79 - 65 - 90	Yes (1) No (2)	Mand (3)	Ulceration (3)	NR (3)	NR (3)	3 - 4 - 7	Surg (2) Surg + Rad (1)	FOD - 6 (1) FOD - 12 (1) Lost - FU (1)
Moxley et al.[25] - (1997) - USA- English	CR	1	F	74	No	Mand	Exophytic mass	Yes	Yes	10	Surg	NR
Block & Scheufler[26]- (2001) - USA- English	CR	1	M	72	Yes	Mand	Gingival hyperplasia	Yes	No	1	Surg	FOD - 18
Shaw et al.[27]– (2004) - United Kingdom- English	CR	2	M-F	67 - 69	NR (2)	Mand (2)	Exophytic mass (2)	Yes (2)	Yes (1) No (1)	NR	Surg (2)	NR
Czerninski et al.[28] (2006) - Israel- English	CR	2	M-F	80 - 52	Yes (1) NR (1)	Mand (2)	Ulceration (2)	Yes (2)	NR (2)	5 - 3	Surg (1) Surg + Chemo (1)	FOD - 18 (1) Died (1)
Abu El-Naaj et al.[29]- (2007) - Israel- French	CR	2	M-F	70 - 72	Yes (1) No (1)	Mand (2)	Ulceration (1) Exophytic mass (1)	Yes (2)	No (2)	15 - 12	Surg (1) Surg + Rad (1)	NR

Chimenos Küstner et al.[30] – (2008)- Spain- English	CR	1	F	62	Yes	Mand	Exophytic mass	Yes	NR	NR	Surg	NR
del Valle et al.[31]- (2008)- Spain- English	CR	1	M	76	No	Mand	Ulcertaion	Yes	Yes	5	Surg	NR
Gallego et al.[32]- (2008)- Spain- English	CR	1	F	81	No	Ma	Exophytic mass	No	No	3	Surg	FOD - 12
Kwok et al.[33]- (2008)- United Kingdom- English	CR	3	M (2) F (1)	62- 71- 67	Yes (3)	Mand (3)	Ulceration (1) Inflammation (1) Granulation tissue (1)	NR (3)	No (2) Yes (1)	0,25 - 6 - 1	Surg (3)	Died (2) FOD - 24 (1)
Schache et al.[34]- (2008)- United Kingdom- English	CR	1	M	77	NR	Mand	Exophytic mass	Yes	No	5	Surg	NR
Gallego et al.- (2009)[35]- Spain- English	CR	1	F	70	No	Mand	Ulceration	NR	No	10	Surg	FOD - 12
Gulati et al.[36]- (2009)- United Kingdom- English	CR	1	F	62	Yes	Mand	Leukoplakia	NR	Yes	8	Surg	Died
Meijer et al.[37]- (2010)- Netherlands- English	CR	1	F	65	NR	Mand	Exophytic mass	No	No	4	Surg	FOD - 36
Moshref et al.[38]- (2011)- Iran- English	CR	1	F	67	No	Mand	Exophytic mass	Yes	Yes	1,3	Surg + Rad + Chemo	NR

Bhatavadekar[39] - (2012)- USA- English	CR	1	M	54	No	Mand	Ulceration	Yes	No	1	Surg	NR
Carini et al.[40]- (2012)- Italy- English	CR	1	F	70	NR	Mand	Ulceration	Yes	No	3	Surg + Rad + Chemo	WD
Jané-Salas et al.[41]- (2012)- Spain- English	CR	2	M (2)	42 - 79	Yes (1) No (1)	Tong (2)	Ulceration (2)	NR (2)	NR (2)	1,4 - 9	Surg (2)	FOD - 6 (1) FOD - 12 (1)
Marini et al.[42]- (2013)- USA- English	CR	1	F	51	No	Mand	Exophytic mass	Yes	Yes	4	Surg	FOD - 60
Moergel et al.[53]- (2013)- Germany- English	RTS	15	M (7) F (8)	66,1*	Yes (6) No (5) NR (4)	Mand (14) Max (1)	Exophytic mass (10) Ulceration (4) Inflammation (1)	Yes (13) No (2)	NR (15)	4,45*	NR (15)	FOD - 80 (5)*
Chainani-Wu et al.[43]- (2015)- USA- English	CR	1	F	60	No	Mand	Normal mucosa	Yes	Yes	4	Surg	FOD - 24
Nariai et al.[44]- (2015)- Japan- English	CR	1	F	58	Yes	Mand	Exophytic mass	Yes	No	3	Surg	FOD - 24
Bhandari et al.[18]- (2016) - India- English	CR	1	F	71	No	Max	Erythematous soft tissue	Yes	Yes	2	Surg	FOD - 11
Kaplan et al.[54]- (2016)- Israel- English	RTS	5	M (2) F (3)	59- 77- 73- 71- 44	No (5)	Mand (3) Max (2)	Ulceratio (1) Exophytic mass (3) NR (1)	Yes (2) No (3)	Yes (1) No (4)	NR (5)	Surg (1) Surg + Rad (2) Surg + Chemo (2)	Died (1) Lost FU (1) FOD - 24 (1) FOD - 18 (1) WD - 12 (1)

Raiser et al.[45]- (2016)- Israel- English	CR	2	F (2)	55 - 70	NR (2)	Mand (2)	Exophytic mass (2)	Yes (2)	No (2)	NR	Surg (1) Surg + Rad (1)	FOD - 86 (1) FOD - 36 (1)
Noguchi et al.[46]- (2017)- Japan- English	CR	1	F	65	No	Mand	Exophytic mass	Yes	Yes	7	Surg	FOD 12
Ito et al.[47]- (2018)- Japan- English	CR	1	M	62	Yes	Max	Ulceration	NR	Yes	5	Surg	FOD 24
Carreira-Nestares et al.[48]- (2018)- Spain- Spanish	CR	1	F	85	Yes	Mand	Ulceration	NR	NR	NR	Surg + Rad + Chemo	NR
Oh et al.[49]- (2018)- Korea- English	CR	1	M	43	No	Mand	Ulceration	Yes	No	1	NR	NR
Malthiéry et al.[50]- (2019)- France- English	CR	1	M	73	No	Mand	Exophytic mass	Yes	Yes	NR	Surg	FOD 48
Noguchi et al.[51]- (2019)- Japan- English	CR	1	F	78	No	Mand	Exophytic mass	Yes	Yes	2	Surg	FOD 48
Granados et al.[52]- (2020)- Spain- English	CR	4	M (3) F (1)	83- 60- 54- 64	Yes (2) No (2)	Mand (4)	Ulceration (1) Verrucous Lesion (1) NR (2)	Yes (4)	Yes (1) NR (3)	8 - 2 - NR (2)	Surg (1) Surg + Rad (2) Surg + Rad + Chemo (1)	Died (1) NR (3)

TOTAL (sum or average)	CR (31) RTS (2)	63	M (28) F (35)	66,7	Yes (20) No (31) NR (12)	Mand(56) Max (5) Tong (2)	Exophytic mass (29) Ulceration (23) Inflammation (2) Verrucous Lesion (1) Leukoplakia (1) Normal Mucosa (1) Gingival Hyperplasia (1) Erythematous soft tissue (1) Granulation tissue (1) NR (3)	Yes (44) No (7) NR (12)	Yes (16) No (20) NR (27)	4,5	Surg (32) Surg + Rad (7) Surg + Rad + Chemo (4) Surg + Chemo (3) NR (17)	FOD - 24.8 months** Died (6) WD (2) Lost Fu (2) NR (16)

CR: Case Report; RTS: Retrospective Study; M: Male; F: Female; OSCC: Oral squamous cell carcinoma; Mand.:Mandible; Max.:Maxilla; Tong : Tongue; FOD: Free of disease; WD: with disease; Lost FU: lost follow-up; Sur: Surgery; Rad: Radiotherapy; Chemo: Chemotherapy; NR: No related. * Average age of the patients, but the individual value was considered when calculating the total average of the studies. ** average not including Moergel et al.[53] since authors did not show precise individual values.

Table 2. Risk of bias was categorized as High (H) when the study reacheds up to 49% score "yes", Moderate (M) when the study reached 50% to 69% score "yes", and Low (L) when the study reached more than 70% score "yes".

Joanna Briggs Institute 2017/ Critical Appraisal Checklist for Case Reports

	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Total
Friedman & Vernon[23]	🟢	🟢	🔴	🟢	🔴	🔴	🟡	🟢	🟢 (57%)
Clapp et al.[24]	🟢	🔴	🔴	🟢	🟢	🟢	🟡	🟢	🟢 (57%)
Moxley et al.[25]	🟢	🟢	🟢	🟢	🟢	🔴	🟡	🟢	🟢 (85%)
Block & Scheufler[26]	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢 (100%)
Shaw et al.[27]	🟢	🔴	🔴	🟢	🟢	🔴	🟡	🔴	🟢 (42%)
Czerninski et al.[28]	🟢	🔴	🟢	🟢	🟢	🟢	🟡	🟢	🟢 (85%)
Abu El-Naaj et al.[29]	🟢	🔴	🔴	🟢	🟢	🔴	🟡	🟢	🟢 (57%)
Chimenos Küstner et al.[30]	🟢	🔴	🔴	🟢	🟢	🔴	🟡	🟢	🟢 (57%)
del Valle et al.[31]	🟢	🟢	🔴	🟢	🟢	🔴	🟡	🟢	🟢 (71%)
Gallego et al.[32]	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢 (100%)
Kwok et al.[33]	🟢	🟢	🔴	🟢	🔴	🟢	🟡	🟢	🟢 (71%)
Schache et al[34]	🟢	🔴	🔴	🟢	🟢	🔴	🟡	🔴	🟢 (42%)
Gallego et al.[35]	🟢	🔴	🟢	🟢	🟢	🟢	🟡	🟢	🟢 (85%)
Gulati et al.[36]	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢 (100%)
Meijer et al.[37]	🔴	🟢	🔴	🟢	🟢	🟢	🟡	🟢	🟢 (71%)
Moshref et al.[38]	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🔴	🟢 (85%)
Bhatavadekar[39]	🟢	🟢	🟢	🟢	🔴	🔴	🟡	🔴	🟢 (57%)
Carini et al.[40]	🔴	🔴	🟢	🟢	🟢	🟢	🟡	🟢	🟢 (71%)
Jané-Salas et al.[41]	🟢	🟢	🔴	🟢	🟢	🟢	🟡	🟢	🟢 (85%)
Marini et al.[42]	🟢	🟢	🟢	🔴	🟢	🟢	🟡	🟢	🟢 (85%)
Chainani-Wu et al.[43]	🟢	🟢	🟢	🔴	🟢	🟢	🟡	🟢	🟢 (100%)
Nariai et al.[44]	🟢	🟢	🟢	🔴	🟢	🟢	🟡	🟢	🟢 (85%)
Bhandari et al.[18]	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢 (100%)
Raiser et al.[45]	🔴	🔴	🔴	🟢	🟢	🟢	🟡	🟢	🟢 (57%)
Noguchi et al.[46]	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢 (100%)
Ito et al.[47]	🟢	🟢	🟢	🟢	🟢	🟢	🟡	🟢	🟢 (100%)
Carreira-Nestares et al.[48]	🟢	🔴	🟢	🟢	🟢	🟢	🟡	🔴	🟢 (71%)
Oh et al.[49]	🟢	🔴	🟢	🟢	🔴	🔴	🟡	🟢	🟢 (57%)
Malthiéry et al.[50]	🟢	🔴	🔴	🟢	🟢	🟢	🟡	🟢	🟢 (71%)
Noguchi et al.[51]	🟢	🔴	🟢	🟢	🟢	🟢	🟡	🟢	🟢 (85%)
Granados et al.[52]	🟢	🔴	🔴	🟢	🟢	🟢	🟡	🟢	🟢 (71%)

Q 1: Were patient's demographic characteristics clearly described?; Q 2: Was the patient's history clearly described and presented as a timeline?; Q 3: Was the current clinical condition of the patient on presentation clearly described?; Q 4: Were diagnostic tests or methods and the results clearly described?; Q 5: Was the intervention(s) or treatment procedure(s) clearly described? Q 6: Was the post-intervention clinical condition clearly described?; Q 7: Were adverse events (harms) or unanticipated events identified and described?; Q 8: Does the case report provide takeaway lessons?. Yes (🟢), No (🔴), Not applicable (🟡).

Table 3. Risk of bias was categorized as High (H) when the study reaches up to 49% score "yes", Moderate (M) when the study reached 50% to 69% score "yes", and Low (L) when the study reached more than 70% score "yes".

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		Moergel et al.[53]	Kaplan et al.[54]
1.	Was the sample frame appropriate to address the target population?	🟢	🟢
2.	Were study participants sampled in an appropriate way?	🟢	🟢
3.	Was the sample size adequate?	🔴	🔴
4.	Were the study subjects and the setting described in detail?	🟢	🟢
5.	Was the data analysis conducted with sufficient coverage of the identified sample?	🟢	🟢
6.	Were valid methods used for the identification of the condition?	🔴	🔴
7.	Was the condition measured in a standard, reliable way for all participants?	🔴	🔴
8.	Was there appropriate statistical analysis?	🟢	🟢
9.	Was the response rate adequate, and if not, was the low response rate managed appropriately?	🟡	🟡
	Total	🟢(62,5%)	🟢(62,5%)

Yes (🟢), No (🔴), Not applicable (🟡).

DISCUSSION

Two literature reviews were previously published about OSCC around DI [55,56]. The first review was published in 2012 [55] with 14 papers and the second in 2016 [56] with 23 papers. Both studies are narrative literature reviews, and since it is not a systematic review, a rigorous search was not applied to the databases, and the PRISMA [19] guidelines were not followed.

OSCC is the most common malignant tumor of the head and neck region [1,2]. It affects mainly men over 50 years of age with a male:female ratio of 2:1. Women are often diagnosed 10 years older than men [1,2,5,57]. However, in this systematic review there was no difference in age between genders and women were the most affected group (55.5%), with a male: female ratio of 1:1,25. Interestingly, the prevalence of oral

rehabilitation using DI is higher among women over 50 years than men at same age [58-62]. In some countries, such as the United States of America, an impressive increase of 728.6% in DI among women from 2000 to 2016 have been reported [58]. Possibly, this may be related to the fact that women are more concerned with oral health and with aesthetic appearance. Consequently, a higher prevalence of OSCC surrounding DI can be expected in this group.

Tobacco and alcohol have been described as the major risk factors for OSCC [63,64]. The risk of developing OSCC increases proportionally with the duration and frequency of cigarette exposure, particularly in individuals with a history of more than 20 packs a year [65,66]. On the other hand, after 20 years of smoking cessation, the risk of OSCC is no longer significantly higher than in non-smokers [67]. Alcohol does not appear to play a direct role in carcinogenesis, but synchronous exposure to tobacco increases the risk of cancer by 5 to 13-fold [65,66]. Interestingly in this systematic review, 49% of the patients had no history of tobacco and alcohol consumption. In addition, 2 patients quit smoking more than 20 years ago and 4 consumed alcohol eventually and therefore were not included in the group with higher risk factors.

Besides tobacco and alcohol, other etiological factors are reported to be possible involved in the carcinogenesis of OSCC, such as chronic inflammation or persistent soft tissue trauma. Although the inflammation process is part of the host's defense to environmental stimuli, it promotes the accumulation of chemokines, cytokines, prostaglandins, and free radicals in the tissue microenvironment. This inflammatory process can lead to the activation of oncogenes and / or inactivation of tumor suppressor genes that regulate cell survival and proliferation [10,68-76]. Inflammatory mediators can cause DNA damage and genetic instability, predisposing the development of neoplasms [10,73,76].

Leaching of Titanium (Ti) particles into peri-implant tissues is quite common and can occur because of several factors, such as friction during implant insertion, corrosion of the implant surface, friction at the implant-abutment interface, among others [77]. These metallic nanoparticles induce inflammatory effects due to their immunomodulatory capacity, exerted mainly on macrophages, through the increase of DNA damage, oxidative stress and protein carbonylation [78,79]. Also, macrophages are abnormally induced, causing excessive inflammation and immune suppression [80,81]. Beyond that, oral epithelial cells can suffer DNA damage due to debris / Ti particles, contributing to

the disruption of epithelial homeostasis and potentially compromising the oral epithelial barrier [82].

Schache et al. [34] suggested that DI can facilitate the spread of malignant cells from OSCC to the bone through the interface of the implant with the mucosa, after microscopic analysis of the specimen. Nariai et al. [44] reported a bone invasion of OSCC at the bone interface around the DI, however, no downward invasion along that interface was observed. Most cases of OSCC invading bone have been reported through the alveolar bone crest and cortical plate in toothless patients [83,84]. On the other hand, the potential route of invasion in dentate patients was reported only in extensive lesions and did not compromise the periodontal membrane [84]. Healthy periodontal tissues can be a natural barrier against tumor progression that slows bone infiltration [31]. In 69.8% of the cases reported in this systematic review, there was evidence of bone loss around DI in several cases. This may suggest that DI and the lesions resulting from it can provide a favorable environment for the rapid bone progression of OSCC that originate in the epithelium of the adjacent mucosa.

Still in the context of chronic inflammation, PMI and PI are considered inflammatory processes that involve the supporting tissues of the dental implant. PMI is considered a reversible inflammatory reaction with a prevalence of up to 80% and is a precursor lesion of peri-implantitis [85]. On the other hand, PI is a chronic inflammation that involves soft and hard tissues with progressive loss of support bone [86-88]. Compared to PMI, PI is less prevalent and may affect approximately 1.1% to 85% of individuals [85,89]. These prevalence variations may be in part due to different diagnostic criteria [88]. In addition, almost half (43.9%) of PI cases occur after 5 years of DI installation [89]. In this review, the average years for the appearance of OSCC around DI was 4.5 years. In 25% of the cases reported in this review, PI was the first clinical hypothesis before the definitive diagnosis of OSCC. The majority of OSCCs around DI presented as an exophytic mass (46%), which is not the classic clinical presentation of oral cavity OSCC. Besides that, clinical features of PMI and PI may vary in individuals, ranging from mild gingival erythema to granular mass or ulceration of the soft tissues around the implants [18].

Other relevant issue is the possible role of chronic inflammation secondary to autoimmune reactions in the process of carcinogenesis in patients without classical risk factors, may explain the development of OSCC surrounding DI. In this systematic review, 65.5% of women had OPMD, being OLP the most common (52.6%). OLP is a chronic

inflammatory disease that affects the oral mucosa with peculiar remissions and recurrences [90-92]. The pathogenesis of OLP is still not completely understood and its potential for malignancy is controversial [93,94]. The malignancy rate of OLP is variable in different studies, ranging from 0.9% [93], 1.09% [94] to 0%-12% [95]. These differences may be due to many studies that did not use a rigorous diagnostic criteria or even did not perform biopsies to confirm the diagnosis, consequently compromising data interpretation [91]. Considering that OLP is a chronic inflammatory autoimmune disease and DI promotes an inflammatory process in adjacent tissues, there may be a synergistic relationship between these factors in the development of OSCC. Another possible relationship to be analyzed is the difficulty in differentiating an initial OLP from a Proliferative verrucous leukoplakia (PVL). The epidemiological, clinical and histopathological characteristics of the initial OLP may overlap with those of PVL, leading to misdiagnosis [96,97]. PVL has high rates of malignant transformation ranging from 33.3% to 100% of cases [99-100] and affects mainly elderly non-drinker and non-smoker women over 60 years of age [101,102]. The delay in the diagnosis of patients with potentially malignant disorders may impact the treatment and outcomes of these individuals.

Jané-Salas et al. [41] reported the presence of OSSC on lateral border of the tongue in contact with mandibular DI in two patients. The first one was a 42-year-old man who quit smoking more than 20 years ago and undergone previous gastroplasty to treat morbid obesity. The other patient was a 79-year-old man with no risk factors and no relevant medical history. In both cases, patients reported frequent trauma due to DI in the areas where the neoplastic lesions appeared, despite the adjustments had been performed. The authors suggested that the nutritional deficiencies secondary to the gastroplasty of the first patient could promote absorption deficiency of vitamins and nutrients which in association with the local inflammation caused by DI may explain the tumor development.

The poor prognosis of OSCC is related to late diagnosis and the advanced clinical stage [103]. In initial and non-metastatic disease, the 5-year survival rate is about 90%, whereas in advanced tumor with metastases do not exceed 36% [4]. Unfortunately, in the last few decades there has been no improvement in survival outcomes in patients with OSCC, emphasizing the need to precocious diagnosis and better understand the pathophysiology of this disease in order to increase patient survival and decrease morbidity [104]. The early diagnosis of OSCC around DI is a challenge because these

lesions in the early stages may resemble the most frequent peri-implant lesions, such as PMI and PI. Patients may also not have the classic risk factors and the lesion may be devalued by the individual or even by the health professional. In addition, these lesions can be hidden by the prosthesis on implant, delaying the diagnosis. It is of utmost importance that, before DI installation, the patient's risk factors be considered, and a cost-benefit assessment be individualized. All patients, particularly those with known risk factors for OSCC, must have a regular check-up with a detailed physical examination of the oral cavity and a biopsy should be performed when a persistent and suspected lesion is observed. In addition, DI supported prostheses must be designed to facilitate removal allowing meticulous clinical inspection of the underlying tissues associated with periodic radiographic monitoring.

CONCLUSIONS

Most patients with OSCC around to DI were women, non-smokers, non-drinkers and almost half of them had OPMD. It is important to emphasize that these lesions may present clinical and radiographic features that could resemble peri-implantitis, which can lead to delay in the diagnosis and subsequent treatment. OSCC around the DI seems to be into the spectrum of the classic OSCC and should be considered particularly in persistent lesions.

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SUPPLEMENTARY MATERIAL

Appendix 1. Search strategies with appropriated key words and MeSH terms.

Database	**Search** (Search date: November 20th, 2019; Updated search: March 20th, 2020)
Pubmed	("Carcinoma, Squamous Cell"[Mesh] OR "Squamous Cell Carcinomas" OR "Squamous Cell Carcinoma" OR "Squamous Carcinoma" OR "Squamous Carcinomas" OR "Epidermoid Carcinoma" OR "Epidermoid Carcinomas" OR "Mouth Neoplasms"[Mesh] OR "Oral Neoplasm" OR "Oral Neoplasms" OR "Cancer of Mouth" OR "Mouth Cancers" OR "Oral Cancer" OR "Oral Cancers" OR "Cancer of the Mouth" OR "Mouth Cancer") AND ("Dental Implants"[Mesh] OR "Dental Implant" OR "Peri-Implantitis"[Mesh] OR "Peri Implantitis" OR "Peri-Implantitides" OR "Periimplantitis" OR "Periimplantitides")
Scopus	TITLE-ABS-KEY (*"Carcinoma, Squamous Cell"* OR *"Squamous Cell Carcinomas"* OR *"Squamous Cell Carcinoma"* OR *"Squamous Carcinoma"* OR *"Squamous Carcinomas"* OR *"Epidermoid Carcinoma"* OR *"Epidermoid Carcinomas"* OR *"Mouth Neoplasms"* OR *"Oral Neoplasm"* OR *"Oral Neoplasms"* OR *"Cancer of Mouth"* OR *"Mouth Cancers"* OR *"Oral Cancer"* OR *"Oral Cancers"* OR *"Cancer of the Mouth"* OR *"Mouth Cancer"*) AND (*"Dental Implants"* OR *"Dental Implant"* OR *"Peri-Implantitis"* OR *"Peri Implantitis"* OR *"Peri-Implantitides"* OR *"Periimplantitis"* OR *"Periimplantitides"*)
Embase	('carcinoma, squamous cell'/exp OR 'carcinoma, squamous cell' OR 'squamous cell carcinomas' OR 'squamous cell carcinoma'/exp OR 'squamous cell carcinoma' OR 'squamous carcinoma'/exp OR 'squamous carcinoma' OR 'squamous carcinomas' OR 'epidermoid carcinoma'/exp OR 'epidermoid carcinoma' OR 'epidermoid carcinomas' OR 'mouth neoplasms'/exp OR 'mouth neoplasms' OR 'oral neoplasm' OR 'oral neoplasms' OR 'cancer of mouth' OR 'mouth cancers' OR 'oral cancer'/exp OR 'oral cancer' OR 'oral cancers' OR 'cancer of the mouth' OR 'mouth cancer'/exp OR 'mouth cancer') AND ('dental implants'/exp OR 'dental implants' OR 'dental implant'/exp OR 'dental implant' OR 'peri-implantitis'/exp OR 'peri-implantitis' OR 'peri implantitis'/exp OR 'peri implantitis' OR 'peri-implantitides' OR 'periimplantitis'/exp OR 'periimplantitis' OR 'periimplantitides')
Google Scholar	"Squamous Cell Carcinomas"OR "Epidermoid Carcinoma" OR "Mouth Neoplasms","Dental Implant" OR ","Peri Implantitis" OR "Peri-Implantitides" OR "Periimplantitis" OR "Periimplantitides"

Appendix 2. Excluded articles and reasons for exclusion (n=7).

Reference	Author/Year	Reasons for exclusion
1	Verhoeven, et al. (2007)	2
2	Agostini, et al (2011)	1
3	Javed et al. (2012)	5
4	Nieto, et al. (2014)	5
5	Salgado-Peralvo (2016)	5
6	Beck-Mannagetta, et al. (2018)	5
7	Bornestein, et al. (2018)	4

1- Patients with benign tumors around dental implants (n=1);
2- Patients with metastasis around implants (n=1);
3- Malignant neoplasms other than squamous cell carcinoma (n=0);
4- Squamous cell carcinoma in a patient without dental implant (n=1);
5- Reviews, letters, conference abstracts, personal opinions, book chapters (n=4).

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ARTIGO: Epidemiological profile and clinical implications of oral squamous cell carcinoma adjacent to dental implants

CAPÍTULO 2- Artigo submetido ao periódico Oral Oncology

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ABSTRACT

Objectives: Describe the epidemiological profile of patients with oral squamous cell carcinoma (OSCC) around dental implants (DI), investigate the spectrum of clinical and pathological characteristics, and discuss the implications of diagnosis delay of these lesions.

Methods: Retrospective analysis of patients treated of OSCC adjacent to DI at A.C. Camargo Cancer Center between 2009 and 2020.

Results: 31 patients were identified, being women the majority (58.1%). The mean age of the patients was 68.8 years. Never smoker corresponds to 46.9% and never alcohol consumer to 54.9% of the sample. OPMD was reported in 45.2% of patients, affecting mainly women (78.5%). Leukoplakia (63.7%) followed by oral lichen planus (36.3%) were the most common OPMD found in women. OSCC adjacent to DI occurred in the inferior gingiva/alveolar mucosa in 48.3% of cases, and ulceration was the most common clinical appearance (87%). Peri-implantitis (PI) was initial clinical diagnosis in 16.1% of cases.

Conclusions: OSCC adjacent to DI were more common in women over 70 years old, non-smokers and non-drinker, and the majority had oral leukoplakia before the diagnosis of OSCC. OSCC may present clinical and radiographic features that resemble PI which can delay the diagnosis and impair the prognosis.

Keywords: Dental Implants; Mouth Neoplasms; Oral Squamous Cell Carcinoma; Diagnosis; Peri-Implantitis.

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INTRODUCTION

Dental implants (DI) gained great popularity in dentistry in recent years as they recover the patient´s masticatory function and aesthetic appearance, improving the quality of life [1]. The overall success of DI survival varies between 70-90% in 5 years, even in high-risk populations [2-4]. However, as a result of the increase in the number of DI installation, interactions between the implants and the host might reach clinical relevance, particularly with long-term use [5-8]. Complications related to DI may occur, such as inflammatory diseases including peri-implant mucositis (PMI) and peri-implantitis (PI) and, consequently, impairing the outcomes [9,10]. Besides, appearence such as squamous cell carcinoma adjacent to DI have also been reported in the last decades [5-8].

Squamous cell carcinoma (SCC) is the most common histological subtype in oral cancer, accounting for about 90% of cases [11,12], affecting mainly men over 50 years old [13,14]. The main risk factors for OSCC are smoking and alcohol consumption, which are associated with the patient's lifestyle [15,16]. The mechanism underlying the occurrence of OSCC adjacent to DI is not yet well established. It has been suggested that metallic nanoparticles could induce inflammatory effects due to their immunomodulatory capacity, causing damage to DNA [17-19]. Leaching of metal ions in the oral cavity can occur due to friction during implant insertion, friction at the implant-abutment interface, corrosion of the implant surface, among others [20].

The prevalence of OSCC adjacent to DI is approximately 1.5% [5]. The clinical presentation of those lesions in the early stages may resemble PMI or PI [21]. Additionally, some patients may not have the classic risk factors, which may result in underdiagnosis of these cases [22,23]. Therefore, the objectives of the present study were to describe the epidemiological profile of patients with OSCC adjacent to DI, investigate the spectrum of clinical and pathological characteristics, and discuss the implications resulting from the delay in the diagnosis of this lesion.

MATERIAL AND METHODS

Patient Population

This retrospective study reviewed the clinical and histopathological data from Department of Head and Neck Surgery and Otorhinolaryngology and from Department of Stomatology of the A.C. Camargo Cancer Center Hospital, São Paulo, Brazil. A total of 970 records of patients with oral squamous cell carcinoma from January 2009 to January 2020 was reviewed. Of those, 31 individuals met the eligibility criteria for the research. The study included fully completed and readable medical records of patients who had OSCC close to or in contact with DI, of any gender, ethnicity and age group who had diagnostic imaging (radiography and / or tomography of the head and neck) prior to surgery. Patients with OSCC in other regions that were not close to or in contact with DI were excluded from the sample, as well as patients who had no available imaging diagnosis.

The demographic variables (age, gender, race and schooling level), risk habits (tobacco and alcohol consumption), clinical features (aspect of the lesion, anatomic site, tumor stage, oral hygiene status, history of potentially malignant disorders and previous history of oral malignancy or malignant tumors in other places), histopathological diagnosis, therapeutic modality (surgery, radiotherapy, and/or chemotherapy), and follow-up status were retrieved from patients' medical charts. The disease was staged according to the American Joint Committee on Cancer (AJCC) (TNM) classification system, 8th edition [24]. Classification of neck lymph nodes was performed according to the neck dissection classification by the American Academy of Otolaryngology Head and Neck Surgery (AA-OHN) [25]. Tumor cell differentiation was determined using the World Health Organization (WHO) classification scheme. The histopathological information of the current study was based on initial surgical pathologic report.

Data collection and statistical analysis

Data were collected using REDCap (Research Electronic Data Capture) software and further analyzed by descriptively and inferentially. A descriptive analysis using absolute frequencies and percentages for categorical variables, and mean, standard deviation (mean ± SD), median and percentiles for numerical variables was performed. Locoregional failure (LRF) was defined as persistence of disease or re-appearance of disease either at the primary site and/or draining regional lymph nodes. Disease free

survival (DFS) was defined as the time from surgery to reappearance of disease at either the primary, regional or distant sites. Overall Survival (OS) was defined as the time from diagnosis to death from any cause. The LRF, DFS and OS were calculated using the product-limit method of Kaplan-Meier. To assess possible associations between qualitative variables, the chi-square test or Fisher's exact test were used, when appropriate. To assess the association between age and qualitative variables, the Mann-Whitney non-parametric test was used. All tests were two-tailed, with a probability value of <0.05 considered statistically significant. All analysis was performed on Statistical Package for Social Sciences (SPSS) version 25.0.

RESULTS

The initial diagnosis of OSCC in areas adjacent to DI was performed by a dental surgeon in 22 (71%) of the cases. The mean time between the installation of the DI and diagnosis of OSCC was 4.7 years, whereas the mean time of evolution of the lesion was about 4.6 months. Women were diagnosed with an mean age of more than 10 years older than men (73.5 vs. 62.3 years) (p= .007). Smoking habit was more common in males 12 (92.3%) than in females 6 (33.3%) (p = 0.004). Former and current smoker patients (58.1%) were younger them those who never smoked (41.9%) mean of 8.6 years (p = .011). Seventeen (54.8%) patients had no history of alcohol consumption, and 15 (88.2%) were women. Personal history of previous oral cancer was present in 5 (16.1%) patients, all of whom were women, and the mean time between the first neoplasia and the OSCC around DI was 3.7 years. Fourteen (45.2%) patients had OPMD, 11 (78.5%) were women, and among them, leukoplakia was the most common lesion (7 cases, 63.7%), followed by oral lichen planus (OLP) (4 cases, 36.3%). The sociodemographic data and risk factors are shown in **Table 1**.

Table 1. Sociodemographic data and Risk Factors

Features	Number of cases n=31 (%)
Age	
Median (interquartile range)	68,8 ± 12.12 (39.9-95.1)
Sex	
Male	13 (41.9)
Female	18 (58.1)
Ethnic background	
Black	1 (3.3)
White	25 (80.6)
Others	5 (16.1)
Educational	
Illiterate	1 (3.2)
Grade school	8 (25.8)
High school	8 (25.8)
College	7 (22.6)
Uninformed	7 (22.6)
Tobacco consumption	
Current smoker	2 (6.5)
Former smoker	16 (51.6)
Never	13 (41.9)
Alcohol consumption	
Social drinking	6 (19.3)
Drinking	6 (19.3)
Never	17 (54.9)
Uninformed	2 (6.4)
Oral hygiene	
Poor	1 (3.2)
Moderate	2 (6.5)
Good	13 (41.9)
Uninformed	15 (48.4)
Previous History of Oral Malignancy	
Yes	5 (16.1)
No	26 (83.9)
Previous History of Cancer in Other sites	
Yes	6 (19.4)
No	25 (80.6)
Previous periimplantitis diagnosis	
Yes	5 (16.1)
Uninformed	26 (83.9)
Oral Potentially Malignant Disorders	
Oral Lichen Planus	4 (13)
Leukoplakia	10 (32.2)
None	14 (45.1)
Uninformed	3 (9.7)

Most common location of the OSCC adjacent to DI in women was the lower gingiva / alveolar mucosa (9 cases, 50%), followed by the upper gingiva / alveolar mucosa (6 cases, 33.3%) and lateral border of the tongue (3 cases, 16.7%). Among men, the most common location was the border of the tongue (7 cases, 53.9%), followed by the lower gingiva / alveolar mucosa (5 cases, 38.5%) and floor of mouth (1case, 7.7%). There is a statistically significant relationship between the location of OSCC and gender ($p = 0.015$). When assessing the location of OSCC in smokers (former and current smoker) and never smokers, no statistically significant association was found ($p = 0.584$). Among 10 patients with OSCC on the lateral border of the tongue, 4 (40%) reported a history of frequent trauma in these areas before diagnosis. Bone loss was present in 22 of the patients (70.9%). There was no statistically significant relationship between TNM clinical stage and smoking status ($p = 0.612$). Eighteen patients (58%) who had OSCC in gingiva/ alveolar mucosa and underwent surgery, bone invasion was identified 5 of them (27.7%). The clinicopathological features are show in **Table 2**.

Table 2. Clinicopathological Features

Features	Number of cases n=31 (%)
Anatomic site	
Floor of mouth	1 (3.2)
Superior gingiva/ alveolar mucosa	6 (19.3)
Inferior gingiva/alveolar mucosa	14 (45.1)
Border of tongue	10 (32.2)
Clinical aspect of the lesion	
Plaque	4 (13)
Ulceration	27 (87)
Clinical T stage	
Tis	1 (3.2)
T1	4 (12.9)
T2	11 (35.5)
T3	3 (9.7)
T4a	10 (32.3)
Uninformed	2 (6.4)
Clinical N stage	
N0	20 (64.5)
N1	7 (22.5)
N2a	2 (6.5)
Uninformed	2 (6.5)
Clinical M stage	
M0	29 (93.5)
Uninformed	2 (6.5)
Clinical Staging	
I	4 (12.9)
II	9 (29)
III	1 (3.2)
IVa	14 (45.2)
IVb	1 (3.2)
Uninformed	2 (6.5)
Histologic differentiation	
G1	11 (35.5)
G2	19 (61.3)
Uninformed	1 (3.2)
Surgical margins	
Negative	27 (87.1)
Positive	2 (6.4)
Uninformed	2 (6.4)

Surgery, alone or combined with other therapies, was the main therapeutic modality, which was performed in 30 patients (96.7%), and the mean time from diagnosis to surgery was 33.5 days. The treatment and toxicities are show in Table 3. Modified neck

dissection was performed in 22 patients (70.9%), being in 15 of them (68.1%) unilateral selective neck dissection from level I to level III. Only 7 of these 22 patients (31.8%) had positive lymph nodes microscopically (**Table 3)**.

Table 3. Treatment and Toxicities

Features	
Therapeutic modality	Number of cases n=31 (%)
Surgery	19 (61.3)
Surgery + radiotherapy	7 (22.6)
Surgery + radiotherapy + chemotherapy	4 (12.9)
Chemotherapy	1 (3.2)
Surgical Treatment	Number of cases n=30 (%)
Marginal mandibulectomy	4 (13.3)
Segmental mandibulectomy	5 (16.7)
Hemimandibulectomy	5 (16.7)
Hemimaxillectomy	4 (13.3)
Hemipelviglossectomy	8 (26.7)
Glossopelvimandibulectomy	3 (10)
Total glossectomy	1 (3.3)
Neck dissection	Number of cases n=22 (%)
SND (I-III)	15 (68.1)
SND (I-IV)	1 (4.5)
bilateral SND (I-IV)	1 (4.5)
Radical neck dissection	5 (22.9)
Radiotherapy techniques	Number of cases n=11 (%)
3D-CRT	2 (18.1)
IMRT	9 (81.9)
Toxicities of radiotherapy	
Oral mucositis	8 (72.7)
Xerostomia	6 (54,5)
Dysgeusia	6 (54.5)
Odynophagia	5 (45.4)
Trismus	3 (27.2)
Osteoradionecrosis	1 (9)
Candidiasis	1 (9)
No	1 (9)
Chemotherapy	Number of cases n=5 (%)
CDDP weekly	4 (80)
CDDP 3-week	1 (20)

SND: selective neck dissections; 3D-CRT: 3-dimensional conformal radiotherapy; IMRT: intensity modulated radiotherapy; CDDP: cisplatin.

Five patients (16.6%) had LRF, being all of them women and 3 (60%) were smokers. Four patients (13.3%) presented distant metastasis at follow-up, being 2 (50%) in the lung and the other 2 (50%) in the axillary lymph nodes. The mean time for LRF was 88.9 months (Figure 1-A). There was a statistical trend for females having a shorter LRF than males (p=0.060) (Figure 1-B). Current and former smokers had shorter LRF (50.7 months) compared to never smokers (96.6 months); however without statistical significant difference (p = 0.499) (Figure 1-C).

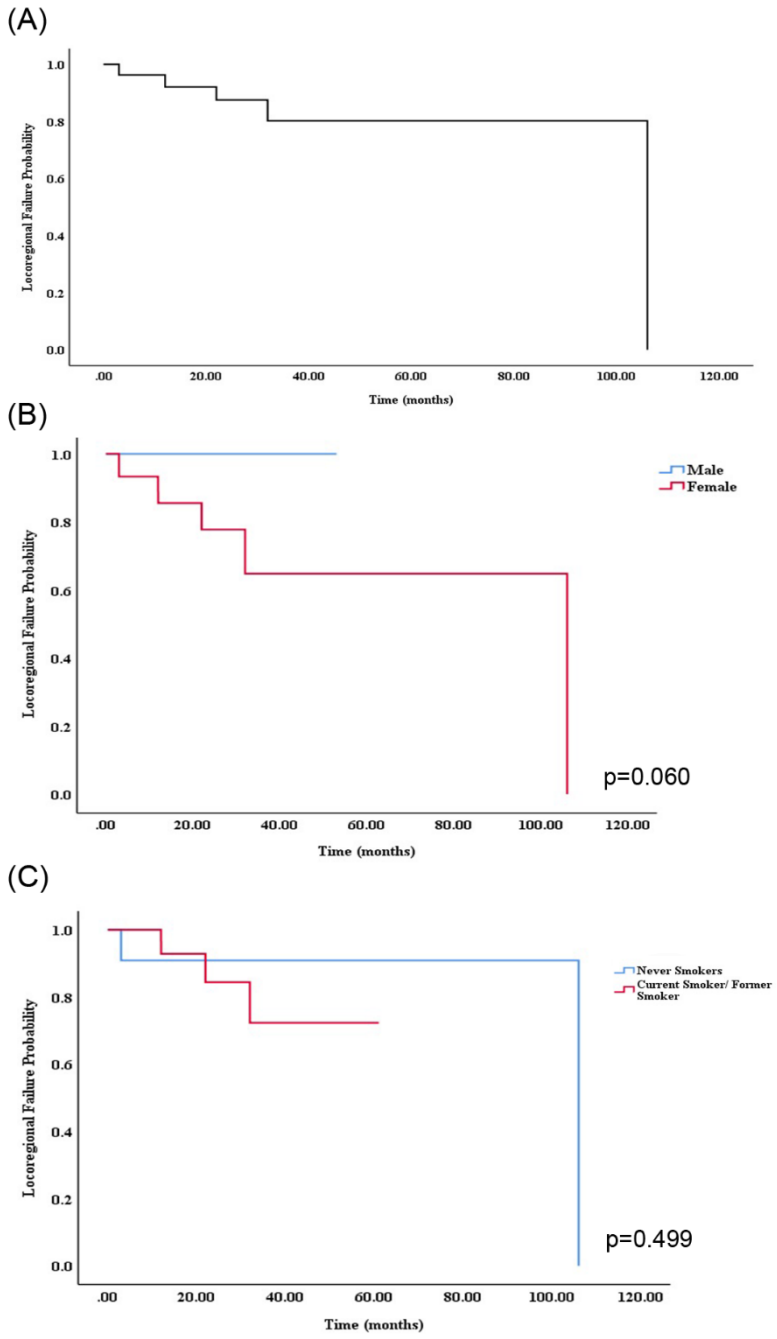

Figure 1. (A) Kaplan-Meier analysis for locoregional failure, (B) comparison of 5-year-for locoregional failure according to sex, (C) comparison of 5-year-for locoregional failure according to smoking status.

As regards to OS, the mean time for the entire group was 103.7 months (Figure 2-A). Females had a similar OS compared to males (p=0.753) (Figure 2-B), as well as current and former smokers to never smokers (p=0.840) (Figure 2-C).

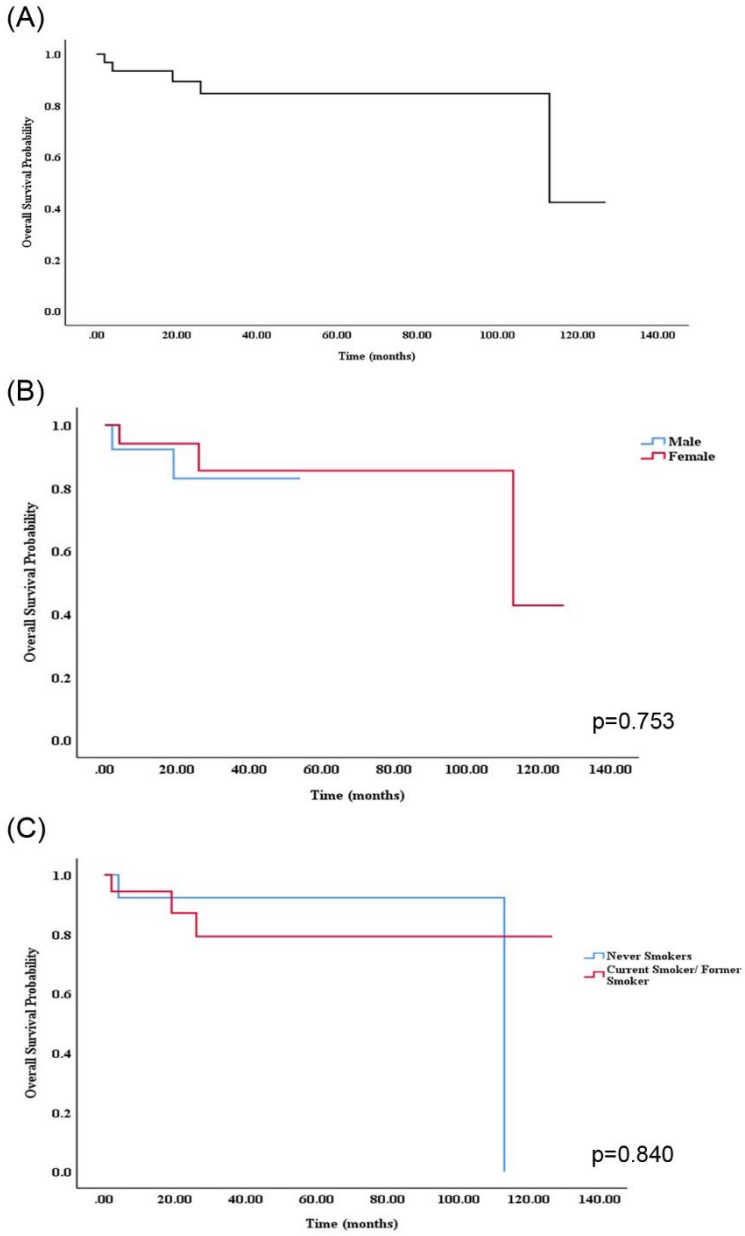

Figure 2. (**A**) Kaplan-Meier analysis for disease overall survival, (**B**) comparison of 5-year- for overall survival according to sex, (**C**) comparison of 5-year-for overall survival according to smoking status.

The mean DSF was 81.6 months (**Figure 3-A**). Females had longer DFS (69.1 months) than males (49.4 months), however without statistical difference (p=0.130) (**Figure 3-B**). Although DFS also was shorter in current smokers and former smokers than never smokers (47.8 vs 86.2 months), the difference was not statistically significant (p=0.660) (**Figure 3-C**).

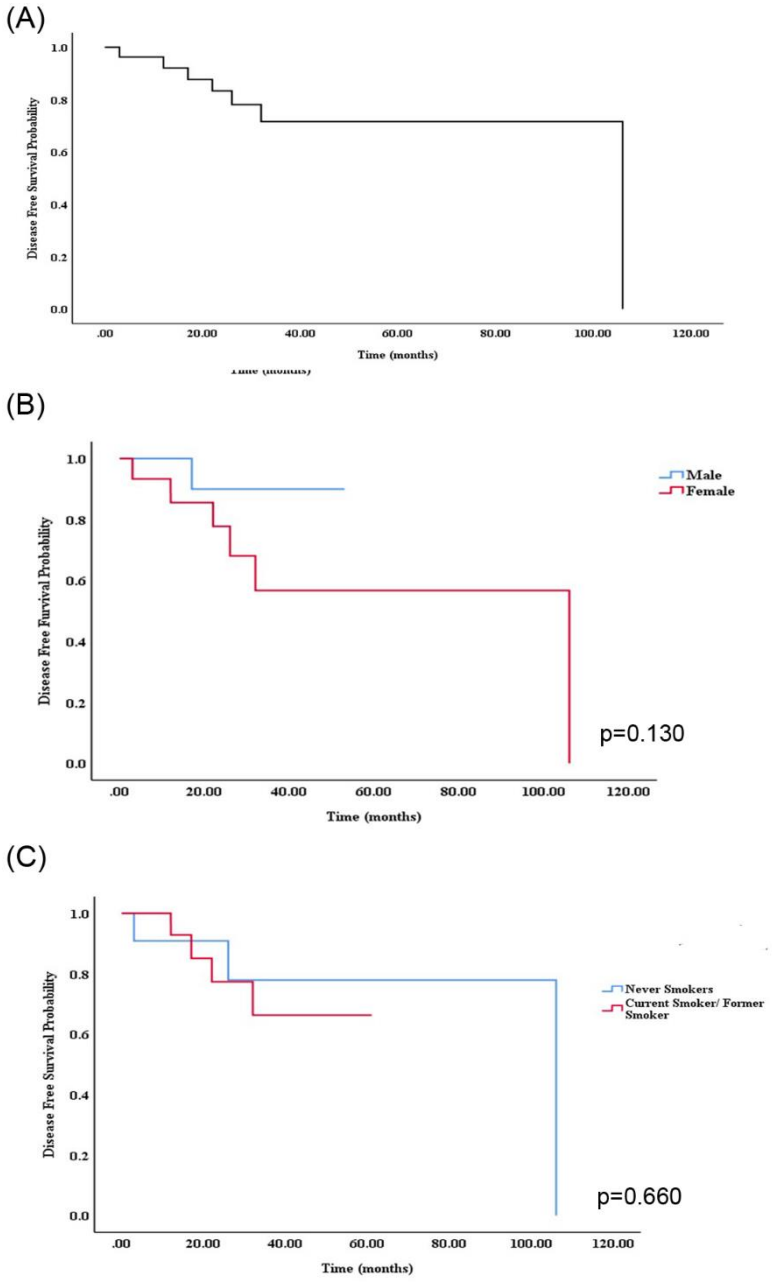

Figure 3. (A) Kaplan-Meier analysis for disease free survival, (**B)** comparison of 5-year- for disease free survival according to sex, (**C**) comparison of 5-year-for disease free survival according to smoking status.

DISCUSSION

OSCC adjacent to DI was first reported in 1983 [26], and since then several other cases have been described in the literature [5-8,19,27-29]. OSCC adjacent to DI is estimated at 0.00017 / million / year in the United States of America (USA) [19], and represents only 1.5% of oral cancer [5]. DI is very important in prosthetic rehabilitation worldwide and it is estimated that this market will profit about US $ 9.8 billion by 2022 [30]. In the last decade, 9 million DI were installed in the USA [6], an increasing of 738.2% from 1999 to 2016 [31]. The prevalence of OSCC cases adjacent to DI in this study was 3.1%, twice than reported by Kaplan et al. [5]. Therefore, even a condition being so far rare, can be clinically relevant as a consequence of the increasing number of DI installed.

OSCC is often associated to tobacco and alcohol consumption, affecting mostly men with a mean age of 60 years [13-14]. Interestingly, studies have shown that OSCC adjacent to DI predominantly affects women over 60 years, and without those classical risk factors [5,32,33]. We found similar results in this study, the majority of patients were women (58.1%), with a mean age of 73.5 years and with no history of smoking (66.7%) and drinking (83.3%). This change in the epidemiological profile is probably due to the increasing of DI installation among women over 50 years [34,35]. Therefore, an increased prevalence of OSCC surrounding DI could be expected in this population.

In this cohort, former and current smokers were diagnosed with OSCC adjacent to DI 8.6 years (mean) earlier than never smokers, and represent 58.1% of the sample. Nevertheless, smoking habits are associated with OSCC in approximately 90% of cases. [36,37]. OSCC is a heterogeneous group of neoplasms that result from genetic and epigenetic changes, whose main risk factors are smoking and alcohol consumption [38]. There is a synergistic effect of tobacco and alcohol on carcinogenesis of oral cancer, since alcohol may increase the permeability of the epithelium, dissolving and facilitating the penetration of tobacco [39]. Currently, there is a lack of data regarding smoking and alcoholism in the OSCC adjacent to DI. Other risk factors related to an increased likelihood of developing OSCC are oral potentially malignant disorders (OPMD), which are more common in males [40]. However, considering the patients diagnosed with OPMD (45,1%) in our sample, the majority were female (78,5%). The rates of malignant transformation of OPMD are higher among females, with an overall rate of 13.1% in women [40].

The most common OPMD in our study was leukoplakia (32.3%) followed by oral lichen planus (OLP) (13%). Leukoplakia occurs less frequently in the gingiva and alveolar ridge and is less likely to have dysplasia when compared to leukoplakia on the lateral border of the tongue or floor of the mouth [40]. Although OLP has been considered a OPMD, its real capacity for malignant transformation is questionable, and when reported, the rate does not exceed 1% 52[41]. Several studies have described history of OLP prior to the diagnosis of OSCC adjacent to the DI [23,41-44]. It is important to emphasize that OLP has clinical and even histopathological similarity to proliferative verrucous leukoplakia (PVL), mainly in its initial stages [45]. Therefore, those overlaps features may difficult the diagnosis of PVL [46]. Then, the accurate diagnosis is necessary since PVL has a very higher risk for malignant transformation, reaching till 100% of malignancy rates [45-47].

Chronic inflammation caused by persistent trauma to the peri-implant soft tissues, nutritional deficiencies [48] autoimmune diseases [25], and the leaching of metal ions into the oral cavity have been speculated as potential etiologic factors for OSCC development adjacent to DI [17-19]. The correlation between chronic inflammation and malignancy has been found for some types of tumors, such as Barret's esophagitis and esophageal cancer [49], and Crohn's disease and colon cancer [50]. Peri-implant tissues are areas with constant inflammation [25], and may result in overexpression of oncogenes and inactivation of tumor suppressor genes that regulate cell survival and proliferation [48, 51-52]. Cytokine mediators, such as prostaglandins, interleukins and tumor necrosis factor, can irreversibly damage the DNA and, consequently, predisposing to genetic instability and cancer [52,53]. Jané-Salas et al. [48] reported two cases of OSCC on the lateral border of the tongue in contact with DI in two male patients without the classical risk factors. Both patients reported frequent DI trauma at the tongue border before diagnosis. One of the patients underwent gastroplasty prior to diagnosis and the authors suggested that nutritional deficiencies combined with local chronic inflammation could be synergistic factors in the carcinogenesis. In this study, the lateral border of the tongue was the primary site for in 32.2% of patients and 40% of these had a history of trauma in the region caused by DI, before the diagnosis of OSCC. Due to the multiple factors involved in the carcinogenesis process, it is very difficult to prove whether this relationship is pure coincidence or not.

In vitro studies have shown that leaching of metal ions can promote inflammatory process and cellular changes [54-.56]. Leaching of metal ions in the oral cavity can occur

due to such as friction during implant insertion, friction at the implant-abutment interface and corrosion of the implant surface, for instance [20]. Titanium (Ti) particles may induce chromosomal instability in human fibroblasts, similar to heavy metals and low radiation exposure [54]. Ti was considered an inert material, however, hypersensitivity reactions I or IV, have recently been described [57-58]. Inflammation induced by Ti nanoparticles cause DNA damage, oxidative stress and protein carbonylation [55,56]. In addition, DNA damage in oral epithelial cells contributes to the disruption of epithelial homeostasis and compromising the epithelial barrier [56]. International Agency for Research on Cancer (IARC) classifies titanium dioxide (TiO2) as a potentially carcinogenic agent, but its clinical relevance is still little known and no relationship causal effect has been proven in OSCC carcinogenesis adjacent DI.

OSCC adjacent to DI may initially present as mild gingival erythema, granular or verrucous mass, or ulceration, with progressive alveolar bone loss [21]. Those clinical features make the clinical diagnosis of OSCC adjacent to DI practically indistinguishable from PMI or PI. PMI is an inflammatory reaction confined to soft tissues adjacent to DI with no signs of support bone loss [5]. PI occurs more frequently after 5 years of DI installation and is a destructive inflammatory process that leads to the formation of the peri-implant pouch and progressive loss of DI support bone [59]. These inflammatory lesions of peri-implant tissues are very common, with a prevalence of up to 1.1% to 85% [59]. In this current study, 16.1% of patients were treated as PI before the definitive diagnosis of OSCC. However, in 83% of medical records, there was no description of treatments prior to the diagnosis of OSCC and, therefore, the prevalence of PI in the patients from this study may be underestimated. The mean time from the DI installation and the appearance of OSCC was 4.7 years, which can also be a confounding factor added to the signs and symptoms of the injury, since it is similar to the mean time of the appearance of the PI.

The prognosis of patients with OSCC is directly related to clinical staging at diagnosis [60]. The 5-year mortality rates based on staging are striking, with survival being less than 50% in advanced disease, compared with 80% in early stage tumors [60]. The average time since the clinical manifestation to the diagnosis of OSCC is around 6 months [60]. Our patients were diagnosed with an average time of 4.6 months, where 51.6% were Tis, T1 and T2 and 64.5% were N0. The diagnosis of OSCC in earlier stages possibly influenced the therapeutic approach, since 61.3% of patients did not receive any adjuvant treatment. Probably, the approach of these patients by an integrated and

experienced multidisciplinary team, in an institution specialized in combating cancer, partially explains the results mentioned above.

Professionals should be aware of unresponsive treatment to PI and consider other clinical hypothesis of diagnosis including OSCC. A rigorous clinical evaluation must be performed, in addition to detailed radiographic image exams, accompanied by a biopsy and a histopathological analysis. Malignancy may not be suspected until the lesion progress and cause other signals and symptoms such as pain and large bone destruction. Consequently, the diagnosis of OSCC is established in advanced stages, which usually requires more aggressive treatments, compromising clinical outcomes, worsens the patient's prognosis and quality of life [21,61].

DI indication must be individualized and some aspects, particularly the presence of known risk factors for OSSC, such as tobacco and alcohol consumption, and the presence of OPMD should be considered. Dental professionals must play an important role in preventing OSCC, as well as in the diagnosis of pre-malignant lesions and/or early stage tumors adjacent to DI and make a potentially curative treatment possible [61]. All patients should have a regular check-up with a detailed physical examination of the oral cavity. ID-supported prostheses should be designed to facilitate removal, allowing clinical inspection of the underlying tissues associated with periodic radiographic monitoring.

CONCLUSIONS

OSCC adjacent to DI were more common in women over 70 years old, non-smokers and non-drinker, and with previous history of oral leukoplakia. In addition, OSCC may present clinical and radiographic features that resemble PI which can delay the diagnosis and impair the prognosis. OSCC adjacent to DI seems to be into the spectrum of the classic oral squamous carcinoma and should be considered particularly in persistent peri-implant lesions.

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ARTIGO: Oral cancer adjacent to dental implants mimicking benign lesions particularly peri-implantitis: A Case Series Study

Running title: Oral cancer adjacent to dental implants

CAPÍTULO 3- Artigo submetido ao periódico British Dental Journal

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ABSTRACT

Despite the long-term survival rates of the osseointegrated dental implants, several biological complications are confirmed to affect the peri-implant tissues, such as peri-implant mucositis and peri-implantitis. Occasionally, the clinical features of these more common inflammatory processes may be similar to peri-implant malignancies, leading to misdiagnosis. Thus, the objective of this study was to present a case series of oral cancer located adjacent to dental implants, aimed to identify the reasons for initial misinterpretation of diagnosis and the key points that could call the attention for early recognition and management. **Clinical reports:** The current series reported thirteen patients (10 females and 3 males) diagnosed with oral cancer around dental implants. Among the differential diagnosis established, a malignant or premalignant lesion was not considered in 10 out of the 13 patients. Peri-implantitis was the most common preliminary diagnosis, followed by mycoses, viral infections, and traumatic ulcers. Alarming, the meantime for the diagnosis of oral cancer was 21.5 months. **Conclusion:** The clinical presentation of peri-implant oral malignancy may mimic peri-implant mucositis, peri-implantitis, and other benign diseases that are more common in the oral cavity. Suspicious lesions with treatment failure that persist for more than two weeks require biopsy and histopathological analysis, in order to establish an early definitive diagnosis, consequently improving the prognosis and quality of life of the patients.

Keywords: Oral cancer, implant, peri-implantitis, peri-implant mucositis and diagnosis.

INTRODUCTION

Oral cancer is among the top ten most prevalent cancer worldwide [1]. Oral squamous cell carcinoma (OSCC) amount to more than 90% of the histological subtype [2]. Due to most OSCCC are diagnosed in advanced clinical stages, the 5-year survival low rate is of 50%, indicating that half of the patients die due to disease progression [3]. Therefore, it is well established that early diagnosis allow a less aggressive treatment, leading to reduced morbidity and mortality rates [4].

OSCC predominantly affects males between 50 and 60 years old, in a 2:1 male to female ratio [2]. Females, when affected, are typically a decade older than males [5]. The major risk factors are tobacco smoking and its association with alcohol consumption [6]. However, as some patients report no exposure to these specific risk factors, other possible causes have been proposed, such as genetic predisposition, nutritional deficiencies, immunosuppression, high-risk human papillomavirus infection, and chronic inflammation [7].

Chronic trauma of oral mucosa, as a consequence of ill-fitting dentures [8], sharp teeth, faulty restoration, dental malocclusion, or malpositioned implants, has been associated with increased mitosis and chronic inflammation, DNA damage and consequent genetic and epigenetic alterations [9]. Nonetheless, the scientific literature does not provide any evidence demonstrating a cause-effect relationship between trauma and oral carcinogenesis [10].

In terms of localization, OSCC occurs most frequently on the lateral border of the oral tongue and on the floor of the mouth, whereas it is less expected to occur on the palate, the retromolar area, and the gingiva [2]. Although peri-implant malignancy represents only 1.5% of oral cancer cases [11], their clinical presentation can mimic peri-implant mucositis, peri-implantitis, or other more common benign lesions, which may result in a delayed diagnosis [12]. Therefore, this article aims to report a case series of 13 OSCC located adjacent to dental implants, in order to identify the reasons for initial misinterpretation of diagnosis and the key points that could call the attention for early recognition and management.

CLINICAL REPORTS

Thirteen patients diagnosed with OSCC adjacent to dental implants were retrospectively reviewed during a period of 9 years (2010–2019). The patients were referred to two oral medicine services: the A.C. Camargo Cancer Center, São Paulo, Brazil (n=7), and the Piracicaba Dental School, University of Campinas (UNICAMP), Piracicaba, Brazil (n=6).

Among the differential diagnosis established, a malignant or premalignant lesion was not considered in 9 out of the 13 patients. Peri-implantitis was the most common preliminary diagnosis (36.4%) **(Figure1)**, followed by mycoses (18.2%), viral infections (9.1%) and traumatic ulcer (9.1%) **(Figure 2)**. Consequently, the patients received several types of treatments such as conventional peri-implantitis management (Patients 1–4), ketoconazole (Patients 5 and 6), acyclovir (Patient 7), and hyaluronic acid and *Aloe vera* gel (Patient 8). As no resolution was achieved the patients were referred to our services.

In only two patients (# 9 and 10) the hypothesis of OSCC was considered, while leukoplakia was the diagnosis in one subject (Patient 11) **(Figure 3)**. The histopathological diagnosis of OSCC was established through an incisional biopsy in all thirteen patients. The period between the subjects become aware of the oral lesion and the diagnosis of OSCC varied significantly, ranging from 1 to 120 months (mean, 21.5 months).

Sociodemographic and clinical data are summarized in **Table 1**. Females were more affected accounting for 76.9% of cases (n=10) (Ratio 1:3.3). Overall, the mean age at the time of diagnosis was 73.4 years (ranging from 59 to 90 years). Eight patients (61.5%) had past history of exposure to known risk factors for oral cancer. Interestingly, only one patient (# 7) reported regular consumption of tobacco for 15 years. Two subjects (# 4 and 5) were ex-smokers: Patient 4 had used tobacco for 4 years and had stopped 40 years before data collection, and patient 5 had used tobacco for 25 years and quit smoking 10 years earlier. Potentially malignant disorders were previously presented in two cases: Patient 5 had been diagnosed with proliferative verrucous leukoplakia and patient 11 had been diagnosed with leukoplakia affecting the alveolar ridge. Furthermore, the other 4 patients had a previous history of oropharynx (Patient 1), palate (Patient 2), tongue and floor of the mouth (Patient 9) and lip (Patient 13) squamous cell carcinoma.

Eleven patients had lesions in the alveolar ridge (84.6%), one in the palate (7.7%), and one in the lateral border of the oral tongue (7.7%). Ulcers or ulcerated mass were the

most common clinical presentation, representing 46.2% of cases (n=6), followed by white and red plaques (38.5%, n=5) and exophytic lesions (15.4%, n=2). Panoramic radiographs could not be retrieved in three cases. Radiographic examination identified bone involvement in 50% of cases (n=5). A radiolucent lesion due to bone destruction was the most frequently observed radiographic characteristic. In some cases, the lesions had a "moth-eaten" aspect.

All patients underwent surgical treatment of OSCC, which consisted of wide resection with macroscopic margins of at least 1cm and neck dissection. Patients with perineural infiltration, vascular embolization, or lymph node metastasis without extracapsular spread were submitted to postoperative radiotherapy. Moreover, patients with positive surgical margins or with metastatic lymph nodes with extracapsular spread underwent postoperative chemoradiation.

Ten patients remained alive and there was no available follow-up information for 3 cases. A total of 3 subjects (25%) experienced local recurrence within follow-up period ranging from 1 to 96 months (mean of 37.8 months).

Table 1. Sociodemographic and clinical data.

Patient	Gender, age	Risk factor	Implant site	Lesion description	Lesion site	Initial diagnosis	Evolution (months)	Recurrence	Follow-up (months)
1	M, 85	PSCC	46	Exophytic white lesion with an irregular white surface	Lower and right alveolar ridge and floor of the mouth	Peri-implantitis	24	Yes, twice	NA
2	F, 81	PSCC	31, 32,33, 43	Ulcer with white plaques	Lower and left alveolar ridge	Peri-implantitis	12	Yes	14
3	F, NA	-	26	Swelling with infiltrative ulcer	Posterior left palate and alveolar ridge	Peri-implantitis	7	No	33
4	M, 61	Ex-smoker	31, 32, 41, 42	Swelling with infiltrative ulcer	Lower anterior alveolar ridge, floor of the mouth and lip skin	Peri-implantitis	12	No	62
5	F, 59	Ex-smoker, PVL	47, 46	Homogenous white plaque	Right, posterior, ventral surface of the tongue	Fungal infection	12	No	NA
6	F, 77	-	41,31, 33	Heterogeneous white plaques	Inferior alveolar ridge	Fungal infection	NA	No	96
7	M, 74	Smoker	14,15, 16	White and red ulcerated lesion	Gingiva and alveolar mucosa in the right posterior region	Viral infection	NA	No	72
8	F, 64	–	45,46, 47	Exophytic lesion with central ulcer and irregular surface	Inferior and right alveolar ridge	Traumatic ulcer	12	NA	NA
9	F, 84	PSCC	43, 31, 33	Exophytic lesion with irregular white surface	Lower and left alveolar ridge	OSCC	3	No	50
10	F, 65	-	33, 34	Erythematous ulcer	Lower and anterior alveolar ridge	OSCC	1	Yes, twice	26
11	F, 68	Leuco-plakia	11,13, 15,17	Leukoplakia	Alveolar ridge, deep groove to jugal mucosa and right hard palate	Leukoplakia	120	No	12
12	F, 90	–	33, 43	Raised white plaque with verruciform surface	Lower alveolar ridge	NA	12	No	12
13	F, 73	PSCC	33, 31	Raised plaque with verruciform surface	Lateral and left alveolar ridge	NA	NA	No	1

NA, not available; OSCC, oral squamous cell carcinoma; PSCC, previous squamous cell carcinoma; PVL, proliferative verrucous leukoplakia.

DISCUSSION

Research over the past decades has allowed elucidate the underlying mechanisms involved in the complex process of oral carcinogenesis [13]. Novel findings revealed targetable pathways resulted in the development of therapeutic approaches that are more precise, effective, and enduring, such as target therapy [14] and immunotherapy [15]. Despite the innovative treatments, the tumor response rate and overall survival remain unsatisfactory, in part due to most patients are diagnosed and treated at advanced clinical stages [16]. With this in mind, we explore the unusual clinical presentation of OSCC located adjacent to dental implants, in order to provide clinicians with key knowledge for early diagnosis.

General dentists, prosthodontists, oral/maxillofacial surgeons, and periodontists are crucial health professionals in dealing with oral cancer screening, as demonstrated by the fact that patients who never visit a dentist are 2.5 times more likely to present with OSCC [17]. Routine oral cavity examinations ensure early screening, considered that in dental offices, dentists have the means for a thorough clinical examination, such as good illumination and intraoral mirrors, besides the skills needed to recognize such conditions [18].

Detection of malignant lesions begins with the medical history, which is necessary for the identification of high-risk patients. The main risk factors for oral cancer are a history of tobacco and alcohol abuse, potentially malignant disorders, and/or previous malignancies, predominantly squamous cell carcinoma due to field cancerization [2]. This term refers to the potential development of cancer at multiple sites covered by squamous epithelium (e.g. oral cavity, pharynx, larynx, esophagus, and lungs) as a consequence of molecular alterations and long-term exposure to environmental carcinogens [19]. Moreover, dental professionals must educate their patients about oral cancer risk factors and motivate the suspension of harmful habits [12].

It is important to recognize that elderly smokers may have experienced dental loss due to periodontal disease, which makes them prone to implants and prosthetic rehabilitation. Thus, some implant-rehabilitated patients constitute the clinical profile of oral cancer patients [20]. An essential point is that screening must be systematic for all patients, as an increased incidence of oral cancer in young patients has been reported in the literature [21]. In addition, a particular group of OSCC patients has been identified and must be considered: older women who were not exposed to the traditional risk factors,

with an unknown etiology for cancer [7]. This is allusive to our series, in which most of the patients were female and the frequency of tobacco and alcohol consumption was low. The higher prevalence of females in our sample may be in part explained by the fact that most dental implants are placed in women [20].

Complete physical examination includes the bimanual palpation of the neck to detect primary or metastatic alterations in the cervical lymph nodes. If a nodule is palpable, the location, number, size, consistency, tenderness, and fixation should be assessed [22]. The intraoral examination requires adequate lighting, gloves, dental mirror, gauze, and a ruler or periodontal probe, and should be systematic for all structures of the oral cavity. Special attention should be given to the most frequent sites of OSCC: lateral border of the oral tongue and floor of the mouth, by thoroughly inspecting and palpating the structures and grasping the tip of the tongue with a piece of gauze [23]. Any alteration should be described according to the following parameters: anatomic site, size, color, outline, texture, symptom, and evolution [24].

OSCC affecting the peri-implant mucosa might resemble peri-implant mucositis and peri-implantitis in terms of clinical and radiological aspects [11]. While peri-implantitis is an infectious and inflammatory disease that affects soft and hard tissues surrounding an endosseous implant, peri-implant mucositis affects the soft tissues in the absence of peri-implant bone loss. Both alterations are characterized by swelling, redness, bleeding and pocket formation [25, 26]. In a retrospective study, Kaplan et al. [11] reported that out of the total number of oral cancer cases, 1.5% were peri-implant malignancies, in contrast to the low incidence reported in the literature [27], suggesting that peri-implant malignancy is underreported and not unusual as previously thought. In the present case series, most of the patients were initially diagnosed with peri-implantitis, leading to unnecessary, ineffective, and dangerous treatments such as debridement and antiseptic or antibiotic therapy.

Although ulcers and tumors with raised exophytic margins are the most common clinical presentation of OSCC, other aspects such as leukoplakia, leukoerythroplakia, and erythroplakia may be observed [2]. The differential diagnosis for lesions with a leukoplastic appearance are 1) frictional keratosis, which disappears after elimination of the suspected mechanical irritation; 2) candidiasis, a pseudomembrane that can be easily wiped away and disappears after antifungal treatment and denture repair or replacement; 3) hairy leukoplakia, which is mainly located on the borders of the oral tongue and presents specific histopathology features (positiveness for Epstein-Bar virus); and 4)

restoration-associated lesions, which disappear after replacement of the restoration. On the other hand, differential diagnostics for red lesions are 1) candidiasis; local irritation, which disappears after elimination of the etiology; and 2) erosive lichen planus, multifocal lesions with periphery bordered by fine white radiating striae that respond to corticosteroid management [28-30].

The above evidence was exemplified in our series, in which patients 5, 6, 7, and 8 were initially diagnosed with a traumatic ulcer, fungal infection, and viral infection respectively, without response after elimination of the trauma, antifungal treatment, or viral management. In fact, only two cases were initially suspected to be OSCC (Patients 9 and 10). It is imperative to recognize that time to diagnosis has a critical impact on the patient´s prognosis and the current study showed a meantime for the diagnosis of 21.5 months, which is alarming given the fast proliferation of neoplastic squamous cells and the high risk of metastases to the regional lymph nodes [2].

Combining all presented, if a diagnosis of inflammatory, infectious, or iatrogenic disease is considered, it is necessary to eliminate potential causes, provide the appropriate treatment, and re-evaluate the patient in 10–14 days. Usually, these alterations resolve or reduce in size during this period. On the other hand, any lesion that persists for more than 2 weeks and does not respond to conventional treatment should be considered suspicious. Thus, referral to an oral medicine specialist, oral/maxillofacial surgeons or head and neck surgeon, should be contemplated, and the biopsy and histopathological analysis will allow the establishment of the definitive diagnosis [24] **(Figure 4)**.

CONCLUSION

The clinical presentation of peri-implant oral cancer may mimic peri-implant mucositis, peri-implantitis, and other more common benign lesions in the oral cavity, leading to a significant delay in diagnosis and treatment. Oral health professionals have an important role in recognizing high-risk patients and suspicious lesions. Previous malignancies, exposure to tobacco and alcohol, and potentially malignant disorders are the main risk factors. Suspicious lesions that persist for more than 2 weeks, requires biopsy and histopathological analysis in order to establish an early definitive diagnosis, contributing to reduce morbidity and mortality rates and improving quality of life.

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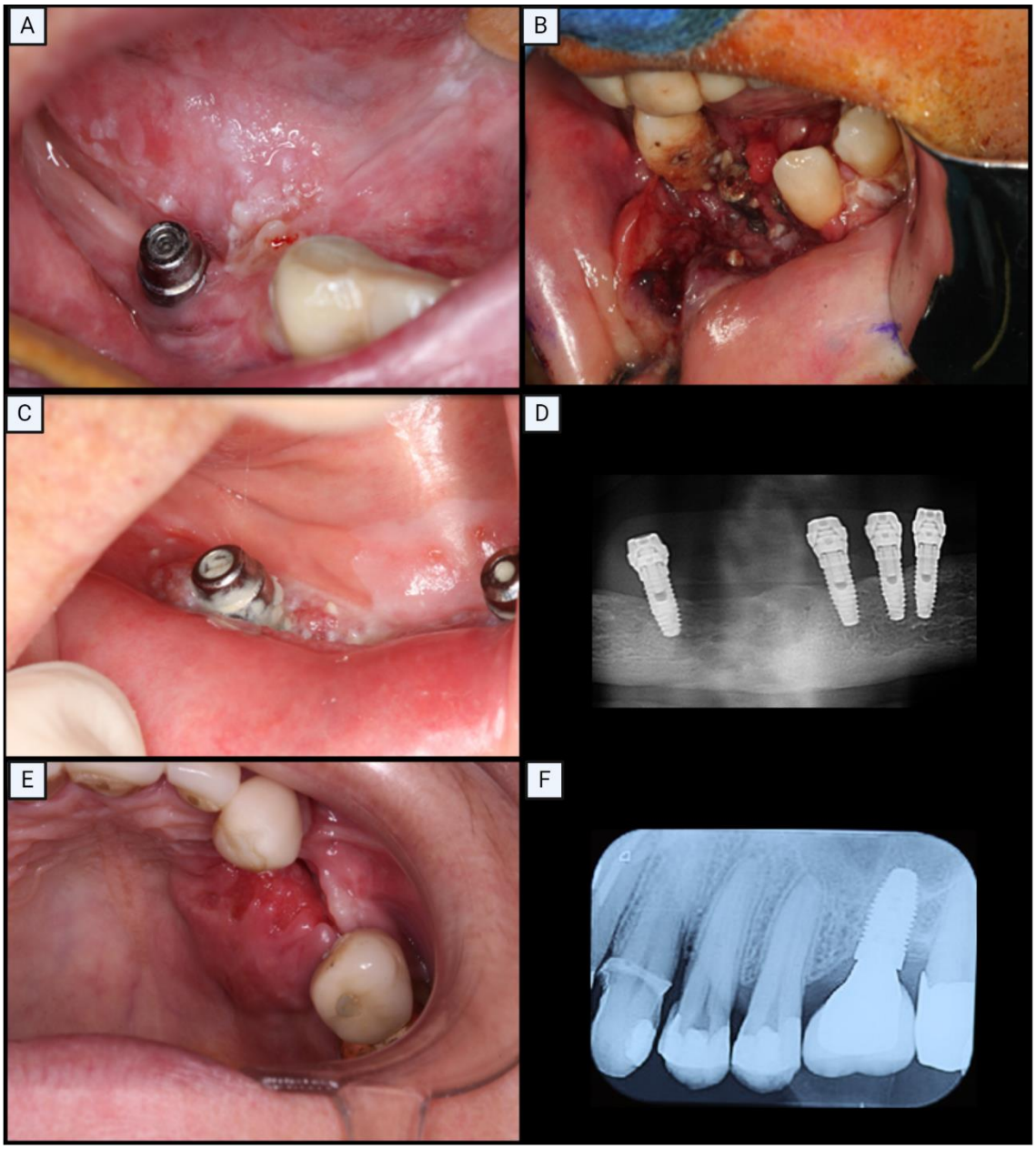

Figure 1. Clinical and radiographic features of cases initially diagnosed as peri-implantitis. (A) Patient 1 presented an exophytic lesion with an irregular white surface in the lower and right alveolar ridge adjacent to implant 46. White plaques extended to the floor of the mouth. The lesion was detected during prosthetic maintenance. **(B)** Intraoperative photo of Patient 4, showing a swelling with an infiltrative ulcer around implants 31, 32, 41 and 42. The lesion involved the lower anterior alveolar ridge, floor of the mouth and lip skin. **(C)** Oral examination of Patient 2, demonstrating an ulcer with white plaques measuring 4 cm approximately in the region of the alveolar ridge adjacent to implants 43, 32 and 33. **(D)** Radiographic evaluation on Patient 2 showed bone destruction with a “moth-eaten” aspect. **(E)** Patient 3 presented a swelling with an

infiltrative ulcer in the region of the posterior left palate, adjacent to implant 26. **(F)** Radiographic assessment of Patient 3 showed a radiolucent lesion.

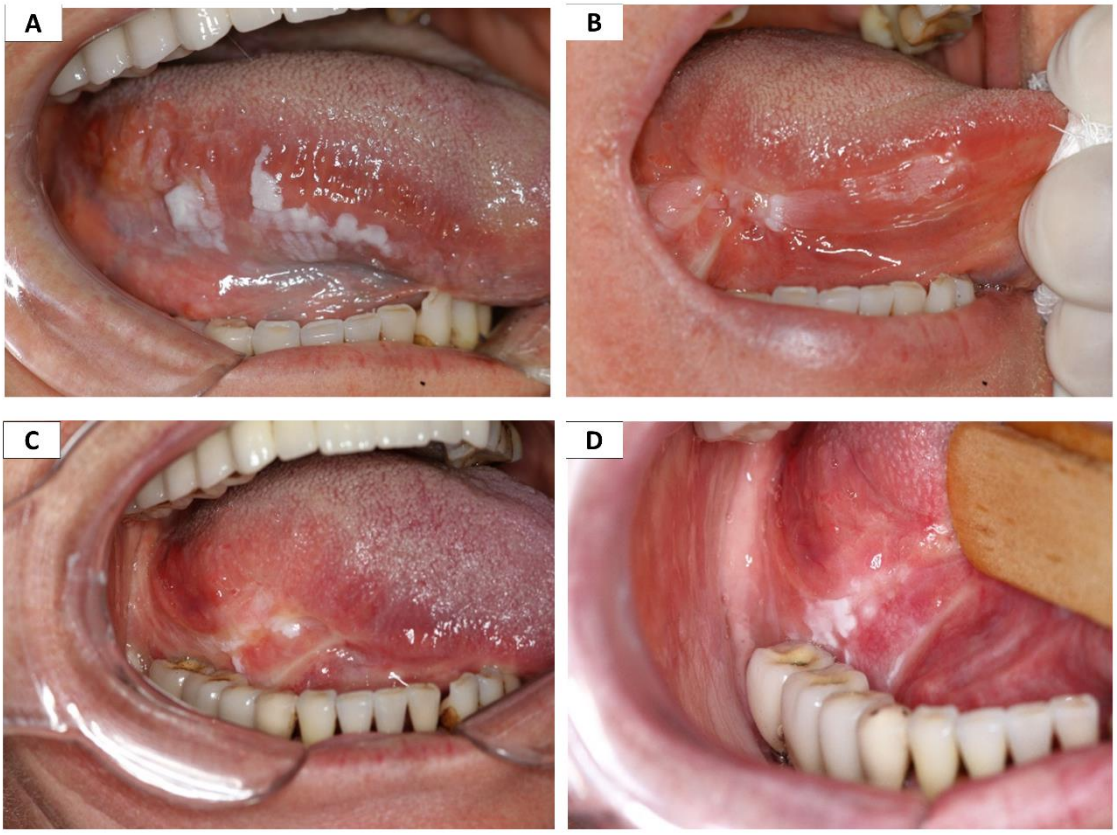

Figure 2. Clinical characteristics of cases initially diagnosed as viral or fungal infections. (A) Oral squamous cell carcinoma diagnosed and treated in the right ventrolateral border of the tongue of Patient 5. **(B)** Six years later, Patient 5 presented local recurrence adjacent to implants 47 and 46. The lesion was a homogenous white plaque. **(C)** Heterogeneous non-scrapable white plaques on the inferior alveolar ridge adjacent to anterior implants of Patient 6. **(D)** Patient 7 presented an extensive white and red ulcerated lesion located on the gingiva and alveolar mucosa in the right posterior region. The lesion was unsuccessfully treated with acyclovir.

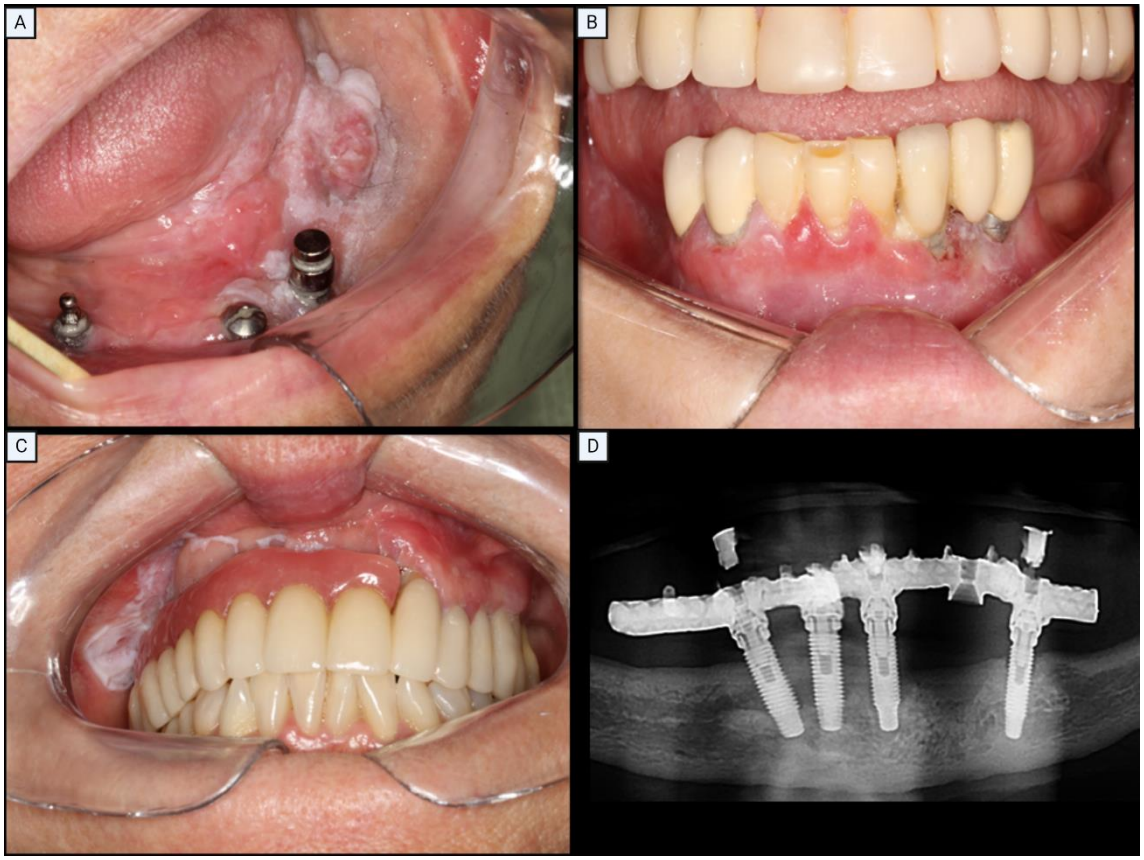

Figure 3. Clinical and radiographic features of oral squamous cell carcinoma around implants. (A) Patient 9 presented an exophytic lesion with an irregular white surface involving the lower left alveolar ridge around implants 43, 31 and 33. **(B)** Patient 10 presented an erythematous ulcer around implants 33 and 34. **(C)** Oral examination of Patient 11, showing leukoplakia in the alveolar ridge, deep groove to the jugal mucosa and right hard palate adjacent to implants 11,13,15 and 17. **(D)** Radiographic evaluation of Patient 13 showed a radiolucent lesion between implants 33 and 3.

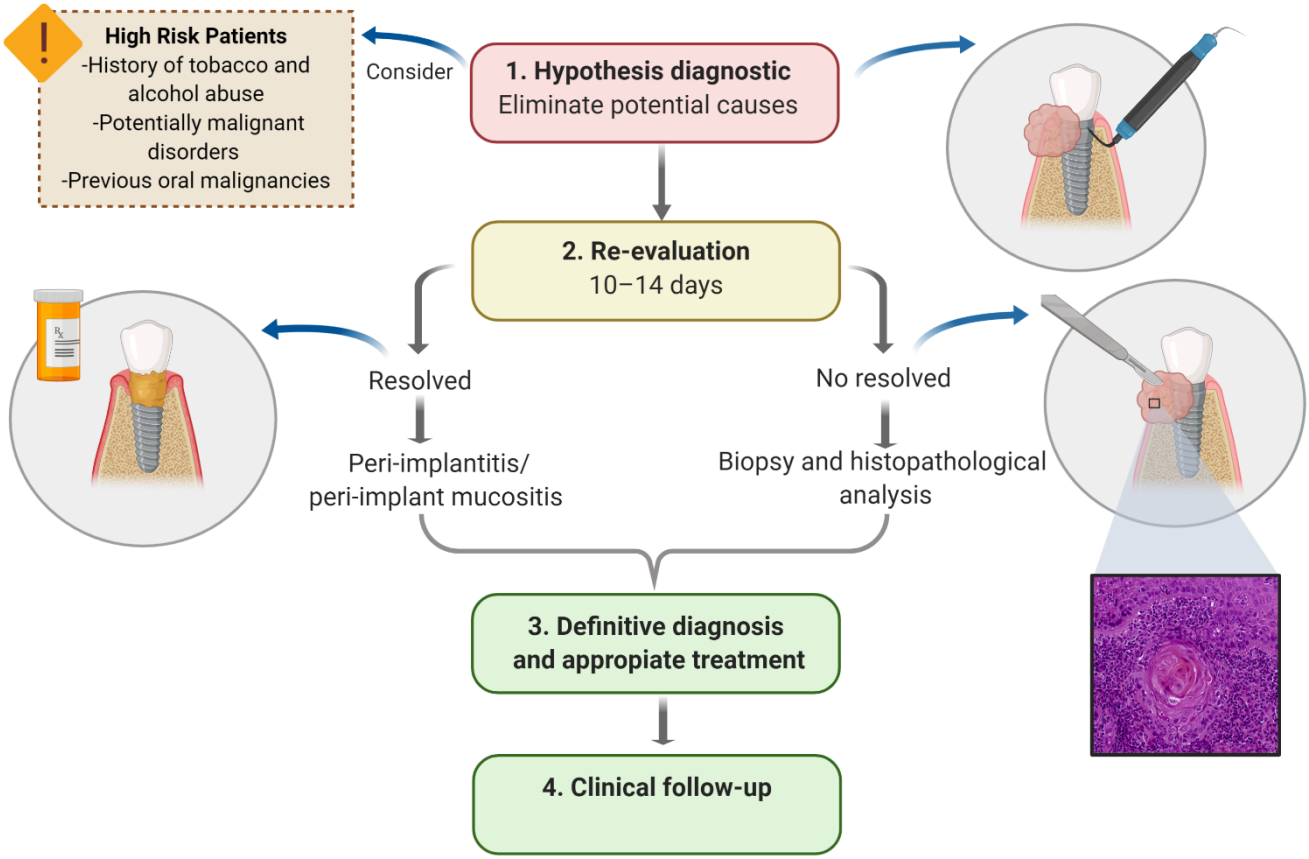

Figure 4. Guide to diagnostic steps for conducting suspicious lesions around dental implants. Anamnesis and intraoral examination will guide the diagnostic hypotheses **(1)**. After eliminating potential causes of inflammatory or infection hypotheses, the patient should be evaluated within 14 days **(2)**. If the lesion resolves or reduces in size it confirms the diagnosis and requires management accordingly. Keep periodic monitoring. On the other hand, if there is no resolution, the lesion becomes suspicious and must be biopsied for possible confirmation of malignancy **(3)**. According to the histopathological diagnosis, appropriate treatment must be established, and close follow-up are essential **(4)**.

ARTIGO: Potentially malignant disorder in patients with oral squamous cell carcinoma around dental implants is lichen planus or proliferative verrucous leukoplakia?

CAPÍTULO 4- Artigo submetido ao periódico Medicina Oral Patologia Oral y Cirugia Bucal

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Dear Editor

Oral squamous cell carcinoma (OSCC) is one of the most common malignancy worldwide corresponding to approximately 354.864 new cases per year[1]. It occurs particularly in males with age above 50 years and with history of tobacco and alcohol consumption[2]. More recently, an increasing incidence of OSCC in younger people with age under 40 years has been observed[3]. Interesting that these patients normally do not have the known risk factors for oral cancer and they are more often females[3]. Several studies have been conducted in order to better understand the possible etiologic factors of OSCC in these group of patients[3]. Other intriguing group of patients with higher risk for developing OSCC is representing by females with ages above 60 years and also without habits of tobacco and alcohol abuse. These patients normally are diagnosed with proliferative verrucous leukoplakia (PVL), a type of leukoplakia described by Hansen et al.[4] with very risk high of recurrence and malignant transformation.

In the past years, some reports of OSCC around dental implants (DI) have been published. Although it is well known that about 90% of oral cancer affect men smokers and/or drinkers, the clinical profile of patients with OSCC around DI is different from that. The involved patients are generally non-smokers and non-drinkers elderly women. Curiously, some reports have described that an important percentage of these patients have previous history of potentially malignant disorders, particularly oral lichen planus (OLP) [5-9].

Reviewing these reports, it was possible to notice that most of these studies do not show the peculiar clinical characteristics of OLP, such as bilateral involvement, and do not present its microscopical features[5-8]. Gallego et al.[5] reported a case of an 81-year-old woman who was referred for evaluation of white lesion on the palate, tongue and buccal mucosa with evolution time of 1 year. The patient had no history of tobacco or alcohol consumption. The authors mentioned that a biopsy was taken and microscopic diagnosis of lichen planus was established. However, the lesion was not bilateral, a crucial feature for considering lichen planus. In addition, the age of the patient was above that what is expected for lichen planus patients.

Marini et al.[6] reported a patient with previous OLP located in the left side of the mouth. The diagnosis of OLP was based on the patient history. The authors emphasized that the only risk factor that could be related to development of oral cancer was the presence of OLP. In addition, the authors reported that an interesting observation was the

fact that the oral cancer arose in an area not previously affected by lichen planus. Raiser et al.[7] presented two patients with OSCC around DI. Both patients were women with ages of 55 and 70 years. Interesting that the authors also affirmed that the diagnosis of OLP was based on the history reported by the patients. There was no information if diagnosis of lichen planus was confirmed microscopically and if the lesions were bilateral and which sites of the oral cavity were affected.

As described above the diagnosis of OLP in some papers was based only in the clinical history described by the patients. This approach should be avoided since OLP may be clinically similar to initial manifestation of PVL, as reported by our group [10]. In addition, although both lesion affect more frequently women, there are some differences between them. Patients with PVL are often older and the lesions occur more frequently in gingiva and mucosa of the alveolar ridge. On the other hand, OLP normally affects buccal mucosa and lateral border of the tongue bilaterally[11,12].

Therefore, it is recommended to consider initial manifestation of PVL in elderly women patients with striated lesion who are going to underwent DI. The differentiation between OLP and PVL, which must consider age of the patients, clinical aspects and site of occurrence of the lesions, and microscopical features, are essential since the disease progression and rate of malignant transformation are completely different between them. It is well known that, besides the controversy regarding the malignant transformation in OLP, the risk is low being under 1%. On the other hand, in PVL the risk is very high ranging from 50 to 100% [11,12].

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3 DISCUSSÃO

O aparecimento de CEC adjacente aos ID é estimado em 0,00017 / milhão / ano nos Estados Unidos da América (EUA) (Bhatavadekar, 2012), representando apenas 1,5% do total de CEC oral (Kaplan et al., 2017). O ID é importante na reabilitação protética em todo o mundo e estima-se que este mercado lucrará cerca de US $ 9,8 bilhões em 2022. Na última década, 9 milhões de ID foram instalados apenas nos EUA (Bhatavadekar, 2012), um aumento de 738,2% entre 1999 e 2016 (Elani et al., 2018). Os casos de CEC adjacentes aos ID no nosso estudo retrospectivo foi de 3,1%, o dobro do relatado por Kaplan et al. (2017). Portanto, mesmo uma condição até agora rara, pode ser clinicamente relevante como consequência do crescente número de ID instalados.

O CEC é a neoplasia maligna mais comum da região da cabeça e pescoço (Moore et al., 2000; Bray et al., 2018). Afeta principalmente homens acima de 50 anos com uma proporção de homens: mulheres de 2: 1. As mulheres são frequentemente diagnosticadas 10 anos mais velhas que os homens (Moore et al., 2000; Warnakulasuriya, 2009; Bray et al., 2018). No entanto, todos os nossos estudos demonstraram uma prevalência do sexo feminino - e uma proporção homem: mulher em média de 1: 1.3. Na RS não houve diferença de idade entre os sexos, porém, o estudo retrospectivo demonstrou significância estatística (p=0.007), onde às mulheres foram diagnosticadas em média 10 anos mais velhas que os homens. Curiosamente, a prevalência de reabilitação oral de pacientes com ID é maior entre mulheres acima de 50 anos do que homens na mesma idade (Ortega-Lopes et al., 2011; Elani et al., 2018; Ducommun et al., 2019). Nos Estados Unidos da América, foi relatado um aumento impressionante de 728,6% em DI entre as mulheres de 2000 a 2016 (Elani et al., 2018). Possivelmente, isso pode estar relacionado ao fato de as mulheres estarem mais preocupadas com a saúde bucal e com a aparência estética. Consequentemente, pode-se esperar uma maior prevalência de CEC em torno do ID neste grupo.

Tabaco e álcool têm sido descritos como os principais fatores de risco para o desenvolvimento do CEC, estando o tabagismo associado ao CEC geralmente em 90% dos casos (Blot, 1999; Franco et al., 1989; Petersen, 2009). O risco de desenvolver CEC aumenta proporcionalmente com a duração e a frequência da exposição ao cigarro, particularmente em indivíduos com histórico de mais de 20 maços/ano (Garrote et al., 2001; Castellsagué et al., 2004). O álcool não parece ter um papel direto na carcinogênese,

mas a exposição síncrona ao tabaco aumenta o risco de câncer em 5 a 13 vezes, uma vez que o álcool pode aumentar a permeabilidade do epitélio, dissolvendo e facilitando a penetração do tabaco (Garrote et al., 2001; Castellsagué et al., 2004). Interessantemente, em nossa RS, 49% dos pacientes não tinham histórico de consumo de tabaco e/ou álcool. Nosso estudo retrospectivo demostrou achados semelhantes, onde 41,9% dos pacientes eram não fumantes e 54,9% eram não etilistas, já na série de casos, apenas 15% dos pacientes eram ex tabagistas. Atualmente, há uma falta de dados sobre os fatores de riscos relacionados ao desenvolvimento do CEC adjacente ao ID. Inflamação crônica causada por trauma persistente nos tecidos moles peri-implantares, deficiências nutricionais (Jané-Salas et al., 2012) doenças auto-imunes (Gallego et al., 2008), e a lixiviação de íons metálicos na cavidade oral é uma etiologia potencial para o desenvolvimento do CEC adjacente ao ID (Gandini et al., 2008; Hafez et al., 2011; Yesensky et al., 2018).

A lixiviação de partículas de titânio (Ti) nos tecidos peri-implantares é bastante comum e pode ocorrer devido a vários fatores, como atrito durante a inserção do implante, corrosão da superfície do implante, atrito na interface implante-pilar, entre outros (Suárez-López et al., 2018). Essas nanopartículas metálicas induzem efeitos inflamatórios devido à sua capacidade imunomoduladora, exercida principalmente em macrófagos, através do aumento de danos ao DNA, estresse oxidativo e carbonilação de proteínas (Noronha Oliveira et al., 2018; Suárez-López et al., 2018). Além disso, os macrófagos são induzidos anormalmente, causando inflamação excessiva e supressão imunológica (Dubey et al., 2015; Huang, 2017). Além disso, as células epiteliais orais podem sofrer danos no DNA devido a detritos/partículas de Ti, contribuindo para a ruptura da homeostase epitelial e comprometendo potencialmente a barreira epitelial oral (Suárez-López et al., 2017).

Ainda no contexto da inflamação crônica, a mucosite peri-implantar (PMI) e a PI são considerados processos inflamatórios que envolvem os tecidos de suporte do ID. A PMI é considerada uma reação inflamatória reversível com prevalência de até 80% e é uma lesão precursora da PI que envolve além dos tecidos moles o tecido duro ao redor do ID (Zitzmann e Berglundh, 2008). Comparado à MPI, a PI é menos prevalente e pode afetar aproximadamente 1,1% a 85% dos indivíduos (Zitzmann e Berglundh, 2008; Dreyeret al., 2018). Além disso, quase metade (43,9%) dos casos de peri-implantite ocorre após 5 anos de instalação do ID (Dreyeret al., 2018). Nosso estudo de RS encontrou um tempo média de 4,5 anos da instalação do ID ao aparecimento do CEC, o que foi parecido com o tempo de 4,7 anos encontrado no nosso estudo retrospectivo. Em

25% dos casos relatados na revisão, a PI foi a primeira hipótese clínica antes do diagnóstico definitivo de CEC e 16,1% no estudo de coorte. Porém, esses números podem estar subestimados, já que a maioria dos casos relatos na revisão não apresentavam informações de tratamento prévio, bem como os prontuários médicos incluídos no estudo retrospectivos. Já a série de casos mostra mais fidedignamente essa confusão no diagnóstico, já que o principal diagnóstico diferencial foi a PI. O CEC adjacente ao ID pode apresentar-se inicialmente como eritema gengival leve a alterações hiperplásicas granulares e/ou ulceração de tecidos moles, com perda óssea alveolar progressiva (Bhandari et al., 2016). Essas características clínicas tornam o diagnóstico clínico de CEC adjacente ao ID praticamente indistinguível do PMI ou PI.

Outra questão relevante é o possível papel da inflamação crônica secundária a reações autoimunes no processo de carcinogênese em pacientes sem fatores de risco clássicos, podendo explicar o desenvolvimento de CEC adjacente ao ID. Em nossa RS, 52,6% das mulheres apresentavam LPO e 13% no estudo retrospectivo. O OLP é uma doença inflamatória crônica que afeta a mucosa oral com remissões e recorrências peculiares (Scully et al., 1998). A patogênese da LPO ainda não está completamente esclarecida e seu potencial para malignidade é controverso, não passando de 1% (Aghbari et al., 2017; Fitzpatrick et al., 2014). Considerando que a LPO é uma doença autoimune inflamatória crônica e o ID pode promover processos inflamatórios em tecidos adjacentes, pode haver uma relação sinérgica entre esses fatores no desenvolvimento do CEC. Outra possível relação a ser analisada é a dificuldade em diferenciar LPO de leucoplasia verrucosa proliferativa (LVP), principalmente nas fases iniciais onde pode apresentar clinicamente aspecto liquenóide, o que enfatizamos no capítulo quatro deste estudo. As características epidemiológicas, clínicas e histopatológicas da LVP inicial podem se sobrepor às do LPO, levando a erros de diagnóstico (Lopes et al., 2015). A LVP apresenta altas taxas de transformação maligna, variando de 33,3% a 100% dos casos e afeta principalmente mulheres idosas, não etilistas e não tabagistas, com mais de 60 anos (Morton et al., 2007). O atraso no diagnóstico de pacientes com DOPM pode afetar o tratamento e os resultados desses indivíduos.

O mau prognóstico do CEC está relacionado ao diagnóstico tardio e ao estágio clínico avançado (Forastiere et al., 2001). Na doença inicial e não metastática, a taxa de sobrevida em 5 anos é de cerca de 90%, enquanto no tumor avançado com metástases não excede 50% (Siegel et al., 2014). Infelizmente, nas últimas décadas, não houve melhora nos resultados de sobrevida em pacientes com CEC, enfatizando a necessidade de

diagnóstico precoce e melhor compreensão da fisiopatologia dessa doença, a fim de aumentar a sobrevida do paciente e diminuir a morbidade (Siegel et al., 2014. O diagnóstico precoce do CEC adjacente ao ID é um desafio, pois essas lesões nos estágios iniciais podem se assemelhar a lesões inflamatórias mais comuns em torno do ID. Os pacientes também podem não ter os fatores de risco clássicos e a lesão pode ser desvalorizada pelo indivíduo ou mesmo pelo profissional de saúde. Além disso, essas lesões podem ser ocultadas pela prótese sobre implante, atrasando o diagnóstico. É de extrema importância que, antes da instalação do ID, os fatores de risco do paciente sejam considerados e uma avaliação de custo-benefício seja individualizada. Todos os pacientes, particularmente aqueles com fatores de risco conhecidos para CEC, devem fazer um check-up regular com um exame físico detalhado da cavidade oral e uma biópsia deve ser realizada quando for observada uma lesão persistente e suspeita. Além disso, as próteses suportadas por ID devem ser projetadas para facilitar a remoção, permitindo uma inspeção clínica meticulosa dos tecidos subjacentes associados à monitorização radiográfica periódica.

4 CONCLUSÃO

- O CEC adjacente ao ID foi mais prevalente entre as mulheres;
- A maioria dos pacientes diagnosticados com CEC adjacente ao ID não apresentavam fatores de risco clássicos, como fumar e beber;
- A maioria das mulheres apresentou DOPM antes do diagnóstico de CEC;
- Às DOPM mais comuns foram, o LPO e a leucoplasia;
- O tempo médio da instalação do ID ao aparecimento do CEC foi de 4,5 a 4,7 anos;
- O tempo médio de evolução da lesão da percepção clínica ao diagnóstico final foi entre 4,6 a 6 meses;
- O CEC adjacente ao ID pode apresentar características clínicas e radiográficas que se assemelham à PI, o que pode levar a um atraso no diagnóstico;
- Os aspectos clínicos mais comuns do CEC adjacente ao ID foram massa exofítica e ulceração;
- O CEC adjacente ao ID parece estar dentro do espectro do CEC oral clássico e deve ser considerada particularmente em lesões peri-implantares persistentes;
- Pode ocorrer uma dificuldade em diferenciar LPO de LVP, principalmente nas fases iniciais onde pode apresentar clinicamente um aspecto liquenóide. Portanto, recomenda-se considerar a manifestação inicial de LVP em mulheres idosas com lesão estriada que serão submetidas ao tratamento reabilitador com ID.

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

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ANEXOS

Anexo 1 – Comprovante de submissão Artigo 2.1

De: **Critical Reviews in Oncology/Hematology** <eesserver@eesmail.elsevier.com>
Date: qui., 18 de jun. de 2020 às 18:20
Subject: Submission Confirmation
To: <malopes@fop.unicamp.br>

*** Automated email sent by the system ***

Dear Lopes,

Your submission entitled "Oral squamous cell carcinoma around dental implants: A systematic review" has been received by Critical Reviews in Oncology/Hematology

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Anexo 2 – Comprovante de submissão Artigo 2.2

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Date: qua., 17 de jun. de 2020 às 16:46
Subject: Submission Confirmation
To: <malopes@fop.unicamp.br>

*** Automated email sent by the system ***

Re: "Epidemiological profile and clinical implications of oral squamous cell carcinoma adjacent to dental implants"
Joab Cabral Ramos, DDs., MSc student; Fábio A Alves, D.D.S, Ph.D.; Luiz P Kowalski, M.D., Ph.D.; Alan R Santos-Silva, D.D.S, Ph.D.; Pablo A Vargas, D.D.S, Ph.D.; Marcio A Lopes, D.D.S, Ph.D.
Original Research Article

Dear Professor Lopes,

Your submission entitled "Epidemiological profile and clinical implications of oral squamous cell carcinoma adjacent to dental implants" has been received by journal Oral Oncology

You will be able to check on the progress of your paper by logging on to Elsevier Editorial Systems as an author. The URL is https://ees.elsevier.com/oo/.

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Kind regards,

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Anexo 3 – Comprovante de submissão Artigo 2.3

9th Jun 2020

Dear Dr Miranda Galvis,

Title: Oral Cancer Adjacent to Dental Implants Mimicking Benign Lesions Particularly Peri-implantitis: A Case Series Study
Corresponding Author: Dr Miranda Galvis

Thank you for submitting the above manuscript for consideration in the British Dental Journal. The manuscript number we have assigned to you is MSS-2020-752. It is important that you keep this number, as this will be your reference should you need to contact us.

If you have any queries regarding your paper please click on the link below or contact me.

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Yours sincerely,

Jonathan Coe
Editor
British Dental Journal
bdjmanuscripts@nature.com

Anexo 4 – Comprovante de submissão Artigo 2.4

Med Oral Patol Oral Cir Bucal, Ref. 24095, 2020-06-17

medoral.es <medoral@medoral.es>
Ter, 16/06/2020 20:11
Para: joab.cabral@hotmail.com <joab.cabral@hotmail.com>
2020-06-17

Reference: 24095

Dear Dr. Joab Ramos,
Your manuscript entitled "Letter to Editor: Potentially malignant disorder in patients with oral squamous cell carcinoma around dental implants is lichen planus or proliferative verrucous leukoplakia? " has been successfully submitted online and has been forwarded to the referees for evaluation. In due time, you will be informed as to its possible publication in Med Oral Patol Oral Cir Bucal.

You can download the pdf of the article at:
http://www.medoral.es/pdf/documentos_generados/finder/files/24095/24095.pdf

For any comment or problems do not reply to this email. Send an email to:
articles_medoral@medoral.es

Yours sincerely.

Professor Jose V. Bagan
Editor Med Oral Patol Oral Cir Bucal
Indexed in: Indexed in: Science Citation Index Expanded, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, Scopus, Embase and Emcare, Indice Médico Español, IBECS, Dialnet, Latindex

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

PERFIL EPIDEMIOLÓGICO E IMPLICAÇÕES CLÍNICAS DO CARCINOMA ESPINOCELULAR ORAL ADJACENTE À IMPLANTES DENTÁRIOS

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Anexo 6 – Certificado de aprovação do Comitê de Ética

COMITÊ DE ÉTICA EM PESQUISA
FACULDADE DE ODONTOLOGIA DE PIRACICABA
UNIVERSIDADE ESTADUAL DE CAMPINAS

CERTIFICADO

O Comitê de Ética em Pesquisa da FOP-UNICAMP certifica que o projeto de pesquisa "**Perfil epidemiológico e comportamento clínico do carcinoma espinocelular em áreas adjacentes a implantes dentários**", CAAE **04040818.0.0000. 5418**, dos pesquisadores **Joab Cabral Ramos, Márcio Ajudarte Lopes, Fábio de Abreu Alves** e **Luiz Paulo Kowalski**, satisfaz as exigências das resoluções específicas sobre ética em pesquisa com seres humanos do Conselho Nacional de Saúde – Ministério da Saúde e foi aprovado por este comitê em 18/12/2018.

The Research Ethics Committee of the Piracicaba Dental School of the University of Campinas (FOP-UNICAMP) certifies that research project "**Epidemiological profile and clinical behavior of squamous cell carcinoma adjacent to dental implants**", CAAE **04040818.0.0000. 5418**, of the researcher's **Joab Cabral Ramos, Márcio Ajudarte Lopes, Fábio de Abreu Alves** and **Luiz Paulo Kowalski**, meets the requirements of the specific resolutions on ethics in research with human beings of the National Health Council - Ministry of Health, and was approved by this committee on the 18th of December of 2018.

Profa. Fernanda Miori Pascon
Vice Coordenador
CEP/FOP/UNICAMP

Prof. Jacks Jorge Junior
Coordenador
CEP/FOP/UNICAMP

Nota: O título do protocolo e a lista de autores aparecem como fornecidos pelos pesquisadores, sem qualquer edição.
Notice: The title and the list of researchers of the project appears as provided by the authors, without editing.

Anexo 7 – Certificado de aprovação do Comitê de Ética

A.C.Camargo Cancer Center
Centro Integrado de Diagnóstico, Tratamento, Ensino e Pesquisa

COMITÊ DE ÉTICA
EM PESQUISA - CEP

APROVAÇÃO

Os membros do Comitê de Ética em Pesquisa da Fundação Antônio Prudente – A.C.Camargo Cancer Center, em sua última reunião de **21/05/2019, aprovaram** a realização do projeto nº. **2718/19** intitulado: **"PERFIL EPIDEMIOLÓGICO E COMPORTAMENTO CLÍNICO DO CARCINOMA ESPINOCELULAR EM ÁREAS ADJACENTES A IMPLANTES DENTÁRIOS."**

Pesquisador Responsável: Fábio de Abreu Alves

Aluno: Joab Cabral Ramos (coparticipante)

Informações a respeito do andamento do referido projeto deverão ser encaminhadas ao CEP dentro de 06 meses em relatório (modelo CEP).

São Paulo, 24 de maio de 2019.

Atenciosamente,

Dra. Sandra Caires Serrano
1ª. Vice-Coordenadora do Comitê de Ética em Pesquisa