Original Article
Application of technical strategies for surgical management of adult intrinsic pontine gliomas: a retrospective series

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Abstract: Object: The authors retrospectively analyzed the surgical treatment of adult intrinsic pontine gliomas in their department, and to enhance the understanding of technical strategies to treat this disease. Methods: 7 patients with intrinsic pontine gliomas were recruited for this study, between January 2011 and June 2013. All patients underwent preoperative MRI and Diffusion Tensor Imaging Fiber Tracking (DTI-FT). In addition, multimodal Intraoperative Neuromonitoring (IOM) and Intraoperative Neuronavigation were also applied during microsurgery. Results: 7 patients with intrinsic pontine gliomas were treated at the West China Hospital of Sichuan University. Mean age, mean duration of symptoms prior to diagnosis, and mean duration of follow-up average time were 38.0 years, 2.0 months, and 23.4 months, respectively. The main presentations were progressive cranial nerve deficits and long tract signs. Total resection was achieved in 3 patients, subtotal resection in 2, and partial resection in 2. Postoperative pathological examination revealed: astrocytoma (WHO II) in 4 cases, anaplastic oligoastrocytoma (AO, WHO III) in one case, and anaplastic astrocytoma (AA, WHO III) in two cases. Postoperative radiotherapy were administered to all patients, and 4 patients with astrocytoma (WHO II) rejected chemotherapy. After 11-39 months of follow-up, patient symptoms were resolved or stable without aggravation except one patient died because of rapidly progressive glioma at 11 months after operation. MRI in other patients showed residual tumor size to be unchanged or without obviously recurrence. Conclusion: Combining preoperative MRI with preoperative DTI-FT, surgery can be better assessed and the operation for adult intrinsic pontine gliomas can be maximally and safely resected with the aid of Multimodal IOMs and Intraoperative Navigation during microsurgery.

Keywords: Adult intrinsic pontine gliomas, diffusion tensor imaging fiber tracking (DTI-FT), multimodal intraoperative neuromonitoring (IOM), intraoperative neuronavigation

Introduction

Brainstem gliomas (BSG) primarily occur in children and account for 10-30% of all posterior fossa tumors [1]. However, these tumors are uncommon and constitute only 2% of all brain tumors in adults [2]. The prognosis varies in these heterogeneous groups of tumors. In adults, age less than 40 years, duration of symptoms greater than 3 months prior to diagnosis, Karnofsky Performance Status (KPS) greater than 70, low grade histology, presence of necrosis, and lack of contrast enhancement on MRI were definite prognostic factors [3]. Due to its vital structures in the brainstem, surgical treatment of brainstem gliomas remains a challenge. However, the volume of the pons is relatively larger than the medulla oblongata and midbrain, in which nuclei and fiber tracts disperse rather than concentrate in the medulla oblongata or midbrain. This advantage makes radical resection of intrinsic pontine gliomas feasible. In other words, under the premise of protecting neurological function, surgeons can utilize the above mentioned characteristics of the pons to obtain maximal resection of tumors. To our knowledge, the literature on the surgical management of intra-axial pontine gliomas is rare. We reported 7 patients who underwent excision of adult intrinsic non-exophytic pontine gliomas, as confirmed by postoperative pathological examination, to highlight some of the

Table 1. Summary of clinical characteristics in 10 patients with intrinsic pontine gliomas

Case No.	Age/sex	Duration of symptoms prior to diagnosis (months)	Symptoms & Signs		
			Cranial Nerve Palsy	Long tract signs	Hydro-cephalus
1	41, F	2	Facial numbness	Left-sided weakness	None
2	19, M	3	Diplopia, strabismus, facial paralysis, trigeminal neuralgia	Right-sided weakness	None
3	41, F	3	Diplopia, strabismus, facial paralysis	Right-sided weakness	None
4	50, F	2	Diplopia, facial paralysis	bilateral limb weakness	None
5	22, M	1	Diplopia, strabismus	Right-sided weakness and numbness	None
6	23, M	2	Facial paralysis and numbness	none	Yes
7	70, F	1	Choking cough	Right-sided weakness	None
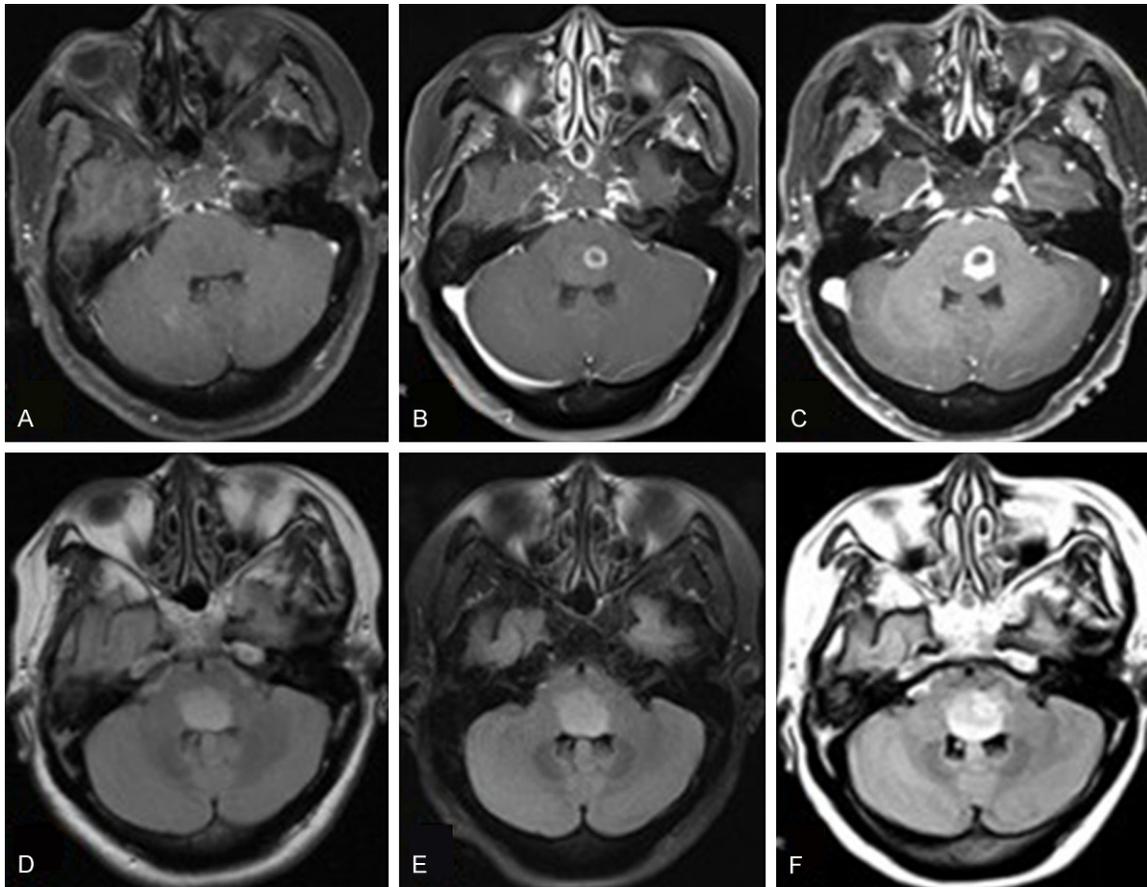
Figure 1. Magnetic resonance images showing the changes of tumor size in three different time points before surgery in Case 6. The first visit (60 days preoperatively) showed no enhancing lesions on contrast-enhanced axial MRI (A) though T2-Fluid Attenuation Inversion Recovery (FLAIR) sequence (D) showing a hyperintensity of the pons; the second visit (40 days preoperatively) showed an apparent enhanced lesion in the center of the pons (B) but not much change on FLAIR sequencing (E). The last visit (3 days preoperatively) showed that the enhancing lesion became larger and moved towards the surface of the pons (C) with a "ringlike" pattern, and a slight change on FLAIR sequence (F). Considering the aggravation of the neurological deficit, the patient underwent surgery at the last visit.

surgical advancements by the application of technical strategies to make removal, or even complete resection, possible.

Methods

General data

The data of 23 patients with adult pontine gliomas were analyzed between January 2011 and June 2013, 16 cases (completely diffuse without contrast-enhancement-6 cases, exophytic 7 cases, and those located in the ventral pons-3 cases) were excluded in this study. The remaining 7 cases with intrinsic pontine gliomas, who underwent microsurgical treatment, were retrospectively reviewed (**Table 1**). These patients included 3 males and 4 females, with a mean age of 38.0 years. The course of the

disease was between 1 and 3 (average 2.0 months). Patients underwent routine admission examinations, including clinical history, neurologic examination, and laboratory testing. Signs and symptoms consisted of typical cranial nerve deficits (including V-VII and IX-XII) in all patients, long-tract signs in 6, and slight hydrocephalus in one cases. Visual disturbances, limb weakness, and gait disorders were the primary symptoms in the majority of cases. No patients received radiotherapy or chemotherapy. All patients had a preoperative Karnofsky performance status (KPS) of greater than 80%.

Radiological and surgical management

Magnetic resonance imaging (MRI) studies, including T1-weighted, T2/Fluid Attenuation
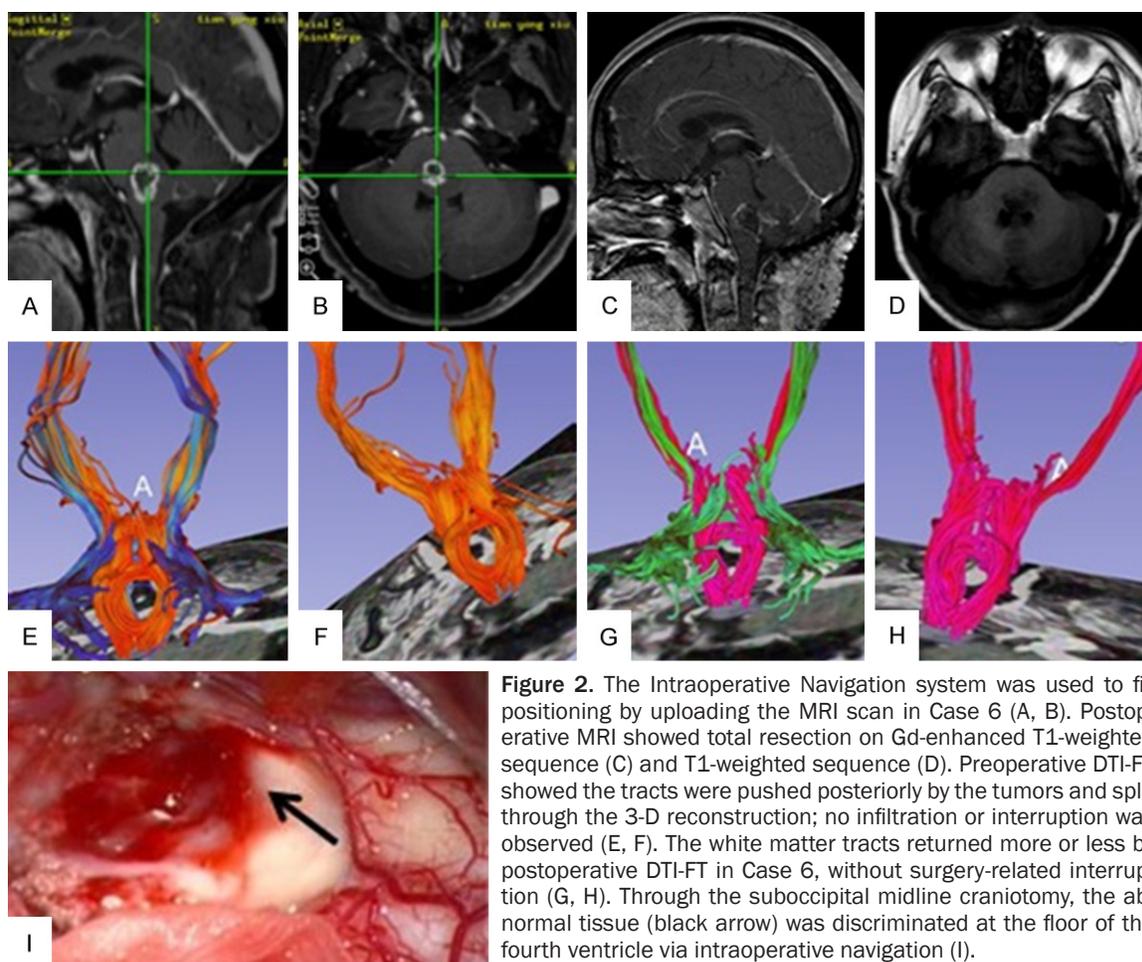
Figure 2. The Intraoperative Navigation system was used to fix positioning by uploading the MRI scan in Case 6 (A, B). Postoperative MRI showed total resection on Gd-enhanced T1-weighted sequence (C) and T1-weighted sequence (D). Preoperative DTI-FT showed the tracts were pushed posteriorly by the tumors and split through the 3-D reconstruction; no infiltration or interruption was observed (E, F). The white matter tracts returned more or less by postoperative DTI-FT in Case 6, without surgery-related interruption (G, H). Through the suboccipital midline craniotomy, the abnormal tissue (black arrow) was discriminated at the floor of the fourth ventricle via intraoperative navigation (I).

Inversion Recovery (FLAIR) weighted, and Gd-enhanced T1-weighted sequences were performed in all patients. Additionally, Diffusion Tensor Imaging Fiber Tracking (DTI-FT) was also conducted for each patient.

The treatment strategy for the pontine gliomas of surgery was tailored to the individual patient. All patients underwent surgery through the suboccipital midline or suboccipital retrosigmoid approach based on the location of the tumor in the pons. Multimodal Intraoperative Neuromonitoring (IOM) was applied during microsurgery. Motor evoked potentials (MEPs), somatosensory evoked potential (SEPs), brainstem auditory evoked potential (BAEPs), and brainstem mapping (BSM) were introduced. Electrophysiological stimulation of the tumor bed or floor of the fourth ventricle was repeated to confirm preservation of brainstem nuclei and fiber tracts.

Intraoperative Navigation systems were also used during microsurgery including fixing the location prior to tumor resection, differentiating tumor from normal brain tissue during the operation, and knowing the extent of tumor resection after surgery (**Figure 2A**, **2B**, **2I**).

Results

Radiological investigation

All the lesions in this report were hyperintense in T2 sequences and slightly hypointense on T1-weighted images. Gd-enhanced T1-weighted sequence showed a contrast-enhanced tumor in the pontine interior in 6 cases, with a "ring-like" pattern in 4 cases. In case 4, we clearly observed that the tumors became enlarged, via the dynamic MRI in different periods (**Figure 1**); the dynamic MRI showed no obvious change at the 20-day intervals in case 5 (**Figure 4A**, **4B**). Postoperative MRI demonstrated complete resection to be achieved in 3 patients, subtotal resection in 2 patients, and partial resection in 2 patients. MRI characteristics are shown in **Table 2**.
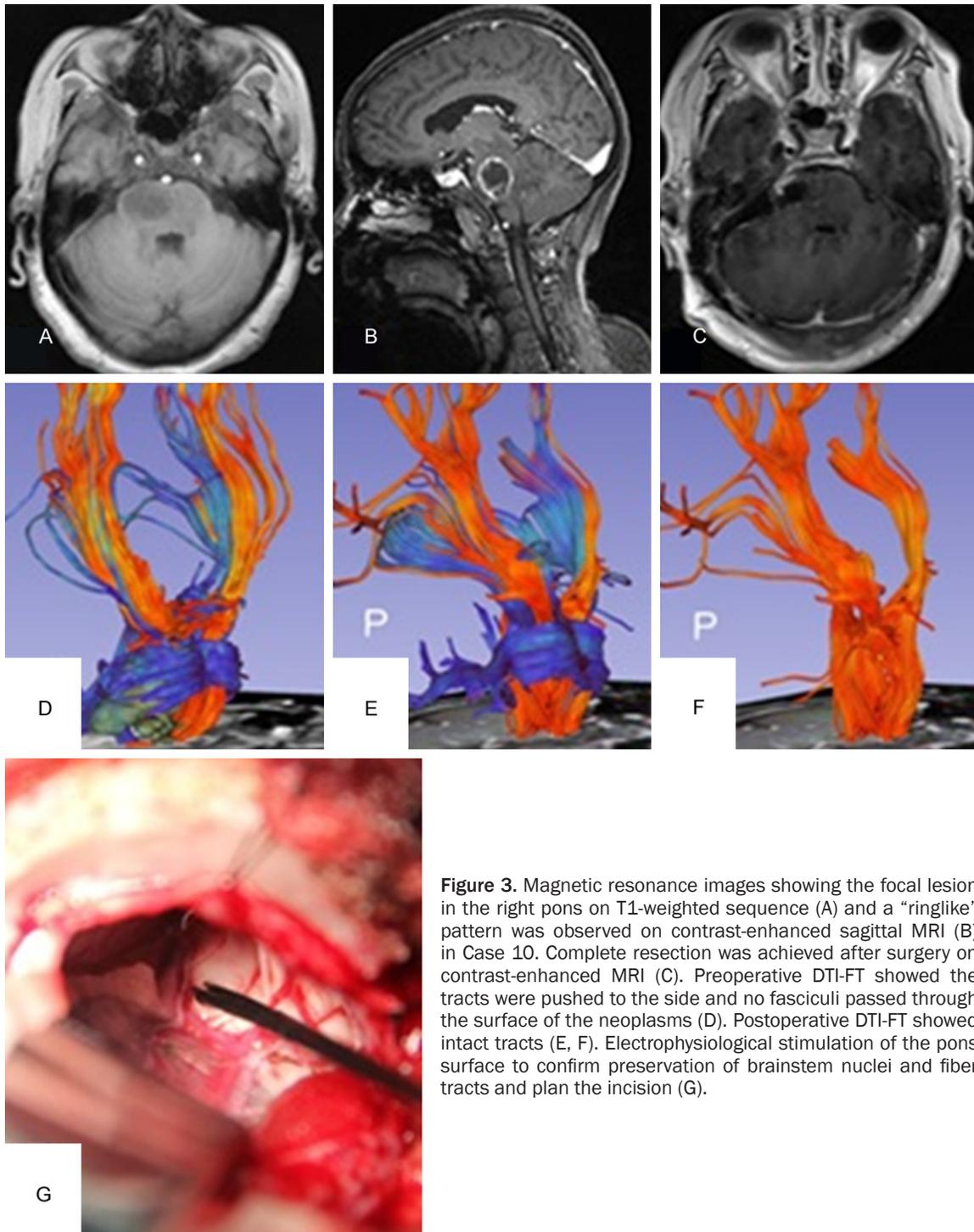
Figure 3. Magnetic resonance images showing the focal lesion in the right pons on T1-weighted sequence (A) and a "ringlike" pattern was observed on contrast-enhanced sagittal MRI (B) in Case 10. Complete resection was achieved after surgery on contrast-enhanced MRI (C). Preoperative DTI-FT showed the tracts were pushed to the side and no fasciculi passed through the surface of the neoplasms (D). Postoperative DTI-FT showed intact tracts (E, F). Electrophysiological stimulation of the pons surface to confirm preservation of brainstem nuclei and fiber tracts and plan the incision (G).

The results of the preoperative DTI-FT were abnormal in all patients, involving the pyramidal tracts, transverse pontine fibers, and medial lemnisci, which were displaced, or infiltrated. The tracts were pushed posteriorly by the tumors and split through the 3-D reconstruction (**Figures 2E**, **2F**, **3D**). The white matter tracts kept intact by the examination of postop-erative DTI-FT in 3 cases (**Figures 2G**, **2H**, **3E**, **3F**).

Intraoperative neuromonitoring

Once the pons was exposed, a hand-held bio-polar concentric stimulating probe was used to deliver single stimuli to map the facial nerve
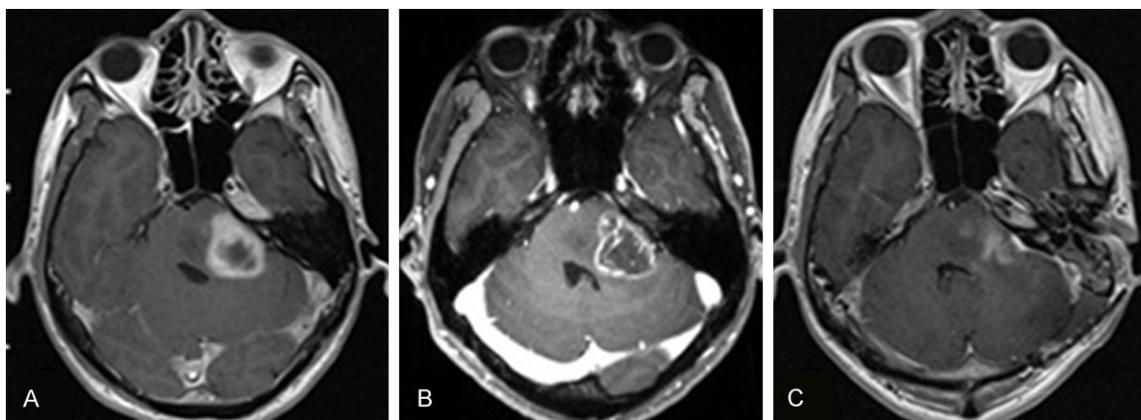
Figure 4. Magnetic resonance images showing the focal lesions in the left pons in Case 9 (A, B). Postoperative MRI showed subtotal resection (C). Dynamic MRI showed no obvious change at 20-day intervals (A, B), considering the superficial location of tumor and slight aggravation of neurologic dysfunction; the patient underwent surgery at the second visit.

Table 2. Summary of radiological, treatment, pathological and follow-up factors

Case No.	Radiological study		Resec-tion Type	Pathological outcome*	Follow up (m)	KPS score#	Postoperative neurological functions
	En-hanced on MRI	Fasciculi type					
1	No	Push	Subtotal	Astrocytoma (II)	39	90	Stable
2	Yes	Push	Partial	Astrocytoma (II)	38	90	Stable, relief of trigeminal neuralgia
3	Yes	Push	Total	AA (III)	25	80	Transient aspiration
4	Yes	Push	Total	AO (III)	16	80	Facial palsy aggravation
5	Yes	Push, infiltrated	Partial	Astrocytoma (II)	11	80	Stable
6	Yes	Push	Subtotal	Astrocytoma (II)	19	80	Transient aspiration and hiccup, slightly-right-sided weakness
7	Yes	Push	Total	AA (III)	16	80	Improved

*There were representing of astrocytoma (WHO II), anaplastic oligoastrocytoma (AO, WHO III), anaplastic astrocytoma (AA, WHO III) respectively. #Karnofsky Performance Status (KPS) Score, at 3 months post-operation.

motor nucleus, to determine the safest entry route to remove the tumor (**Figure 3G**). Continuous intraoperative recording of motor evoked potentials (MEPs) and somatosensory evoked potentials (SEPs) were stable during the operation in all patients. No new neurological deficit occurred within 24 hours after surgery.

Surgery outcomes and histological analysis

All patients underwent surgery via the suboccipital midline approach or suboccipital retrosigmoid approach based on the location of the tumor. The aim of surgery was to maximally and safely remove the tumor. There were no surgery-related deaths. 3 patients underwent total resection and 2 underwent subtotal resection (**Figures 2C**, **2D**, **3C**, **4C**). Given the involvement of important fasciculi in pons and the diffusion of tumor, 2 patients received partial resection.

Histologic analysis revealed astrocytoma (WHO II) in 4 cases, anaplastic oligoastrocytoma (AO, WHO III) in one case, anaplastic astrocytoma (AA, WHO III) in 2 cases (**Figure 5**).

Follow-up and postoperative evaluation

Follow-up was performed at 3 months, 9 months, and then once a year after the operation. During the follow-up period, all patients underwent clinical assessments including neurological examination (to observe changes in neurologic dysfunction) and cranial MRI (to understand whether the gliomas recurred or progressed). Within 24 hours after surgery, the neurological functional status improved in 2 patients (Cases 2 and 7), maintained stable in 2 patients (Cases 1 and 5). During the second 24 hours after surgery, 3 patients (Case 3, 4 and 6) were found new neurological deficits
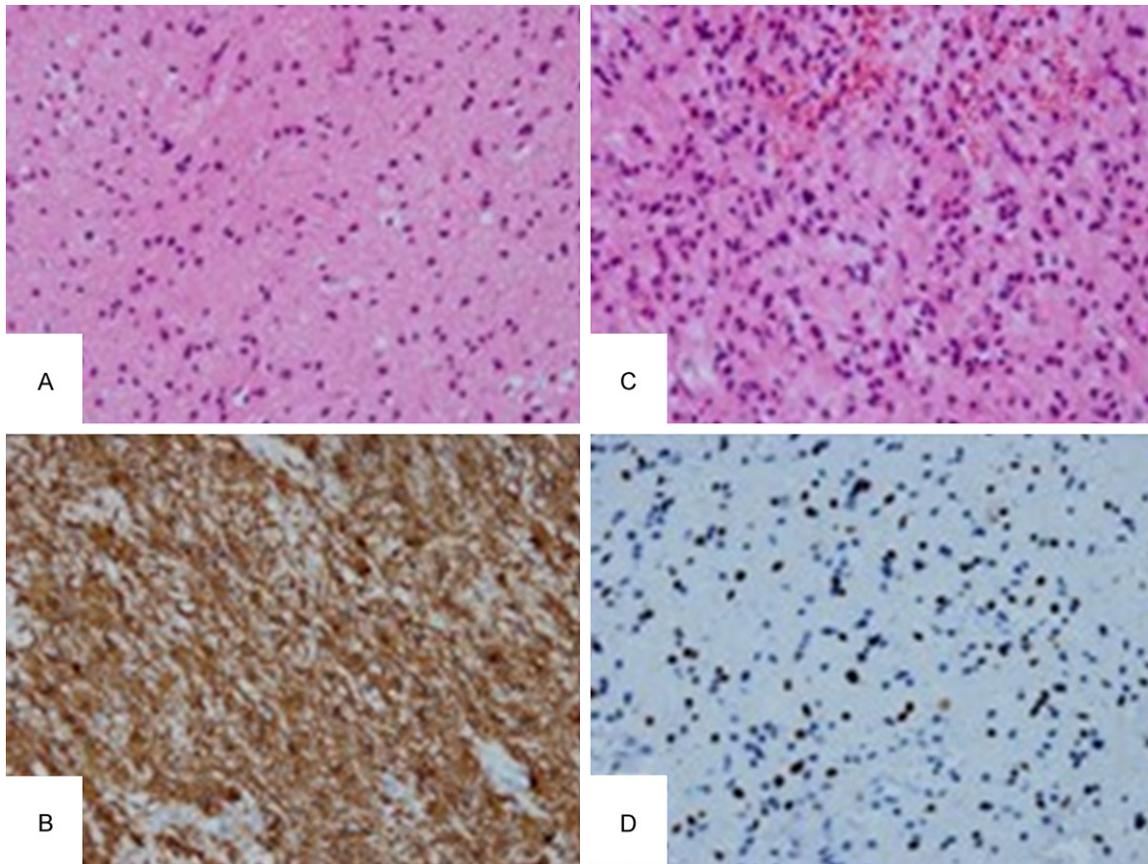
Figure 5. Photomicrographs obtained during pathologic examination of tumor tissue demonstrating glioma (A, C) (H & E staining at 200 ×). Results of immunohistochemistry testing for GFAP (B) and Oligo-2 (D) revealing the glial cells classified as astrocytomas (WHO Grade II) and anaplastic oligoastrocytoma (AO, WHO III) in Case 9 and Case 6. (immunohistochemical staining at 400 ×).

including transient hiccups, transient aspiration, aggravation of facial palsy and slight limb movement disorder, compared with the preoperative state. During the follow-up period, the new neurological dysfunctions resolved gradually, and the neurological dysfunctions deteriorated in 1 patient at 9 months after surgery (Case 5). The rest patients' symptoms either became stable or improved during the follow-up period of 11-39 months. Postoperative radiotherapy (the conventional median dose is 50-55 Gy, using fractions of 1.8-2 Gy) were given to all patients, and 4 patients with astrocytoma (WHO II) rejected chemotherapy. One patient (Case 5) died because the lesion was proved to be completely diffuse change and showed rapidly progress at 9 months after operation. MRI in other patients showed residual tumor size to be unchanged or without obviously recurrence.

Discussion

The present status of treatment of brainstem gliomas is not optimistic, with the majority of brainstem gliomas having a poor outcome [4]. Conventional radiotherapy, although standard, has been disappointing to date; chemotherapy is not routinely used [5]. Surgical management remains a controversial issue [5]. According to the classification of brainstem gliomas in children and adults, based on imaging characteristics and clinical presentation, subtypes excluding the most common diffuse brainstem gliomas, may benefit from surgery under the accomplishment of relative information warrants [3, 6]. Focal, superficial, and exophytic lesions may be amenable to complete resection. Nevertheless, most disagree with progressive resection in intrinsic brainstem gliomas, due to the potential risk of destroying vital fascicule and the attendant risk for significant

morbidity outweighing the therapeutic benefit of tumor debulking in high-grade gliomas [7-9].

In view of the unsatisfactory treatment outcomes of brainstem gliomas, better surgical methods are necessary as we investigate other treatments, such as targeted therapy in diffuse brainstem gliomas [10, 11]. Considering that most gliomas involve the pons [12], which have relatively scattered white matter tracts in anatomical structures other than midbrain and medulla oblongata, the possibility of surgical intervention in intrinsic pontine gliomas may be possible as long as sufficient preoperative preparation is performed. In this report, preoperative MRI, or even dynamic MRI if necessary, and preoperative DTI-FT were utilized in all cases to demonstrate the advantages of technical strategies for removing adult intrinsic pontine gliomas, including repeated physical examination. Multimodal IOMs and Intraoperative Neuronavigation were also used to reach maximal safe resection margins in all patients.

For this report, 6 patients demonstrated contrast-enhanced lesions within the pons on Gd-enhanced T1-weighted sequencing by preoperative MRI and 4 showed a typical "ringlike" pattern suggesting central necrosis [3, 13]. Patients with grade II tumors showed enhancement suggesting potential malignant transformation [14]. One patient exhibited a focal non-enhenced lesion in the right of the pons (Case 1). In 6 patients, diffuse enhancing pontine lesions were demonstrated in one cases (Cases 5), and focal enhancing lesions in 5 cases by reference to the previous classification [15, 16]. Obviously, not all patients met operative criteria due to diffuse infiltration, tumors that were not superficial, or suspected malignancy. Surgical treatment was hesitated in 4 cases, accounting for one case (Cases 5) with diffuse change, one case (Cases 4) with smaller lesion located in the center of the pons, 1 case (Cases 6) with slight neurological dysfunction, and 1 case (Cases 7) of a 70-year-old patient with comorbidities. 2 patients underwent dynamic MRI because there was no explicit surgery indication at the first visit. The time interval between first visit to operation was 2 months in one patient (Case 4), and repeated MRI showed tumor progression, extending towards the surface of the brainstem. One patient (Case 6) that did not demonstrate obvious change was thought to have a low-grade lesion or a short interval time.

Unfortunately, the assessment of white matter tract involvement by tumor was limited in routine MRI scans. However, DTI-FT could remedy this defect. DTI-FT was a promising method for visualizing the relationship between the functional tracts and the tumor and to choose a trajectory to the target area that would minimize the chances of creating new neurological deficits. Preoperative DTI-FT and postoperative DTI-FT could improve the accuracy of prognosis of functional recovery after surgery [17, 18]. Tumor involvement of the white matter tracts were categorized into deviation, deformation, infiltration, or apparent tract interruption [19]. Unquestionably, patients with serious tract interruption were likely to have a poor prognosis. All patients underwent preoperative DTI-FT, of which deviation or deformation was shown in 6 cases, and coexisting displacement and infiltration in one cases (Case 5). No tract interruption was found in our report. The enhancing portion of the tumors were close to the brainstem surface in the diffuse gliomas, while there were hardly any fasciculi passing through the surface of the neoplasms, although few tracts were infiltrated in the deep location by 3D reconstruction of the DTI-FT, suggesting the feasibility of the operation. However, Chen et al demonstrated that DTI may not reliably distinguish tumor "infiltration" from "edema" in brainstem lesions [20]. Therefore, it was impossible to define a clear boundary between surrounding normal parenchyma, edema and infiltrated tumor; the main goal of surgery was to partially debulk tumor, to confirm the diagnosis and improve symptoms [21]. In one patient (Cases 4) with a smaller lesion in the center of the pons, complete division of the fiber tracts on the tumor's surface was seen, as compared to the findings at the first visit, which provided the space to operate with the avoidance of vital structures. Postoperative DTI-FT were performed in 3 cases showing no obvious interruption tracts related to surgery, and split tracts returned in 2 cases with total resection. Compared to preoperative physical examination, there were no new nerve deficits within 24 hours, corroborating the preservation of vital structures.

In case 4, the time from the first visit to the operation was two months; thus, it was not always true that earlier surgery was better for the patient (i.e. as soon as the gliomas were found). Under the condition of using preopera-

tive MRI and DTI-FT, the appropriate timing of surgery management for adult intrinsic pontine gliomas could be definite based on the following reasons: (1) Fiber tracts can be pushed away and adequate room is applied to excision when the lesions are large enough. (2) Larger tumors are closer to the surface of the pons, which can diminish the damage of deep-seated nuclei. (3) It is easier to choose the operative approach when tumors are larger. (4) The rare blood supply of the cortex in the pons surface, caused by larger occupying lesions can delineate the incision. Therefore, surgical interventions were performed on the second or third admission to the clinic in two cases; with hesitating operation in the first visit including 1 case with a smaller lesion located in the center of the pons, and 1 case with slight neurologic dysfunction. Operative timing is important to minimize the surgical complications. The morbidity caused by early aggressive surgery and improper operative timing is more risky compared to the deficits led by the growth of tumors themselves, which is confirmed by clinical observation. With the help of Multimodal IOMs and Intraoperative Navigation during microsurgery, maximal safe resection can be achieved, including accurate positioning, and the extent of tumor resection.

Brainstem auditory-evoked potentials (BAEPs) and SEPs have represented the classical setting of intraoperative neurophysiological monitoring during brainstem surgery. However, BAEPs and SEPs together can monitor only approximately 20% of the brainstem, and cannot provide specific information on the descending motor pathways [22]. Multimodal IOMs including SEP, MEP, and brainstem mapping of the cranial motor nucleus (CMNs) provide more comprehensive protection. Although there is no sufficient evidence correlating neurophysiological data with postoperative neurological outcome, and the warning criteria is not established yet, continuous monitoring of MEPs and SEPs is real-time and important for preservation of pyramidal tracts and the medial lemniscus and proprioceptive function, respectively [22-24]. Furthermore, recent work has achieved better results for lower-extremity MEP (LE-MEP) monitoring by using direct MEP (dMEP) during supratentorial surgery [25]. The mapping of the facial nerve motor nucleus in the brainstem helps to select a safe route to the target area. Continuous intraoperative recording of motor evoked potentials (MEPs) and somatosensory evoked potentials (SEPs) were stable during the operation in all cases. The new neurological deficits found the next day after surgery were likely the result of nerve edema.

Additionally, the application of Intraoperative Navigation systems in microsurgery is becoming widely involved in the uploading of CT, MRI scan or DTI [26]. Benign lesions in brainstem are also used for selection of the operative approach, decreasing postoperative morbidity, and understanding the extent of resection [27]. However, there was existing white matter tract shift under the process of tumor resection; the real-time intraoperative update by uploading DTI data may be more precise [20]. Of course, meticulous microsurgical technique plays an equally important role in intrinsic pontine gliomas under the guidance of preoperative MRI, preoperative DTI-FT, Multimodal IOMs, and Intraoperative Navigation during microsurgery.

In fact, adult intrinsic pontine gliomas can be maximally resected as long as complete preoperative evaluation is performed, followed by adjuvant radiation and chemotherapy. To date, chemotherapy has only been shown to be effective in supratentorial gliomas [28]. The patient (Case 5) who survived only 11 months was regarded to be the result of completely diffuse change glioma, rapidly progressive, and refusal of more adjuvant treatment. The remaining patients were alive at the last follow-up (11, 19, and 39 months). A second surgery was considered, especially for patients whose recurrent tumors showed eccentric growth along the operative trajectory after their first surgery. Radiotherapy should be considered individually for recurrent tumor in the follow-up period. However, we cannot make any elaborate survival analysis due to limited cases or the short follow-up period in some situations. Modifications will be implemented in future studies, including gathering more homologous cases, increasing the size of the comparison group, and extending the follow-up period.

Conclusion

Combining preoperative MRI with preoperative DTI-FT, surgery can be better assessed and the operation for adult intrinsic pontine gliomas can be maximally and safely resected with the aid of Multimodal IOMs and Intraoperative

Navigation during microsurgery. Total resection is extremely difficult for infiltrative gliomas, more treatment technical strategies, such as fluorescence imaging technique, for intrinsic pontine gliomas are still deserved to explore in the future.

Disclosure of conflict of interest

None.

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