Endoscopic endonasal surgery to treat intrinsic brainstem lesions: correlation between anatomy and surgery*

Thomaz E. Topczewski[1], Alberto Di Somma[1,2], Diego Culebras[1], Luis Reyes[1], Jorge Torales[1], Ana Tercero[3], Cristobal Langdon[4], Isam Alobid[4], Ramon Torne[1], Pedro Roldan[1], Alberto Prats-Galino[2], Joaquim Enseñat[1]

[1] Institut Clínic de Neurociències (ICN), Department of Neurological Surgery, Hospital Clínic de Barcelona, Universidad de Barcelona, Barcelona, Spain

[2] Laboratory of Surgical Neuroanatomy (LSNA), Faculty of Medicine, Universitat de Barcelona, Barcelona, Spain

[3] Institut Clínic de Neurociències (ICN), Department of Neurology, Hospital Clínic de Barcelona, Universidad de Barcelona, Barcelona, Spain

[4] Rhinology Unit and Smell Clinic, Otorhinolaryngology Department, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain

Rhinology 59: 2, 191 - 204, 2020

https://doi.org/10.4193/Rhin20.064

***Received for publication:**

February 22, 2020

Accepted: September 29, 2020

Abstract

Objective: The endoscopic endonasal approach (EEA) has been proposed as an alternative in the surgical removal of ventral brainstem lesions. However, the feasibility and limitations of this approach to treat such pathologies are still poorly understood. This study aimed to report our experience in five consecutive cases of intrinsic brainstem lesions that were managed via an EEA, as well as the specific anatomy of each case.

Methods: All patients were treated in a single center by a multidisciplinary surgical team between 2015 and 2019. Before surgery, a dedicated anatomical analysis of the brainstem safe entry zone was performed, and proper surgical planning was carried out. Neurophysiological monitoring was used in all cases. Anatomical dissections were performed in three human cadaveric heads using 0° and 30° endoscopes, and specific 3D reconstructions were executed using Amira 3D software.

Results: All lesions were located at the level of the ventral brainstem. Specifically, one mesencephalic cavernoma, two pontine cavernomas, one pontine gliomas, and one medullary diffuse midline glioma were reported. Cerebrospinal fluid leak was the major complication that occurred in one case (medullary diffuse midline glioma). From an anatomical standpoint, three main safe entry zones were used, namely the anterior mesencephalic zone (AMZ), the peritrigeminal zone (PTZ, used in two cases), and the olivar zone (OZ). Reviewing the literature, 17 cases of various brainstem lesions treated using an EEA were found.

Conclusions: To our knowledge, this was the first preliminary clinical series of intrinsic brainstem lesions treated via an EEA presented in the literature. The EEA can be considered a valid surgical alternative to traditional transcranial approaches to treat selected intra-axial brainstem lesions located at the level of the ventral brainstem. To achieve good results, surgery must involve comprehensive anatomical knowledge, meticulous preoperative surgical planning, and intraoperative neurophysiological monitoring.

Key words: brainstem, endoscopic endonasal approach, anterior mesencephalic zone, peritrigeminal zone, olivar zone, cavernoma, brianstem glioma

Introduction

The brainstem is among the most challenging structures to access during surgery because it is located deep in the posterior fossa near the ventral skull base, and because it is closely adjacent to perforating arteries, white matter tracts [1-3], and some important functional nuclei.

Many pathologies involve the brainstem; for example, brainstem gliomas comprise 1.4% of all intracranial tumors, and 5% of all

Table 1. Single center cases of brainstem lesions approached via an extended endoscopic endonasal approach.

Case	Patients	Pathology	Location	Clinical status	Entry point	Safe Entry Zone of the Brainstem	Surgical Complications	Immediate post-operative status	Subsequent treatment	Last follow-up
Case #1	M, 38	Cavernoma	Ventral midline midbrain	Isolated third-nerve palsy	Ventral midbrain, right side	Anterior Mesencephalic Zone (AMZ)	None	Improved	None	Improved
Case #2	F, 29	Cavernoma	Pons	Headache and hypoesthesia on the right side of the face	Ventral pons, right side	Peritrigeminal Zone (PTZ)	None	Improved	None	Improved
Case #3	M, 27	Astrocytoma IDH-1 mutated	Pons	Dizziness and diplopia	Ventral pons, right side	Peritrigeminal Zone (PTZ)	None	Improved	VPS, CT and RT	Stable
Case #4	F, 43	Diffuse midline glioma H3-K27M mutation	Medullary	Headache and dizziness	Right medullary	Olivar Zone (OZ)	CSF leak	Stable	VPS, CT and RT	Progression
Case #5	F, 32	Cavernoma	Pons	Left sixth nerve palsy	Ventral pons, left side	Peritrigeminal Zone (PTZ)	None	Stable	None	Stable

M, Male; F, Female; IDH, isocitrate dehydrogenase; VPS, ventriculo-peritoneal shunt; CT, chemiotherapy; RT, radiotherapy; AMZ, anterior mesencephalic zone; OZ, olivar zone.

vascular anomalies occur in this area. When planning operations that involve brainstem lesions, surgeons must consider multiple surgical and anatomical factors to minimize the risk of injury to vital zones and vascular structures [4-7]. To minimize morbidity, they must select the appropriate surgical route to resect intrinsic brainstem lesions; as such, they require a proper knowledge of anatomical structures and safe-entry zones [8-13]. To plan the most appropriate procedure for each patient, they must consider the pathology and its natural history, the patient's life expectancy and wishes, existing deficits, and the likelihood of introducing new deficits.

Recently, neurosurgeons have been able markedly to improve skull base surgery, including brainstem surgery, thanks to developments in optical techniques, frameless stereotactic systems, intraoperative Doppler imaging, neuromonitoring techniques, and dissecting instruments [14, 15]. As a result, the minimally invasive endoscopic endonasal approach (EEA) was recently devised to provide a valid surgical window to the posterior fossa [16-29]. The expanded EEA permits exposure of the clivus and craniovertebral junction, which are located immediately anterior to the brainstem [16-29]. Hence, both extradural and intradural pathologies have been treated using the EEA, as have both extra-axial and intra-axial pathologies. The detailed anatomy of the EEA to the brainstem was recently described, and several case reports have been presented in the literature [30-32]. However, the surgical feasibility and limitations of the EEA to treat intrinsic brainstem lesions have not been described in detail.

Therefore, in the present study, we reported the cases of five consecutive patients with brainstem lesions that were approached via an EEA. Furthermore, detailed, 3-dimensional (3D) anatomical visualization and analysis were performed.

Materials and methods

Patient population

We retrospectively analyzed five consecutive adult patients who had brainstem lesions that were approached via an EEA (two men and three women; mean age: 33.8 years, range: 27–43 years). All procedures were performed between 2015 and 2019 at the Division of Neurosurgery of the Clinical Hospital, Barcelona (Spain). Written informed consent was obtained from all patients.

All patients underwent complete neuroradiological examination, including diffusion tensor imaging (DTI) sequencing to localize the lesion and the ascending and descending fibers before surgery. Preoperative magnetic resonance imaging (MRI) was also carried out to localize the tumor using the neuronavigation system. The following data were recorded: demographic data, comprehensive preoperative assessment, pathology features, prior and/or adjunctive treatments, diagnostic results, outcomes, complications, and follow-up with subsequent treatments (Table 1).

Anatomic dissection & 3-dimensional analysis

Before surgery, an anatomical visualization and detailed 3D analysis of each entry zone was carried out at the Laboratory of Surgical Neuroanatomy of the Human and Embryology Unit, University of Barcelona (Spain) using three preserved cadaveric heads whose arterial system had been injected with red latex. This procedure was previously approved by the Institutional Review Board of the University of Barcelona. Before the dissection, all specimens underwent a multi-slice helical computed tomography scan (SOMATOM Sensation 64; Siemens, Malvern, PA, USA) with 0.6-mm thick axial spiral sections and a 0° gantry angle. In one specimen, MRI was performed to achieve proper reconstruction of the brainstem and its vital surrounding neurovascular structures. The virtual 3D model was created using Amira 3D for life sciences (ThermoFisher Scientific, Hillsboro, OR, USA).

Endoscopic endonasal surgery to the brainstem

All patients underwent brainstem surgery via an EEA. The surgical procedures were performed according to the techniques described in previous publications [32-35].

Dedicated instrumentation, such as proper dissecting instruments and an intraoperative image guidance system, allows surgeons to perform brainstem surgery more safely and effectively using this approach.

In most procedures, the patient was placed in the supine position with their head mildly flexed, rotated approximately 10° towards the surgeon, and elevated above the thorax to optimize venous outflow. Intraoperative neuronavigation was recorded. At this point, the patient's nose was packed with lidocaine-soaked Cottonoids® or a nasal decongestant such as oxymetazoline. The abdomen was also prepared and draped in case a fat and/or fascia graft was necessary.

Both ENT surgeons and neurosurgeons performed the operation simultaneously using the two nostrils and four hands technique, which conferred advantages in all surgical phases.

In all cases, the initial steps of the surgical procedures were the same until the posterior wall of the sphenoid sinus was reached, as described previously [36-38]. After the main anatomical landmark of the sphenoid sinus posterior wall was identified, the procedure continued depending on the underlying pathology, as described in the case presentations below.

In the transtuberculum–transplanum approach, the main anatomic landmarks of the initial drilling were the sella and the superior intercavernous sinus because the approach to the brainstem required drilling of the posterior portion of the planum, the tuberculum sellae, and the sella itself, exposing the pituitary gland. The lateral limits were the optic canals.

In the transclival approach, the limits depended on the location of the lesion. If the lesion was in the upper clivus, the superior limit was the dorsum sellae and the posterior clinoids. Pituitary gland transposition was sometimes necessary. The inferior limit was determined by the surgeon based on what they wished to expose. If the lesion was in the middle clivus, the limits were the Dorello's canal down to the jugular foramens. The lateral limits were the paraclival carotid arteries. If the lesion was in the lower clivus, the drilling was limited by the jugular foramens and cervicomedullary junction, and laterally by Rosenmuller's fossa.

Skull base reconstruction was performed in a multilayer fashion. That is, fat tissue and fascia lata were inserted intradurally, with another fascial layer being placed extracranially and reinforced with fat. Finally, vascularized pedicled nasoseptal flaps were overlaid to complete the reconstruction. The nasal packing was placed bilaterally on the floor of the nasal cavities to ensure hemostasis. Lumbar drainage was used to ensure the reconstruction did not fail; this was removed 3 days after surgery.

Neuromonitoring of somatosensory evoked potentials (SSEPs), motor evoked potentials (MEPs), brainstem auditory evoked potentials, and dedicated cranial nerve electromyography was performed in all cases.

Results

All five brainstem lesions were approached via an extended EEA. All lesions were located at the level of the ventral brainstem. Specifically, we reported one mesencephalic cavernoma, two pontine cavernomas, one pontine glioma and one medullary diffuse midline glioma. At the last follow-up, two patients were stable, two had improved, and one had suffered tumor progression. Tumor biopsy was performed in two cases, while gross total or complete removal was achieved in the other three. The data are summarized in Table 1.

Case #1

A 38-year-old man presented with isolated right third-nerve palsy without any other non-ocular signs. MRI revealed a ventral midline mesencephalon cavernous malformation. The neurological status of the patient remained substantially stable during the 3 weeks after acute onset (Figure 1) [39]. We decided to intervene because the initial bleeding had caused third nerve palsy and superficial ventral location of the cavernoma.

After considering the advantages and disadvantages of various surgical routes to the brainstem, we decided to approach the lesion via an extended EEA, mostly because the cavernoma showed a pial presentation, surfacing at the ventral mesencephalon and thus conducive to a purely translesional resection via a direct anterior approach that avoided the need to traverse intact neural tissue.

From an anatomical standpoint, the brainstem entry zone used was the exophitic portion of the cavernoma itself. We duly considered the structures of the anterior mesencephalic zone (AMZ) and conducted the procedure guided by data from intraoperative neurophysiological monitoring.

Once the interpeduncular fossa was entered, the endoscope was moved further into the surgical field, allowing a clear visu-

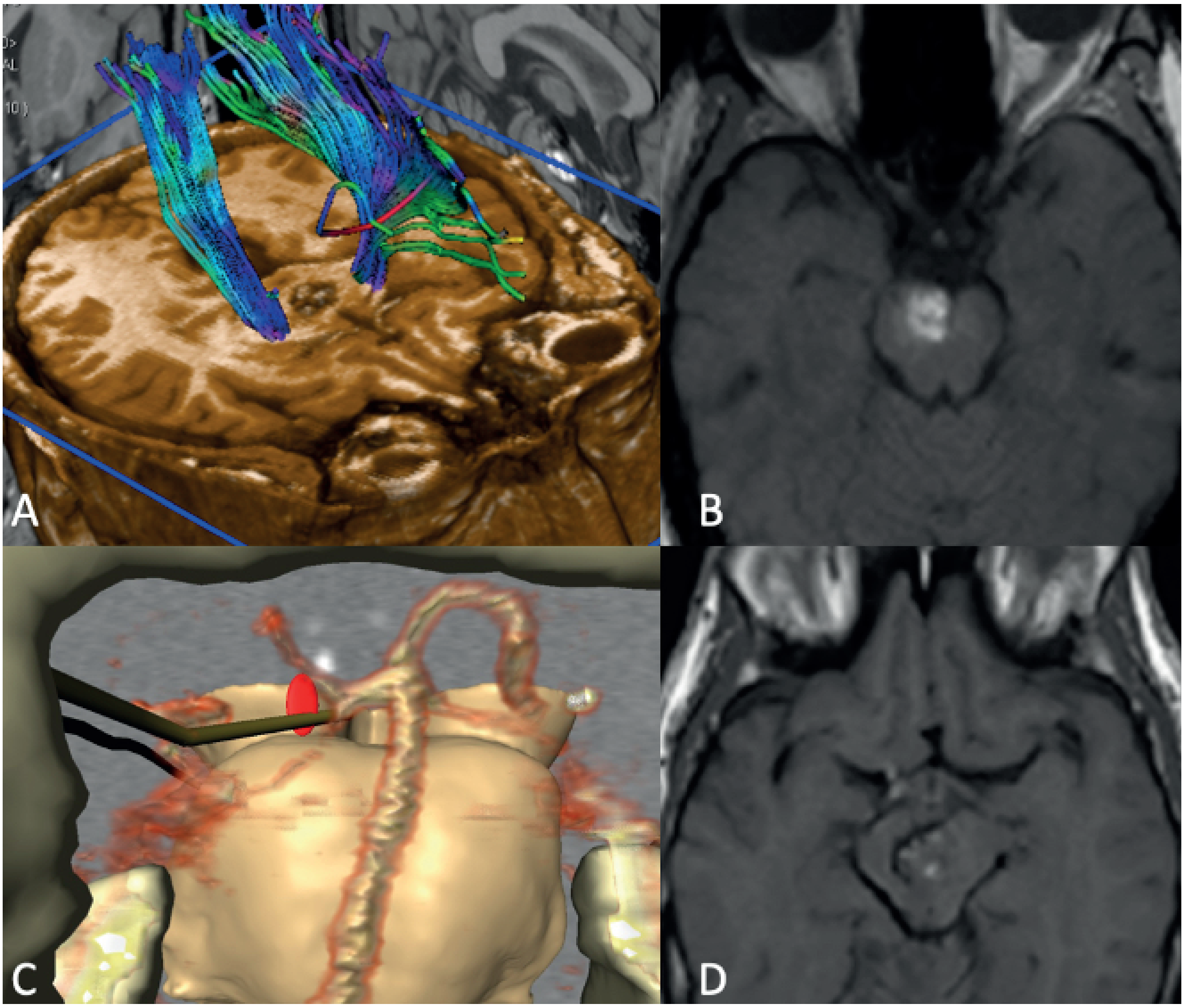

Figure 1. Neuroradiological study and anatomical 3D visualization of the entry zone to the brainstem via endoscopic endonasal approach in Case #1. Diffusion tensor imaging (a) was performed to show the relationship between the mesencephalic cavernoma and right corticospinal tract. Axial preoperative imaging (b) showed spontaneous bleeding of the cavernoma, while postoperative axial magnetic resonance imaging (d) revealed gross total removal. (c) Dedicated reconstruction showed the position of the anterior mesencephalic zone.

alization of the basilar artery in the center of the surgical field, the mammillary bodies superiorly, the cerebral peduncles and posterior communicating arteries laterally, and the oculomotor nerves and posterior cerebral arteries inferiorly. The hematoma overlying the cavernous malformation was encountered on the ventral surface of the midbrain. Both pituitary gland transposition and posterior clinoidectomy could have been used as adjunct techniques after the start of the procedure had the surgical corridor been too narrow. However, it sufficed to remove a small portion of normal pituitary gland to perform a standard transtuberculum-transplanum approach that resulted in comfortable exposure of the cavernoma and surrounding neurovascular structures. The cavernoma itself created virtual space between the mesencephalon and basilar artery, as well as between the posterior communicating arteries and perforators. With gentle suction and sharp dissection, the hematoma was evacuated and the cavernoma removed piecemeal, decompressing the brainstem. Evacuating the hematoma together with fragments of the cavernoma eliminated this virtual space (Figure 2). The anatomical orientation made it too risky to attempt any other surgical maneuver, so the surgery was stopped before we could inspect the surgical cavity. This resulted in subtotal removal of the cavernoma. After surgery, the patient's oculomotor symptoms were entirely resolved, and no new neurological or endocrinological deficits appeared.

Six years later, at the time of writing the present report, the patient was stable, without any other neurological or endocrinological symptoms or signs.

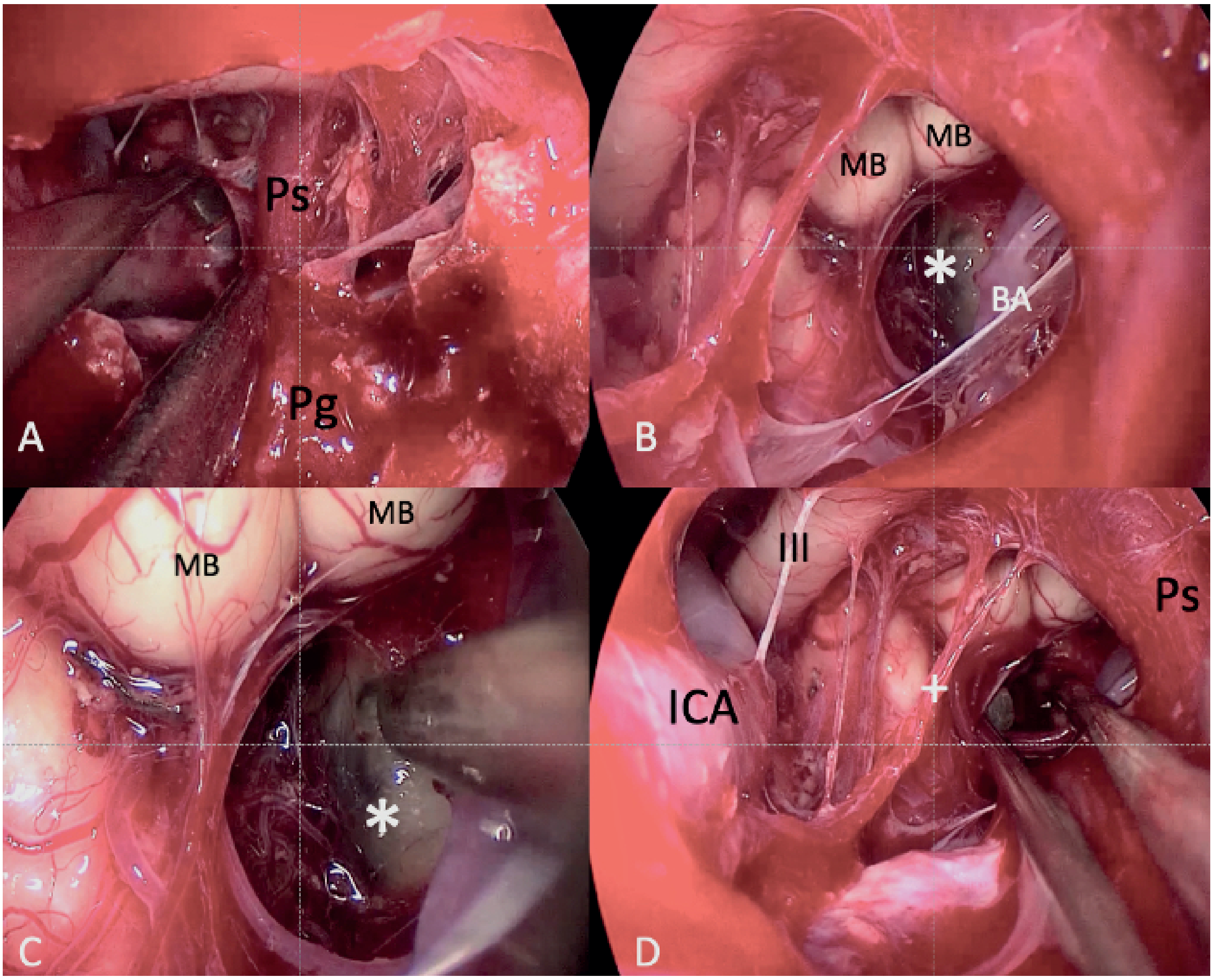

Figure 2. Intraoperative endoscopic endonasal pictures showing cavernoma removal and the main neurovascular structures of the surgical field. (a, b) The cavernoma was reached with minimal displacement of the pituitary stalk, and debulking was carried out using a microdissector and suction (c, d). Ps, pituitary stalk; Pg, pituitary gland; MB, mammillary body; ICA, internal carotid artery; BA, basilar artery; III, oculomotor nerve; +, superior hypophyseal artery; *, mesencephalic cavernoma.

Case #2

A 29-year-old woman presented with headache and hypoesthesia on the right side of the face. MRI revealed a ventral right-sided pons cavernous malformation with recent bleeding. Surgical treatment was chosen based on clinical radiological data showing ventral superficial localization of the lesion. All feasible approaches to the ventral brainstem were considered and it transpired that the endoscopic transclival approach would allow a direct route to the lesion without impinging on important neurological structures (Figure 3).

From an anatomical standpoint, the brainstem entry zone corresponded to the peritrigeminal zone, which was also used to access a pontine lesion reported below (case #3; Table 1).

The dura was opened in the midline using a feather blade, and the basiclival plexus was then opened using a controlled bipolar cautery. Upon completion of the dural opening, a clearly discolored portion of the pons was visible. Microdissectors and suction were then used to circumferentially dissect the arachnoid around the cavernoma that had erupted to the surface. The lesion was gently removed using suction, angled dissectors, and curettes (Figure 4).

The patient showed improved symptoms until the last follow-up 3 years after the surgery. No other neurological or endocrinological symptoms or signs were reported. The last MRI showed no complications.

Case #3

A 27-year-old man presented with dizziness and diplopia caused by a sixth cranial nerve (CN) palsy. Computed tomography (CT) and MRI showed a brainstem lesion compatible with an

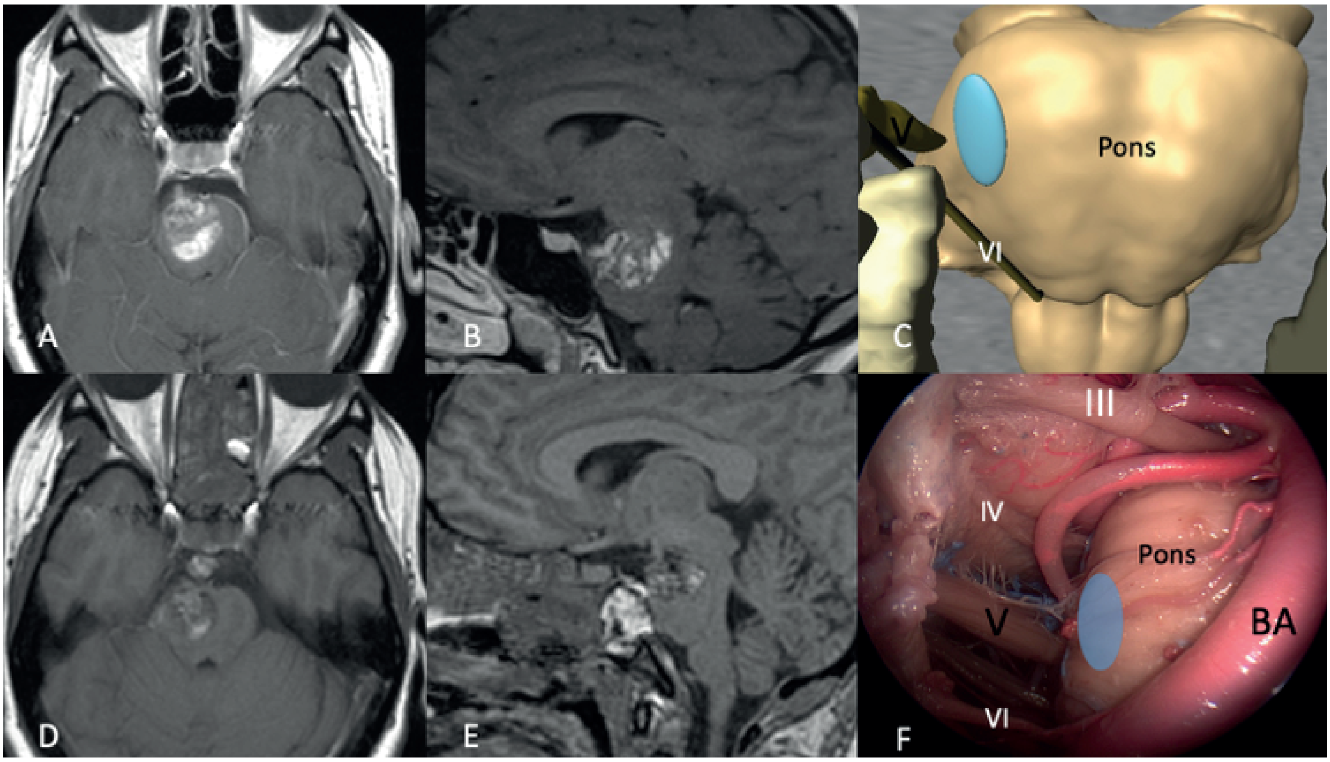

Figure 3. Preoperative axial (a) and sagittal (b) magnetic resonance images showing a pontine cavernoma in Case #2. Postoperative axial (d) and sagittal (e) magnetic resonance images showing removal of the lesion. 3-dimensional analysis and anatomical pictures have been provided. Blue circle, peritrigeminal safe entry zone; V, trigeminal nerve; BA, basilar artery; IV, trochlear nerve; III, oculomotor nerve; VI, abducens nerve.

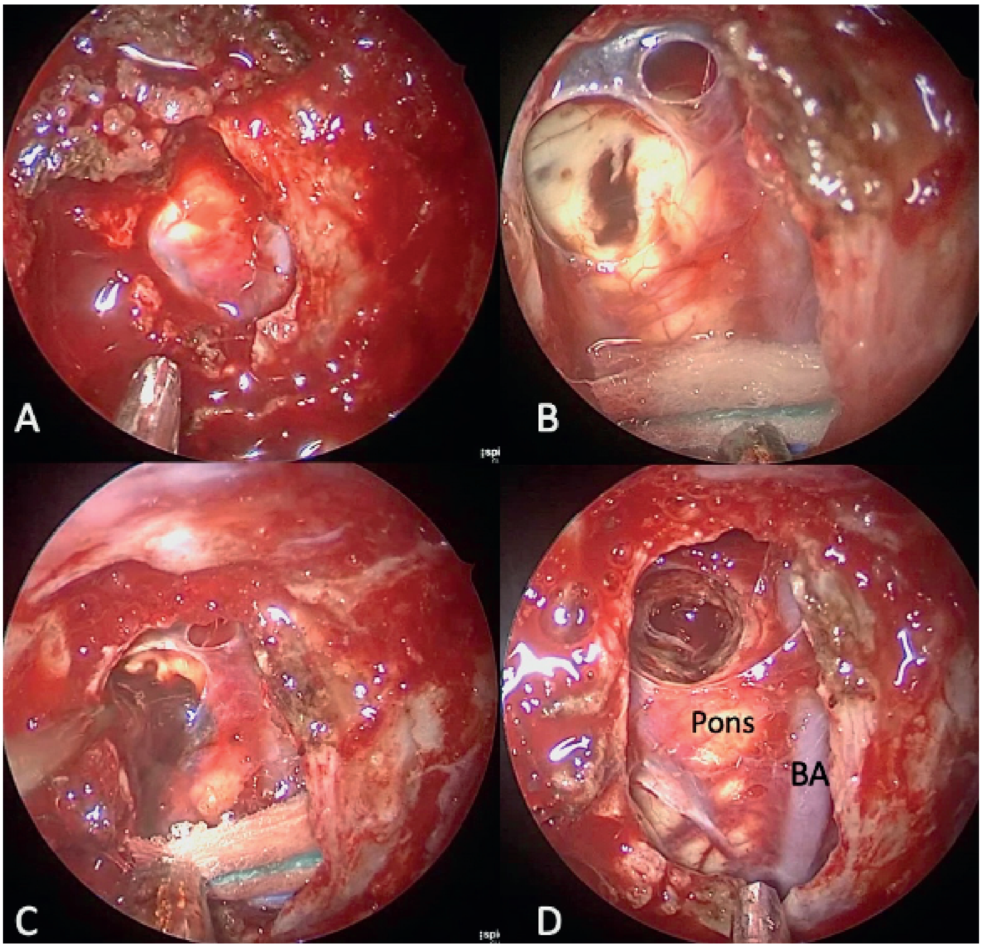

Figure 4. Endoscopic endonasal removal of pontine cavernoma (Case #2). The cavernoma was approached through its exophytic portion in the ventral pons, respecting the peritrigeminal safe entry zone (a-c). The surgical cavity can be observed after removal of the cavernoma (d). BA, basilar artery.

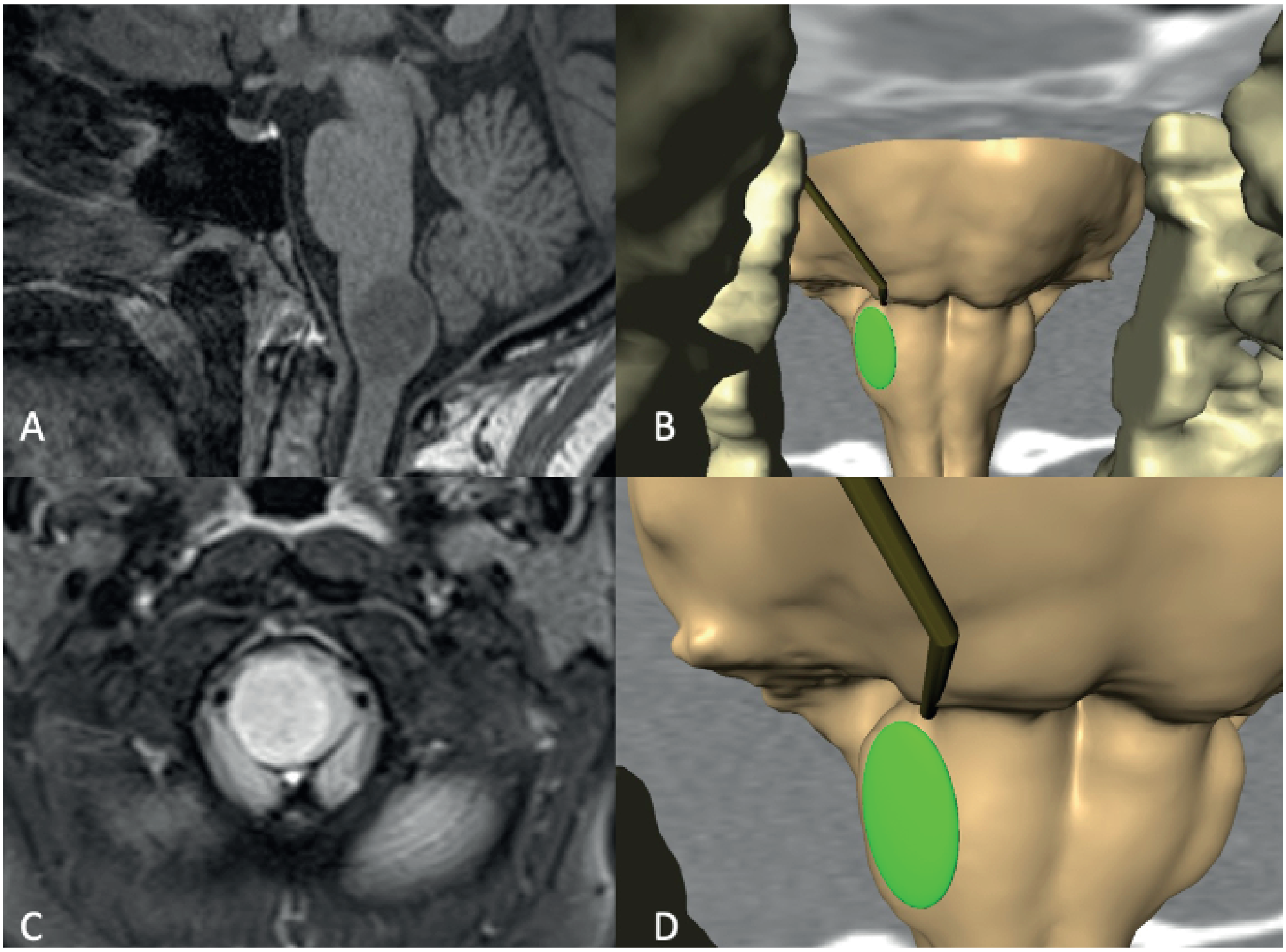

Figure 5. Preoperative magnetic resonance study of Case #4 showing a medullary non-contrast-enhancing lesion with its exophytic portion at the level of the ventral brainstem (a, c). Detailed 3D anatomic analysis showed the position of the olivar zone and its relationship with the tumor (b, d).

astrocytoma and inceptive hydrocephalus. To allow better specification of the lesion, the neuro-oncology committee opted to take a biopsy. After analyzing the images and concluding that an anterior approach to a ventral superficial component of the lesion was feasible via the peritrigeminal zone (PTZ), we decided to adopt an endoscopic endonasal transclival approach because it allowed direct access to the lesion.

An external ventricular drainage was placed immediately before the beginning of surgery. Neuronavigation was used during the approach until the lesion was reached. A superior and middle clivectomy was then performed. A biopsy was carried out in the PTZ and guided by neurophysiological monitoring.

The patient improved on the first day after surgery. During the following days, he required a ventricular peritoneal shunt, but showed no neurological or endocrinological deficits. Pathology confirmed an astrocytoma with an isocitrate dehydrogenase-1 mutation. The patient received subsequent radiotherapy and chemotherapy. In the last MRI images, the lesion showed discrete diminution in size. After 1 year and 8 months, at the time of writing the present report, the patient was stable.

Case #4

A 43-year-old woman presented with headache and dizziness. MRI revealed a medullary non-contrast-enhancing lesion (Figure 5). DTI showed that the corticomedullary and corticospinal tracts were pushed posterolaterally. The case was discussed by the neuro-oncology committee, who decided that a biopsy would ensure better treatment because it would allow the lesion to be specified on a molecular basis. After review of the MRI, it was decided that surgery was possible without additional neurological deficits to the patient. Considering all feasible approaches, an endoscopic endonasal transclival route was elected because it allows direct entry via the olivar zone (OZ). Neuromonitoring of the sixth CN and the lower CNs (tenth to twelfth), MEPs, and SSEPs was used, and intraoperative neuronavigation facilitated identification of anatomical landmarks.

The basopharyngeal fascial flap was lifted by cutting the fascia from the medial limit of one Eustachian tube to the other. The longus capitis and rectus capitis muscles were then raised with the fascial flap. This allowed the lower clivus to be removed to the foramen magnum using a diamond drill, exposing the

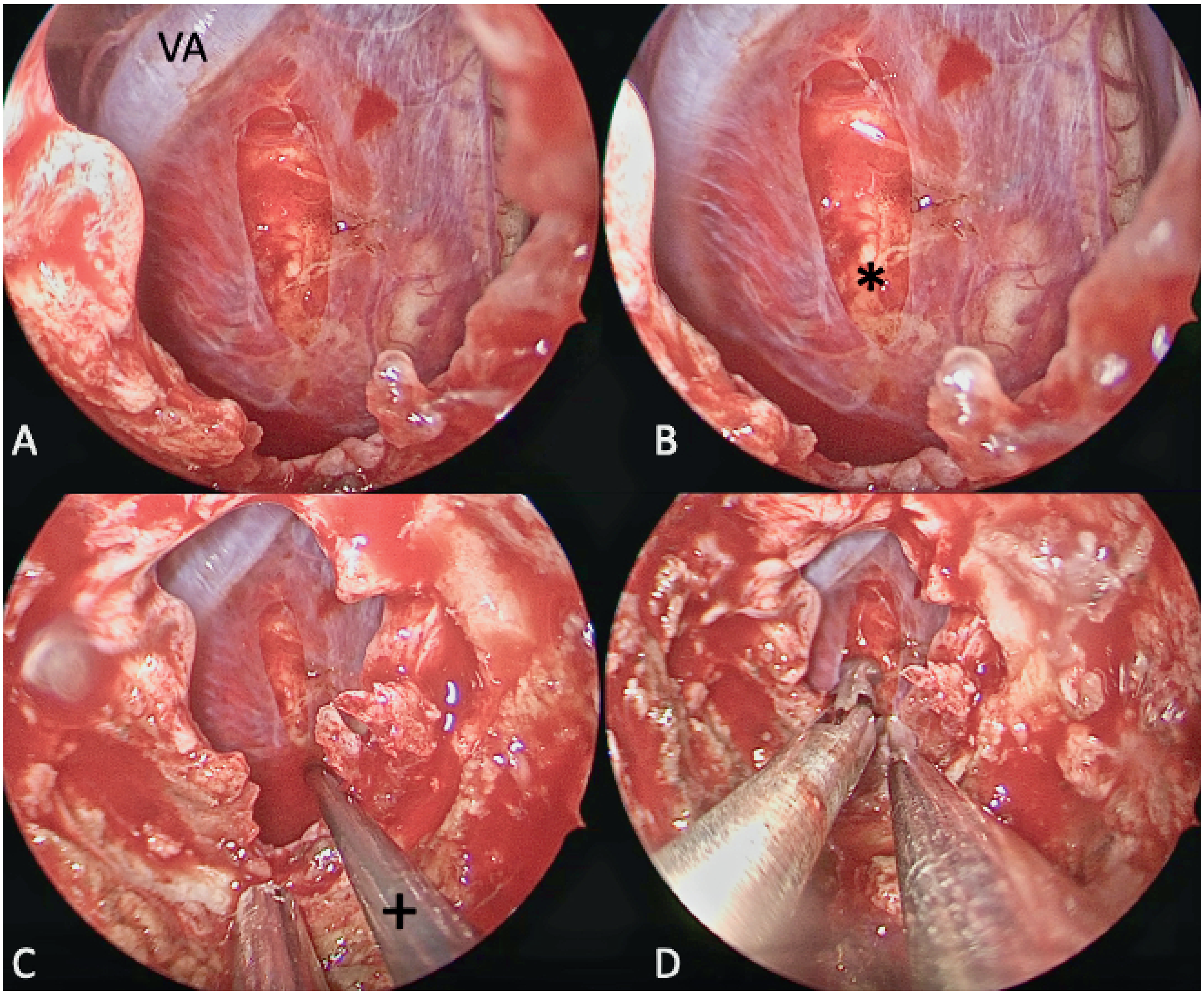

Figure 6. Endoscopic endonasal biopsy for a ventral medullary tumor (a, b). The use of direct neuromonitoring was mandatory immediately before tumor biopsy (c, d). VA, vertebral artery; +, direct neurophysiologic pointer; *, exophytic portion of the tumor.

underlying dura.

To perform a tumor biopsy, the dura was opened in a linear fashion and a small piece of the lesion was sent for pathology analysis (Figure 6). After surgery, the patient was neurologically stable with no new deficits. Pathology found a diffuse midline glioma with H3-K27M mutation, so the patient underwent chemotherapy and radiotherapy after surgery (details in Table 1).

As a complication, subacute hydrocephalus was diagnosed after detecting a cerebrospinal fluid (CSF) leak, which was solved with revision surgery and by means of a ventriculo-peritoneal shunt.

After 10 months, the patient presented progression of the lesion despite the oncological treatment. The patient died 1 year after diagnosis.

Case #5

A 32 year-old woman presented with a medical history of low grade brainstem astrocytoma treated with surgery and radiotherapy when she was 12 years old. A brainstem cavernoma was diagnosed several years later during control MRI.

The patient presented to the ER complaining of sudden diplopia. A left sixth CN palsy was diagnosed. On the CT scan, a medullary pontine hemorrhage was observed. The patient was discharged without any other neurological deficits. Fifteen days later, she returned to the ER because of right hemiparesis. An MRI was carried out subsequently and corroborated the cavernoma hemorrhage with a ventral superficial portion.

Because the patient had two recent episodes of hemorrhage, neurological deficits, and superficial cavernoma, surgery was considered the best option. Before surgery, the patient's hemiparesis improved, but her sixth CN palsy did not.

Considering that the lesion had a ventral position, the endoscopic endonasal transclival approach was elected, which allowed a straight route without impinging on important neurological structures. The approach was similar to the one used in Cases

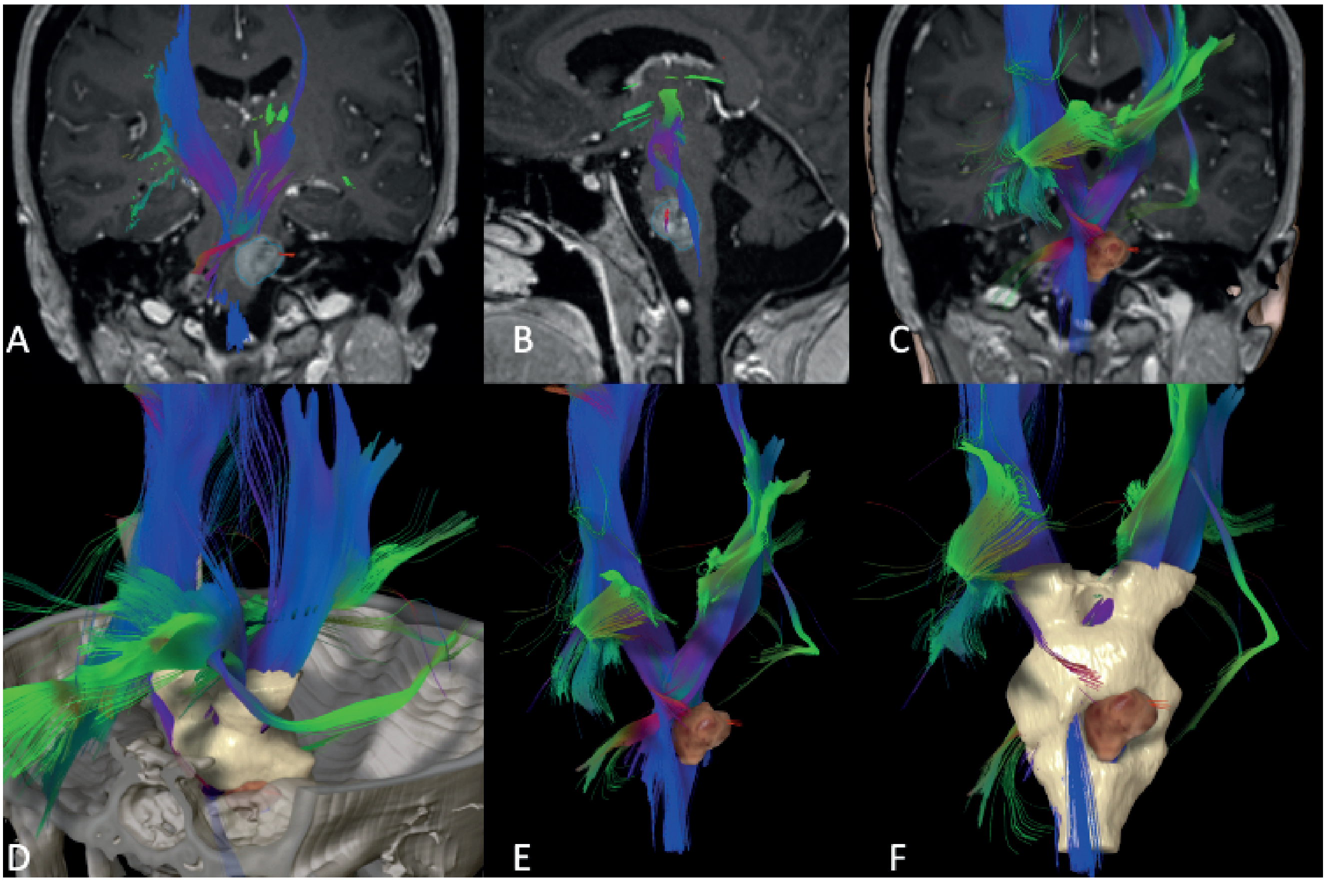

Figure 7. Comprehensive neuroradiological study in Case #5. A lesion at the level of the pons was visible, causing compression and displacement of the corticospinal tracts to the right side.

2 and 3. The entry zone was the PTZ and the procedure was guided by neuronavigation and intraoperative neuromonitoring. The surgery was carried out without complications and the patient was stable after the surgery, retaining the sixth CN palsy but with no new neurological deficits. At the last follow-up 7 months after the surgery, the patient was stable.

3D reconstruction and relevant neuroanatomy

The anatomy of the brainstem area has been detailed in recent publications [40] in a study that adopted an extended transtuberculum-transplanum route to access the AMZ endonasally. In some cases, the pituitary gland needed to be transposed. However, this access route to the AMZ can be blocked medially by the exiting third cranial nerve from the brainstem and laterally by the medially coursing cavernous carotid artery.

When exposing the pons, sufficient lateral exposure is vital to identify the relevant anatomy, such as the pontine midline. It also partially exposes the PTZ. However, surgeons must pay particular attention to the abducens nerve, which courses upwards in a medial-to-lateral trajectory, through the basilar plexus and dura mater, to reach Dorello's canal at the level of the petrous apex.

The superior segment of the medulla can easily be exposed, while its inferior part cannot. The relatively small size of the medulla and the superficiality of the corticospinal tract (CST) limit surgical maneuverability at this level. A safe entry zone, namely the OZ, can be used to access the medulla to allow tumor biopsy, especially if the lesion is displacing the CST away from the biopsy area.

Finally, the use of neuronavigation and intraoperative electrophysiological monitoring should be mandatory in cases like those above to ensure accurate localization of the cortical incision and real-time feedback during dissection.

Discussion

Intrinsic brainstem pathologies are not routinely removed because, from an ethical standpoint, any surgery should improve the natural history of the treated disorder without adding morbidity to the patient. When surgeons need to access a lesion through critical neural pathways, they risk causing temporary or permanent deficits in patients. To optimize the resection of lesions while decreasing risk to the patient, surgeons must select an approach that allows direct access to the lesion, ideally via the shortest distance, although this is not always possible, with minimal disturbance to adjacent neural pathways [12]. Although surgical treatment of intra-axial brainstem tumors remains

Table 2. Cases of intra-axial brainstem lesions approached via an endoscopic endonasal corridor.

Author & Year	Patients	Pathology	Location	Clinical status	Entry point	Immediate post-operative status	Late outcome
Sanborn MR, 2012	M, 17	Cavernoma	Ventromedial pons	Headache, facial numbness, tingling; left-sided hemiparesis, right sixth nerve palsy, dysphagia	Right ventromedial pons	Minimally worsened; CSF leak	No further signs of CSF leak, hemiparesis improved
Kimball MM, 2012	F, 59	Cavernoma	Ventral midpons eccentric to the right	Intermittent dysarthria, right facial weakness, left arm and leg weakness	Right ventromedial pons	Stable; CSF leak	Improved
Rajappa P, 2013	M, 16	Anaplastic ependymoma	Pontomedullary junction	Headaches, dysphagia, left hemiparesis	Tumor visible at BS surface	Three surgical intervention, progressive worsening	Death
Enseñat J, 2014 (Case #1)	M, 38	Cavernoma	Ventral midline midbrain	Isolated third-nerve palsy	Ventral midbrain, right side (anterior mesencephalic zone)	Improved	Improved
Linsler S & Oertel J, 2015	F, 29	Cavernoma	Ventral pons	numbness and tingling right arm and leg; loss of fine motor control	Ventral pons	Motor control loss and tingling disappeared	Stable
Dallan I, 2015	M, 15	Cavernoma	Ventral pons	Headache and right cranial nerve VI, VII and VIII palsies	Right paramedian pons	Improvement	Stable
Nayak NR, 2015	F, 60	Cavernoma	Ventral Medulla	2/5 right deltoid weakness and less severe distal right upper extremity weakness	Hemorrhagic staining in the medulla	Unchanged	Stable
Fomichev D, 2016	N/A	Endodermal cyst	Ventral Pons	headaches, dizziness, shaky gait, taste disturbances on a tongue, diplopia, left side numbness	Right paramedian pons	Improvement	Stable
Gómez-Amador JL, 2016	M, 29	Cavernoma	Ventral Pons	Headache, nausea, horizontal diplopia; facial palsy, dysarthria, dysphonia, dysphagia, and left hemiparesis	Right paramedian pons	Palate deviation improved	Improved
He S, 2016	F, 20	Cavernoma	Ventral Midbrain	Headache, nausea and vomiting. left-sided hemiparesis, restriction of eye movements	Right midbrain	Improved oculomotor symptoms	Improved
Alikhania P, 2017	F, 26	Cavernoma	Ventral Medulla	Imbalance and dizziness; imbalance and swallowing difficulty; minimal (grade 4/5) weakness in the right hemibody	Right medulla	Initial worsening	Improved
Erickson N, 2018	M, 21	Cavernoma	Ventral Pons	Right sided hemiparesis	Infero-medial pons area	Stable	Improved
Fernandes Cabral DT, 2018	F, 56	Glioma	Ventral Pons	right-side hemiparesis and left facial numbness; 4/5 strength on the right upper and 3/5 on the right lower extremity.	Exophitic component	new abducens nerve palsy and hemiparesis worsening	Death
Current Case #2	F, 29	Cavernoma	Ventral Pons	Headache and hypoesthesia on the right side of the face	Right pons (peritrigeminal zone)	Improved	Improved
Current Case #3	M, 27	Astrocytoma IDH-1 mutated	Ventral Pons	Dizziness and diplopia	Right pons (peritrigeminal zone)	Improved	Stable
Current Case #4	F, 43	Diffuse midline glioma H3-K27M mutation	Medullary	Headache and dizziness	Right medulla (olivar zone)	Stable, CSF leak	Progression
Current Case #5	F, 32	Cavernoma	Pons	Left sixth nerve palsy	Left pons (peritrigeminal zone)	Stable	Stable

M, Male; F, Female; IDH, isocitrate dehydrogenase.

controversial, it may be indicated for open biopsy or resection of lesions with a large exophytic component.

In cases of brainstem neoplasia, oncologists prefer to have a biopsy performed because the molecular specifications of the tumors influence both prognosis and treatment. In the case of cavernomas, surgeons and patients must make decisions together based on the risks of the procedure, the previous clinical situation of the patients (neurological deficits due to cavernoma hemorrhage), and the anatomical position of the lesions.

Endoscopic endonasal surgery to treat intrinsic brainstem lesions

Recently, Essayed et al. [40] described the potential indications and limitations of the EEA to treat such lesions. Their purely anatomical report provided a first step towards the application of this route to treat ventral brainstem lesions. Nevertheless, exposing or visualizing these structures does not confirm that they can be safely accessed and dissected. Conversely, based on an understanding of brainstem anatomy from the endonasal perspective, Weiss el al. [30] proposed that fiber dissection using 7T-MRI neuronavigation was correlated with significant improvement. However, the actual clinical relevance of their result is uncertain because it was based solely on cadaveric dissections and 7T MRIs.

Several advancements have rendered brainstem endonasal endoscopic surgery more feasible, and it is now commonly used worldwide in extended approaches previously unthinkable. Experienced endoscopic neurosurgeons can use microsurgical dissection to decrease the incidence of neurovascular injury and damage to the brainstem tracts or nuclei. Image-guidance and intraoperative neuromonitoring allow a better view of the tracts and nuclei in each individual patient and prevent undesirable injuries.

Anatomical analysis of safe entry zone during EEA to the brainstem in the present series

The anatomic dissections and specific 3D reconstructions focused on safe entry zones. In our five cases, we used the AMZ, the PTZ (in three cases), and the OZ.

The AMZ is a limited area of the cerebral peduncle bounded medially by the oculomotor tract and nerve and laterally by the corticospinal tract. Such a narrow corridor takes advantage of the distribution of corticospinal tract fibers mainly in the intermediate three-fifths of the peduncle and the fact that the red nucleus and the nigrostriatal circuit are in a deep medial location. The entry point inside the interpeduncular cistern is limited superiorly by the posterior cerebral artery (PCA) and inferiorly by the main trunk of the superior cerebellar artery (SCA) (Figure 1). Conversely, the PTZ, which was used in two of the present cases, is located in front of the trigeminal nerve entry zone, lateral to the corticospinal tract and anterior to the motor and sensory nuclei of the trigeminal nerve. The fibers of the sixth, seventh, and eighth CNs run downward and are located posterior to the trigeminal nuclei (Figure 3).

Specific considerations regarding our results

In the present study, we reported the first single-center experience of endoscopic endonasal surgery to treat five heterogeneous cases of intrinsic brainstem lesions. Three cases were cavernous malformations and three were localized at the level of the pons.

Reviewing the literature, 17 patients with intrinsic brainstem pathologies treated via an EEA were found, (eight women, seven men, one N/A; mean age: 32.5 years), including the patients in the present study. The data extracted from these studies, which mainly comprised case reports, are summarized in Table 2 (Figure 7) [32, 39, 41-51]. An analysis revealed that, in most cases (69%), the diagnosis was a cavernous malformation, followed by an intrinsic brainstem glioma (19% of cases). Regarding localization, lesions resected via the EEA were more frequently located at the level of the pons. In 14 cases (87.5%), the final outcome was improved or stable, while death was reported in two cases (12.5%), both of which involved glioma. The most frequent complication was CSF leak, which occurred in three cases (18.75%).

The two pathologies reported in the present study—cavernoma and intrinsic brainstem glioma—should be considered separately (Table 2).

In cases of cavernoma, we approached via the exophytic region, considering the structures of the AMZ and the PTZ, which are both considered safe entry zones. Surgeons must understand the anatomy of the entry zones to avoid injuring brainstem tracts and nuclei during dissection and resection of the lesion. Conversely, surgery of intrinsic cavernomas is a matter of debate and timing. Even with a perfect understanding of the safe entry zones and tracts, as well as the positions of the nuclei, surgeons must use neuronavigation and intraoperative neuromonitoring to minimize the risk of new deficits to the patient, even if they have extensive experience [52-55].

With regards to the outcomes of brainstem cavernomas, our patients improved in the immediate post-operative period, as did most of the nine patients with cavernomas reported in the literature, wherein only one had worsened and one had remained stable at the last follow-up.

Concerning the gliomas in our series, following the decision of our neuro-oncology committee, we decided to perform biopsies to ensure a more specific treatment and prognosis based on molecular data, and because we thought the procedure was feasible while maintaining the safety of the patients. We thought that we could enter through the PTZ and OZ, respectively. As with cavernomas, surgeons must fully understand the surgical anatomy of the safe entry zones. However, in the specific case of glioma surgery, total resection is challenging and dangerous because surgeons often cannot ascertain when and where to stop to ensure total resection. Furthermore, prognosis is no better in patients who undergo surgery of that magnitude, especially if the resection is not total.

Regarding the specific clinical results of our preliminary series, two patients remained stable; in another, diplopia improved during the immediate post-operative period and follow-up. One patient showed progression of the tumor.

Specific to the EEA, the risk of postoperative CSF leak can be minimized using a multilayer vascularized skull base reconstruction and lumbar drain. However, the role of lumbar drainage is a matter of debate in skull base surgery, with guidelines and relevant articles on this procedure being published recently [56, 57]. In all cases presented in the present series, multilayer vascularized reconstruction and placement of a lumbar drain were used, and we reported one case of CSF leak (20% of our cases). Among all reported cases, CSF leak has occurred in three patients (18.75%).

Study limitations

Our case series included only a few cases with heterogeneous presentation, so strong conclusions cannot be drawn. However, this preliminary series represents the first report of a single-center experience of endoscopic endonasal surgery to the brainstem, although it lacked a high level of evidence [58].

Conclusion

In the present study, we demonstrated, in a real surgical scenario, that EEAs offer adequate access to the brainstem. Being in the midline and in the retroclival area, the pons can be exposed easily via the EEA route. In particular, cavernous malformations can be treated using this approach, combined with a ventral route and with the PTZ as a safe entry zone. Other classic brainstem safe entry zones, such as AMZ in the mesencephalon and OZ in the medulla, are accessible when using the anterior endoscopic trajectory. To our knowledge, this was the first single-center study to adopt the endoscopic endonasal perspective in intra-axial brainstem surgery. As such, the EEA can be considered a valid surgical alternative to traditional transcranial approaches to treat select intra-axial brainstem lesions located at the level of the ventral brainstem. Comprehensive anatomical knowledge, thorough preoperative surgical planning, and intraoperative neurophysiological monitoring are essential to accomplish good results.

Acknowledgements

This project was partially supported by grants from the "Instituto de Salud Carlos III" (PI19/00592) and the "Fundacio La Marato de TV3" (Reg. 95/210; Codi projecte: 201914).

Authorship contribution

All authors contributed equally to the final paper.

Conflict of interest

Dr. Di Somma is consultant for Brainlab AG (Munich, Germany). No other conflict of intersts of the authors.

References

1. Cavalcanti DD, Preul MC, Kalani MY, Spetzler RF. Microsurgical anatomy of safe entry zones to the brainstem. J Neurosurg. 2016;124(5):1359-76.
2. Matsushima K, Yagmurlu K, Kohno M, Rhoton AL. Anatomy and approaches along the cerebellar-brainstem fissures. J Neurosurg. 2016;124(1):248-63.
3. Yagmurlu K, Rhoton AL, Tanriover N, Bennett JA. Three-dimensional microsurgical anatomy and the safe entry zones of the brainstem. Neurosurgery. 2014;10 Suppl 4:602-19; discussion 19-20.
4. Bricolo A, Turazzi S. Surgery for gliomas and other mass lesions of the brainstem. Adv Tech Stand Neurosurg. 1995;22:261-341.
5. Porter RW, Detwiler PW, Spetzler RF, Lawton MT, Baskin JJ, Derksen PT, et al. Cavernous malformations of the brainstem: experience with 100 patients. J Neurosurg. 1999;90(1):50-8.
6. Garcia RM, Ivan ME, Lawton MT. Brainstem cavernous malformations: surgical results in 104 patients and a proposed grading system to predict neurological outcomes. Neurosurgery. 2015;76(3):265-77; discussion 77-8.
7. Han SJ, Englot DJ, Kim H, Lawton MT. Brainstem arteriovenous malformations: anatomical subtypes, assessment of "occlusion in situ" technique, and microsurgical results. J Neurosurg. 2015;122(1):107-17.
8. Abla AA, Turner JD, Mitha AP, Lekovic G, Spetzler RF. Surgical approaches to brainstem cavernous malformations. Neurosurg Focus. 2010;29(3):E8.
9. Almefty KK, Spetzler RF. Management of brainstem cavernous malformations. World Neurosurg. 2015;83(3):317-9.
10. 10. Cavalcanti DD, Figueiredo EG, Preul MC, Spetzler RF. Anatomical and Objective Evaluation of the Main Surgical Approaches to Pontine Intra-Axial Lesions. World Neurosurg. 2019;121:e207-e14.
11. Garrett M, Spetzler RF. Surgical treatment of brainstem cavernous malformations. Surg Neurol. 2009;72 Suppl 2:S3-9; discussion S-10.
12. Kalani MY, Yagmurlu K, Martirosyan NL, Cavalcanti DD, Spetzler RF. Approach selection for intrinsic brainstem pathologies. J Neurosurg. 2016;125(6):1596-607.
13. Konovalov A, Samii M, Porter RW, Spetzler RF, Houteville JP, Yoshimoto T, et al. Brainstem cavernoma. Surg Neurol. 2000;54(6):418-21.
14. Cappabianca P. Neuroendoscopy: a modern perspective. World Neurosurg. 2012;77(1):3-4.
15. Zada G, Cappabianca P. Raising the bar in transsphenoidal pituitary surgery. World Neurosurg. 2010;74(4-5):452-4.
16. Kaen A, Cárdenas Ruiz-Valdepeñas E, Di Somma A, Esteban F, Márquez Rivas J, Ambrosiani Fernandez J. Refining the anatomic boundaries of the endoscopic endonasal transpterygoid approach: the "VELPPHA area" concept. J Neurosurg. 2018:1-9.
17. Freeman JL, Sampath R, Quattlebaum SC, Casey MA, Folzenlogen ZA, Ramakrishnan VR, et al. Expanding the endoscopic transpterygoid corridor to the petroclival region: anatomical study and volumetric comparative analysis. J Neurosurg. 2017:1-10.
18. Koutourousiou M, Fernandez-Miranda JC, Vaz-Guimaraes Filho F, de Almeida JR, Wang EW, Snyderman CH, et al. Outcomes of Endonasal and Lateral Approaches to Petroclival Meningiomas. World Neurosurg. 2017;99:500-17.
19. Beer-Furlan A, Abi-Hachem R, Jamshidi AO, Carrau RL, Prevedello DM. Endoscopic

trans-sphenoidal surgery for petroclival and clival meningiomas. J Neurosurg Sci. 2016;60(4):495-502.
20. Jean WC, Felbaum DR, Anaizi A, DeKlotz TR. Endoscopic Endonasal Approach for Transclival Resection of a Petroclival Meningioma: A Technical Note. Cureus. 2016;8(6):e641.
21. Muto J, Prevedello DM, Ditzel Filho LF, Tang IP, Oyama K, Kerr EE, et al. Comparative analysis of the anterior transpetrosal approach with the endoscopic endonasal approach to the petroclival region. J Neurosurg. 2016;125(5):1171-86.
22. Beer-Furlan A, Vellutini EA, Balsalobre L, Stamm AC. Endoscopic Endonasal Approach to Ventral Posterior Fossa Meningiomas: From Case Selection to Surgical Management. Neurosurg Clin N Am. 2015;26(3):413-26.
23. Ditzel Filho LF, Prevedello DM, Dolci RL, Jamshidi AO, Kerr EE, Campbell R, et al. The Endoscopic Endonasal Approach for Removal of Petroclival Chondrosarcomas. Neurosurg Clin N Am. 2015;26(3):453-62.
24. Jacquesson T, Simon E, Berhouma M, Jouanneau E. Anatomic comparison of anterior petrosectomy versus the expanded endoscopic endonasal approach: interest in petroclival tumors surgery. Surg Radiol Anat. 2015;37(10):1199-207.
25. Moussazadeh N, Kulwin C, Anand VK, Ting JY, Gamss C, Iorgulescu JB, et al. Endoscopic endonasal resection of skull base chondrosarcomas: technique and early results. J Neurosurg. 2015;122(4):735-42.
26. Mesquita Filho PM, Ditzel Filho LF, Prevedello DM, Martinez CA, Fiore ME, Dolci RL, et al. Endoscopic endonasal surgical management of chondrosarcomas with cerebellopontine angle extension. Neurosurg Focus. 2014;37(4):E13.
27. Van Gompel JJ, Alikhani P, Tabor MH, van Loveren HR, Agazzi S, Froelich S, et al. Anterior inferior petrosectomy: defining the role of endonasal endoscopic techniques for petrous apex approaches. J Neurosurg. 2014;120(6):1321-5.
28. Fernandez-Miranda JC, Morera VA, Snyderman CH, Gardner P. Endoscopic endonasal transclival approach to the jugular tubercle. Neurosurgery. 2012;71(1 Suppl Operative):146-58; discussion 58-9.
29. de Notaris M, Cavallo LM, Prats-Galino A, Esposito I, Benet A, Poblete J, et al. Endoscopic endonasal transclival approach and retrosigmoid approach to the clival and petroclival regions. Neurosurgery. 2009;65(6 Suppl):42-50; discussion -2.
30. Weiss A, Perrini P, De Notaris M, Soria G, Carlos A, Castagna M, et al. Endoscopic Endonasal Transclival Approach to the Ventral Brainstem: Anatomic Study of the Safe Entry Zones Combining Fiber Dissection Technique with 7 Tesla Magnetic Resonance Guided Neuronavigation. Oper Neurosurg (Hagerstown). 2019;16(2):239-49.
31. Essayed WI, Singh H, Lapadula G, Almodovar-Mercado GJ, Anand VK, Schwartz TH. Endoscopic endonasal approach to the ventral brainstem: anatomical feasibility and surgical limitations. J Neurosurg. 2017:1-8.
32. Fernandes Cabral DT, Zenonos GA, Nuñez M, Celtikci P, Snyderman C, Wang E, et al. Endoscopic Endonasal Transclival Approach for Resection of a Pontine Glioma: Surgical Planning, Surgical Anatomy, and Technique. Oper Neurosurg (Hagerstown). 2018;15(5):589-99.
33. Solari D, Villa A, De Angelis M, Esposito F, Cavallo LM, Cappabianca P. Anatomy and surgery of the endoscopic endonasal approach to the skull base. Transl Med UniSa. 2012;2:36-46.
34. Cappabianca P, Cavallo LM, Esposito F, De Divitiis O, Messina A, De Divitiis E. Extended endoscopic endonasal approach to the midline skull base: the evolving role of transsphenoidal surgery. Adv Tech Stand Neurosurg. 2008;33:151-99.
35. Cavallo LM, Messina A, Cappabianca P, Esposito F, de Divitiis E, Gardner P, et al. Endoscopic endonasal surgery of the midline skull base: anatomical study and clinical considerations. Neurosurg Focus. 2005;19(1):E2.
36. Kassam A, Snyderman CH, Mintz A, Gardner P, Carrau RL. Expanded endonasal approach: the rostrocaudal axis. Part II. Posterior clinoids to the foramen magnum. Neurosurgical focus. 2005;19(1):E4.
37. Kassam A, Snyderman CH, Mintz A, Gardner P, Carrau RL. Expanded endonasal approach: the rostrocaudal axis. Part I. Crista galli to the sella turcica. Neurosurgical focus. 2005;19(1):E3.
38. Solari D, Chiaramonte C, Di Somma A, Dell'Aversana Orabona G, de Notaris M, Angileri FF, et al. Endoscopic anatomy of the skull base explored through the nose. World neurosurgery. 2014;82(6 Suppl):S164-70.
39. Enseñat J, d'Avella E, Tercero A, Valero R, Alobid I. Endoscopic endonasal surgery for a mesencephalic cavernoma. Acta Neurochir (Wien). 2015;157(1):53-5.
40. Essayed WI, Singh H, Lapadula G, Almodovar-Mercado GJ, Anand VK, Schwartz TH. Endoscopic endonasal approach to the ventral brainstem: anatomical feasibility and surgical limitations. J Neurosurg. 2017;127(5):1139-46.
41. Nayak NR, Thawani JP, Sanborn MR, Storm PB, Lee JY. Endoscopic approaches to brainstem cavernous malformations: Case series and review of the literature. Surg Neurol Int. 2015;6:68.
42. Alikhani P, Sivakanthan S, Ashour R, Tabor M, van Loveren H, Agazzi S. Endoscopic endonasal resection of a medullary cavernoma: a novel case. Br J Neurosurg. 2017:1-3.
43. He SM, Wang Y, Zhao TZ, Zheng T, Lv WH, Zhao LF, et al. Endoscopic Endonasal Approach to Mesencephalic Cavernous Malformations. World Neurosurg. 2016;90:701.e7-.e10.
44. Dallan I, Battaglia P, de Notaris M, Caniglia M, Turri-Zanoni M. Endoscopic endonasal transclival approach to a pontine cavernous malformation: case report. Int J Pediatr Otorhinolaryngol. 2015;79(9):1584-8.
45. Erickson N, Siu A, Sherman JH, Gragnaniello C, Singh A, Litvack Z. Endoscopic Transnasal Transclival Approach to a Pontine Cavernoma with Associated Developmental Venous Anomaly. World Neurosurg. 2018;118:212-8.
46. Gómez-Amador JL, Ortega-Porcayo LA, Palacios-Ortíz IJ, Perdomo-Pantoja A, Nares-López FE, Vega-Alarcón A. Endoscopic endonasal transclival resection of a ventral pontine cavernous malformation: technical case report. J Neurosurg. 2016:1-6.
47. Kimball MM, Lewis SB, Werning JW, Mocco JD. Resection of a pontine cavernous malformation via an endoscopic endonasal approach: a case report. Neurosurgery. 2012;71(1 Suppl Operative):186-93; discussion 93-4.
48. Linsler S, Oertel J. Endoscopic Endonasal Transclival Resection of a Brainstem Cavernoma: A Detailed Account of Our Technique and Comparison with the Literature. World Neurosurg. 2015;84(6):2064-71.
49. Sanborn MR, Kramarz MJ, Storm PB, Adappa ND, Palmer JN, Lee JY. Endoscopic, endonasal, transclival resection of a pontine cavernoma: case report. Neurosurgery. 2012;71(1 Suppl Operative):198-203.
50. Fomichev D, Kalinin P, Gavrushin A. Endoscopic Transnasal Transclival Resection of Endodermal Cyst on Ventral Surface of Brainstem. World Neurosurg. 2016.
51. Rajappa P, Margetis K, Sigounas D, Anand V, Schwartz TH, Greenfield JP. Endoscopic endonasal transclival approach to a ventral pontine pediatric ependymoma. J Neurosurg Pediatr. 2013;12(5):465-8.
52. Li D, Yang Y, Hao SY, Wang L, Tang J, Xiao XR, et al. Hemorrhage risk, surgical management, and functional outcome of brainstem cavernous malformations. J Neurosurg. 2013;119(4):996-1008.
53. Gross BA, Batjer HH, Awad IA, Bendok BR, Du R. Brainstem cavernous malformations: 1390 surgical cases from the literature. World Neurosurg. 2013;80(1-2):89-93.
54. Zaidi HA, Mooney MA, Levitt MR, Dru AB, Abla AA, Spetzler RF. Impact of Timing of Intervention Among 397 Consecutively Treated Brainstem Cavernous Malformations. Neurosurgery. 2017;81(4):620-6.
55. Rajagopal N, Kawase T, Mohammad AA, Seng LB, Yamada Y, Kato Y. Timing of Surgery and Surgical Strategies in Symptomatic Brainstem Cavernomas: Review of the Literature. Asian J Neurosurg. 2019;14(1):15-27.
56. Wang EW, Zanation AM, Gardner PA, Schwartz TH, Eloy JA, Adappa ND, et al. ICAR: endoscopic skull-base surgery. Int

Forum Allergy Rhinol. 2019;9(S3):S145-S365.
57. Zwagerman NT, Wang EW, Shin SS, Chang YF, Fernandez-Miranda JC, Snyderman CH, et al. Does lumbar drainage reduce postoperative cerebrospinal fluid leak after endoscopic endonasal skull base surgery? A prospective, randomized controlled trial. J Neurosurg. 2018:1-7.
58. Rutka JT. Editorial. Classes of evidence in neurosurgery. J Neurosurg. 2017;126(6):1747-8.

Alberto Di Somma
Institut Clínic de Neurociències (ICN)
Department of Neurological Surgery
Hospital Clínic de Barcelona
Universidad de Barcelona
Barcelona
Spain

E-mail:
albertodisomma87@gmail.com

Supplementary data

Video 1: Endoscopic endonasal surgery to treat a ventral midbrain cavernoma (Case #1, see Table 1 for details). Dissection was performed in the retrosellar area to expose the mammillary bodies and the surface of the midbrain. Using gentle suction and sharp dissection, the hematoma was evacuated and the cavernoma removed piecemeal, decompressing the brainstem.

Video 2: Endoscopic endonasal surgery to treat a ventral pontine cavernoma (Case #2, see Table 1 for details). The lesion was gently removed using suction, angled dissectors, and curettes.

Video 3: Endoscopic endonasal biopsy for a diffuse midline glioma (Case #4, see Table 1 for details). After opening the dura, direct neurophysiological stimulation was performed according to specific data reported in the neuronavigation system. Due to a trigger of the XII cranial nerve, the entry site was modified and a small piece of the lesion was sent for pathology analysis.

Link to Videos: https://www.dropbox.com/sh/q1magyblux9pz7s/AACSvCChxp0QRpKXbawGl2sna?dl=0