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CLINICAL ARTICLE

Microsurgical management of midbrain gliomas: surgical results and long-term outcome in a large, single-surgeon, consecutive series

Carlo Serra, MD,[1,3] Hatice Türe, MD,[2] Zeynep Fırat, MD,[4] Victor E. Staartjes, MD, PhD,[3] Cumhur Kaan Yaltırık, MD,[1] Gazanfer Ekinci, MD,[4] Aydin Sav, MD,[5] and Uğur Türe, MD[1]

Departments of [1]Neurosurgery, [2]Anesthesiology, [4]Radiology, and [5]Pathology, Yeditepe University School of Medicine, Istanbul, Turkey; and [3]Department of Neurosurgery, Clinical Neuroscience Centre, University Hospital Zürich, University of Zürich, Switzerland

OBJECTIVE The authors report on a large, consecutive, single-surgeon series of patients undergoing microsurgical removal of midbrain gliomas. Emphasis is put on surgical indications, technique, and results as well as long-term oncological follow-up.

METHODS A retrospective analysis was performed of prospectively collected data from a consecutive series of patients undergoing microneurosurgery for midbrain gliomas from March 2006 through June 2022 at the authors' institution. According to the growth pattern and location of the lesion in the midbrain (tegmentum, central mesencephalic structures, and tectum), one of the following approaches was chosen: transsylvian (TS), extreme anterior interhemispheric transcallosal (eAIT), posterior interhemispheric transtentorial subsplenial (PITS), paramedian supracerebellar transtentorial (PST), perimedian supracerebellar (PeS), perimedian contralateral supracerebellar (PeCS), and transuvulotonsillar fissure (TUTF). Clinical and radiological data were gathered according to a standard protocol and reported according to common descriptive statistics. The main outcomes were rate of gross-total resection; extent of resection; occurrence of any complications; variation in Karnofsky Performance Status score at discharge, 3 months, and last follow-up; progression-free survival (PFS); and overall survival (OS).

RESULTS Fifty-four patients (28 of them pediatric) met the inclusion criteria (6 with high-grade and 48 with low-grade gliomas [LGGs]). Twenty-two tumors were in the tegmentum, 7 in the central mesencephalic structures, and 25 in the tectum. In no instance did the glioma originate in the cerebral peduncle. TS was performed in 2 patients, eAIT in 6, PITS in 23, PST in 16, PeS in 4, PeCS in 1, and TUTF in 2 patients. Gross-total resection was achieved in 39 patients (72%). The average extent of resection was 98.0% (median 100%, range 82%–100%). There were no deaths due to surgery. Nine patients experienced transient and 2 patients experienced permanent new neurological deficits. At a mean follow-up of 72 months (median 62, range 3–193 months), 49 of the 54 patients were still alive. All patients with LGGs (48/54) were alive with no decrease in their KPS score, whereas 42 showed improvement compared with their preoperative status.

CONCLUSIONS Microneurosurgical removal of midbrain gliomas is feasible with good surgical results and long-term clinical outcomes, particularly in patients with LGGs. As such, microneurosurgery should be considered as the first therapeutic option. Adequate microsurgical technique and anesthesiological management, along with an accurate preoperative understanding of the tumor's exact topographic origin and growth pattern, is crucial for a good surgical outcome.

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KEYWORDS brainstem; glioma; mesencephalon; microneurosurgery; midbrain; tumor

Brainstem surgery presents one of the most arduous challenges in neurosurgery, and surgical series on this topic in the literature are scarce compared with other brain regions. Consequently, there is no standard of reporting.[1–10] Several studies report generally about "brainstem lesions," notwithstanding the fact that the word "brainstem" indicates a highly complex group of structures, hosting several nuclei crucial for somatomotor and somatovisceral functions, and major white matter tracts connecting the brain with the periphery,[11–19] all of which

ABBREVIATIONS DTI = diffusion tensor imaging; eAIT = extreme anterior interhemispheric transcallosal; EOR = extent of resection; ETV = endoscopic third ventriculostomy; GTR = gross-total resection; HGG = high-grade glioma; ioMRI = intraoperative MRI; KPS = Karnofsky Performance Status; LGG = low-grade glioma; OS = overall survival; PeCS = perimedian contralateral supracerebellar; PeS = perimedian supracerebellar; PFS = progression-free survival; PITS = posterior interhemispheric transtentorial subsplenial; PST = paramedian supracerebellar transtentorial; TS = transsylvian; TUTF = transuvulotonsillar fissure.

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are within a small volume. In fact, each part of the brainstem is unique from almost any surgically relevant aspect. The midbrain, pons, and medulla oblongata differ in their macro-, micro-, and functional anatomy, in both their pathoclisis (preferential vulnerability to pathological processes) and topographic anatomical relations. Differing pathoclisis results in a different incidence and distribution of histotypes in each of the three segments (e.g., low-grade tumors are much more common in the midbrain than in the pons). Histotype and anatomical relations of a target lesion dramatically affect the difficulty of surgery. For example, a pons glioma poses completely different surgical challenges from those of a midbrain glioma, and a midbrain glioma in turn poses completely different challenges from those of a midbrain cavernoma. In short, the topography and histopathology of the target lesion are crucial criteria for surgical decision-making. Thus, they are also crucial for identifying homogeneous patients' subgroups within the larger population of patients harboring brainstem lesions.

In light of these considerations, neurosurgical reporting and debate about brainstem surgery should be standardized according to topography and histopathology. As such, the topographic focus of this article is exclusively on the midbrain, whereas the histopathological focus is on gliomas only, a topic currently lacking solid data in the literature.

Here, we systematically present our surgical indications, technique, and results in a large, single-surgeon, consecutive series of patients undergoing microneurosurgery for midbrain gliomas. Oncological results and descriptions of long-term clinical outcome are also reported in detail.

Methods

Data of patients undergoing surgery by the senior author (U.T.) at our institution for a brainstem lesion from March 2006 through June 2022 were extracted from our prospective ongoing surgical registry and were retrospectively reviewed to identify patients harboring a midbrain glioma. The histopathology of lesions resected before 2017 was reviewed according to the WHO classification of 2016.[20] Written informed consent was obtained from all patients, and the study was performed according to the ethical standards of the Declaration of Helsinki and approved by our institutional review committee.

Surgical Indications and Technique

For surgery to be a consideration, the tumors had to be focal and either growing or causing symptoms. Patients having diffuse periaqueductal tumors causing hydrocephalus were offered endoscopic third ventriculostomy (ETV) or, in one case only, subtotal resection because of progressive evolution. Patients with asymptomatic and nonenhancing lesions underwent primarily follow-up only.

Because the whole outer surface of the midbrain is in contact with the subarachnoid space, virtually any midbrain lesion can be reached through either a transcisternal or transcallosal transventricular approach. Several combined variables determine the choice of surgical approach: the involved midbrain's region (cerebral peduncle, tegmentum, central mesencephalic structures, and tectum[21]) (Fig. 1); size; extension and pattern of growth of the lesion; presence of cystic components or contrast medium enhancement; distance to the midbrain surface; suspected histopathology; relationship of the lesion to the splenium and deep venous system; tentorial angle; patient age; presence of disturbances in the circulation of CSF; and need for 3T intraoperative MRI (ioMRI).

The use of diffusion tensor imaging (DTI) is crucial in choosing the surgical approach as it gives essential information about the position and displacement of relevant tracts.[22,23] All operations were done with endoscopic assistance and intraoperative ultrasound for real-time intraoperative orientation and under continuous intraoperative neuromonitoring and mapping according to a protocol including somatosensory and motor evoked potentials and direct subcortical stimulation. Neuronavigation and 3T ioMRI were introduced at our institution in January 2018 and are routinely performed unless contraindicated. To improve operative planning, preoperative MRI scans were loaded into OsiriX software[24] to obtain a 3D reconstruction of the surgically relevant structures. Surgery aimed for the maximal possible resection according to one of the following 7 approaches (Fig. 1).

The transsylvian (TS) approach, via a pterional approach (with orbitotomy if needed)[25] is appropriate for lesions reaching the ventral surface of the cerebral peduncle, as was the case in 2 patients with large tegmental tumors in our series. In both cases, the oculomotor nerve impeded the trajectory and had to be mobilized at its entrance into the roof of the cavernous sinus (Fig. 2).

The extreme anterior interhemispheric transcallosal (eAIT)[26,27] approach is ideal for lesions of the upper part of the aqueduct. It consists of a variation of the anterior interhemispheric transcallosal approach,[28] in which the craniotomy is placed more anterior than usual so that the callosotomy can be done at the transition between the genu and body of the corpus callosum. This variation allows a steep angle of approach to reach the top of the aqueduct via a transcallosal transforaminal pathway.

The posterior interhemispheric transtentorial subsplenial (PITS) approach entails the same previously described steps[29,30] to reach thalamic tumors abutting the cisternal surface.[31] It is performed with the patient in a lateral oblique or prone oblique position (if ioMR is required), with the patient positioned on (or with the head rotated toward) the side of the tumor.[30] As such, it can also be performed in patients with occlusive hydrocephalus. The approach is ideal for reaching the tectum, particularly if the tumor extends caudally. The approach is directed through the interhemispheric fissure along the medial surface of the cuneus, aiming at the splenium. Once reached, the quadrigeminal cistern is opened to release CSF and achieve adequate gravity relaxation of the ipsilateral hemisphere. At this point, the tentorium is cut (under Doppler guidance) perpendicular to the hiatus to achieve the necessary exposure of the dorsal surface of the midbrain. The approach allows limited view and control of the tumor if it grows in a cranial direction along the inferior surface of the splenium (Fig. 3).

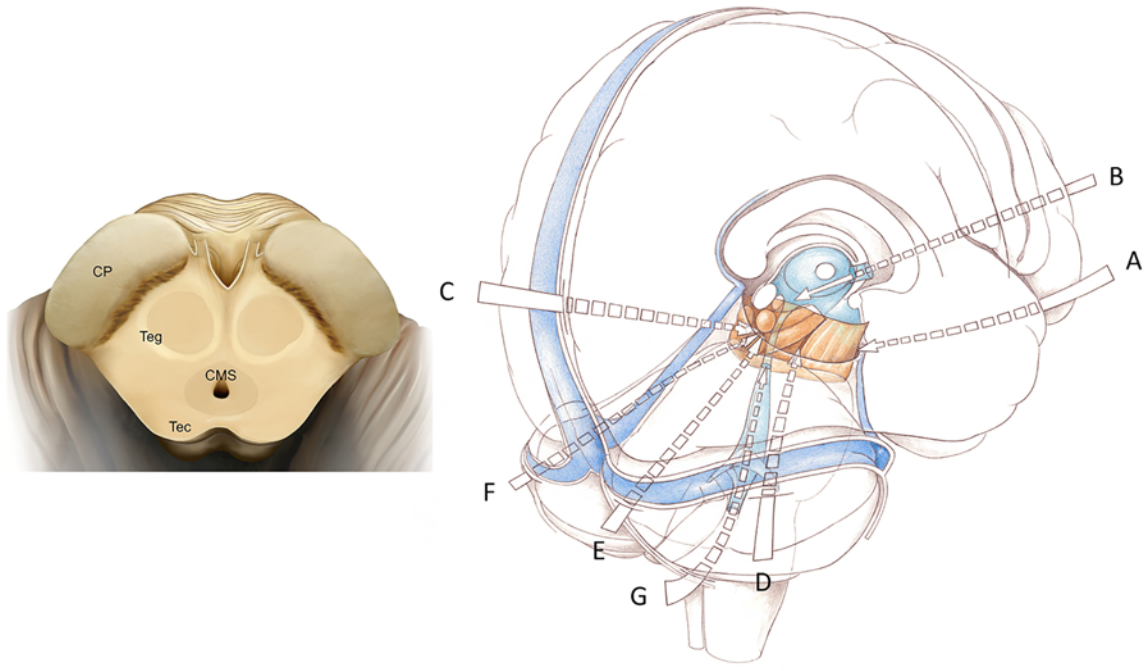

FIG. 1. Left: Topographic subdivision of the midbrain. CMS = central mesencephalic structures; CP = cerebral peduncle; Tec = tectum; Teg = midbrain tegmentum. **Right:** Artist's depiction of the surgical approaches available to reach the subregions of the midbrain. The TS (*A*), eAIT (*B*), PITS (*C*), PST (*D*), PeS (*E*), PeCS (*F*), and TUTF (*G*) approaches. © Uğur Türe, published with permission. Figure is available in color online only.

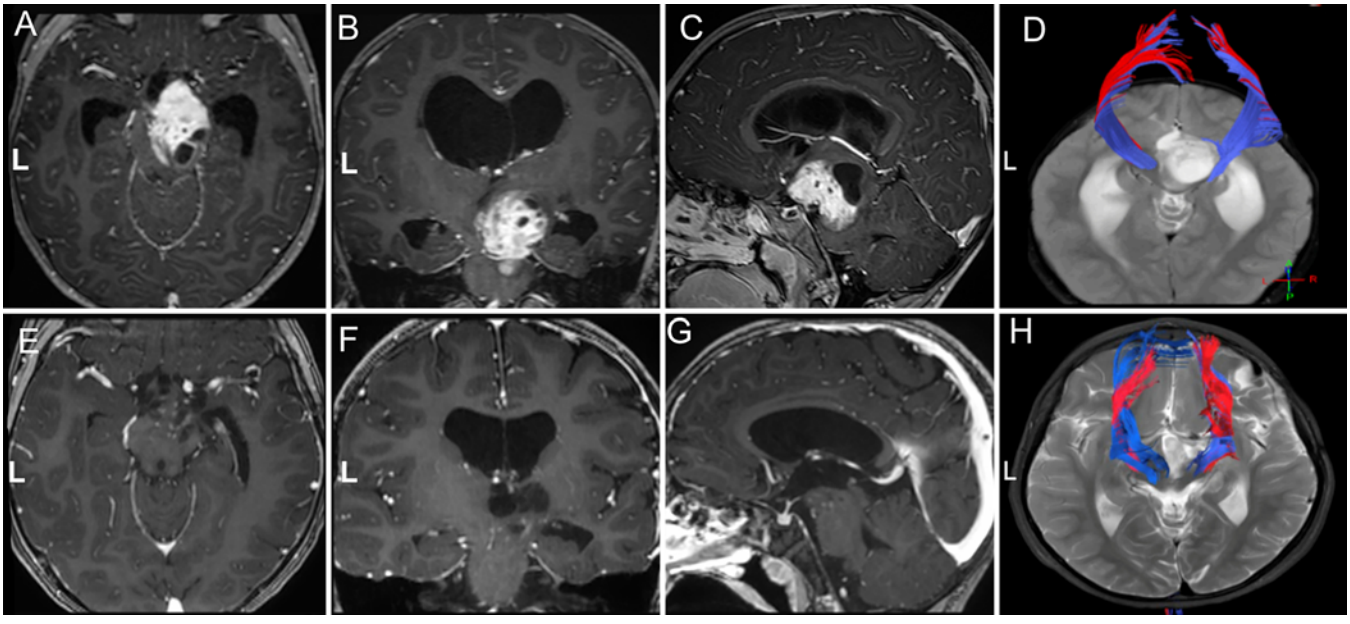

FIG. 2. A 4-year-old male had been experiencing progressive left hemiparesis over the previous 12 months. He eventually underwent MRI, which showed a lesion in the cerebral peduncle that was growing ventrally into the subarachnoid space, divaricating the fibers of the right cerebral peduncle. This anatomical element prompted a TS approach. The operation was uneventful, and the lesion was removed. On histological examination, the lesion proved to be a pilocytic astrocytoma (WHO grade I). Intraoperative inspection and, most noticeably, postoperative imaging (see *lower row*) indicated a tegmental origin of the tumor as also proved by DTI showing that the pyramidal tract was intact. **A–C:** Preoperative axial (A), coronal (B), and sagittal (C) T1-weighted MR images with gadolinium. **E–G:** Postoperative axial (E), coronal (F), and sagittal (G) T1-weighted MR images obtained at 3 months, showing GTR and remission of the hydrocephalus. **D:** By demonstrating lateral dislocation of the peduncular fibers on one hand, the preoperative DTI study clearly indicates the tegmental origin of the tumor on the other hand. It prohibits a lateral approach and suggests, on the contrary, an anterolateral TS approach. **H:** Postoperative DTI scan showing intact pyramidal tracts. Left (L) in the images corresponds to the patient's left. Figure is available in color online only.

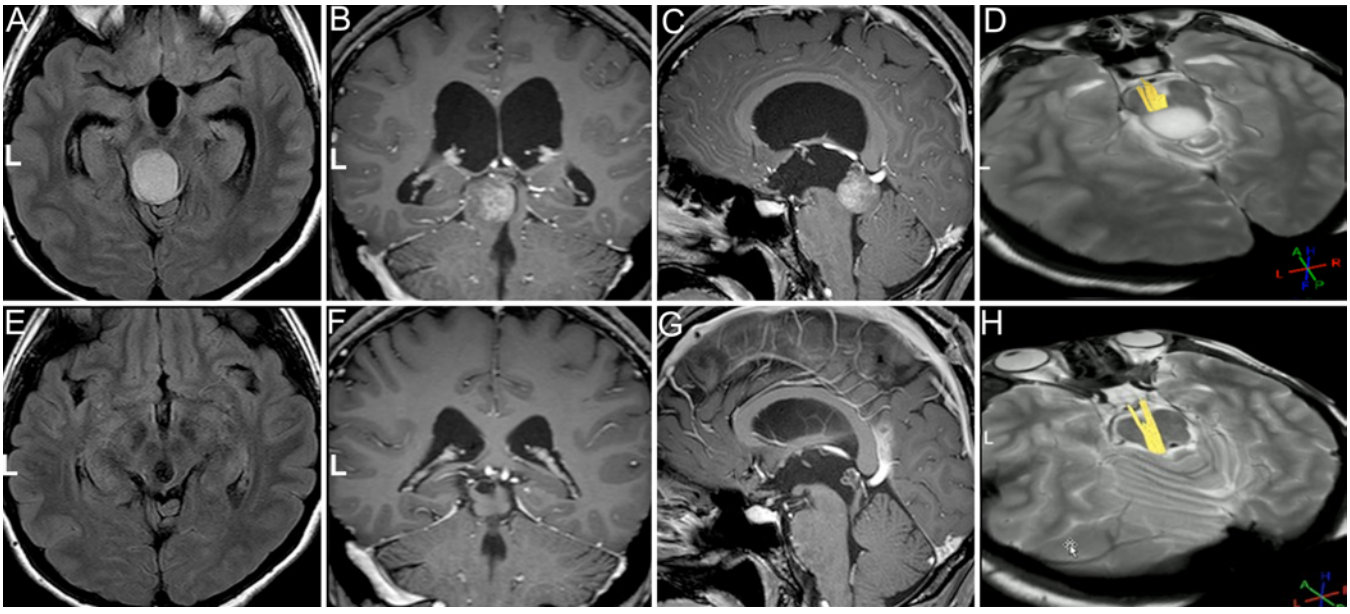

FIG. 3. A 23-year-old woman presented with severe headache and nausea. MRI showed a lesion in the left tectum that was responsible for subocclusive hydrocephalus. Given the tentorial angle and the relation of the tumor to the splenium, a PITS approach with the patient in the lateral oblique position was chosen. Complete resection was achieved, with no new neurological deficit. Histopathology revealed a pilocytic astrocytoma (WHO grade I). **A–D:** Preoperative axial FLAIR (A) and coronal (B) and sagittal (C) T1-weighted MR images with gadolinium and preoperative DTI study (D). **E–H:** Postoperative axial FLAIR (E) and coronal (F) and sagittal (G) T1-weighted MR images and DTI study (H) illustrating the position of the superior cerebellar peduncle. Postoperative imaging allowed us to not only assess the GTR and resolution of the hydrocephalus but also to clarify the tumor's topographic origin, which in this case corresponded to the left superior colliculus. Left (L) in the images corresponds to the patient's left. Figure is available in color online only.

The paramedian supracerebellar transtentorial (PST) approach, described for mediobasal temporal tumors by our group in 2012,[32] can be tailored for midbrain gliomas and is our first choice for tegmental tumors. It is based on a paramedian suboccipital craniotomy ideally performed with the patient in the semisitting position, now a standard and safe position.[33] If the patient has a spontaneous atrial right-left shunt, then the lateral or semilateral position is also a viable alternative, the latter being the position of choice if 3T ioMRI is to be done. Promptly releasing CSF from the cisterna magna as a first step allows the brain to relax with gravity. In this way, the transverse fissure opens without the need for retraction, the tentorium is cut parallel to the surgical trajectory, and the dorsolateral surface of the midbrain is reached. Particular care is given to preserve the paramedian cerebellar hemispheric tentorial bridging veins. This approach is designed to attack tegmental tumors through the posterolateral midbrain surface (Fig. 4).

The perimedian supracerebellar (PeS) approach (Fig. 5), previously described for thalamic tumors,[30] uses the same principles of the PST to reach the dorsal surface of the tectum via a more median pathway, which can be tailored according to the anatomy of the cerebellar hemispheric tentorial bridging veins. A linear median occipital incision is made, and an asymmetrical perimedian craniotomy is carried out. The craniotomy is relatively large and encompasses both sides (hence the name "perimedian"), the transverse sinus, and the torcular, but it extends asymmetrically more on the side of the pathology. The PeS approach is done with the patient in a semisitting position. The approach is particularly appropriate for patients in whom the tumor originates from the superior colliculus and from there grows cranially under the splenium (Fig. 5).

The perimedian contralateral supracerebellar (PeCS) approach, a variation of which has already been described for thalamic tumors,[30,34] can also be tailored for midbrain gliomas. The skin incision and craniotomy are the same as those for the PeS approach, the only difference being that the asymmetrical craniotomy extends more toward the side contralateral to the lesion. No tentorial incision is needed. In the present series, the approach was done in only one case with the patient in the semisitting position (Fig. 6).

The transuvulotonsillar fissure (TUTF) approach is carried out via an inferior median suboccipital approach and opening of the uvulotonsillar fissure to enter the fourth ventricle as described by Yaşargil.[7] From there, it allows the surgeon to gain access to lesions of the inferior portion of the aqueduct that protrude into the fourth ventricle. This approach can be done with the patient either prone or in the semisitting position (Fig. 7).

Since the introduction of 3T ioMRI in our clinical practice, we tend to privilege those approaches that allow positioning of the patient compatible with 3T ioMRI. Once

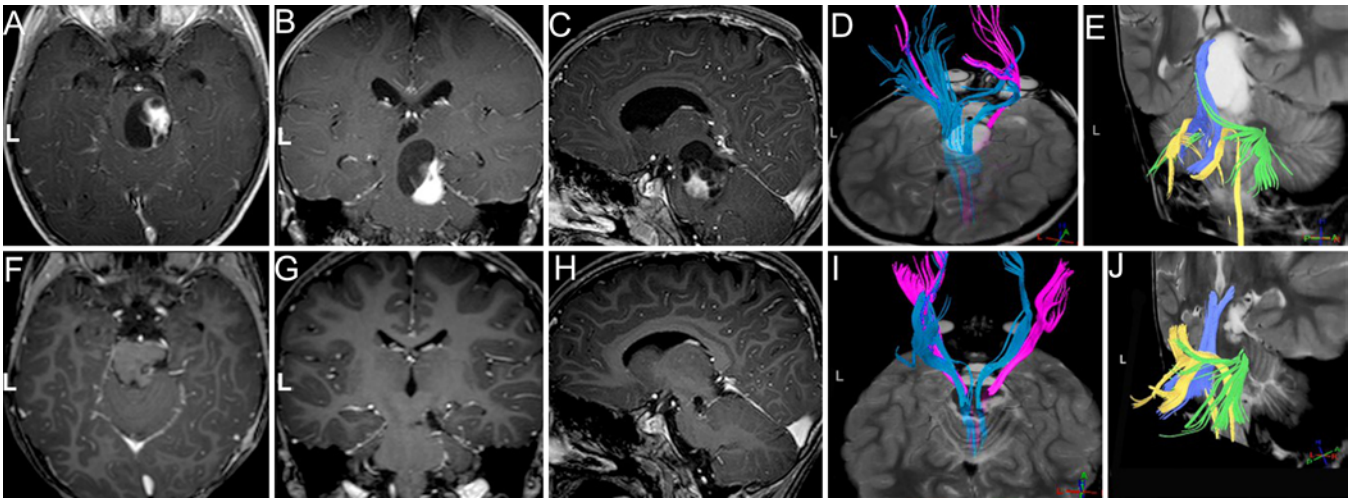

FIG. 4. A 4-year-old male had been experiencing left hemiparesis for 10 days. MRI showed a lesion originating from the tegmentum on the right side, while DTI showed posterior dislocation of the medial lemniscus thereby prohibiting a median posterior approach. The patient underwent a PST approach in the lateral position. Postoperative MRI confirmed GTR. Postoperatively, the patient had no new neurological deficits. Histopathological examination revealed a pilocytic glioma (WHO grade I). **A–E:** Preoperative axial (A), coronal (B), and sagittal (C) T1-weighted MR images with gadolinium and DTI studies (D and E) and showing the pyramidal tract (*pink*), medial lemniscus (*blue*), and the superior (*violet*), medius (*green*), and inferior (*yellow*) cerebellar peduncles. **F–J:** Postoperative axial (F), coronal (G), and sagittal (H) T1-weighted MR images with gadolinium and DTI studies (I) and (J), which confirm the tegmental origin of the tumor and preservation of the most relevant white matter tracts. Left (L) in the images corresponds to the patient's left. Figure is available in color online only.

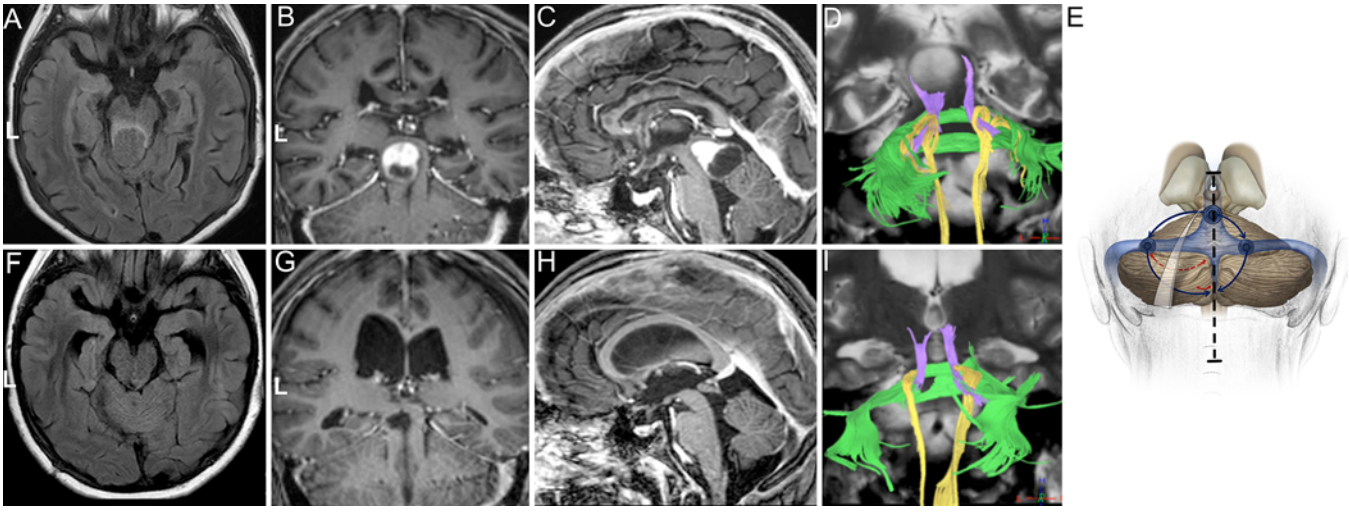

FIG. 5. An 11-year-old female presented with hydrocephalus and right hemiparesis, dizziness, and hand tremor at another institution, where she underwent placement of a ventriculoperitoneal shunt (hyperdrainage was visible on preoperative MRI). The patient was then referred to our center, where she underwent surgery via a PeS approach in the semisitting position, and the shunt was removed. Surgery was uneventful, and the patient promptly recovered with no new neurological deficits. Histopathology revealed a pilocytic glioma (WHO grade I). **A–D:** Preoperative axial FLAIR (A) and coronal (B) and sagittal (C) T1-weighted MR images with gadolinium and preoperative DTI study (D). **F–I:** Postoperative axial FLAIR (F) and coronal (G) and sagittal (H) T1-weighted MR images with gadolinium, confirming that the lesion originated from the left inferior colliculus and that relevant white matter tracts (I) were left untouched by the surgical approach (superior [*violet*], medius [*green*], and inferior [*yellow*] cerebellar peduncles). **E:** Artist's depiction of the perimedian craniotomy. Left (L) in the images corresponds to the patient's left. Panel E: © Uğur Türe, published with permission. Figure is available in color online only.

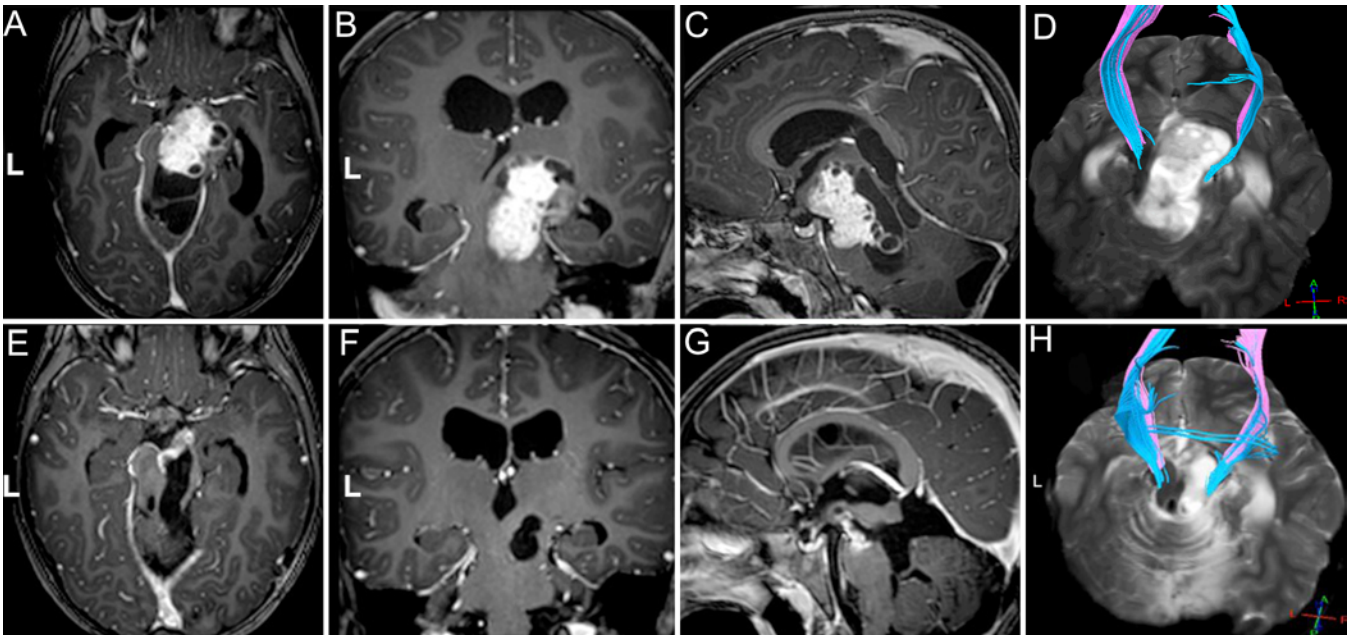

FIG. 6. A 4-year-old male presented to our institution after three unsuccessful surgeries at other institutions. He had oculomotor paresis on the right side and left hemiparesis. MRI showed a right tegmental lesion with a ventral extension into the subarachnoid space and a dorsal extension in the cisterna of the quadrigeminal plate. The lesion also had a significant craniocaudal extension toward the diencephalon cranially and deep in the cerebellomedullary fissure caudally. Given fiber displacement, as visible on DTI, a PeCS approach from the left side was chosen, which, combined with a TUFT needed for the caudal portion, led to a satisfactory EOR (95.8%). The patient experienced transient worsening of his third cranial nerve paresis and slight hemiparesis in the immediate postoperative period. On follow-up, however, he showed significant clinical improvement, particularly of the hemiparesis, which only 3 months after surgery was Medical Research Council grade 4+ and did not significantly hamper his activities. The third cranial nerve paresis required oculoplastic surgical treatment. **A–D:** Preoperative axial (A), coronal (B), and sagittal (C) T1-weighted MR images with gadolinium and DTI study (D). **E–H:** Postoperative axial (E), coronal (F), and sagittal (G) T1-weighted MR images with gadolinium and DTI study (H). Left (L) in the images corresponds to the patient's left. Figure is available in color online only.

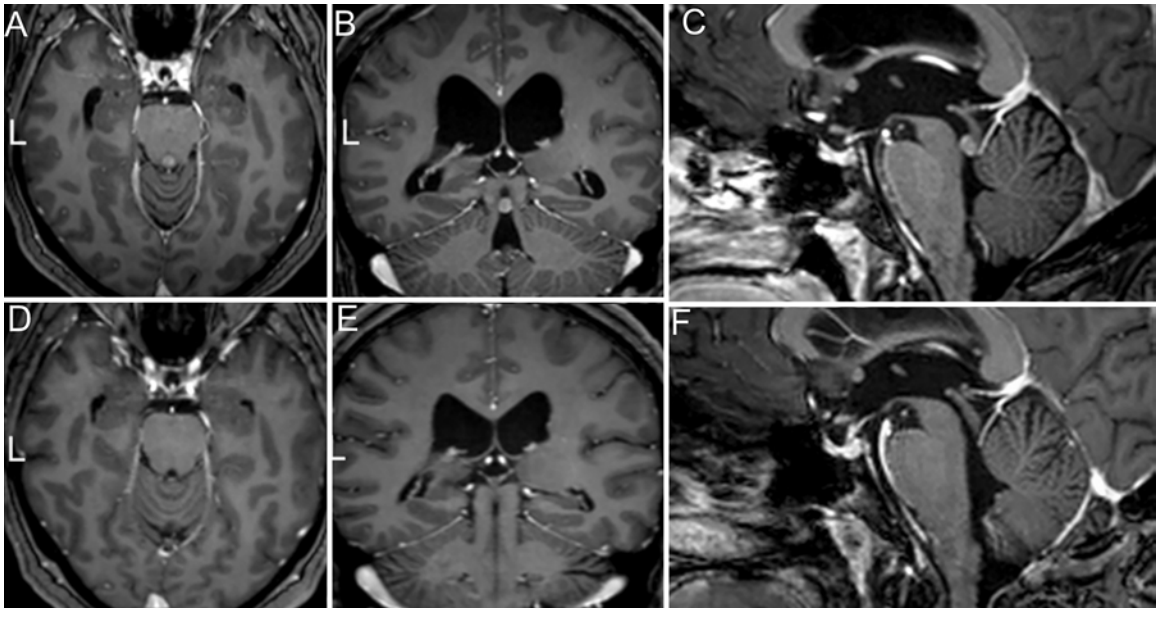

FIG. 7. A 47-year-old female presented with a 1-year history of headache, dizziness, and cognitive decline. MRI revealed a small, purely aqueductal tumor in the lower third of the cerebral aqueduct, causing hydrocephalus. The tumor was completely removed via a TUTF approach with the patient in a semisitting position. Surgery was uneventful, and the patient fully recovered. **A–C:** Preoperative axial (A), coronal (B), and sagittal (C) T1-weighted MR images with gadolinium. **D–F:** Postoperative axial (A), coronal (B), and sagittal (C) T1-weighted MR images with gadolinium. Left (L) in the images corresponds to the patient's left.

reached, tumors are removed piecemeal by successive central debulking with an ultrasonic aspirator (Sonopet, Stryker) and then peripheral preparation. Tumor tissues can be distinguished based on their appearance as well as on the tumor's consistency as revealed by gentle suction. As a rule, the use of bipolar coagulation is avoided, and hemostasis is achieved with tumorectomy and continuous saline irrigation in the surgical cavity.

Patient Data and Outcome Assessment

Routinely, all our patients with midbrain lesions undergo an imaging protocol consisting of preoperative, immediate postoperative (< 24 hours), and late postoperative (3 months) 3T MRI including DTI tractography of the corticospinal tract, medial lemniscus, and superior cerebellar peduncle. The extent of resection (EOR) was assessed volumetrically on the immediate postoperative MRI with OsiriX software.

All patients underwent neurological examination and assessment of their Karnofsky Performance Status (KPS) at admission, immediately after surgery, at discharge, and at 3 months postoperatively, and at any successive clinical follow-up time point. We defined transient and permanent neurological deficits as new, surgery-related deficits evident at discharge and at the 3-month postoperative follow-up, respectively. Follow-ups were repeated thereafter depending on the histopathology of the lesion. If required, adjuvant therapy was administered according to international standard guidelines. Progression-free survival (PFS) was defined as the interval between the date of surgery and the need for reintervention or adjuvant treatment. Overall survival (OS) was considered the interval between the date of surgery and death. Patient data are reported according to common descriptive statistics.

Lastly, we explored preoperative radiological factors associated with anatomical topographic localization, histopathological grading, PFS, and OS. Recorded radiological features of the gliomas are reported in Supplementary Table 1. For both radiological and histopathological features, we carried out decision-tree analysis based on recursive partitioning. We generated optimal decision trees in a cross-validated fashion, with a maximum depth of three layers. Statistical analyses were carried out in R, a language and environment for statistical computing (R Core Team 2022). The rpart package was used to generate decision trees, while we used the survival and survminer packages for survival analysis.

Results

Patient Characteristics

In the study period, 286 patients underwent surgery for a brainstem lesion. Of these, 77 had a midbrain lesion, 57 of which were gliomas. Of these 57 patients, 54 underwent microsurgery aimed at the maximal possible resection, whereas 3 patients with a diffuse periaqueductal glioma causing hydrocephalus underwent ETV only.

The mean symptom duration before diagnosis was 19.5 months (median 6.5 months, range 4 days–11 years). A detailed description of presenting symptoms is reported in Supplementary Table 2. Symptoms appeared to differ significantly according to the glioma's site of origin. Patients with tegmental glioma were more likely to present with hemiparesis, whereas those with tectal gliomas or gliomas in the central mesencephalic structures were more likely to present with headache and ocular movement disorders. Of the 54 patients undergoing open microsurgery (male/female ratio 33:21; 28 [52%] pediatric patients; median age 16 years, range 2–54 years), 6 had a high-grade glioma (HGG) and 48 had a low-grade glioma (LGG). Neurofibromatosis type 1 was not detected in any of the 54 patients in the study cohort. Among the 14 patients with histology other than WHO grade I tumors, in 2 patients who underwent surgery early in the series, IDH1 and H3K27M status could not be determined retrospectively due to the paucity of available histological material. Instead, the remaining 12 patients had wild-type IDH1 status. H3K27M was positive in all 3 WHO grade IV diffuse midline gliomas. Further details on histopathology are available in Supplementary Table 2.

Radiological Features

All gliomas in our series were confined within one of three topographic areas: 22 (41%) in the tegmentum, 7 (13%) in the central mesencephalic structures, and 25 (46%) in the tectum. None of the tumors originated in the cerebral peduncle or presented a thalamopeduncular pattern, whereas 1 tumor had a diffuse periaqueductal pattern. In the latter case, the patient initially underwent only an ETV because of hydrocephalus, and microsurgery became necessary only later as a result of documented radiological progression of the disease. Three tectal tumors, all originating from the superior colliculus, extended into the thalamus cranially. This was not the case for tegmental tumors, which at the most displaced but did not infiltrate either the pons or thalamus.

Preoperative radiological and demographic features allowed us to build decision trees that could identify with high precision the topography and WHO grading of the lesion (Supplementary Fig. 1).

Surgery and Surgical Results

Gross-total resection (GTR; EOR > 99%) was achieved in 39 (72%) of the 54 patients, near-total resection (EOR 95%–99%) in 7 (13%), and subtotal resection (EOR < 95%) in 8 (15%). The average EOR was 98.0% (median 100%, range 82%–100%). The mean preoperative lesion volume was 8.5 cm^3 (median 6.8 cm^3, range 0.2–30.8 cm^3), and the mean postoperative lesion volume was 0.5 cm^3 (median 0.4 cm^3, range 0.0–1.2 cm^3). Detailed results according to surgical approach and tumor location appear in Table 1.

Clinical Outcome

There was no surgical mortality. Eleven patients (20.4%) were discharged with a neurological status worse than that at admission. Nine of these patients experienced a transient deterioration (5 hemiparesis, 3 ocular movement disturbance, and 1 patient with new deficits of cranial nerves III and VII), which recovered at the 3-month postoperative control. The remaining 2 patients did not experience recovery. One of these patients, harboring an HGG, under-

TABLE 1. Summary of surgical and clinical outcomes in the patient series according to tumor topography and surgical approach

Tumor Origin	No. of Tumors	Op Approach	No. of Approaches	Mean Preop Vol, cm^3	GTR, %	Mean EOR (median, range), %	New ND: TD/PD, %	KPS Score, Median (range)			Worse/Stable/Better KPS Score, %	
								Admission	Discharge	3 mos	Discharge	3 mos
Tegmentum	22	TS	2	12.6	50.00	97.20	0/0	75 (70–80)	75 (70–80)	95 (90–100)	0/100/0	0/0/100
		eAIT	2	5.8	50.00	94.50	0/0	90 (90–90)	90 (90–90)	100 (100–100)	0/100/0	0/0/100
		PITS	3	18.3	33.00	94.4 (95.1, 88–100)	33/0	70 (70–90)	80 (70–90)	100 (80–100)	0/66/33	0/0/100
		PST	14*	10.5	58.30	97.5 (100, 86.2–100)	21/7	70 (60–90)	70 (60–90)	90 (70–100)	14/64/22	0/7/93
		PeCS + TUTF	1	29.8	0.00	95.80	100/0	60	60	90	0/100/0	0/0/100
Aquaduct	7	eAIT	4	0.7	100.00	100.00	0/0	90 (90–90)	90 (90–90)	100 (100–100)	0/100/0	0/0/100
		TUTF	2	3.4	100.00	100.00	0/0	90 (90–90)	90 (90–90)	100 (100–100)	0/100/0	0/0/100
		PITS	1	2.9	0.00	82.00	0/0	90	90	100	0/100/0	0/0/100
Tectum	25	PITS	19†	6.7	76.50	96.8 (100, 71.1–100)	26/5	90 (70–90)	90 (30–90)	100 (40–100)	26/48/26	5/16/79
		PST	2	3.3	100.00	100.00	0/0	85 (80–90)	90 (90–90)	100 (100–100)	0/50/50	0/0/100
		PeS	4	11	100.00	100.00	25/0	90 (80–90)	90 (70–90)	100 (90–100)	25/50/25	0/25/75

ND = neurological deficit; PD = permanent deficit; TD = transient deficit.
* One PST case required a second PITS as a second step.
† One PITS case required a PeS as a second step.

went a PITS approach in the lateral position for a lesion of the right superior colliculus but did not awake from surgery. Postoperative MRI revealed an extensive infarction in the vascular territory of both anterior cerebral arteries. Digital subtraction angiography did not show any anomalies, not even azygos anterior cerebral arteries. The patient ended up in a minimally conscious state. The remaining patient presented with a right-sided facio-brachio-crural hemiparesis due to a tegmental diffuse midline glioma (WHO grade IV). After surgery, the patient experienced a worsening of his symptomatology, which did not recover over the course of follow-up. The mean length of hospital stay was 8.5 days (median 8, range 4–33 days). The mean KPS scores were 82 (median 90, range 60–90) at admission, 82 at discharge (median 90, range 30–90), and 94 at the 3-month follow-up (median 100, range 40–100). Only 1 patient had a permanent KPS score deterioration at the 3-month follow-up.

At the last follow-up (mean 72 months, median 62, range 3–193 months) 5 patients, all of whom had an HGG, had died (mean survival 23 months, median 24, range 9–31 months). The remaining patient with an HGG was still alive 100 months after the first surgery. Excluding the patients who died, the mean KPS score at last follow-up was 97 (median 100, range 80–100). Of the 49 patients still alive at the last follow-up, 42 experienced an improvement in their KPS score compared with preoperative levels, whereas 7 had neither improvement nor deterioration. None of the patients with an LGG experienced a deterioration in KPS score in the long term.

Ten patients had a recurrence of their tumor. The tumor recurred in 4 of 39 patients with a grade I tumor and in 6 of 6 patients with an HGG. Salvage chemotherapy was performed in 5 of the latter 6 patients (except for the patient experiencing major morbidity whose KPS score contraindicated any form of therapy). A second surgery for recurrence was required in 3 patients with a grade I glioma at 3, 9, and 11 months after the first surgery, and in 1 patient with a grade III tumor 5 months after the first surgery. The remaining patient with a grade I tumor who had a recurrence underwent radiotherapy because of ill-defined tumor borders that made further surgery unsuitable.

Not surprisingly, histopathological grades appeared to be significantly associated with OS and PFS (Supplementary Figs. 2 and 3).

CSF Disturbances

Of the 14 patients (25.9%) who presented at diagnosis without hydrocephalus, none developed hydrocephalus postoperatively. Overall, 40 patients (74.1%) presented at diagnosis with ventricular dilation. Twelve patients (22.2%) underwent some form of CSF diversion at other institutions and were then referred to our center for microsurgical removal. Of the 28 patients (51.9%) presenting primarily at our institution with ventricular dilation, 1 initially underwent ETV only because of a glioma with diffuse periaqueductal pattern, which later required surgery because of radiological progression. The remaining 27 patients (50%) underwent direct microsurgical removal of their tumors. In 2 of these patients (3.7% overall), because of favorable anatomical conditions and surgical

angle (both PITS), microsurgical opening of the lamina terminalis (in 1 case) or of the lamina terminalis and tuber cinereum (in the second case) was performed, aiming at improving CSF flow. Neither patient developed CSF disturbance in the postoperative period. Of the remaining 25 patients, in only 2 (3.7% overall) was some form of CSF diversion necessary in the early postoperative period (< 30 days), and in 2 more patients within 90 days of surgery. In 21 of the 27 patients, the ventricular dilatation resolved as a consequence of tumor removal only.

Discussion

In this study, we present one of the largest, single-surgeon series of patients undergoing open microsurgery for midbrain gliomas. All 54 patients underwent microsurgical removal with endoscope assistance according to a strict transcisternal or transcallosal-transventricular philosophy.

Midbrain Gliomas and Midbrain Pathoclisis

Midbrain gliomas are rare and inconsistently reported. Consequently, relevant data in the literature are not sufficient to draw conclusions about their natural history, prognosis, and best treatment, and suggested management policies differ greatly from center to center. As a result, the literature does not have any numerically consistent case series that are homogeneous for baseline characteristics and pattern of care on which to base solid therapeutic decisions.

From an oncological point of view, one could ask whether midbrain gliomas actually represent a distinct entity deserving to be recognized as such. The answer, at least as far as the literature up to the late 2000s is concerned, appears to be negative for midbrain and any other gliomas, apparently being only intrinsic histological features of gliomas crucial for prognosis.[20] More recently, however, emerging data indicate that molecular and topographical features of gliomas can have an impact on the prognosis of the patient.[20] This is not so much by virtue of a differential surgical morbidity resulting from a different anatomical situation but because of intrinsic conditions of the neoplasm itself, as determined by the anatomical situation. In support of this hypothesis, the consolidated evidence shows that gliomas of the midbrain are, for the most part, benign, whereas those of the pons are more malignant.[35]

In the classifications of CNS tumors in use until 2016, the prognosis of a patient with a glioma seemed to be determined primarily by histological elements. In the classification introduced in 2016,[20] however, topographical elements also begin to appear (for example, the concept of a diffuse midline glioma). Such elements become even more numerous in the classification of 2021,[20] for example, the concepts of diffuse midline glioma, diffuse hemispheric glioma, and supratentorial ependymoma. These designations begin to confirm the theory of pathoclisis, the selective vulnerability of certain anatomical regions to certain pathological conditions as a result of regional-specific genetics, a concept introduced by Vogt and Vogt in neurology[36] and popularized in neurosurgery by Yaşargil.[37]

Consistent with this emerging evidence, we have noted that midbrain gliomas tend to remain confined within one of the four topographical areas (tectum, central mesencephalic structures, tegmentum, and cerebral peduncle) but seem to preferentially avoid the cerebral peduncle as a site of origin, at least in our series and those of Bricolo[38] and Yaşargil.[7] Moreover, in our series, patients younger than 5 years invariably had a tegmental glioma, whereas small paucisymptomatic gliomas in adult patients were mainly aqueductal.[27] Our data also indicate that both recurrence and progression of histologically benign gliomas and the occurrence of HGGs are not absolute rarities in the midbrain, data that have been seldom reported in the literature.[39–41]

These indications should be interpreted with caution, and their generalizability outside the cohort of the present study cannot be ensured. However, if confirmed in larger series, they can define new nosological entities in neuro-oncology. Because of the scarcity of case series and the increasingly urgent need to collect topographic data about gliomas, we believe that glioma series should be reported, paying careful attention to anatomotopographic features for clinical, oncological, and, as we will further discuss, also for surgical purposes.

Topographic Anatomy Dictates Surgical Approach

Pool[42] was the first to accurately report a surgical series of brainstem gliomas. Nonetheless, Epstein and Wisoff,[3] Hoffman and colleagues,[43] Yaşargil,[7] and Bricolo and Turazzi[1] must be credited as the surgeons who most significantly contributed to the development of brainstem glioma surgery. A nonexhaustive list of surgical approaches includes the transsylvian, subtemporal (with or without a tentorial incision), median, and lateral infratentorial supracerebellar approaches. As a rule, we strictly avoid any kind of transcortical approach because of the destructive consequences on the transversed brain parenchyma. We also do not recommend the subtemporal approach, as it requires a retraction of the temporal lobe, which endangers the vein of Labbé and the basal temporal veins. This risk must be weighed with the fact that the areas reachable through a subtemporal approach can be safely accessed via a supracerebellar approach, with the notable advantage of avoiding any kind of retraction on healthy brain parenchyma.

From a neurosurgical point of view, the midbrain has some very peculiar features. First, its whole surface is in contact with subarachnoid spaces and cisterns and, as such, it can be reached from any direction without traversing other uninvolved structures. Second, the centripetal vascularization pattern of the midbrain is rather constant and favorable for surgery.[13,37] Lastly, neoplastic lesions tend to remain confined within one of the four topographic areas of the midbrain (Fig. 1).

Once a lesion is deemed amenable to resection (see *Methods*), the first step is assessing the exact topography of the tumor, as every subarea of the midbrain can be preferentially reached via one or more of the 7 surgical approaches described above.

We never encountered glioma originating from the cerebral peduncle. Tegmental gliomas occurred rather frequently, most often expanding posteriorly through the tectum into the quadrigeminal cistern or growing in a craniocaudal direction, displacing the thalamus, pons, or

both. The PST approach through the lateral midbrain surface is our first choice for this type of glioma. Care should be paid to the red nucleus, which can cause characteristic morbidity if damaged.

Gliomas in the tectum were approached mostly via a PITS approach or a PeS approach if a PITS approach was not feasible. Tectal gliomas can show two rather diverging growing patterns: a diffuse MRI pattern (so-called "diffuse glioma," although the tumor is still confined within one compartment only), which is managed conservatively, and a focal pattern, which is more frequent and more amenable to surgical removal, as it invariably originates from one colliculus only. Differentiating between these two entities can be challenging, and sometimes the true origin of the glioma may become evident only intraoperatively or on postoperative MRI. So-called diffuse tectal gliomas are in fact mostly located in the periaqueduct and can be recognized as such, as close MRI inspection invariably reveals a dorsally located thin layer of normal tissue corresponding to the quadrigeminal plate. They can sometimes even be misdiagnosed as aqueductal tumors. The latter, however, are usually benign and well circumscribed and thus can be safely removed via an eAIT approach,[26,27] whereas removing a tectal lesion causes an upward gaze palsy, although transient. In our experience, most midbrain lesions can be classified at least from a macroscopic morphological point of view as follows: focal tumors, which are amenable to resection, as they show a focal origin and expansive growth; purely aqueductal tumors, which are purely aqueductal, well circumscribed, and amenable to resection; and diffuse periaqueductal tumors, which are a minority, are characteristically located around the aqueduct and are not suitable for complete resection.

Preoperative images should be carefully studied to clearly determine whether a tumor has a focal origin and expansive growth. On imaging, midbrain gliomas, particularly large ones, may appear to involve the whole midbrain or even infiltrate neighboring segments of the brainstem, diencephalon, or even the pineal gland. On closer inspection, in a high percentage of patients, lesions will prove to have a focal origin, and it is likely that with the introduction of 7T MRI in the clinical routine, visualization will significantly improve. Most gliomas show, on a macroscopic scale at least, an expansive growth so that they displace rather than truly invade surrounding midbrain subareas or the thalamus or pons. This occurrence is indirectly confirmed by the clinical observation that paresis at diagnosis occurred in a minority of our patients only and was always mild. If infiltration with fiber disruption occurs, a much higher rate of severe hemiparesis should be expected, and no immediate postoperative recovery is likely to happen. Moreover, in all our patients, preoperative DTI invariably revealed an intact corticospinal tract, medial lemniscus, and superior cerebellar peduncle. On the contrary, fiber dislocation may happen and can be studied preoperatively with appropriate DTI protocols. Sometimes a tumor may even divaricate fibers and emerge at the surface, abutting the cisternal space, thereby suggesting the most appropriate surgical approach (see Fig. 2). In no instance in our series did a glioma show a growth pattern along white matter tracts.

All this information eventually dictates the most appropriate entry point. In our experience, the dynamic interaction between tumor morphology and growth pattern, with an understanding of the topography of the involved area rather than brainstem anatomy only, dictates the so-called safe entry zone and thus the approach. As an example of this concept, in 2 patients in our series (Fig. 2), the ventral outgrowth of a tegmental glioma through the cerebral peduncle into the subarachnoid space eventually created an entry zone formally within the cerebral peduncle itself. Understanding these peculiar features is crucial as, if properly recognized, they dictate the surgical indications and allow a selective tumorectomy without damaging surrounding otherwise healthy parenchyma. In those rare cases in which tumors show truly infiltrative growth, no surgery can be offered.

Finally, we feel that it is important to emphasize one further aspect that emerged from the analysis of our data, as we believe it is relevant for planning of the surgical strategy: patients with midbrain glioma presenting at diagnosis with hydrocephalus due to glioma-induced narrowing/occlusion of the ventricular system do not seem to require additional treatment for hydrocephalus other than removal of the tumor itself. This was the case in 21 of the 27 patients who presented primarily at our institution with hydrocephalus, which resolved after tumor removal without the need for any further and potentially harmful treatment.

Clinical Outcome

Our short-term surgical and long-term oncological results support the choice of microneurosurgical removal as the first-line therapeutic approach for patients with midbrain gliomas. First, although our data indicate that midbrain lesions show a trend toward a benign histology (72% of WHO grade I gliomas), they also indicate that both recurrence and progression of histologically benign gliomas and the occurrence of HGGs are not rarities in the midbrain, data that have been seldom reported in the literature.[39–41] This finding should prompt the team of treating physicians to obtain whenever feasible the highest possible EOR, a crucial parameter for treating gliomas. Our study indicates that this is not only possible but possible with low morbidity, which makes the surgical option attractive not only to patients with HGGs but also, if not especially, to those with low-grade tumors: at last follow-up (mean 72 months, median 62, range 3–193 months) of the 48 patients harboring a WHO grade I or II glioma, none had died and none had experienced deterioration of their KPS score. On the contrary, 42 of these 48 patients had improved KPS scores, including those 4 who had a treated recurrence. These excellent long-term clinical results substantiate our policy of offering surgery as the first choice for patients with midbrain gliomas.

Meaningful comparisons of these results with those reported in the literature are difficult because of the heterogeneity, both punctual and over the years, of the nosological and outcome criteria adopted in the various studies. This applies for both surgical as well as radiotherapic series. Radiotherapy has also been proposed as possible upfront therapy, with satisfactory oncological and clinical

results,[44,45] although we believe that this strategy might probably not be applicable for a cohort like ours with 52% of pediatric patients. We believe that our series offers some advantages over the available literature. Above all is the homogeneity of the cohort with regard to pathology treated, anatomical location, and treatment protocol. With the length of follow-up and the number of patients included, our study offers itself as a benchmark for future surgical series to adopt the same anatomical and clinical rigor.

Limitations

The present study was conducted in a tertiary referral center highly specialized in the surgical treatment of deep-seated lesions and with national and international referral. The study therefore carries with it the limitations of monocentric, single-arm, cohort studies.

Conclusions

Microneurosurgical removal of midbrain gliomas is feasible with good resection and clinical results. Adequate microsurgical technique, anesthesiological management, and accurate preoperative understanding of the tumor's exact topographic origin and growth pattern are crucial for a good surgical outcome. In our experience, these elements determine surgical indications and eventually dictate the appropriate safe-entry zone, which in turn dictates the surgical approach required to reach 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: U Türe, Serra, H Türe. Acquisition of data: U Türe, H Türe, Fırat, Yaltırık, Ekinci, Sav. Analysis and interpretation of data: U Türe, Serra, Fırat, Staartjes, Ekinci, Sav. Drafting the article: U Türe, Serra. Critically revising the article: U Türe, Serra, Staartjes. Reviewed submitted version of manuscript: U Türe, Serra, Staartjes. Approved the final version of the manuscript on behalf of all authors: U Türe. Statistical analysis: Staartjes, Yaltırık. Administrative/technical/material support: U Türe, H Türe, Fırat, Ekinci, Sav. Study supervision: U Türe, Sav.

Supplemental Information

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Correspondence

Uğur Türe: Yeditepe University School of Medicine, Kadiköy, Istanbul, Turkey. drture@yahoo.com.