

## Ossifying fibroma of the nose and paranasal sinuses

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**Background:** The purpose of this work was to perform a systematic review regarding ossifying fibroma and its multiple variants of the paranasal sinuses, and to identify any clinical differences between the multiple variants.

**Methods:** A search of the U.S. National Library of Medicine (PubMed) database was performed for the non-Medical Subject Heading (MeSH) search term "ossifying fibroma." The bibliographies of the retrieved manuscripts were searched to identify additional potentially relevant articles. Finally, textbooks of head and neck pathology were searched to identify peer-reviewed literature that addresses the histopathology of ossifying fibroma and its variants. Abstracts were screened by 2 of the authors to identify reports of ossifying fibroma lesions (and its variants) that involved the paranasal sinuses. Extracted data from case reports or case series included the clinical presentation, age, gender, site of involvement, surgical approach, treatment outcome, follow-up period, and recurrence rate. Information derived from cases is summarized in tables, and simple descriptive statistics were applied to the data.

**Results:** A total of 137 distinct patients were identified in 103 reports. Extracted data did not show any appreciable difference in clinical presentation or outcomes. Data on recurrence of these lesions was often limited by a lack of follow-up.

**Conclusion:** Although differentiation between the subtypes of ossifying fibroma can be made histologically, and a diverse nomenclature exists, there does not appear to be any overriding clinical significance to the histopathologic differentiation of OF variants. © 2013 ARS-AAOA, LLC.

**Key Words:**

ossifying fibroma; cemento-ossifying fibroma; juvenile aggressive ossifying fibroma; aggressive psammomatoid ossifying fibroma; fibro-osseous lesion; paranasal sinuses

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A variety of benign fibro-osseous lesions can develop in the head and neck. Examples of such lesions include fibrous dysplasia, osteoma, and ossifying fibroma (OF). The classification of these lesions has evolved substantially over the last decades, but their appropriate classification and treatment are continued subjects of confusion and controversy. OF is a common benign fibro-osseous lesion that develops in the nose and paranasal sinuses. It is considered

a benign, locally aggressive neoplasm that requires surgical excision.

OF has traditionally been considered to be a slow growing tumor. However, the biologic behavior of these lesions may be quite variable. Often OF lesions do not cause significant symptoms, but are incidentally discovered when imaging is performed for another indication. Because they may grow for long periods while clinically silent, OF may not be diagnosed until the tumor has become quite large and is causing facial distortion or is compressing important adjacent anatomic structures. Signs and symptoms of OF include proptosis, diplopia, cheek swelling, headaches, nosebleeds, nasal obstruction, epiphora, and rhinorrhea. These tumors may also cause serious complications including massive mucocele formation, visual loss, and intracranial infections.<sup>1-4</sup> When visualized endoscopically, these lesions appear as smooth, rounded, mucosally covered masses.<sup>5</sup> However, if the lesion does not involve the nasal cavity, intranasal examination and endoscopy may not provide helpful diagnostic information. Thus radiologic studies are essential for diagnostic and treatment planning purposes.

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Several variants of OF have been described. These variants include cemento-ossifying fibroma (COF), juvenile active ossifying fibroma (JAOF), and aggressive psammomatoid ossifying fibroma (APOF). These histopathological variants of OF may have different clinical behavior that impacts the surgical approach and subsequent follow-up. The objectives of this report are to review the classification and diagnosis of these lesions and to analyze the clinical behavior of OF variants to inform clinical decision-making.

### Nomenclature for OF lesions

The nomenclature surrounding ossifying fibroma is diverse and often confusing. In 1971, the World Health Organization (WHO) published their first "Histological Typing of Odontogenic Tumours, Jaw Cysts and Allied Lesions."<sup>6</sup> This classification separated tumors into 3 main categories: (1) neoplasms and other tumors related to the odontogenic apparatus; (2) neoplasms and other tumors related to bone; and (3) epithelial cysts. Within the second category lay a subcategory of osteogenic neoplasms, namely OF.

OF lesions have woven or metaplastic bone as their primary component. However, within certain OF lesions, hard tissue identifiable as woven or metaplastic bone is seen mixed with cementum-like tissue. In 1995 the WHO<sup>7</sup> renamed the group of lesions "cemento-ossifying fibroma" (COF). Tumors in which the main mineralized component is cementum are known as cementifying fibromas. Tumors in which the main mineralized component is bone are known as OFs. Tumors with a mix of mineralized components are labeled COFs.

Cementifying lesions may not produce cementum, but rather, "cementum like-material." The round calcified structures, similar to cementum found in some OFs are also referred to as "ossicles" or "psammoma-like spherules."<sup>8</sup> Lesions containing these structures are sometimes referred to as "psammomatoid ossifying fibroma," but the WHO now considers COF and psammomatoid ossifying fibroma to be synonymous.<sup>9</sup> Various authors have attached additional terms to the pathologic diagnosis of OF. For example, some lesions within the OF spectrum have been labeled in the literature as APOF or JAOF. Such nomenclature is potentially confusing. For example, not all JAOFs are diagnosed in juveniles, not all JAOFs exhibit locally aggressive behavior, and not all lesions classified as JAOF have the same histopathologic features.<sup>10,11</sup> Thus, our understanding of OF lesions is impaired by a diverse nomenclature and a lack of a general consensus on strict histological classifications of these lesions.

In this review, clinical information from published reports of these lesions has been collated in an attempt to identify clinical differences between the different variants of OF. We have divided these variants into 3 categories, based on the authors' identification of the lesion. The categories are: (1) ossifying fibroma (OF); (2) cementifying fibroma or cemento-ossifying fibroma (COF), and; (3) ag-

gressive psammomatoid ossifying fibroma, psammomatoid ossifying fibroma or juvenile active ossifying fibroma (referred to in this review as APOF).

### Methods

A search of the U.S. National Library of Medicine (PubMed) database was performed for the non-Medical Subject Heading (MeSH) search term "ossifying fibroma." Limits were set for humans and English language, identifying 470 manuscripts. These reports were screened by 2 of the authors to identify reports of OF lesions (and its variants) that involved the paranasal sinuses. Reports for lesions that involved only the maxillary alveolus were excluded, yielding 107 reports. The bibliographies of the retrieved manuscripts were searched to identify additional potentially relevant articles. Finally, textbooks of head and neck pathology were searched to identify peer-reviewed literature that addresses the histopathology of ossifying fibroma and its variants. A total of 103 reports with relevant clinical data were ultimately reviewed. Extracted data from case reports or case series included the clinical presentation, age, gender, site of involvement, surgical approach, treatment outcome, follow-up period, and recurrence rate. Information derived from cases is summarized in tables, and simple descriptive statistics were applied to the data.

### Results

A total of 137 cases of fibro-osseous lesions of the nasal cavity and paranasal sinuses were reviewed in the literature. The clinical characteristics of the lesion categories are displayed in Table 1.

#### OF

The literature review revealed 55 cases of OF in the paranasal sinuses.<sup>1,3,12-53</sup> The mean age of presentation was 29.9 years, with a range of 7 to 75. The male to female ratio was found to be 1 to 1.04, with 4 reports not identifying the gender of the patient. Facial swelling was the most common presenting sign, followed by nasal obstruction, proptosis, and headache. Most OFs of the paranasal sinuses occurred in the ethmoid and maxillary sinuses, followed by the nasal cavity. Multiple areas of presentation were common.

The clinical behavior of OF is similar to COF and APOF, based upon published cases. OF lesions were treated with a variety of external and endoscopic surgical approaches. Average follow-up for these cases was 30.8 months, with a range of 2 weeks to 17 years. Follow-up was available in 37 of 55 patients. Twenty-nine were noted to be free of disease during follow-up. One patient died in the postoperative period, but the cause of death was not specified in the report.<sup>39</sup> Two patients exhibited recurrences after total resection and 3 patients showed recurrence after subtotal resection.<sup>18,33,34,43,48</sup> Three other patients who underwent subtotal resection showed no change or progression of residual disease during follow-up.<sup>1,31,32</sup>

**TABLE 1.** Clinical characteristics of fibro-osseous lesions: literature review reports

	Ossifying fibroma	Aggressive psammomatoid ossifying fibroma	Cemento-ossifying fibroma
Sex, n (%)			
Female	26 (48)	20 (34)	13 (57)
Male	24 (44)	39 (66)	9 (39)
Not recorded	4 (8)	0 (0)	1 (4)
Mean age at presentation, years	29.9	16.9	22.8
Most common presenting sign/symptom (n)	Nasal obstruction (15)	Facial swelling (17)	Facial swelling (11)
	Facial swelling (14)	Nasal obstruction (17)	Proptosis (11)
	Proptosis (12)	Proptosis (17)	Nasal obstruction (6)
Most common location (n)	Maxillary sinus (13)	Ethmoid sinus (30)	Maxillary sinus (23)
	Ethmoid sinus (13)	Maxillary sinus (19)	Ethmoid sinus (20)
Approach to resection, n (%)			
Open	41 (75)	44 (75)	17 (74)
Endoscopic	8 (15)	6 (10)	2 (9)
Not recorded	6 (10)	9 (15)	4 (17)
Extent of resection, n (%)			
Total	29 (53)	42 (71)	14 (61)
Subtotal	12 (22)	8 (14)	3 (13)
Biopsy	0 (0)	2 (3)	1 (4)
Not recorded	14 (25)	7 (12)	5 (22)
Mean follow-up time, months	26.2	24.5	30.8
Status at follow-up, n (%)			
Free of disease	28 (51)	29 (49)	12 (52)
No change in disease	4 (7)	5 (8)	1 (4)
Not recorded	18 (33)	21 (36)	10 (44)
Recurrence of disease	1 (2)	4 (7)	0 (0)
Progression of disease	3 (5)	0 (0)	0 (0)
Deceased	1 (2)	0 (0)	0 (0)

### APOF

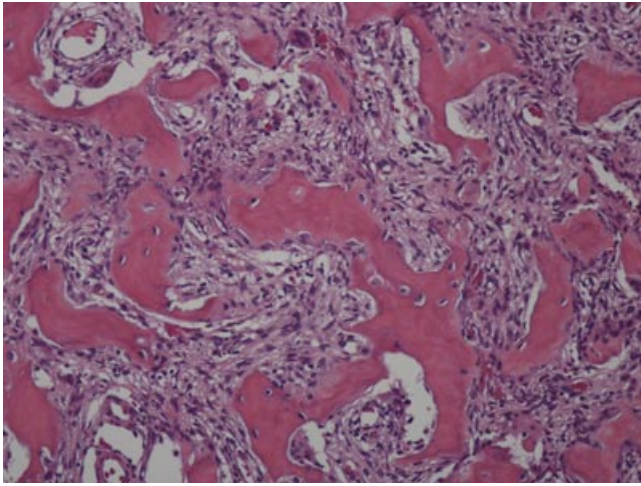
Fifty-nine cases of APOF were identified in 40 separate reports.<sup>2,4,11,22,33,54–89</sup> The average age at presentation was 16.9 years, with a range from 15 months to 68 years. There was a male to female ratio of approximately 2 to 1. The most common presenting signs and symptoms were facial swelling, nasal obstruction, and proptosis. APOF lesions most often presented in the ethmoid sinus, followed by the maxillary sinus, orbit, and frontal sinus. Many lesions had multiple sites of involvement and multiple presenting symptoms.

APOF has a reputation for aggressive behavior and recurrence that could be due to an aggressive growth rate and biologic behavior, advanced disease at presentation, or a greater rate of incomplete resection.<sup>11</sup> However, the reports reviewed in this study did not reveal a higher rate of recurrence, nor evidence of more advanced disease at

presentation. Of the 59 APOF cases identified in the literature, follow-up data was available in 38 reports. The average follow-up time was 24.5 months, with a range of 3 to 72 months. Twenty-nine of 38 cases with follow-up had no recurrence after excision. One case recurred 4 months after resection. This patient underwent re-resection, and remained disease-free over a follow-up period of 7 years.<sup>11</sup> Two other cases experienced recurrences after reported total excision.<sup>33,74</sup> One patient had a subtotal resection and presented 4 months later with disease noted to be more extensive than preexcision.<sup>89</sup> There are no reports in the literature of metastatic disease.

### COF

Twenty-three cases of COF of the paranasal sinuses were identified in our literature review.<sup>5,28,68,90–108</sup> The average



**FIGURE 1.** The lesion shows varying amount of trabeculae of lamellar bone or woven bone, characteristically with osteoblastic rims and some osteoclasts, a few multinucleated giant cells and varying amounts of fibroblastic stroma. Cementum-like bodies (psammomatoid spherules) are not present.

age of presentation was 22.8 years, with a range of 5 to 53 years. Male to female ratio was noted to be 1 to 1.44, with 1 report not identifying the gender of the patient. Clinically, symptoms depend on the exact location of the lesion. The most common presentations included facial swelling and proptosis, followed by headache. In contrast to APOF, COF most often presented in the maxillary and ethmoid sinuses, and was much less commonly found in the sphenoid sinus, frontal sinus or orbit.

Early recurrence rates for sinonasal COF appear to be low. Follow-up was specified in 13 of 23 patients identified in this review. The average follow-up time was 26.2 months, with a range of 6 to 120 months. On follow-up, 12 patients were noted to be free of disease. As with the other OF lesions, there are no reports of metastatic disease.

## Pathology

### *Histopathology of OF*

Grossly, OF is often oval or circular, gray or white, with a firm shell. Histologically, the lesion consists of 2 main components: (1) fibrous stroma; and (2) bone element.<sup>12</sup> The fibrous stroma generally consists of fibroblasts and collagenous fibers. Bone elements include mineralized bodies, woven bone, and lamellar bone. Tumors in which the main mineralized component is bone are known as OFs. This is in contrast to tumors in which the main mineralized component is cementum, which are known as cementifying fibromas. Figure 1 displays a representative histologic picture of OF.

### *Histopathology of APOF*

Histologically, APOF appears as a benign fibro-osseous proliferation consisting of irregular bony spicules and spherules of variable shape and size admixed with a cellular fibrous stroma. The most distinctive feature or component is the presence of mineralized ossicles resembling

cementum or calcified “psammomatoid” bodies with variable numbers or shapes. The ossicles are demarcated with a central blue to black appearance surrounded by a pink rim and some have concentric lamination depending on degree of calcification. The ossicles exist within or at the periphery of bony trabeculae or cellular stroma. There are osteoclasts present in association with ossicles, and osteoblasts rimming the periphery. The bony trabeculae also vary in shape and size. Trabeculae are composed of lamellar bone with associated osteoclast and osteoblast rimming. The transition zone between the ossicles and bony trabeculae often can be identified. The cellular stroma are arranged in a fascicular to storiform growth pattern composed of round of polyhedral to spindle-shaped cells with prominent basophilic nuclei and indistinct cellular borders. Mitosis can be seen but is not prominent, and there are no atypical mitotic figures. Giant cells are occasionally present.

### *Histopathology of COF*

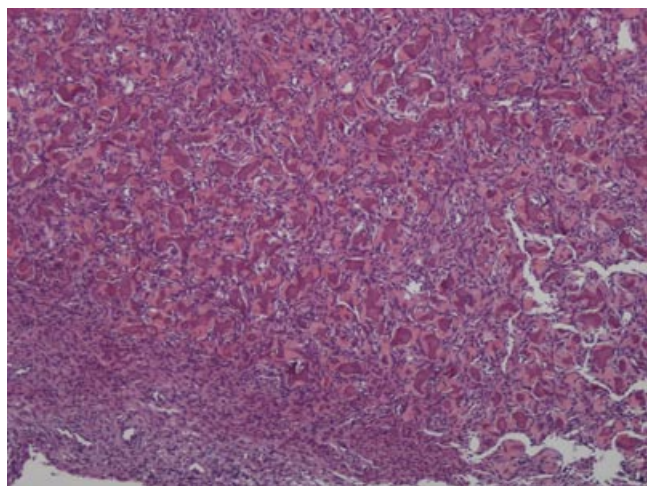
Histologically, COF may have overlapping features with APOF, and the 2 lesions may be confused. COF can be divided into 3 basic subtypes.<sup>109</sup> The first type has equal amounts of calcified material and fibroblastic stroma. The calcified structures are composed of bony trabeculae with prominent osteoblastic rims and some osteoclasts. Cementum-like bodies are scattered throughout the lesion. The connective tissue consists of spindle fibroblastic cells in a storiform pattern. The second type consists mostly of a storiform cellular pattern, with little bony trabeculae, and often without osteoblastic rimming. The third type represents a combination of the above 2 subtypes, which are seen interspersed throughout large lesions.<sup>110</sup> The variation of the histopathologic components of the lesion may also depend upon the age of the tumor. Figure 2 displays the histology of a lesion that may be defined as COF or APOF.

### *Radiology of OF lesions*

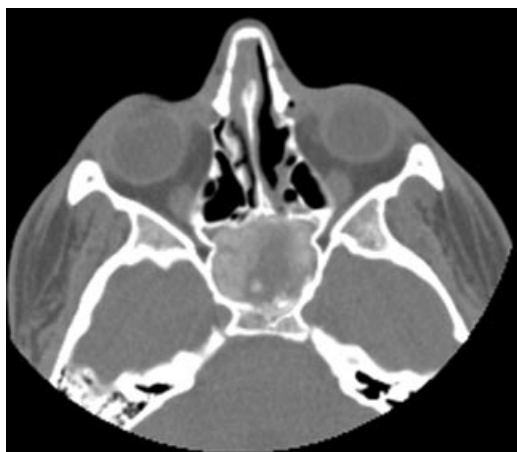
The OF variants have significantly overlapping radiologic characteristics; thus, even with magnetic resonance imaging (MRI) and computed tomography (CT) the OF, COF, and APOF lesions cannot be reliably differentiated. In OF, CT usually shows an eggshell-thin rim of bone surrounding a lytic area.<sup>18</sup> On MRI, fibro-osseous lesions usually have low to intermediate signal intensity on T1 imaging, and variable intensity on T2 imaging. The outer layer of the lesion usually enhances with contrast, although incomplete enhancement of the shell has been reported.<sup>111</sup>

Imaging findings in APOF lesions are slightly different from OF on CT. The lesions are expansile and circumscribed by a thick shell of bone density with a multiloculated internal appearance and a content of varying density (see Fig. 3).<sup>112</sup> The psammomatoid ossicles that are present in these lesions may give the lesion a ground glass appearance. On MRI, an APOF is hypointense to muscle on T1- and T2-weighted images. The well-demarcated bony walls are isointense to soft tissue on T1-weighted images and





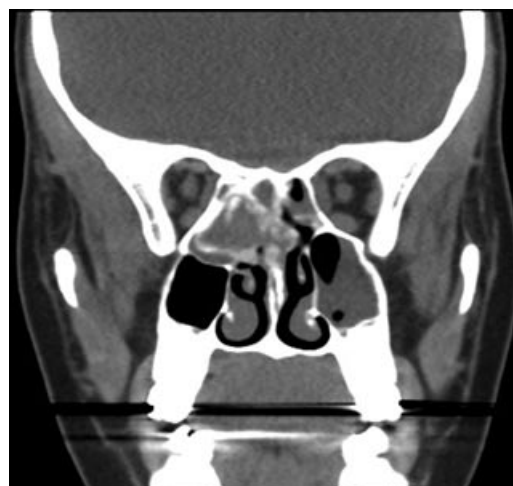
**FIGURE 2.** Histologically, COF-APOF is composed of varying amounts and types of calcified material and varying amounts of fibroblastic stroma. The calcified structures may present as cementum-like (psammomatoid) basophilic deposits (round bodies or spherule forms), trabeculae of lamellar bone or woven bone, characteristically with prominent osteoblastic rims and some osteoclasts. Cementum-like bodies (psammomatoid spherules) are scattered throughout the lesion. The connective tissue consists of spindle fibroblastic cells in storiform pattern can be closely packed to nearly acellular. Mitosis can be seen. COF-APOF = cemento-ossifying fibroma-aggressive psammomatoid ossifying fibroma.



**FIGURE 3.** Axial CT scan of JAOF. Note the heterogeneity within the lesion. CT = computed tomography; JAOF = juvenile active ossifying fibroma.

hypointense on T2-weighted images.<sup>2</sup> Occasionally, these lesions will have a hyperintense area on T2-weighted imaging, consistent with a cyst or mucocele.<sup>2</sup> The bony walls tend to enhance with gadolinium, suggesting that the area is part of the proliferative process as opposed to a reactive hyperostosis.<sup>2</sup>

Imaging findings in COF are very similar to APOF. On CT, the lesions are also expansile and circumscribed by a thick shell of bone density with a multiloculated internal appearance and a content of varying densities (see Fig. 4).<sup>112</sup> The cementum-like bodies appear radiolucent or like ground glass. On MRI, a COF is hypointense to muscle on T1- and T2-weighted images. The well-demarcated bony walls are isointense to soft tissue on T1-weighted im-



**FIGURE 4.** Coronal CT scan of COF. Note the similar characteristics between this and JAOF. COF = cemento-ossifying fibroma; CT = computed tomography; JAOF = juvenile active ossifying fibroma.

ages and hypointense on T2-weighted images.<sup>12</sup> As with other OF lesions, the bony walls tend to enhance with gadolinium, suggesting that it is part of the proliferative process as opposed to a reactive hyperostosis.<sup>12</sup> Thus, the imaging findings cannot reliably distinguish between OF, APOF, and COF.

## Discussion

Based upon this review of published case reports and case series, the exact histologic differentiation of these lesions does not appear to be clinically important. There do not appear to be any clinical signs or symptoms that distinguish OF, COF, and APOF. For all of these lesions the ethmoid and maxillary sinuses are the most commonly involved sites, but any of these lesions can develop at any site within the paranasal sinuses, and there does not appear to be a predilection of any of these lesions for involvement of a particular sinus.

OF lesions can develop at any time along the life span, with the mean age of presentation in young adulthood. There do not appear to be any differences among the lesions with regard to patient age at diagnosis. Based on our review, it appears that APOF is more likely to develop in males, whereas OF and COF do not appear to have a gender predilection. Recurrence rates for APOF, COF, and OF appear to be low, and appear to be equivalent, based upon limited follow-up data in published reports. Despite the labels “aggressive” and “active” attached to APOF, we did not identify any reason to label APOF as more aggressive than the other ossifying fibromas. Also, we found no information to suggest that APOFs are more extensive at the time of diagnosis. The location or extent of disease at the time of diagnosis is probably more important than the histopathology.

Many questions remain regarding the appropriate treatment of OF lesions. The data accumulated in this review

is based upon case reports and case series that have inconsistent or even nonexistent follow-up. Because there are no systematic studies that have followed large cohorts of these patients for prolonged periods of time, significant knowledge gaps remain with respect to the natural history and recurrence rates for these lesions. If a tumor cannot be completely resected, when should re-resection be considered? Should one wait for recurrence of symptoms or radiologic progression of disease? Is there harm in observing a patient with residual disease after subtotal resection? Even if complete resection achieved, it is unclear from published data if these patients should be followed with serial imaging and for how long such follow-up should continue. Systematic study of these lesions could reveal that there are indeed some differences in biologic behavior among the various histologic subtypes of ossifying fibroma.

OFs are benign tumors, and some benign tumors can undergo malignant transformation over time. But we do not know the malignant transformation rate for these rare lesions. Similarly, although radiation therapy has not been advocated for these lesions, some other bony tumors are treated with radiation. Does radiation therapy ever have a role for these lesions? The answers to many of these questions will only come from long-term multi-institutional studies that follow large cohorts of ossifying fibroma patients over a period of years.


### Management of OF lesions

When faced with a patient with an apparent fibro-osseous lesion of the paranasal sinuses, the first priority is to secure a diagnosis. If OF is suspected radiologically, the next step is to obtain a surgical biopsy, with an adequate specimen to allow the pathologist to make an accurate diagnosis. The purpose of this biopsy is to confirm the diagnosis of OF and exclude other entities such as a sarcoma that may require an altered treatment approach.

The goal of treatment for OF should be complete surgical removal, preferably on the first attempt. Re-resection of

these lesions is made more difficult by scarring and distortion of anatomic structures and tissue planes. These impair surgeon orientation and visualization, as well as the ability to distinguish tumor from adjacent normal tissue. Resection may be accomplished with a purely endoscopic approach, or through various transfacial, transoral, or craniotomy approaches. There is no evidence suggesting an open approach is superior to an endoscopic approach, or vice versa. The surgical approach should be dictated by the location of the lesion and the ability to perform complete removal. However, the goal of complete surgical excision should be tempered by the possible risks of attempting a complete excision. Most cerebrospinal fluid (CSF) leaks can be repaired intraoperatively, provided the surgeon is prepared and possesses the requisite technical skill and experience. Furthermore, bony removal in the sphenoclivar region can be performed safely and effectively in experienced hands. But such a decision should only be made after carefully weighing the risks of complications such as optic nerve or cavernous carotid injury. If complete removal could lead to injury of these structures, a less aggressive surgical approach with subtotal resection may be the most appropriate management choice. Surveillance for tumor recurrence seems prudent in all patients, using serial nasal endoscopy and yearly noncontrast sinus CT.

### Conclusion

Differentiation of OF subtypes can be made histologically, and a diverse nomenclature exists, but there does not appear to be any overriding clinical significance to the histopathologic differentiation of OF variants. Total resection remains the goal of treatment of these lesions; however, surgery in this setting should be carefully weighed against patient morbidity for benign disease. Patients who have undergone resection, whether total or subtotal, should be followed for recurrence with long-term nasal endoscopy and serial imaging. 

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