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Stereotactic Gamma Knife Radiosurgery for Extracranial Arteriovenous Malformations

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Abstract

Introduction: Head and neck extracranial arteriovenous malformations (AVMs) are rare pathological conditions which pose diagnostic and reconstruction challenges. Stereotactic radiosurgery (SRS) is nowadays an established treatment method for brain AVMs, with high obliteration and low complication rates. Here we describe the first report of head extracranial AVMs successfully treated by Gamma Knife (GK) as a retrospective historical cohort. ***Methods:*** Over a 9-year period, 2 cases of extracranial AVMs were treated by GK Perfexion (Elekta Instruments AB, Stockholm, Sweden) at a single institution. A stereotactic frame and multimodal imaging, including digital subtraction angiography (DSA), were used. The prescribed dose was 24 Gy at the 50% isodose line. ***Results:*** The first case was of a patient with pulsating tinnitus and left superficial parotido-condylian AVM. Embolization achieved partial obliteration. Tinnitus disappeared during the following 6 months after GK. The second case was a patient with repetitive gingival hemorrhages and right superior maxillary AVM, fed by the right internal maxillary and facial arteries. Embolization achieved partial obliteration with recurrence of symptoms. GK was further performed. DSA confirmed complete obliteration in both patients. ***Conclusions:*** Single-fraction GK radiosurgery appears to be safe and effective for extracranial AVMs. We recommend prescribing doses that are comparable to the ones used for brain AVMs (i.e., 24 Gy). A stereotactic frame is an important tool to ensure higher accuracy in the context of these particular locations. However, in selected cases, a mask could be applied either for single fraction purposes (if in a non-mobile location) or for hypofractionation, in case of larger volumes. These findings should be validated in larger cohorts, inclusively in terms of dose prescription.

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Introduction

Arteriovenous malformations (AVMs) in general are characterized by the presence of abnormal connections between the arterial and venous system, while lacking the intervening capillaries. The high-pressure, high-flow arteriovenous shunts are considered to form as a result of pathologic vascular development between the 4th and 6th gestational week [1]. Their natural history, as well as their respective prevalence, are not completely elucidated. The size of AVMs may vary over time, including increasing, decreasing, or even disappearing [2]. The risk of hemorrhage is 2–4% per year [3]. Morbidity rates also vary depending on the study, ranging between 4 and 30% [4].

The management of intracranial AVMs includes observation, microsurgical excision, endovascular treatment, and stereotactic radiosurgery (SRS). These treatment techniques can be used alone or in combination, in the frame of a multimodal approach [3, 5]. Microsurgery directly approaches the AVM, using a sequence of steps which are well defined and include coagulation and clipping of the arterial pedicle, followed by nidus ablation and exclusion of the abnormal drainage vein [6]. Endovascular treatment is based upon injection of embolization agents (coils, glue, Onyx). SRS is a non-invasive approach and generates a progressive obliteration, usually after a mean period of 2 years. The adverse radiation effects (AREs) are considered low and 5-year obliteration rates vary between 70 and 80% [7–10]. Multidisciplinary management is considered the key for optimal patient treatment.

Head and neck AVMs are extremely rare [11]. Their particularities are mainly related to diagnosis challenges and reconstructive issues [12]. Furthermore, from a stereotactic point of view, they are situated either outside the frame space or in mobile regions. Only two previous reports have described radiotherapy (RT) [13] and Cyberknife (CK; Accuray, Madison, WI, USA) SRS [14] as a treatment for these rare conditions.

Here, we present the first report of 2 cases of extracranial AVMs, treated with single fraction Gamma Knife (GK; Elekta Instruments AB, Stockholm, Sweden) SRS. The clinical context, as well as the course after treatment, is described. Both were located in the lower part of the face, which is even more rare, accounting for approximately 17% of cases, as previously reported [14]. We hypothesized that using similar radiation doses as for brain AVM would achieve obliteration with minimal complication rates.

Methods

Patient Population

This is a retrospective historical cohort of 2 cases with extracranial AVMs. According to Swiss regulations, for this type of report there is no need for ethical committee approval. In fact, for describing series of less than or equal to 3 cases, there is no need for ethical committee agreement if they are retrospective historical cohorts. We previously published the results of our center for the overall series of AVMs treated with GK as first intention treatment or in the context of multimodal management [15].

Radiosurgery Treatment

Both patients were treated with a Leksell Gamma Knife Perfexion™ (Elekta Instruments) by the same operators (M.L., C.T.) during the specified timeframe. Dosimetry planning was performed using Leksell Gamma Plan (LGP version 10.0 and 11.0; Elekta Instruments).

We always apply the Leksell Model G stereotactic frame (Elekta Instruments) under local anesthesia. All patients undergo stereotactic imaging on the day of GK. We use multimodal stereotactic imaging for target definition: digital subtraction angiography (DSA), followed by MRI (including time-of-flight, TOF, sequences, 0.6-mm slices) and CT-angiography.

Mandibular Fixation

A mandibular fixation was performed in illustrative case 1 (see the Results section) to ensure the absence of any undesired movements and its use has been previously reported [16]. In fact, in 2016 we published a paper on our technique of jaw immobilization in patients with mandibular lesions [16]. The same approach was applied here (case 1).

As an important aspect, the Leksell G stereotactic frame was still applied in both cases. The mandibular fixation is further used before and during stereotactic neuroimaging, and also during the GK treatment, so as to ensure immobilization and reproducibility between the patient's jaw position at the time of MRI, DSA, and CT, and during ongoing radiation delivery.

The Fiducial Box

The fiducial box is classically used to acquire the stereotactic neuroimaging during the treatment day, particularly for MRI and CT, as in usual GK procedures.

Potential Collisions

There were no collisions in either of the illustrated cases.

Follow-Up Course

Follow-up MRI and clinical outpatient visits are performed at 6, 12, 24, and 36 months. When the AVM is considered obliterated on the MRI, an angiography is scheduled as a gold standard to confirm definitive obliteration.

Results

Illustrative Case 1

A 40-year-old patient complained of left-sided pulsating tinnitus, which appeared 4 years before SRS. MRI and

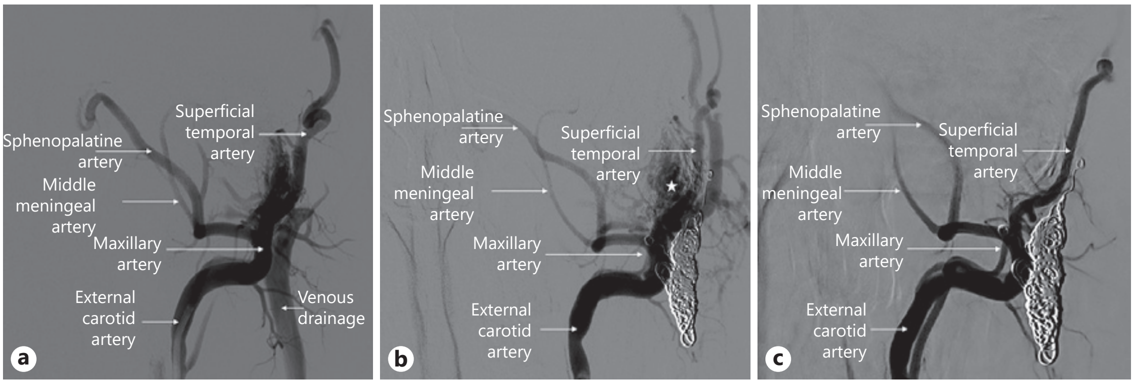

Fig. 1. Case 1: DSA prior to (**a**), at the time of (**b**), and 3.5 years after (**c**) the GK SRS – left superficial parotido-condylian AVM.

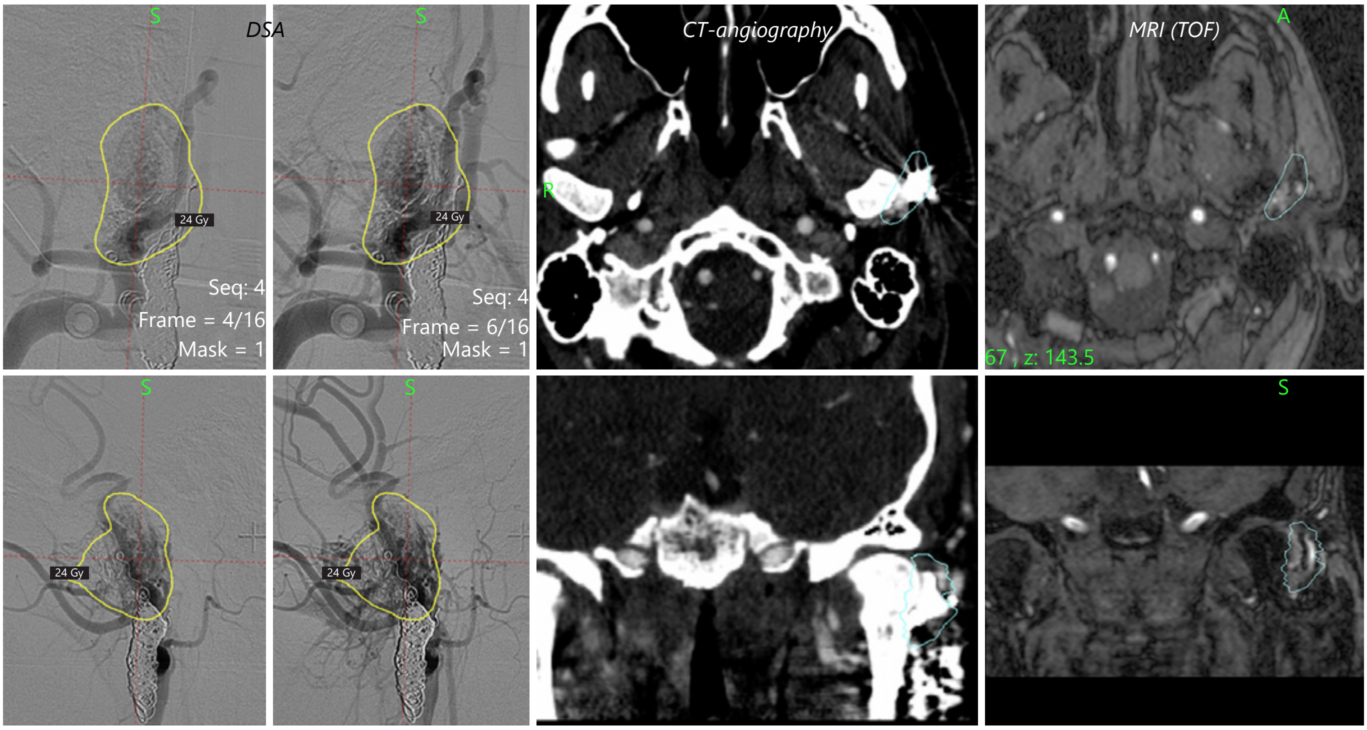

Fig. 2. Case 1: GK treatment plan, showing multimodal imaging (DSA, MRI-TOF, and CT-angiography).

angiography revealed a left superficial parotido-condylian AVM draining into the left internal jugular vein. Twelve months from the initial diagnosis, an uneventful embolization with an estimated obliteration rate of approximately 90–95% was performed. The occlusion was achieved using coils via the external jugular vein and the AVM nidus was occluded by the Onyx transarterially. Following this procedure, the patient reported partial improvement of his tinnitus.

The control digital subtraction angiography (DSA) was performed 2 months later, revealing vascular neo-recruitment associated with the reconstitution of the two posterior thirds of the nidus. Moreover, after the segmental occlusion of the left external jugular vein, the venous drainage pattern was altered, with the major draining by the inferior ophthalmic vein and the ipsilateral pterygoid plexus.

SRS by GK was further performed. The target volume (TV) was 3.76 cm^3 and the prescription isodose volume

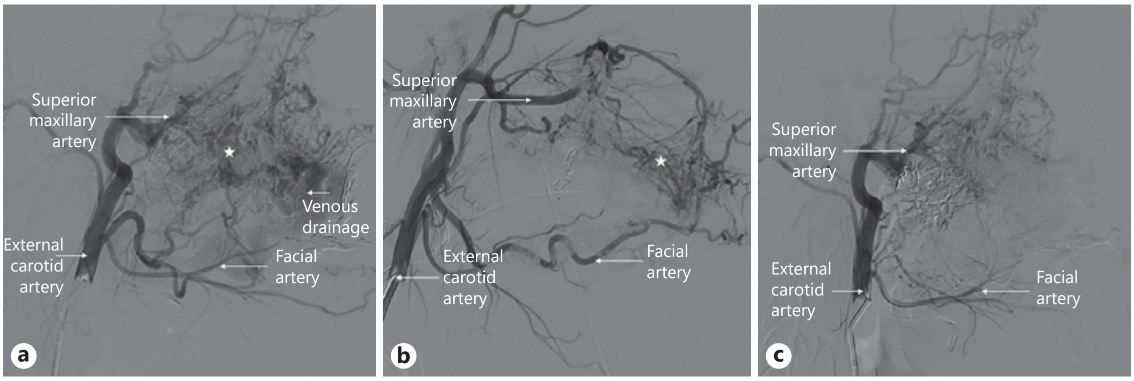

Fig. 3. Case 2: DSA prior to (**a**), at the time of (**b**), and 3.5 years after (**c**) the GK SRS – right superior maxillary AVM.

(PIV) was 6.42 cm^3. The maximum marginal dose prescribed was 24 Gy at the 50% prescription isodose line (Fig. 1, 2). The conformity, the selectivity, the Paddick, and the gradient index were 1.000, 0.586, 0.586, and 2.447, respectively.

After GK, the pulsatile tinnitus disappeared within 2 months and no new symptoms or signs reappeared during the follow-up period of 3.5 years. MRI performed 7 months after GK showed the disappearance of the arteriovenous shunt. The result was confirmed 1 month later with DSA, which proved the complete disappearance of the left parotido-condylian AVM (Fig. 1). The last MRI at 3.5 years after the GK confirmed the absence of recurrence of the arteriovenous shunt.

Illustrative Case 2

A 16-year-old female examined for repetitive gingival hemorrhages was diagnosed with a right superior maxillary AVM fed by the right internal maxillary and facial arteries. Endovascular embolization using Onyx, coils, and histoacryl via the afferents from the right external carotid artery was performed leading to approximately 90% obliteration with temporary diminution of the gingival bleeding.

Five months later, the daily gingival hemorrhage had recurred. DSA revealed the nidus reconstitution with multiple diffuse afferents from the facial and both internal maxillary arteries draining via the right facial vein with reflux into the right angular vein. Because of important recanalization, a second embolization was performed, leading to 95% obliteration with minimal residual venous drainage via the left facial vein. Two months after the second embolization, SRS by GK was performed on the residual AVM. The TV was 4.21 cm^3 and the PIV was of 4.32 cm^3. The maximum marginal dose was 24 Gy at the 50% prescription isodose (Fig. 3, 4). The conformity, the selectivity, the Paddick, and the gradient index were 0.990, 0.965, 0.956, and 2.7, respectively.

The post-GK clinical course was complicated by an acute oral mucositis (Fig. 5), which appeared in the first week following GK. A short-term (1 week) corticosteroid treatment was successful, with immediate disappearance of the symptoms. No other AREs were experienced by the patient. Ultimately, 7 months after GK, DSA confirmed a major reduction of the AVM nidus (Fig. 3). An eventual additional treatment for the persistence of the minimal arteriovenous shunt with early venous enhancement of the right superior maxillary artery was evoked. However, the patient remains asymptomatic up to 3 years after SRS, with no gingival hemorrhage reappearance. The final conclusion was that the AVM was obliterated, and that the MRI changes are those classically encountered after SRS by GK.

Discussion

To the best of our knowledge, here we report the first cases of extracranial AVMs treated with SRS by single-fraction GK. These are rare entities characterized by continual growth leading to the focal destruction of superficial and deep underlying tissue [14, 17]. Compared to the well-established role of SRS in the management of cerebral AVMs, very little is known about its therapeutic effect on extracranial AVMs. The most common reported treatment in these particular instances remains endovascular therapy [18] followed or not by surgical resection, depending on the context [19]. It has been previously ac-

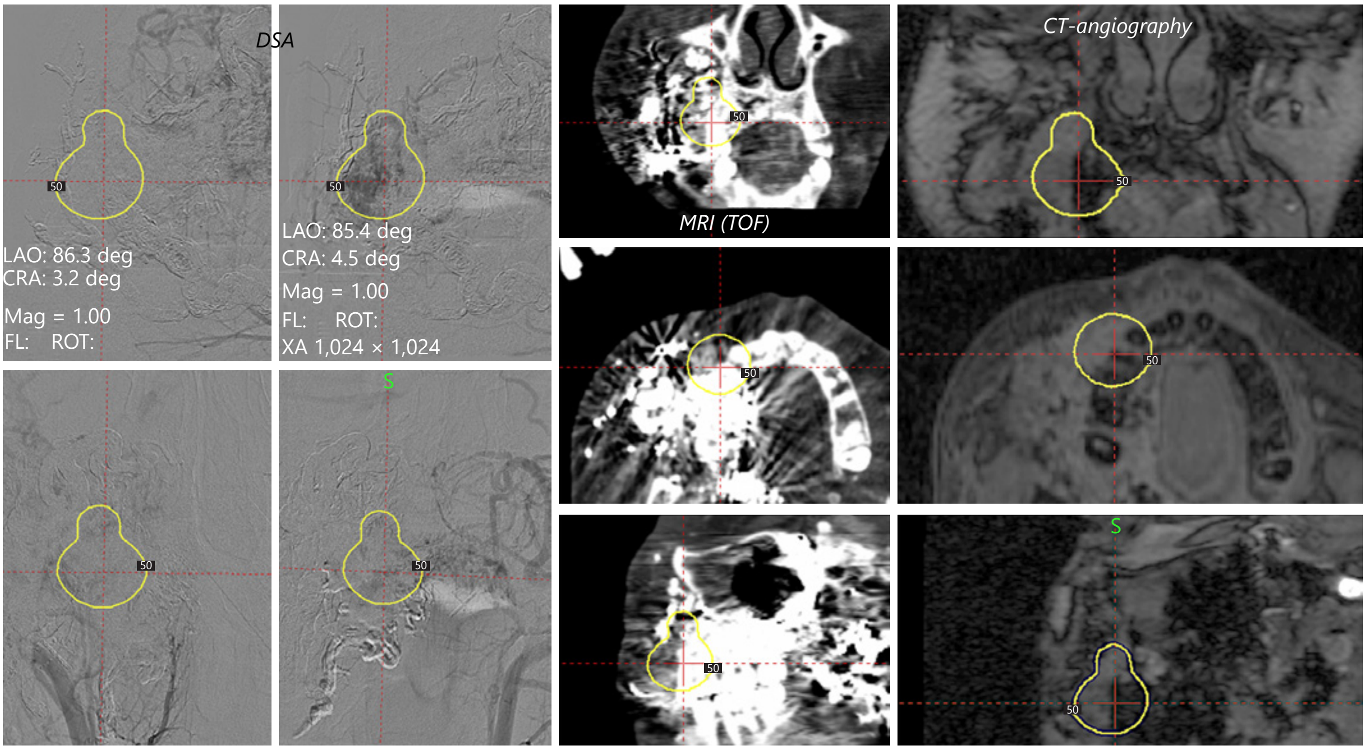

Fig. 4. Case 2: GK treatment plan, showing multimodal imaging (DSA, MRI-TOF, and CT-angiography).

Fig. 5. Transient oral mucositis (arrows) as an ARE in case 2.

knowledged that multiple embolizations appear to increase safety in the treatment of extracranial AVMs and suggest an additional positive effect besides bleeding control [18]. However, reported recurrence rates are as high as 81% [12]. In our experience, both cases were managed with combined therapies, including embolization with further SRS in a single fraction. The prescribed marginal dose was 24 Gy at the 50% isodose line, which is the optimal dose for obtaining cerebral AVMs with SRS [7], as discussed below [8, 20, 21]. The selectivity index was considered less relevant in these cases, due to the absence of critical and risk structures surrounding the lesions, and the potential use of larger collimators to decrease the treatment time, etc. One case experienced the disappearance of pretherapeutic tinnitus and the other case experienced a transient ARE, in the form of an oral mucositis, which disappeared 1 week after corticosteroid treatment. Both patients now have more than 3 years of follow-up with no other side effects being documented. The AVMs are considered obliterated.

SRS is a safe and effective alternative to surgical resection in the management of cerebral AVMs, primarily in patients considered to be of high surgical risk [22–24]. The most important factor associated with nidus obliteration is the prescribed radiation dose [7]. The documented rates of obliteration range from 60 to 70% for margin doses of 15–16 Gy, and more than 90% for margin doses of 20–25 Gy [25]. The marginal dose of more than 20 Gy is classically associated with higher obliteration rates ($p = 0.001$) [26]. Partially embolized AVMs are typically associated with lower obliteration rates after GK [27].

To the best of our knowledge, to date only two case reports have described the use of SRS for the treatment of the extracranial AVMs. Saito et al. [14] documented the first case of extracranial AVMs at the level of the tongue, treated by CK. The patient was previously treated by embolization, lingual artery ligation, and partial nidus resection, as part of a complex management strategy. However, DSA revealed the persistence of the AVM nidus, despite all of these therapies. The treatment by CK, with a 22-Gy marginal dose prescription for a TV of 0.130 mL, was performed in two fractions with a 24-h interval (as an equivalent to 16 Gy in a single fraction). A complete obliteration of the AVM was documented by DSA at 34 months after the CK SRS [14]. The second case was reported by Koyfman et al. [13], who published a case of left infratemporal fossa and right-sided tongue AVMs treated by stereotactic body RT (SBRT). Although two extensive surgical resections and 8 embolizations were realized, the clinical status of the patient was aggravated. He developed left-sided vision and hearing loss and intractable facial pain. The SBRT using a 24-Gy prescription dose to 88.8 and 92.4% isodose lines (left and right TVs) to the treatment volume of 0.177 mL was realized in three fractions (one fraction per week). The clinical course was satisfactory. After 4.5 years of follow-up, facial symmetry was improved and the size and pulsatility of the left buccal AVM was diminished, but not fully obliterated [13].

A question this raises is whether these patients might benefit from single versus hypofractionated SRS. The balance between the prescribed dose and the TV, as well as the 12-Gy isodose volume (relevant for the radiobiology of AVMs, AREs, and obliteration) [28] should be further taken into account. We favored a therapeutic dose of 24 Gy at the 50% isodose line in a single session, based on the previously published data regarding the prescribed dose as a major factor for further obliteration. However, such a dose should be validated in larger cohorts. In these reports including 2 patients, no osteonecrosis was encountered. We do not consider stage-volume SRS or hypofractionation in cases where a single-session SRS is feasible. In our present case reports, both the TV and PIV were small. Furthermore, the surrounding tissues did not contain major risk structures. If needed, larger TVs could be also treated with the new Leksell GK ICON, using a hypofractionated SRS approach [29]. This approach is performed using a mask, so caution should be further taken for lesions close to the mandible and the potential array of movement. Although one of the arguments usually put forward for the use of fractionation is the avoidance of complications, side effects were reported both in our series, using a single fraction, as well as in the other two series, using a fractionated SBRT or multiple sessions of CK SRS.

Indeed, even if SRS seems a promising complementary treatment for extracranial AVMs, it is not complication free. Considering the early complications, Saito et al. [14] reported a minimal inflammation of the oral cavity, pharynx, and larynx, which was successfully treated by a frozen sodium azulene sulfonate ball orally and dexamethasone sodium phosphate intravenously [14]. Similarly, in our second patient, the post-SRS period was complicated by a transient oral mucositis, which was successfully treated by corticosteroids. Koyfman at al. [13] described the development of intractable facial pain in the month following SRS which necessitated the insertion of an intrathecal pain pump [13]. Follow-up of these 4 patients treated by SRS ranged from 7 to 54 months (7, 34, 42, and 54 months, respectively); however, only minor AREs were reported in the form of the moderate xerostomie, mild trismus, and skin fibrosis [13]. Other risks related to such treatment strategies might be gum/tooth loss as late effects. With the current follow-up period, we did not encounter such AREs. Another concern is related to late progression of these frequently growing vascular malformations. Targeting the vascular lesion after embolization (with the risk of recanalization) could be a real problem.

As an alternative to minimally invasive techniques, such as SRS and embolization, microsurgical resection can also be proposed [30]. As an example, Panda et al. [31] reported 12 patients with head and neck AVMs, with 10 undergoing embolization which was followed by surgery. Complete excision was achieved in 8 cases while partial resection was achieved in 2 cases; 3 patients had complications while being treated (the most common were pain, bleeding, and failure of the reconstruction flap requiring revision surgery) [31].

The limitations of the current report are mostly related to the limited number of cases. Furthermore, the retrospective nature with the inherent bias remains a concern. One could also discuss the absence of a long-term angiography with further absence of recanalization. Another question that should be considered is, outside the brain, how accurate is the assumption of uniform density in the dose calculation algorithm used by the Gamma Plan? In this sense, we did not perform any dose correction for tissue inhomogeneity prior to delivery. An open question is also whether radio-opaque shielding could ever be introduced between the AVM and normal, adjacent structures, such as teeth or tongue, to reduce the chance of radiation-related side effects.

Conclusions

The role of single-fraction SRS in the management of extracranial AVMs is not well established. Our series of 2 cases adds to the sparse literature. To the best of our knowledge, only few cases of the head and neck AVMs treated by SRS or SBRT have been reported. The results in terms of obliteration and complication rates are rather promising. Radiosurgery could become an alternative to embolization, which is currently the most used therapeutic method. We recommend performing single-fraction SRS while prescribing a marginal dose of 24 Gy by analogy to intracranial cerebral AVMs. We recommend the use of a stereotactic frame due to the need for special accuracy in these cases. We consider that the mask could be used in selected cases, either in the setting of single-fraction treatments, or in cases when higher volumes need to be treated to avoid multiple endovascular and/or surgical interventions, with their potential further impact on the patient's esthetics. We recommend a multidisciplinary team, with special help from neuroradiology colleagues, also to help addressing the particular angiographic context. We conclude, based on our experience, that radiosurgery can be considered as a first or second alternative in these rather challenging cases.

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Statement of Ethics

The research presented here was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and the appropriate guidelines for human studies as well as according to animal welfare regulations, including the Animal Research: Reporting of in vivo Experiments (ARRIVE) guidelines, and was approved by the appropriate institutional review bodies. For this type of study, formal ethical committee approval is not necessary.

Conflict of Interest Statement

Constantin Tuleasca is a scientific advisor for Elekta Instruments AB, Stockholm, Sweden, without any relation to the present manuscript. The other authors report no conflicts of interest.

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Author Contributions

Each author: (1) made substantial contributions to the conception or design of the work, or to the acquisition, analysis, or interpretation of data for the work; (2) participated in drafting the work or revising it critically for important intellectual content; (3) approved the final version to be published, and (4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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