**CLINICAL REVIEW**

# Nasal juvenile angiofibroma: current perspectives with emphasis on management

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**Abstract**

Juvenile angiofibroma (JA) is an uncommon, vascular, benign, locally aggressive tumor. It is found almost exclusively in young males. Common presenting symptoms include nasal obstruction and epistaxis. The evaluation of patients with JA relies on diagnostic imaging. Preoperative biopsy is not recommended. The mainstay of treatment is resection combined with preoperative embolization. Endoscopic surgery is the approach of choice in early stages while in advanced stages open or endoscopic approaches are feasible in expert hands. Postoperative radiotherapy (RT) or stereotactic radiosurgery are considered for lesions that have been subtotally resected. Patients with apparently incompletely resectable JAs are best managed with moderate dose RT alone. There is no advantage to performing a subtotal resection followed by RT versus RT alone and the former is more morbid. Chemotherapy and hormone therapy are ineffective. The present review aims to update the current state of knowledge related to this rare disease.

## Introduction

The cellular, vascular and locally aggressive tumor that characteristically develops in the posterior nasal cavity of adolescent males[1], is generally referred to as juvenile nasopharyngeal angiofibroma Because of previous uncertainty regarding the precise origin of the tumor, it has been described using various names in the literature. Chelius[2] in 1847 described this lesion as a "fibrous nasal polyp which commonly occurs in persons around the time of puberty". It has also been known as juvenile nasopharyngeal angioma (Chaveau)[3], vascular fibroma (Frieberg)[4], juvenile nasopharyngeal hemangiofibroma[5], juvenile fibroangioma[6] and juvenile fibroma.[7] However, given the origin of the tumor from the pterygopalatine fossa close to the vidian canal canal, the term juvenile angiofibroma (JA) seems preferable and is used here.

JA is regarded as a benign tumor.[1] Sarcomatous, malignant transformation is extremely rare and attributable to prior radiotherapy (RT).[8.9] Transformation of a tumor in the absence of previous RT has been recently described.[9] JA may be associated with significant morbidity due to the particular anatomic location and locally destructive growth pattern. Management may be complex because of increased risk of severe hemorrhage. The present review therefore aims to explore the management of JA in the light of current knowledge and in conjunction with epidemiologic, pathobiologic and diagnostic aspects.

## Epidemiology

JA comprises about 0.05 % of all head and neck tumors with an incidence of approximately 1:150000.[10,11] It is the most common benign tumor presenting in the nose and nasopharynx and is almost exclusively seen in young males between the ages of 9 and 19 years.[10] Occasional cases in older males have been reported.[12] Exceptional cases in females have also been described[13,14,15,16] but should be subjected to rigorous pathologic and genetic review. The incidence seems higher in the Middle East and India than in Europe.[10,11,17]

## Etiopathogenetic considerations

Hormonal and genetic factors have been considered to explain the almost exclusive occurrence of JA in young males.[18]

Hormonal influences are controversial. On the one hand, JA expresses various levels of estrogen, progesterone and androgen receptors;[19] and an etiopathogenetic role for testosterone has been advocated.[20,21,22] Riggs *et al*.[23] observed that exogenous testosterone can cause tumor growth at any time, even decades following treatment. On the other hand correlations between proliferative index, hormonal receptors, age at diagnosis and tumor stage or bleeding, have not been established.[19,24,25] The significance of puberty-induced testosteronelevels in tumor development thus remains unclear.

Investigations of possible genetic events,[18,26] are usually based on small numbers of patients and clinical correlation is lacking. Chromosomal numerical gains and losses have been detected in both endothelial and stromal components of JA.[26] These include deletions in chromosome 17, which affect regions of the TP53 suppressor gene and *HER-2/NEU* oncogene.[27] Wnt pathways may also be involved via somatic or germ-line mutations of *CTNNB1*and *APC*, respectively.[28] Ponti *et al*.[29] reported nuclear staining for β-catenin in JAs, which is of interest because β-catenin is a coactivator of androgen receptors, whereas altered APC expression was only seen in JAs associated with familial adenomatous polyposis (FAP). Except for the association with FAP,[18,28,30] JA may develop in patients with Gardner's syndrome and chromosomal aberrations have been reported.[31]

JA overexpresses receptors for vascular endothelial growth factor (VEGFR2),[29] which may explain the growth of the tumor vascular component. Immuno-expression of stromal tenascin-C (TNC) in tumor stroma correlates with vascular density and higher tumor stage, and possibly influences angiogenesis.[32] Loss of syndecan-2 has also been reported, which could enhance the migration of tumor cells and account for difficulties in surgical control of tumor margins.[32] Other investigations drew attention to a correlation between overexpression of FGF18 and AURKB in stromal cells and down regulation of androgen receptors in endothelial cells.[26]

A possible role for human herpes simplex virus-8 (HSV-8), Epstein-Barr virus (EBV) and human papilloma virus (HPV) has also been considered.[25] Although JA does not appear to be associated with HSV-8 or EBV there is evidence of HPV infection at DNA and protein levels.[33] HPV is also likely to increase cell proliferation rate in JA[33],

and may be a possible etiologic or aggravating factor effecting early presentation/recurrent disease and accounting for variability in clinical behavior, respectively.[33]

Except for gender and age preference, the characteristic location of JA is intriguing. This could be explained if the tumor is regarded as a vascular malformation related to incomplete regression of the first branchial arch artery. Remnants of the artery may be preserved at the area of the sphenopalatine foramen, the typical site of JA, and could be sensitive to growth stimulation around puberty resulting in JA.[34] The notion is further explored in 'Pathology' below and can be reconciled with molecular events, though some authors consider it unlikely.[32]

**Site of origin and progression routes**

JA usually originates in the posterior nasal cavity, near the basisphenoid and the superior margins of the sphenopalatine foramen. The tumor shows an expansive and destructive growth pattern; and spreads to adjacent nasal cavity, nasopharynx, paranasal sinuses, orbit and skull base through foramina and fissures. Normal tissues are displaced and affected by pressure rather than invasion. Dumbbell-shaped extension into the pterygopalatine space, masticator space and infratemporal fossae often occurs.[35] Cavernous sinus or intracranial extension is noted in 10-20% of the cases.[36] Intradural involvement is exceptional.

**Pathology**

Grossly, JAs appear as rounded or lobulated, reddish or red-purple masses, sessile or pedunculated.[37,38] They are well circumscribed (Figures 1A and B), though non-encapsulated, and there may be areas of ulceration or purulent exudate on the surface. Depending on degree of vascularity, the cut surface appears solid or spongy with smooth "cysts/ openings" corresponding with distended vessels.

Histologically, JA shows vascular and stromal components (Figure 1C).[37,39] The vessels range from narrow-caliber and slit-like to irregularly outlined, ectatic channels in 'stag horn' or 'pericytomatous' arrangements (Figure 1D). They are lined by a single endothelial layer and variously surrounded by poorly-developed, 'myoid' cells variably resembling smooth muscle fibres (Figures 1A-H). Elastic laminae or definite muscular coats are not seen, and a structural 'leaky' appearance (Figure 1I) accounts for the finding

of thrombi therein and clinical bleeding even after minor manipulation. The stroma is often moderately cellular and collagenous (Figure 1C). The cells are spindled, plump, stellate or angular often with dispersed chromatin and small nucleoli (Figures 1J and 1K); and varying in distribution between different tumors and areas of the same tumor. Multinuclear forms may be detected. The interstitial matrix ranges from fibrillary to hyalinised; myxoid areas may be present (Figure 1L). Overall, cytology is bland, and significant atypia or mitotic activity is not seen (Figure 1J). Necrosis, if present, is attributable to pre-operative embolization. Embolic material may be seen in vascular lumina (Figure 1A). Small nerves and seromucinous glands can be trapped within the growing tumor. The overlying epithelium is often respiratory epithelium, with areas of squamous metaplasia or ulceration. The latter results in reactive changes, like mixed inflammatory-cell infiltration and formation of vascular granulation tissue.

Electron microscopy shows a focal lack of pericytes, discontinuous basement membranes and irregular muscular coat, which reinforces the notion of 'leaky' vessels and suggests that JA is a vascular malformation rather than a neoplasm.[40] Stromal cells are often fibroblasts, though myofibroblasts are also present. The latter are demonstrable on immunohistochemistry for smooth muscle actin.[41,42] The vascular endothelium expresses CD34, CD31, von Willebrand factor, and endoglin.[43,44] The stromal cells do not stain for CD34. It has been suggested that microvessel density in JA assessed by means of immunohistochemistry for endoglin, correlates with recurrence.[44] Confirmation is desirable but clinical value, if any, remains to be seen. The expressioin of androgen receptors, VEGFR2 and tenascin in JA, has already been mentioned (see 'Etiopathogenesis').

The histological diagnosis of JA does not usually pose a problem for the experienced head and neck pathologist, particularly when excised specimens are examined. Inflammatory sinonasal polyps, pyogenic granuloma,[45,46] glomangiopericytoma and solitary fibrous tumor should be considered in the differential diagnosis but in our opinion, the diagnostic difficulties have been over-emphasised, even in cases of hyalinised inflammatory sinonasal polyps.[47,48,49,50] Distinction from the rare sinonasal, vascular leiomyoma may be more challenging, though clinical setting, gender, age and site should be of help. Diagnosis on superficial incisional biopsies may pose difficulties, particularly in the presence of superficial ulceration, but such biopsies must be avoided when JA is suspected (see 'Clinical Features and Diagnosis' below).

## Clinical Features and Diagnosis

Recurrent, unprovoked, painless, profuse, unilateral epistaxis (60%) and unilateral nasal obstruction (80%) with rhinorrhea, is the usual clinical presentation. Nasal examination is recommended for every young male with these symptoms to exclude JA. Less common symptoms include headaches (25%) secondary to the obstruction of the paranasal sinuses; and conductive hearing loss secondary to serous otitis media from compression of the Eustachian tube. Progressive expansion leads to sinonasal symptoms and facial swelling (10-40%).[51] Visual and neurological deficits may appear when the orbit, skull base or endocranium are affected.[52] Symptoms are generally present for 6 months to a year before diagnosis and theaverage delay between symptom onset and surgery is around 12-14 months.[54]

Modern imaging techniques enable earlier recognition; patients present at an earlier stages, and compressive and neurological symptoms are less frequent. Still, up to 40% of cases are diagnosed at an advanced-stage (see 'Staging' below) with up to 17% showing intracranial extension.[53] Delay in presentation is attributable to the association of indolent symptoms of JA with more common diseases such as rhinitis, sinusitis and antrochoanal polyps.

Pre-operative diagnosis is based on clinical and imaging features; incisional biopsy may lead to massive bleeding and is not recommended.[55] Rhinoscopy usually reveals a reddish lobulated mass located at the back of the nasal cavity and the cavum, often lobulated and firm (Figure 2).

## Imaging

Routine pre-operative imaging confirms the diagnosis, defines tumor extension and staging, and assists in treatment planning. In addition, it is used post-operatively to assess tumor persistence or recurrence.[56]

Computed tomography (CT), magnetic resonance imaging (MRI) and angiography assist in defining location, relationship to important neurovascular structures and assessment of blood supply to select the least traumatic approach for hemostatic control (Figures 3 and 4). CT is superior in outlining bony landmarks, and demonstrating bone erosion and invasion of the sphenoid, a significant predictor of recurrence. CT is more accurate for intraoperative image-based navigation. It is useful to get a CT-

angiogram for navigation since this will provide superior visualization of the internal carotid artery. MRI is more useful for assessing soft tissues, invasion of bone marrow and intracranial extension; it is also the preferred modality for follow-up due to potential for differentiating postoperative reparative processes from recurrence.

CT often shows a soft tissue mass with bone remodelling or destruction, which originates near the sphenopalatine foramen and extends into adjacent nasopharynx and pterygopalatine fossa. The Holman-Miller sign, which is the forward bowing of the posterior wall of the maxilla, is found in 80% of JAs but can also occur with other benign or malignant tumors. The pathognomonic sign of JA is erosion of the upper medial pterygoid plate which is found in 98% of JAs.[56] Contrast injection enables diffuse, avid enhancement.

On MRI, JA shows low and medium to high signal intensities on pre-contrast T1- and T2-weighted sequences, respectively. Intra-lesional signal voids and intense enhancement following contrast injection reflect flow in enlarged vessels in keeping with a diagnosis of JA. Diffusion coefficient (ADC) values are high and degenerative/cystic components may be seen. The use of MRI and fat-suppression sequences assists in detecting bone marrow edema, inversely related to surgical success. MRI is also useful in detecting intracranial, dural and intracavernous extension and shows the relations of the tumor to the internal carotid arteries and pituitary. Detection of dural involvement may be challenging, but should be suspected if enhancement is seen on post-contrast T1-weighted images. Also, contrast-enhanced fluid-attenuated inversion recovery (FLAIR) sequences are reported to be sensitive in detecting leptomeningeal spread.[57] MRI may finally assist in distinguishing fluid collections and inflammatory mucosal thickening of the paranasal sinuses from intra-sinus tumor extension.

Kukwa *et al.*[58] reported expression of somatostatin receptors (SSTRs) in JA and suggested that SST analogues with an affinity for SSTR2 may be used in pre- and postoperative assessment via (99m)TC-octreotide scintigraphy.

**Angiography and embolization**

Bilateral carotid angiography is required to assess the vascular supply of JA and allow embolization of feeding vessels prior to surgery.[59] Occlusion of feeders reduces intra-operative bleeding, a major cause of morbidity, and may shrink the tumor. This

enables better visualization of the surgical field, particularly in an endoscopic setting, facilitates dissection [60] and increase chances of complete resection, a factor influencing recurrence.[61] Most authors endorse embolization, though a few question its value on the basis of possible distortion of tumor boundaries, leading to incomplete resection.[62,63]

Reservations apart, pre-operative embolization is now regarded as an important component of management. It results in a 70% reduction of intra-operative blood loss, thus alleviating morbidity and need for blood transfusions.[60,64,65,66] Blood loss is significant with JA (mean, 1,449 ml), and reinforces careful selection and preoperative workup of patients.[53] Wasl *et al.*[67] reported that homologous blood transfusion can be avoided with pre-operative cell saver and autologous blood banking. Others support the latter, but caution against the former because of possible autoinoculation.[68]

The vascular supply of JA largely derives from the external carotid artery and its internal maxillary and ascending pharyngeal.[69] Occasionally, JA is supplied by both external carotid arteries.[59.70] Bilateral embolization of the internal maxillary arteries may be performed in such cases, to prevent collateral blood supply. It is also noted that embolizing deep temporal branches of the external carotid artery that supply the temporalis muscle may compromise reconstruction. As tumors enlarge, additional blood supply is derived from branches of the internal carotid artery, predominantly the vidian artery. Although feeders from the internal carotid artery may be embolized[51], the risk of serious complications such as stroke, visual loss, facial paralysis, or carotid dissection is increased and is not routinely performed. The ophthalmic artery is not embolized due to the risk of visual loss.

Embolization should be performed 24-48 hours before surgery (Figure 4).[71] It is usually effected via super-selective catheterization of supplying arterial branches. Embolic substances include poly vinyl alcohol (PVA), coils, micro-particles or liquid glue. The ethylene–vinyl alcohol co-polymer (Onyx®), shows technical advantages enabling deep penetration into the tumor, with more extensive tumor necrosis, embolization of large portions of the tumor via fewer catheterizations and safe withdrawal of the catheter despite possible substantial reflux.[72] Successful arterial embolization with any of these embolic agents may be limited by vessel tortuosity, vasospasm, or prior sacrifice of the internal maxillary artery or external carotid artery. If the tumor feeding

vessels are not accessible or cannot be safely embolized, direct intra-tumoral embolization under, radiographic control may be undertaken.[73,74,75]

Embolization is not without complications, the most serious being loss of vision secondary to occlusion of the central retinal artery.[76,77] The majority of complications are transient and amenable to clinical management.[78] Transient hair loss in the occipital region from radiation exposure can be seen following embolization.[79]

If preoperative tumor embolization cannot be performed, attempts should be made to reduce intraoperative bleeding via isolation and ligation of feeding vessels (mainly internal maxillary artery) as part of the surgical approach before proper tumor dissection begins. Hypotensive general anesthesia, the use of radiofrequency coblation and other hemostatic devices, and meticulous dissection as well as diathermy of the sphenopalatine artery would be helpful.[80,81,82,83] Other surgical strategies for minimizing intraoperative blood loss include dividing the tumor into vascular segments, cauterization of the vidian artery contribution, and staging of surgery.[70]

Advanced tumors with encasement of the internal carotid artery are at increased risk of vascular injury during surgery. Assessment of collateral blood flow and balloon occlusion testing of the artery can help identify patients who can tolerate sacrifice of the artery if an injury occurs. Such information is helpful in determining the extent of surgery. In such cases, angiographic sacrifice of the artery can be performed preemptively or only if an injury occurs. Most young patients will tolerate sacrifice of one carotid artery. Preoperative stenting of the vessel has also been used to decrease the risk of injury when there is tumor encasement by paragangliomas and could be applied to JA.[84]

**Staging systems**

Various systems have been proposed; most are based on tumor expansion and intracranial extension (Table 1).[11,85] Although none is universally endorsed[86], that suggested by Radkowski *et al.*[87](modification of Sessions *et al.*[88]) enjoys popularity. Snyderman *et al*. introduced an interesting alternative that also emphasizes the significance of residual vascularity of the tumor following embolization.[89]

**Management**

Surgical resection is regarded as the treatment of choice for all stages of uncomplicated primary and recurrent JA.[53] Radiotherapy (RT) should be reserved for advanced tumors with a high risk of significant morbidity or residual/recurrent disease in neurocritical areas.[64] Hormone therapy and chemotherapy have been explored with little or no success. Spontaneous regression of untreated JA has been reported,[92,93,94,95,96] and observation of residual tumors that are difficult to resect is warranted until continued growth is confirmed.[97]

**Surgery**

Surgery aims to achieve tumor exposure and complete resection with the least possible morbidity. The extent of the initial resection influences recurrence rates. Multiple approaches based on tumor location and stage have been suggested.[98] All have advantages and limitations, and selection often depends on surgical skill and experience. It is likely that experienced surgeons would use more conservative approaches for the resection of large JA. A detailed description of the different potential surgical approaches is beyond the scope of this review but it is noted that preferences are shifting from open surgery to endoscopic approaches.[99,100]

Conventional open surgery has a role in the management of JAs with significant intracranial and infratemporal or temporal fossa extension, or encasement of the optic nerve or internal carotid artery entrapment. It is usually reserved for patients with Radkowski IIIB tumors.[99,100,101,102] Anterior open approaches include transfacial and transpalatal approaches. External facial or palatal incisions can be avoided in most cases with the use of midfacial degloving approaches. Augmentation of the midfacial degloving approach with a craniofacial-subcranial approach or preauricular-subtemporal-infratemporal approach may be necessary for large tumors with extension to the anterior cranial fossa or middle cranial fossa, respectively. The facial translocation approach provides maximal access for midline tumors with lateral extension but has significant morbidity; equivalent results are obtained with a midfacial degloving approach combined with a lateral infratemporal approach.[103] A lateral transorbital approach with lateral orbitotomy is an alternative for limited lateral skull base involvement. The midfacial degloving approach provides simultaneous access through the nasal cavity and maxillary sinus on one or both sides. A disadvantage of this approach is the relatively poor access to the skull base behind the tumor. Although most intracranial lesions can be safely

dissected from the dural surface, the complete extirpation of these tumors may be difficult if bleeding is severe. In these cases the standard facial translocation approach is applicable.[104] Anterior and standard facial translocations, and the preauricular-subtemporal-infratemporal and craniofacial-subcranial approaches are further examined. The versatile facial translocation is the method of choice for large tumors extending to the infratemporal fossa or paranasal sinuses. It allows osteotomies that enable exposure of the sinonasal area and infratemporal fossa; and approaching the tumor from lateral and antero-posterior perspectives.[104] Poor access to the skull base behind of the tumor is a disadvantage. Although most intracranial lesions can be safely removed because the pushing tumor border is easily dissected from the dura, complete extirpation may be difficult if bleeding is severe. In these cases the standard facial translocation approach is applicable.[104] The preauricular-subtemporal-infratemporal approach provides lateral access for tumors that extend into the masticator space, infratemporal fossa, middle cranial fossa, parasellar region, or involve the greater wing of the sphenoid bone.[105] An orbitozygomatic osteotomy and elevation of the temporalis muscle provide exposes the subtemporal skull base and lateral orbit (greater wing of sphenoid). Following excision of tumor, the temporalis muscle can be transposed to cover an exposed carotid artery or middle fossa dura. The craniofacial-subcranial approach is appropriate for intracranially extending JAs affecting the floor of anterior fossa, sellar region or optic chiasm.[106] It is noted that the open procedures do not substantially affect the facial and cranial growth of the young patients.[107]

Transnasal endoscopic approaches are now increasingly used avoiding facial incisions and achieving low long-term morbidity and low recurrence rates. They are valuable in treating early and carefully selected, advanced JAs.[70,108] When compared with open resection, they result in significantly less intra-operative blood loss.[109,110] They do not preclude surgical cure[64,65,111,112,113,114] and may allow access to deep structures not fully visualized during open surgery[115,116] En bloc resection is not necessary to achieve surgical cure and by contrast, piecemeal resection can facilitate the approach to difficult anatomic areas. Initially, endoscopic approaches were used for the management of small (Radkowski stages I, II) tumors.[117,118,119,120,121,122] The increase of endoscopic surgical skills together with advances in surgical instrumentation, imaging and surgical navigation systems enabled, however, the indication of these approaches even for Radkowski stages IIIA, B or UPMC stages IV and V [64,65,113,114,116,123,124,125,126].

Despite endoscopic advances, challenges remain and there is no consensus on the management of advanced JA. Although craniofacial approaches have been the standard treatment, a recent review of surgical outcomes for JA with intracranial involvement, indicated that endoscopic resection is feasible in expert hands.[53] Lateral extension of JA into the infratemporal fossa may be a relative contra-indication for endoscopic surgery[98] but the absence of adhesions to surrounding tissues may enable retraction of the tumor into the nasal cavity.[51,64] Even limited intracranial penetration/dural invasion may be endoscopically approachable.[53] The debate continues and employing endoscopy combined with transnasal, transfacial and transcranial approaches may be a reasonable compromise.[127]

Staging of surgery due to excessive intraoperative blood loss may be necessary for advanced tumors with significant blood supply from the internal carotid artery (UPMC stage IV and V), especially in young patients with a small blood volume. In such cases, it is preferable to excise the extracranial component of the tumor at the first stage and address the intracranial component or internal carotid artery involvement in subsequent stages.

**Radiotherapy**

In general, surgical excision is the preferred treatment for all JA, regardless of stage, and RT should be avoided due to the unknown long-term effects in a young patient population. RT may be considered for advanced, incompletely resectable JA and cases with a high morbidity of resection. Examples include tumors with significant intracranial extension and encasement of the internal carotid artery. The dose fractionation schedule is approximately 36 Gy at 1.8 Gy per once-daily fraction. Lower doses correlate with higher recurrence rates.[128] Intensity modulated RT (IMRT) may employed to create a conformal dose distribution to minimize the dose to adjacent tissues. Alternatively, proton RT may be used to create an even tighter dose distribution to further reduce the risk of late effects in these young patients. Local control rates after definitive RT range from 85% to 91% with low riskof severe late complications.[83,129,130,131]

Stereotactic radiosurgery (SRS) is not appropriate as a sole modality to treat JAs because treating a large incompletely resected mass with a single high dose of irradiation would likely result in a higher risk of late complications.[130,131,132] However, it could be considered for minimal, well-defined residual tumor following incomplete resection. The

disadvantages of SRS is a risk of marginal miss because of the necessarily tight dose distribution and a higher risk of late complications compared with conventionally fractionated RT. Stereotactic hypofractionated RT using 5 or fewer fractions has the same disadvantages compared with SRS.

In patients with advanced stage JA that are considered unresectable due to involvement of critical structures, an alternative to primary RT, is excision of the extracranial portion of the tumor, leaving a small residuum in critical areas. This may minimize the radiation field and potential morbidity of RT. A potential disadvantage of primary RT for large "inoperable" tumors is the difficulty of subsequent surgery if there is progressive tumor growth. However, the likelihood of progression after RT is low and the risk of increased complications after 36 Gy at 2 Gy per fraction is probably modest.[125] RT after unanticipated incomplete resection or recurrent JA after prior surgery is a reasonable option.[129,133,134,135] As is the case with other benign tumors such as paragangliomas and meningiomas, the tumor either slowly regresses incompletely or remains stable after successful RT. The main risk following RT is a radiation induced malignancy such as a sarcoma. The risk is probably about 1 in 500 with a latency period of 7 to 10 years or longer.[8,129,132,136] Other potential complications of RT include growth retardation, panhypopituitarism, temporal lobe necrosis, cataracts, and radiation keratopathy.[131] However, the risk of late complications is very low with the dose-fractionation schedules employed. In contrast, if a patient is at high risk for severe complication associated with surgery, it occurs immediately during the procedure or perioperatively.[131]

**Chemotherapy and hormonal therapy**

Chemotherapy or hormonotherapy are not routinely recommended.[137]

Chemotherapy has been suggested for recurrences and selected cases with aggressive growth.[138,139]

Hormonal therapy holds attraction because of the possible involvement of androgen receptors in the etiopathogenesis of JA (see above). In post-puberal patients, flutamide, an androgen receptor antagonist, has been used preoperatively to achieve partial regression of the tumor from adjacent vital structures and allow a more conservative surgical approach.[140] However, others failed to confirm these results.[141]

Expression of somatostatin (SST) receptors in JA suggests that their sub-typing may allow the use of specific SST analogues to treat residual, recurrent and inoperable tumors.[58]

Expression of other receptors[55,142] indicates similarly variable potential. Tamoxifen, an estrogen receptor antagonist, inhibits proliferation of cultured JA stromal cells[142]; however, the side effects of Tamoxifen preclude from its clinical application in JA. Bevacizumab, a monoclonal antibody that inhibits VEGF-A, may also be of value, but clinical data are lacking.[143] An untested, though intriguing option would be glucocorticoids as they seem able to downregulate VEGF, and reduce microvascular density and tumor volume; and their receptors are upregulated in JA.[144]

**Results and follow-up**

Most, if not all, recurrences are due to incomplete resection of the primary tumor.[145] The rate of residual disease varies from 13% to 50%.[64] Although it may be difficult to distinguish between residual tumor and new tumor growth[144] the likelihood of a second primary JA is remote. Residual disease may not grow or even undergo involution[60,146] On post-operative CT and/or MRI residual/recurrent disease appears as areas of contrast enhancement, but healing processes may show similar appearances and distinction is a major radiological challenge.[11,126,147]

Chagnaud *et al*.[147] formulated guidelines for follow-up. If the patient is asymptomatic, rhinoscopy is negative and imaging shows no residual mass 3 to 4 months after surgery, clinical review alone is recommended. If the clinical signs/symptoms suggest recurrent/residual tumor, a mass is visualized on rhinoscopy, and CT or MRI confirm tumor and indicate its extent, a second operation is performed. Finally, if the patient is asymptomatic, rhinoscopy is negative and enhancement outside the nasopharyngeal cavity is seen on the first radiological examination 3 or 4 months post-operatively, further imaging is undertaken 3 to 6 months later. Then, if the enhancement has decreased in size and/or intensity, a third imaging study follows after 6 months; in case of resolution clinical review is adequate; if the enhancement remains stable, periodical imaging twice a year is recommended; if the enhancement has increased in size, second surgery or RT are indicated. Langdon *et al.*[126] do not support further surgery for intracranial remnants, unless there is a measurable tumor growth or new symptoms.

Recurrence is usually observed within 6 to 36 months after primary therapy [53,110,126,148] which supports a minimum follow-up of 3 years.[11] Most investigators use a combination of rhinoscopy and MRI for at least 5 years post-operatively, but periods of follow-up vary between institutions.[64,149] Nevertheless early detection relates to better outcomes and some authors advocate imaging within the first month post-operatively (even immediately after packing is removed) to detect residual disease.[150] This may improve its distinction from later healing processes.[111] Early detected residual disease usually requires minimally invasive surgery and the need for repeating embolization or RT can be avoided.

Recurrences are observed in approximately 18–45% of the patients and depending on size, extent of tumor and surgical approach; most patients (86%) would be expected to be free of disease during long-term follow-up.[10,17,53,118] The likelihood of recurrence is particularly high in patients with intracranial extension.[145] Endoscopic recurrence rates appear lower than those of open surgery, although this may reflect the bias of early-stage tumors being more likely to be treated endoscopically. However there is no difference in recurrence rate when controlling for tumor extent.[109,114] Recurrence rates for patients with stage I and II lesions is between 0 and 7% according to the majority of publications.[62,65,113,114,124] Encouraged by these results, technological progress and increasing endoscopic skills, some authors approached advanced JA endoscopically with similar outcomes.[64,126]

Recurrence rates appear related to involvement of specific sites. The more sites involved, the higher the probability of tumor persistence.[126] Involvement of the skull base, extension into the pterygoid fossa and basisphenoid, erosion of the clivus, intracranial extension medial to the cavernous sinus, invasion of the sphenoid diploe through a widened pterygoid canal, feeders from the internal carotid artery, young age and incomplete surgery are factors associated with increased risk of recurrence.[40,108,110,14,151] Howard *et al*.[152] emphasized the significance of residual tumor in the basisphenoid and base of pterygoids and that meticulous removal led to cure in the majority of cases. Lloyd *et al*.[56] reported that 60% of JA expand posteriorly along the pterygoid canal with invasion of the cancellous bone of the sphenoid, and noted that 93% of recurrences occurred in patients with invasion of sphenoid diploe. Meticulous subperiosteal dissection and drilling of these areas assist in complete removal and avoiding recurrences.[64,111,148,149] Thakar *et al*[153], reported that involvement of the vidian canal is almost universal in JA

and may not be detected on CT; this site may still harbor microscopic residual tumor after an apparently complete resection and should receive particular surgical attention to reduce for the chances of recurrence.

Second surgery, whether open or endoscopic, appears the best option if chances for extirpating residual/recurrence tumor are reasonably high.[60] Attempts at removing remnants from critical areas (cavernous sinus, internal carotid artery) do not seem justified because of significant morbidity.[65,148,151] While residual or recurrent tumor may also be treated with RT or SRS with acceptable morbidity, a 'wait and see' policy may be adopted.[53,64] Prospective investigations are needed to determine the optimal strategy

## Conclusion

JA is a rare and complex disease that may cause significant morbidity in young patients. Improved surgical and RT techniques, and advances in imaging and pre-operative embolization have influenced management. Treatment planning depends on patient age, low likelihood of spontaneous involution, expected surgical morbidity, RT side effects and risk of recurrence. The benign yet aggressive nature of the tumor poses a dilemma as price of cure must not be worse than the disease itself. Surgery is the main therapeutic option. Patients should be treated at centers with expertise in skull-base surgery to achieve best results in regards to complete resection and low morbidity. Endoscopic excision is preferable for early stage tumors due to decreased morbidity. The selection of open or endoscopic approaches for more advanced tumors is very dependent on the experience of the surgical team. In these cases the best results may be achieved with a combination of open and endoscopic approaches. RT or SRS after incomplete resection is valuable for long-term control of extensive JA involving vital structures. Although definitive RT is a treatment option for extensive, incompletely resected JA, resectability is subjective based on the abilities of the surgical team. Hormone therapy and chemotherapy have been nearly abandoned because of ineffectiveness and significant toxicity.

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## FIGURE LEGEND

**FIGURE 1**. Histology of a typical JA. The photomicrographs are from sections of routinely processed tissue, which were stained with hematoxylin and eosin. Zooming on the electronic format of the photomicrographs would allow appreciation of detail, less perceptible on prints. **(A)** Non-encapsulated front of tumor (asterisk). Pre-existing glands and an embolized vessel are seen at the lower left and right of the picture, respectively.

**(B)** Evidence of osteo-destruction. The arrow indicates fragment of pre-existing bone incorporated within the growing tumor. **(C)** Core of tumor. Dilated lumina of 'empty' thin-walled vessels and collagenous stroma (asterisk) are seen. **(D)** 'Stag horn' vessel. **(E)** Poorly-developed 'myoid' coat of a vessel. Although variably demarcated, its increased eosinophilia allows distinction from adjacent stroma. Ocassional cells resemble attenuated smooth muscle fibres (arrow). **(F)** The increased cellularity of a tangentially sectioned coat (asterisk) further distinguishes it from adjacent stroma. **(G)** Moderately-developed 'myoid' coats. In comparison with Fig. 1E, cells resembling attenuated smooth muscle fibres show more abundant cytoplasm. **(H)** Moderately-developed 'myoid' coat demarcated from adjacent stroma. Compare with Fig. 1E. **(I)** Vessel with incomplete myoid' coat shows possible 'gaps' in the continuity of the endothelial lining and leakage of plasma (arrows). **(J)** Nuclear features of spindled stromal cells. Note absence of mitoses. A possible multinuclear form is arrowed. **(K)** Stellate and angular stromal cells (arrows). **(L)** Myxoid matrix (asterisk) around vessels.

**FIGURE 2.** Endoscopic nasal view of the right nasal fossa during endoscopic surgery in a patient with JA. The tumor appears as lobulated, pedunculated mass with smooth and focally hemorrhagic surface, located in the posterior nasal cavity. MT: middle turbinate; IT: inferior turbinate; S: septum; T: tumor

**FIGURE 3. (A)** Coronal view of right external carotid angiogram prior to embolization. Vascularization of JA effected by distal branches of the internal maxillary artery. **(B)** Coronal view of right external carotid angiogram, after particulate and coil embolization of feeders. Devascularization of the tumor is almost complete.

**FIGURE 4.** Coronal CT **(A)**, axial CT **(B)**, T1-weighted postcontrast **(C)** and T2-weighted **(D)** MRI images show a large mass centered in the posterior nasal cavity with widening of and extension into the pterygopalatine fossa. There is also extension to the pterygoid plates/process posteriorly. Post-resection coronal **(E)** and axial images **(F)** show complete resection of the tumor following an endoscopic approach.