Natural history of cavernous sinus meningiomas

Aymeric Amelot, MD, PhD,^{1,2} Remy van Effenterre, MD, PhD,^{1,2} Michel Kalamarides, MD, PhD,^{1,2} Philippe Cornu, MD, PhD,^{1,2} and Anne-Laure Boch, MD, PhD^{1,2}

¹Department of Neurosurgery, Groupe Hospitalier Pitié-Salpêtrière, APHP; and ²Université Paris VI–Pierre et Marie Curie, Paris, France

OBJECTIVE Meningiomas confined to the cavernous sinus (MCSs) are benign tumors. Due to the high risk of severe complications, the intracavernous surgical procedure was abandoned in favor of radiotherapy. However, the choice of treatment remains complicated due to the fact that the natural history of this lesion has not yet been described.

METHODS The authors studied the natural history of this lesion using a prospective series of 53 consecutive patients suffering from MCSs. The median follow-up duration was 10.2 years (range 2–25 years), from 1990 to 2016.

RESULTS Patients ranged in age from 30 to 72 years (mean 53 years). The meningiomas were diagnosed by major symptoms (mainly oculomotor palsy and neuralgia experienced in 28 patients), minor symptoms (headache, intermittent diplopia in 15 patients), or incidental findings (10 patients). Simple symptomatic treatment (short courses of corticosteroids and carbamazepine) allowed patients to become asymptomatic in 19 (67.9%) of 28 cases experiencing major symptoms, and for 12 (80%) of 15 patients with initial minor symptoms ($p < 0.0001$). All patients with incidental findings remained asymptomatic. Forty four (83%) of 53 MCSs did not show any significant growth and 42 (80%) of 53 patients were not symptomatic at the end of follow-up ($p < 0.001$). The radiographic progression-free survival rates ($\pm$ SD) at 5, 10, and 20 years were $90\% \pm 4.2\%$, $82\% \pm 5.7\%$, and $70\% \pm 10.2\%$, respectively. Five patients (9.4%) with no evidence of any effect of the initial medical treatment desired additional conventional radiation therapy.

CONCLUSIONS Because of the capricious, unpredictable, and slow growth of MCSs, together with high growth variability from one patient to the next, the symptomatic medical treatment of these tumors is a highly effective method. This series shows that these lesions are naturally, clinically, and radiologically indolent.

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KEYWORDS cavernous sinus meningioma; treatment; natural history; corticosteroids; oncology

TUMORS involving the cavernous sinus (CS) are rare lesions, which represent less than 1% of all intracranial tumors. Meningiomas are the most common tumors of the CS (MCSs; 41%), accounting for 1.8% of all intracranial meningiomas.^{19,20} The symptoms caused by MCSs are related to compression of neighboring cranial nerves (CNs): VI (80%), V, IV, III (30%), and II.^{10,22}

There are many heterogeneities for the definition of MCSs. MCSs with an extracavernous extension (sella, temporal, clivus), sphenocavernous meningiomas secondarily invading the CS, and meningiomas strictly confined to the CS are studied and described without any anatomical distinctions and without any details on the initial location,

although both are different entities. In this work we have exclusively studied the meningiomas confined to the CS.

MCSs appear as an entity that is based only on radiological diagnosis. In typical forms, biopsy is unnecessary. The diagnosis is retained on MRI: a slender and nonglobular lesion, expanding the CS, typically enhanced in a dove-tail-shape during Gd contrast injection (Fig. 1). If there is any doubt about the diagnosis and whether it is a different lesion, the meningioma can be confirmed by a CT scan that allows for an examination of specific radiological criteria such as lateral edge sphenoid hyperostosis and/or a slightly thickened clinoid.²⁷

Due to various associated risks such as venous bleeding

ABBREVIATIONS CN = cranial nerve; CS = cavernous sinus; MCS = meningioma of the CS; PFS = progression-free survival.

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FIG. 1. Axial brain T1-weighted MRI with Gd in CS meningeiomas showing examples in patients with an incidental finding (A), minor symptoms (B), and major symptoms (C).

(which is difficult to control), wounds in the internal carotid artery, intratumoral bleeding, and morbidity caused by accidental damage to the oculomotor nerve or trigeminal nerve, surgical approaches to the CS have practically been abandoned.²³ Surgery is sometimes necessary and recommended only for extracavernous portions of sphenocavernous meningeiomas. Radiation therapy is now the standard treatment of MCSs, but its mid- and long-term complications should not be underestimated.

What complicates the choice of a treatment strategy for MCSs is an essential point: the poorly studied natural history of the disease. Indeed, it is not conceivable to randomize therapeutic lesions that lead to little or no symptoms, or for which the symptoms are fluctuating. Unfortunately, while the knowledge of the natural history of MCSs is the prerequisite for adapting a therapy, it is also the least studied aspect in the literature. No study specifically dedicated to the growth of meningeiomas confined to the CS could be found in the literature. All radiotherapy series analyze the development of tumors under treatment and claim to have obtained frequent stabilization or decreases in tumor volume. However, these series never compare the results to those of a control group, i.e., untreated MCSs.

The aim of our work was to determine the natural history of MCSs through a consecutive series of 53 patients with this lesion. All patients were treated symptomatically, presenting a low expandability of their tumor, and were closely followed up both radiographically and clinically. This prospective study, with a median follow-up > 10 years, will aid in gaining insights into the treatment of such tumors.

Methods

The local ethics committee of La Pitié Salpêtrière Hospital approved this study. Written consent was obtained and recorded in each patient's medical file.

Study Population

From 1990 to 2016, 90 adults harboring MCSs were diagnosed by 3 neurosurgeons and their cases were subsequently followed. Fifty-three patients treated for meningeiomas confined to the CS, newly diagnosed using brain MRI, were included. Thirty-seven patients who had a me-

ningioma that expanded beyond the CS with an extracavernous portion (i.e., sphenoid, sella, temporal, clinoid, etc.) or invading the CS secondarily were excluded from this study.

At diagnosis, all patients were clinically evaluated with particular attention to both an ophthalmological (visual acuity, visual field, and coordimetric examinations according to Hess-Lancaster) and CN examination. Medication history investigations focused on hormonal intake (such as cyproterone acetate or treatment of menopause) were performed. Radiological examination included brain MRI, and sometimes, if deemed necessary, a CT scan.

Follow-Up

All patients were followed-up prospectively with a neurological examination and a neuro-ophthalmological assessment at 6 weeks to assess the effectiveness of symptomatic treatment when it was established. Furthermore, follow-up examinations were systematically performed at 6 months, every year for 3 years, then every 2 years afterward. Each time, the patient underwent MRI and a clinical examination. The median follow-up duration of our series was 10.8 ± 5.55 years (range 2–25.2 years). Six patients (11%) were followed < 5 years, 19 patients (35.9%) between 5 and 10 years, and 28 patients (52%) > 10 years, including 10 patients (18.5%) > 15 years, with a maximum of 25 years. In the course of follow-up evaluations, some patients worsened clinically or radiologically because of their tumor. In these cases, the initial course of observation without intervention was modified accordingly to interventional radiotherapy: 3 patients by radiotherapy (36 Gy), and 2 others by Gamma Knife radiosurgery (16 Gy). Even if these cases could be considered outside the bounds of analysis of natural history in the strict sense, the study of such patients was continued.

MRI and Tumor Volume

During initial evaluation and follow-up, the tumor volume was assessed by 3D gradient echo T1-weighted post-Gd sequences, with 0.7-mm slice thickness and no gap, by manual segmentation using OsiriX software (version 4.1.2, OsiriX). Tumor progression was defined as a > 20% increase in volume, and tumors that showed < 20% reduc-

TABLE 1. Patient characteristics (n = 53)

Variable	Value (%)
Sex	
Male	7 (13.2)
Female	46 (86.8)
Mean age at diagnosis $\pm$ SD (yrs)	53 $\pm$ 9.5
Clinical presentation	
CN VI palsy	18 (33.9)
CN III palsy	7 (13.2)
CN V neuralgia	3 (5.7)
Headache	9 (16.9)
Pituitary insufficiency	3 (5.7)
Acuity visual impairment	10 (18.8)
Incidental findings	10 (18.8)
Minor symptoms	15 (28.3)
Major symptoms	28 (52.8)
Side	
Rt	21 (39.6)
Lt	32 (60.3)
Follow-up (yrs)	
Median $\pm$ SD	10.8 $\pm$ 5.5
<5	6 (11.3)
5–10	19 (35.8)
>10	28 (52.8)

All data given as number of patients (%) unless otherwise indicated.

tion and < 20% increase in volume were categorized as stable.⁴

Statistical Analyses

Statistical analyses were performed using Stata (version 11, StataCorp). Associations between different group parameters or patient groups were analyzed with the Fisher's exact test. Sex and initial clinical presentation were considered categorical variables, while age and lesion volume were considered continuous variables. Clinical and radiographic progression-free survival (PFSs) were plotted according to the Kaplan-Meier method. All tests were 2-sided, and *p* values < 0.05 were considered significant.

Results

Epidemiology

From 1990 to 2014, 53 patients with MCSs were included in the study and evaluated. There were 46 women (87%) and 7 men (13%; sex ratio 6:1). At the time of diagnosis, the patients ranged in age from 30 to 72 years, with a mean age of 53 $\pm$ 9.5 years (Table 1). Forty-one of the 46 women were postmenopausal. A treatment with progestogens (norgestrel acetate or cyproterone acetate) was observed at the examination in 12 patients.

Clinical Presentation

Clinical presentations included visual impairment, CN deficits, headaches, ocular signs, and pituitary insufficiency.

CN deficit was the most frequent initial symptom. The mean duration of symptoms at diagnosis was 13 $\pm$ 8.9 months.

Incidental Findings

For 10 patients (18.9%), the diagnosis of MCS was made fortuitously during imaging conducted for other investigations (incidental finding), such as after trauma, stroke, epilepsy, or otorhinolaryngological diseases.

Minor Symptoms

Fifteen patients (28.3%) had symptoms that we described as "minor," characterized by intermittent and irregular appearances, or, alternatively, with no clear implication from meningioma. Minor symptoms were distributed as follows: 4 patients described intermittent diplopia in the lateral view, with no infringement of CN VI objectively confirmed by ophthalmological examination; 1 patient described moderate and inconstant paresthesias in the territory of CN V, with no facial nerve pain or hypoesthesia; another patient complained of visual acuity impairment; and 9 patients complained of simple retroorbital headache.

Major Symptoms

Twenty-eight patients (53%) had a symptomatology at diagnosis that can be qualified as "major," that is, permanent or debilitating symptoms and clearly attributable to the meningioma. Twenty-three patients (40.7%) presented with impaired oculomotor nerve function: 14 patients (26.4%) had CN VI palsy, 7 patients (13%) had CN III palsy, and 2 patients had both CN VI and CN II palsy. No abnormality of CN IV was detected (Table 1). Trigeminal signs and symptoms were present in 2 patients (3.8%) with neuralgia. Unilateral visual acuity was impaired in 2 patients (3.7%) due to an invasion of the optic canal. Three patients had amenorrhea-galactorrhea due to disconnection hyperprolactinemia.

Correlation of Symptoms With Initial Radiological Findings

The side of the lesion was divided into right (*n* = 21) and left (*n* = 32) halves. The mean meningioma volume at diagnosis was 5.6 $\pm$ 2.9 cm³ (range 1.8–12.7 cm³; Fig. 1). Meningiomas diagnosed due to minor symptoms were significantly larger (mean volume 6.76 $\pm$ 2.7 cm³) than those diagnosed due to major symptoms (mean volume 4.5 $\pm$ 1.9 cm³) or fortuitously (mean volume 4.2 $\pm$ 1.9 cm³; *p* < 0.004).

Efficiency of Initial Treatment

The discontinuation of progestin (norgestrel acetate or cyproterone acetate) was recommended for all patients.

The patients in the incidental findings group underwent clinical and radiological follow-up without treatment. None of the 25 patients in this group (*n* = 10) or minor symptoms group (*n* = 15) complained of a new disorder in short-term follow-up. The cessation of hormonal treatment modestly improved visual acuity in 1 patient (Figs. 2 and 3). Twenty-four (85.7%) of 28 patients in the major symptoms group received methylprednisolone at a decreasing

FIG. 2. Follow-up years for the incidental findings group (dark gray = asymptomatic).

dose for 6 weeks; 3 patients (5.6%) received bromocriptine for endocrine disorders, and 1 patient (1.8%) received carbamazepine for neuralgia.

Symptom Improvement

At the control consultation at 6 weeks, 22 patients (78.6%) improved and demonstrated a regression of their major symptoms ($p < 0.0001$, Pearson's chi-square test) as a direct consequence of their medical treatment (corticosteroids/carbamazepine or bromocriptine). These patients were distributed as follows: 13 patients with CN VI palsy, 4 patients with CN III palsy, 2 patients with CN V neuralgia, and 3 patients with disconnection hyperprolactinemia. After cessation of this initial symptomatic treatment, 18 patients (64.3%) did not experience relapse of their disorders; 1 had a recurrence of CN V neuralgia, which required resumption of carbamazepine treatment, and 3 patients with initial CN VI palsy relapsed after cessation of corticosteroids, but the installation of an eyeglass prism to limit diplopia allowed them to resume a normal life (Fig. 2).

No Symptom Improvement

Six patients did not improve after the initial symptomatic treatment: 2 patients had CN VI palsy associated with visual acuity loss, 3 patients had CN III palsy, and 1 patient had isolated CN VI palsy.

Clinical Correlation With Radiological Findings

The mean volume of meningiomas in patients whose condition was improved by medical treatment was $4.4 \text{ cm}^3 \pm 1.8 \text{ cm}^3$ versus $4.3 \pm 2.06 \text{ cm}^3$ in patients who did not improve ($p = 0.92$, Student t-test).

Development of New Symptoms

None of the patients in the incidental findings group developed symptoms over a mean follow-up of 10.4 years (Fig. 2). Twelve of the 15 patients in the minor symptoms group remained asymptomatic over a mean follow-up of 11.5 ± 5.08 years. The patient who initially experienced a decrease in visual acuity did not get worse. One patient presented with recurrence of CN VI palsy 5.6 years after initial manifestation of her minor symptoms; this pa-

tient decided to accept her diplopia, and refused all other treatment. Twelve years later, 1 patient presented with an invasion of the optic canal associated with decreased visual acuity; decompression could not be performed due to medical contraindications (Figs. 3 and 4A).

Nineteen (67.9%) of the 28 patients in the major symptoms group became asymptomatic after discontinuing initial corticosteroid treatment over a mean follow-up of 10.3 ± 5.2 years; $p < 0.0001$, Pearson's chi-square test; Fig. 4B). Fifteen patients never experienced recurrence (CN VI, $n = 9$; CN V, $n = 1$; CN III, $n = 2$; disconnection hyperprolactinemia, $n = 3$) and 4 patients (CN III, $n = 1$; CN V, $n = 1$; CN VI, $n = 2$) experienced a recurrence during the natural history of their meningioma (mean 3.7 years after diagnosis), which required the reintroduction of a symptomatic treatment (Fig. 4A).

Currently, 9 patients remain symptomatic. Two patients have sustained a visual acuity loss, 2 other patients continue to experience CN III palsy (which remained stable and well tolerated over the follow-up), and 5 patients (CN VI, $n = 3$; CN III, $n = 2$) with no or temporary effectiveness of the initial symptomatic treatment have secondarily undergone treatment using radiotherapy (mean 5.8 years). The clinical PFS rates at 5, 10, and 20 years were $94\% \pm 3.3\%$, $81\% \pm 5.3\%$, and $81\% \pm 4.7\%$, respectively.

Tumor Growth, Initial Symptoms, and Radiographic PFS

According to the criteria previously defined to assess progression of meningiomas (Fig. 4B and C), radiographic PFS rates at 5, 10, and 20 years were $90\% \pm 4.2\%$, $82\% \pm 5.7\%$, and $70\% \pm 10.2\%$, respectively.

None of the meningiomas increased in volume in the incidental findings group. Twelve meningiomas (80%) in the minor symptoms group exhibited no increase in volume. Three meningiomas (20%) increased moderately (mean growth 60% in 10.7 years): two of them were without any symptoms, and the other developed CN VI symptoms. Twenty-two patients (78.6%) in the major symptoms group had meningiomas whose volume did not increase. Five patients (19%) had meningiomas that progressed (mean growth 35% in 10.2 years); only 2 of these patients experienced an aggravation of their symptoms: 1 in CN III and 1 in CN VI.

FIG. 3. Follow-up data for patients in minor and major symptomatic groups (*dark gray* = become asymptomatic, *light gray* = became or remain symptomatic). γ = Gamma Knife surgery; II–VI = CNs; HyperP = hyperprolactinemia; M = medical symptomatic treatment; R = radiotherapy.

FIG. 4. **A:** Kaplan-Meier curve for development of new symptoms. **B and C:** Kaplan-Meier curves of years to progression of cavernous sinus meningiomas within the whole series (B) and according to incidental findings (C; 18.8 months, *dashed line*), minor symptoms (15.6 months, *black line*), and major symptoms (20.2 months, *gray line*). Figure is available in color online only.

Second Oncological Treatment

An oncological treatment was required for 5 patients (9.4%) because of the failure of medical treatment (persistent symptoms despite medical treatment) or rapid recurrence of symptoms. Each of these patients is described in Table 2. Only 1 of the 5 patients showed improved symptoms (diplopia and ptosis) after the second oncological treatment.

Three patients initially had a CN VI palsy that worsened during follow-up and accepted treatment either with radiotherapy ($n = 1$) or radiosurgery ($n = 2$). The average time until this secondary treatment was necessary was 8 years (successively after 5.7 and 12 years). Diplopia did not improve after such treatment, although 1 of the meningiomas decreased (30%) and the 2 others were stable. One of these patients developed a new meningioma 7 years later, located on the irradiation fields (pterion) and possibly radiation-induced.

Two patients initially had a CN III palsy that worsened with time and agreed to treatment with radiotherapy. After treatment, diplopia and ptosis were partially improved in 1 patient and unchanged in the other. The average duration of this secondary treatment was 2 years. One patient developed radiation-induced hyposialorrhea.

Discussion

Natural History of Meningiomas Confined to the CS

Clinical Improvement

Our series reveal several findings and conclusions that were poorly explored in the literature until now. First, at tumor diagnosis, many of our patients with meningiomas confined to the CS have few or no outward symptoms. Second, when they are symptomatic (diplopia, more rarely trigeminal neuralgia), we recommend ceasing possible hormonal treatments and, instead, establishing a simple symptomatic treatment with corticosteroids in the short term (1–2 months). This approach allows for symptom disappearance in more than 70% of patients. Third, after cessation of corticosteroids, there is usually no recurrence,

but in cases of recurrence, a second treatment may be effective; alternatively, the use of a prism may be considered. Fourth, in the long term, there is limited clinical follow-up. And fifth, in case of the appearance of new symptoms, a new medication with corticosteroids, prescribed on the same terms, may have similar efficacy.

To our knowledge, we are the first to describe the natural history of meningiomas confined to the CS and to significantly describe the efficacy of short-term corticosteroid treatments. However, very few cases reported the use of corticosteroid treatment for CN palsy caused by CS meningioma.^{16,26} Moreover, the effect of corticosteroids was described on headaches and CN VI palsy, but the follow-up time of patients was very short in these reports.

The mechanism of action of corticosteroids is unknown, but we assume that they decrease inflammation concomitant with the meningioma. In some cases, patients also benefited from discontinuation of hormonal treatment. It is likely that corticosteroids diminish the congestion of the CS.

Growth of Meningioma

The evolution of CS meningioma is unpredictable and irregular: 10 (18.9%) of 53 increased in size, 38 (71.7%) remained stable, and 5 (9.4%) decreased. Unlike any other cerebral localization, we cannot model or establish growth rate profiles in the CS. Some lesions will not evolve over 10 years, while others will increase gradually and slowly, or more quickly. In any case, imaging follow-up appears appropriate to establish the unique evolution of the tumor in each patient.

In this work, we observed that clinical symptoms, either initial or recurrent, sensitive or resistant to symptomatic treatment, were independent of the initial size and growth of the meningioma. Again, this is a novel finding due to the lack of observational series in the literature.

Surgical Removal

It is difficult to compare the series published in the literature. Indeed, as we previously suggested, surgical stud-

TABLE 2. Patients with oncological treatment during follow-up

Pt No.	Initial CN Deficit	Efficiency of Initial Corticosteroids	Time w/o Recurrence (yrs)	Time Before 2nd Tx (yrs)	Efficiency of 2nd Tx on CN Deficit	Lesion Vol Evolution After 2nd Tx (yrs FU)	Secondary Complication
1	III	–		Radiotherapy (2)	+ (partially)	Unchanged (3)	
2	III	–		Radiotherapy (2)	–	Unchanged (6)	Pituitary deficiency
3	VI	+	18	Radiosurgery (2)	–	Unchanged (2)	
4	VI	+	4.5	Radiosurgery (5)	–	Unchanged (5)	
5	VI	–		Radiotherapy (15)	–	Decreased 30% (9)	Meningioma radio-induced

FU = follow-up; Pt = patient; Tx = treatment.

ies propose heterogeneous definitions for the MSC, gathering all meningiomas involving the CS without anatomical distinction.^{1,3,4,8} As now acknowledged, surgery of the CS is a hazardous treatment associated with a very high rate of morbidity and death. Although some authors still recommend radical and gross-total surgeries accompanied by vascular bypass for treating these lesions, the radical resection has been practically abandoned.^{23,28} This is confirmed by the lack of recent surgical series reported in the literature. However, our experience indicates that there may be some surgical indications for extracavernous-portion meningiomas, for instance, when visual acuity is impaired after invasion, compression, or swelling of the optic canal.

Radiotherapy Treatment

Initial deficits in CNs usually improve in about 20%–42% of patients after primary radiotherapy.^{18,24} Clinical improvement varies depending on the initial symptom, i.e., diplopia or neuralgia.^{6,14,18,24} Many authors reported more stable symptoms characterized by a so-called “lack of deterioration.”^{12,21} It is noteworthy that the efficacy of radiotherapy on neuralgia may be explained not only by its oncological effects; radiation could directly act on CN V as thermocoagulation, thus resulting in partial denervation.^{5,6,21,24,25}

Survival without tumor progression (PFS) is variable according to studies, and ranges from 87% to 99% at 5 years and from 70% to 90% at 10 years.^{15,17} More recently, other studies have reported a control of growth in 60%–96% of lesions at 2 years,^{9,11} a decrease in volume by 20%,⁵ and radiological progression after radiotherapy in 5%–11% of lesions.^{5,7,15} In the present study, only 1 of 5 patients undergoing radiation therapy had a meningioma whose volume decreased (by 30%). The efficacy of radiotherapy on growth of these meningiomas must be consistent with the natural history of this entity, which has an unpredictable and irregular development. Thus, the efficacy attributed to radiotherapy (including the “stabilization” of meningiomas) might be the result of the natural history of spontaneously indolent tumors.

In 1979, a pioneering study by van Effenterre and colleagues reported 8 irradiated meningiomas confined to the CS with mitigated results.²⁷ Since then, with the benefit of distance and hindsight, the authors have noted a frequent spontaneous clinical improvement of symptoms and a low spontaneous evolution without treatment, limiting the treatment to symptomatic treatment as long as possible. This does not mean that radiotherapy has no further

indication in CS meningiomas. If our study confirms a cautious approach to avoid unnecessary radiation, we do believe that radiation therapy has its place as a second-line therapy after failure of symptomatic treatment. We believe that trigeminal neuralgia is often improved by irradiation more frequently than the deficits of the oculomotor nerves.¹³ CN VI deficits are improved by treatment with short-term corticosteroids and/or the placement of a prism. Therefore, radiation may not always be a preferred choice as it may be ineffective. Given the natural history of meningiomas and efficacy of symptomatic treatment, delayed radiotherapy may be beneficial for the patient.

Conclusions

The meningioma confined to the CS appears to be a capricious lesion, with an unpredictable and slow evolution that varies between patients, yet which is never life-threatening. It can remain unnoticed for a long time with little or no symptoms, and can be treated, if necessary, with simple treatments, such as short-term corticosteroids, carbamazepine, and prisms. The challenge for treating this lesion is functional outcomes (mostly diplopia and neuralgia); consequently, the motto “First, do no harm” should guide our treatment. We propose the following approach. First, as a first-line symptomatic treatment, cessation of any hormone therapy (norgestrel acetate or cyproterone acetate), carbamazepine for neuralgic pain, short-term corticosteroids for diplopia, and prism placement in the case of failure. Second, follow up long-term clinical and radiological outcomes. Third, if diplopia recurs, symptomatic short-term treatment may be tried again. Fourth, radiotherapy may be considered in cases in which the radiological follow-up is important and symptomatic, including neuralgia, and for very debilitating deficits after failure of symptomatic treatment. And fifth, the smallest possible surgery should be performed and only in cases of extracavernous compressive invasion (toward CN II in particular), and should respect the intracavernous contingency of the tumor.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Amelot, Boch. Acquisition of data: Amelot, van Effenterre, Kalamarides, Boch. Analysis and interpretation of data: Amelot, van Effenterre, Boch. Drafting the article: Amelot, van Effenterre, Cornu, Boch. Critically revising the article: Amelot, Kalamarides, Cornu, Boch. Reviewed submitted version of manuscript: Amelot, van Effenterre, Cornu, Boch. Statistical analysis: Amelot. Administrative/technical/material support: Amelot, van Effenterre, Kalamarides, Boch. Study supervision: Amelot, Kalamarides, Boch.

Correspondence

Aymeric Amelot: Groupe Hospitalier Pitié-Salpêtrière, Paris, France. aymmed@hotmail.fr.