Juvenile Nasal Angiofibromas: A Comparison of Modern Staging Systems in an Endoscopic Era

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Abstract

Objectives To compare the clinical utility of four juvenile nasal angiofibroma (JNA) staging systems in a large cohort of patients.

Design Retrospective case series.

Setting Tertiary referral academic center.

Participants Pediatric patients undergoing surgical resection of JNAs between January 2008 and June 2015.

Main Outcome Measures Intraoperative blood loss and transfusions, number of staged operations, postoperative residual disease, and recurrent disease.

Results In total, 34 patients were identified; all underwent preoperative embolization followed by surgery. Of the 34 patients, 33 (97%) underwent an exclusively endoscopic surgical approach, with 6 (18%) requiring planned staged operations. Ten (29%) patients had residual disease and three (9%) required further surgical resection. Using the area under the curve (AUC) of receiver operating characteristic curves, the University of Pittsburgh Medical Center (UPMC) staging system was most predictive of patients who required staged procedures, received intraoperative transfusions, and had residual postoperative disease (AUC: 0.89, 0.88, 0.86, respectively).

Conclusions The UPMC JNA staging system accounts for both route of skull base extension and tumor vascularity, which are two important tumor attributes in the age of preoperative embolization and endoscopic endonasal surgery. The UPMC staging system is a reliable modern staging system that closely reflects prognostic information and aids in surgical planning.

Keywords

- angiofibroma
- endoscopy
- surgery
- standards
- prognosis
- retrospective study
- skull base pathologies

Introduction

With an increasing shift toward endoscopic endonasal approaches over external approaches for the treatment of juvenile nasal angiofibromas (JNA), the surgical management of JNAs has followed the trend for most sinonasal and skull base pathologies.^{1,2} Despite the changing landscape of surgical approaches, there continue to be multiple staging systems

for JNAs, most of which were adopted prior to the era of endoscopic removal.

Traditional staging systems such as the Radkowski and Andrews staging systems, which are the two most commonly used ones, are primarily based on the size and the extent of disease.^{3,4} On the other hand, the Onerci and University of Pittsburgh Medical Center (UPMC) staging systems are two relatively new staging systems that account for the use of

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endoscopic approaches.^{5,6} The UPMC staging system is unique in including the residual vascularity of the tumor following embolization as a prognostic factor as well as the route of intracranial extension. Definitions of these four staging systems are shown in ►Table 1.^{3–6} An initial report suggests that the UPMC system is superior to other staging systems for prediction of perioperative morbidities and tumor recurrence, but its clinical use within the field of skull base surgery has been limited.⁶

Staging systems are important for the classification and management of tumors. A universal staging system assists with treatment planning and patient counseling regarding risks, outcomes, and prognosis. Additionally, staging systems help to develop standards of care. Given the need for a single and comprehensive JNA staging system, the aim of this study is to compare the clinical utility of four commonly used JNA staging systems, with a secondary aim of identifying the most clinically applicable staging system.

Methods

University of Pittsburgh Institutional Review Board approval was obtained for this retrospective study. Patient records were reviewed between January 2008 and June 2015. Patients who were included in prior staging publications, above 18 years of age at the time of surgery, without available imaging, or without complete angiographic or operative details were excluded from this analysis. Detailed inspection of preoperative, perioperative, and postoperative clinical factors were reviewed.

In regards to preoperative review, basic patient demographics, prior history of treatment, and all preoperative imaging were reviewed to establish the sites and extent of disease. All tumors were staged according to the four staging systems: Andrews, Radkowski, Onerci, and UPMC. Descriptions and outcomes of preoperative angiography and embolization were thoroughly reviewed. Arterial blood supply to the tumor, laterality of blood supply, type of embolic material used, and the angiographer's description of residual vascularity were recorded. Less than 5% residual blood flow to the tumor was considered to be complete embolization.

We recorded the type of operative intervention, surgical approach, estimated intraoperative blood loss, need for intraoperative blood transfusion, and number of staged surgeries. Endoscopic surgery was defined as approaches that utilized endoscopy for visualization. These included transnasal and transmaxillary approaches. When multiple operations were required for definitive therapy, estimated blood loss across all stages was compiled for each patient. Both intraoperative and acute postoperative complications were tabulated in addition to permanent sequelae of surgery. Patients were assessed for postoperative residual disease and postoperative recurrence. Postoperative residual disease was defined as endoscopically visualized gross residual disease or radiographic evidence of disease immediately following surgery. Recurrence of disease was defined as patients who demonstrated regrowth of tumor following complete surgical resection. All postoperative imaging was reviewed and length of follow-up was recorded.

Table 1 Juvenile nasal angiofibroma staging systems

Staging system	Stage				
	I	II	III	IV	V
Andrews ¹	Limited to NP	Invading PPF or maxillary, ethmoid, or sphenoid sinus with evidence of bone destruction	Invading ITF or orbit: IIIA: no intracranial extension IIIB: extradural (parasellar) extension	Intracranial, intradural tumor: IVB: without infiltration of cavernous sinus, pituitary fossa, or optic chiasm IVB: with infiltration of cavernous sinus, pituitary fossa, or optic chiasm	NA
Radkowski ²	IA: limited to nose or NP IB: extends into one or more sinuses	IIA: minimal extension into medial PMF IIB: full occupation of PMF with local mass effect IIC: extension into ITF, cheek, or posterior to pterygoid plates	Erosion of skull base: IIIA: minimal skull base involvement IIIB: extensive intracranial extension, with or without invasion into cavernous sinus	NA	NA
Onerci ³	Nose, NP, ethmoid, and sphenoid sinuses or minimal extension into PMF	Maxillary sinus involvement, full occupation of PMF, extension to anterior cranial fossa, limited extension into ITF	Deep extension into cancellous bone at pterygoid base or body and GW of sphenoid, significant lateral extension into ITF or pterygoid plates, orbital, cavernous sinus obliteration	Intracranial extension between pituitary gland and ICA, tumor localization lateral to ICA, middle fossa extension and extensive intracranial extension	
UPMC ⁴	Nasal cavity, medial PPF	Paranasal sinuses, lateral PPF; no residual vascularity	Skull base erosion, orbit, ITF involvement; no residual vascularity	Skull base erosion, orbit, ITF involvement; residual vascularity	Intracranial extension with residual vascularity; M: medial extension L: lateral extension

Abbreviations: GW, greater wing; ICA, internal carotid artery; ITF, infratemporal fossa; NP, nasopharynx; PMF, pterygomaxillary fossa; PPF, pterygopalatine fossa; UPMC, University of Pittsburgh Medical Center.

Table 2 Patient demographics and clinical characteristics

Characteristic	Values
No. of patients	34
Age, median (25th–75th percentile), y	14.5 (12.4–16.3)
Sex	All male
Previous treatment at another institution, no.	10
Surgery alone	5
Surgery and preoperative embolization	2
Surgery and radiation	1
Radiation alone	1
Embolization alone	1
Preoperative embolization, %	100
Median time between preoperative embolization and surgery, h	24
No. of staged operations (range)	6 (2–3)
Follow-up, median (25th–75th percentile), mo	13.8 (2.6–41.1)
Residual tumor, no.	10
Stable (observation)	7
Required further surgery	3
Other adjuvant therapies	0

The UPMC staging system was independently correlated with outcome variables using a Spearman rank correlation. Areas under the curve (AUC) from receiver operator curves (ROC) were used to assess for differences amongst the different staging systems. A *p*-value of 0.05 was used to determine statistical significance where appropriate (GraphPad Prism software, version 6 for Macintosh; GraphPad Software Inc., La Jolla, California).

Results

In total, 34 patients were found to meet inclusion criteria; a summary of their clinical characteristics is shown

Table 3 Postoperative complications and permanent postoperative sequelae

Perioperative complication	n	Permanent sequelae	n
Trigeminal nerve numbness	6	Dry eye	3
Temporary sixth nerve palsy	3	Chronic nasal crusting	3
Trismus	3	Synechiae	2
Carotid sacrifice	1	Horner syndrome	2
Cerebrospinal fluid leak	1	Frontal sinus obstruction	2
Visual loss (unilateral)	1	Visual loss (unilateral)	1
Wound infection	1	Dacryocystitis	1
Temporary sixth and third nerve palsy	1	V ₂ neuralgia	1
Dry eye	1	Eustachian tube dysfunction	1

Table 4 Sites of residual disease^a

Location	n	%
Cavernous sinus	4	22.2
Infratemporal fossa	4	22.2
Middle cranial fossa	3	16.7
Orbit	2	11.1
Inferior orbital fissure	2	11.1
Petrous carotid	2	11.1
Meckel's cave	1	5.6

^aSome patients had multiple sites of residual disease.

in ▶Table 2. All patients were male and had an average age of 14.5 years. Approximately 30% of patients had prior therapy. All patients underwent preoperative embolization and all but one (3%) patient underwent an endoscopic approach. Perioperative complications and permanent sequelae are listed in ▶Table 3.

Approximately, 29% (10/34) of patients had residual postoperative tumor, 70% (7/10) of whom did not require further intervention. The most common sites of residual disease were the cavernous sinus and infratemporal fossa (▶Table 4). Of the three patients that required further surgery, all demonstrated intracranial disease; none of these had a second recurrence. None of the patients were treated with additional radiation therapy.

The UPMC staging system had an excellent correlation with intraoperative blood loss ($r = 0.84$, $p < 0.0001$). Statistical significance was also demonstrated between the UPMC staging system, and intraoperative transfusion, postoperative residual disease, and postoperative length of stay ($p < 0.0001$, $p = 0.0002$, and $p = 0.026$, respectively; ▶Table 5).

The distribution of patients across the four staging systems is listed in ▶Table 6. Approximately 82% (28/34) of patients had evidence of preoperative skull base erosion. Among the four staging systems, the UPMC staging system was most predictive of patients with the need for staged procedures, the need for intraoperative transfusions, and with residual postoperative disease (AUC: 0.89, 0.88, 0.86, respectively; ▶Table 7).

Table 5 UPMC staging system and perioperative clinical parameters

Perioperative clinical parameter	UPMC stage					
	I	II	III	IV	V	
	n = 1	n = 5	n = 5	n = 11	n = 12	p-Value
Intraoperative blood loss (median), mL	40	136	422	1231	4501	<0.0001
Intraoperative transfusion	0	0	1	6	11	<0.0001
Staged operations	0	0	0	0	6	0.0009
Postoperative residual disease	0	0	0	2	8	0.0002
Postoperative length of stay, d	2	2	3.2	2.8	7.9	0.026

Abbreviation: UPMC, University of Pittsburgh Medical Center.

Discussion

The primary goals of staging systems are to provide prognostic information for treatment planning and patient counseling. Additionally, staging systems encourage uniform reporting within the literature to allow comparison of results and establish standards of care. With a multitude of staging systems for JNA, the prognostication and comparison of JNAs across different institutions are convoluted and there is a clear need for a universal staging system. A recent review of more than 10 JNA staging systems suggests that while traditional staging systems may correlate well with surgical approach and prognosis, several more recently developed staging systems may be more accurate.⁷ Additionally, despite the increasing evidence of improved outcomes associated with preoperative embolization and endoscopic resection, the majority of staging systems do not account for these advances in management.^{8,9} This study demonstrates the exemplary clinical applicability of the UPMC staging system to serve as a modern staging system as compared with three

other staging systems in an advanced stage patient population and provides impetus for this staging system's use.

The primary goal of this study is to compare four different JNA staging systems for the most important perioperative outcomes: intraoperative blood loss and postoperative residual disease. Intraoperative blood loss is an important morbidity (need for transfusion) that also contributes to operative complications such as neural or vascular injury. Given the potential for significant blood loss from these vascular lesions, a strong correlation between intraoperative blood loss and a staging system is paramount in both surgical planning and patient counseling. Moreover, JNA staging systems should also closely correlate with postoperative residual disease and tumor recurrence since further treatment may be required. In line with the authors' prior report from 2010, the UPMC staging system was most predictive of the need for an intraoperative transfusion, the need for a staged procedure, and the likelihood of postoperative residual disease.⁶

Table 6 Distribution of staging systems

Staging system	Stage				
	I	II	III	IV	V
Andrews	1	6	IIIA: 7 IIIB: 8	IVA: 0 IVB: 10	–
Radkowski	IA: 1 IB: 0	IIA: 4 IIB: 2 IIC: 5	IIIA: 10 IIIB: 12	–	–
Onerci	5	2	16	11	
UPMC	1	5	5	11	12

Abbreviation: UPMC, University of Pittsburgh Medical Center.

Table 7 Receiver operator characteristic curves: area under the curve

Staging system	Staged operation	Intraoperative transfusion	Postoperative residual disease
Andrews	0.851	0.844	0.783
Radkowski	0.714	0.703	0.681
Onerci	0.830	0.766	0.810
UPMC	0.893	0.880	0.863

In addition to serving as a guide for perioperative outcomes, the UPMC staging system can aid in treatment planning with consideration of the route of intracranial extension and the tumor's position relative to the internal carotid artery, a unique feature that distinguishes this staging system. This information is critical in planning the optimal surgical approach: medial extension requires an anterior approach, whereas lateral extension may be supplemented with a lateral approach. The source of residual blood supply may also influence the selection of a surgical approach. Though this study consisted of a population who primarily underwent endoscopic surgery, thoughtful consideration of the contributing blood supply to these highly vascular tumors should be considered, regardless of surgical approach.

While the UPMC staging system is not applicable in cases where preoperative angiography and embolization is not available, we propose that this should be part of the standard of care. In addition to the prognostic information from preoperative angiography, preoperative embolization can effectively down stage tumors to a UPMC stage III tumor (without residual vascularity) that is associated with less perioperative risk. Multiple institutions and systematic reviews have demonstrated a significant difference in intraoperative blood loss following preoperative embolization.^{8–11} In centers where preoperative angiography and embolization is not available, early stage tumors (e.g., UPMC stage I and II) may be resected without these preoperative adjuncts.

An effective staging system should also account for the relative risk of perioperative complications. Examining this relationship was a secondary goal of this study, but given the retrospective nature of this study and a wide range of different postoperative complications, these results were too underpowered to provide meaningful statistical results. It is worth noting that arguably the most devastating consequences (e.g., visual loss, carotid artery sacrifice, and cerebrospinal fluid leak) occurred in patients with UPMC stage V disease.

Although these results suggest that the UPMC staging system is the most clinically applicable of the available JNA staging systems, a potential limitation of this study is the advanced stage of disease within our patient population. Though the study size was relatively robust, the majority of patients had skull base erosion at the time of presentation, and this reflects a potential referral bias. Although almost all patients were managed with endoscopic techniques, the UPMC staging system probably has validity for open surgical approaches as well. These limitations could be addressed by a larger multi-institutional study.

In addition, the median follow-up time of this study is relatively short at 13.8 months. In the setting of 10 patients with residual disease, 2 with stage IV disease, and 8 with stage V disease, the regrowth rates of residual disease will be important to follow over years to come both for patient counseling and in the development of postoperative surveillance guidelines. With large tumors, tumor nodules may be left inadvertently due to the multilobular nature of the tumor or left intentionally due to proximity to critical structures. The former can usually be removed surgically if regrowth is

noted. Small residuals may be less likely to regrow. In our experience, the majority of patients who require additional treatment demonstrate significant regrowth on serial scans within 1 to 2 years. In this study, significant regrowth that required further surgical resection occurred within 14 months postoperatively. Due to the age of the patients and the unknown long-term consequences of stereotactic radiotherapy, radiation therapy is not recommended in these patients if surgery (or observation) is an option.

In conclusion, it is apparent that recent shifts in management paradigms for JNAs should be accompanied by a universal staging system that accounts for these changes in practice. The UPMC staging system fits this need by more reliably correlating with prognostic outcome measures while incorporating modern treatment practices such as preoperative embolization and endoscopic approaches. The UPMC staging system is also helpful in surgical planning and should be considered as a contemporary clinical tool in both the management and reporting of JNAs.

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