ENT Updates

ORIGINAL ARTICLE

ENT UPDATES 12(1):17-28
DOI: 10.5152/entupdates.2022.22179

Endoscopic Treatment of Juvenile Angiofibromas: Experience of a Tertiary Center from 1993 to 2020

ABSTRACT

Objective: Juvenile angiofibromas are benign tumors that almost exclusively affect male adolescents. Over the last decades, there is an evolution from open surgery to less-invasive endoscopic techniques.

Methods: The medical records of 39 consecutive patients who underwent endoscopic sinus surgery for a juvenile angiofibroma were retrospectively analyzed.

Results: The distribution of the tumor stages according to the classification system of Radkowski was as follows: 1 in stage IA, 5 in IB, 7 in IIA, 13 in IIB, 5 in IIC, 4 in IIIA, and 4 in IIIB. Preoperative angiography with embolization was performed in all but 1 patient. The mean postoperative follow-up time was 32 months. Five patients (12.8%) had a recurrence after a mean period of 9 months (range 3-24 months), of which 2 initially had incomplete macroscopic tumor removal due to intracranial extension. The mean operating time was 106 minutes (range 35-400 minutes). The mean duration of hospitalization was 4.3 days (range 1-9 days). Two patients (5.1%) had postoperative bleeding out of the internal maxillary artery for which a reintervention and blood transfusion was needed.

Conclusions: Endoscopic surgery for juvenile angiofibromas is an effective and safe technique with good outcomes and low postoperative morbidity. This technique should be used as the first choice in the treatment of small to medium-sized tumors (I-IIB) and is a worthy alternative to open surgery for advanced tumor stages (IIC-IIIB) when performed by an experienced surgeon.

Keywords: Juvenile angiofibroma, endoscopic sinus surgery, embolization

INTRODUCTION

Juvenile angiofibromas (JAs) are rare, histologically benign vascular tumors that affect male adolescents. It represents 0.05-0.5% of all head and neck tumors. The incidence is higher in the Middle East and India compared to Europe.[1] A retrospective national demographic study in Denmark showed an incidence rate of 0.4 cases per 1 million inhabitants per year and 3.7 cases per 1 million men aged 10-24 years per year.[2]

The term juvenile nasopharyngeal angiofibroma is increasingly replaced in literature by juvenile angiofibroma. It was so named because the tumor was thought to originate in the nasopharynx. The site of origin however is not in the nasopharynx but at the level of the sphenopalatine foramen or posteriorly in the pterygopalatine fossa, behind the pterygopalatine ganglion, at the level of the anterior opening of the pterygoid canal.[3,4] The JA extends into the nasal cavity which leads to specific nasal complaints in affected patients. In the case of unilateral nasal obstruction and epistaxis in a male adolescent, one should be aware of a possible JA. Further expansion occurs in different directions, through fissures and foramina, following the way of lowest resistance into the nasopharynx, the paranasal sinuses, the infratemporal fossa, the orbit, and the intracranial space. The significant vascularization, the locally aggressive and destructive nature, and the possibility of recurrence lead to significant morbidity associated with this tumor.

The JA consists of a fibrous stroma with mesenchymal cells and irregular vascular structures.[5] It is unclear whether the JA is a true neoplasm, a developmental disorder, or a vascular malformation. Some authors describe the JA as a vascular malformation, due to

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Cite this article as: Poels L, Van Gerven L, Jorissen M. Endoscopic treatment of juvenile angiofibromas: Experience of a tertiary center from 1993 to 2020. *ENT Updates.* 2022;12(1):17-28.

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Received: *January 30, 2022*
Accepted: *April 12, 2022*

incomplete regression of the first branchial artery.[6,7] This blood vessel is formed between days 22 and 24 and should regress completely. It forms a temporary connection between the internal carotid artery and the branches of the internal maxillary artery. If regression is incomplete, the embryological residue—situated at the site of the sphenopalatine foramen—could be responsible for the vascular component of JA by growth at adolescent age.[7] Moreover, the tumor arises at the site where, during embryogenesis, the buccopharyngeal membrane—the connection between the ectoderm (stomatodeum) and the endoderm (primitive gut)—adheres and where the membranous viscerocranium (palatine bone, vomer, pterygoid plate) and the cartilaginous neurocranium (sphenoid) meet. Further, the almost exclusive occurrence of these tumors in male adolescents suggests that hormonal components play a role in the development of JA.

The diagnosis of a JA is usually suspected during clinical examination, that is, a red mass in the nasal cavity in a male adolescent with complaints of nasal obstruction and/or epistaxis. Confirmation of the diagnosis is obtained through imaging, usually a combination of computed tomography (CT) and magnetic resonance imaging (MRI). The most specific sign of JA on both CT and MRI is the widening of the pterygomaxillary fissure.[4]

Various classification systems for staging have been described, among which the staging systems by *Sessions*, *Fisch*, *Chandler*, *Andrews,* and *Radkowski*[8-12] rely on the anatomical localization and/or extension of the tumor. Newer staging systems are those of *Onerci* and *Snyderman*.[13-14] In parallel with the evolution of less-invasive surgical techniques, *Snyderman* developed a prognostic classification system based on the route of cranial base extension and the vascularity of the tumor.[14]

Surgical treatment, preceded by selective embolization by means of angiography, is preferred. Several open surgical techniques and approaches have been described in the past, including a transpalatal approach, medial maxillectomy (by lateral rhinotomy or midfacial degloving), and craniofacial resection.[15] Over the last decades, there is an evolution from open surgery to less-invasive endoscopic-assisted or exclusive endoscopic techniques.[16] The first to describe endoscopic approach for JA was Jorissen.[17] Initially, the endoscopic technique was used for limited tumors, Radkowski stages I-IIA only. The indications for endoscopic surgery gradually expanded to more advanced stages, especially for the treatment of JA with extension into the infratemporal fossa (IIC) and even with intracranial extension (III).

MAIN POINTS

- Endoscopic surgery for a juvenile angiofibroma (JA) is an effective and safe procedure with good outcomes (recurrence rate of 12.8% in our series) and low postoperative morbidity.
- Endoscopic surgery is the preferred technique for the treatment of small to medium-sized tumors (I-IIB).
- Endoscopic surgery is an worthy alternative to open surgery for advanced tumor stages (IIC-IIIB) in the hands of an experienced surgeon.

The aim of this study was to analyze all cases of JA treated by endoscopic surgery in our tertiary center from 1993 to 2020 including presentation, staging, preoperative embolization, treatment, and follow-up. Moreover, we attempted to clarify the possibilities and limitations of endoscopic surgery in the treatment of JA.

METHODS

Patients

The medical records of all 39 patients who underwent endoscopic sinus surgery for a JA at University Hospitals Leuven between 1993 and 2020 were retrospectively analyzed.

Pre-operative Work-Up

The JA was suspected during anamnesis and clinical examination (including nasal endoscopy) and confirmed on CT and MRI with axial, sagittal, and coronal planes. A pre-operative embolization through angiography was generally performed 24-48 hours prior to surgery. The procedure involved a selective catheterization of the external and internal carotid artery with visualization of the vasculature of the tumor after contrast injection. By using supra-selective catheterization and embolization of the afferent branches with microparticles (polyvinyl alcohol or trisacryl gelatin) and/or vascular coils, an attempt was made to devascularize the tumor. A control angiography was performed to evaluate the occlusion of the embolized branches and to estimate residual opacification.

Staging

Tumors were staged using the classification systems according to *Sessions*, *Chandler*, *Andrews,* and *Radkowski* based on preoperative radiological and peroperative macroscopic extension of the tumor.[8,10-12] In addition, the tumors were also classified according to the newer University of Pittsburgh Medical Center staging system.[14] For the discussion of the results, we opted to work with the Radkowski staging system in order to compare our results with the results of other studies (Table 1).

Surgical Procedure

All procedures were performed endoscopically. The procedure was carried out under general anesthesia with controlled hypotension. Cottonoids, soaked with cocaine and epinephrine, were intranasally applied for 15 minutes to obtain vasoconstriction and decongestion. The exact surgical procedure depended on the individual presentation of the tumor, but a standard number of surgical steps were completed for each procedure. Only classic cold steel endoscopic sinus surgery instrumentation was

Table 1. Radkowski Staging System[12]

Stage	Description
IA	Limited to the nasal cavity and/or nasopharynx
IB	Extension into one or more paranasal sinuses
IIA	Minimal extension into the pterygopalatine fossa
IIB	Full occupation of the pterygopalatine fossa
IIC	Extension into the infratemporal fossa or posterior of the pterygoid plates
IIIA	Erosion of the skull base with minimal intracranial extension
IIIB	Extensive intracranial extension

used, except for 1 patient with an advanced stage JA in which we used coblation.

The endoscopic procedure (pull and release technique) was performed as follows: First, the limits of the tumor were explored. For this purpose, an infundibulotomy and ethmoidectomy were carried out with the creation of a large maxillary antrostomy. The posterior part of the middle turbinate was resected. The sphenoid was opened along the superolateral wall, and the anterior wall was removed. A resection of the posterior half of the inferior turbinate was usually carried out, especially when the JA expanded into the inferior part of the pterygopalatine fossa and/or infratemporal fossa. The tumor was dissected from the nasopharynx medially, and when the nasal septum was affected, it was partially resected. The posterior wall of the maxillary sinus was then removed in order to gain access to the pterygopalatine and infratemporal fossa. The internal maxillary artery was detected in the retromaxillary fat and clipped. The tumor was mobilized for visualization of the insertion site. The JA was then further dissected from its attachment to the surrounding structures. In case of invasion of the pterygoid process, further dissection in the posterior direction was necessary. In case of extension into the inferior part of the sphenoid sinus, the inferior wall of the sphenoid sinus was also removed. The tumor was then mobilized medially and inferiorly and was subsequently removed (complete or piecemeal resection) through transnasal or transoral route depending on the size. A thorough inspection of residual tumor tissue was always performed. A prophylactic curettage at the level of the pterygoid process, the basisphenoid, and sometimes the vomer and the clivus was additionally carried out in those patients with (suspicion of) extension of the JA into these sites.

Follow-Up

Patients were postoperatively monitored by MRI immediately after surgery and nasal endoscopy every 2 months in the first year and every 4 months in the second year after surgery. Thereafter, patients were no longer routinely followed up. Additional radiological imaging was only performed on grounds of clinical suspicion of recurrence.

Statistical Analysis

Descriptive statistics were used throughout the study using Microsoft Excel.

Ethics

This study was approved by the ethics advisory board of Biomedical Sciences of the KU Leuven. Explicit informed consent not necessary for the ethics advisory board given the retrospective character of the study and given the anonymity of patients is guaranteed.

RESULTS

Demography

All 39 patients who underwent endoscopic surgery for a JA were of the male sex. The age ranged between 11 and 31 years with a median age of 17 years. A left-sided JA was observed in 16 patients, and a right-sided one in 22 patients. In 1 patient, the JA had a bilateral extension. Thirty-six patients underwent their first surgery, and 3 patients were referred for a recurrence which was previously treated with surgery elsewhere.

Presentation

The most frequent symptom was nasal obstruction in 33 cases (84.6%), followed by epistaxis in 19 cases (48.7%). Less frequent symptoms were nasal secretions in 10 cases (25.6%), headache in 7 cases (17.9%), postnasal drip, and hypo- or anosmia in 4 cases (10.2%). Rather rare symptoms at initial presentation were snoring, jaw swelling, and epiphora. An overview of the symptoms at the initial presentation is shown in Figure 1.

Extension and Staging

An overview of the extent of the tumors is shown in Figure 2. Based on radiographic investigations and peroperative findings, the tumors were classified according to the above-described classification schemes (Figure 3). The distribution of the patients following the Radkowski staging was as follows: 13 patients in stages IA-IIA, 13 patients in stage IIB, 5 patients in stage IIC, 4 patients in stage IIIA, and 4 patients in stage IIIB. Of the 39 patients, 26 patients (66.7%) were treated endoscopically for more advanced stages (IIB-IIIB), of which 13 patients were with extension into the infratemporal fossa (IIC) or erosion of the skull base with minimal (IIIA) or extensive intracranial extension (IIIB).

Preoperative Embolization and Peroperative Blood Loss

All but 1 patient underwent an angiography with embolization prior to surgery. Until 2003, the average time between embolization and surgery ranged from 1 to 6 days, later the interval ranged between 24 and 48 hours. The external carotid artery (with branches of internal maxillary artery and ascending pharyngeal artery) contributed in all cases to the blood supply. In 6 cases, the vascularization of the tumor through the branches of the external carotid artery was bilateral. The main contribution, i.e. in 37 of the 39 cases (94.9%), came from the internal maxillary artery - not only from the distal branches (sphenopalatine artery and the artery of the pterygoid canal), but also from the proximal branches (meningeal artery and accessory meningeal artery) - followed by the ascending pharyngeal artery (53.8%). In 1 case, there was also contribution of the facial artery. Contribution of the internal carotid artery (with branches of mandibular artery, inferolateral trunk, and ophthalmic artery) was observed in 21 of the 39 cases (53.8%) of which the mandibular artery in 13 cases, the inferolateral trunk in 7 cases, and the ophthalmic artery in 2 cases. In 3 cases, the artery of the pterygoid canal arised, cfr initial text from the internal carotid artery. Twenty-three patients had a successful devascularization of the tumor, in 9 patients devascularization was almost complete, and in 6 patients devascularization was incomplete, mainly due to a significant contribution of the internal carotid artery to the blood supply. The preoperative embolization was uncomplicated in all cases.

The peroperative blood loss was limited or conform to the procedure in most cases and was documented in 21 cases, ranging from 200 cm^3 to 2500 cm^3. More than 500 cm^3 of blood loss was observed in 14 cases (35.9%), and more than 1000 cm^3 of blood loss in 7 cases (17.9%). One patient had severe peroperative bleeding for which the external carotid artery was ligated via an external approach, and 1 patient had venous bleeding from the cavernous sinus which was treated conservatively. These patients needed a peroperative transfusion of packed cells with normalization of hemoglobin levels during their hospital stay.

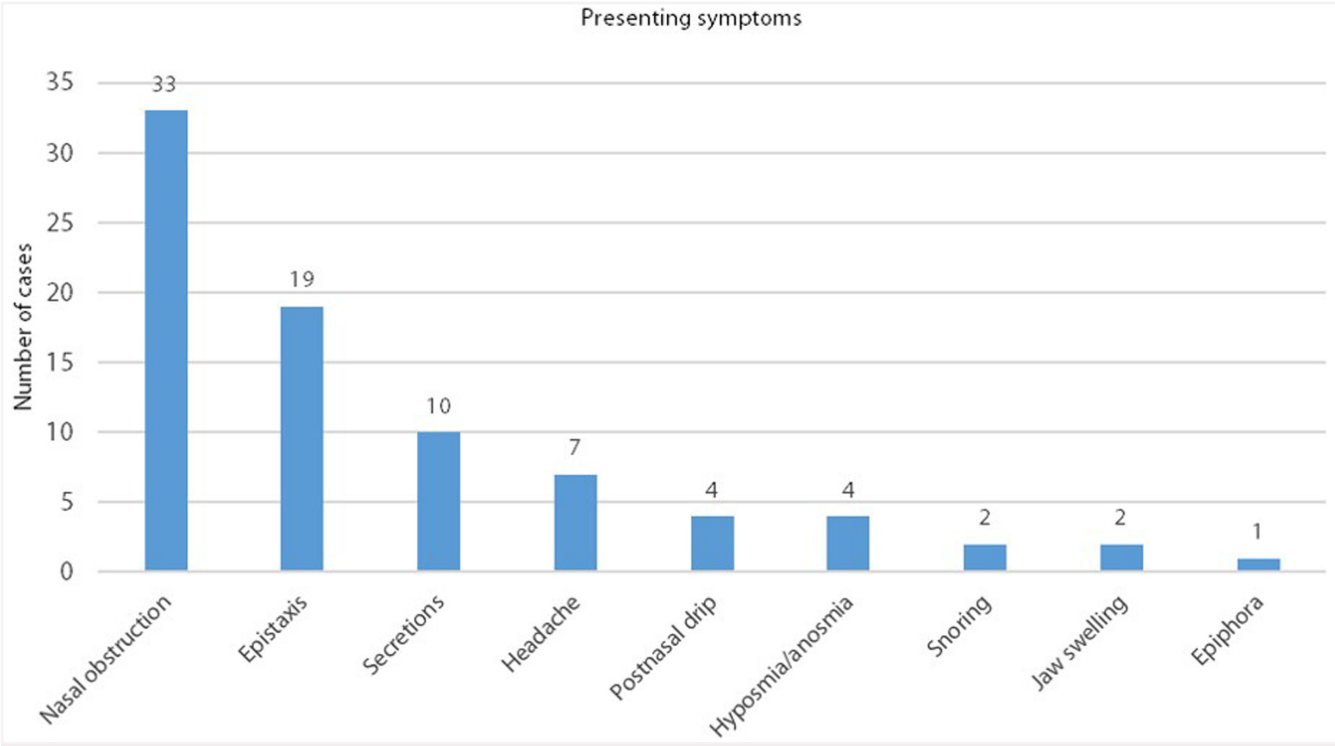

Figure 1. Symptoms at initial presentation.

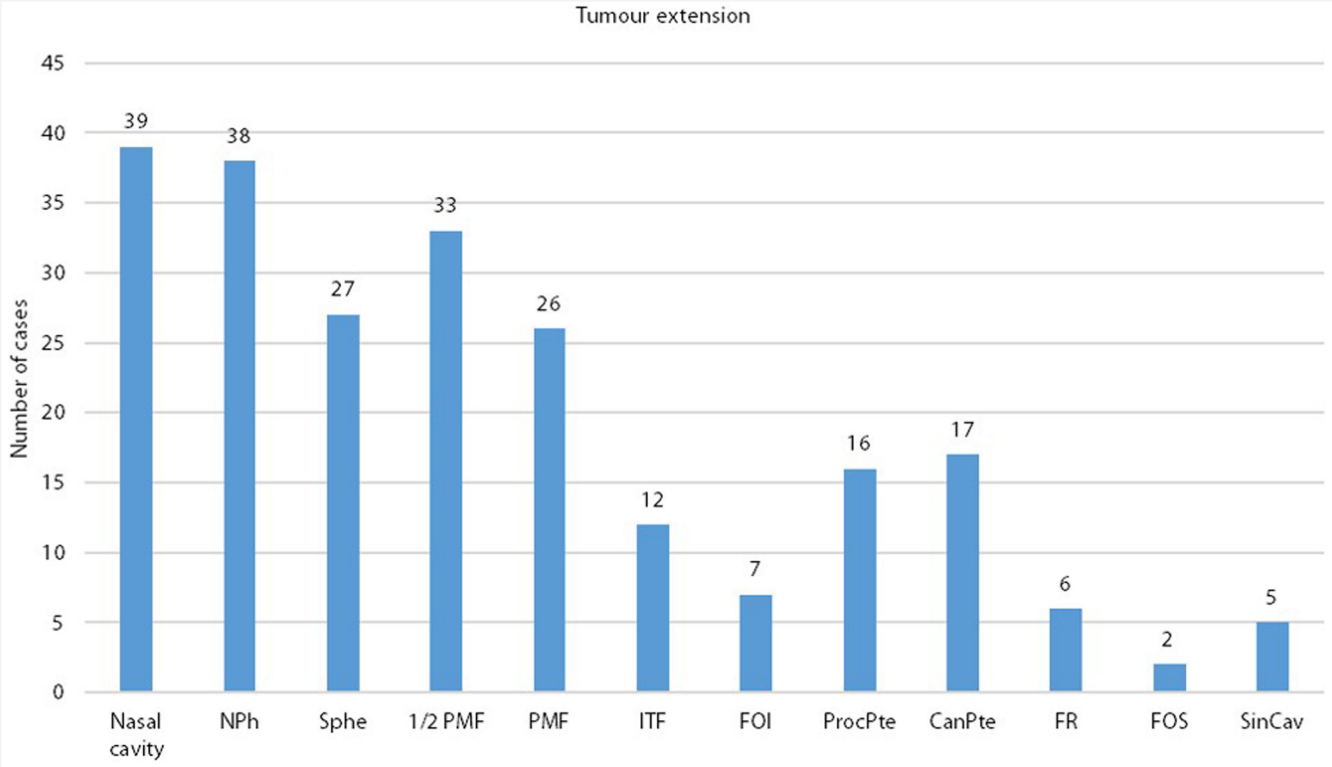

Figure 2. Extension and anatomical localization of JA based on imaging and peroperative findings. JA, juvenile angiofibromas; Nph,nasopharynx; Sphe, sphenoid sinus; ½ PMF, minimal extension into the pterygomaxillary fossa; PMF, pterygomaxillary fossa; ITF, infratemporal fossa; FOI, inferior orbital fissure; ProcPte, pterygoid process; CanPte, pterygoid canal; FR, foramen rotundum; FOS, superior orbital fissure; SinCav, cavernous sinus.

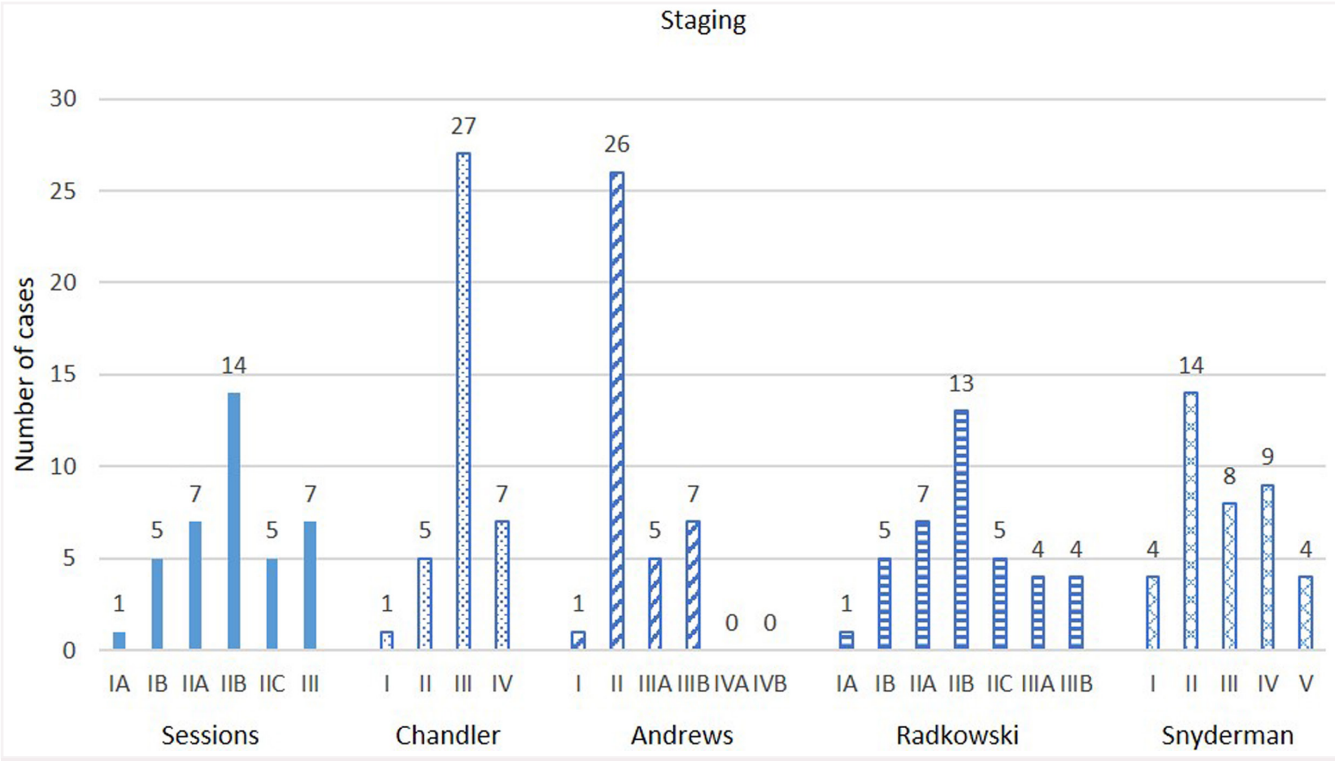

Figure 3. Staging according to Sessions, Chandler, Andrews, Radkowski, and Snyderman[8,10-12,14]

Postoperative Complications

Hypoesthesia in the region of the maxillary nerve (V2) was reported by most patients with recuperation within several weeks to months. Two patients needed a reintervention and transfusion of packed cells due to bleeding of the internal maxillary artery. One patient had a postoperative infection. One patient experienced temporary velopharyngeal insufficiency. No major postoperative complications were seen.

Operating Time and Duration of Hospital Stay

The duration of the surgery was reported in 35 cases with an average duration of 106 minutes (range 35-400 minutes). The mean duration of hospitalization was 4.3 days, ranging from 1 day in patients with limited tumors (IA-IIA) to 9 days in 1 patient with an advanced stage JA (IIIB, year of surgery 2002).

Tumor Recurrence

In 5 out of 39 patients (12.8%), a recurrence was observed after an average time of 9 months (range from 3 to 24 months) (Table 2). Among all endoscopically treated patients, there was a complete macroscopic removal of the tumor in 37 cases (94.9%). In 2 cases, 1 with initial stage IIIA (patient A, year of surgery 1994) and 1 with initial stage IIIB (patient B, year of surgery 2015), the tumor was removed incompletely with the progression of residual tumor tissue after 4 and 3 months, respectively. In patient A, residual tumor tissue growth was seen at the body of the sphenoid bone. After initial watchful waiting strategy, he underwent an embolization of the internal carotid artery after 9 months in Zurich (Switzerland) with sustained tumor regression after 60 months (cfr Table 2). In patient B, residual tumor tissue growth was seen at the greater wing of the sphenoid bone, extending into the middle cranial fossa, more specifically into the

Table 2. Overview of Recurrences

Patient	Age	Staging	Macroscopic Tumor Removal	Timing of Recurrence After Surgery	Treatment	Disease Status
A	13	IIIA	No	4 months	Embol (9 months)	RD (60 months)
B	14	IIIB	No	3 months	1/WW (8 months) 2/ ESS after embol	NED (20 months)
C	17	IIB	Yes	6 months	ESS after embol (2 months)	NED (32 months)
D	17	IIIA	Yes	9 months	1/WW (14 months) 2/ ESS after embol	NED (30 months)
E	13	IIB	Yes	24 months	WW	SD (60 months)

ESS, endoscopic sinus surgery; WW, watchful waiting; embol, embolization; RD, disease regression; NED, no evidence of disease; SD, stable disease.

carvernous sinus and close to the internal carotid artery and Meckel's cavum and also reaching into the inferior orbital fissure. After an 8-month wait-and-see policy, patient B underwent a new endoscopic surgery procedure preceded by embolization. After this surgery, the patient showed no tumor recurrence after 20 months of follow-up. Further follow-up was elsewhere due to a move abroad. In addition, we noted 3 recurrences after 6, 9, and 24 months of tumors with initial stage IIB (patient C, year of surgery 1995), IIIA (patient D, year of surgery 2000), and IIB (patient E, year of surgery 2005), respectively. Patient C had a recurrence in the pterygopalatine fossa with extension in the pterygoid muscles, pterygoid process, and greater wing of the sphenoid bone. He underwent a new endoscopic surgery procedure with preoperative embolization 2 months after the diagnosis of tumor recurrence. Patient D had a recurrence at the level of the sphenopalatine foramen with extension into the pterygopalatine fossa, pterygoid process, and sphenoid sinus. He was monitored for 14 months, whereafter we proceeded to surgical treatment by endoscopic approach with preoperative embolization. In both patients, there was no evidence of tumor recurrence after a follow-up of 32 and 30 months, respectively. In patient E, a small recurrence in the pterygopalatine fossa was detected on MRI at 24 months follow-up. The MRI was done because of complaints of nasal obstruction and epistaxis. Given the rapid subjective improvement of the reported symptoms, the small size of the recurrence and the absence of tumor tissue in the nasal cavity and paranasal sinuses during nasal endoscopy, we suspected that the recurrence could not be responsible for the symptoms of the patient. The tumor remained stable on MRI at 60 months follow-up.

DISCUSSION

Surgery

The surgical treatment of a JA is a major challenge for surgeons despite the benign character, because of the significant vascularization and the local extent of the tumor and its occurrence mainly at younger age. Over the past few decades, there is an evolution from open surgical techniques to minimally invasive endoscopic approaches. The first to describe the transnasal endoscopic approach for JA was Jorissen .[17] Shortly thereafter, this technique was also described by Kamel.[18] Initially, the endoscopic technique was used for the treatment of tumors limited to the nasal cavity, the nasopharynx, sphenoid, and limited extension in the pterygopalatine fossa (Radkowski IIA). A number of benefits are attributed to the endoscopic technique, more specifically, good visualization of the tumor, and adequate assessment of the totality of the resection. Moreover, there is no adverse effect on the growth of the facial skeleton, there are no external scars, and the length of hospital stay is short.[19] One of the disadvantages assigned to the endoscopic approach could be the longer duration of the surgery as compared to open surgery.[20] It is remarkable that in our study, the mean duration of surgery, reported in 35 cases, was only 106 minutes (range 35-400 minutes). This is shorter than for most other studies, presumably because blood loss was limited since all procedures were preceded by embolization (except for 1) and carried out by an experienced surgeon. In a systematic review by Khoueir et al.[21] the mean operating time was 168.35 minutes. A shorter surgical time could also be explained if on average less advanced tumors were treated in our series; however, 13/39 of our patients were treated for advanced stage tumors (IIC-IIIB). In the systematic review, the tumors were not stratified by tumor stage.

Preoperative Embolization and Peroperative Blood Loss

Peroperative bleeding is a feared complication in the surgical treatment of various pathologies because of associated morbidity and mortality. Hemostasis is of particular interest in the endoscopic treatment of the JA. First, the JA intrinsically has a higher bleeding risk due to the vascular nature of the tumor. On the other hand, good peroperative bleeding control is important in endoscopic surgery to maintain a good overview and to obtain adequate tumor resection. Various methods are used to reduce the peroperative blood loss, such as preoperative embolization, local vasoconstriction, controlled hypotension, and the clipping of the internal maxillary artery.

The peroperative blood loss in our study was limited in most cases. Larger losses of 1000-2500 cm^3 were only reported in 4 cases, which could be explained by larger tumor size and/or significant contribution of the internal carotid artery with incomplete devascularization of the tumor. In our study, no complications were reported after the embolization procedure.

Preoperative embolization is a safe procedure and results in a significant decrease in intraoperative blood loss and blood transfusions.[22-23] Embolization of the branches of the internal carotid artery is possible but is associated with potential intracranial complications, making devascularization of tumors, with significant contribution of the internal carotid artery, rather difficult and often subtotal. The interval between embolization and the surgical procedure can be up to a maximum of 48 hours because of the risk of recanalization.[24] Although preoperative embolization has numerous advantages in reduction of intraoperative blood loss and therefore contributes to better visualization of the surgical field, an adverse effect of preoperative embolization is described by McCombe[25] concerning completeness of the resection, especially for deep invasion of the sphenoid. The hypothesis is that devascularization leads to a decrease in tumor size which leads to retraction of the tumor in the spongious bone of the sphenoid and a higher risk of incomplete resection. Rapid residual tumor tissue growth can occur during revascularization of the tumor in the immediate postoperative period. However, in our center, preoperative embolization is part of the standard preoperative workup of JA in order to limit blood loss during surgery. This not only increases safety during the procedure but also improves the chance of complete resection through better visualization. In our opinion, it is mainly the expansion of the tumor at the level of the basisphenoid that determines the risk of recurrence. Curettage and or drilling of the basisphenoid and other bony structures where the JA seems adherent is an indispensable step to avoid any residual tumor tissue and thus prevent recurrence. This step is systematically built into our endoscopic treatment of JA. Q3

Recurrence

One of the primary outcome parameters of our study was the recurrence rate. Since JA is a unifocal and benign disease, recurrence of a JA is considered as growth of macroscopic or microscopic residual tumor tissue.[19] Incomplete resection and the

growth rate of the tumor at the time of surgery are the main determining factors for recurrence.[4,26] Residual tumor tissue, however, can remain stable or involute so that revision surgery with complete removal of the residual tumor tissue is not always necessary.[27-28] These cases should be followed systematically by nasal endoscopy and imaging depending on the follow-up regimen. Treatment is indicated in cases of tumor progression or symptoms.[20,26] Incomplete resection is frequently seen in cases of tumor invasion in the infratemporal fossa, the sphenoid sinus, the base of the pterygoid process (especially deep invasion) and the clivus, the cavernous sinus (medial), the foramen lacerum, and the anterior cranial fossa.[22] Other factors associated with a higher risk of recurrence are age and blood supply from the internal carotid artery.[26] With increasing age, a decreased growth potential is reported.[29] Residual vascularization of the tumor after preoperative embolization and expansion near the internal carotid artery reduces the extent of surgery and leads to a higher risk of residual tumor tissue.[14] However, as discussed above, some authors believe that preoperative embolization compromises the completeness of the resection due to the retraction of the tumor in the spongious bone of the sphenoid.[21]

In our study, we noted an incomplete resection in 2 cases (5.1%) with the growth of residual tumor tissue and recurrence in 3 patients (7.7%). Most recurrences in our study occurred within 1 year (80%). Besides 1 patient with incomplete macroscopic tumor removal due to intracranial tumor extension (patient B, surgery in 2015), no recurrence was seen in our center after endoscopic sinus surgery in the last 15 years (patient E, surgery in 2005). Important to note is that in our study we performed 1 MRI immediately after surgery but then the patients were monitored for recurrence with nasal endoscopy. It is possible that more recurrences would have been detected if patients were systematically monitored with radiological imaging. Given the social costs and the limited therapeutic implications of asymptomatic residual tumor tissue, we prefer to follow our patients clinically and request additional imaging only if a recurrence is suspected. The average recurrence rate of 12.8% is in accordance with other studies (Table 3). After the single-center series of Huang et al (66 cases) and Ardehali et al (47 cases), our series is the largest series of patients (37 cases) treated endoscopically for JA.[34,35] Recurrence rate in the study of Huang et al. was 28.3% and in the study of Ardehali et al 19.1%. Important to notice is that in these series the absolute number and proportion of patients treated for more advanced stages (IIC-IIIB) was larger compared to our study. In a systematic review of the exclusive endoscopic treatment of the JA by Khoueir et al[21] a mean recurrence rate of 17.7% (7.7% residue and 10% relapse) was reported.[21]

Indications

The increasing experience with endoscopic techniques and the development of appropriate instruments has led to the widespread use of this technique in the approach of the JA with cautious expansion of indications. Initially, significant extension of the JA into the pterygopalatine fossa (IIB), the infratemporal fossa (IIC), and intracranial extension (III) was considered a contraindication for an endoscopic approach by many surgeons. Over the past decades, in numerous published studies, tumors at stage IIB-IIIB were treated endoscopically (Table 3). Jorissen et al[30] concluded that the endoscopic technique is a good alternative to open surgery for small- to medium-sized tumors (I-IIB) and also considered an expansion to stage IIC. A retrospective study by Roger et al in which 20 patients were exclusively treated by endoscopic surgery showed successful endoscopic treatment of small to medium-sized tumors (I-IIB). They consider the endoscopic approach as the preferred technique for these tumors. They also state that IIC-IIIA tumors can be treated endoscopically.[31] Similar results were published by Önerci et al.[32] Although there was a successful endoscopic treatment of 3 tumors with extension into the infratemporal fossa and 1 tumor with extension lateral into the cavernous sinus (IIIB), Nicolai et al concluded that only patients with very limited expansion in the infratemporal fossa, orbital or extradural parasellar region (limited Andrews stage IIIA-IIIB tumors) may be safely treated endoscopically.[33] Ardehali et al[34] consider the endoscopic resection as a safe, effective technique for the treatment of tumors of stage I-IIIA. Huang et al[35] state that the endoscopic approach was successful for IIB tumors and some IIC-IIIB tumors. Langdon et al[36] noted good long-term results in a large multicentre retrospective study in which 74 patients with tumors stage IIIA-IIIB were endoscopically treated. In our study, 13 patients were treated for more advanced tumor stages (IIC-IIIB).

Limits

For several years, surgeons wonder about the limits of endoscopic sinus surgery for the JA. So far, there is no clear consensus, but larger studies gradually appear reporting on successful treatment of the JA with extension into the infratemporal fossa (IIC) and with intracranial extension (III). Our study shows that advanced tumors are no contraindication for endoscopic surgery. Several arguments can be pushed forward. Firstly, a JA is usually located extradural without invasion of the brain parenchyma. Tumor growth near the skull base is mostly expansion, with possible pressure erosion on the surrounding bone and less-frequent real tumor invasion, so the tumor can be "easily" dissected from the surrounding structures.[32,34] In addition, endoscopy offers the possibility to inspect the area thoroughly after the resection of the JA.[37] Additional curettage or drilling at places where the tumor seems adherent prevents leaving residual tumor tissue behind. In contrast with this minimally invasive technique, extensive open surgery is associated with significant morbidity which is hard to defend when treating a benign tumor that occurs in young patients. The possibility of stabilization or spontaneous involution of residual tumor tissue makes the endoscopic technique for the treatment of the JA, even for stages IIC-IIIB, a worthy alternative to open surgical treatment. Obviously, expertise is important as there is a significant learning curve associated with endoscopic sinus surgery in general and endoscopic treatment of a JA in particular. Cases with extensive tumor growth best end up in the hands of an experienced surgeon. Preoperative embolization is very important to have a good overview during surgery. The patient must always be informed about the possibility of conversion to an open technique in case of peroperative unfavorable conditions. Figure 4 shows the preoperative MRI of a patient with a JA Radkowski stage IIIB. We were able to completely resect the tumor via endoscopic approach. Postoperative MRI showed no evidence of residual tumor.

We encounter the limits of both open surgical techniques and endoscopic approaches in case of extensive intracranial extension into the middle cranial fossa, extension into the lateral of the cavernous sinus, and around the internal carotid artery and optic

Table 3 Overview of Studies with ESS for JA

Author(s), year	Number of Cases	Stage	FU (months)	Recurrence	Recurrence (%)
Schick et al (1999)[40]	5	*Andrews*	19 (5-39)	No recurrence	0
		5 × II			
Jorissen et al (2000)[30]	13	*Radkowski*	35.3 (12-72)	1 × IIC after 6months, ESS: NED (32)	15.40
		2 × IA		1 × IIIA after 4months, ICA embolization: regression (48 months)	
		2 × IB			
		2 × IIA			
		2 × IIB			
		4 × IIC			
		1 × IIIA			
Roger et al (2002)[31]	20	*Radkowski*	22	1 × IIC: SD (30 months)	10
		2 × IA		1 × IIIA: SD (36 months)	
		2 × IB			
		5 × IIA			
		1 × IIB			
		1 × IIC			
		9 × IIIA			
Önerci et al (2003)[32]	12	*Radkowski*	At least 6	1 × IIIA SD (18 months)	16.70
		8 × IIC		1 × IIIA SD (36 months)	
		4 × IIIA			
Nicolai et al (2003)[33]	15	*Andrews*	51.2 (24-96)	1 × I after 24 months: AWD (66 months)	6.70
		2 × I			
		9 × II			
		3 × IIIA			
		1 × IIIB			
Wormald et al (2003)[41]	7	*Radkowski*	45	No recurrence	0
		1 × I			
		2 × IIA			
		3 × IIB			
		1 × IIC			
Munoz del Castillo et al (2004)[42]	11	*Fisch*	48	2 × II, ESS	36.30
		1 × I		2 × III, ESS, of which later one secondary recurrence, midfacial degloving	
		8 × II			
		2 × III			
Hofmann et al (2006)[20]	21	*Fisch*	51.7 (5-120)	1 × II: FOS (61 months)	57.10
		1 × I		1 × IIIA: FOS (38 months)	
		15 × II		1 × II : FOS (120 months)	
		5 × IIIA		1 × II after 23 months, ESS: NED (109 months)	
				1 × IIIA after 14 months, gamma knife radiosurgery	

(*Continued*)

Table 3 Overview of Studies with ESS for JA (*Continued*)

Author(s), year	Number of Cases	Stage	FU (months)	Recurrence	Recurrence (%)
				1 × II after 6 months, 3 × ESS: NED (36 months)	
Sciaretta et al (2006)[43]	9	*Radkowski*	23 (6-75)	1 × IIA after 20 months, ESS: NED (30 months)	11.10
		1 × IA			
		4 × IIA			
		1 × IIB			
		2 × IIC			
		1 × IIIA			
Tosun et al (2006)[15]	9	*Radkowski*	20.6 (12-56)	No recurrence	0
		2 × IA			
		2 × IB			
		3 × IIA			
		2 × IIIA			
Borghei et al (2006)[44]	25	*Radkowski*	33 (13-57)	1 × IIB after 19 months, ESS: NED (28 months)	4
		5 × IA			
		9 × IB			
		4 × IIA			
		5 × IIB			
Eloy et al (2007)[45]	6	*Radkowski*	67	1 × IB, ESS after 36 months: NED (39 months)	33.30
		1 × IA		1 × IIB: regression (48 months)	
		1 × IB			
		4 × IIB			
Andrade et al (2007)[46]	12	*Andrews*	24 (12-60)	No recurrence	0
		8 × I			
		4 × II			
Gupta et al (2008)[47]	28	*Radkowski*	At least 12 (12-65)	1 × IIC, open surgery	3.60
		6 × I			
		14 × IIA			
		6 × IIB			
		2 × IIC			
Midilli et al (2009)[48]	12	*Andrews*	92 (12-251)	No recurrence	0
		2 × IB			
		6 × IIA			
		1 × IIB			
		2 × IIIC			
		1 × IIIA			
Hackmann et al (2009)[49]	15	nd	48 (12-120)	1 recurrence	6.70
Bleier et al (2009)[50]	10	*Andrews*	24.4 (3.6-88.4)	No recurrence	0
		1 × I			
		8 × II			
		1 × IIIA			

(*Continued*)

Table 3 Overview of Studies with ESS for JA (*Continued*)

Author(s), year	Number of Cases	Stage	FU (months)	Recurrence	Recurrence (%)
Ardehali et al (2010)[34]	47	*Radkowski*	33.1 (3-74)	1 × IA	19.10
		21 × IA-IIB		1 × IB	
		22 × IIC		2 × IIA	
		3 × IIIA		3 × IIC	
		1 × IIIB		2 × IIIA	
Frympas et al (2012)[51]	10	*Radkowski*	23.7 (3-70)	1 × IIB after 9 months, ESS: NED (25 months)	10
		1 × IA			
		2 × IB			
		1 × IIA			
		2 × IIB			
		2 × IIC			
		2 × IIIA			
Huang et al (2014)[35]	66	*Radkowski*	55 (6-182)	1 × IB	28.30
		4 × IA		4 × IIB	
		5 × IB		3 × IIC	
		6 × IIA		2 × IIIA	
		11 × IIB		7 × IIIB	
		24 × IIC		6/66 patients with no data	
		6 × IIIA			
		10 × IIIB			
Langdon et al (2015)[36]	74	*Radkowski*	37.9 (2-196)	1× radiotherapy, 1× surgery, 16× conservative: SD (35.6 months)	33.30
		56 × IIIA		20/74 patients with no data	
		18 × IIIB			

JA, juvenile angiofibromas; ESS, endoscopic sinus surgery; NED, no evidence of disease; SD, stable disease; ICA, internal carotid artery; AWD, alive with disease; FOS, free of symptoms.

nerve. Besides surgery, radiotherapy is also found to be effective in the treatment of JA.[38] Given the significant side effects of radiotherapy and the adverse long-term effects, radiotherapy is only considered in very sophisticated cases where surgery is contraindicated. A possible role of angiogenesis inhibitors is more recently pushed forward as a treatment option in difficult or

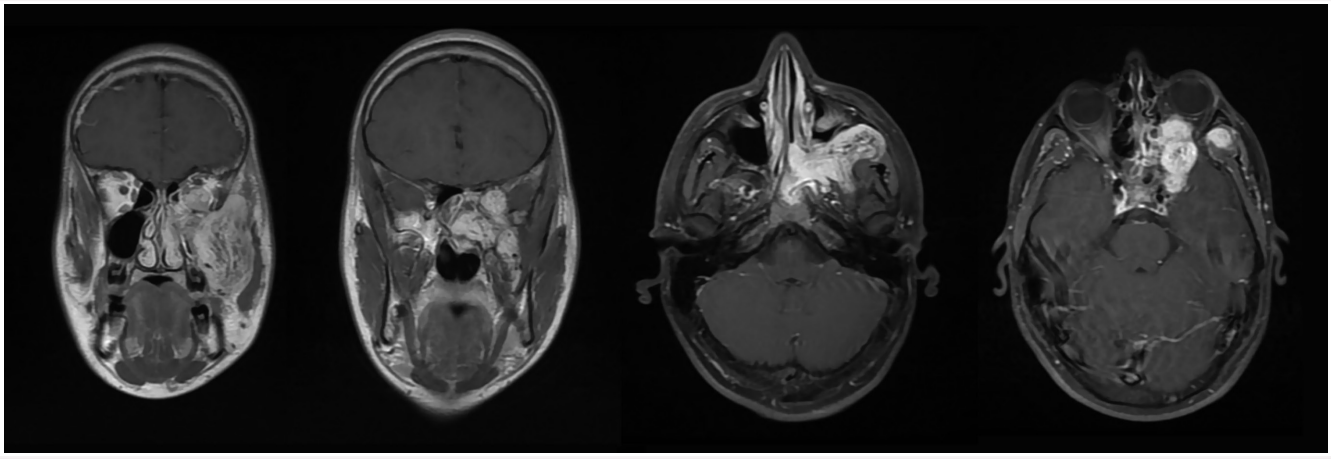

Figure 4. Preoperative magnetic resonance imaging (T1+contrast) of a patient with an advanced stage juvenile angiofibroma. Extension into infratemporal fossa, masticator space, inferior orbital fissure, orbit, and near the optic nerve.

challenging surgical cases. Angiogenic growth factors, such as vascular endothelial growth factor, play a role in the pathogenesis of the JA.[19,39] Currently, it concerns experimental treatments in literature, which may yield promising results in the future when dealing with inoperable JA.

CONCLUSION

The results of this study indicate an average recurrence rate of 12.8% after endoscopic surgery for a JA. These results are consistent with the results of similar studies. Based on these findings, we conclude that endoscopic sinus surgery is the preferred technique for the treatment of small to medium-sized tumors (I-IIB) and is a worthy alternative to open surgery – in the hands of an experienced surgeon – for advanced tumor stages (IIC-IIIB).

Ethics Committee Approval: This study was approved by the ethics advisory board of Biomedical Sciences of the K.U. Leuven.

Informed Consent: Patient consent was waived. Anonymity and confidentiality of patients were guaranteed.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – L.P., L.V.G., M.J.; Design – L.P., L.V.G., M.J.; Supervision – L.V.G., M.J.; Materials – L.P., M.J.; Data Collection and/or Processing – L.P., L.V.G., M.J.; Analysis and/or Interpretation – L.P., L.V.G., M.J.; Literature Review – L.P., M.J.; Writing - L.P.; Critical Review – L.V.G., M.J.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

REFERENCES

1. Lund VJ, Stammberger H, Nicolai P, et al. European position paper on endoscopic management of tumours of the nose, paranasal sinuses and skull base. *Rhinol Suppl*. 2010;22:1-143.
2. Glad H, Vainer B, Buchwald C, et al. Juvenile nasopharyngeal angiofibromas in Denmark 1981-2003: diagnosis, incidence, and treatment. *Acta Otolaryngol*. 2007;127(3):292-299. [CrossRef]
3. Neel HB III, Whicker JH, Devine KD, Weiland LH. Juvenile angiofibroma: review of 120 cases. *Am J Surg*. 1973;126(4):547-556. [CrossRef]
4. Lloyd G, Howard D, Phelps P, Cheesman A. Juvenile angiofibroma: the lessons of 20 years of modern imaging. *J Laryngol Otol*. 1999;113(2):127-134. [CrossRef]
5. Mills S, Gaffey M, Frierson Jr H. *Tumours of the Upper Aerodigestive Tract and Ear*. Washington, DC: Armed Forces Institute of Pathology under the Auspices of Universities Associated for Research and Education in Pathology, 2000.
6. Beham A, Beham-Schmid C, Regauer S, Auböck L, Stammberger H. Nasopharyngeal angiofibroma: true neoplasm or vascular malformation? *Adv Anat Pathol*. 2000;7(1):36-46. [CrossRef]
7. Schick B, Plinkert PK, Prescher A. Aetiology of angiofibromas: reflection on their specific vascular component. *Laryngorhinootologie*. 2002;81(4):280-284. [CrossRef]
8. Sessions RB, Bryan RN, Naclerio RM, Alford BR. Radiographic staging of juvenile angiofibroma. *Head Neck Surg*. 1981;3(4):279-283. [CrossRef]
9. Fisch U. The infratemporal fossa approach for nasopharyngeal tumours. *Laryngoscope*. 1983;93(1):36-44. [CrossRef]
10. Chandler JR, Goulding R, Moskowitz L, Quencer RM. Nasopharyngeal angiofibromas: staging and management. *Ann Otol Rhinol Laryngol*. 1984;93(4 Pt 1):322-329. [CrossRef]
11. Andrews JC, Fisch U, Valavanis A, Aeppli U, Makek MS. The surgical management of extensive nasopharyngeal angiofibromas with the infra-temporal fossa approach. *Laryngoscope*. 1989;99(4):429-437. [CrossRef]
12. Radkowski D, McGill T, Healy GB, Ohlms L, Jones DT. Angiofibroma. Changes in staging and treatment. *Arch Otolaryngol Head Neck Surg*. 1996;122(2):122-129. [CrossRef]
13. Onerci M, Oğretmenoğlu O, Yücel T. Juvenile nasopharyngeal angiofibroma: a revised staging system. *Rhinology*. 2006;44(1):39-45.
14. Snyderman CH, Pant H, Carrau RL, Gardner P. A new endoscopic staging system for angiofibromas. *Arch Otolaryngol Head Neck Surg*. 2010;136(6):588-594. [CrossRef].
15. Tosun F, Ozer C, Gerek M, Yetiser S. Surgical approaches for nasopharyngeal angiofibroma: comparative analysis and current trends. *J Craniofac Surg*. 2006;17(1):15-20. [CrossRef]
16. 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(4):859-869. [CrossRef]
17. Jorissen M. The role of endoscopy in the management of paranasal sinus tumours. *Acta Otorhinolaryngol Belg*. 1995;49(3):225-228.
18. Kamel RH. Transnasal endoscopic surgery in juvenile nasoparhyngeal angiofibroma. *J Laryngol Otol*. 1996;110(10):962-968. [CrossRef]
19. Renkonen S, Hagström J, Vuola J, et al. The changing surgical management of juvenile nasopharyngeal angiofibroma. *Eur Arch Otorhinolaryngol*. 2011;268(4):599-607. [CrossRef]
20. Hofmann T, Bernal-Sprekelsen M, Koele W, Reittner P, Klein E, Stammberger H. Endoscopic resection of juvenile angiofibromas – long-term results. *Rhinology*. 2005;43(4):282-289.
21. Khoueir N, Nicolas N, Rohayem Z, Haddad A, Abou Hamad WA. Exclusive endoscopic resection of juvenile nasopharyngeal angiofibroma: a systematic review of the literature. *Otolaryngol Head Neck Surg*. 2014;150(3):350-358. [CrossRef]
22. Herman P, Lot G, Chapot R, Salvan D, Huy PT. Long-term follow-up of juvenile nasopharyngeal angiofibromas: analysis of recurrences. *Laryngoscope*. 1999;109(1):140-147. [CrossRef]
23. Gruber A, Bavinzski G, Killer M, Richling B. Preoperative embolization of hypervascular skull base tumours. *Minim Invasive Neurosurg*. 2000;43(2):62-71. [CrossRef]
24. De Vincentiis M, Gallo A, Minni A, Torri E, Tomassi R, Della Rocca C. Preoperative embolisation in the treatment protocol for rhinopharyngeal angiofibroma: comparison of the effectiveness of various materials. *Acta otorhinolaryngol ital*. 1997;17(3):225-232.
25. McCombe A, Lund VJ, Howard DJ. Recurrence in juvenile angiofibroma. *Rhinology*. 1990;28(2):97-102.
26. Tyagi I, Syal R, Goyal A. Recurrent and residual juvenile angiofibromas. *J Laryngol Otol*. 2007;121(5):460-467. [CrossRef]
27. 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(2):238-239. [CrossRef]
28. 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(11):1191-1193. [CrossRef]
29. Stansbie JM, Phelps PD. Involution of residual juvenile nasopharyngeal angiofibroma (a case report). *J Laryngol Otol*. 1986;100(5):599-603. [CrossRef]
30. Jorissen M, Eloy PH, Rombaux PH, Bachert CL, Daele J. Endoscopic sinus surgery for juvenile nasopharyngeal angiofibroma. *Acta Otorhinolaryngol Belg*. 2019;54(2):201-219.
31. 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(8):928-935. [CrossRef]

32. Önerci TM, Yücel OT, Ögretmenoglu O. Endoscopic surgery in treatment of juvenile nasopharyngeal angiofibroma. *Int J Pediatr Otorhinolaryngol*. 2003;67(11):1219-1225. [CrossRef]
33. Nicolai P, Berlucchi M, Tomenzoli D, et al. Endoscopic surgery for juvenile angiofibroma: when and how. *Laryngoscope*. 2003;113:775-782.
34. Ardehali MM, Samimi Ardestani SH, Yazdani N, Goodarzi H, Bastaninejad S. Endoscopic approach for excision of juvenile nasopharyngeal angiofibroma: complications and outcomes. *Am J Otolaryngol*. 2010;31(5):343-349. [CrossRef]
35. Huang Y, Liu Z, Wang J, Sun X, Yang L, Wang D. Surgical management of juvenile nasoparhyngeal angiofibroma: analysis of 162 cases from 1995 to 2012. *Laryngoscope*. 2014;124(8):1942-1946. [CrossRef]
36. Langdon C, Herman P, Verillaud B, et al. Expanded endoscopic endonasal surgery for advanced stage juvenile angiofibromas: a retrospective multi-center study. *Rhinology*. 2016;54(3):239-246. [CrossRef]
37. Carrau RL, Snyderman CH, Kassam AB, Jungreis CA. Endoscopic and endoscopic-assisted surgery for juvenile angiofibroma. *Laryngoscope*. 2001;111(3):483-487. [CrossRef]
38. Cummings BJ, Blend R, Keane T, et al. Primary radiation treatment for juvenile nasopharyngeal angiofibroma. *Laryngoscope*. 1984;94(12 Pt 1):1599-1605.
39. Brieger J, Wierzbicka M, Sokolov M, Roth Y, Szyfter W, Mann WJ. Vessel density, proliferation, and immunolocalization of vascular endothelial growth factor in juvenile nasopharyngeal angiofibromas. *Arch Otolaryngol Head Neck Surg*. 2004;130(6):727-731. [CrossRef]
40. Schick B, El Rahman El Tahan A, Brors D, Kahle G, Draf W. Experiences with endonasal surgery in angiofibroma. *Rhinology*. 1999;37(2):80-85.
41. Wormald PJ, Van Hasselt A. Endoscopic removal of juvenile angiofibromas. *Otolaryngol Head Neck Surg*. 2003;129(6):684-691. [CrossRef]
42. Jurado RA, Bravo-Rodriguez F, Delgado AF, Lopez VP. *Endoscopic surgery of nasopharyngeal angiofibroma*. *Acta Otorinolaringol Esp*. 2004;55(8):369-375.
43. Sciarretta V, Pasquini E, Farneti G, Frank G, Mazzatenta D, Calbucci F. Endoscpic sinus surgery for the treatment of vascular tumours. *Am J Rhinol*. 2006;20(4):426-431. [CrossRef]
44. Borghei P, Baradaranfar MH, Borghei SH, Sokhandon F. Transnasal endoscopic resection of juvenile nasopharyngeal angiofibroma without preoperatieve embolization. *Ear Nose Throat J*. 2006;85(11):740-746. [CrossRef]
45. Eloy P, Watelet JB, Hatert AS, de Wispelaere J, Bertrand B. Endonasal endoscopic resection of juvenile nasopharyngeal angiofibroma. *Rhinology*. 2007;45(1):24-30.
46. Andrade NA, Pinto JA, Nóbrega Mde O, Aguiar JE, Aguiar TF, Vinhaes ES. Exclusively endoscopic surgery for juvenile nasopharyngeal angiofibroma. *Otolaryngol Head Neck Surg*. 2007;137(3):492-496. [CrossRef]
47. Gupta AK, Rajiniganth MG, Gupta AK. Endoscopic approach to juvenile nasopharyngeal angiofibroma: our experience at a tertiary care center. *J Laryngol Otol*. 2008;122(11):1185-1189. [CrossRef]
48. 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(3):401-408. [CrossRef]
49. Hackman T, Snyderman CH, Carrau R, Vescan A, Kassam A. Juvenile nasopharyngeal angiofibroma: the expanded endonasal approach. *Am J Rhinol Allergy*. 2009;23(1):95-99. [CrossRef]
50. Bleier BS, Kennedy DW, Palmer JN, Chiu AG, Bloom JD, O'Malley BW. Current management of juvenile nasopharyngeal angiofibroma: a tertiary center experience 1999-2007. *Am J Rhinol Allergy*. 2009;23(3):328-330. [CrossRef]
51. Fyrmpas G, Konstantinidis I, Constantinidis J. Endoscopic treatment of juvenile nasopharyngeal angiofibromas: our experience and review of the literature. *Eur Arch Otorhinolaryngol*. 2012;269(2):523-529. [CrossRef]