# Contemporary management of juvenile angiofibroma

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**Purpose of review**
To illustrate the latest developments and trends in the management of juvenile angiofibroma.

**Recent findings**
Endoscopic surgery is currently the primary management strategy for juvenile angiofibroma. Recent reports on the use of multiportal approaches have contributed to further extend its indications. Studies from different countries suggest that the lesion can display variable growth rates not only in relation to patient age. The same concept applies to residual lesions. For this reason, retreatment of persistent juvenile angiofibromas is indicated when serial imaging clearly shows that the lesion is growing. When redo surgery is potentially associated with high morbidity for the critical relationships of the lesion with adjacent structures, stereotactic or intensity-modulated radiation therapy can be an alternative. Early use of MRI in the postoperative course is a highly effective way to detect residual lesions.

**Summary**
Contemporary management of juvenile angiofibroma should primarily rely on endoscopic surgery to obtain radical tumor resection. Recent evidence on the behavior of residual postoperative juvenile angiofibroma and the development of conformal RT techniques have helped to clarify the role of watchful waiting and radiotherapy (RT) as alternatives to aggressive procedures in cases with critical extension of the lesion. Although radical excision is the primary therapeutic objective, the benign nature of juvenile angiofibroma and the reported tendency of small residual lesions to remain stable or involute, especially in postpubertal patients, should always be kept in mind to avoid unnecessary morbidity.

**Video abstract**
In the video, two of the authors describe the content of the review and present the main topics discussed in the article. http://links.lww.com/COOH/A37.

**Keywords**
endoscopic surgery, juvenile angiofibroma, juvenile angiofibroma follow-up

## INTRODUCTION

Juvenile angiofibroma is a benign expansive lesion typically affecting young men [1]. Its etiopathology is controversial as it shows features typical of tumors (i.e. chromosomal abnormalities) and characteristics suggesting a malformative nature (i.e. constant origin along the course of the first branchial artery; leaky vascular walls) [1–8].

In view of clinical and molecular evidence, sexual hormones have been advocated as a possible trigger for tumor growth and angiogenesis [1,9]. However, the precise mechanism explaining this relationship is far from being fully elucidated [1,10,11].

Remarkably, increasing evidence supports the hypothesis that the clinical behavior of juvenile angiofibroma can vary significantly according to geographical area [11,12]. Some authors suggest that this heterogeneity may be justified by the diversity of juvenile angiofibroma biological and genetic features in different countries [6,11,13▪].

Surgery is the current mainstay of treatment, whereas other treatment modalities find a role in selected circumstances [14–16]. Preoperative transarterial embolization followed by endoscopic transnasal resection has progressively emerged as the optimal approach to combine radical excision with limited morbidity [1,15,17,18]. Moreover, several reports suggest that most small postsurgical juvenile angiofibroma residues behave indolently, showing size stability or even regression, especially

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## KEY POINTS

- Contemporary management of juvenile angiofibroma should primarily rely on endoscopic surgery to obtain radical tumor resection.
- Recent evidence on the behavior of residual postoperative juvenile angiofibroma and the development of conformal RT techniques have helped to clarify the role of watchful waiting and RT as alternatives to aggressive procedures in cases with critical extension of the lesion.
- Although radical excision is the primary therapeutic objective, the benign nature of juvenile angiofibroma and the reported tendency of small residual lesions to remain stable or involute, especially in postpubertal patients, should always be kept in mind to avoid unnecessary morbidity.

in postpubertal patients, thus supporting a wait and see approach in selected cases [19▪,20,21].

## CLINICAL BEHAVIOR, PATTERN OF GROWTH AND DIAGNOSIS

The typical clinical presentation of juvenile angiofibroma includes unprovoked and relapsing epistaxis with nasal obstruction occurring in young men. Most advanced cases can also present with sinonasal disturbances, ocular or neurologic symptoms, and facial swelling as a consequence of sinus drainage blockage, intraorbital/intracranial growth and large infratemporal/temporal extension or remodeling of the maxillofacial skeleton [1], respectively.

Juvenile angiofibroma typically grows within the compartments adjacent to the site of origin by dislocating soft tissues and enlarging bony fissures and foramina. Furthermore, juvenile angiofibroma has a specific propensity to grow into the cancellous bone of the sphenoid [16]. The vidian canal and, consequently, the pterygoid process, are typically involved by juvenile angiofibroma and require particular attention during surgery as tumor nests can insidiously invade the medullary portion of the pterygoid root and adjacent floor of the middle cranial fossa [22,23].

Diagnosis is based on its typical clinical presentation and should be confirmed with contrast-enhanced imaging. Information from history, clinical examination with nasal endoscopy and contrast-enhanced computed tomography (CT) or MRI are usually sufficient for reliable diagnosis, without resorting to biopsy, which is discouraged because of a high risk of uncontrollable bleeding.

## TREATMENT PLANNING

### Imaging and staging

Thorough assessment of local extension of the lesion, which is typically performed with contrast-enhanced MRI or CT [16,24], is essential for planning surgery. Both techniques are equally effective in delineating the areas involved by the tumor [16]. On the contrary, while bony remodeling and destruction are equally well depicted by CT and MRI [15], MRI is superior in demonstrating permeation of the cancellous bone, a finding to be taken into due consideration to avoid neglected residues at the pterygoid root, sphenoid greater wing or clivus [1,15,16,24]. MRI is also highly superior to CT in assessing the involvement of cavernous sinus and orbital apex, as well as the relation between the lesion and dura [1,15,16].

On the basis of the pattern of extension, juvenile angiofibroma can be staged using one of the many different available systems [18,25–30]. Those proposed by Andrews *et al.* [25] and Radkowski *et al.* [26] have been most frequently employed. More recently, staging systems have focused on amenability of the lesion to endoscopic surgery [18,27,28,31]. All classifications reflect the increasing difficulty of approaching lesions extending laterally to the infratemporal fossa and cranially to the skull base or the intracranial compartment. Snyderman *et al.* [18] proposed to include the presence of residual vascularity after lesion embolization as a criterion to identify high-stage lesions [31]. The classification introduced by Janakiram *et al.* [29] is meant to guide the selection of surgical approach.

### Angiography and embolization

Management of intraoperative bleeding is probably the most challenging aspect of juvenile angiofibroma surgery. Hence, preoperative angiography and embolization of juvenile angiofibroma are endorsed by most authors [1,14,17,18,32,33]. Preoperative angiography is the best tool to depict vascularization of juvenile angiofibroma, which predominantly receives vascular supply via the external carotid artery (ECA) system [34▪]. Feeders from the internal carotid artery (ICA) system should also be expected in large juvenile angiofibromas [34▪]. According to a recent meta-analysis, bilateral vascular supply is observed in 30.6% of cases, but in series including a high rate of advanced lesions it can rise as high as 69%, thus supporting the need for bilateral angiographic evaluation [34▪].

Embolization is mainly performed with transarterial techniques and recent evidence has demonstrated significant reduction (up to 70%) of

intraoperative blood loss [33,35]. Polyvinyl-alcohol particles are the most frequently used material for transarterial embolization, which must be planned 24–72 h before surgery to avoid revascularization [17]. Other employed materials are coils, microparticles, liquid glue or the ethylene-vinyl alcohol copolymer Onyx (ev3, Irvine, CA, USA) [17]. The risk of complications after embolization is not negligible, ranging from 2.4 to 59.4% for major and minor complications, respectively [36]. Severe neurological complications are related to inadvertent reflux of embolization material through inconstant anastomoses with the ICA system, whereas other ischemic complications can be attributed to the ECA system (e.g. nasal/tonsillar necrosis and alopecia) [36,37]. Some authors have reported successful surgical treatment of juvenile angiofibroma at all stages with acceptable blood loss without embolization [38–40]. In these series, bleeding was controlled by ligating the ECA via a transcervical approach and/or clipping the main afferent vessels before beginning to dissect the lesion during the endoscopic procedure [38,39]. Remarkably, ECA ligation precludes the possibility of future transarterial embolization. Residual vascularization of juvenile angiofibroma after embolization is usually related to the presence of feeders from ICA [34▪]. Although embolization of ICA branches is technically feasible, it is related with a high risk of severe complications (stroke, visual loss, facial paralysis or carotid dissection) [1,41,42]. In such cases, direct embolization has been proposed, even though it is marred by a high risk of severe complications [43]. The introduction of Onyx has renewed interest in the technique, as this embolization material is less subject to inadvertent migration [17]. Finally, in cases of ICA encasement, staged surgery or leaving residual tumor are the options that should be considered.

### Surgical approach planning

The goal of surgical treatment is complete removal of juvenile angiofibroma. The need for delayed revision surgery should be minimized as scarring and loss of surgical landmarks significantly increase the difficulty of surgery. Alternative treatment modalities such as radiotherapy can be considered to treat residual juvenile angiofibroma in critical locations [44].

Endoscopic surgery is currently the primary management strategy for juvenile angiofibroma. The advantages in comparison to traditional approaches include better visualization of deep anatomical structures and tumor limits, lower intraoperative blood loss and recurrence rate, and shorter hospitalization [32]. Open approaches such as transpalatal, transfacial through lateral rhinotomy, mid-facial degloving and Le Fort I osteotomy, or infratemporal type D may still be preferred to manage large juvenile angiofibromas with intracranial extension although they are associated in different way with facial scarring, cerebrospinal fluid (CSF) leak, facial and infraorbital nerve damage, lacrimal dysfunction, facial deformities, trismus, dental malocclusion and alteration of craniofacial growth [1,16,29,45,46]. Moreover, multiportal approaches (i.e. combination of transnasal-transmaxillary, transorbital, transoral and/or transcranial corridors) have recently evolved in the attempt to reduce surgical morbidity [39,47–50].

In case of involvement of critical areas, the risks of surgery against the possible ensuing morbidity should be carefully evaluated. In fact, the risks related to aggressive surgery may outweigh the problems associated with intentionally leaving juvenile angiofibroma residues in critical areas, especially in patients who are at the end of their stature growth cycle or sexual development [19▪]. In this scenario, residues are expected to grow slowly, remain stable or even regress, as spontaneous involution of residual/primary juvenile angiofibromas has been described [19▪,45]. Staged resection to address different components of large juvenile angiofibroma can mitigate surgical morbidity by reducing blood loss and need for multiple transfusions [15,16]. In addition, radiotherapy could be considered to treat symptomatic or growing juvenile angiofibroma residues [44,46].

## ENDOSCOPIC SURGERY

The endoscopic approach to juvenile angiofibroma follows a number of key principles. First, the lesion must be extensively exposed without traumatizing its surface [35], through a middle turbinectomy, ethmoidectomy, wide antrostomy and sphenoidotomy [35]. The posterior maxillary wall is removed to access the pterygopalatine and infratemporal fossae [35]. Further lateral and caudal exposure can be achieved following the concept of modular endoscopic medial maxillectomy [51]. Posterior septectomy allows wide exposure of the nasopharynx and facilitates a bi-nostril, four-handed technique [16]. A sublabial-transantral approach through the anterior maxillary wall may be considered in alternative [52]. To increase exposure and ease the procedure, multibloc resection may also be helpful in multicompartmental juvenile angiofibroma [14,45,52].

At this point, detection and control of maxillary artery and its branches is undertaken. Subsequently, attention should be focused on identifying the correct dissection plane between juvenile angiofibroma

and surrounding tissues. Remarkably, identification of juvenile angiofibroma surface is obtained by incising the periosteum of the posterior maxillary wall [16]. Hemostatic materials can be used to control bleeding from venous plexuses. Hemostasis is also facilitated by continuous irrigation with warm water (40–45°C) and/or temporary packing with cottonoids [16]. Careful dissection and gentle traction allow to progressively pull out projections of juvenile angiofibroma that extend beyond the field of exposure [16].

As previously mentioned, the pterygoid root is considered the hotspot of juvenile angiofibroma and can harbor hidden lesion nests that might be overlooked during surgery [23]. Extensive drilling of this area is recommended to prevent persistence, which frequently occurs at this site [23].

Cavernous sinus involvement can be related to invasion through the foramen rotundum or orbital apex, which can be managed endoscopically with the help of hemostatic materials and intraoperative ultrasound doppler to map the course of the ICA [16]. When juvenile angiofibroma encases the ICA, surgical dissection is hazardous; a balloon occlusion test should be performed, a two-step surgery must be considered and the possibility to leave residual lesion must be discussed with the patient, parents or legal guardian [16].

Intracranial extension is present in 10–20% of advanced lesions, but transdural growth is exceedingly rare [1,16]. Intracranial juvenile angiofibroma can be gently pulled and detached from dura, thus obviating the need for more extensive procedures [1,16,45].

Whenever ICA remains extensively exposed in the surgical field, the vessel should be covered with vascularized tissue (i.e. naso-septal flap) to avoid arteritis and spontaneous carotid blowout.

### Complications

The complications of endoscopic surgery for juvenile angiofibroma are essentially related to the extent of the procedure. Sectioning of the vidian and palatine nerves leads to reduced lacrimation and palatal hypoesthesia, respectively [53]. Type D endoscopic medial maxillectomy has been associated with hypoesthesia in the region of the infraorbital nerve and anterior superior alveolar nerve and increased risk of nasolacrimal duct stenosis [53,54,55]. Extended procedures with dissection along the trigeminal nerve may elicit the trigeminocardiac reflex, which may cause fatal alterations of cardiac rhythm [56]. Dissection along the ICA may cause rupture of the vessel.

## POSTOPERATIVE MANAGEMENT AND FOLLOW-UP

Follow-up aims at evaluating the presence and growth of residual juvenile angiofibroma. Presence of juvenile angiofibroma after surgery should be considered persistence resulting from incomplete excision rather than recurrence.

Early postoperative contrast-enhanced CT can identify persistent juvenile angiofibroma within 48–72 h after surgery [45,57]. In our experience, early postoperative MRI provided an excellent rate of identification of residual juvenile angiofibromas (unpublished data). In patients with positive early imaging, immediate redo surgery should be considered to take advantage of the absence of postsurgical remodeling of tissues surrounding the residue [57] (Fig. 1).

The growth kinetics of juvenile angiofibroma is variable and probably related to hormonal changes, as it can shift from rapid growth during infancy–adolescence to slower evolution/spontaneous regression following sexual development [19▪]. Relevant growth of persistent juvenile angiofibroma is unlikely in postpubertal patients, being anecdotally reported only in a 36-year-old individual undergoing testosterone supplementation [58]. The optimal follow-up frequency proposed by Rowan *et al.* [19▪] is every 6 months, who reported a median time to progression after surgery of 7.5 months. On the basis of these observations, it can be hypothesized that at the end of puberty patients with negative postoperative imaging may have a very low chance of developing a recurrence, and long-term surveillance is probably not mandatory [19▪]. On the contrary, juvenile angiofibroma should be monitored closely during puberty until overall stability or nonrelevant growth of the lesion is demonstrated [19▪].

## NONSURGICAL MANAGEMENT

### Radiotherapy

The current role of radiotherapy in the management of primary or persistent juvenile angiofibroma is limited to lesions involving critical intracranial structures not amenable to surgery because of morbidity concerns [44,59]. As previously mentioned, watchful waiting could also be a reasonable alternative in properly selected cases of persistent juvenile angiofibroma [1,19▪,45].

The main issue limiting the employment of radiotherapy is the poorly known long-term effects of treatment, as only about 200 cases have been described [44]. Radiotherapy is usually administered with reduced radiation doses (35–50 Gy) and offers a rate of local control of an 85–92% [44,60]. Complications include malignant transformation of juvenile

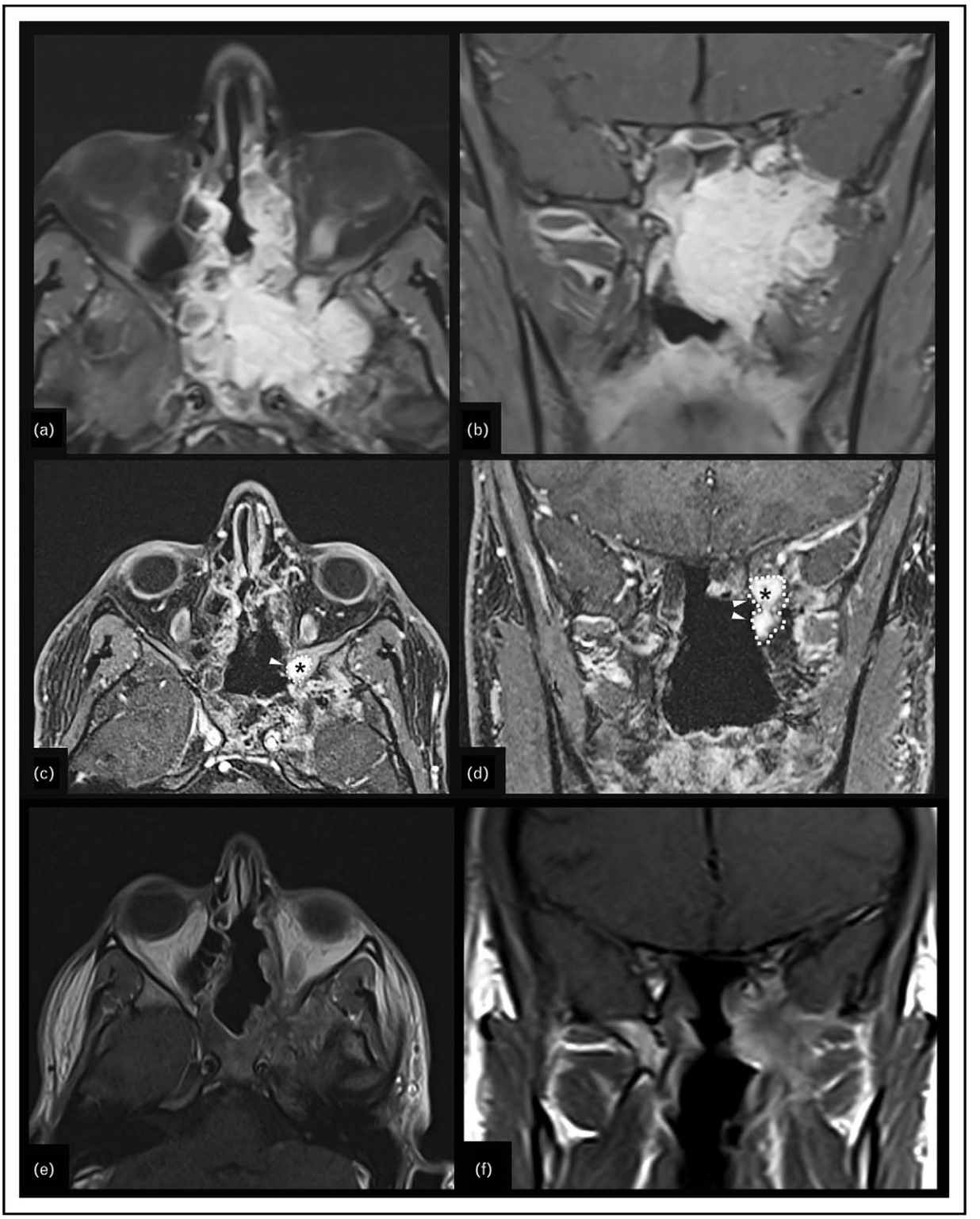


**FIGURE 1.** The figure illustrates the case of an 18-year-old patient who had undergone endoscopic resection of JA 2 years before at another center; JA imaging is shown before (a, b) and after revision surgery (c, d). Figures a and b (axial and coronal T1 weighted sequences) show the extension of the growing recurrent lesion before surgery performed at our Institution. Surgical dissection was very challenging because of the presence of abundant scar tissue surrounding the lesion. Despite apparent radical resection, 48 h after surgery an unexpected persistent JA was recognized by postoperative MRI as highly contrast-enhancing tissue on axial (c) and coronal (d) T1 sequences (marked with asterisk and dotted outline). Further revision surgery was performed 1 day later and complete removal of JA was achieved, as confirmed by postoperative MRI on axial (e) and coronal (f) T1 sequences. JA, juvenile angiofibroma.

angiofibroma, cutaneous or thyroid neoplasms, cataract, xerostomia, caries, brain necrosis and growth retardation [44]. Of note, most complications are reported in older series that included patients treated with nonconformal radiotherapy techniques or higher cumulative radiation doses [44,59].

Radiosurgery has also been described as a possible treatment for small, well-defined, residual juvenile angiofibromas [61]. However, even this technique is not free of complications and a case of delayed CSF leak has been reported [62].

### Chemotherapy and hormonal therapy

The use of medical therapy, hormonal or cytotoxic, in juvenile angiofibroma has been attempted with the aim of either interrupting the growth of the lesion before/after surgery or reducing tumor size and facilitating its excision [10].

Currently, chemotherapy does not have a role in the treatment of juvenile angiofibroma because of its toxicity [63]. Hormonal therapy offers the possibility to achieve a reduction in tumor volume of 17–29% [10,63–66]. The proposed treatment, which is based on a daily regimen of 10 mg/kg of flutamide administered for 6 weeks [10], targets testosterone and dihydrotestosterone receptors. Unfortunately, prepubertal patients, who would benefit the most from this therapy, respond poorly to treatment [10]. Moreover, CSF-leak has been described as a possible complication of hormonal therapy in a case of juvenile angiofibroma involving the anterior skull base [67].

## FUTURE PERSPECTIVES

Increasing knowledge in the field of molecular biology of juvenile angiofibroma is paving the way toward implementation of treatment with medical therapy. Some preclinical evidence suggests a possible role of AZD4547 and propranolol in the future therapy of juvenile angiofibroma by virtue of the ability to target the stromal component of juvenile angiofibroma, reducing activity of fibroblasts and mesenchymal–endothelial transition, respectively [2,68]. Bevacizumab, an antivascular-endothelial-growth-factor (VEGF) antibody, is an intriguing option in view of the high expression of VEGF in juvenile angiofibroma cells [1,3–5]. Glucocorticoids are interesting agents as they downregulate the activity of VEGF [69].

## CONCLUSION

Contemporary management of juvenile angiofibroma should primarily rely on endoscopic surgery to obtain radical tumor resection. Indeed, recent evidence on the behavior of residual postoperative juvenile angiofibroma in relation with patient growth [19▪], and the development of low-morbidity conformal RT techniques [44], has helped to better define the role of watchful waiting and RT as alternatives to extended procedures with potential high morbidity in cases with critical extension of the lesion. Although radical excision is the primary therapeutic objective, the benign nature of juvenile angiofibroma and the reported tendency of small residual lesions to remain stable or involute [19▪] should always be kept in mind in the decision-making process.

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### Conflicts of interest

*There are no conflicts of interest.*

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