

CLINICAL REVIEW

Nasal juvenile angiofibroma: current perspectives with emphasis on management

Fernando López, MD, PhD, FEBORL-HNS,^{1,2} **Asterios Triantafyllou**, PhD, FRCPATH,^{3,4} **Carl H. Snyderman**, MD, MBA,⁵ **Jennifer L. Hunt**, MD,⁶ **Carlos Suárez**, MD, PhD,² **Valerie J. Lund**, MD, CBE, FRCS, FRCSEd,⁷ **Primož Strojjan**, MD, PhD,⁸ **Nabil F. Saba**, MD, FACP,⁹ **Iain J. Nixon** MD, MBChB, FRCS (ORL-HNS), PhD,¹⁰ **Kenneth O. Devaney**, MD, JD, FCAP,¹¹ **Isam Alobid**, MD, PhD,¹² **Manuel Bernal-Sprekelsen**, MD, PhD,¹² **Ehab Y. Hanna**, MD,¹³ **Alessandra Rinaldo**, MD, FRCSEd *ad hominem*, FRCS (Eng, Ir) *ad eundem*, FRCSEd Glasg,¹⁴ **Alfio Ferlito**, MD, DLO, DPath, FRCSEd *ad hominem*, FRCS (Eng, Glasg, Ir) *ad eundem*, FDSRCS *ad eundem*, FHKCORL, FRCPATH, FASCP, IFCAP.¹⁵

1. Department of Otolaryngology, Hospital Universitario Central de Asturias, Oviedo, Spain
2. Instituto Universitario de Oncología del Principado de Asturias, University of Oviedo, and Fundación para la Investigación Biosanitaria de Asturias, Oviedo, Spain
3. Pathology Department, Liverpool Clinical Laboratories, Liverpool, UK
4. School of Dentistry, University of Liverpool, Liverpool, UJ
5. Department of Otolaryngology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
6. Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, AR, USA
7. Professorial Unit, Ear Institute, University College London, London, UK
8. Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia
9. Department of Hematology and Medical Oncology, The Winship Cancer Institute of Emory University, Atlanta, GA, USA

10. Departments of Surgery and Otolaryngology, Head and Neck Surgery, Edinburgh University, UK

11. Department of Pathology, Allegiance Health, Jackson, MI, USA

12. Department of Otolaryngology, Hospital Clínic, University of Barcelona Medical School, Barcelona, Spain

13. Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

14. University of Udine School of Medicine, Udine, Italy

15. Coordinator of the International Head and Neck Scientific Group

This article was written by members and invitees of the International Head and Neck Scientific Group (www.IHNSG.com).

Address for correspondence:

Fernando López MD, PhD, FEBORL-HNS
Department of Otolaryngology
Hospital Universitario Central de Asturias
Avenida de Roma s/n
33011 - Oviedo (Asturias) - Spain
email: flopez_1981@yahoo.es

Running title: Management of juvenile angiofibroma

Keywords: embolization, endoscopy, juvenile nasopharyngeal angiofibroma, nasal tumors, surgery

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 males¹, 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. Chelius² 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 (Friebert)⁴, juvenile nasopharyngeal hemangiofibroma⁵, juvenile fibroangioma⁶ 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 testosterone levels 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 JA³³,

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 spindle, 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 expression 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 the average 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 dissection⁶⁰ 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 embolized⁵¹, 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 endorsed⁸⁶, 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 surgery⁹⁸ 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 be 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 risk of 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 cells¹⁴²; 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 growth¹⁴⁴ 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.

References

1. Nonogaki S, Campos HG, Butugan O, et al. Markers of vascular differentiation, proliferation and tissue remodeling in juvenile nasopharyngeal angiofibromas. *Exp Ther Med* 2010;1:921-926
2. Chelius MS. *A systemic of surgery (Vol 2)*. London:Renshaw; 1847; p 726.
3. Chaveau UC. Histoire des Maladies du Pharynx. *Arch Int Laryng* 1906;21:889
4. Friedberg SA. Vascular fibromas of the nasopharynx. *Arch Otolaryngol* 1940;31:313-326
5. Seid AB, Vorster WF. Juvenile nasopharyngeal haemangiofibroma. *S Afr Med J* 1972;46:517-518
6. Capps FC. Juvenile fibroangioma of the postnasal space in service personnel. *Proc R Soc Med* 1971;64:47-54
7. Heck WE, Mcnaught RC. Case report the transpalatal approach for juvenile fibroma. *Calif Med*. 1951;75:430-431
8. Makek MS, Andrews JC, Fisch U. Malignant transformation of a nasopharyngeal angiofibroma. *Laryngoscope* 1989;99:1088-1092
9. Allensworth JJ, Troob SH, Lanciault C, Andersen PE. High-grade malignant transformation of a radiation-naïve nasopharyngeal angiofibroma. *Head Neck* 2016 Apr;38 Suppl 1:E2425-7. doi: 10.1002/hed.24378. Epub 2016 Feb 3.
10. Gullane PJ, Davidson J, O'Dwyer T, Forte V. Juvenile angiofibroma: a review of the literature and a case series report. *Laryngoscope* 1992;102:928-933
11. Lund VJ, Stammberger H, Fokkens WJ, et al. European position paper on the anatomical terminology of the internal nose and paranasal sinuses. *Rhinol Suppl* 2014;24:1-34
12. Parikh V, Hennemeyer C. Microspheres embolization of juvenile nasopharyngeal angiofibroma in an adult. *Int J Surg Case Rep* 2014;5:1203-1206
13. Midilli R, Karci B, Akyildiz S. Juvenile nasopharyngeal angiofibroma: analysis of 42 cases and important aspects of endoscopic approach. *Int J Pediatr Otorhinolaryngol* 2009;73:401-408

14. Madhavan Nirmal R, Veeravarmal V, Santha Devy A, Ramachandran CR. Unusual presentation of nasopharyngeal (juvenile) angiofibroma in a 45 year old female. *Indian J Dent Res* 2004;15:145-148
15. Llorente JL, López F, Suárez V, Costales M, Suárez C. Evolution in the treatment of juvenile nasopharyngeal angiofibroma. *Acta Otorrinolaringol Esp* 2011;62:279-286
16. Patrocínio JA, Patrocínio LG, Borba BH, Bonatti Bde S, Guimaraes AH. Nasopharyngeal angiofibroma in an elderly woman. *Am J Otolaryngol* 2005;26:198–200
17. Danesi G, Panciera DT, Harvey RJ, Agostinis C. Juvenile nasopharyngeal angiofibroma: evaluation and surgical management of advanced disease. *Otolaryngol Head Neck Surg* 2008;138:581–586
18. Coutinho-Camilo CM, Brentani MM, Nagai MA. Genetic alterations in juvenile nasopharyngeal angiofibromas. *Head Neck* 2008;30:390-400
19. Liu Z, Wang J, Wang H, et al. Hormonal receptors and vascular endothelial growth factor in juvenile nasopharyngeal angiofibroma: immunohistochemical and tissue microarray analysis. *Acta Otolaryngol* 2015;135:51-57
20. Lee DA, Rao RB, Meyer JS, Prioleau PG, Bauer WC. Hormonal receptor determination in juvenile nasopharyngeal angiofibromas. *Cancer* 1980;46:547–51
21. Hwang HC, Mills SE, Patterson K, Gown AM. Expression of androgen receptors in nasopharyngeal angiofibroma: an immunohistochemical study of 24 cases. *Mod Pathol* 1998;11:1122-1126
22. Montag AG, Tretiakova M, Richardson M. Steroid hormone receptor expression in nasopharyngeal angiofibromas. Consistent expression of estrogen receptor beta. *Am J Clin Pathol* 2006;125:832-837
23. Riggs S, Orlandi RR. Juvenile nasopharyngeal angiofibroma recurrence associated with exogenous testosterone therapy. *Head Neck* 2010;32:812-815
24. Gatalica Z. Immunohistochemical analysis of steroid hormone receptors in nasopharyngeal angiofibromas. *Cancer Lett* 1998;127:89-93

25. Carlos R, Thompson LDR, Netto AC, et al. Epstein–Barr virus and human herpes virus-8 are not associated with juvenile nasopharyngeal angiofibroma. *Head Neck Pathol* 2008;2:145-149
26. Silveira SM, Custódio Domingues MA, Butugan O, Brentani MM, Rogatto SR. Tumor microenvironmental genomic alterations in juvenile nasopharyngeal angiofibroma. *Head Neck* 2012;34:485-492
27. Schick B, Veldung B, Wemmert S, et al. p53 and Her-2/neu in juvenile angiofibromas. *Oncol Rep* 2005;13:453-457
28. Guertl B, Beham A, Zechner R, Stammberger H, Hoefler G. Nasopharyngeal angiofibroma: an APC-gene-associated tumor? *Hum Pathol* 2000;31:1411-1413
29. Ponti G, Losi L, Pellacani G, et al. Wnt pathway, angiogenic and hormonal markers in sporadic and familial adenomatous polyposis-associated juvenile nasopharyngeal angiofibromas (JNA). *Appl Immunohistochem Mol Morphol* 2008;16:173-178
30. Valanzano R, Curia MC, Aceto G, et al. Genetic evidence that juvenile nasopharyngeal angiofibroma is an integral FAP tumour. *Gut* 2005;54:1046-107
31. Schick B, Wemmert S, Bechtel U, et al. Comprehensive genomic analysis identifies MDM2 and AURKA as novel amplified genes in juvenile angiofibromas. *Head Neck* 2007;29:479-487
32. Renkonen S, Heikkilä P, Haglund C, Mäkitie AA, Hagström J. Tenascin-C, GLUT-1, and syndecan-2 expression in juvenile nasopharyngeal angiofibroma: correlations to vessel density and tumor stage. *Head Neck* 2013;35:1036-1042
33. Mishra A, Sachadeva M, Jain A, Shukla NM, Pandey A. Human papilloma virus in juvenile nasopharyngeal angiofibroma: possible recent trend. *Am J Otolaryngol* 2016;37:317-322
34. Schick B, Plinkert PK, Prescher A. Aetiology of angiofibromas: reflection on their specific vascular component. *Laryngorhinootologie* 2002;81:280-284
35. Chandler JR, Goulding R, Moskowitz L, Quencer RM. Nasopharyngeal angiofibromas: staging and management. *Ann Otol Rhinol Laryngol* 1984;93:322-329

36. Bakshi SS, Bhattacharjee S. Juvenile nasopharyngeal angiofibroma. *J Pediatr Hematol Oncol* 2016 May 9. [Epub ahead of print]
37. Sternberg SS. Pathology of juvenile nasopharyngeal angiofibroma; a lesion of adolescent males. *Cancer* 1954;7:15-28
38. Martin H, Ehrlich HE, Abels JC. Juvenile nasopharyngeal angiofibroma. *Ann Surg* 1948;127:513-536
39. Johncilla M, Jo VY. Soft tissue tumors of the sinonasal tract. *Semin Diagn Pathol* 2016;33:81-90
40. Beham A, Beham-Schmid C, Regauer S, Aubock L, Stammberger H. Nasopharyngeal angiofibroma: true neoplasm or vascular malformation? *Adv Anat Pathol* 2000;7:36-46
41. Beham A, Kainz J, Stammberger H, Auböck L, Beham-Schmid C. Immunohistochemical and electron microscopical characterization of stromal cells in nasopharyngeal angiofibromas. *Eur Arch Otorhinolaryngol* 1997;254:196-199
42. Beham A, Fletcher CD, Kainz J, Schmid C, Humer U. Nasopharyngeal angiofibroma: an immunohistochemical study of 32 cases. *Virchows Arch A Pathol Anat Histopathol* 1993;423:281-285
43. Beham A, Regauer S, Beham-Schmid C, Kainz J, Stammberger H. Expression of CD34-antigen in nasopharyngeal angiofibromas. *Int J Pediatr Otorhinolaryngol* 1998;44:245-250
44. Wang JJ, Sun XC, Hu L, et al. Endoglin (CD105) expression on microvessel endothelial cells in juvenile nasopharyngeal angiofibroma: tissue microarray analysis and association with prognostic significance. *Head Neck* 2013;35:1719-1725
45. Smith SC, Patel RM, Lucas DR, McHugh JB. Sinonasal lobular capillary hemangioma: a clinicopathologic study of 34 cases characterizing potential for local recurrence. *Head Neck Pathol* 2013;7:129-134
46. Guo R, Folpe AL. Extensively myxoid and hyalinized sinonasal capillary hemangiomas: a clinicopathologic study of 16 cases of a distinctive and potentially confusing hemangioma variant. *Am J Surg Pathol* 2015;39:1584-1590

47. Hourani R, Taslakian B, Shabb NS, et al. Fibroblastic and myofibroblastic tumors of the head and neck: comprehensive imaging-based review with pathologic correlation. *Eur J Radiol* 2015;84:250-260
48. Cox DP, Daniels T, Jordan RC. Solitary fibrous tumor of the head and neck. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;110:79-84
49. Gengler C, Guillou L. Solitary fibrous tumour and haemangiopericytoma: evolution of a concept. *Histopathology* 2006;48:63-74
50. Yokoi H, Arakawa A, Kuribayashi K, Inoshita A, Haruyama T, Ikeda K. An immunohistochemical study of sinonasal hemangiopericytoma. *Auris Nasus Larynx* 2011;38:743-476
51. López F, Suárez V, Costales M, Suárez C, Llorente JL. Treatment of juvenile angiofibromas: 18-year experience of a single tertiary centre in Spain. *Rhinology* 2012;50:95-103
52. Bernal-Sprekelsen M, Alobid I, Guilemany JM. Juvenil angiofibroma. *Acta Otorrinolaringol Esp* 2007;58:84-95
53. Leong SC. A systematic review of surgical outcomes for advanced juvenile nasopharyngeal angiofibroma with intracranial involvement. *Laryngoscope* 2013;123:1125-1131
54. Paris J, Guelfucci B, Triglia JM, Moulin G, Zanaret M, Triglia JM. Diagnosis and treatment of juvenile nasopharyngeal angiofibroma. *Eur Arch Otorhinolaryngol* 2001;258:120-124
55. Scholfield DW, Brundler MA, McDermott AL, Mussai F, Kearns P. Adjunctive treatment in juvenile nasopharyngeal angiofibroma: how should we approach recurrence? *J Pediatr Hematol Oncol* 2016;38:235-239
56. Lloyd G, Howard D, Lund VJ, Savy L. Imaging for juvenile angiofibroma. *J Laryngol Otol* 2000;114:727-730
57. Griffiths PD, Coley SC, Romanowski CA, Hodgson T, Wilkinson ID. Contrast-enhanced fluid-attenuated inversion recovery imaging for leptomeningeal disease in children. *AJNR* 2003;24: 719-723.

58. Kukwa W, Andrysiak R, Kukwa A, et al. (99m)TC-octreotide scintigraphy and somatostatin receptor subtype expression in juvenile nasopharyngeal angiofibromas. *Head Neck* 2011;33:1739-1746
59. Wu AW, Mowry SE, Vinuela F, Abemayor E, Wang MB. Bilateral vascular supply in juvenile nasopharyngeal angiofibromas. *Laryngoscope* 2011;121:639-643
60. Glad H, Vainer B, Buchwald C, et al. Juvenile nasopharyngeal angiofibromas in Denmark 1981-2003: diagnosis, incidence, and treatment. *Acta Otolaryngol* 2007;127:292-299
61. Siniluoto TM, Luotonen JP, Tikkakoski TA, Leinonen AS, Jokinen KE. Value of preoperative embolization in surgery for nasopharyngeal angiofibroma. *J Laryngol Otol* 1993;107:514-521
62. Mann WJ, Jecker P, Amedee RG. Juvenile angiofibromas: changing surgical concept over the last 20 years. *Laryngoscope* 2004;114:291-293
63. Li JR, Qian J, Shan XZ, Wang L. Evaluation of the effectiveness of preoperative embolization in surgery for nasopharyngeal angiofibroma. *Eur Arch Otorhinolaryngol* 255:430-432
64. Nicolai P, Berlucchi M, Tomenzoli D. Endoscopic surgery for juvenile angiofibroma: when and how. *Laryngoscope* 2003;113:775-782
65. Onerci TM, Yucel OT, Ogretmenoglu O. Endoscopic surgery in treatment of juvenile nasopharyngeal angiofibroma. *Int J Pediatr Otolaryngol* 2003;67:1219-1225
66. Santaolalla F, Araluce I, Zabala A, López A, Garay M, Sanchez JM. Efficacy of selective percutaneous embolization for the treatment of intractable posterior epistaxis and juvenile nasopharyngeal angiofibroma (JNA). *Acta Otolaryngol* 2009;129:1456-1462
67. Wasl H, McGuire J, Lubbe D. Avoiding allogenic blood transfusions in endoscopic angiofibroma surgery. *J Otolaryngol Head Neck Surg* 2016;45:25
68. Mair EA, Battiatà A, Casler JD. Endoscopic laser-assisted excision of juvenile nasopharyngeal angiofibromas. *Arch Otolaryngol Head Neck Surg* 2003;129:454-459

69. Mehan R, Rupa V, Lukka VK, Ahmed M, Moses V, Shyam Kumar NK. Association between vascular supply, stage and tumour size of juvenile nasopharyngeal angiofibroma. *Eur Arch Otorhinolaryngol* 2016 Jun 11. [Epub ahead of print]
70. Hackman T, Snyderman CH, Carrau R, Vescan A, Kassam A. Juvenile nasopharyngeal angiofibroma: The expanded endonasal approach. *Am J Rhinol Allergy* 2009;23:95-99
71. De Vincentiis M, Gallo A, Minni A, Torri E, Tomassi R, Della RC. Preoperative embolisation in the treatment protocol for rhinopharyngeal angiofibroma: comparison of the effectiveness of various materials. *Acta Otorhinolaryngol Ital* 1997;17:225-232
72. Lutz J, Holtmannspötter M, Flatz W, et al Preoperative embolization to improve the surgical management and outcome of juvenile nasopharyngeal angiofibroma (JNA) in a single center: 10-year experience. *Clin Neuroradiol* 2015 Jan 29. [Epub ahead of print]
73. Tranbahuy P, Borsik M, Herman P, Wassef M, Casasco A. Direct intratumoural embolisation of juvenile angiofibroma. *Am J Otolaryngol* 1994;15:429-435
74. Borota L, Mahmoud E, Nyberg C, Ekberg T. Combined percutaneous and transarterial devascularisation of juvenile nasopharyngeal angiofibroma with protection of internal carotid artery: A modification of the technique. *Interv Neuroradiol* 2015;21:390-396
75. Herman B, Bublik M, Ruiz J, Younis R. Endoscopic embolization with onyx prior to resection of JNA: a new approach. *Int J Pediatr Otorhinolaryngol* 2011;75:53-56
76. Onerci M, Gumus K, Cil B, Eldem B. A rare complication of embolization in juvenile nasopharyngeal angiofibroma. *Int J Pediatr Otorhinolaryngol* 2005;69:423-428
77. Ramezani A, Haghhighatkhah H, Moghadasi H, Taheri MS, Parsafar H. A case of central retinal artery occlusion following embolization procedure for juvenile nasopharyngeal angiofibroma. *Indian J Ophthalmol* 2010;58:419-421
78. Ogawa AI, Fornazieri MA, da Silva LV, et al. Juvenile angiofibroma: major and minor complications of preoperative embolization. *Rhinology* 2012;50:199-202
79. Gavagan L, Ti J, Thornton J. Is hair loss a reality in neuro-interventional radiology? *Radiat Prot Dosimetry* 2011;147:68-71

80. Ye D, Shen Z, Wang G, Deng H, Qiu S, Zhang Y. Analysis of factors in successful nasal endoscopic resection of nasopharyngeal angiofibroma. *Acta Otolaryngol* 2016;136:205-213
81. El Sharkawy AA. Endonasal endoscopic management of juvenile nasopharyngeal angiofibroma without angiographic embolization *Eur Arch Otorhinolaryngol* 2013;270:2051-2055
82. Cannon DE, Poetker DM, Loehrl TA, Chun RH. Use of coblation in resection of juvenile nasopharyngeal angiofibroma. *Ann Otol Rhinol Laryngol* 2013;122:353-357
83. Piazza P, Di Lella F, Bacciu A, Di Trapani G, Ait Mimoune H, Sanna M. Preoperative protective stenting of the internal carotid artery in the management of complex head and neck paragangliomas: long-term results. *Audiol Neurootol* 2013;18:345-352
84. McLaughlin EJ, Cunningham MJ, Kazahaya K, Hsing J, Kawai K, Adil EA. Endoscopic Radiofrequency Ablation-Assisted Resection of Juvenile Nasopharyngeal Angiofibroma: Comparison with Traditional Endoscopic Technique. *Otolaryngol Head Neck Surg* 2016;154:1145-1148
85. Alshaikh NA, Eleftheriadou A. Juvenile nasopharyngeal angiofibroma staging: An overview. *Ear Nose Throat J* 2015;94:E12-22
86. Blount A, Riley KO, Woodworth BA. Juvenile nasopharyngeal angiofibroma. *Otolaryngol Clin North Am* 2011;44:989-1004
87. Radkowski D, McGill T, Healy GB, Ohlms L, Jones DT. Angiofibroma: changes in staging and treatment. *Arch Otolaryngol Head Neck Surg* 1996;122:122-129
88. Sessions RB, Bryan RN, Naclerio RM, Alford BR. Radiographic staging of juvenile angiofibroma. *Head Neck Surg* 1981;3:279-283
89. Snyderman CH, Pant H, Carrau RL, Gardner P. A new endoscopic staging system for angiofibromas. *Arch Otolaryngol Head Neck Surg* 2010;136:588-594
90. Andrews JC, Fisch U, Valavanis A, Aeppli U, Makek MS. The surgical management of extensive nasopharyngeal angiofibromas with the infratemporal fossa approach. *Laryngoscope* 1989;99:429-437

91. Onerci M, Öğretmenoğlu O, Yücel T. Juvenile nasopharyngeal angiofibroma: a revised staging system. *Rhinology* 2006;44:39-45
92. Weprin LS, Siemers PT. Spontaneous regression of juvenile nasopharyngeal angiofibroma. *Arch Otolaryngol Head and Neck Surg* 1991;117:796-799
93. Scholtz AW, Appenroth E, Kammen-Jolly K, Scholtz LU, Thumfart WF. Juvenile nasopharyngeal angiofibroma: management and therapy. *Laryngoscope* 2001;111:681-687
94. Tosun F, Onerci M, Durmaz A, Ugurel S. Spontaneous involution of nasopharyngeal angiofibroma. *J Craniofac Surg* 2008;19:1686-1689
95. Jacobsson M, Petruson B, Ruth M, Svendsen P. Involution of juvenile nasopharyngeal angiofibroma with intracranial extension. A case report with computed tomographic assessment. *Arch Otolaryngol Head Neck Surg* 1989;115:238-239
96. Dohar JE, Duvall AJ 3rd. Spontaneous regression of juvenile nasopharyngeal angiofibroma. *Ann Otol Rhinol Laryngol* 1992;101:469-471
97. Mishra SC, Shukla GK, Bhatia N, Pant MC. A rational classification of angiofibromas of the postnasal space. *J Laryngol Otol* 1989;103:912-916
98. Hosseini SM, Borghei P, Borghei SH, Ashtiani MT, Shirkhoda A. Angiofibroma: an outcome review of conventional surgical approaches. *Eur Arch Otorhinolaryngol* 2005;262:807-812
99. Donald PJ, Enepekides D, Boggan J. Giant juvenile nasopharyngeal angiofibroma: management by skull-base surgery. *Arch Otolaryngol Head Neck Surg* 2004;130:882-886
100. Cloutier T, Pons Y, Blancal JP, et al. Juvenile nasopharyngeal angiofibroma: does the external approach still make sense? *Otolaryngol Head Neck Surg* 2012;147:958-963
101. Enepekides DJ. Recent advances in the treatment of juvenile angiofibroma. *Curr Opin Otolaryngol Head Neck Surg* 2004;12: 495-496
102. Fagan JJ, Snyderman CH, Carrau RL, Janecka IP. Nasopharyngeal angiofibromas: selecting a surgical approach. *Head Neck* 1997;19:391-399

103. Suárez C, Llorente JL, Muñoz C, García LA, Rodrigo JP. Facial translocation approach in the management of central skull base and infratemporal tumors. *Laryngoscope* 2004;114:1047-1051
104. Janecka IP, Sen CN, Sekhar LN, Arriaga M. Facial translocation: a new approach to the cranial base. *Otolaryngol Head Neck Surg* 1990;103:413-419
105. Llorente JL, Nazar G, Cabanillas R, Fernández de León R, Suárez C. Subtemporal preauricular approach in the management of infratemporal and nasopharyngeal tumours. *J Otolaryngol* 2006; 35:173-179
106. Bales C, Kotapka M, Loevner LA, et al. Craniofacial resection of advanced juvenile nasopharyngeal angiofibroma. *Arch Otolaryngol Head Neck Surg* 2002;128:1071-1078
107. Lang DA, Neil-Dwyer G, Evans BT, Honeybul S. Craniofacial access in children. *Acta Neurochir (Wien)* 1998;140:33-40
108. Douglas R, Wormald PJ. Endoscopic surgery for juvenile nasopharyngeal angiofibroma: where are the limits? *Curr Opin Otolaryngol Head Neck Surg* 2006;14:1-5
109. Boghani Z, Husain Q, Kanumuri VV, et al. Juvenile nasopharyngeal angiofibroma; a systematic review and comparison of endoscopic, endoscopic-assisted, and open resection in 1047 cases. *Laryngoscope* 2013;123:859-869
110. Bleier BS, Kennedy DW, Palmer JN, Chiu AG, Bloom JD, O'Malley BW, Jr. Current management of juvenile nasopharyngeal angiofibroma: a tertiary center experience 1999-2007. *Am J Rhinol Allergy* 2009;23:328-330
111. Nicolai P, Villaret AB, Farina D. Endoscopic surgery for juvenile angiofibroma: a critical review of indications after 46 cases. *Am J Rhinol Allergy* 2010;24:e67-72
112. Nicolai P, Schreiber A, Bolzoni Villaret A. Juvenile angiofibroma: evolution of management. *Int J Pediatr.* 2012;2012:412545
113. Hofmann T, Bernal-Sprekelsen M, Koele W, Reittner P, Klein E, Stammberger H. Endoscopic resection of juvenile angiofibromas long term results. *Rhinology* 1995;43: 282-289

114. Pryor SG, Moore EJ, Kasperbauer JL. Endoscopic versus traditional approaches for excision of juvenile nasopharyngeal angiofibroma. *Laryngoscope* 2005;115:1201-1207
115. Khalifa MA, Ragab SM. Endoscopic assisted antral window approach for type III nasopharyngeal angiofibroma with infratemporal fossa extension. *Int J Ped Otorhinolaryngol* 2008;72:1855–1860
116. Gupta K, Rajiniganth MG. Endoscopic approach to juvenile nasopharyngeal angiofibroma: our experience at a tertiary care centre. *J Laryngol Otol* 2008;122:1185-1189
117. Roger G, Tran Ba Huy P, Froehlich P, et al. Exclusively endoscopic removal of juvenile nasopharyngeal angiofibroma: trends and limits. *Arch Otolaryngol-Head Neck Surg* 2002;128:928-935
118. Carrau RL, Snyderman CH, Kassam AB, Jungreis CA. Endoscopic and endoscopic assisted surgery for juvenile angiofibroma. *Laryngoscope* 2001;111:483-487
119. Newlands SD, Weymuller EA. Endoscopic treatment of juvenile nasopharyngeal angiofibroma. *Am J Rhinol* 1999;13:213-219
120. Mitskavich MT, Carrau RL, Snyderman CH, Weissman JL, Fagan JJ. Intranasal endoscopic excision of a juvenile angiofibroma. *Auris Nasus Larynx* 1998;25:39-44
121. Bernal-Sprekelsen M, Vázquez AA, Pueyo J, Carbonell Casasús J. Endoscopic resection of juvenile nasopharyngeal fibromas. *HNO* 1998;46:172-174
122. Tseng HZ, Chao WY. Transnasal endoscopic approach for juvenile nasopharyngeal angiofibroma. *Am J Otolaryngol* 1997;18:151-154
123. Bernal-Sprekelsen M, Massegur Solench H, Tomás Barberán M. Paediatric endoscopic sinus surgery (PESS): review of the indications. *Rev Laryngol Otol Rhinol* 2003;124:145-150
124. Wormald PJ, Van Hasselt A. Endoscopic removal of juvenile angiofibromas. *Otolaryngol Head Neck Surg* 2003;129:684-691
125. Pasquini E, Sciarretta V, Frank G, et al. Endoscopic treatment of benign tumours of the nose and paranasal sinuses. *Otolaryngol Head Neck Surg* 2004;131:180-186

126. Langdon C, Herman P, Verillaud B, et al. Expanded endoscopic endonasal surgery for advanced stage juvenile angiofibromas: a retrospective multi-center study. *Rhinology*. 2016 Apr 9. [Epub ahead of print]
127. Liu JK, Husain Q, Kanumuri V, Khan MN, Mendelson ZS, Eloy JA. Endoscopic graduated multiangle, multicorridor resection of juvenile nasopharyngeal angiofibroma: an individualized, tailored, multicorridor skull base approach. *J Neurosurg* 2016;124:1328-1338
128. Amdur RJ, Yeung AR, Fitzgerald BM, Mancuso AA, Werning JW, Mendenhall WM. Radiotherapy for juvenile nasopharyngeal angiofibroma. *Pract Radiat Oncol* 2011;1:271-278
129. Reddy KA, Mendenhall WM, Amdur RJ, Stringer SP, Cassisi NJ. Long-term results of radiation therapy for juvenile nasopharyngeal angiofibroma. *Am J Otolaryngol* 2001;22:172-175
130. McAfee WJ, Morris CG, Amdur RJ, Werning JW, Mendenhall WM. Definitive radiotherapy for juvenile nasopharyngeal angiofibroma. *Am J Clin Oncol* 2006;29:168-170
131. Lee JT, Chen P, Safa A, Juillard G, Calcaterra TC. The role of radiation in the treatment of advanced juvenile angiofibroma. *Laryngoscope* 2002;12:1217-1220
132. Kasper ME, Parsons JT, Mancuso AA, et al. Radiation therapy for juvenile angiofibroma: evaluation by CT and MRI, analysis of tumour regression, and selection of patients. *Int J Radiat Oncol Biol Phys* 1993;25:689-694
133. Chakraborty S, Ghoshal S, Patil VM, Oinam AS, Sharma SC. Conformal radiotherapy in the treatment of advanced juvenile nasopharyngeal angiofibroma with intracranial extension: an institutional experience. *Int J Radiat Oncol Biol Phys* 2011;80:1398-404
134. Álvarez FL, Suárez V, Suárez C, Llorente JL. Multimodality approach for advanced-stage juvenile nasopharyngeal angiofibromas *Head Neck* 2013;35:209-213

135. Koppersmith RB, Teh BS, Donovan DT, et al. The use of intensity modulated radiotherapy for the treatment of extensive and recurrent juvenile angiofibroma. *Int J Pediatr Otorhinolaryngol* 2000;52:261-268
136. Chen KT, Bauer FW. Sarcomatous transformation of nasopharyngeal angiofibroma. *Cancer*. 1982;49:369-371
137. Gates GA, Rice DH, Koopmann Jr CF, Schuller DE. Flutamide-induced regression of angiofibroma. *Laryngoscope* 1992;102:641-614
138. Goepfert H, Cangir A, Lee YY. Chemotherapy for aggressive juvenile nasopharyngeal angiofibroma. *Arch Otolaryngol* 1985;111:285-289
139. Schick B, Kahle G, Hassler R, Draf W. Chemotherapy of juvenile angiofibroma—an alternative? *HNO* 1996;44:148–152
140. Thakar A, Gupta G, Bhalla AS, et al. Adjuvant therapy with flutamide for presurgical volume reduction in juvenile nasopharyngeal angiofibroma. *Head Neck* 201;33:1747-1753
141. Labra A, Chavolla-Magana R, Lopez-Ugalde A, Alanis-Calderon J, Huerta-Delgado A. Flutamide as a preoperative treatment in juvenile angiofibroma (JA) with intracranial invasion: report of 7 cases. *Otolaryngol Head Neck Surg* 2004;130:466-469
142. Schick B, Długaiczek J, Wendler O. Expression of sex hormone receptors in juvenile angiofibromas and antiproliferative effects of receptor modulators. *Head Neck* 2014;36:1596-1603
143. Saylam G, Yücel OT, Sungur A, Onerci M.. Proliferation, angiogenesis and hormonal markers in juvenile nasopharyngeal angiofibroma. *Int J Pediatr Otorhinolaryngol* 2006;70:227-234
144. Wendler O, Długaiczek J, Birk S, Schick B. Anti-proliferative effect of glucocorticoids on mesenchymal cells in juvenile angiofibromas. *Head Neck* 2012;34:1615-1621
145. Renkonen S, Hagström J, Vuola J, et al. The changing surgical management of juvenile nasopharyngeal angiofibroma. *Eur Arch Otorhinolaryngol* 2011;268:599-607

146. Jones GC, DeSanto LW, Bremer JW, Neel HB. Juvenile angiofibromas. Behavior and treatment of extensive and residual tumours. *Arch Otolaryngol Head Neck Surg* 1986;112:1191-1193
147. Chagnaud C, Petit P, Bartoli J, et al. Postoperative follow-up of juvenile nasopharyngeal angiofibromas: assessment by CT scan and MR imaging. *Eur Radiol* 1998;8:756-764
148. Tyagi I, Syal R, Goyal A. Recurrent and residual juvenile angiofibromas. *J Laryngol Otol* 2007;121:460-467
149. Sciarretta V, Pasquini E, Farneti G, Frank G, Mazzatenta D, Calbucci F. Endoscopic sinus surgery for the treatment of vascular tumors. *Am J Rhinol* 2006;20:426-431
150. Kania RE, Sauvaget E, Guichard J, Chapot R, Huy PT, Herman P. Early postoperative CT scanning for juvenile nasopharyngeal angiofibroma: detection of residual disease. *AJNR Am J Neuroradiol* 2005;26:82-88
151. Herman P, Lot G, Chapot R, Salvan D, Huy PT. Long-term follow-up of juvenile nasopharyngeal angiofibromas: analysis of recurrences. *Laryngoscope* 1999;109:140–147
152. Howard DJ, Lloyd G, Lund V. Recurrence and its avoidance in juvenile angiofibroma. *Laryngoscope* 2001;111:1509-1511
153. Thakar A, Hota A, Bhalla AS, Gupta SD, Sarkar C, Kumar R. Overt and occult vidian canal involvement in juvenile angiofibroma and its possible impact on recurrence. *Head Neck* 2016;38:E421-425

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. Occasional 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.