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Early Postoperative Magnetic Resonance in the Diagnosis of Persistent Juvenile Angiofibroma

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Objectives/Hypothesis: Despite improvements in the treatment of juvenile angiofibroma (JA), the rate of persistence (pJA) is still not negligible. In the present study, we assessed the value of early postoperative magnetic resonance imaging (MRI) in depicting unintentional pJAs and designed a MRI-driven decisional flow-chart for pJA management and follow-up.

Study Design: Observational study.

Methods: Patients undergoing early postoperative MRI after endoscopic resection of JA in the Unit of Otorhinolaryngology – ASST Spedali Civili, University of Brescia from 2007 to 2017 were enrolled. MRI was defined as negative or positive based on defined radiological criteria. The diagnostic performance of MRI was evaluated.

Results: The analysis included 26 patients, with a mean age of 16.5 years (range, 11–25). Early MRI was negative for pJA in 21 (80.8%) patients and positive in five (19.2%). No patient with a negative finding was found positive at subsequent follow-up MRIs. The accuracy of a positive finding was confirmed by pathologic examination (three cases) or follow-up MRIs (two cases). The diagnostic performance of MRI was excellent with sensitivity and specificity of 100%. An MRI-driven flow-chart for pJA management and follow-up was designed.

Conclusions: Early postoperative MRI demonstrated a high diagnostic accuracy in the detection of unintentional pJA. Our MRI-driven strategy and decisional flow-chart could aid in the decision-making process in the management of pJA and definition of postoperative surveillance.

Key Words: Juvenile angiofibroma, persistent juvenile angiofibroma, magnetic resonance, postoperative magnetic resonance, transnasal endoscopic surgery.

Level of Evidence: 4

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INTRODUCTION

Juvenile angiofibroma (JA) is a rare vascular lesion affecting adolescent males. The origin of JA is controversial, sharing features common to both vascular malformations and benign tumors, and the most credited hypothesis is that it develops from incomplete regression of the first branchial artery.[1–8] Transnasal endoscopic resection following embolization is the mainstay of treatment in the large majority of JAs.[1,9–12] However, despite continuous refinements in surgical technique, an unintentional persistence of JA (pJA) is present during postoperative surveillance in up to 7% of cases.[12,13] The prevalent current opinion is that all post-surgical recurrent lesions are actually persistent disease resulting from incomplete excision, and not de novo disease.[13–15] Although pJA can be theoretically left in many locations, the pterygoid root is the most frequently involved site due to the well-known propensity of JA to grow in the cancellous bone of the sphenoid.[16–18]

Early postoperative detection of pJA could enable immediate redo surgery before the formation of scar tissue and prevent possible regrowth of the lesion. This strategy was first described by Kania et al. using contrast-enhanced computer tomography (CT) and later recommended in the European position paper on sinonasal tumors, favoring the use of magnetic resonance imaging (MRI).[19–23] Contrast-enhanced MRI is the gold standard for preoperative assessment of JA and the imaging technique of choice for postoperative surveillance due to its high soft-tissue resolution and lesion enhancement after gadolinium injection. Moreover, thanks to 3D, T1-weighted, fat saturated, contrast-enhanced sequences with high spatial resolution, MRI is more efficient even in depicting permeation into the medullary bone than contrast-enhanced CT scan.[1,9,12,14,15,22,24,25]

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If surgical principles guiding treatment in primary lesions are well established, management of pJAs and guidelines on surveillance is still controversial. pJA may be identified by imaging techniques or endoscopy during the postoperative course. In our recent report on a relatively large series of 74 patients, the evolution and management of pJA were analyzed[12] in the attempt to better understand the behavior, optimize treatment, and minimize morbidity of pJA. As an additional aid to the management of unintentional pJAs, the present study focuses on the role of early postoperative MRI after endoscopic resection.

The aims of the present study were to: 1) assess the diagnostic performance of early postoperative MRI in the detection of unintentional pJAs after surgery; 2) define the risk of recurrence after a negative early postoperative MRI. The implications for the management of pJA and follow-up will also be discussed.

MATERIALS AND METHODS

All patients treated for JA from 2007 to 2017 at the Unit of Otorhinolaryngology – ASST Spedali Civili, University of Brescia, were prospectively enrolled in the study. The study was conducted according to the principles of the revised Declaration of Helsinki and in compliance with Good Clinical Practice and local Ethics Committee regulations (approved by the "Comitato Etico Provinciale della Provincia di Brescia").

Preoperative work-up consisted of general clinical assessment, endoscopic examination, and preoperative MRI. Transarterial embolization with polyvinyl alcohol particles and endoscopic resection of JA were performed following the general principles described in previous publications.[9,12,15,22,23]

TABLE I.
Demographic and Clinical Characteristics of the Series.

	n	
Number of patients	26	
Age at surgery (mean, range)	16.5 years, 11–25 years	
Radkowski classification (n, %)	IA	2 (7.7%)
	IB	1 (3.8%)
	IIB	3 (11.6%)
	IIC	5 (19.2%)
	IIIA	13 (50%)
	IIIB	2 (7.7%)
Snyderman classification (n, %)	I	3 (11.6%)
	II	6 (23.1%)
	III	10 (38.4%)
	IV	6 (23.1%)
	V	1 (3.8%)
Previous treatment (n, %)	None	24 (92.3%)
	Surgery	2 (7.7%)
Early post-op magnetic resonance: (n, %)	Negative	Score 0: 19 (73%)
		Score 1: 2 (3.9%)
		Score 2: 1 (3.9%)
	Positive	Score 3: 5 (19.2%)

Postoperative MRI (hereby defined "early postoperative MRI") for detection of unintentional pJA was scheduled prior to discharge, according to availability of the Unit of Radiology; presence of nasal packing did not contraindicate MRI acquisition. All MRI studies were performed with a 1.5 Tesla scanner (Siemens Magnetom Aera, Siemens Healthcare, Erlangen, Germany). The study protocol included a turbo-spin-echo T2-weighted sequence in axial, coronal and, if needed, sagittal plane (TR 5200 ms, TE 106 ms), a turbo-spin-echo T1 unhenhanced sequence on axial or coronal plane (TR 430 ms, TE 14 ms) and a 3D gradient echo fat-saturated (VIBE) sequence. The slice thickness of the spin-echo sequences never exceeded 3 mm, and the isotropic voxel of 3D VIBE ranged between 0.6 and 0.7 mm. Early image acquisition after contrast agent injection (3D VIBE) was used to differentiate highly enhancing lesions from mucosal thickenings and postoperative changes.

JA persistence was defined using the following radiological criteria: 1) highly contrast-enhancing nodular tissue with intermediate T2 signal; 2) nodular shape in at least two perpendicular planes reconstructed from 3D sequences; 3) site of the lesion already involved by JA at the pre-treatment imaging.[12] Images were prospectively analyzed by an expert head and neck radiologist (M.R.) who assigned score 0 when no criteria were satisfied and score 1 to 3 based on the number of criteria satisfied. A novice radiologist who was not previously involved in the prospective interpretation of early postoperative MRIs was asked to retrospectively and blindly review all images. Inter-rater agreement among examiners (M.R. and I.Z.) was calculated through percentage of agreement, unweighted and linear weighted Cohen's κ.

Depending on general conditions, site and size of pJA, surgery- and general anesthesia-related risks, and opinion of the patient and/or parents, patients with score 3 underwent either redo surgery or radiological surveillance until stability/regression of pJA and/or postpuberal age. Patients with score 0 to 2 followed a standard wait and scan protocol with MRI every 6 months for at least 3 years after surgery.

Follow-up MRI was evaluated by the same head and neck radiologist (M.R.), applying the aforementioned radiologic criteria. The last MRI was considered the final result of comparison. Endoscopic outpatient examinations were performed in all patients to follow healing of the surgical field; thereafter, nasal endoscopy was performed concomitantly with radiological examinations.

The diagnostic performance of early postoperative MRI was calculated considering as "positive" those cases fulfilling all three radiological criteria (score 3) and "negative" those which had at least one criteria not satisfied (score 0 to 2). This was justified by the uniformity of management of positive cases for whom immediate redo surgery was first considered, and negative cases for whom a wait and scan policy was adopted.

Gold standard evaluations to establish whether or not an unintentional pJA was left were: 1) definitive histopathology in cases undergoing immediate redo surgery; and 2) the latest follow-up MRI in all other cases. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV), accuracy, and Youden's J index were calculated accordingly.

RESULTS

From 2007 to 2017, a series of 42 patients underwent endoscopic resection for JA in the Unit of Otorhinolaryngology – ASST Spedali Civili, University of Brescia. Among these, 26 patients underwent early postoperative MRI and were enrolled in the study. Table I summarizes the characteristics of the cohort. Early postoperative MRI was always performed within 5 days (mean 2 days; range, 1–5 days) after surgery. Thirty-three patients of the series and 20 of those with early postoperative MRI had already been included in our previous study.[12]

Early postoperative MRI was negative in 21 (80.8%) patients and showed the presence of a lesion suspicious for pJA in five (19.2%). Among the positive patients, three underwent immediate redo surgery and diagnosis was confirmed at pathologic examination. The first was a 16-year-old boy operated on in another institution 2 years before with a large and growing residual lesion (Radkowski IIIA, Snyderman IV). Early postoperative MRI showed a 1.9 cm pJA in the inferior orbital fissure. Revision surgery was performed 3 days later to prevent the potential need of future revisions due to previously documented growth and the risk of orbital/trigeminal symptoms. Identification of the pJA was quite challenging and lasted 130 minutes due to the presence of abundant scar tissue caused by the treatment performed 2 years before. The second was a 12-year-old prepubescent boy (Radkowski IIIA, Snyderman III) who had a 9 mm pJA in the contralateral pterygoid root. He underwent revision 4 days after surgery and the operating time was 37 minutes (Fig. 1). The last was a 16-year-old (Radkowski IIC, Snyderman II); a 8 mm pJA was left in the ipsilateral pterygoid root in a favorable site close to the surgical margin; redo surgery was easily performed

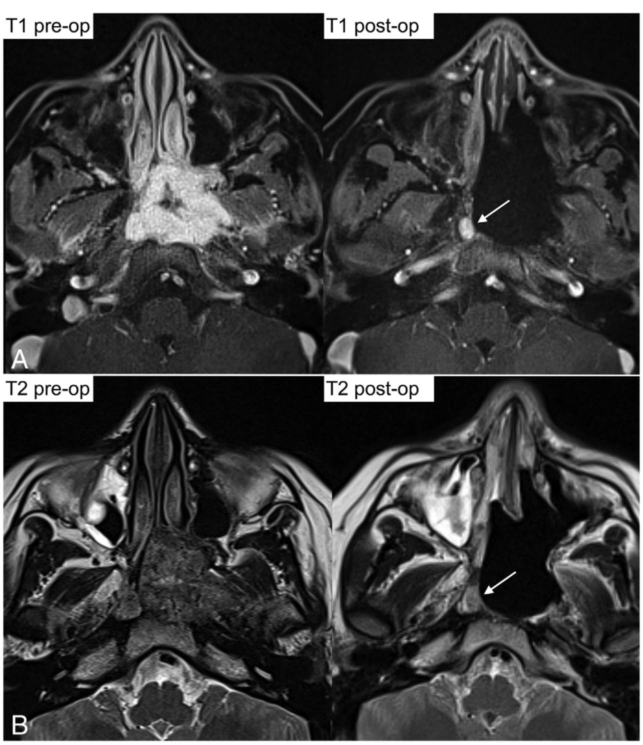

Fig. 1. Preoperative (pre-op) and early postoperative (post-op) contrast-enhanced T1 fat-saturated and T2 axial sequences of a 12-year-old boy affected by juvenile angiofibroma (Radkowski IIIA, Snyderman III). The white arrow shows a 9 mm highly contrast-enhancing nodular shaped lesion with intermediate T2 signal in the right pterygoid root, a site already involved by juvenile angiofibroma at the preoperative MRI.

2 days after primary treatment and lasted 27 minutes. In all patients, no perioperative complications or significant blood loss occurred. Except for the first patient who had scars due to the previous treatment, in the other two patients the identification of persistence was rapid thanks to the easy dissection of tissue in the absence of scarring and precise identification of the site from radiological information.

A wait and scan strategy was used for two cases with positive postoperative MRI based on the patient's status and pJA features. Both these patients were included in our previous study focused on evolution of pJAs.[12] The first was a 15-year-old boy (Radkowski IIIA, Snyderman IV) who had postoperative hemodynamic instability due to massive blood loss (6000 mL). The patient has been now under surveillance with MRI for 4 years with an overall growth of pJA of 5 mm (from 32 to 37 mm). The second was 22-year-old (Radkowski IIC, Snyderman IV) who refused revision surgery for a 6 mm pJA; follow-up was stopped 3 years later due to disease stability and patient age. Neither patient showed disease-related symptoms and both had a non-critical site of pJA (pterygoid root).

In all patients with score 0 negative early postoperative MRI, the absence of pJA was confirmed in all subsequent MRI studies during the following 3 years. One patient showed score 1 at early postoperative MRI satisfying only the third criterion (Fig. 2), and one score 2 for both criteria 1 and 2. Both these patients were considered negative for pJA because not fulfilling all the criteria and were defined disease-free at MRI performed 6 months after surgery and during the 3-year follow-up.

In only two cases was the novice radiologist's rate (score 1 in both cases) different to that of the expert head and neck radiologist (score 0 in both cases). Inter-rater agreement was optimal, with percentage of agreement, unweighted and linear weighted Cohen's κ being 92.3%, 0.855, and 0.932.

All patients enrolled in the present study underwent surveillance with endoscopy and contrast-enhanced MRI every 6 months for 3 years. One patient with persistent lesion was followed 4 years. At the time of the study, all patients were asymptomatic after a mean of 73 (36–151) months from surgery.

The diagnostic performance of early postoperative MRI was optimal: since no false results were observed, sensitivity, specificity, PPV, NPV, accuracy, and Youden's J index were all 100%. Based on the accuracy of early postoperative MRI, a proposal for a flow-chart for pJA management and follow-up was designed (Fig. 3).

DISCUSSION

Herein, we assessed a sample of 26 patients who underwent early postoperative MRI after endoscopic resection of JA. Diagnostic performance of early MRI was excellent and all patients with residual disease were identified within 5 days from surgery, allowing a prompt decision on whether to propose redo surgery or a wait and scan policy. None of the patients who were negative at early MRI assessment presented a positive finding at

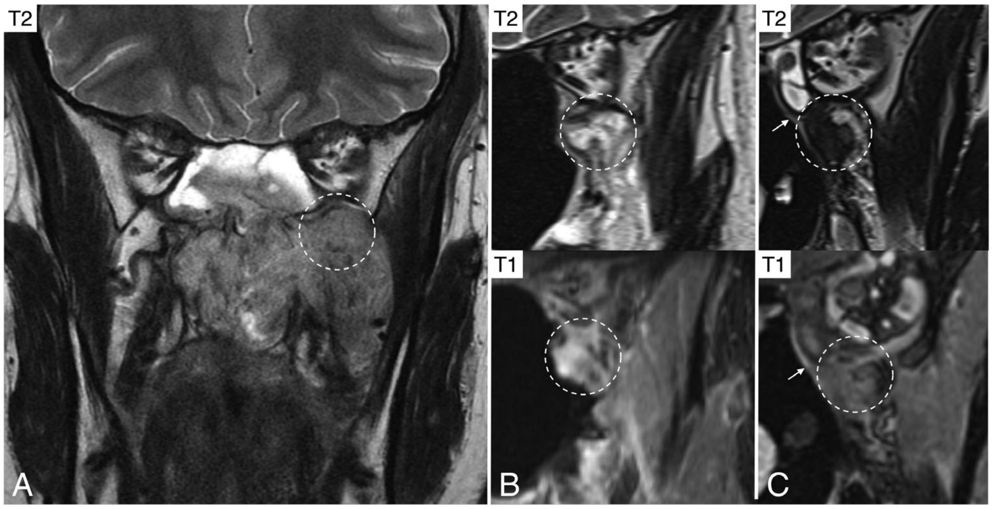

Fig. 2. Preoperative T2 coronal image of a juvenile angiofibroma (Radkowski IIIA, Snyderman IV) in a 17-year-old patient (A). Early postoperative magnetic resonance shows a tissue with high T2 signal and contrast-enhanced on T1 fat-saturated sequences (white dashed circle) in a site previously involved by the lesion; not having a nodular shape and intermediate signal in T2, the tissue meets only the third diagnostic criterion (B). Six months after surgery magnetic resonance shows retracted and hypointense tissue in T2, without enhancement after gadolinium injection in T1 (white dashed circle), and covered by a thin mucosal layer (with arrows) (C).

subsequent imaging evaluations. Our results show that MRI is highly accurate not only in preoperative work-up and surveillance, but also for postoperative baseline imaging. The rationale to perform MRI early after surgery is to reduce the potential risk of false positives due to contrast-enhancing inflammatory or scar tissue, which, being part of the postoperative healing process, are absent early after surgery. The present study validated MRI as the imaging technique of choice for early detection of unintentional pJA: high soft tissue resolution, lesion enhancement after gadolinium injection, and 3D fat saturated sequences render MRI superior to contrast-enhanced CT[19] and particularly effective in this specific setting. In addition, knowledge of the disease, which has progressively improved over the last decade, combined with the availability of a highly-reliable radiological technique early detecting residual disease, allowed for refinements in the management of pJA and identification of low-risk patients who do not need long-term surveillance.

Three simple and reproducible radiological criteria were validated to define the presence of pJA on MRI. When all these criteria are met, MRI should be considered positive for persistence until proven otherwise. By providing reliable information on the presence or absence of pJA, MRI enables adequate counseling of the patient and family about the complete excision and possible need for redo surgery or watchfully monitor the residual lesion. In case of positive early MRI, the decision-making process is based on parameters related to patient status (e.g., age, postoperative hemodynamic stability) and pJA features (e.g., size, critical location). Early surgical re-intervention based on precise radiological information provides the surgeon with a scar-free surgical bed where a quick and safe resection can be achieved. Conversely, in our long-standing experience,[9,12,15,22,23] revision surgery performed at a later stage is more challenging due to the presence of scar tissue, which hinders easy identification of pJA. Another relevant point to consider is that the growth of residues over time is definitively rare, in particular after puberty, as demonstrated by the experience gained over the years through pJA monitoring after surgery.[12,14] Post-adolescent age, postoperative hemodynamic instability, and the preference of the patient or parents should orient toward active surveillance, especially if the persistence is located in critical areas. However, a wait and scan policy would require long-term radiological surveillance, at least until stability/regression is proven or postpuberal age is reached. This encourages complete excision of JA whenever it can be achieved with a reasonable cost/benefit balance in settings of both primary and early revision surgery.

Overall, prepuberal age, hemodynamic stability, and favorable size and site of the persistence should favor early redo surgery. Of note, the pros and cons of each policy should be extensively discussed with the patients and parents, and their preference may be crucial in dubious situations. In extreme scenarios (i.e., growing residues in critical areas), non-surgical approaches, such as radiotherapy or medical treatments (antiandrogens, corticosteroids, beta-blockers, and antiVEGF), can be considered.[2–5,26–35] The current role of radiotherapy is limited to lesions involving critical intracranial structures not amenable to surgery despite the high control rates reported because of morbidity concerns.[15,26,27] The main issue limiting its use in JA is the young age of patients and the poorly known long-term effects, even if usually administered with low radiation doses and with a technique like intensity-modulated radiotherapy or radiosurgery.[26,28]

Current opinion based on the knowledge of the nature and behavior of JA is that all post-surgical recurrent lesions are actually persistences resulting from

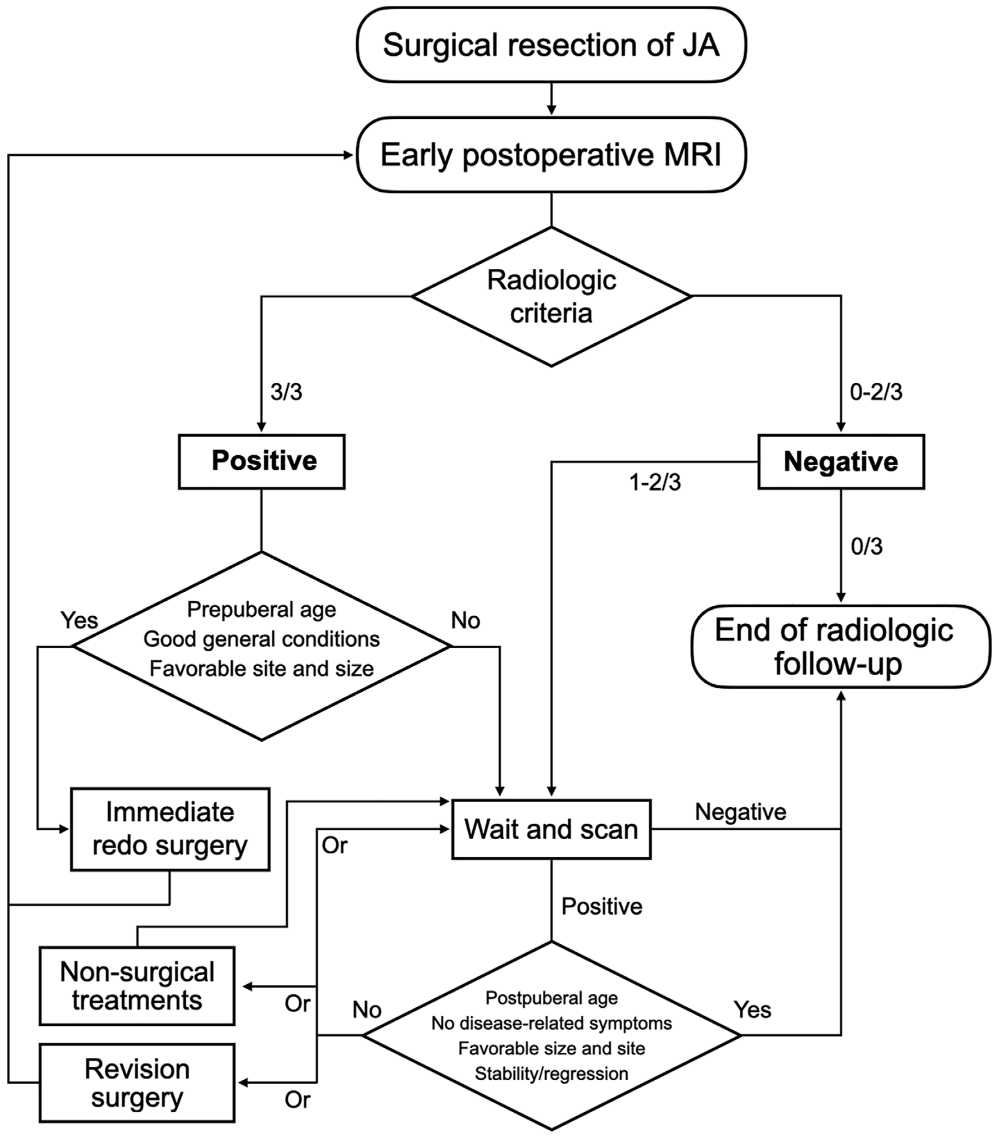

Fig. 3. Decisional flow-chart for postoperative management and follow-up of patients treated for juvenile angiofibroma. JA: juvenile angiofibroma; MRI: magnetic resonance imaging.

incomplete excision, rather than de novo disease. This was corroborated by our results, as among patients who had negative early postoperative MRI, none showed any pJA during radiological follow-up. Therefore, the excellent specificity and negative predictive value of early postoperative MRI led us to conclude that MRI-demonstrated complete excision does not require further radiological investigation and follow-up. In addition to being a cost-effective strategy, this would also have a positive impact on the psychological stress of the young patient and his family, as the patient can be reliably defined as "cured" within days after surgery.

Although early postoperative MRI reduces the potential risk of false positives for the absence of remodeling processes, in some cases suspicious areas can be identified, as seen in two patients in our study. In both cases, however, not all diagnostic criteria were met and the change of signal on the MRI acquired 6 months after surgery confirmed complete excision of the lesion. This result supports a strategy of wait and scan in situations not fulfilling all the three diagnostic criteria for pJA.

Based on our findings, we propose a flow-chart for management of patients after JA resection (Fig. 2). When early postoperative MRI clearly shows persistence (score 3), we suggest to consider immediate revision surgery, depending on the abovementioned factors. An additional MRI for negative uncertain cases (score 1 and 2) should be performed to verify the absence of pJA. An exclusive endoscopic follow-up until complete healing is adequate when postoperative MRI is negative (score 0). Prolonged radiological surveillance is required only for cases of persistence until it is demonstrated to be stable/reduced in size or postpuberal age is reached. Finally, in the event that pJA shows significant growth or in the presence of persistence-related symptoms, re-treatment should be considered.

The following limitations of the study should be highlighted. Since the start of patient enrollment in 2007, not all cases of JA undergoing surgery received early postoperative imaging due to limited availability of slots on our MRI scanners. Early postoperative MRI was definitively introduced into our JA patient management protocol starting in 2015, and therefore, performed systematically in all patients. Finally, our conclusions are based on the analysis of a small number of patients and, although justified by the rarity of the disease, would need to be validated by further studies on larger series.

CONCLUSION

The results of the present long-term prospective study strongly support the use of postoperative MRI within 5 days from surgery as the imaging technique of choice for early detection of unintentional pJA. Although guidelines for diagnosis and treatment of JA are well established in the scientific community, management of pJA and definition of postoperative surveillance are still debated. Our MRI-driven strategy and decisional flowchart, based on a long-standing experience, can help to clarify outstanding issues and aid in the decision-making process in the management of pJA.

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