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Non-neoplastic jaw cysts: a 30-year epidemiological study of 2150 cases in Italian population

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Abstract.

Non-neoplastic jaw cysts (NJCs) are one of the most common lesions in oral cavity, but there are only few detailed and extended epidemiological data based on the 2017 WHO classification. The aim of this study was to perform an epidemiologic analysis of all NJCs treated from 1990 to 2019 at the Marche Polytechnic University, and to compare these data with those published in the literature. This retrospective study considered 2060 patients treated from 1990 to 2019. The NJCs were classified according to the 2017 WHO classification, and the main clinicopathological variables were analysed (sex, age, diagnosis, site of onset, size, and recurrences). Of 2150 total lesions, there were 2095 primary cysts and 55 recurrences; males are more frequently affected than women (M/F ratio of 1.73:1). The mean age of occurrence was 46.6 years, with a peak of frequency in the fifth decade. The mandible was more frequently involved than the maxilla, with a mean size of 1.9 cm. Radicular cyst was the most frequently diagnosed cyst (56.6%), followed by dentigerous cyst (23.4%) and odontogenic keratocyst (12.9%). This is the first epidemiological study on NJCs in Italian population according to 2017 WHO classification.

Introduction

Non-neoplastic jaw cysts (NJCs) are one of the most frequent lesions that occur in maxillofacial region and that affect jaws and are mainly represented by odontogenic cysts. NJCs are characterized by the presence of a pathological cavity, having semifluid or fluid content that could be either partially or completely covered by odontogenic epithelial tissue.[1] In 2017, the World Health Organization (WHO) published a new histological classification of NJCs.[2] The main difference from the previous classification was the reintroduction of the odontogenic keratocyst (OKC) and the calcified odontogenic cyst (COC) into the cyst group.[3] Since NJCs are very common lesions, it is crucial to diagnose them and to perform a differential diagnosis in order to determine the most appropriate treatment and follow-up.[4] NJCs are commonly detected by clinical and radiologic exams, although the final diagnosis depends on histopathology. Despite many studies have reported on the NJCs, there are only few detailed and extended epidemiological data that are based on the 2017 WHO classification.[2, 5] The healthcare organization of Marche region (Italy) is structured with only one tertiary referral center for Head and Neck pathology.[6] For this reason, it is possible to collect data on NJCs in this region with a certain degree of accuracy, resulting in a more accurate estimation of their epidemiology in Italy.

Thus, the aim of this retrospective study was to perform a comprehensive epidemiologic analysis of all NJCs surgically treated and diagnosed by a single center in Marche region over a 30-year period, from 1990 to 2019. The collected data were also compared with those of previously published works to provide a better epidemiologic representation of these lesions.

Materials and Methods

This study included patients surgically treated for NJCs from January 1990 to December 2019. Variables such as age, sex, site distribution, size, pathologic diagnosis and relapses were considered. The size of NJCs was determined by measuring the maximum diameter on the

macroscopic surgical specimen. Site distribution was classified in maxillary and mandibular. Regarding the position of the cysts, the following regions were used: anterior, posterior (premolar and molar area), and mandibular angle-ramus. For all the missing data, the wording No Data Available (NDA) was set. Histopathological slides were re-evaluated by two pathologists to confirm the diagnosis, according to the 2017 WHO criteria. Any disagreement was settled by consensus, including a third investigator. Statistical analysis was performed using the software R (R version 3.5.3, Copyright (C) 2019 The R Foundation for Statistical Computing). Chi-squared test and Fisher's exact test were used for grouped variables. One-way analysis of variance and Bonferroni post hoc test were used for continued variables, Kruskal-Wallis and Dunn post hoc tests were used for grouped variables. The level of significance was set at $p < 0.05$. This study was conducted in accordance with the "Ethical Principles for Medical Research Involving Human Subjects" statement of the Helsinki Declaration. This study received exemption from the institutional review board, because of its retrospective nature.

Results

2060 patients were treated for NJCs from January 1990 to December 2019, giving a total of 2095 primary cysts and 55 recurrent cysts. NJCs represented 12.1% of all surgical head and neck specimens recorded at the Institute of Pathology, Marche Polytechnic University, Italy.

A total of 7 misdiagnosed cases were found: 2 cases of OKCs were actually orthokeratinized odontogenic cysts (OOCs), 3 cases of DCs were OKCs, 2 cases of glandular odontogenic cysts (GOCs) were DCs. Furthermore, 2 DCs proved to be unicystic ameloblastomas, and therefore have been excluded. Table 1 summarizes the distribution of NJCs in relation to clinicopathological data. Male were more frequently affected than women, with a male/female (M/F) ratio of 1.7:1. The mean age of occurrence for primary and recurrent NJCs were 46.6 and 47.7 years, respectively, without significant differences ($p > 0.05$). The peak of frequency was in the fifth decade (Figure 1),

while the mean age of occurrence for collateral inflammatory cyst (ICC) was significantly lower than the other NJCs (p = 0.0006). The mandible was more frequently involved than the maxilla; in particular, the posterior mandibular and the anterior maxillary regions were the most commonly affected sites (Figure 2). The mean size of primary and recurrent cysts was 1.9 cm (range 0.3-6.5) and 2.1 cm (range 0.4-6.0), respectively, showing no significant difference (p > 0.05). OKCs were significantly larger than other NJCs, with a mean value of 2.2 cm (p = 0.0028). The mean follow-up time was 11.3 months (range 0-120), and the mean onset time for the first recurrence was 4.8 years (range 1-18). 48 subjects developed recurrences (33 males and 15 females) and 6 of them showed multiple recurrences over the years, for a total of 55 recurrent cysts. In particular, all cases of multiple recurrences were OKCs (2 recurrences in 5 patients and 3 recurrences in 1 patient). Table 2 summarized the distribution of recurrent NJCs in relation to clinicopathological data. OKC was the most common recurring cyst with 49 cases. The mean size of recurring cysts was 2.1 cm (range 0.4-6.0), showing no significant differences between mandible and maxilla (p > 0.05). Furthermore, no difference between the size of primary and recurrent cysts was found (p > 0.05).

The three most common type of NJCs were radicular cyst (RC), dentigerous cyst (DC), and OKC, representing 92.8% of all NJCs (Table 1). RC was the most frequently diagnosed cyst, with 1216 cases, 182 of which were residual cysts (ReC). RCs were more common in males (M/F ratio of 1.7) and slightly more frequent in mandible. DC was the second most common cyst, showing 502 cases and a M/F ratio of 2.0. The DCs were significantly more common in the mandible than maxilla. OKC represented the third most frequent cyst (277 cases), with a M/F ratio of 1.5. Like the previous NJCs, OKCs were significantly more frequent in the mandible. All the other NJCs showed a low frequency, reaching a total of 155 cases (7.2%).

Discussion

In this study was conducted for the first time an extended epidemiological analysis of NJCs in Italian population according to the 2017 WHO Classification of Head and Neck tumours. NJCs are one of the most frequently treated lesions in oral and maxillofacial surgical practice. Indeed, previous studies showed that 11.5-21.6% of the surgical specimens in head and neck pathology services had a diagnosis of NJCs.[2-4, 7-9] We found that 12.1% of all surgical specimens in the head and neck pathology service were NJCs; however, the comparison with other reports would be difficult, given that several studies have evaluated data from oral pathology services, which receive numerous specimens from public health structures and/or private dental practitioners.[10]

Males were more frequently affected by NJCs, showing a M/F ratio of 1.7:1, in agreement with most results in literature (Table 1),[3, 4, 9-11] although other studies did not find a significant sex difference.[5, 8, 12] We found a mean onset age of 46.6 years, a frequency peak in the 5th decade of life (Figure 1), and several cases were reported in elderly patients (75 years or over). The ages reported here were higher compared with those reported in the literature, in which the mean age of diagnosis ranged from 28 to 43 years (Table 3).[3, 4, 10, 13-22] A possible explanation could be given by a greater number of diagnoses in elderly people. Indeed, NJCs could be asymptomatic and characterized by a small rate growth, remaining therefore undiagnosed for many years. Furthermore, the life expectancy in Marche region is the highest in Italy and one of the highest in the world.[6] The mandible was the most commonly affected site by NJCs with 832 cases. Despite the localization of a significant number of cysts not being recorded, these results were consistent with those reported by some studies,[3, 9] but in contrast with others.[2, 4, 11] Posterior mandible and anterior maxilla were the most frequently affected sites, in agreement with most of the literature (Table 3).[2, 3, 9, 11, 14] The mean size of primary and recurrent cysts was similar (1.9 vs 2.1 cm, respectively), showing no significant difference, while OKC were significantly larger than other cysts, similarly to what is reported in literature.[23, 24]

The RCs was the most frequent NJC, accounting for 56.6% of the total, in agreement with literature data (Table 3).[2-5, 7-12, 14] These lesions arise from proliferation of the epithelial rests of Malassez, as consequence of the chronic inflammation of peri-radicular tissues.[8] Therefore, the prevalence of RCs could be related to the high incidence of caries in those countries in which most of the studies were conducted.[25] Alternatively, most of the samples analyzed by pathology services come from general dental practitioners that could more easily treat simple cysts like RCs, but less frequently complex lesions such as OKCs.[26] The DC was the second most common lesion, accounting for 23.4% of all NJCs. According to most of the literature, this is the most common developmental cyst,[2, 7, 9, 12, 21, 27] although some authors reported that OKCs were more frequent than DCs,[4, 16] while in other studies OKC were not considered as the authors followed the 2005 WHO classification.[3] Larger OKCs were found mainly in the mandible angle-ramus, followed by the mandibular posterior region, as reported by others.[28] Furthermore, no association between OKC size and recurrences were found, in accordance with previous studies.[23]

OKC was the most common recurring cyst with 49 cases, although we found also 4 unusual recurrences of DCs and inflammatory cysts (Table 2). As reported in literature and in this study, OKCs or even unicystic ameloblastomas could be misdiagnosed as DCs, given their histological similarities. Therefore, a careful correlation of radiographic and histological findings is required for an accurate diagnosis.[29] We hypothesize that these unusual recurrences could be due to several causes, such as an inadequate treatment method, the large size of the lesion, or the position of these lesions, all related to the greater risk of not completely removing the epithelial odontogenic tissue. The high recurrence rate of OKC could be related to two main reasons: (a) the presence of satellite/daughter cysts left beyond the enucleated cyst; (b) the development of unrelated OKCs in patients affected by nevoid basal cell carcinoma syndrome that could be misinterpreted as a recurrence.[30]

To date this is the second extended epidemiological study of NJCs based on the 2017 WHO Classification of Head and Neck tumours, and the first conducted in Italian population. More studies using this classification are needed in order to provide reliable epidemiological data and the clinical and pathological characteristics of NJCs.

Conflict of interest.

The authors declare that they have no competing interest.

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Table 1. Clinical and pathological data of NJCs (1990-2019). Data regarding ReCs are reported in italics, since these cysts are now considered a subgroup of RCs. Please note that the exact location of many cysts was unknown. NDA = No Data Available; RC = radicular cyst; ReC = residual cyst; ICC = collateral inflammatory cyst; OOC = orthokeratinized odontogenic cyst; GOC = glandular odontogenic cysts; GC = gingival cyst; LPC = lateral periodontal cyst; COC = calcifying odontogenic cyst; NDC = nasopalatine duct cyst.

Cyst	n. of cases	Sex M	Sex F	Mean age (range)	Number (mean size; size range) Mandible Total	Mandible Anterior	Mandible Posterior	Mandible Angle-ramus	Maxilla Total	Maxilla Anterior	Maxilla Posterior	NDA
RC	1216	764	452	46.6 (7-93)	398 (1.8;0.4-6.5)	16 (1.5; 0.7-2.0)	75 (1.9; 0.7-5.0)	14 (2.0; 1.0-3.0)	363 (2.0;0.4-6.0)	39 (1.3; 0.5-3.0)	28 (1.5; 0.4-3.5)	455
ReC	*182*	*126*	*56*	*52.6 (18-86)*	*58 (1.8 (0.5-4.0)*	*2 (2.0)*	*17 (1.8; 1.0-3.5)*	*1.7 (1.4-2.0)*	*69 (2.2; 0.8-5.0)*	*7 (1.5; 0.8-2.5)*	*4 (2.7; 2.2-3.5)*	*55*
ICC	31	22	9	31.0 (9-69)	11 (1.6;0.7-3.2)	2 (2.0; 0.8-3.2)	4 (1.9; 0.9-3.0)	0	9 (1.8; 0.6-4.0)	3 (1.2; 0.6-1.5)	0	11
DC	502	333	169	47.0 (5-87)	196 (1.8;0.5-6.5)	5 (1.4; 0.7-2.0)	36 (1.8; 0.6-3.0)	8 (2.2; 1.0-5.0)	96 (2.2; 0.7-4.7)	12 (2.2; 0.7-4.5)	5 (1.8; 0.7-3.0)	210
OKC	277	164	113	44.3 (7-84)	208 (2.2;0.5-6.0)	5 (1.4; 0.8-2.5)	12 (2.7; 1.0-5.0)	26 (2.0; 0.7-4.0)	60 (2.3; 0.5-4.5)	1 (1.5)	2 (1.5)	9
LPC	17	10	7	44.8 (7-75)	5 (2.1; 1.5-2.5)	2 (1.8; 1.5-2.0)	0	1 (2.5)	6 (2.7;2.0-4.0)	1 (2.0)	1 (1.6)	6
GC	24	13	11	54.4 (24-73)	8 (2.0; 0.5-3.5)	2 (1.4; 0.5-2.2)	0	0	7 (1.8;0.3-3.0)	1 (0.3)	2 (2.3; 1.5-3.0)	9
GOC	25	17	8	46.7 (22-79)	6 (1.6; 1.0-2.0)	2 (1.4; 1.3-1.5)	2 (1.5; 1.0-2.0)	0	12 (2.5; 0.6-6.5)	0	1 (2.0)	7
COC	16	7	9	48.9 (14-90)	6 (2.3; 1.0-3.5)	0	0	1 (3.5)	1 (0.6)	0	0	9
OOC	26	21	5	50.5 (16-76)	13 (1.9; 0.4-3.0)	1 (1.5)	4 (1.5; 0.4-2.0)	1 (2.8)	7 (1.8; 0.7-3.0)	0	1 (1.0)	6
NDC	16	11	5	48.9 (13-76)	0	0	0	0	16 (1.4; 1.0-3.0)	16 (1.0-3.0)	0	0
Total	2150	1362	788	46.6 (5-93)	851 (1.9;0.4-6.5)	35 (1.5; 0.5-3.2)	133 (1.9;0.4-5.0)	51 (2.1; 0.7-5.0)	577 (2.0;0.3-6.5)	73 (1.5; 0.3-4.5)	40 (1.6; 0.4-3.5)	722

Table 2. Clinical and pathological data of recurrent cysts (1990-2019). "n. of cases" refers to the number of surgical samples, while "Sex" category reports the number of patients (differences in OKC are due to multiple recurrences).

| Cyst	n. of cases	Sex		Mean age (range)	Number (mean size; size range)	
		M	F		Mandible	Maxilla
OKC	49	29	13	47.6 (14-78)	39 (2.1; 0.5-6.0)	10 (2.4; 0.8-4.5)
DC	2	2	0	67 (57-77)	2 (1.1; 1.0-1.2)	-
OOC	2	2	0	51.5 (47-56)	2 (1.2; 0.4-2.0)	-
ICC	1	0	1	25	-	1 (1.7)
RC	1	0	1	29	-	1 (2.0)
Total	55	33	15	47.7 (14-78)	43 (2.0; 0.4-6.0)	12 (2.3; 0.8-4.5)

Table 3. Distribution of odontogenic cysts and comparison with other studies. Mand. = mandible, Max. = maxilla.

Author [(Reference)]	M/F ratio	Mean age	Max.	Mand.	RC (*ReC*)	DC	OKC	Other cysts
Daley [7]	-	-	-	-	65.0%	23.0%	4.7%	10.0%
Mosqueda-Taylor [27]	1.1	-	-	-	42.1% (*2.2%*)	33.0%	21.5%	3.4%
Meningaud [21]	1.9	41.8	346	1044	58.1% (*4.6%*)	22.3%	19.1%	0.5%
Varinauskas [20]	1.2	35.8	536	314	86.2% (*9.3%*)	13.8%	-	-
Jones and Franklin [8]	1.3	-	-	-	62.7% (*9.3%*)	17.9%	9.8%	9.6%
Grossmann [12]	1.0	-	1379	1330	61.0%	25.3%	7.2%	6.5%
Ochsenius [11]	1.1	-	1753	1191	61.9% (*11.2%*)	18.5%	14.3%	5.8%
Tortorici [19]	1.2	35.1			84.5%	11.4%	1.3%	2.8%
Prockt [26]	0.9	-	381	297	73.7% (*4.1%*)	21.4%	4.0%	0.9%
Avelar [15]	1.4	28.9	223	284	58.2% (*5.9%*)	30.7%	-	11.2%
de Souza [17]	0.8	31.0	499	428	66.3% (*4.9%*)	20.1%	6.4%	7.2%
Nuñez-Urrutia [22]	1.4	42.0	161	257	54.5% (*4.3%*)	21.8%	-	23.7%
Ramachandra [16]	1.7	30.3	134	118	40.1%	17.7%	21.8%	20.4%
Sharifian [14]	1.3	28.6	605	615	45.8% (*8.0%*)	24.7%	19.4%	10.1%
Açikgöz [25]	1.2	-	227	232	68.4% (*13.7%*)	26.6%	3.3%	1.7%
Selvamani [13]	1.2	28	88	65	72.6% (*3.3%*)	20.3%	5.2%	1.9%
Tekkesin [4]	1.4	36.3	2701	2387	64.6% (*9.5%*)	10.4%	20.6%	4.4%
Khosravi [9]	1.3	29.5	746	857	48.0% (*13.0%*)	26.3%	23.0%	2.7%
Johnson [10]	1.2	43.4	-	-	45.7%	22.4%	-	31.9%
Demirkol [18]	1.4	32.7	80	69	66.4% (*3.4%*)	26.9%	6.1%	0.6%
Jaeger [5]	1.1	-	421	534	65.9%	24.8%	6.8%	2.5%

Lo Muzio [3]	1.7	37.7	846	1124	55.0% (*11.1%*)	40.9%	-	9.1%
Tamiolakis [2]	1.6	42.3	2583	2504	71.4% (*14.1%*)	14.5%	8.2%	5.9%
Present Study	1.7	46.6	577	851	56.6% (*8.5%*)	23.3%	12.9%	7.2%

Figure 1. Distribution of RCs, DCs, and OKCs according to age.
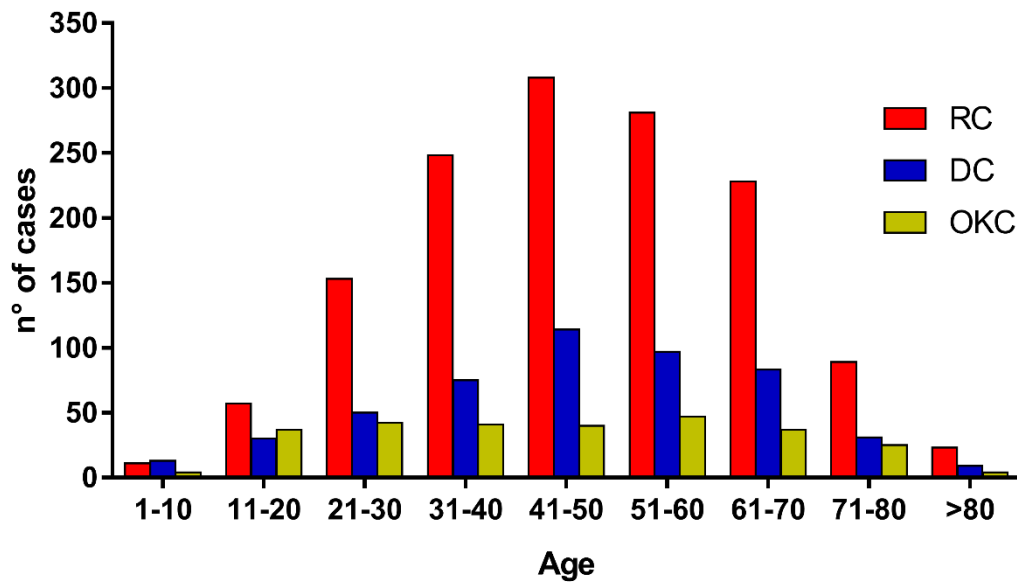
Figure 2. Site distribution of NJCs by percentage in maxilla (orange areas) and mandible (blue areas). The mandible and maxilla have been separated into anterior area, posterior area, and mandibular angle-ramus (separated by dotted lines).