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Research Article

Oral Cancers Adjacent to Dental Implants: A Descriptive Study

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ABSTRACT

Background: Trauma and chronic inflammation are controversial factors because of their potential role as an initiator or as an aggravating factor in the oral carcinogenesis process. Dental implants are related to chronic inflammatory processes and could act as a potential risk factor for oral cancer.

Objective: To analyze the oral cancer cases adjacent to dental implants.

Methodology: A PubMed database search on studies of oral cancers adjacent to dental implants was conducted.

Statistical analysis: The descriptive statistic included means, standard deviations, ranges and percentages. For the comparison of continuous variables, the Student's t-test was used and, for the comparison of categorical variables the Pearson Chi-square test was applied.

Results: Thirty studies describing 62 cases of oral cancer adjacent to dental implants were included in this review. These cancers were observed more frequently in patients with an average age of almost 67 years, female gender and mandibular location. The most prevalent harmful habit was the combined consumption of tobacco and alcohol and the most common oral risk lesion was leukoplakia. Almost all were oral squamous cell carcinomas and half were moderately differentiated.

Conclusion: Oral cancers adjacent to dental implants seem to have similar characteristics than tumors not related to dental implants.

Introduction

Oral pharyngeal cancer is the sixth most common cancer in the world responsible for approximately 4% of cases and 3.5% of all cancer deaths [1]. The etiological factors most strongly associated with the oral cancer risk are the consumption of tobacco and/or alcohol intake and the existence of potentially malignant disorders of the oral mucosa. Other related factors are prolonged and accumulative sun exposure, especially in lip cancer, infectious agents such as human papillomavirus or Candida fungus, poor diet and nutrition, or immunosuppression conditions [2]. Trauma and chronic inflammation of oral tissues are controversial factors in terms of their role as an initiator or as an aggravating factor in the oral carcinogenesis process [3]. Implant rehabilitation has become a therapeutic option very demanded by patients. However, the placement of dental implants can lead to the appearance of chronic inflammatory processes (periimplantitis) and act as a potential risk factor for oral cancer [4]. The aim of this study was to analyze the oral cancer cases adjacent to dental implants.

Materials and Methods

A search of oral cancer studies and dental implants in the PubMed database was carried out combining the terms of the Medical Subjects Headings (MeSH) "dental implant abutment design" OR "dental implant" OR "dental implants" AND "mouth neoplasms". After this initial search, 217 articles were found between 1968 and 2018.

Only studies with full-text availability were considered (n=149). The exclusion criteria were a) studies on rehabilitation with dental implants of the oncology patient (n=110) and b) studies with non-usable data (n=9). After applying the inclusion and exclusion criteria, 30 studies remained for this review (Figure 1).

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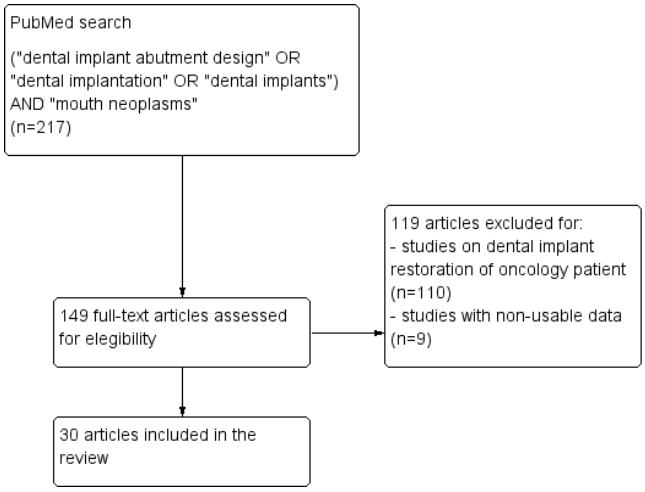

Figure 1: Study flow diagram.

Statistical analysis

The data were processed with the statistical program IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY). The descriptive statistic included means, standard deviations, ranges and percentages. For the comparison of continuous variables, the Student t-test was used and for the comparison of categorical ones, the Pearson Chi-square test was applied. A *P*-value < 0.05 was considered as the minimum level of significance.

Results

Table 1 shows the studies with cases of oral cancer adjacent to dental implants considering the country of origin, the age and gender of the patients, the histological type of tumor, the maxilla or mandible location, the degree of tumor differentiation, the tobacco and/or alcohol consumption, the existence of oral risk lesions and the time elapsed since the implant placement and the diagnosis of oral cancer. The 30 studies analyzed describe 62 oral cancer cases adjacent to dental implants [5-34].

Table 1: Description of the studies on oral cancers adjacent to dental implants according to age, gender, histological type of tumor, location, degree of tumor differentiation, harmful habits, oral risk lesions and the time elapsed since implant placement to the diagnosis of oral cancer.

First author, year	Country	n	Mean age	Gender	Histological type	Location Differentiation	Harmful habits	Oral risk lesion	Time Imp-OC
Friedman, 1983 [5]	USA	1	65 yrs	1M	OSCC	Mnd WD	Tob	na	12m
Clapp, 1996 [6]	USA	3	78 yrs	1M, 2F	3OSCC	3Mnd na, 2MD	No,Alc,Tob+ Alc	No,pOC	36m,48m, 84m
Moxley, 1997 [7]	The Netherlands	1	74 yrs	1F	OSCC	Mnd na	na	ExL	156m
Block, 2001 [8]	USA	1	72 yrs	1M	VeCa	Mnd WD	Tob	Leu	5m
Shaw, 2004 [9]	UK	2	63 yrs	1M, 1F	2OSCC	2Mnd na, MD	2na	pOC,ExL	63m,24m
Czerninski, 2006 [10]	Israel	2	66 yrs	1M, 1F	2OSCC	2Mnd WD, MD	Tob,na	OLP,pOC	36m,36m
Dib, 2007 [11]	Brazil	1	67 yrs	1F	OSCC	Mnd na	na	na	na
Verhoeven, 2007 [12]	The Netherlands	1	67 yrs	1F	OSCC	Mnd PD	na	na	na
Poggio, 2007 [13]	Italy	1	75 yrs	1F	Plasmac.	Mnd na	na	ONe	36m
Abu El-Naaj, 2007 [14]	Israel	2	71 yrs	1M, 1F	2OSCC	2Mnd na	No,na	No,OLP	144m,180m
Eguia del Valle, 2008 [15]	Spain	1	76 yrs	1M	OSCC	Mnd WD	No	No	60m
Gallego, 2008 [16]	Spain	1	81 yrs	1F	OSCC	Mnd MD	na	OLP	36m
Schache, 2008 [17]	UK	1	77 yrs	1M	OSCC	Mnd MD	No	No	60m
Kwok, 2008 [18]	UK	3	67 yrs	2M, 1F	3OSCC	3Mnd 2WD, MD	3Tob+Alc	2na, 1pOC	3m,72m, 12m
Chimenos-Küstner, 2008 [19]	Spain	1	62 yrs	1F	OSCC	Mnd na	na	na	2m

McGuff, 2008 [20]	USA	1	38 yrs	1F	Sarcoma	Uma na	No	No	11m
Gulati, 2009 [21]	UK	1	62 yrs	1F	OSCC	Mnd MD	Tob	pOC	96m
Gallego, 2009 [22]	Spain	1	70 yrs	1F	OSCC	Mnd WD	No	No	120m
De Ceulaer, 2010 [23]	The Netherlands	3	70 yrs	1M,2F	3OSCC	3Mnd 2WD, 1MD	3na	3pOC	24m,7m,6m
Meijer, 2010 [24]	The Netherlands	1	65 yrs	1F	OSCC	Mnd MD	na	pOC	48m
Orhan, 2011 [25]	Turkey	1	69 yrs	1F	OSCC	Mnd na	na	na	na
Bhatavadekar, 2011 [26]	India	1	54 yrs	1M	OSCC	Uma na	No	No	12m
Pfammatter, 2012 [27]	Switzerland	1	55 yrs	1F	OSCC	Mnd na	na	na	na
Jané-Salas, 2012 [28]	Spain	2	61 yrs	2M	2OSCC	2Mnd na, MD	2No	2No	24m,108m
Marini, 2013 [29]	Italy	1	51 yrs	1F	OSCC	Mnd MD	na	OLP	48m
Moergel, 2014 [30]	Germany	15	66 yrs	7M,8F	15OSCC	14Mnd, 1Uma 15na	10na, 4Tob+Alc, 1Alc	9Leu,3OLP, 2Ery,1na	42m,48m, 43m,120m, 43m,7m,5m, 115m,42m, 29m,97m, 43m,110m, 6m,51m
Bhandari, 2016 [31]	India	1	71 yrs	1F	OSCC	Uma WD	No	No	19m
Nariai, 2016 [32]	Japan	1	58 yrs	1F	OSCC	Mnd na	na	pOC	36m
Raiser, 2016 [33]	Israel	3	66 yrs	1M, 2F	2OSCC,1BcL	2Mnd, 1Uma 2na, WD	No, 2na	No, 2OLP	3na
Kaplan, 2017 [34]	Israel	7	69 yrs	2M,5F	7OSCC	5Mnd, 2Uma 7na	4na, 2No, 1pOC	4na, 2No, 1pOC	12m,156m, 5m,9m,7m, 9m,12m

Time IM-OC: Time between implant placement and oral cancer diagnosis; **n:** number of cases; **yrs:** years; **m:** months; **USA:** United States of America; **UK:** United Kingdom; **M:** male; **F:** female; **OSCC:** oral squamous cell carcinoma; **VeCa:** verrucous carcinoma; **Plasmac.:** plasmacytoma; **BcL:** B-cell lymphoma **na:** data not available; **Mnd:** Mandible; **Uma:** Upper maxilla; **WD:** well-differentiated; **MD:** moderately differentiated; **PD:** poorly differentiated; **No:** none; **Tob:** tobacco consumption; **Alc:** alcohol intake; **pOC:** previous oral carcinoma; **ExL:** Exophytic leukoplakia; **Leu:** Leukoplakia; **Ery:** erythroplasia **OLP:** oral lichen planus; **ONe:** Other neoplasms.

The description of the different parameters considered in the 62 oral cancers adjacent to dental implants is presented in (Table 2). Patients had a mean age of 66.85±11.34 years (range 38 to 90 years). By gender, 38 (61.3%) were female and 24 (38.7%) male. The most frequent histological tumor type was oral squamous cell carcinoma (OSCC) with 93.6% of cases (58/62). The remaining 6.4% were other tumors such as verrucous carcinoma, plasmacytoma, sarcoma or B-cell lymphoma. Fifty-five tumors (88.7%) were located in the mandible, while 7 (11.3%), in the upper maxilla. Regarding the degree of tumor differentiation, 50% of them were moderately differentiated (MD) and 45.8% were well-differentiated tumors (WD). The combined consumption of tobacco and alcohol was the most frequent harmful habit (25.9%). 25.5% of the patients did not report any previous oral risk lesion, meanwhile, 21.6% had oral leukoplakias as a risk lesion. Finally, the mean time between implant placement and diagnosis of oral cancer was 48.64±45.63 months (range 2 to 180 months). When comparing the different parameters of the study (Table 3), male patients had a higher mean age than that of women, although without statistically significant differences (P=0.56). Similarly, patients with tumors in the mandible, had a higher mean age than that of patients with tumors in the upper maxilla, albeit no statistically significant association was found (P=0.12). On the other hand, oral cancers in males and those located in the mandible suffered a greater diagnostic delay than those of women and those located in the upper maxilla, though without statistically significant differences (P=0.75 and P=0.18, respectively). When analyzing the possible relationship between gender and tumor location, in most women, tumors were located in the mandible; whereas, in the majority of men, they were located in the upper maxilla. However, no statistically significant

association was found (*P*=0.41). The majority of the males reported tobacco and/or alcohol consumption while the majority of the females did not have harmful habits, even if without statistically significant differences (*P*=0.86).

Table 2: Description of different parameters analyzed in the 62 oral cancers adjacent to dental implants.

Parameter	
Age X±SD (range)	66.85±11.34 years (38-90 years)
Gender	
Male n (%)	24 (38.7)
Female n (%)	38 (61.3)
Histological tumor type	
OSCC n (%)	58 (93.6)
Verrucous carcinoma n (%)	1 (1.6)
Plasmacytoma n (%)	1 (1.6)
Sarcoma n (%)	1 (1.6)
B-cell lymphoma n (%)	1 (1.6)
Location of tumor	
Upper maxilla	7 (11.3)
Mandible	55 (88.7)
Degree of tumor differentiation[a]	
WD n (%)	11 (45.8)
MD n (%)	12 (50.0)
PD n (%)	1 (4.2)
Harmful habits[b]	
None n (%)	13 (48.2)
Tobacco n (%)	5 (18.5)
Alcohol n (%)	2 (7.4)
Tobacco+Alcohol n (%)	7 (25.9)
Oral risk lesion[c]	
None n (%)	13 (25.5)
Previous OSCC n (%)	10 (19.6)
Exophytic leukoplakia n (%)	3 (5.9)
Leukoplakia n (%)	11 (21.6)
Erythroplakia n (%)	2 (3.9)
Oral lichen planus n (%)	10 (19.6)
Other neoplasms n (%)	2 (3.9)
Time dental implant-oral cancer X±DE (range)	48.64±45.63 months (2-180 months)

X±SD: mean±standard deviation; **OSCC:** oral squamous cell carcinoma; **WD:** well-differentiated; **MD:** moderately differenciated; **PD:** poorly differentiated; [a]38 cases without data; [b]35 cases without data; [c]11 cases without data.

Table 3: Association between different parameters of the study.

Parameters	Gender		
	Male	Female	*P* value
Age			
X±SD, years (n)	67.92±12.01 (24)	66.18±11.01 (38)	0.56
	Tumor location		
	Mandible	Upper maxilla	*P* value
Age			
X±SD, years (n)	67.64±10.69 (55)	60.71±15.14 (7)	0.12
	Gender		
	Male	Female	*P* value
Time implant-oral cancer*			
X±SD, months (n)	50.96±46.70 (24)	46.97±45.52 (38)	0.75
	Tumor location		
	Mandible	Upper maxilla	*P* value
Time implant-oral cancer*			
X±SD, months (n)	51.51±46.19 (55)	25.17±35.52 (7)	0.18
	Tumor location		
Gender	Mandible	Upper maxilla	*P* value
Male n (%)	20 (36.4)	4 (57.1)	
Female n (%)	35 (63.6)	3 (42.9)	0.41
	Harmful habits		
Gender	No	Yes	*P* value
Male n (%)	6 (46.2)	8 (57.1)	
Female n (%)	7 (53.8)	6 (42.9)	0.86

X±SD: mean±standard deviation; ***Time implant-oral cancer:** Time between implant placement and oral cancer diagnosis; **n:** number of cases; **(%):** percentage.

Discussion

In the present review on oral cancers adjacent to dental implants, data from 30 studies have been included. In this review, patients with oral cancer adjacent to dental implants had a mean age of almost 67 years, an age very close to that published in several studies [5, 10-12, 18, 30, 33]. However, five studies described cases of oral cancer adjacent to implants in subjects older than 75 years [6, 13, 15-17]. The youngest patient with a tumor adjacent to a dental implant was a 38-year-old patient who had a sarcoma, a tumor with a much more aggressive biological behavior than oral squamous cell carcinoma, the most common neoplasm in the oral cavity [20]. Most oral cancer studies situate the age range of patients between 60 and 80 years old [15]. Oral tumors adjacent to dental implants seem to appear at the same ages as those with oral tumors not related to dental implants [4]. Oral cancers adjacent to dental implants were more frequent in women than in men, an apparently contradictory finding since oral cancer has a predilection for males [2]. This finding should be interpreted with caution since this work is a descriptive study of the cases of oral peri-implant cancer published in the literature. However, it seems that women have a higher risk of developing a second primary carcinoma around dental implants [32].

93.6% of the neoplasms adjacent to dental implants were oral squamous cell carcinomas (OSCCs), the most common histological type in the oral cavity. Isolated cases of other histological types (verrucous carcinoma, plasmacytoma, sarcoma, B-cell lymphoma) have been described in tumors around implants [8, 13, 20, 33]. Nevertheless, the fact of being a carrier or not of dental implants does not affect the histological type most frequently found in oral cancers [4]. The majority of cases of oral cancer adjacent to dental implants were located in the mandible with respect to the upper maxilla. Implant placement in the mandible could induce a series of bony changes potentially predisposing to the onset of cancer. Specifically, the mandible has areas rich in bone marrow, in which there are variations in blood circulation that could condition the entrapment of tumor cells, creating the appropriate conditions for possible tumor development [27]. Another possible explanation would be that dental implants located in the mandible were subjected to occlusal loads greater than that of the dental implants in the upper maxilla, inducing a possible continuous trauma that would favor chronic inflammation and infection of the mandibular bone [34]. Also, in cancers located in the maxilla, there was a higher percentage of males and younger patients compared to cases located in the mandible. However, in both cases no statistically significant differences were observed. These are probably casual

findings related to the characteristics of the cases described in the literature [4].

Regarding the degree of tumor differentiation, 50% of the carcinomas adjacent to the dental implants were moderately differentiated tumors, while another 45.8% were well-differentiated tumors. The percentage of well-differentiated tumors in oral cancers not related to dental implants is lower, showing that they are lesions in more advanced stages due to diagnostic delay [32]. The appearance of lesions in relation to dental implants causes concern in the patient thinking that he can lose the implant and demanding attention. This attitude contributes to the earlier diagnosis of these lesions and could justify the high percentage of well-differentiated tumors [28]. Oral cancer is closely related to harmful habits. In this review, 51.8% of patients with cancers adjacent to dental implants had a history of tobacco and/or alcohol consumption and in 25.9% of cases, there was a combined consumption of tobacco and alcohol, which, per se, implies an exponential increase in the oral cancer risk [6,16,32]. In the present review, gender had no significant influence on harmful habits. Apart from these well-known classic factors of oral cancer, chronic trauma is a controversial factor as regards its possible role as the unique initiator of carcinogenesis or as an aggravating factor along with other factors. Chronic trauma could facilitate tumor growth since malignant cells grow more rapidly in areas of high cell proliferation, such as bone regeneration areas mediated by host growth factors that occur around a dental implant. Periimplantitis is a major complication of implant therapy. It is a chronic inflammatory condition that can cause loss of supporting bone in the tissues surrounding a dental implant. The gingival tissue around the implant experiences constant inflammation that may compromise implant stability. This inflammation can play an important role in the development of cancer due to the action of inflammatory cytokines such as interleukin 1, interleukin 6 and tumor necrosis factor [3]. In the implant placement, the periodontal ligament may be affected, producing an implant-bone interface that could facilitate the development of carcinoma at this level [25, 28, 32].

The presence of previous risk lesions before oral cancers related to dental implants was also analyzed. 25.5% of patients did not have any previous oral risk lesion. Before the development of cancer, oral potentially malignant disorders were observed, such as different types of leukoplakia (27.5% of the cases), oral lichen planus (19.6%) or erythroplasia (3.9%). Leukoplakia and, above all, erythroplakia are lesions with high rates of malignant transformation in which the implant placement in patients with these lesions could be situations that contribute to malignant degeneration [30]. In the case of oral lichen planus, it should be borne in mind that these patients are usually treated with corticosteroids for important periods of time, which could induce immunosuppression states that would favor malignant transformation [29]. Special mention deserves 19.6% of cases in which patients had had an oral squamous cell carcinoma before. This high percentage reveals the phenomenon of field cancerization in the case of oral cancer in which there is a high probability of developing second primary tumors. The implant placement could be a precipitating factor, in combination with others, for the start of a new process of oral carcinogenesis [24].

With respect to the time elapsed between the placement of the implants and the diagnosis of oral cancer, it was just over 4 years (48.64 months) with an interval between 2 and 180 months. It refers to the moment of diagnosis, not necessarily the appearance of the lesion. Probably there is a delay in the diagnosis of the neoplasm when initially confused with an inflammatory peri-implant lesion. Any lesion that appears in relation to dental implants, although in most cases it will be an inflammatory lesion, requires correct diagnosis, treatment and a periodic follow-up [3]. If after the treatment, the lesion is not resolved satisfactorily, it is mandatory to perform a biopsy and histopathological study, especially in hyperplastic lesions with peri-implant bone resorption [15,26,28,30,31]. Finally, the mean diagnostic delay was lower in women (46.97 months) than in men (50.96 months), although statistical significance was not reached. New studies are needed in larger population samples and longer follow-up times that allow establishing the true influence of dental implant placement on the oral cancer risk.

In conclusion, oral cancers adjacent to dental implants were observed more frequently in patients with an average age of almost 67 years, of female gender and with tumors of mandibular location. The most common harmful habit was the combined consumption of tobacco and alcohol and the most frequent oral risk lesion was leukoplakia. Almost all (93.6% of cases) were oral squamous cell carcinomas and half were moderately differentiated.

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