Oral Oncology 75 (2017) 39–45

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

A multicenter study of malignant oral and maxillofacial lesions in children and adolescents

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ARTICLE INFO

Keywords:
Oral oncology
Oral lesions
Neoplasms
Child
Adolescent
Epidemiology

ABSTRACT

Objectives: To investigate the frequency of malignant oral and maxillofacial lesions among children and adolescents from representative geographic regions of Brazil.
Materials and Methods: A retrospective study was conducted on biopsies obtained from 1990 to 2016 at six Brazilian oral and maxillofacial pathology referral centers. A total of 85,105 biopsy specimens from children and adolescents were analyzed. Gender, age, anatomical location, symptomatology and histopathological diagnosis were evaluated. Data were analyzed using descriptive statistical methods.
Results: Fifty-eight (0.06%) malignant oral and maxillofacial lesions were diagnosed in children (19%) and adolescents (81%). The lesions were more frequent among females (60.3%) and adolescents. The most prevalent lesions were mucoepidermoid carcinomas (22.4%), osteosarcomas (13.8%), squamous cell carcinomas (12.1%), and Burkitt's lymphomas (12.1%). The most commonly affected sites were the palate (19%), mandible (13.8%), and maxilla (13.8%). Almost half the patients were asymptomatic.
Conclusion: Pediatric oral and maxillofacial malignant lesions were infrequent and showed wide diversity, with a prevalence of mucoepidermoid carcinomas. Analysis of malignant lesions in children and adolescents helps pediatric dentists and oncologists to obtain a better understanding of such lesions and to reduce the time for diagnosis, with a consequent improvement of prognosis.

Introduction

Children and adolescents constitute about a third of the world's population and their health status is important for every country [1]. They represent the future, and ensuring their healthy growth and development should be a major concern of all societies [2]. Cancer in children and adolescents represents a group of diseases considered rare, with an incidence of 0.01% in the age range of 0–19 years in developed countries [3]. When compared to adult malignancies, it corresponds to 2–3% of all malignant tumors [4]. Brazil has a young population and the current estimate of its total population is 207 million inhabitants. Brazilian demographic data for 2017 show that 30.98% of the population is in the 0–19 year age range [5]. In this country, cancer represents the first leading cause of death (8% of the total) by disease among children and adolescents [6].

Over the last four decades, extremely significant progress has been

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http://dx.doi.org/10.1016/j.oraloncology.2017.10.016
Received 28 September 2017; Accepted 19 October 2017
Available online 05 November 2017
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made in the treatment of childhood and adolescence cancer. Nowadays, about 80% of children and adolescents with cancer can be cured if diagnosed early and treated at specialized centers, most of them having a good quality of life after treatment [7,8].

The world's population should reach 9.7 billion by 2050 [9], being accompanied by a high incidence of oral and systemic diseases. Several studies on the epidemiology of malignant lesions among children and adolescents have been conducted worldwide [3,10–15]. The incidence of oral lesions among children and adolescents requires attention in terms of public health policies for the diagnosis and treatment of diseases, promoting a better quality of life. For childhood cancers in particular, a classification of cancers by histological type is important in order to understand the etiology and progression of the disease and has led to new studies about the health of pediatric patients [16,17].

Epidemiological studies based on histopathological results of oral and maxillofacial biopsies provide more accurate data [18–22]. The objective of the present study was to determine the frequency of malignant and maxillofacial oral lesions in children and adolescents from representative geographic regions of Brazil.

Material and methods

Study design and ethical approval

A total of 85,105 histopathological records of oral and maxillofacial biopsies were analyzed in a retrospective study. The records were obtained from six oral diagnostic referral centers in four regions of Brazil (Southeast, Northeast, South and Midwest) (Table 1). The study was approved by the Ethics Committee of Federal University of Minas Gerais (Approval No. 016/2003). The patient's identity remained anonymous according to the Declaration of Helsinki.

Sample

A total of 85,105 biopsy records from patients aged 0–19 years were analyzed. The malignant oral and maxillofacial lesions were analyzed regarding gender, age, anatomical location, symptomatology, and histopathological diagnosis. The patients were stratified by age, i.e., 0–9 years: children, and 10–19 years: adolescents [23] in order to evaluate the distribution of lesions according to age. The anatomical sites involved were divided into lips, maxilla, mandible, palate, floor of the mouth, tongue, cheek mucosa, parotid gland, temporomandibular joint, and extraoral sites.

Exclusion criteria were lack of information about age (≤19 years of age) or gender and lack of a histopathological diagnosis. Malignant oral and maxillofacial lesions were classified according to the 2017 classification of the World Health Organization (WHO) [24]. The cases were analyzed by six independent oral and maxillofacial pathologists with more than 20 years of experience. Immunohistochemical analysis was performed when routine hematoxylin-eosin staining was not sufficient to establish the final diagnosis of the lesions.

Data analysis

Descriptive and quantitative data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 22.0 (SPSS Inc., Chicago, IL, USA).

Table 1
Sources of the reviewed cases.

Institution	Years	Lesions biopsied during the study period	Oral lesions diagnosed in patients (0–19 Y)	Malignant lesions diagnosed in patients (0–19 Y)	%[a]
UFMG[b]	1996–2016	35,118	2487	26	0.07
UFG[c]	1996–2016	10,246	1507	15	0.14
UPE[d]	1990–2016	6250	1109	12	0.19
UFPel[e]	1996–2016	16,182	1832	3	0.01
UFRGS[f]	1996–2016	14,606	2164	1	0.006
UFSC[g]	2006–2016	2703	312	1	0.03
Total		85,105	9411	58	0.406

[a] Percent of the sample of malignant lesions at each center.
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Results

A total of 85,105 patients were diagnosed with oral and maxillofacial lesions at the centers studied; of these, 9411 (11.0%) were 0–19 years old, with malignant lesions being detected in 58 cases. This value represented 0.06% of all diagnoses made at all centers and 0.61% of the diagnoses made in the age range of 0–19 years at all centers; and 5.3% of neoplasms of the total sample of children and adolescents. The average percentage of malignant lesions at all centers was 0.40%.

Among the malignant cases studied, 44.8% (n = 26) were from the Federal University of Minas Gerais, 25.9% (n = 15) from the Federal University of Goiás, 20.7% (n = 12) from the University of Pernambuco, 5.1% (n = 3) from the Federal University of Pelotas, 1.7% (n = 1) from the Federal University of Rio Grande do Sul, and 1.7% (n = 1) from the Federal University of Santa Catarina (Table 1).

The most prevalent lesions were mucoepidermoid carcinomas (MEC) (22.4%), osteosarcomas (OS) (13.8%) (Fig. 1), squamous cell carcinomas (SCC) (12.1%), and Burkitt's lymphomas (BL) (12.1%) (Fig. 2); 60.3% (n = 35) of the cases were females. The highest frequency of lesions (81.0%) was observed in the age group of 10–19 years. Most of the lesions proved to be asymptomatic (43.1%). The lesions affected different sites, the most common being the palate (19%), mandible (13.8%), and maxilla (13.8%) (Table 2).

Eleven cases of Langerhans cell histiocytosis were detected at the centers studied. However, since there is no consensus about the classification of this disease as malignant, these cases were not included in the sample of malignant lesions. For this kind of lesion, females were slightly more affected (54.5%) than males. Children were more affected (72.7%) than teenagers; most cases were asymptomatic (63.3%) and the mandible (63.6%) was the most common anatomical region.

Worldwide studies of oral and maxillofacial biopsied lesions involving children and adolescents have reported variations in the geographic distribution, prevalence, age, period of data collection, number of lesions and most prevalent malignant lesions (Table 3).

Discussion

Annually, it is estimated that 127,459 deaths are caused by oral cavity malignancies worldwide, 96,720 of which occur in less developed countries [25]. Oral cancer is highly prevalent in India, Pakistan, Afghanistan, Iran, Bangladesh, Sri Lanka, Bhutan, Nepal, Maldives, Brazil, and France. In these countries, it ranks first or second among the different types of cancer [26]. In Brazil, it is estimated that in 2017 about 15,500 new cases of malignancies will occur among all ages [6]. The causes of most childhood malignant diseases remain poorly understood, even though genetic predisposition seems to be more frequent in the pathogenesis of childhood and youth cancers in comparison to adults [27,28].

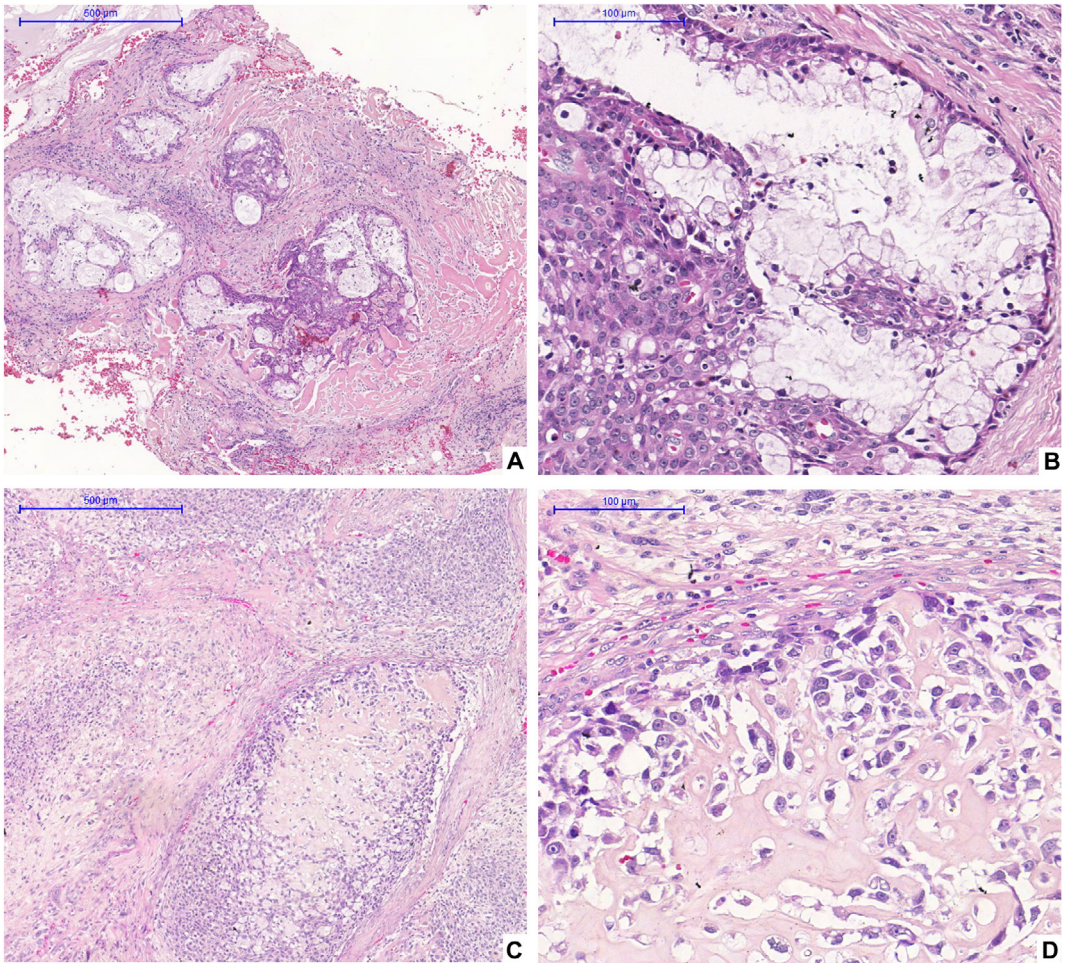

Fig. 1. A and B represent a mucoepidermoid carcinoma. A - Low-power view of the tumor's nests mixed with dense connective tissue (H & E staining, 5× magnification). Tumor's nest composed of the intermediate - basaloid shape and mucus-producing cells- large, cell contain abundant foamy cytoplasm (H & E staining, 20× magnification). C and D represent an osteosarcoma. C- Low-power view of the sheets of round or spindle cells separated by fascicle dense connective tissue (H & E staining, 5× magnification). D - Round cells with pleomorphism, nuclear hiperchromatism and associated with direct production of osteoid that is characterized by eosinophilic and amorphous material (H & E staining, 20× magnification).

In this Brazilian survey, malignant oral and maxillofacial lesions represented 58 (0.61%) cases among 9411 lesions diagnosed in patients in the age group 0–19 years. The data agree with the rate reported in single center studies in Asia, Europe, Africa and America showing a relative frequency of malignant lesions among children and adolescents ranging from 0.14 to 7.74% [18,19,29,30]. The difference of our study is that it reports the frequency of malignant lesions detected at reference centers in a multicenter collaboration. In addition, there is variation between continents regarding the frequency of malignant lesions in the age group studied [17,30,31]. A comparison of the real prevalence of this lesion among different regions may be difficult mainly because of the different periods of analysis in each population and the relative lack of epidemiological studies on this topic [32–34]. Studies reporting prevalence and incidence data were based on the 2005/1992 WHO classification. Although the present study was based on the latest 2017 WHO classification, the prevalence of malignant lesions found was similar to that reported in studies which used the 2005/1992 WHO classification.

The six referral centers with diagnostic services in oral and maxillofacial pathology are located in four different geographic regions of Brazil (Southeast, Northeast, South and Midwest). In the Brazilian states of Minas Gerais, Goiás, Pernambuco, Rio Grande do Sul, and Santa Catarina (geographic areas: 586.522,122 km^2; 340.111,783 km^2; 98.312 km^2; 281.062 km^2; and 95.736,165 km^2, respectively), children and adolescents aged 0–19 years account for 14.15%, 15.14%, 16.39%, 13.15%, and 13.79%, of the population, respectively [5]. Studies involving children and adolescents have been conducted in these different regions and, when the occurrence of lesions in this population was compared, variations were detected in their prevalence and geographic distribution (Table 3).

Salivary gland epithelial neoplasms are rare in children, with a global annual incidence of 3–4 cases per 100,000, accounting for less than 5% of all salivary gland tumors and merely 2% of head and neck malignancies in the pediatric population [35,36]. These are heterogeneous lesions with complex clinical features and distinct biological behavior. To date, only a few studies have been conducted on pediatric salivary gland tumors and less than a handful have assessed the behavior and prognosis of these lesions [36]. According to Hicks and Flaitz [14], Xu et al. [36] and Chiaravalli et al. [37], MEC is the most frequent of all malignant neoplasms of the salivary glands, with a higher prevalence among female adolescents [38], as also observed in the present study. Regarding the location of this neoplasm, despite wide variability, the present study supports previously reported data showing that the palate is the most frequent site [39–41].

The second most frequent malignant neoplasm observed in children and adolescents was OS. As found in studies conducted in China, India and Brazil [20,32,42], this lesion usually affects long bones like the femur, tibia and humerus, and less than 10% of cases occur in the jaws [43,44]. Growth factors may be associated with the development of OS of long bones, and this association is not clear for the jaw lesions since

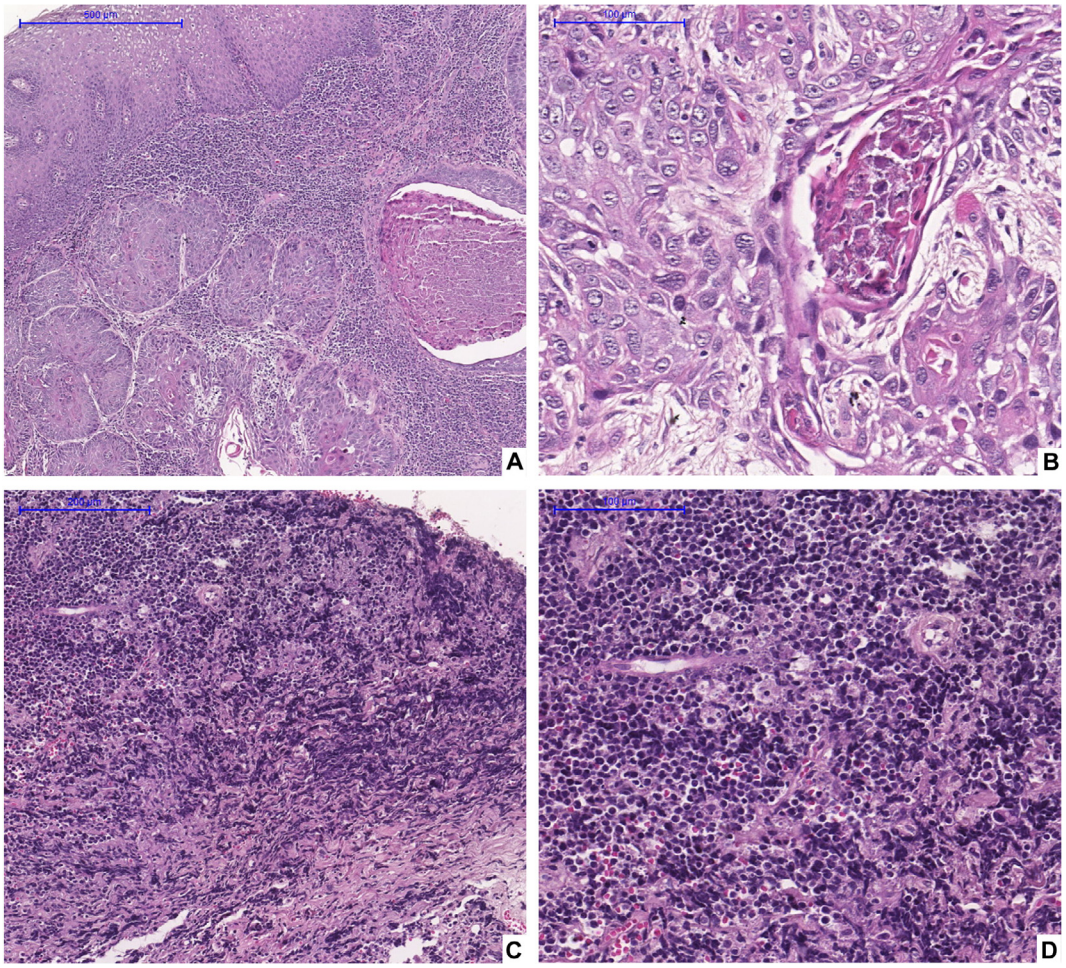

Fig. 2. A and B represent a squamous cell carcinoma. A - Low-power view of the invasive nests mixed with dense connective tissue below the mucosal surface (H & E staining, 5× magnification). B - Neoplastic squamous cells present an abundant eosinophilic cytoplasm, around nuclei and increased nuclear-cytoplasm ratio. Individual cell keratinization and neural invasion neural is also present (H & E staining, 20× magnification). C and D represent a Burkitt's lymphoma. C - Low-power view of the sheet of small cells invaded the dense connective tissue (H & E staining, 5× magnification). D - Cells of Burkitt's lymphoma are small, noncleaved and without evident cytoplasm. Classic "starry-sky" pattern is seen because of the presence of macrophages within of the tumor tissue (H & E staining, 20× magnification).

they appear after the growth phase [45]. Due to the rarity of this bone tumor, there is a lack of data supporting significant differences between genders and anatomical locations, although five cases of this multicenter study affected girls and the mandible was the most common site. All OS were diagnosed here in the second decade of life, in agreement with literature findings indicating an average age of 15 years [44].

Lymphomas represent the third most common cancer in children [46]. In the present study, BL was the third most frequent oral malignancy. Three clinical forms are described by the WHO: endemic, sporadic and related to immunodeficiency [46,47]. The lesions are diagnosed three times more in boys and when they occur in the jaw, the clinical findings are easily recognizable. The frequency of this disease in this Brazilian study agrees with the findings of Dhanuthai et al. [19] from Thailand, and with those of Omoregie and Akpata [48], who diagnosed 38 BL in a study from Nigeria. In surveys conducted where the malaria rate is high, the association of BL with this disease is also very frequent. However, although malaria is endemic in Brazil, none of the patients reported here had this disease.

Seven of the 58 cases of malignancy were oral SCC, occurring in patients with a mean age of 16.7 years. Oral SCC is more common in adolescents than in children. Smoking and alcohol consumption are factors predisposing to this type of cancer, which may also be associated with human papillomavirus (HPV) infection. None of the adolescents of the present sample had a history of smoking or consumption of alcoholic beverages or a medical history of HPV. However, in some Brazilian populations the smoking habit is present since childhood [49]. Some studies have reported similar findings of carcinoma incidence in adolescents [20,50].

In addition, rhabdomyosarcoma (RMS) and leiomyosarcoma (LMS) were prevalent soft tissue malignancies in the present study. Rhabdomyosarcoma is the most common soft tissue sarcoma of children, adolescents and young adults, representing about 3–4% of all cancers affecting children and 35% of cases affecting the head and neck region [51,52]. The incidence of RMS is highest in children aged 1–4 years, falling to a lower rate at 10–14 years, and remaining steady between 15 and 19 years [53]. In our study, adolescents and the cheek region were the most affected. In South America, Lima et al. [54] and Zuñiga et al. [55] observed that RMS was one of the most prevalent injuries in children and adolescents. According to Yadav et al. [56], no clear etiologic factors have been identified to account for the occurrence of these malignant neoplastic growths. There is, however, increasing evidence that gene abnormalities may play a role in the development of RMS. LMS in the head and neck region is rare [57]. The occurrence in the pediatric population is even rarer, as demonstrated by our study, in which only three patients were affected by this neoplasia, in agreement with the literature.

In the present study, two cases of ameloblastic carcinoma were detected, both characterized as *de-novo* lesions. This finding agrees with previous studies, indicating that the malignant transformation of odontogenic tumors is a rare occurrence, especially in the young

Table 2
Clinical data of 58 oral and maxillofacial malignant lesions in children and adolescents in the Brazilian population.

Lesions	*n* (%[b])	Gender		Age group		Symptomatology[a]		Anatomical region each of lesion
		Male (%)	Female (%)	0–9	10–19	Symptomatic	Asymptomatic	
Neurogenic sarcoma	1 (1.7)	–	1	–	1	–	–	Mandible (n = 1)
Leiomyosarcoma	4 (6.9)	2	2	3	1	1	2	Cheek área (n = 2); mandible (n = 1); NI (n = 1)
Rhabdomyosarcoma	3 (5.2)	2	1	1	2	1	1	Parotid duct (n = 1); jugal mucosa (n = 1); NI (n = 1)
Malignant fibrous histiocytoma	1 (1.7)	1	–	1	–	–	–	Cervical region (n = 1)
Fibrosarcoma	1 (1.7)	1	–	–	1	1	–	Mandible (n = 1)
Malignant peripheral nerve sheath tumor	1 (1.7)	–	1	–	1	–	1	Maxilla (n = 1)
Mucoepidermoid carcinoma	13 (22.4)	3	10	1	12	2	8	Palate (n = 6); jugal mucosa (n = 3); maxila (n = 2); parotid gland (n = 1); NI (n = 1)
Adenocarcinoma NOS	3 (5.2)	1	2	2	1	–	2	Upper lip (n = 1); orbital floor (n = 1); parotid gland (n = 1)
Carcinosarcoma	1 (1.7)	–	1	–	1	1	–	NI (n = 1)
Adenoid cystic carcinoma	2 (3.4)	–	2	–	2	–	1	Palate (n = 2)
Primitive neuroectodermal tumor	1 (1.7)	–	1	–	1	–	–	NI (n = 1)
Osteosarcoma	8 (13.8)	3	5	–	8	2	–	Mandible (n = 5); maxila (n = 2); NI (n = 1)
Chondrosarcoma	1 (1.7)	–	1	–	1	–	–	Temporomandibular joint (n = 1)
Ameloblastic carcinoma	2 (3.4)	2	–	–	2	1	1	Mandible (n = 1); maxila (n = 1)
Squamous cell carcinoma	7 (12.1)	2	5	–	7	2	5	Tongue (n = 6); nasal mucosa (n = 1)
Acute lymphoblastic leucemia	2 (3.4)	2	–	1	1	1	1	Parotid gland (n = 1); NI (n = 1)
Burkitt's lymphoma	7 (12.1)	4	3	2	5	–	3	Mandible (n = 3); maxila (n = 3); NI (n = 1)
Total	58 (100)	23 (39.6)	35 (60.3)	11 (19)	47 (81.0)	12 (20.7)	25 (43.1)	–

[a] Symptomatology was not available in some cases.
[b] Percent of the sample of malignant lesions at all centers; NI, not informed.

population [44,49,58]. Both reported cases affected boys in the second decade of life, in agreement with literature data showing a 3:1 ratio male:female ratio and a mean age of 12.6 years [59]. Although mandible and maxilla were equally affected in the present analysis, this lesion is most commonly seen in the mandibular region [44,58,60].

Unfortunately, a limitation of the present study is that staging/grading of the malignant lesions was not available because the investigation involved only diagnostic data from oral diagnostic centers. After the diagnosis, patients were referred to several hospitals throughout the country, so we could retrieve information about staging, grading or treatment. Single or multicenter prospective studies are feasible, even though malignant oral lesions are rare among pediatric patients. The prevalence of oral lesions seems to be dependent on various additional factors. For example, socioeconomic and cultural factors may influence self-care health measures and affect the search for health professionals, so that these lesions may be underdiagnosed. It is important to highlight that the notification of malignant neoplasms is important in order to implement preventive and early-diagnosis

Table 3
Malignant oral and maxillofacial biopsied lesions of children and adolescents in different geographic regions of the world.

Author and year of publication	Country	Period (years)	Age group	Total no. of lesions	Total no. of malignant lesions	%[a]	Most prevalent malignant lesions
Jones and Franklin, 2006	UK	30	0–16	4406	31	0.70	LCH, MEC, multiple endocrine neoplasia syndromes, neurosarcoma, RMS, and SCC
Dhanuthai et al., 2007	Thailand	15	0–16	1251	11	0.87	BL
Lima et al., 2008	Brazil	20	0–14	625	8	1.28	RMS, neuroblastoma, and LCH
Shah et al., 2009	USA	15	0–16	5457	8	0.14	–
Wang et al., 2009	China	20	0–14	797	7	0.87	OS
Al Yamani et al., 2011	Saudi Arabia	12	0–18	155	12	7.74	Lymphoma
Jaafari-Ashkavandi and Ashraf, 2011	Iran	5	0–18	142	35	24.6	Lymphoma
Saxena et al., 2012	India	6	0–18	61	4	6.55	OS
Zuñiga et al., 2012	Chile	15	0–16	542	4	0.73	Undifferentiated malignant tumor, RMS, malignant schwannoma, and NHL
Jaafari-Ashkavandi et al., 2014	Iran	19	0–18	576	11	1.90	Lymphoma
Ha et al., 2014	Australia	58	0–16	1305	9	0.68	LCH
Krishnan et al., 2014	India	10	0–15	97	4	4.12	Malignant round cell tumor, RMS, OS, and Ewing's sarcoma
Perry et al., 2015	USA	20	0–16	20	1	5	RMS
Omoregie and Akpata, 2014	Nigeria	21	0–16	1013	65	6.41	BL
Pêssoa et al., 2015	Brazil	15	0–19	360	1	0.27	Chondrosarcoma
Martins-Filho et al., 2015	Brazil	18	0–18	564	3	0.53	MEC, OS, and MPNST
Cavalcante et al., 2016	Brazil	12	0–16	1240	9	0.72	SCC
Ataíde et al., 2016	Brazil	15	0–16	2539	9	0.35	LCH and lymphoma
Patil et al., 2017	India	10	0–17	2959	5	0.16	MEC

[a] Percent of the sample of malignant lesions; BL, Burkitt's lymphoma; LCH, Langerhans cell histiocytosis; MEC, mucoepidermoid carcinoma; MPNST: malignant peripheral nerve sheath tumor; NHL, Non-Hodgkin lymphoma; OS, osteosarcoma; RMS, rhabdomyosarcoma; SCC, squamous cell carcinoma.

measures leading to more effective treatments for this population and improving prognosis.

Conclusion

Mucoepidermoid carcinoma was the most frequent disease. Our findings add to the literature of pediatric malignant oral and maxillofacial lesions. Due to the rarity of these malignancies, it is important to recommend that, whenever possible, the pediatric population should be referred to specialized centers. Also, it is a fundamental goal of pediatric dentists and oncologists dealing with these tumors to develop broad international cooperative schemes and especially to ensure an active networking with otolaryngologists and head and neck surgeons with an in-depth experience about malignant oral and maxillofacial tumors in adults. Thus, larger, international prospective cooperative efforts are needed.

Conflict of Interest

None declared.

Acknowledgements

This work was supported by the Brazilian National Council for Scientific and Technological Development [Grant Number CNPq #309322/2015-4]. The authors thank the Coordination for the Improvement of Higher Education Personnel (CAPES). RAM, ACB and MDM are research fellows of CNPq. Mrs. E. Greene provided English editing of the manuscript.

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