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Juvenile Angiofibroma: What Is on Stage?

Maurizio Bignami, MD; Giacomo Pietrobon, MD; Alberto D. Arosio, MD; Enrico Fazio, MD; Larissa Nocchi Cardim, MD; Sabina Strocchi, MD, PhD; Stefano Molinaro, MD; Edoardo Agosti, MD; Apostolos Karligkiotis, MD; Paolo Battaglia, MD; Paolo Castelnuovo, MD, FACS, FRCS(Ed); Andrea Giorgianni, MD

Objectives/Hypothesis: The aim of the present study is to validate and compare four of the most widely used staging systems for juvenile angiofibroma on a homogeneous cohort of patients.

Study Design: Retrospective case series.

Methods: A retrospective review of patients treated with endoscopic or endoscopic-assisted surgical resection between 1999 and 2020 was carried out. Each case was classified according to the following staging systems: Andrews-Fisch (1989), Radkowski (1996), University of Pittsburgh Medical Center (2010), and Janakiram (2017). Spearman's rank correlation test and areas under the curve of receiver operator curves were used to assess the correlation between outcomes of interests (blood loss, surgical time, need for transfusion, and persistence of disease) and stage of disease.

Results: Seventy-nine patients were included, with a median follow-up time of 25 months (range 12–127 months). Median surgical time was 217 minutes (range 52–625). Median blood loss was 500 mL (range 40–5200) and 27 patients (34.2%) required blood transfusions. Seven patients (8.9%) showed persistence of disease. All classification systems showed a similar association with blood loss, surgical time, persistence of disease, and need for transfusion.

Conclusions: Involvement of the infratemporal fossa and intracranial extension was identified as red flags for surgical planning and preoperative counseling, as associated with increased risk for transfusion and persistent/recurrent disease, respectively. No classification system was found to be better than the others in predicting the most important outcomes. Therefore, the simplest and most easily applicable system would be the preferred one to be used in clinical practice.

Key Words: Juvenile angiofibroma, embolization, endoscopy.

Level of Evidence: Level 4 case series

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INTRODUCTION

Juvenile angiofibroma (JA) is a rare, benign, and locally aggressive vascular lesion, which accounts for 0.05% of all head and neck lesions.[1] The transnasal endoscopic resection nowadays represents the mainstay of treatment in the majority of cases,[2,3] often preceded by preoperative embolization.[4,5] Despite being a benign vascular lesion, JA is challenging for the surgeon with the need of accurate preoperative planning, potential dramatic intraoperative bleeding, and the possibility of persistence of disease. These issues have compelled over the years various surgeons to find a universally accepted classification system, which could provide prognostic information and guide preoperative counseling. Indeed, more than 10 different staging systems have been proposed throughout the years,[6] but none of them has become the gold standard so far.

Given the lack of consensus about this topic, the aim of the present study was to validate four of the most widely used staging systems[7–10] on a cohort of patients treated for JA, with the intent to identify, if any, the most informative and predictive classification with regard to complications and persistence of disease.

MATERIALS AND METHODS

Study Design

A retrospective review of patients treated between 1999 and 2020 in two university hospitals (Pavia and Varese) by the same surgical team was carried out. Only patients affected by histologically proven JA who underwent preoperative intra-arterial embolization (PIAE) and endoscopic or endoscopic-assisted surgical resection were included in the study. The following data were collected: age at surgery, imaging studies, surgical technique, duration of surgery, blood loss, need for

From the Department of Otorhinolaryngology, Department of Surgery (M.B.), ASST Lariana, University of Insubria, Como, Italy; Head and Neck Surgery & Forensic Dissection Research Center (HNS&FDRc), Department of Biotechnology and Life Sciences (M.B., A.K., P.B., P.C.), University of Insubria, Varese, Italy; Department of Head and Neck Surgery and Otorhinolaryngology (G.P.), European Institute of Oncology IRCCS, Milan, Italy; Division of Otorhinolaryngology, Department of Biotechnology and Life Sciences (A.D.A., E.F., P.B., P.C.), University of Insubria, Varese, Italy; Division of Otorhinolaryngology, Department of Surgical Specialties (A.D.A., A.K., P.B., P.C.), ASST Sette Laghi, Ospedale di Circolo, Varese, Italy; Department of Radiology (L.N.C.), ASST Sette Laghi, Del Ponte Hospital, Varese, Italy; Department of Neuroradiology (L.N.C., S. M., A.G.), ASST Sette Laghi, Circolo Hospital, Varese, Italy; Medical Physics Department (S.S.), ASST Sette Laghi, Varese, Italy; and the Division of Neurosurgery, Department of Biotechnology and Life Sciences (E.A.), University of Insubria, Varese, Italy.

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Send correspondence to Alberto D. Arosio, MD, Department of Otorhinolaryngology-Head and Neck Surgery, University of Insubria, Italy Via Guicciardini, 9 - Varese, Italy. E-mail: albertodaniele.arosio@gmail.com

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perioperative transfusion, intraoperative and postoperative complications, outcomes, and follow-up. Pre- and post-embolization angiograms were reviewed for evidence of residual vascularity from the internal carotid artery (ICA), which was not quantified but based on identifiable vessels coming from the artery, according to Snyderman et al.[9] Based on the analysis of preoperative imaging, angiography, and intraoperative findings, all the lesions were retrospectively classified according to the following staging systems (Table I): Andrews-Fisch,[7] Radkowski,[8] University of Pittsburgh Medical Center (UPMC),[9] and Janakiram.[10] Exclusion criteria were as follows: 1) JA surgically removed without preoperative embolization; 2) missing relevant data (e.g., preoperative imaging, surgical report, postoperative radiologic control); 3) less than 12 months of follow-up.

The study was performed in compliance with the Helsinki declaration, and all patients gave written consent to have their data included. The study was approved by the Institutional Review Board (Insubria Board of Ethics, approval number 0033025/2015).

Preoperative Assessment and Surgical Management

Preoperative work-up included general clinical assessment, endoscopic endonasal examination, and preoperative evaluation with computed tomography scan and contrast-enhanced magnetic resonance imaging (MRI). Preoperative angiography was accomplished 24 to 48 hours prior to the surgical procedure in all cases, and devascularization was performed with slow-infusion polyvinyl alcohol particles (Contour, Boston Scientific) using a blank roadmap visualization to achieve as distal penetration as anatomically possible, until complete stasis of the flow within each feeding vessel was obtained. At the end of the procedure, control angiography was performed from both ICA and ECA to assess the percentage of tumor feeders embolized. Successful embolization was determined as lack of contrast in the vascular territory of the embolized vessel. All surgeries were performed by the same surgical team and all patients were treated with endoscopic or endoscopic-assisted approach. Surgical resection was performed according to general principles detailed in previous papers.[11,12]

Postoperative Surveillance

All patients underwent early postoperative MRI after removal of the nasal packing and within 72 hours after surgery. This is part of the protocol employed in our institution, and it is aimed at obtaining a valuable baseline postoperative imaging, devoid of the inevitable inflammatory changes taking place subsequently and possibly confounding the recognition of persistence/relapse of disease.[13,14] Residual disease was defined as radiographic and/or endoscopic evidence of disease immediately following surgery. Follow-up included MRI performed yearly for at least 3 years to assess eventual recurrent tumor, as well as periodic nasal and nasopharyngeal endoscopy performed every 4 months in the first year and every 6 months thereafter.

TABLE I.
Four Staging System for Juvenile Angiofibroma Considered for the Present Study.

Staging System	Stage I	Stage II	Stage III	Stage IV	Stage V
Andrews et al.[7]	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: IVA: without infiltration of cavernous sinus, pituitary fossa, or optic chiasm IVB: with infiltration of cavernous sinus, pituitary fossa, or optic chiasm	NA
Radkowski et al.[8]	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
Snyderman et al.[9] (UPMC)	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)
Janakiram et al.[10]	IA: pterygoid wedge and/or paranasal sinus IB: with extension to nasopharynx	IIA: with extension in nasal cavity and/or minimal involvement of infratemporal PPF IIB: involvement of ITF IIC: involvement of ITF with extension to cheek/pterygoid fossa/inferior orbital fissure/laterally along the greater wing of the sphenoid	IIIA: involvement of quadrangular space/Meckel's cave IIIB: involvement of cavernous sinus/engulfing carotid artery	IVA: prestyloid parapharyngeal tumor extension above the lower border of the mandible IVB: intracranial intradural extension	Massive parapharyngeal, maximal intracranial extensions, and bilateral JNA

GW = greater wing; ICA = internal carotid artery; ITF = infratemporal fossa; NA = not applicable; NP = nasopharynx; PMF = pterygomaxillary fossa; PPF = pterygopalatine fossa; UPMC = University of Pittsburgh Medical Center.

Statistical Analysis

The outcomes of interest of the study were blood loss, surgical time, persistence of disease, and need for transfusion. Correlation between stage of disease according to the four considered classifications and quantitative variables (i.e., blood loss and surgical time) was assessed by means of Spearman's rank correlation test. Results are expressed with Spearman's rho. The areas under the curve (AUC) of receiver operator curves (ROCs) were used to assess the differences among the staging systems in predicting persistence of disease or need for transfusion. Youden Index (J) was used as main summary statistic for identification of optimal cutoff point for each classification system to predict the outcome of interest. A P value of .05 was used to determine statistical significance where appropriate.

RESULTS

Characteristics of the Study Population

A total of 79 patients were included in the study. All patients were males. The median age at surgery was 16 years (range 10–63). Distribution of stages according to each staging system is reported in Table II.

All patients underwent preoperative PIAE. No postprocedural bleeding or thromboembolic cerebral ischemic complications occurred, nor other complications related to vascular microcatheterization (e.g., vascular dissections, groin hematomas) were observed. In 31 cases (39.2%), residual vascularization from ICA branches was noticed after the procedure. These cases were classified as stage IV and V according to the UPMC classification in 25 and 6 cases, respectively.

A purely transnasal endoscopic resection was carried out in 77 patients (97.5%); an endoscopic-assisted procedure was employed in the remaining two cases (2.5%), with midfacial degloving and lateral rhinotomy in one case each. No patient underwent any other form of treatment (e.g., radiotherapy).

Median surgical time considering the entire series was 217 minutes (range 52–625 minutes). Median blood loss was 500 mL (range 40–5200 mL). Twenty-seven patients (34.2%) required blood transfusion perioperatively. Median blood loss in this latter group of patients was 1480 mL. Postoperative course was uneventful for all patients but one, who experienced bleeding of the surgical site and required urgent revision surgery (revision of ligation of the maxillary artery), without need for blood transfusions.

Median follow-up was 25 months (range 12–127 months). During the surveillance, seven patients presented persistence of disease (8.9%), which was located in the cavernous sinus (5 cases, 6.3%), middle cranial fossa (1 case, 1.3%) and the pterygopalatine fossa (1 case, 1.3%). In this group of patients, median blood loss was 1750 mL and 6 out of 7 patients (85.7%) required blood transfusions perioperatively. All persistent lesions were identified in the early postoperative MRI and in all cases a wait-and-see policy was adopted. One patient (1.3%) with symptomatic persistent disease in the cavernous sinus required revision surgery 22 months after the first operation, with complete resection of the disease and no further evidence of persistence. All the other patients with persistent disease remained asymptomatic after a median follow-up of 54 months (range 12–80 months), without any radiological volume increase over time of the residual JA.

Analysis of Complication and Outcomes

Spearman's rank correlation test showed similar association of all the four classification systems with blood loss (Spearman's $\rho = 0.546$, 0.564, 0.618, and 0.541 for Andrews-Fisch, Radkowski, UPMC, and Janakiram's classification, respectively). Conversely, considering surgical time, the test showed a weaker association of Radkowski's classification (Spearman's $\rho = 0.362$), while the others showed similar association (Spearman's $\rho = 0.512$, 0.495, and 0.554 for Andrews-Fisch, UPMC, and Janakiram, respectively).

All the four classification systems were able to predict persistence of disease, with AUC ranging between 0.836 and 0.905. The lowest value of sensitivity was observed for UPMC classification (71%). Optimal cutoff points identified for each classification corresponded to the presence of skull base and/or intracranial extension of disease: stage IIIB (Andrews), IIIA (Radkowski), V (UPMC), and IIIA (Janakiram).

All four classification systems were able to predict the need of transfusion, with AUC ranging between 0.799 and 0.840. The lowest value of sensitivity was observed

TABLE II.
Distribution of Patients Among the Four Considered Classification Systems.

	Stage				
Staging Systems	I	II	III	IV	V
Andrews et al.[7]	6/79 (7.6%)	30/79 (38%)	IIIA: 25/79 (31.7%) IIIB: 7/79 (8.9%)	IVA: 1/79 (1.2%) IVB: 10/79 (12.6%)	NA
Radkowski et al.[8]	IA: 3/79 (3.8%) IB: 7/79 (8.9%)	IIA: 26/79 (32.9%) IIB: 7/79 (8.9%) IIC: 21/79 (26.5%)	IIIA: 11/79 (13.9%) IIIB: 4/79 (5.1)	NA	NA
Snyderman et al.[9] (UPMC)	15/79 (19%)	12/79 (15.2%)	13/79 (16.5%)	25/79 (31.6%)	14/79 (17.7%)
Janakiram et al.[10]	IA: 0/79 (0%) IB: 16/79 (20.3%)	IIA: 19/79 (24%) IIB: 21/79 (26.5%) IIC: 7/79 (8.9%)	IIIA: 2/79 (2.6%) IIIB: 9/79 (11.4%)	0/79 (0%)	5/79 (6.3%)

NA = not applicable; UPMC = University of Pittsburgh Medical Center.

for Andrews's classification (58%), while the lowest value of specificity was observed for UPMC classification (67%). Optimal cutoff points identified for each classification corresponded to extension of the disease into the infratemporal fossa (ITF) (stage IIC, IV, and IIC for Radkowski, UPMC, and Janakiram classification, respectively), except for Andrews's classification (stage IIIB: extradural parasellar extension).

DISCUSSION

Juvenile angiofibroma represents a challenging disease for the head and neck surgeon, because of its local aggressiveness and threatening potential for bleeding. Moreover, patients' young age requires an especially careful preoperative work-up in order to minimize the risk of perioperative blood transfusions and persistent disease, which could adversely affect their subsequent life span.

Throughout the years, several staging systems have been proposed,[6] based on the alleged pathways of growth of the mass, which was finally found to be centered on the vidian canal.[15,16] Such classifications aimed to establish a common ground for comparative studies, providing both elements for proper preoperative planning and prognostic information. In recent years, suggestions for new classifications were proposed by Snyderman[9] and Janakiram.[10] Both authors provided statistical evidence to support the superiority of their staging systems in terms of stratification. The former was backed up by the concept of "residual vascularity," a novelty never considered in previous classification systems, which could account for better correlation with the considered clinical endpoints (blood loss, need for multiple operations, and postoperative persistence and recurrence). The latter took advantage of the likely largest series worldwide, notably in patients treated mostly without PIAE. Nonetheless, universal consensus has not been reached to date. The UPMC study was based on a small cohort of thirty-five patients, while Janakiram's five-staged system appeared to be too complex for routine clinical use. To note, in the last 15 years, other classifications have been published as well, by Onerci et al.,[17] Carrillo et al.,[18] and, most recently, Abdelwahab et al.[19] These last three staging systems were excluded from our analysis because of their limited clinical application and lack of either innovative features or robust numbers.

Despite their advocates and use in clinical studies, none of the classifications proposed so far has ever become the gold standard. Moreover, only Rowan et al.[20] compared different classifications in order to find the most informative about the prognostic potential. However, this was performed in a relatively small cohort of patients (34 cases), with median follow-up of 13 months and an unbalanced distribution of stages of disease, with the majority of patients presenting skull base erosion at the time of presentation, thus representing a potential referral bias. The aim of the present study was to investigate on the prognostic potential of four of the most commonly used classification systems on a large cohort of patients affected by JA, with homogeneous distribution of stages and long mean follow-up.

Mean age of the patients, mean follow-up, need for transfusion, and rate of persistent disease of the present study are comparable to most of the published series,[9–11,18,20,21] thus confirming appropriateness of the treatment provided and allowing for such an analysis to be performed. All patients of this series underwent PIAE, which allowed for the UPMC classification to be correctly applied. In this regard, residual vascularity from branches coming from ICA was noticed in 31 cases (39.2%), similarly to what observed from Syderman et al.[9] Moreover, this study confirmed the efficacy in the use of PIAE considering the absence of any complication observed in such a large number of cases.

Our analysis revealed approximately the same correlation of the four classification systems with both blood loss and operative time, with only Radkowski classification showing the weaker association with the latter variable (Spearman's $\rho = 0.362$). Therefore, as far as the present series is concerned, none of the classifications showed a clear superior association with either increased blood loss or prolonged duration of surgery.

The need for perioperative transfusion is what actually adds morbidity for patients, and therefore it represents an outcome of interest to be evaluated. In this regard, the ROC curve analysis revealed that all the classification systems share the same ability to predict the need for transfusion, as demonstrated by similar values of AUC, ranging between 0.799 and 0.840 (Table III). Moreover, the analysis identified the optimal cutoff point that correlated best with this outcome. For each classification, the optimal cutoff corresponded to the stage defined by the involvement of the ITF by the disease, with the

TABLE III.
Receiver Operator Characteristic Analysis Considering Persistence of Disease and Need of Transfusion.

	Persistence of Disease					Need for Blood Transfusion				
Staging System	Sn (%)	Sp (%)	AUC	*P*	Cut-off*	Sn (%)	Sp (%)	AUC	*P*	Cutoff*
Andrews et al.[7]	86	83	0.905	<.0001	≥IIIB	58	94	0.840	<.0001	≥IIIB
Radkowski et al.[8]	86	88	0.900	<.0001	≥IIIA	81	71	0.799	<.0001	≥IIC
Snyderman et al.[9] (UPMC)	71	88	0.836	<.0001	≥V	85	67	0.824	<.0001	≥IV
Janakiram et al.[10]	86	86	0.872	<.0001	≥IIIA	62	87	0.828	<.0001	≥IIC

Sn = sensitivity; Sp = specificity; UPMC = University of Pittsburgh Medical Center.
*Optimal cutoff points for each classification system to predict the outcome of interest identified with the Youden Index summary statistic.

exception of Andrews' classification, for which a higher threshold was identified (i.e., stage IIIB: extradural parasellar extension). With regard to UPMC classification, the analysis identified stage IV as the optimal cutoff point, which includes the extension to ITF with "residual vascularity" of the lesion, which is the novel concept of the classification, not considered in the other staging systems. The clinical correlate of this finding might be related to the presence of the maxillary artery (MA) within the ITF: the increased risk of blood loss and subsequent transfusion may be due to vascularization from additional small arterial branches coming from the artery despite adequate PIAE (e.g., feeding vessels from meningeal arteries) or due to the higher risk of direct damage of the artery itself during the dissection. Therefore, our results suggest that in case of JA encroaching the ITF, adequate preoperative counseling about an increased risk for blood transfusion should be provided to the patients and their parents.

The four classification systems showed similar ability to predict persistence of disease as well, with AUC ranging between 0.799 and 0.840 (Table III). For each classification, the stage corresponding to the optimal cutoff was the one defined by the intracranial extension of the disease. Of note, 14 cases with intracranial extension were included in the present series, with the persistence of disease in 6 cases (42.9%). This emphasizes that intracranial extension does not preclude endoscopic or endoscopic-assisted resection to be performed, as already demonstrated in previous publications.[11] However, in these cases, the clinician should inform the patient about the possibility of incomplete resection or plan a staged procedure in advance. In our series, a wait-and-see policy was employed for all patients with residual disease, considering that the growth of residues over time is rare, in particular after puberty.[22,23] Accordingly, only one patient required revision surgery with removal of a symptomatic remnant in the cavernous sinus.

Some limitations of the present study deserve mention. First, it is based on a retrospective analysis of patients treated over a 20-year period, with intercurrent changes in imaging technology, embolization techniques, and surgical expertise. Second, the mean follow-up is shorter than what reported in other series; however, the prevalent opinion is that postsurgical recurrences are actually persistent disease due to incomplete excision, and most of them are recognized with early postoperative MRI, which is the case also in our series. Finally, even though the sample size is large considering the rarity of the disease, the conclusions of our investigation would need to be validated by further studies on larger series.

CONCLUSION

Despite the fact that more than 10 different staging systems have been proposed throughout the years, none of them has become the gold standard so far. Our study identified the involvement of ITF and the intracranial extension as red flags to consider during surgical planning and preoperative counselling, as associated with increased perioperative risk for transfusion and persistence of disease, respectively. Notably, these factors are considered in each of the four analyzed classification. On the one hand, these findings contradict the hypothesis that classification systems developed prior to the advent of endoscopic techniques, such as the ones proposed by Andrews-Fisch and Radkowski, might be less accurate in evaluating complications and persistence of disease. On the other hand, our results confirm that no classification system is better than the other in predicting the most important outcomes of treatment. Considering these facts, the simplest and most easily applicable classification system would therefore be the preferred system to use in clinical practice. In our opinion, the UPMC classification appears to respond better than the needs, with the advantage of considering PIAE as part of the treatment.

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