Management and Outcome in Patients with Advanced Juvenile Nasopharyngeal Angiofibroma

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Abstract

Objective To report the management outcome in a series of patients with advanced juvenile nasopharyngeal angiofibroma (JNA).

Design Retrospective study.

Setting Tertiary care teaching hospital.

Participants Forty-five patients classified as Radkowski stage IIIA or IIIB who presented to us over the past 10 years.

Main Outcome Measures Surgical approaches used and disease free outcomes in patients with advanced JNA.

Results Surgical access for the extracranial component included open (41.9%) and expanded endonasal approaches (58.1%). Craniotomy (16.3%), endoscopy-assisted open approach (7%), or expanded endonasal approach (20.9%) was performed to excise the skull base or intracranial component. Follow up ranged from 4 to 96 months (mean, 20.3 months). Of 35 patients who underwent imaging at the first postoperative follow up, 25 (71.4%) had negative scans. Three symptomatic patients with residual disease underwent endoscopic excision and had negative scans thereafter. Of two others who had radiation therapy, one was disease free and the other lost to follow up. Five others had stable, residual disease. Three patients (8.6%) with recurrent disease underwent surgical excision, of whom two had minimal, stable residual disease. At the last follow-up, 27 (77.1%) patients had negative scans, and 7 (20%) had stable residual disease with one (2.9%) patient lost to follow-up.

Conclusions Advanced JNA may be successfully treated in most cases with expanded endonasal/endoscopy assisted $\pm$ craniotomy approach after appropriate preoperative evaluation. At follow-up, only symptomatic patients or those with enlarging residue require treatment; periodic imaging surveillance is adequate for those with stable disease.

Keywords

- angiofibroma
- management
- endoscopy
- nasopharynx

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Introduction

Juvenile nasopharyngeal angiofibroma (JNA) is a benign, but locally invasive tumor causing massive epistaxis and nasal obstruction. It originates from the sphenopalatine foramen, Vidian canal, clivus, and/or basisphenoid. Intracranial extension occurs to the middle or anterior cranial fossa and, rarely, to the posterior fossa. In a nationwide study in Denmark, advanced stage tumors accounted for 43% of all JNAs.¹ Higher prevalence rates of 66%² and 74%³ in some case series suggest that prevalence of advanced tumors is dependent upon referral patterns.

At least six different classifications for JNA are currently available in the literature. These include those of Sessions et al,⁴ Chandler et al,⁵ Radkowski et al,⁶ Andrews et al,⁷ Onerci et al,⁸ and University of Pittsburgh Medical Center (UPMC).³ The Radkowski classification, although very popular, does not specify the exact sites and degree of skull base involvement in advanced stage tumors. Identification of the exact skull base sites involved by imaging and classifying tumors accordingly may assist in addressing those sites specifically at surgery, thus reducing the risk of residual tumor.

The surgical management of patients with JNA with intracranial extension is particularly challenging because the extent and vascularity of the tumor can make access and complete excision a difficult proposition. Excision of the extracranial component of the tumor has been traditionally performed using a variety of approaches. These include open approaches, which have visible external incisions, such as lateral rhinotomy, or infratemporal fossa approaches or approaches involving mucosal incisions, such as transpalatal, sublabial, or midfacial degloving incisions.^{9–11} With the advent of endoscopic techniques for tumor removal, these methods are less favored.^{12,13} Removal of the intracranial component of tumors has been either by craniotomy,^{14,15} through the same external incision for removal of the extracranial component,¹¹ or through an expanded endonasal approach.¹⁶

To study the outcome of our management of advanced stage JNA using different approaches, we analyzed the data from all such patients treated by us over the past 10 years.

Material and Methods

We retrospectively reviewed the data of all patients who presented to us over the past 10 years and were classified as Radkowski stage IIIA or IIIB. Age, presenting symptoms, radiological findings, tumor size, laterality, angiogram findings, results of embolization, surgical approach and findings, estimated blood loss, intraoperative and postoperative complications, non-surgical treatment, and residual/ recurrent tumor were noted. Routine postoperative imaging using contrast-enhanced magnetic resonance imaging (MRI) or computed tomography (CT) was performed at 3 months after the initial surgery. Annual or biannual follow-up evaluation was performed using endoscopic examination and imaging.

Definitions

Residual disease was defined as any well-defined enhancing residue noted on the 3-month postoperative follow-up imaging. Recurrent disease was defined as any enhancing tumor seen at the second or later follow-up in a patient in whom the 3-month follow-up imaging revealed no obvious residue. Stable disease was defined as residue or recurrent tumor, which was not evident on rigid nasal endoscopy and which showed no increase in size on serial imaging performed at least 6 months apart in an asymptomatic patient.

Institutional review board and ethics committee approval was obtained for the performance of this study.

Results

Of a total of 56 patients with JNA seen over the past 10 years, 45 (80.4%) patients were diagnosed with Radkowski stage III A or IIIB tumors. The patients' ages ranged from 8 to 36 years with a mean of 16.3 years. Tumor size ranged from 3 to 10.8 cm with a mean length of 5.6 cm in the maximum dimension. Forty-three (95.6%) of the 45 patients went on to have surgery.

Clinical Presentation

Profuse epistaxis was the primary symptom in all except five patients in whom nasal block was the predominant symptom. One patient had total loss of vision of the right eye over a period of 4 months, while another had deterioration of vision in the left eye over a period of 2 months with only perception of light at presentation. The mean duration of symptoms ranged from 1 month to 1 year (mean 7.6 months).

Prior Surgery

Nine patients had undergone definitive prior surgery elsewhere with persistent symptoms postoperatively. Four others had undergone biopsies of their tumors.

Angiography and Embolization

Diagnostic angiography was performed in 41 of the 45 patients studied. In 24 (58.5%) patients, the ipsilateral internal maxillary artery was the primary supply, while in 17 (41.5%) patients, bilateral internal maxillary arteries were the primary supply. Accessory vessel supply, which was seen in 26 (63.4%) patients, was chiefly by branches of the ipsilateral internal carotid artery. One patient (previously reported¹⁷) was found to have a carotidocavernous fistula following surgery performed elsewhere.

Embolization was performed in 32 (78.5%) patients with gelatin sponge particles and in 5 patients with polyvinyl alcohol particles. Coils were additionally used in six patients. Except for two patients, all had <20% residual vascularity, and no patient developed any complication from angiography or embolization.

Surgery (–Table 1)

In 18 cases operated >5 years ago, open approaches like lateral rhinotomy and transpalatal incisions were made for better exposure. In all 25 patients operated over the past 5 years,

endoscopic excision with or without added sublabial incisions (expanded endonasal approach as described by Hackmann et al¹⁶) was the preferred approach. The extracranial component of the tumor was excised by open approaches in 18 (41.9%) patients and an expanded endonasal approach with/without sublabial incisions in 25 (58.1%) patients. The intracranial component of the tumor was removed by an expanded endonasal approach alone in nine (20.9%) patients and an endoscopy assisted open approach in another three (6.9%) patients. Seven (16.3%) patients underwent craniotomy to either remove the intracranial component of the tumor or to provide access to the deep skull base sites adjacent to middle fossa dura. Either a fronto-temporo-orbitozygomatic (FTOZ) craniotomy or frontotemporal craniotomy was performed in these seven patients. In one patient with extensive intracranial tumor, surgery was abandoned because of excessive bleeding. Operative time ranged from 6.5 to 8 hours.

Intraoperative blood loss ranged from 0.5 to 2 L with only 14 (32.6%) patients requiring blood transfusion. All patients who underwent craniotomy were monitored in the neurosurgical intensive care unit for 24 hours postoperatively.

Intracranial Extension

In three patients with stage IIIB lesions, the intracranial extension was entirely extradural. In three patients with stage IIIB lesions, intradural extension was present, necessitating the opening of the dura to excise the tumor in the one patient who underwent craniotomy for tumor excision (►Table 1).

Complications

There was no postoperative neurological deficit in any of the patients. One patient developed a consumptive coagulopathy intraoperatively soon after tumor removal and was appropriately treated with transfusions. One patient who had undergone an external lateral rhinotomy incision developed scarring of the nasal vestibule and stenosis for which he subsequently underwent plastic surgery. No other complications were encountered, and there was no mortality.

Adjuvant Radiation Therapy

Two patients received postoperative radiation therapy because of extensive residual disease. One was a 15-year-old boy who had undergone lateral rhinotomy and craniotomy for excision of a stage IIIA tumor 2 years earlier. He defaulted on follow-up and presented with massive intracranial, intradural recurrence (►Fig. 1). He received external radiation therapy at a dose of

54 Gy, to which he responded well. He had a disease-free follow-up of 4 years after radiotherapy. The other patient underwent radiation therapy elsewhere and did not report for follow-up.

Follow-Up

Follow-up in 40 of 43 patients who underwent surgery, ranged from 4 to 96 months (mean of 20.3 months) (►Fig. 2). All patients underwent rigid nasal endoscopic examination at each follow-up. Thirty-five patients underwent postoperative scanning by contrast-enhanced CT (22 patients) or MRI (9 patients) scanning or both (4 patients) at the first follow-up. Of the 22 patients who initially underwent CT scanning, 11 also had a contrast-enhanced MRI scan at a later date. The imaging results showed one of three outcomes:

No Residual Disease at the Initial Follow-Up

Twenty-five (71.4%) patients had negative scans at the first follow-up (►Fig. 3). Included in this group were five patients who had ill-defined, mildly enhancing or non-enhancing areas in the region of cavernous sinus, pterygopalatine fossa, sphenopalatine foramen, and greater wing of sphenoid, which were asymptomatic and not evident on rigid nasal endoscopy. In these patients, no new symptoms developed, rigid nasal endoscopy showed no evidence of disease, and the enhancement in the tumor bed usually disappeared on the subsequent scans (►Fig. 4)

Residual Disease at the Initial Follow-Up

Ten (28.6%) patients showed varying degrees of residual lesions at different sites following what appeared to be complete excision as judged at surgery (►Table 2). Of these, three patients who had epistaxis underwent endoscopic excision of residual tumor. These patients had no residual or recurrent disease thereafter. In five other asymptomatic patients with enhancing areas near the basisphenoid, cavernous sinus, root of pterygoid, greater wing of sphenoid, and pterygopalatine fossa, there was no enlargement of the lesion over the next 3 years, and they were considered to have stable disease (►Fig. 5). The commonest sites for residual disease were the pterygopalatine fossa, root of pterygoid, basisphenoid, and adjacent cavernous sinus (►Table 2).

Recurrent Disease at Later Follow-Up

Three patients developed a recurrence 2 years and 5 years after primary endoscopic excision of the tumor (►Fig. 6). Repeated scans in the first 2 years and 4 years after the initial

Table 1 Surgical approaches for excision of extracranial and intracranial components of tumor ($n = 43$)

Approaches for excision of extracranial component	Number	Approaches for excision of intracranial component	Number
Expanded endonasal approach with/ without sublabial incision	25	Fronto-temporo-orbitozygomatic craniotomy	3
Lateral rhinotomy approach	16	Frontotemporal craniotomy	4
Transpalatal approach	4	Expanded endonasal approach	9
Midfacial degloving approach	3	Endoscopy assisted open approach	3

Fig. 1 Extensive Stage IIIB JNA, which showed complete resolution following conventional external beam radiation therapy. (A and B) Contrast-enhanced coronal and axial MR scans before the therapy. (C and D) Contrast-enhanced coronal and axial CT scans following therapy. CT, computed tomography; MR, magnetic resonance.

surgery were negative. The three patients who developed recurrence were aged 13 years (two patients) and 14 years (one patient) at the time of first surgery, respectively. They were aged 15 years (two patients) and 19 years (one patient), respectively, at the time of recurrence. The recurrence was excised endoscopically. The overall rate of recurrent disease was 8.6%. Two of the three patients had minimal, asymptomatic, residual disease after repeat surgery for recurrence.

In summary, of a total of 45 patients with stage IIIA or IIIB tumors, 43 underwent surgery (►Fig. 1). Of these only 40 returned for follow-up. Of these 40 patients, 5 patients underwent rigid nasal endoscopy alone and appeared to be disease free. As they did not undergo any imaging at follow-up, they were excluded from the analysis. Of the 35 patients who underwent imaging, 25 had negative scans. Ten patients had residual tumor, of whom five were symptomatic. Of

Fig. 2 Flow chart for follow-up of patients. FU, follow up; LFU, lost to follow-up.

Fig. 3 Preoperative (A) and 3-month postoperative (B) gadolinium-enhanced coronal MR images of a patient with stage III tumor with no residual disease following excision via expanded endonasal approach. MR, magnetic resonance.

Fig. 4 (A and B) Spontaneously resolving residual enhancement in left pterygopalatine fossa (arrows). (A) Contrast CT done 3 months after surgery; (B) contrast CT done 6 months after surgery. CT, computed tomography.

these, three underwent endoscopic excision of small residue and were found to have negative scans on subsequent imaging. Two patients with extensive residual disease went on to have radiation therapy soon after surgery. Of these, one patient had a negative scan at the last follow-up, and one was lost to follow-up. Five patients with residue

Table 2 Sites of residual disease at first follow-up after complete surgical excision ($n = 10$)

Sites of recurrence	No. of patients ^a
Pterygopalatine fossa	4
Basisphenoid	5
Root of pterygoid	5
Pterygoid plates	4
Vidian canal	2
Greater wing of sphenoid	1
Cavernous sinus	4

^aEight patients had more than one site of residual tumor.

were found to have stable disease and are on regular follow-up. Three patients who were initially disease free were found to have recurrent disease. These patients were from the group that had negative scans at the first follow-up. All three underwent surgery, and two had asymptomatic stable disease (with minimal residue) after surgery and are on follow-up, while one is currently disease free with a negative scan.

At the last follow up, 27 (77.1%) patients were disease free, and 7 (20%) patients had stable, asymptomatic, residual disease. One (2.9%) patient who underwent radiation therapy for residual tumor was lost to follow-up.

Discussion

Preoperative Imaging

The first step in the management of JNA with intracranial extension is evaluation of the extent and size of the tumor with imaging using both contrast-enhanced CT and MRI scanning. The need for both modalities is best appreciated in advanced tumors where knowledge of bone erosion/expansion or widening of a foramen in the skull base or proximity to the

Fig. 5 (A and B) Gadolinium enhanced axial MR images showing stable residual disease (arrow) in the left pterygopalatine fossa at 3 months after surgery (A) and 2 years later (B). MR, magnetic resonance.

dura or cavernous sinus is essential for staging and planning the surgical approach. Radiological evidence of bone invasion must also be sought preoperatively as those sites should be drilled out with a high-speed drill at surgery in a thorough manner to prevent residual and recurrent disease.^{10,13}

More recently, emphasis has been placed on preoperative evaluation of the vascularity of the tumor by angiography as supply from the internal carotid artery (which is not usually embolized) can be considerable. In our series, up to 40% of patients with intracranial extension had internal carotid artery supply either from direct branches or through ophthalmic and Vidian branches. Previous studies have shown similar findings.^{3,17,18}

Staging of Tumors

The Radkowski staging system⁶ is one of the most widely used. As this classification was proposed in the pre-endoscopic era, one major limitation is that there is insufficient detail regarding

the various skull base sites involved from stage III A onward. This has resulted in authors interpreting “skull base erosion” in different ways. In the case of Radkowski stage IIIA tumors, while some authors have excluded tumors involving pterygoid plates and anterior wall of sphenoid from this stage,¹⁶ others have included involvement of base of pterygoids, foramen rotundum, and foramen ovale in this stage.² The Onerci⁸ staging system which was developed in the endoscopic era appears to address involvement of specific skull base sites while the UPMC³ staging system addresses the issue of residual vascularity, which occurs following embolization and is related to a larger internal carotid artery supply in advanced tumors.

Reducing Intraoperative Blood Loss

Techniques to reduce bleeding during surgery include the use of hypotensive anesthesia and embolization of the tumor preoperatively. Several authors have extolled the benefits of embolization.^{3,18} However, some authors suggest that

Fig. 6 (A–D) Contrast-enhanced coronal CT images (A–C) in a patient with Stage IIIA tumor (A) with no evidence of disease at 1 year (B) and 4 years (C) after surgery. Note recurrence of tumor at left root of pterygoid after 5 years, seen in the gadolinium enhanced coronal MR image (D).

embolization could increase the likelihood of leaving behind residual tumor because the reduction in blood supply can make it difficult to differentiate tumor from normal tissue.¹⁹

Endoscopic Surgical Approach

A review of the literature on the application of endoscopic techniques for resecting JNA shows that the limits of resection have been progressively raised over time. One of the early reports on the use of a totally endoscopic approach for the treatment of JNA was by Kamel in 1996.²⁰ Hofmann et al²¹ suggested endoscopic removal of large tumors with extension to the orbit and infratemporal fossa. Using a totally endoscopic technique, Onerci et al¹³ operated on four cases with minimal intracranial extension and cavernous sinus involvement. The residual tumor rate was 50% for these four cases. Later, Hackmann et al¹⁶ introduced the expanded endonasal approach for treatment of tumors with varying degrees of intracranial extension without craniotomy. The approach was often combined with sublabial and midfacial degloving incisions. We have also found the expanded endonasal approach useful in the management of advanced JNA.

In most patients with stage IIIA and IIIB tumors, an endoscopic approach with or without craniotomy may be required for total tumor removal. Craniotomy provides better exposure when there is significant tumor extension to the middle cranial fossa and parasellar region lateral to the cavernous sinus. In the present series, this was performed in seven patients. In tumors with compression of the cavernous sinus inferomedially or those with minimal anterior or middle cranial fossa extension, the expanded endonasal approach as described by Hackmann et al¹⁶ may be sufficient. The use of image guidance is particularly important in these cases to prevent complications.

Endoscopic techniques are associated with fewer complications and shortened hospital stay. However, some reports of complications like cerebrospinal fluid (CSF) leak, enophthalmos,²² optic neuropathy,¹² trismus, and facial hypesthesia¹⁶ have been described. In the present series, the overall morbidity was low. One cause for development of complications is prolonged surgery. In the present series, the maximum duration of surgery was 8 hours. Some authors describe a mean duration of surgery of around 12 hours for a combined approach.¹⁴ Endoscopic approaches may take less time, but the duration of surgery is largely dependent on the experience of the surgeon.¹² Overall, the surgical options for management should be individualized, and the particular technique selected will depend upon the anatomical location as well as the level of expertise of the surgical team.

Residual Disease

One of the major problems of treating advanced JNA is the propensity for leaving behind residual tumor despite intraoperative appearance of total tumor excision, especially when the tumor is removed in one piece. The propensity of advanced stage JNA to recur has been noted by several authors, and residual tumor rates of 14%,³ 22%,⁶ 27.5%,² and 37.5%²³ have been reported. The terms "residual" and "recurrent" tumor have often been used interchangeably in the literature on JNA.

True recurrence should refer to tumor that has developed after at least 2 years of negative imaging. This was the case in three patients in our series. The differentiation of residual and recurrent tumor is difficult, and some authors believe that all recurrent tumors are residual tumors with slow growth. To add to the confusion, some authors² suggest that only symptomatic residual tumor be considered as residual tumor/recurrence.

One cause for residual tumor is the presence of significant invasion of the bony skull base, most often the basisphenoid, greater wing of sphenoid, Vidian canal, and the root of pterygoid.^{2,10,13} Additionally, involvement of the cavernous sinus and infratemporal fossa has been shown to be predictive of residual tumor.^{2,3,10} Other factors which have been shown to predispose to residual/recurrent disease include advanced stage,^{3,7,9,15} presence of internal carotid artery supply,^{1,18} early age at presentation,²⁴ and microscopic remnant in the Vidian canal.¹⁰

The treatment of residual disease is controversial. While some authors advocate resection,^{2,10,13} others recommend external radiation therapy.²⁵ Most authors believe that asymptomatic recurrent/residual disease may be left alone, and the patient may be followed up regularly with rigid nasal endoscopy and imaging.^{13,21,23} Long-term follow-up of at least seven of our patients with radiologically stable residual lesions showed that the patients were asymptomatic and had no lesion on rigid nasal endoscopy. As there is always a possibility of spontaneous involution of tumor and because some patients may have asymptomatic residual disease for years, a wait and watch policy is probably best for those with deep-seated, asymptomatic residual tumor.^{2,13}

Role of Radiotherapy

Radiation therapy plays a definite role in control of disease in those with extensive intracranial extension where the potential morbidity from surgery outweigh the benefits. Radiation therapy may be given as the sole modality of therapy,^{26,27} as part of combined modality treatment of advanced stage tumors²⁷ and as treatment for residual disease in deep-seated areas after extensive surgical resection.⁶ The tumor has been shown to regress over several months following the completion of radiotherapy resulting in a completely negative scan. This was seen in one of our patients (→Fig. 5). Radiotherapy may be administered as conventional radiation therapy,^{26,27} intensity modulated radiotherapy (IMRT)²⁵ or radiosurgery.²⁸ Alvarez et al²⁸ successfully treated 10 patients with advanced JNA with gamma knife radiosurgery, following primary surgical resection with no significant complications and good tumor control rate. The use of intensity modulated radiotherapy or radiosurgery appears to produce much less complications than conventional radiation therapy.^{25–28}

In conclusion, the treatment of patients with advanced stage JNA is primarily surgical with preoperative comprehensive multiplanar imaging as well as angiography with embolization. Internal carotid artery supply forms the main accessory supply and is responsible for residual vascularity following embolization. Postoperative follow-up with periodic contrast-enhanced imaging (ideally MR imaging), even in asymptomatic patients, is mandatory to detect residual or early recurrent disease.

Residual/recurrent tumor is largely at the basisphenoid, cavernous sinus, or root of pterygoid. Resection is not essential if the lesion is asymptomatic and not increasing in size on follow-up. Radiation therapy (as either IMRT or radiosurgery) is a useful option for those with extensive residual tumor.

Conflicts of Interest

None.

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