Odontogenic tumors: an 11-year international multicenter study

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Odontogenic tumors (OTs) are a heterogeneous group of lesions originating from the remnants of the tooth-forming apparatus (Nalabolu et al., 2016). The frequency rates of OTs vary from about 1% to 32% of all jawbone tumors (Adebayo et al., 2005; Sekerci et al., 2015).

OTs are divided into benign and malignant categories of unknown etiology (Sekerci et al., 2015; Wright and Tekkesin, 2017). The first internationally accepted classification of OTs was published by the World Health Organization (WHO) in 1971. It was then reviewed and updated in 1992, 2005, and in 2017 (Barnes et al., 2005; Sekerci et al., 2015; El-Naggar et al., 2017).

Several retrospective studies on OTs have been performed in different countries (Mosqueda-Taylor et al., 1997; Adebayo et al., 2005; Jing et al., 2007; Costa et al., 2012; Osterne et al., 2011), demonstrating variations in the clinical presentation of OTs. This multicenter study aimed to determine the prevalence and clinicopathologic presentation of OTs collected from three countries.

This retrospective study was approved by the Research Ethics Committee of the São Leopoldo Mandic Institute and Research Center (protocol number: 3.099.404). The pathology records of the following referral centers were evaluated over a 10-year period (1.1.2004-31-12.2014): Department of Oral Pathology, São Leopoldo Mandic Research Institute and Research Center (Brazil 1); Diagnostic Centre for Oral Diseases, School of Dentistry, Federal University of Pelotas (Brazil 2); Department of Oral and Maxillofacial Diseases, University of Helsinki (Finland); and School of Dentistry, Faculty of Medicine, Tel Aviv University (Israel).

Cases of OTs were selected and classified according to the current WHO classification (2017) (Wright and Vered, 2017). The hematoxylin and eosin-stained sections were re-evaluated. Data regarding histopathological type, gender, age and anatomical site, were obtained from patient records.

The cases of OTs were divided according to the oral pathology center and its corresponding geographical areas. Based on the 10-year analysis, Brazil 1 was the center with the highest number of cases of OTs (437 cases), followed by Israel (163 cases), Finland (115 cases), and Brazil 2 (108 cases). The records of the two Brazilian centers were combined, resulting in 545 cases. A total of 823 cases of OTs were obtained (Figure 1).

Benign OTs (BOTs) were most common (n = 814, 98.9%). In all countries, the most frequent BOT was odontoma (n = 394, 48.4%), followed by ameloblastoma (n = 253, 31.0%). Odontogenic myxoma/myxofibroma (n = 66, 8.1%) was the third most common OT in Brazil and Israel, whereas in Finland, odontogenic myxoma, ameloblastic fibroma and odontogenic fibroma presented the same prevalence. Only 9 malignant OTs (MOTs) (n = 9, 1.0%) were diagnosed in this series. Most cases were found in Israel (six out of nine), including five ameloblastic carcinomas and 1 clear cell odontogenic carcinoma. In Brazil, there was one case of ameloblastic fibrosarcoma and one case of ameloblastic carcinoma, similar to Finland (Tables 1 and 2).

OTs showed virtual equal distribution between males (n = 409, 49.7%) and females (n = 407, 49.4%). The mandible (n = 595, 72.2%) was 2.9 times more affected than the maxilla (n = 199, 24.1%), except for adenomatoid odontogenic tumor (Tables 1 and 2; *Supplementary Table 1).* The age of OTs patients ranged from 0 to 87 years, with a mean age of 22 years (SD = ±

17.2). MOTs affected older patients when compared to BOTs, with a mean age of 55 ± 22.6 years.

In this multicenter study, the most common OT was odontoma, followed by ameloblastoma and odontogenic myxoma, similar to the data from previous publications (Mosqueda-Taylor et al., 1997; Tamme et al., 2004; Buchner et al., 2006; Chrysomali et al., 2013; Servato et al., 2013). However, it is difficult to compare these studies considering that each one is based on different classifications and study designs. It is worthwhile to mention that the prevalence of odontoma may have a bias. In several diagnostic services, the lesion is interpreted as a malformation or a hamartoma rather than a neoplasm, being discovered during routine radiographic examination and surgically treated only in cases with a secondary complication (Tamme et al., 2004).

This series of OTs showed a very similar frequency between males and females. There are studies in the literature reporting this similar incidence of OTs regarding gender (Ladeinde et al., 2005; Chrysomali et al., 2013;); however, some studies have reported a higher prevalence in males (Chrysomali et al., 2013; Nalabolu et al., 2016; Mascitti et al., 2019), while others also have shown females to be more affected (Osterne et al., 2011). There is no plausible explanation for these differences. In association with these results, this multicenter study showed that OTs affected mostly the mandible. The majority of the studies on OTs also demonstrated a strong predilection for the mandible (Sekerci et al., 2015; Mascitti et al., 2019; Rubini et al., 2017). Jaw-specific genetic mechanisms that regulate the evolution and development of upper and lower dentitions appear to differ and this may

provide a partial explanation to the difference in the incidence of OTs in the mandible versus maxilla (Ferguson et al., 2000).

The present study showed that the average age of individuals affected by OTs was 22 ± 17.2 years. Different studies demonstrate that the average age varied, for example from 25.5 (Fernandes et al., 2005) to 46.7 years (Rubini et al., 2017). The variation may be related to the different samples and populations analyzed.

MOTs are extremely rare lesions, with similar reported incidences of 1.1% (Mosqueda-Taylor et al., 1997), 1.18% (Fernandes et al., 2005), and 1.26% (Adebayo et al., 2005). In this study, the malignant lesions were more common in males and in the mandible, affecting individuals of 55 ± 21.6 years. Curiously, there was a much higher prevalence of MOTs in the Israeli series. This could be attributed to the population genetic background or to specific characteristics of the pathology center where the lesions were diagnosed.

The present communication describes a panoramic view of the diagnosis of OTs from different continents, according to its most recent WHO classification. The study of the incidence of OTs in different geographic areas contributes to understand their trends over time. Besides that, this communication specially added the knowledge that the new WHO classification did not significantly impact the distribution of the most diagnosed OTs worldwide.

Conflicts of interests: none to declare.

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Table 1. Frequency of odontogenic tumors by histological type and countries included in this multicenter study.

	Brazil		***Israel***		***Finland***		***Total***	
	n	*%*	n	*%*	n	*%*	**n**	***%***
BENIGN ODONTOGENIC TUMORS								
Ameloblastoma	175	*32.2*	49	*31.2*	29	*25.4*	**253**	***31.0***
Squamous odontogenic tumor	3	*0.5*	-	-	-	-	**3**	***0.4***
Calcifying epithelial odontogenic tumor	9	*1.6*	6	*3.8*	-	-	**15**	***1.8***
Adenomatoid odontogenic tumor	21	*3.9*	2	*1.3*	1	*0.9*	**24**	***2.9***
Ameloblastic fibroma	-	-	2	*1.3*	7	*6.1*	**9**	***1.1***
Primordial odontogenic tumor	-	-	-	-	-	-	**-**	**-**
Odontoma	275	*50.6*	61	*38.8*	58	*50.9*	**394**	***48.4***
Dentinogenic ghost cell tumor	-	-	-	-	-	-	**-**	**-**
Odontogenic fibroma	8	*1.5*	14	*8.9*	7	*6.1*	**29**	***3.6***
Odontogenic myxoma/myxofibroma	40	*7.4*	19	*12.2*	7	*6.1*	**66**	***8.1***
Cementoblastoma	12	*2.2*	4	*2.5*	5	*4.4*	**21**	***2.6***
Total benign odontogenic tumors	**543**	***66.7***	**157**	***19.3***	**114**	***14.0***	**814**	***98.9***
MALIGNANT ODONTOGENIC TUMORS								
Ameloblastic carcinoma	1	*50.0*	5	*83.3*	1	*100*	**7**	***77.8***
Metastasizing (malignant) ameloblastoma	-	-	-	-	-	-	**-**	**-**
Primary intraosseous carcinoma, NOS	-	-	-	-	-	-	**-**	**-**
Sclerosing odontogenic carcinoma	-	-	-	-	-	-	**-**	**-**
Clear cell odontogenic carcinoma	-	-	1	*16.6*	-	-	**1**	***11.1***
Ghost cell odontogenic carcinoma	-	-	-	-	-	-	**-**	**-**
Odontogenic carcinosarcoma	-	-	-	-	-	-	**-**	**-**
Odontogenic sarcoma	1	*50.0*	-	-	-	-	**1**	***11.1***
Total malignant odontogenic tumors	**2**	***22.2***	**6**	***66.6***	**1**	***11.1***	**9**	***1.0***
Total odontogenic tumors	**545**	***66.2***	**163**	***19.8***	**115**	***13.9***	**823**	***100***

n, absolute frequency; **%**, relative frequency; **NOS**, not otherwise specified;

Table 2. Histological type, gender, age and anatomical site of the informed cases of odontogenic tumors from this multicenter study.

	Total		Gender	Age	Anatomic Location
	n	%	Male:Female	Mean age ± SD	Mandible:Maxilla
BENIGN ODONTOGENIC TUMORS					
Odontoma	394	48.4	1:1	16 ±12.8	1.8:1
Ameloblastoma	253	31	1.3:1	31.5 ± 18.2	23:1
Odontogenic Myxoma/Myxofibroma	66	8.1	1:1.5	29 ± 14.2	1.5:1
Odontogenic Fibroma	29	3.6	1:1	21 ± 17.3	2.7:1
Adenomatoid Odontogenic Tumor	24	2.9	1:2.6	14 ± 2.9	1:1.5
Cementoblastoma	21	2.6	1:6.0	26 ± 17.0	19:1
Calcifying Epithelial Odontogenic Tumor	15	1.8	1:2	26 ± 19.2	3.6:1
Ameloblastic fibroma	9	1.1	1:1.25	8.4 ± 3.0	2:1
Squamous Odontogenic Tumor	3	0.4	1:2	39 ±19.9	2:1
Total benign odontogenic tumors	**814**	**98.9**	**1:1**	**21 ± 16.9**	**2.9:1**
MALIGNANT ODONTOGENIC TUMORS					
Ameloblastic Carcinoma	7	77.8	2.5:1	50.8 ± 21.1	**1:0**
Clear Cell Odontogenic Carcinoma	1	11.1	ND	83	Mandible
Odontogenic Sarcoma	1	11.1	Female	40	ND
Total malignant odontogenic tumors	**9**	**1.1**	**1.25:1**	**55 ± 22.6**	**1:0**
Total odontogenic tumors	**823**	**100**	**1:1**	**22 ± 17.2**	**2.9:1**

n, absolute frequency; **%**, relative frequency; **SD**, standard deviation; **ND**, no data.

Table 1 Patient gender and anatomical site of odontogenic tumor.

	Male		***Female***				***Mandible***		***Maxilla***				
BENIGN ODONTOGENIC TUMORS	*n*	***%***	*n*	*%*	*M:F ratio*	*N.I.*	*n*	*%*	*n*	*%*	*Man:Max ratio*	*N.I.*	***Total***
Ameloblastoma	142	56.1	110	43.5	1.3:1	1	239	94.4	10	3.9	23.9:1	4	**253**
Squamous odontogenic tumor	1	33.3	2	66.6	1:2	0	2	66.6	1	33.3	2:1	0	**3**
Calcifying epithelial odontogenic tumor	5	33.3	10	66.6	1:2	0	11	73.3	3	20	3.6:1	1	**15**
Adenomatoid odontogenic tumor	6	25.0	16	66.6	1:2.6	2	9	37.5	14	58.3	1:1.5	1	**24**
Ameloblastic fibroma	4	44.4	5	55.5	1:1.25	0	6	66.6	3	33.3	2:1	0	**9**
Primordial odontogenic tumor	-	-	-	-	-	-	-	-	-	-	-	-	**-**
Odontoma	202	51.2	189	47.9	~1:1	3	243	61.6	135	34.2	1.8:1	16	**394**
Dentinogenic ghost cell tumor	-	-	-	-	-	-	-	-	-	-	-	-	**-**
Odontogenic fibroma	15	51.7	14	48.2	~1:1	0	19	65.5	7	24.1	2.7:1	2	**29***
Odontogenic myxoma/myxofibroma	26	39.4	39	59.0	1:1.5	1	39	59.0	25	37.9	1.5:1	2	**66**
Cementoblastoma	3	14.2	18	85.7	1:6	0	19	90.5	1	4.7	19:1	1	**21**
Total benign odontogenic tumors	**404**	**49.6**	**403**	**49.5**	**~1:1**	**7**	**587**	**72.1**	**199**	**24.4**	**2.9:1**	**27**	**814**
MALIGNANT ODONTOGENIC TUMORS													
Ameloblastic carcinoma	5	71.4	2	28.5	2.5:1	0	7	100	0	0	1:0	0	**7**
Metastasizing (malignant) ameloblastoma	-	-	-	-	-	-	-	-	-	-	-	-	**-**
Primary intraosseous carcinoma, NOS	-	-	-	-	-	-	-	-	-	-	-	-	**-**
Sclerosing odontogenic carcinoma	-	-	-	-	-	-	-	-	-	-	-	-	**-**
Clear cell odontogenic carcinoma	0	0	1	25.0		0	1	100	0	0	1:0	0	**1**
Ghost cell odontogenic carcinoma	-	-	-	-	-	-	-	-	-	-	-	-	**-**
Odontogenic carcinosarcoma	-	-	-	-	-	-	-	-	-	-	-	-	**-**
Odontogenic sarcoma	0	0	1	25.0	0:1	0	0	0	0	0	-	1	**1**
Total malignant odontogenic tumors	**5**	**55.5**	**4**	**44.4**	**1.25:1**	**0**	**8**	**88.8**	**0**	**0**	**1:0**	**1**	**9**
Total odontogenic tumors	**409**	**49.7**	**407**	**49.4**	**~1:1**	**7**	**595**	**72.2**	**199**	**24.1**	**2.9:1**	**28**	**823**

***n**, absolute frequency; **%**, relative frequency; **M**, male; **F**, female; **Man**, mandible; **Max**, maxila; **N.I.**, not informed; **NOS**, not otherwise specified;*
***** one case of odontogenic fibroma was peripheral*

Figure 1. Flowchart showing the sample selection of the multicenter study