Malignant transformation of craniomaxillofacial fibro-osseous lesions: a systematic review

Running title: Malignant transformation of FOLs

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Abstract

The purpose of this study was to perform a systematic review of the literature concerning all documented cases of malignant transformation of craniomaxillofacial fibro-osseous lesions (FOLs). Three electronic databases were searched. Data were evaluated descriptively. Kaplan-Meier survival curves were constructed and compared using the log-rank test. A critical appraisal of included articles was performed through the Joanna Briggs Institute tool. A total 19 studies including 27 patients were selected for data extraction. Twenty-six cases were initially diagnosed as fibrous dysplasia and one as ossyfing fibroma. The mean age at the time of malignant transformation was 38.11 years and the average time from initial diagnosis to malignant transformation was 18.2 years. The male:female ratio was 1:1.2 and the maxilla:mandible ratio was 1.5:1. The histological type of the malignant tumor was predominantly osteosarcoma. Follow-up was available for 21 patients. The 3-year overall survival rate was 51%. Mandible tumors and diagnoses other than osteosarcoma tended to have poor survival rates, but no significant difference was identified. We concluded that between all FOL, only fibrous dysplasia seems to have a considerable increased risk of malignant transformation. Thus, a regular and long follow-up period is advised.

Keywords: fibro-osseous lesions, ossifying fibromas, fibrous dysplasia, survival, malignant transformation.

1 INTRODUCTION

Fibro-osseous lesions (FOLs) of the craniomaxillofacial region comprise a group of developmental, dysplastic and neoplastic alterations characterized by the replacement of bone by cellular fibrous tissue containing varied amount of mineralized tissue. Since FOLs exhibit significant overlap in histological appearance, the correlation of clinical, radiological and histological features is essential to achieve a reliable diagnosis.[1] FOLs include Ossifying Fibromas (OF), Cemento-ossifying Fibroma (COF), Familial Gigantiform Cementoma (FGC), Fibrous Dysplasia (FD) and Cemento-Osseous Dysplasia (COD).[2] FOLs usually present a favorable prognosis, but evidence suggests that some FOL, especially FD, may have a risk of spontaneous malignant transformation.[2]

The management of FOLs can be quite variable depending on the diagnosis, size and location of the lesion and patient status. Complete surgical removal represents the first line of treatment for OF. The main approach to treat patients with FD with aesthetic complications is surgical remodeling; and patients with COD usually do not require treatment, being followed periodically.[2,3] Generally, the risk of malignant transformation is not taken into account by professionals when deciding the frequency and extension of follow-up. This can be expected since there is no agreement concerning the risk of transformation of these lesions. The actual risk of occurrence of malignant tumors derived from FD or their prognosis, is not well defined. Moreover, there is no consensus in the literature about the potential of malignant transformation of OF and COD. The knowledge of this important information can guide professionals in the establishment of more rigorous follow-up regimens if necessary.

The aim of this study was to perform a systematic review of the literature concerning all documented cases of malignant transformation of craniomaxillofacial FOLs. By gathering all these reports, we were able to make a more comprehensive analysis of important aspects related to this event. We believe it is important to critically analyze these data in order to draw well-founded conclusions.

2 METHODS

The present literature review followed the Preferred Report Items for Systematic reviews and Meta-Analyses (PRISMA) Statement guidelines.[4] The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42019117186.

2.1 Literature search strategy

A literature search was performed in September 2018 on the following electronic databases: PubMed/MEDLINE, Scopus and EMBASE. The strategy used in all databases covered the following keywords: ("fibro-osseous lesion" OR "fibrous dysplasia" OR "cemento-osseous dysplasia" OR "osseous dysplasia" OR "ossifying fibroma") AND ("malignant transformation" OR "sarcomatous transformation").

2.2 Inclusion and exclusion criteria

Inclusion criteria comprised cases of craniomaxillofacial FOLs that underwent malignant transformation with sufficient clinical, radiological and histological data to confirm both diagnoses (initial diagnosis of FOL and further diagnosis of the malignant tumor). Randomized and controlled clinical trials, cohort studies, cross-sectional studies, case-control studies, case series, and case reports were screened. The literature search was confined to English-language literature. Exclusion criteria comprised cases of malignant transformation of FOLs located in different locations other than the maxillofacial region, cases with previous history of radiotherapy before malignant transformation and cases in which the diagnosis of a malignant tumor was performed simultaneously with the FOL. Articles published prior to 1990, meeting/conference abstracts and articles with no full text available were also excluded.

2.3 Study selection

Two independent trained reviewers screened titles and abstracts of all studies retrieved through the electronic searches. Those that met the eligibility criteria were selected for full text analysis. If the abstract was unavailable but the title suggested that the study could be related to the subject of this systematic review, the full text was also assessed for eligibility. Following the full text appraisal, studies that fulfilled the eligibility criteria were included. Next, the references of included studies were manually screened for eligibility. Additionally, all studies that had cited these included articles, in Scopus database, were assessed for eligibility. Finally, a hand search in the gray literature was performed using Google Scholar for additional studies that might have been missed during the searches of the electronic databases.

2.4 Data extraction

For each study included, the following data were extracted: authors' name and affiliation (country), year of publication, number of cases reported, age, gender, site, FOL diagnosis, malignant tumor diagnosis and time to malignant transformation. The outcome (alive or deceased) after malignant transformation and follow-up period were also collected when available.

2.5 Analysis

Clinicopathological information was descriptively presented. The difference between median age at malignant transformation was evaluated through the Mann-Whitney test. Based on the information collected, Kaplan-Meier survival curves were constructed. The survival curves were compared using the log-rank test to identify potential prognostic factors.

2.6 Quality assessment

The critical appraisal of included articles was performed through the Joanna Briggs Institute - University of Adelaide tool for case reports.[5] Two independent trained reviewers performed this analysis. The domains evaluated in

this tool includes: (1) description of patient's demographic characteristics and past diagnosis, (2) medical history, (3) current clinical condition, (4) diagnostic tests, (5) intervention/treatment, (6) post-intervention clinical condition, (7) adverse events, and (8) lessons provided by the case report. Each criterion was rated as "yes" (the article fulfilled the criteria), "no" (the article did not fulfilled the criteria), "unclear" or "not applicable". For the full descriptions of all topics included in each domain please refer to the original reference.[5]

3 RESULTS

3.1 Literature search

The flowchart of studies identified, screening, eligibility and inclusion is presented in Figure 1. Briefly, the electronic searches resulted in 755 references following duplicates removal. After applying the inclusion and exclusion criteria 14 studies were included for review. The manual search added 5 more studies, resulting in 19 articles included in this systematic review reporting the malignant transformation of 27 patients with FOLs.[6-24] Only cases that fulfilled all the inclusion criteria within case series studies were included in this review.

3.2 Description of the studies and statistical analysis

Table 1 summarises the data collected from the 19 included studies. Twenty-six patients had FD (96.2%), while only one was initially diagnosed with OF (3.8%). No cases of other FOL with malignant transformation were identified in this review. Among patients with FD, in 6 cases the type of FD was not specified. Five patients had monostotic FD (MFD), 11 patients had polyostotic FD (PFD) and 4 patients had McCune-Albright (MCA) syndrome.

The overall analysis revealed that the mean age at the time of malignant transformation was 38.11 years, ranging from sixteen[16] to sixty years old.[6] The male:female ratio was 1:1.2. Women suffered malignant transformation at a slightly higher age compared to men (40.0 vs 35.6), but this difference was not statistically significant (p=0.42, Mann-Whitney test).

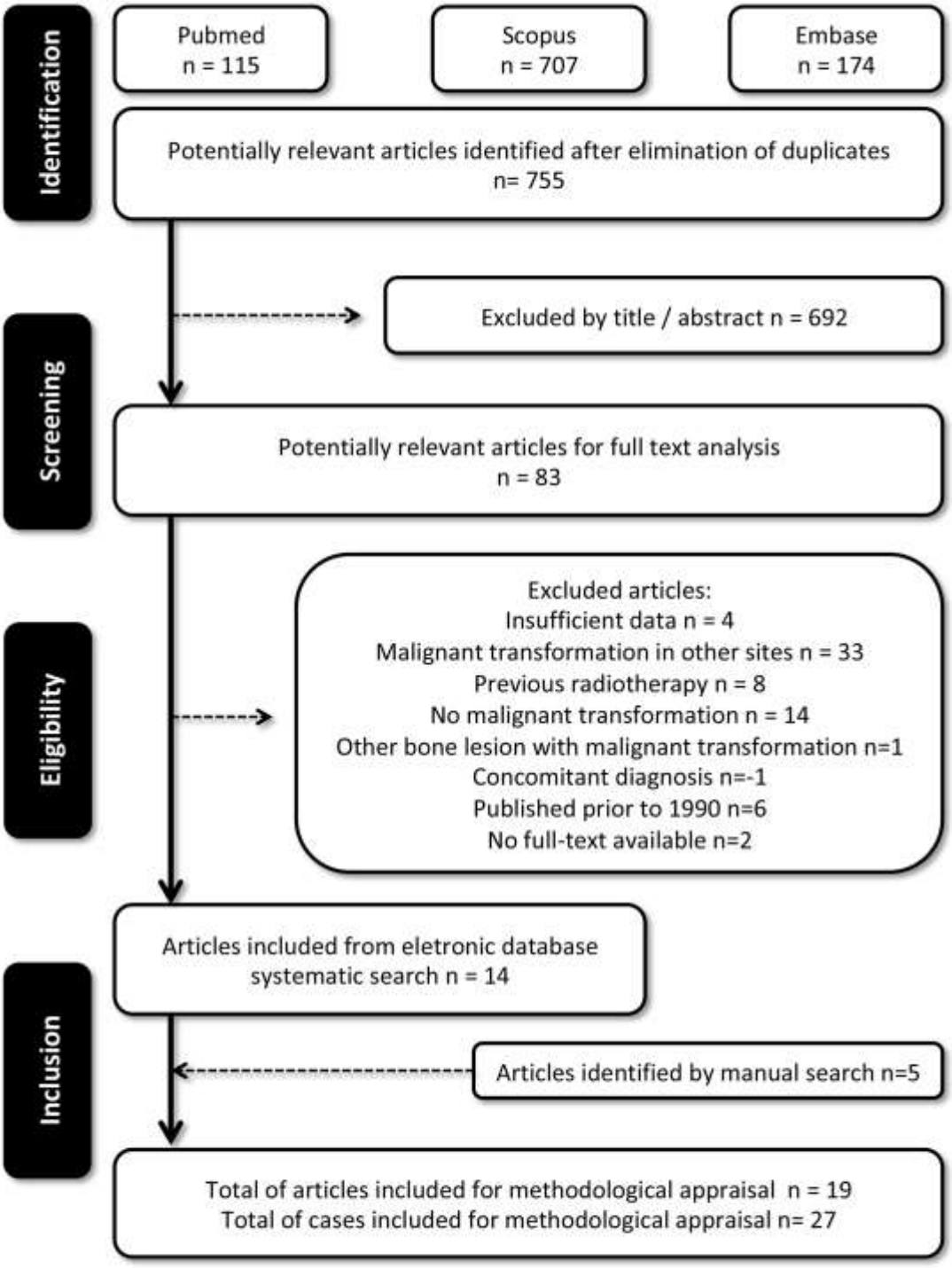

Figure 1. Flow chart of study selection

Table 1. Studies reporting cases of FOL with malignant transformation

Authors/ year	Country	Age (y)	Gender	Site	FOL	Malignant tumor	Time to MT	Follow-	Observations
Pack et al., 2016[24]	USA	39	F	Mand	FD	Osteosarcoma	11y	No response to therapy	The radiographic aspects suggest a COD
Mardekian and Tuluc 2015[23]	USA	59	F	Max	FD	Osteoblastic osteosarcoma	2y	Not informed	FD initial diagnosis was based only on computed tomography aspects
Lee et al., 2015[22]	Korea	47	F	Mand	OF	Low-grade osteosarcoma	3y	Not informed	The tumor recurred three times before MT
Sun et al., 2014[21]	China	55	M	Mand	PFD	Osteosarcoma	50y	3y +8m, died of tumor	Other cases presented in this study were considered as concomitant FD and malignant lesions
		55	M	Max	PFD	Osteosarcoma	42y	4y +3m, died of tumor	
		31	F	Mand	PFD	Osteosarcoma	8y	1y +3m, alive with disease	
		28	F	Max	PFD	Osteosarcoma	20y	5y +2m, died of tumor	
		45	F	Infratemporal fossa	PFD	Osteosarcoma	11y	3y +5m, died of tumor	
		48	F	Infratemporal fossa	PFD	Osteosarcoma	25y	1y +1m, alive with disease	
Cheng et al., 2013[20]	China	55	M	Max	PFD	Osteosarcoma	45y	6m, died of tumor	
		57	F	Max	PFD	Osteosarcoma	43y	1y+11m, free of tumor	
		20	F	Max	PFD	Osteosarcoma	20y	1y +4m, died of tumor	
Ma et al., 2013[19]	China	29	M	Mand	MFD	Osteosarcoma	3y	Not informed	
De Araujo et al., 2012[18]	Brazil	24	F	Mand	MCA Syndrome	Osteosarcoma	19y	1y, disease under control	
Gon et al., 2012[17]	India	16	M	Mand	MFD	Chondroblastic osteosarcoma	10m	Not informed	

Sadeghi et al., 2011[16]	Iran	16	M	Max	FD	Osteosarcoma	4m	1y and 5m, died of tumor	The malignant lesion might have been misinterpreted as a FD
Varghese et al., 2010[15]	UK	47	M	Max	MFD	Osteosarcoma	-	1m, died of tumor	No information on how initial diagnosis was established
Kim et al., 2010[14]	Republic of Korea	50	F	Mand	FD	Osteoblastic osteosarcoma	25y	2y, free of tumor	No information on how initial diagnosis was established
Kanazawa et al., 2009[13]	Japan	38	F	Mand	MCA Syndrome	Osteosarcoma	28y	3y, free of tumor	GNAS mutation was identified in the resected malignant tumor
Reis et al., 2008[12]	Portugal/ USA	52	M	Temporal	PFD	Osteosarcoma	23y	Not informed	No information on how initial diagnosis was established
Amaral et al., 2008[11]	Brazil	38	F	Max; Orbital	PFD	Osteosarcoma	4y	6m, died of tumor	
Kaushik et al., 2001[10]	USA	18	M	Max	MCA Syndrome	Chondroblastic osteosarcoma	14y	4y, free of tumor	
Heller et al., 2001[9]	USA	27	M	Max	MCA Syndrome	Chondrosarcoma	23y	2y, free of tumor	
Beuerlein et al., 1997[8]	USA	29	M	Max	FD	Malignant mesenchymoma	-	3w, died of tumor	No information on how initial diagnosis was established
Cheng and Chen, 1997[7]	Taiwan	29	M	Max	FD	Malignant fibrous histiocytoma	25y	2y +6m, died of tumor	No information on how initial diagnosis was established
Ruggieri et al., 1994[6]	USA	17	F	Max	MFD	Chondroblastic osteosarcoma	8y	8m, died of tumor	Other cases presented in this study had a history of previous radiotherapy
		60	F	Sphenoid	MFD	Fibrosarcoma	2y	5m, died of tumor	

FOL – fibro-osseous lesion, MT – malignant transformation, F – female, M – male, COD – cemento-osseous dysplasia, FD – fibrous dysplasia, PFD – polyostotic fibrous dysplasia, MFD – monostotic fibrous dysplasia, MCA - McCune-Albright, y – year, m – months, w – weeks.

Regarding the site of the FOLs that underwent malignant change, 9 cases occurred in the mandible, 14 occurred in the maxilla, and 4 at other sites, including the temporal, intratemporal fossa and sphenoid. Considering only the jawbones, the maxilla:mandible ratio was 1.5:1. The average period from initial FOL diagnosis to malignant transformation was 18.2 years (analysis made from 25 cases in which the time was reported). This period ranged from 4 months[16] to 50 years.[21]

The histological type of the malignant tumor was predominantly osteosarcoma (85.2%). In five cases of osteosarcoma the tumor's subtype was specified, being 2 cases of osteoblastic osteosarcoma and 3 cases of chondroblastic osteosarcoma. The remaining cases were diagnosed as chondrosarcoma,[9] malignant fibrous histiocytoma,[7] fibrosarcoma,[6] and malignant mesenchymoma.[8] This latter diagnosis was established in 1997 by Beurerlein et al.[8] This nomenclature is no longer accepted by the world health organization (WHO) classification of tumours of soft tissue and bone.[25] We consider that according to the current classification this tumour could be diagnosed as a chondroblastic osteosarcoma.

Concerning the outcome, five studies did not report any follow-up information[15,17,19,22,23] and one study only reported that the patient did not respond to therapy, yet the time of follow-up was not m4ntioned.[21] Among the other reports (n=21), 8 patients remained alive during the follow-up, while 13 died because of the tumor. All cases in which the outcome was available were initially diagnosed as FD. The average survival time for patients who died was 22.1 years and the 3-year overall survival rate was 51%. We observed that lesions located in the mandible and diagnoses other than osteosarcoma tended to have poor survival rates (Figure 2), but no significant difference was identified.

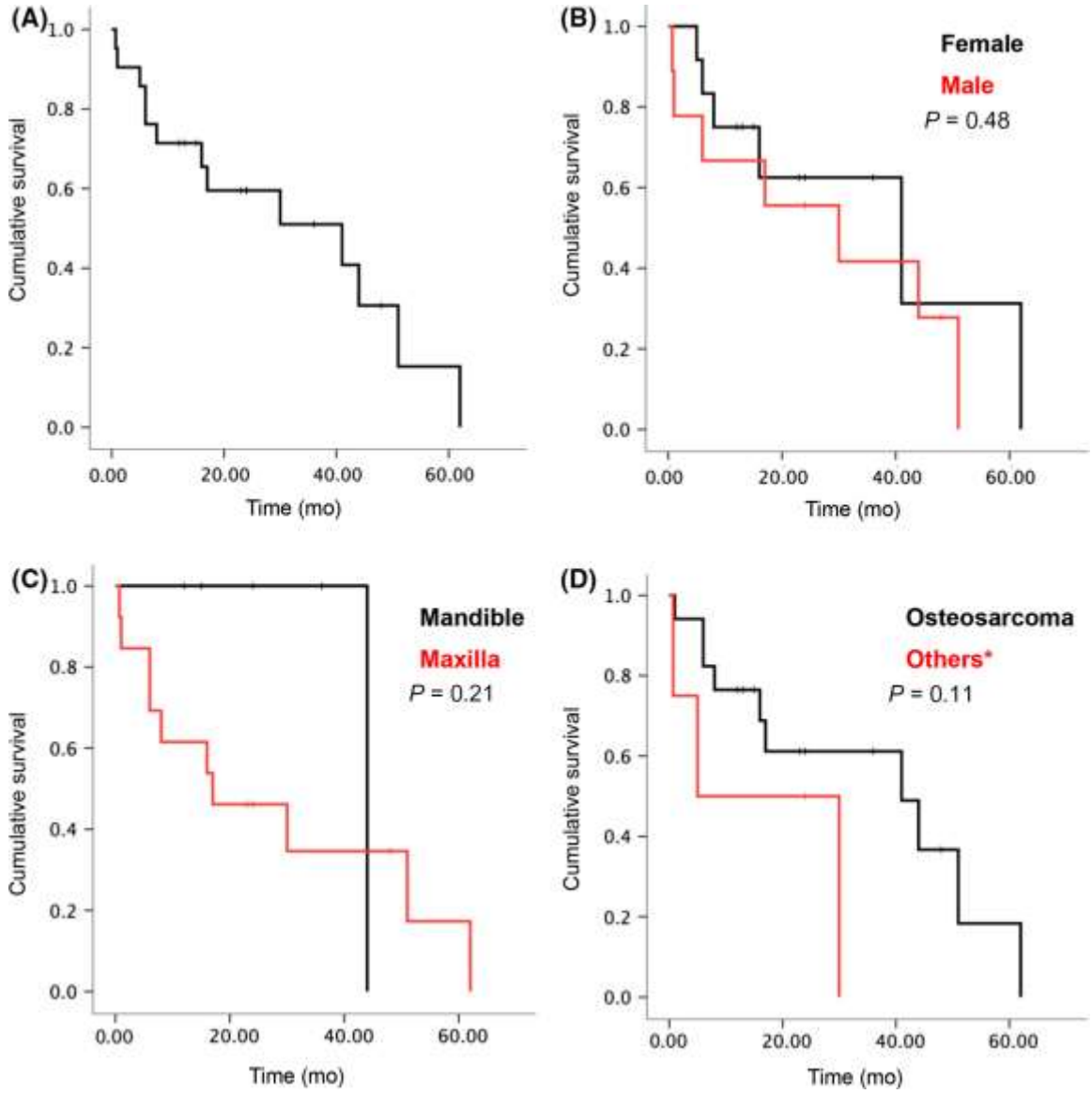

Figure 2. (A) Overall cumulative survival curves of FLO-associated malignant tumors. Survival curves according to (B) gender, (C) site and (D) diagnosis. Curves were compared by the log-rank test.

3.3 Quality assessment

Table 2 shows the results from the quality assessment. Few papers adequately described the patient demographics or previous diagnosis (criterion 1) and most had an incomplete or absent description of patient's medical history. Few studies did not present follow-up information.

Table 2. Quality assessment

Authors/ year	Domain							
	1	2	3	4	5	6	7	8
Pack et al., 2016	No	No	Yes	Yes	Yes	No	NA	Yes
Mardekian et al., 2015	No	No	Yes	Yes	No	No	NA	Yes
Lee et al., 2015	Yes	No	Yes	Yes	Yes	No	NA	Yes
Sun et al., 2014	Yes	No	Yes	Yes	Yes	Yes	NA	Yes
Cheng et al., 2013	Yes	No	Yes	Yes	Yes	Yes	NA	Yes
Ma et al., 2013	Yes	No	Yes	Yes	No	No	NA	Yes
De Araujo et al., 2012	No	No	Yes	Yes	Yes	Yes	NA	Yes
Gon et al., 2012	No	No	Yes	Yes	No	No	NA	Yes
Sadeghi et al., 2011	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Varghese et al., 2010	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kim et al., 2010	No	No	Yes	Yes	Yes	Yes	NA	Yes
Kanazawa et al., 2009	Yes	No	Yes	Yes	Yes	Yes	NA	Yes
Reis et al., 2008	No	No	Yes	Yes	Yes	No	NA	Yes
Amaral et al., 2008	No	No	Yes	Yes	Yes	Yes	NA	Yes
Kaushik et al., 2001	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Heller et al., 2001	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Beuerlein et al., 1997	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cheng and Chen, 1997	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Ruggieri et al., 1994	Yes	No	Yes	Yes	Yes	Yes	NA	Yes

1 - description of patient's demographic characteristics and past diagnosis; 2 - medical history; 3 - current clinical condition; 4 - diagnostic tests; 5 - intervention/treatment; 6 - post-intervention clinical condition; 7 - adverse events; 8 - lessons provided by the case report

4 DISCUSSION

Craniomaxillofacial FOL represents lesions widely debated within the academic community, mainly due to the challenges involved with their diagnosis. The risk of malignant transformation however is not commonly discussed. We believe this is an important issue since it can guide clinicians while establishing follow-up strategies. In the present study we attempted to elucidate the risk of malignant transformation of craniomaxillofacial FOLs through a systematic review of the literature. A total of 27 cases of malignant transformation were identified, including 26 cases of FD and 1 case of OF. A slight predominance of malignant change was observed in women (male:female ratio 1:1.2) an in maxillary lesions. However, it is important to be aware that FD occurs more frequently in the maxilla and paranasal regions compared to the mandible. Moreover, FD lesions are more common in females.[1,2] A recent study by Kato et al., (2018) demonstrated a female:male ratio of 1.46:1 concerning MFD in a representative sample of patients with FOLs. In this study, 66% of FD cases occurred in the maxilla.[26] Therefore, these tendencies observed in the present study might just reflect the predilections observed for the FD initial diagnosis.

The age of the patients at the time of malignant transformation was quite variable (16 to 60 years), as was the period between initial diagnosis and this event. The average time from initial FOL diagnosis to malignant transformation was 18.2 years, ranging from 4 months[16] to 50 years.[21] More than 10 cases took more than 20 years to undergo malignant transformation. These data reveal that patients with FD need regular follow-ups for a long period, not only to monitor aesthetic issues or to identify reactivations, but also to possibly diagnose a malignant tumor at early stages. Symptoms such as abrupt swelling, numbness or pain might raise the suspicion of a malignant transformation,[21] and patients should immediately undergo a new biopsy. Malignant tumors derived from FD were diagnosed mainly as osteosarcomas, however cases of chondrosarcoma, malignant fibrous histiocytoma and fibrosarcoma were also observed. Yet, it is important to have in mind that in some cases the osteoid production by malignant cells is not that evident. This can lead to a misdiagnosis between chondroblastic

osteosarcoma and chondrosarcoma, as well as between fibroblastic osteosarcoma and malignant fibrous histiocytoma or fibrosarcoma. Immunohistochemistry is valuable to identify malignant osteoblasts that are capable of producing neoplastic bone, through osteocalcin and osteonectin for example.[27] Moreover, galectin-1 is a useful marker to differentiate chondroblastic osteosarcoma and conventional chondrosarcoma.[28] We observed that among the reports in which the malignant tumor was not an osteosarcoma, immunohistochemistry for bone markers was not performed.[6,7,9]

The great majority of cases identified in this review were FD. A recent systematic review performed by Li et al., also evaluated cases of craniofacial FD with malignant transformation, and identified a considerable number of cases.[29] However, in this study radiation-induced cases and concomitant cases were also included. In the past, FD was often treated with radiotherapy to control lesion's growth. Therefore, certain reported cases of FD that underwent malignant degeneration are better classified as radiation-induced sarcomas,[30] and therefore were not included in our study. FD is a developmental process caused by postzygotic activating missense mutations in the GNAS gene, provoking abnormal bone formation that occur frequently in gnathic bones but also in long bones, ribs and skull.[2] FD may involve a single bone (MFD) or multiple bones (PFD) and can also be associated with other endocrinopathies in MCA syndrome. In this review we observed that cases of malignant transformation have occurred in all types of FD. Among all studies included in this systematic review, only one evaluated the GNAS status in the malignant tumor resected from a woman with MCA syndrome.[13] Recently, Sugiura et al. (2018) also confirmed the presence of GNAS mutation in an osteosarcoma derived from FD in the hips[31] Other studies have previously demonstrated that GNAS mutations are not detected in conventional osteosarcomas.[32,33] Combined, these data suggest that a positive GNAS mutation status is highly diagnostic for FD and also for FD-derived osteosarcoma. Since 2007, a simple and reliable method of identifying the *GNAS1* mutation in paraffin embedded tissue is available.[34] However, several cases described after that time did not evaluate the GNAS

mutation in the initial sample nor in the malignant tumor.[12,14-21,23,24] We believe that this information is of paramount importance and should be evaluated in further reports.

In our review we encountered well-documented cases of malignant transformation of FD, which confirms that this event, although extremely rare, can occur. Nevertheless, the exact risk of this event is quite difficult to predict. Cheng et al. (2013) observed that the percentage of patients with craniomaxillofacial FD that experienced malignant transformation was 0.93%,[20] while Sun et al., (2014) observed a rate of 2.55% in a 20-year period.[21] Ruggieri et al. (1994) observed that 1.33% of patients diagnosed with FD in any part of the body had a history of malignant transformation not associated with previous radiotherapy.[6] These rates represent the prevalence of the event during a long period of follow-up, and it's hard to estimate the annual incidence of malignant transformation. We detected only 26 cases in the English-language literature, suggesting a rather low frequency. Yet, gnathic osteosarcoma is estimated to occur at a rate of 0.7 cases per million.[35] Therefore, the percentage of events observed in the studies of Cheng, Sun and Ruggieri are higher that one would expect in the general population, reinforcing that patients with FD have in fact a greater risk to develop osteosarcoma. Well-delineated prospective studies are necessary to establish the real incidence of this event.

The patients with FD-associated malignant tumors had a quite poor prognosis. According to The USA National Cancer Data Base Report the 3-year and 5-year survival rates for patients with conventional gnathic osteosarcomas are 65.3% and 59.7%, respectively.[36] Among the reports evaluated herein, a single patient had a follow-up period grater than 5 years.[21] This patient died 5 years and 2 months after diagnosis. We observed a 3-year survival of 51%, which was slightly lower than the rate observed in conventional osteosarcoma of the head and neck. This difference could indicate a more aggressive behavior of FOL-related malignancies. However, we believe that the short follow up periods of several studies might hamper the establishment of such assumptions. More studies with longer follow-up periods are necessary. Our analysis revealed a

tendency of poor prognosis of maxillary tumors, a fact observed in conventional gnathic osteosarcomas.[36] This observation may be because mandibular tumors are surgically removed more easily and complete surgical excision remains the best treatment option for osteosarcomas.[36]

Despite the robust evidence concerning FD sarcomatous degeneration, it appears that other FOL do not share the same risk. OF is slow-growing benign tumor in which sporadic cases present mutations in HRPT2. Recurrences can occur however its potential for malignant transformation is not recognized by the WHO.[2] In this review, only one report of OF that underwent malignant degeneration was identified.[22] The case occurred after a third recurrence in the posterior mandible of a 47-year-old female patient, suggesting that this lesion had an aggressive behavior from the beginning. It appears that patients with multiple recurrences might need a closer follow-up to detect any evidence of malignant transformation. COD is considered a non-neoplastic lesion with probable reactive nature and, although it is not considered an odontogenic lesion, all cases are diagnosed in tooth-bearing regions of the gnathic bones, suggesting at least some odontogenic influence on its etiology.[2,37] Among all craniomaxillofacial FOL, COD is the most prevalent with a mean number of cases per year globally of 5.1, compared to 1.6 for FD.[37] Yet, no case of COD sarcomatous transformation was identified in this review. We believe, however, that the radiographic aspect in the study by Pack et al., (2016) is more compatible with a florid-COD rather than a FD as described by the authors.[24] Cases of concomitant diagnosis of COD and malignant tumors can be found in the literature,[38,39] including one case from our institution.[3] These studies were not included in the systematic review since concomitant lesions were considered an exclusion criteria. Despite these few reports, we considered that the evidence is not sufficient to support that OF or COD have a real risk of malignant transformation. Yet, it is important to mention that some cases of OF and COD, specially juvenile OF and florid COD, might have a local aggressive behavior with extensive bone expansion. Moreover, recurrences after surgical excision can

also occur. Therefore these conditions also deserve careful attention by health professionals even though they do not present a risk of malignant transformation.

Some important pitfalls need to be considered in the context of malignant transformation of FOL. FD presents invariably in early childhood or rarely early in adolescence. Therefore, reports in which the initial diagnosis of FD was made at a more advanced age[7,12,23,24] can raise suspicion of a misdiagnosis. The most important pitfall is related to a misdiagnosis due to similar clinical, radiological and histological features between FD and other lesions. Different conditions such as chronic sclerosing osteomyelitis and low-grade osteosarcomas require a very thorough inspection and correlation of clinical, radiological and microscopic features to differentiate from FD.[40,41] Moreover, the possibility of initial misdiagnosis due to inappropriate tumor sampling in the incisional biopsy also needs to be considered. Therefore, the analysis of the whole specimen is very important to confirm the diagnosis. In the study of Sadeghi et al (2011), the rapid growth and diplopia in the short interval between initial diagnosis and malignant transformation, as well as the poor outcome might suggest that the patient had an osteosarcoma from the beginning.[16] In this study the diagnosis of FD was established in another center, and despite the clinical photos were retrieved, the histopathological slides were not recovered for revision of the diagnosis. Hence, we suggest that the initial diagnosis must be well supported by correlation of clinical, radiological and histopathological features, including a careful analysis of the cytological aspects. Moreover, immunohistochemical analysis of MDM2 and CDK4 can help to distinguish low-grade osteosarcoma from benign histological mimics,[42,43] and could be performed in borderline cases. In this review, it was common to observe that the authors reported that the patient “had a history of” a FOLs.[8,12,14,15] This was observed as the main failure in quality assessment. In some cases with a long history of FD, especially PFD or MCA syndrome, the diagnosis might seem quite clear to the clinicians. However, we believe that in the academic scope it is very important to be rigorous in identifying and reporting the aspects that lead to an initial diagnosis. Ideally, the initial clinical aspect, radiographic exams and histopathological features need to be reported and if

possible illustrated. The GNAS status is also very important to be evaluated in cases of FD to confirm the initial diagnosis and also to endorse that the malignant tumor was derived from this condition.

This review was performed using a systematic approach to cover the literature as comprehensively as possible. Yet, some important limitations and/or bias need to be addressed. We included three major and important electronic databases, however the database Web of Science was not included, which represents a limitation in our search strategy. Moreover, the term “Familial Gigantiform Cementoma” was not included, due to the rarity of this lesion. Yet, this may have led to missed studies on this subject. The language restriction might led to a selection bias known as “Tower of Babel” bias, when only English studies are included. Nevertheless, there is evidences that demonstrate that excluding studies published in languages other than English from systematic reviews have no impact on outcomes compared to reviews that included studies published in other languages.[44] In this review, we also included a date restriction which can be a limitation of the study. This restriction was based in the fact that in the past fibrous dysplasia was often treated with radiation. Studies conducted before the 90’s might not have mentioned radiotherapy as the therapeutic approach once the concept of radiation-induced sarcomas in FD was not completely established.[6]

5 CONCLUSIONS

The initial diagnosis of any FOL must be well supported by clinical, radiographical and histopathological evaluation since some cases evaluated herein raised the suspicion of a low-grade osteosarcoma misdiagnosis. Our analysis revealed that FD demonstrates a risk of malignant transformation that must be taken into account by clinicians. Osteosarcoma was the most common malignant tumor observed in these patients and the malignant change can occur in a very late period after the initial diagnosis of FD. Therefore, a regular and long follow-up is advised.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

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