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Clinical characteristics and prognostic factors of surgical treatment in children with brainstem tumor

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Abstract. – OBJECTIVE: Brainstem tumors present a significant challenge in surgical treatment, and the prognostic factors in children are lacking. This study aimed to investigate clinical characteristics and prognostic factors of surgical treatment in children with brainstem tumors.

PATIENTS AND METHODS: 50 children with brainstem tumors who underwent surgical treatment, including frameless- or frame-based stereotactic biopsy and resection, were included and followed up for clinical and biological analysis. Factors of outcomes were assessed by univariate and multivariate analysis.

RESULTS: 27 cases (54.0%) underwent resection in all children with brainstem tumors. The rate of resection reached as high as 81.8% in children with non-diffuse intrinsic pontine glioma (DIPG), while in children with DIPG, biopsy was performed in the majority, and resection was obtained in the minority with focal necrosis. A rare complication was found following the surgery. Multivariate analysis considered World Health Organization (WHO) grade 3-4, with hazard ratio (HR)=4.48, 95% confidence interval (CI) of 2.84-8.69, *p*=0.001, H3K27M mutation (HR=2.50, 95% CI 1.73-5.69, *p*=0.015), and hydrocephalus (HR=2.17, 95% CI 1.08-5.32, *p*=0.014) as independent adverse prognostic factors. For Kaplan-Meier analysis, children with WHO grade 3-4, Ki-67 LI ≥ 20%, TP53 mutation, H3K27M mutation, DIPG, and hydrocephalus had significantly decreased overall survival (OS).

CONCLUSIONS: A high rate of resection has been obtained in non-DIPG, and surgical intervention is remarkably safe and efficient for children with brainstem tumors. WHO grade 3-4, H3K27M mutation, and hydrocephalus indicate poor prognosis in children with brainstem tumors.

Key Words:
Brainstem tumor, Surgery, DIPG, Frameless system.

Introduction

Brainstem tumor originates from the midbrain, pontine, and medulla, which accounts for 10-20% of tumors affecting the central nervous system in children[1]. Brainstem tumor is a series of rare, highly heterogeneous, and challenging group of brain tumors with poor prognosis[2]. Brainstem tumors usually cause fatal clinical course with a median survival of 10 months and a two-year survival rate of less than 10%[3]. One subtype of them – diffuse intrinsic pontine glioma (DIPG) – is the leading cause of brain tumor-related death in childhood and is associated with a mutation in histone protein H3 genes[4]. Despite a transient benefit of standard radiotherapy, the prognosis is still poor with progressive neurologic deterioration[5].

In recent decades, a concerted effort has been made to improve the prognosis of brainstem tumors. With the efforts of neurosurgeons, surgery is playing an increasingly important role in treatment[6]. Surgery aimed to achieve maximal safe resection for low-grade brainstem gliomas, while craniotomy biopsy is aimed for high-grade gliomas, especially for DIPG[7]. Efficient and specific treatments for brainstem tumors remain challenging, as most of them are of a diffusely infiltrative nature and intolerant to resection. A histological diagnosis is crucial to genetic, molecular studies, and adjuvant treatment, which is required for further therapy, including chemotherapy, radiotherapy, and potential targeted therapy[8]. For a long time, the biological mechanism for these neoplasms remains obscure due to the historically unacceptable morbidity and mortality of surgery (even biopsy)[2].

Following advances in surgical techniques and instruments, more studies[9] have demonstrated that resection of brainstem lesions can be con-

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ducted safely. Now, brainstem tumor resection has been considered an acceptable increasingly applied surgery, due to safety and efficiency[10]. Consequently, more research is needed to improve the prognosis of brainstem tumors with surgical treatment. This study aimed to investigate clinical characteristics and prognostic factors of surgical treatment in children with brainstem tumors.

Patients and Methods

Study Population

This study was conducted on 50 children with brainstem tumors who were hospitalized at Wuhan Children's Hospital between July 2017 and November 2021. The inclusion criteria were: 1) Brainstem tumor patients who were clinically and radiologically (magnetic resonance imaging, MRI) confirmed as involving the mesencephalon, crus cerebri, pons, or medulla oblongata; and 2) patients who underwent the frame-based or stereotactic frameless-based surgery for tumor resection or biopsy. Patients with previous lumbar surgery, tumor, trauma or other neurological diseases were excluded. This study was performed in accordance with the Helsinki Declaration and approved by the ethical committee of Wuhan Children's Hospital.

Surgical Procedure

27 cases underwent tumor resection and 23 cases underwent tumor biopsy. In patients with biopsy, 21 cases received frame-based stereotactic brainstem tumor biopsy, and 2 cases underwent frameless brainstem tumor biopsy. All patients underwent biopsy through the frontal puncture pathway under general anesthesia. All patients were subjected to intraoperative frozen pathology, and postoperative routine head computed tomography (CT) was performed to determine the accuracy of surgical location and bleeding-related complications[11].

Brain stem tumor resection surgery: for localized brainstem tumors, surgical resection was usually used. The boundary of the surgical resection during the operation was determined by the combination of the judgment of neurosurgeons. Electrophysiological monitoring and accurate location through neural navigation were used during surgery if necessary. In this study, four different surgical approaches were used: suboccipital posterior median approach, retrosigmoid sinus approach, Kawase approach, and transcallosal interforniceal approach. To enter the brainstem point is the most important, areas with fewer neural nuclei is usually selected. It is easier to choose areas without nuclei and with the weakest tissue. During the tumor resection process, real-time monitoring of the nucleus and brainstem function is necessary and close cooperation with anesthesiologists and neuroelectrophysiological personnel is required. Gentle operation was performed to minimize continuous traction on the brainstem, and attention was paid to the selection of bipolar electrocoagulation output power, lower power should be selected when entering the brainstem.

For the standard frame-based stereotactic biopsy, the Leksell Frame G stereotactic frame (Elekta lnc., Stockholm, Sweden) was placed on the patient's head preoperatively, and MRI scanning images were transmitted to the stereotactic surgery planning system workstation. The biopsy target and puncture trajectory are designed based on the three-dimensional imaging of the lesion, and the surgery is performed. Under general anesthesia, the surgeon made a burr hole with a diameter of 1 cm at the prescribed site and put a biopsy needle into the brain lesion. A CT scan was performed on all patients after surgery.

For the frameless biopsy, the patients' MRI data were obtained 1-2 days before surgery. All the MRI and CT data were collected into the mobile workstation equipped with a calculator to choose the target and plan the trajectory of the needle biopsy depending on tumor location and surrounding structures, then the surgical plan was planned. The completed biopsy plan was imported into the computer system for mark point registration and error calibration. After the machine arm was in place, a biopsy surgery was performed. After four scalp markers were verified with two test markers, the biopsy needle was securely fixed to the robotic arm, a burr hole was drilled at the entry point, the robotic arm was sent to the target position, and biopsy specimens were collected.

Evaluation and Postsurgical Follow-up

The medical history and demographic data of patients were collected from the hospital. Karnofsky scoring (KPS) score was adopted for the evaluation of clinical observations on pre-surgery. Histologic diagnosis was made on paraffin-embedded tissue and integrated by analysis of H3K27 and TP53 mutational status. Molecular analysis to test for activation of specific pathways was made by immunohistochemistry. For at least two years, all children with brainstem tumors were followed up at the clinic or by phone.

Statistical Analysis

Chi-squared test or Fisher's exact test was hired for data analysis. Beneficial factors affecting overall survival (OS) were identified and tested by univariate and multivariate analysis respectively. Hazard ratio (HR) and 95% confidence interval (CI) were calculated. Survival was calculated using the Kaplan-Meier method. The log-rank test was used to compare differences in survival curves. All statistical analysis was performed using SPSS Software Version 25.0 (IBM Corp., Armonk, NY, USA), and p-value < 0.05 was considered significant.

Results

Clinical Characteristics

Among the 50 children with brainstem tumors, 23 were male and 27 were female respectively. There were 22 children with Grade 1-2 tumors and 28 children with Grade 3-4 tumors. Among 30 children with glioma, 24 children had high-grade glioma and 6 children had low-grade glioma. In high-grade glioma, 17 children were DIPG (Figure 1). The median duration of preoperative symptoms was 3 months (range: 1 to 24 months). The median KPS score was 70 (range: 50 to 90) for all children. H3K27M mutation (50.0%) was frequently observed in children with brainstem tumors, and Ki-67 LI $\geq$ 20% was accounted for 36.0%. Hydrocephalus happened in 28.0% of children on diagnosis (Table I).

Surgical Outcomes

All children were evaluated for whether they were suitable for tumor resection. Resection was performed in 27 cases (54.0%) with brainstem tumors. The rate of resection reached as high as 81.8% in children with non-DIPG, while in children with DIPG, resection was obtained in those with focal tumors. Biopsy was performed in 17 children with diffuse tumors and 6 children with local tumors but difficult for resection. Children with World Health Organization (WHO) grade 3-4 (p=0.002) and H3K27M mutation (p=0.001)

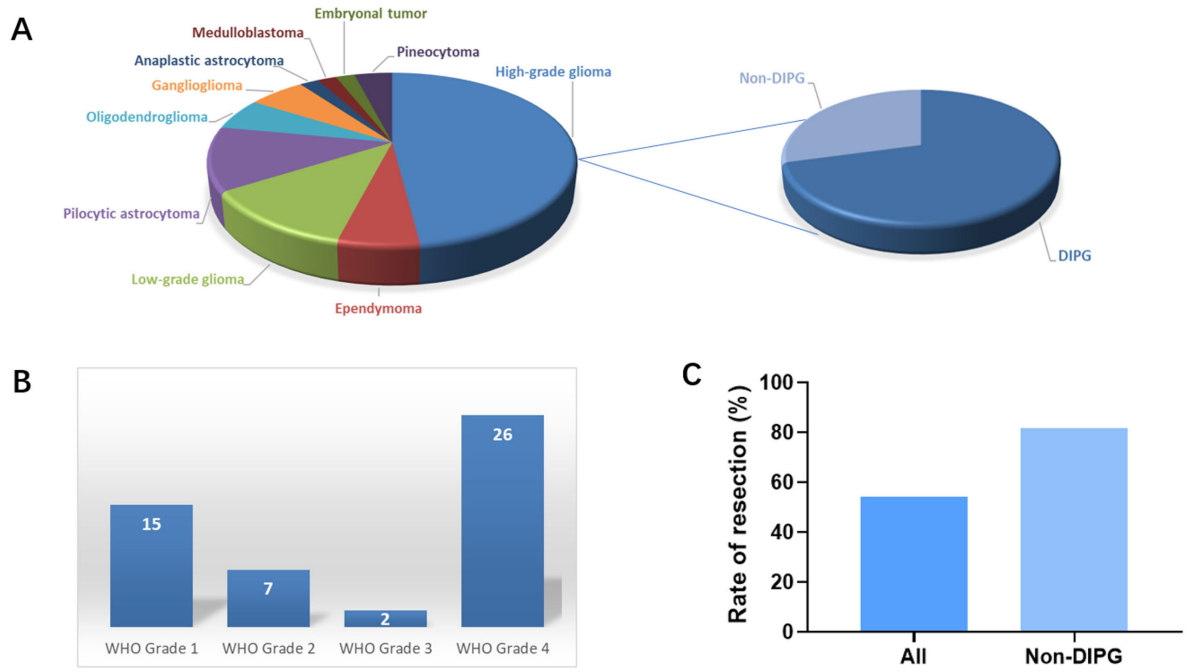

Figure 1. Pie chart of pathological diagnosis of 50 children with brainstem tumors. **A,** 24 cases (48%) were high-grade glioma, 6 cases (12%) were low-grade glioma, 6 cases (12%) were pilocytic astrocytoma, 3 cases were (6%) oligodendroglioma, 3 cases were (6%) ependymoma, 3 cases were (6%) ganglioglioma, 2 cases were (4%) pineocytoma, with one case (2%) of anaplastic astrocytoma, medulloblastoma, embryonal tumor respectively. In high-grade glioma, 17 cases (70%) were diffuse intrinsic pontine glioma (DIPG) and 7 cases (30%) were non-DIPG. **B,** World Health Organization (WHO) grade of 50 children with brainstem tumors. **C**, 27 cases (54.0%) underwent resection in all children with brainstem tumors and 27 cases (81.8%) underwent resection in children with non-DIPG.

Table I. Clinical characteristics.

Characteristics	No. (%) n=50
Sex	
Male	23 (46.0)
Female	27 (54.0)
Age	
< 1 years	5 (10.0)
1-5 years	15 (30.0)
> 5 years	30 (60.0)
Preoperative KPS	
≥70	28 (56.0)
<70	22 (44.0)
Tumorsize	
< 5 cm	31 (62.0)
≥ 5 cm	19 (38.0)
Pathological WHO grade	
1-2	22 (44.0)
3-4	28 (56.0)
Ki-67 LI	
≥ 20%	18 (36.0)
<20%	32 (64.0)
Histone 3 mutation	
H3K27M	25 (50.0)
H3F3A	2 (4.0)
HIST1H3B	2 (4.0)
Location	
Diffuse	17 (34.0)
Pons	15 (30.0)
Midbrain	10 (20.0)
Medulla oblongata	8 (16.0)
Hydrocephalus	
Yes	14 (28.0)
No	36 (72.0)
Surgical treatment	
Resection	27 (54.0)
Biopsy	23 (46.0)

KPS, Karnofsky scoring; WHO, World Health Organization.

were more likely to receive a biopsy. No new symptoms were observed in children with biopsy, and just 3 children had new symptoms after resection (p=0.058) (Table II). Surgical complications were rarely observed, and the only complication is hydrocephalus. No difference was found between children with frame-based *vs.* frameless-guided system. Figure 2 shows the MRI and histopathological image of DIPG before and after brainstem tumor resection. Figure 3 and Figure 4 show the MRI and histopathological images of two cases with non-DIPG before and after brainstem tumor resection.

Prognostic Factors of OS

Univariate analysis showed children with WHO grade 3-4 (HR=6.20, 95% CI 2.78-10.32, p<0.001), H3K27M mutation (HR=5.83, 95% CI 3.59-8.72, p<0.001), and hydrocephalus (HR=3.42, 95% CI 1.77-5.98, p=0.029) significantly had decreased OS. Multivariate analysis considered WHO grade 3-4 (HR=4.48, 95% CI 2.84-8.69, p=0.001), H3K27M mutation (HR=2.50, 95% CI 1.73-5.69, p=0.015), and hydrocephalus (HR=2.17, 95% CI 1.08-5.32, p=0.014) as independent adverse prognostic factors (Table III). For Kaplan-Meier analysis, Figure 5 shows that children with WHO grade 3-4, Ki-67 LI ≥ 20%, TP53 mutation, H3K27M mutation, DIPG, and hydrocephalus had significantly decreased OS.

Discussion

The main risks of brainstem stereotactic biopsy are failure to obtain tumor samples for diagnosis and the emergence of new neurologic deficits after surgery[9]. As reported by previous research, a frameless stereotactic biopsy can obtain a rate of diagnostic tissue from 89% to 99.3%, and a frame-based procedure can provide a diagnostic tissue of 81.3-99.2%[12,13]. We successfully obtained the diagnostic tissue in 100% of cases, confirming the safety of the stereotactic procedure. For brainstem tumors, the surgery strategy aims to achieve the maximal extent of safe resection[7]. We obtained a relatively high rate (81.8%) of resection in children with non-DIPG and a deep degree extent of resection in children with DIPG. It is possible to affirm that stereotactic technique and multidisciplinary discussion were fundamental to prognosis evaluation and therapeutic options.

In 2021, the WHO updated an integrated molecular and histological diagnostic framework for central nervous system (CNS) tumors, the updated molecular classifications have deep implications for prognosis and therapeutic options[14]. The need for accurate molecular diagnosis requires the acquisition of diagnostic tissue, especially for anatomically unresectable brainstem tumors[2]. With the help of magnetic resonance spectroscopy (MRS), the histological grade and treatment plan of tumors could be primarily evaluated before surgery[15]. Stereotactic brain biopsy has been widely applied as an accurate, effective, and safe technique for the identification of brain lesions[16]. This study analyzed clinical characteristics in 50

Table II. Comparison of outcome between patients with resection and biopsy.

Characteristics	Resection (%) n=27	Biopsy (%) n=23	*p*-value
Age <5 year	14 (51.8)	6 (26.1)	239
Preoperative KPS≥70	17 (63.0)	11 (47.8)	295
Duration ≤3 months	6 (22.2)	9 (39.1)	529
WHO grade 3-4	8 (29.6)	20 (74.1)	2
Ki-67 LI ≥ 20%	5 (18.5)	11 (47.8)	54
H3K27M mutation	8 (29.6)	17 (74.0)	1
Tumor size ≥ 5 cm	11 (40.7)	8 (34.8)	812
Hydrocephalus	7 (25.9)	7 (30.4)	700
New symptoms	3 (11.1)	0 (0)	58

KPS, Karnofsky scoring; WHO, World Health Organization.

children with brainstem tumors who underwent surgical treatment and found that children with WHO Grade 3-4, Ki-67 LI ≥ 20%, TP53 mutation, H3K27M mutation, and hydrocephalus had a significantly poor prognosis. The stereotactic frame-based and frameless-based systems were successfully used to acquire brainstem tissue for accurate molecular diagnosis.

DIPG accounts for 10 to 20% of all pediatric brain tumors and accounts for about 80% of all brainstem gliomas[10]. DIPG is a leading cause of death from solid tumors in children with a typical age between 6 and 9 years. Children with DIPG showed significantly decreased OS than non-DIPG. In this study, DIPG accounted for 34.0% of brainstem tumors and 70.8% of high-grade brainstem gliomas in children. Current clinical trials on the efficacy of histone deacetylase inhibitors, BET inhibitors, CDK4/6 inhibitors, other small molecule inhibitors, and oncolytic viruses

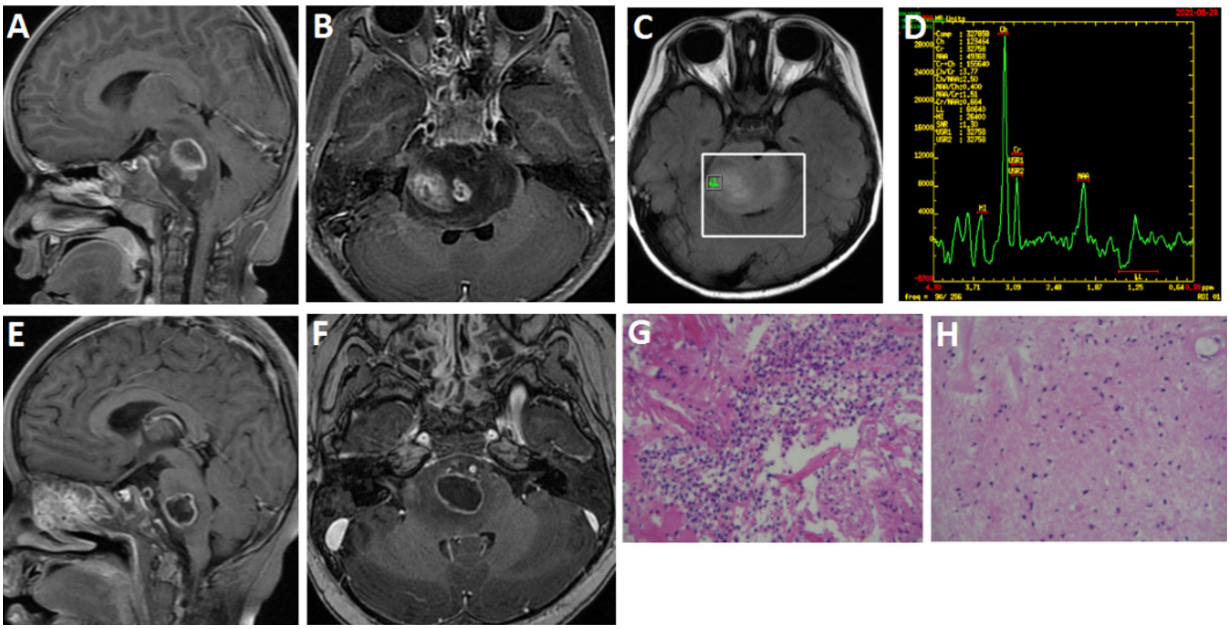

Figure 2. Case presentation pre- and post-operative magnetic resonance (DIPG). **A,** Pre-operative magnetic resonance imaging (MRI) enhanced scan in coronal view. **B,** Pre-operative MRI enhanced scan in axial view. **C**, and **D,** Magnetic resonance spectroscopy (MRS) with an echo time of 144 ms showed a marked increase in the Cho/NAA ratio. **E,** Post-operative MRI enhanced scan in coronal view. **F,** Post-operative MRI enhanced scan in axial view. **G,** and **H,** The histopathological image (Hematoxylin and eosin stain, 100×) showed a diffuse, infiltrative glioma with astrocytic morphology.

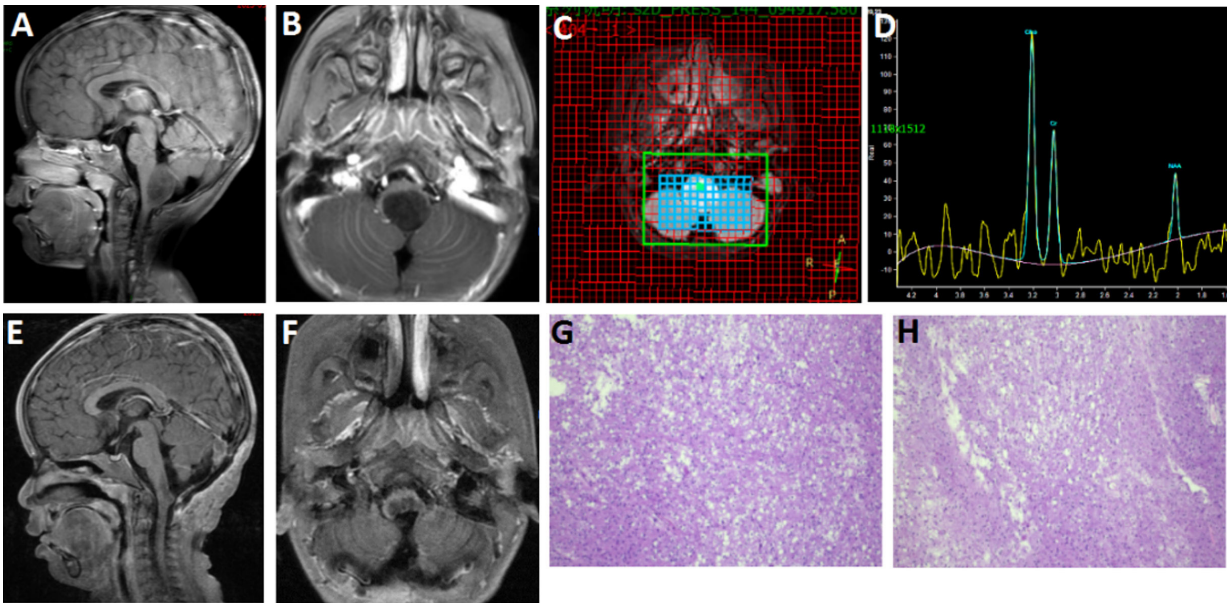

Figure 3. Case presentation pre- and post-operative magnetic resonance (pilocytic astrocytoma). **A,** Pre-operative MRI enhanced scan in coronal view. **B,** Pre-operative MRI enhanced scan in axial view. **C,** and **D,** MRS with an echo time of 144 ms showed an increase in the Cho/NAA ratio. **E,** Post-operative MRI enhanced scan in coronal view. **F,** Post-operative MRI enhanced scan in axial view. **G,** and **H,** The histopathological image (Hematoxylin and eosin stain, 100×) showed infiltrative glioma with hair cell morphology.

have promisingly improved the survival[4]. This study indicates the feasibility of the stereotactic technique, supporting the safety of surgical biopsy for DIPG and highlighting biopsy for accurate diagnosis and treatment decision-making[3]. These findings align with recent publications on the feasibility of biopsy in patients with DIPG and agree with earlier reports[17].

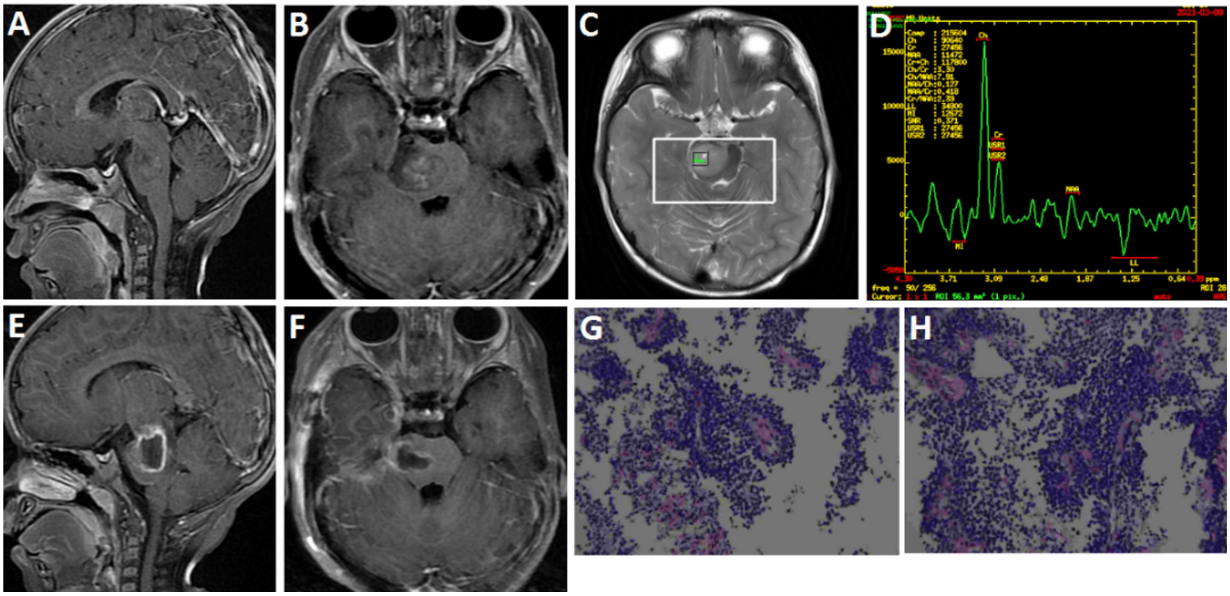

Figure 4. Case presentation pre- and post-operative magnetic resonance (Embryonal tumor). **A,** Pre-operative MRI enhanced scan in coronal view. **B,** Pre-operative MRI enhanced scan in axial view. **C,** and **D,** MRS with an echo time of 144 ms showed a marked increase in the Cho/NAA ratio. **E,** Post-operative MRI enhanced scan in coronal view. **F,** Post-operative MRI enhanced scan in axial view. **G,** and **H,** The histopathological image (Hematoxylin and eosin stain, 100×) showed embryonal tumor with multilayered rosettes morphology.

Table III. Univariate and multivariate analysis of factors associated with OS.

Characteristics	Univariable HR (95% CI)	*p*-value	Multivariable HR (95% CI)	*p*-value
Age <5 year	0.30 (3.15-7.16)	682		
Preoperative KPS ≥70	0.82 (0.23-1.78)	709		
Duration ≤3 months	0.74 (1.92-8.85)	828		
WHO grade 3-4	6.20 (2.78-10.32)	<0.001	4.48 (2.84-8.69)	1
Ki-67 LI ≥ 20%	1.12 (0.86-2.97)	59		
H3K27M mutation	5.83 (3.59-8.72)	<0.001	2.50 (1.73-5.69)	15
TP53 mutation	1.35 (0.97-5.45)	78		
Tumor size ≥ 5 cm	1.63 (0.79-4.18)	452		
Hydrocephalus	3.42 (1.77-5.98)	29	2.17 (1.08-5.32)	14
Resection	0.68 (0.32-1.74)	697		

OS, Overall survival; KPS, Karnofsky scoring; WHO, World Health Organization; HR, hazard ratio; CI, confidence interval.

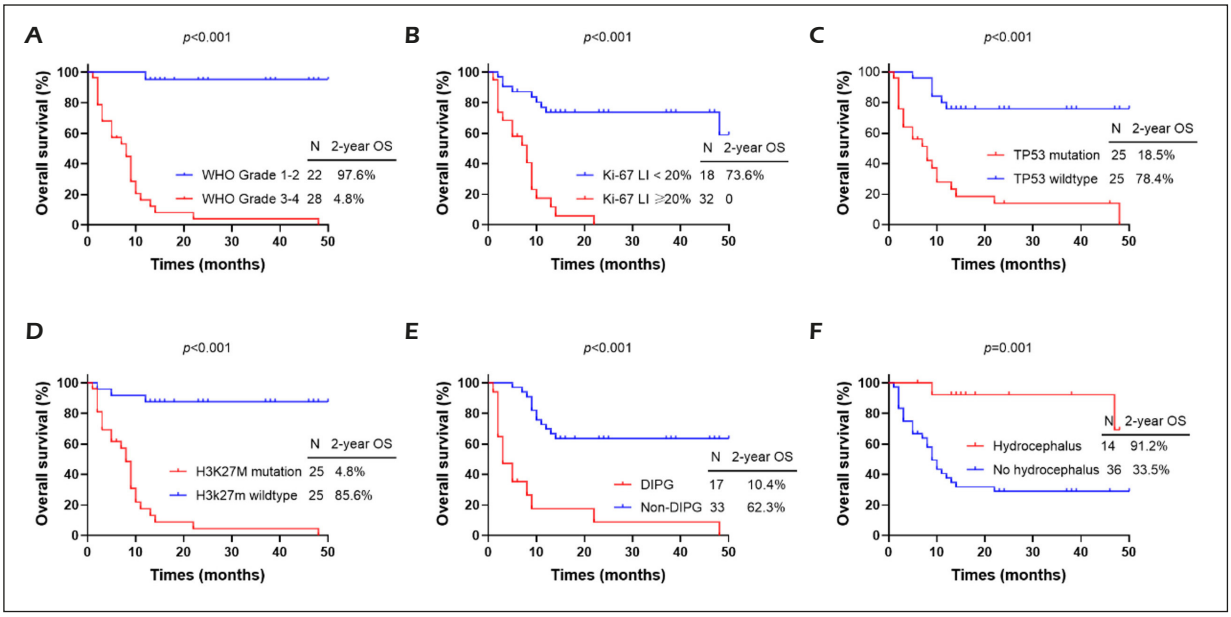

Figure 5. Kaplan-Meier survival curves of overall survival (OS). Children with (**A**) WHO grade 3-4, (**B**) Ki-67 LI ≥ 20%, (**C**) TP53 mutation, (**D**) H3K27M mutation, (**E**) DIPG, and (**F**) hydrocephalus had poor OS.

The clinical advent of molecular profiling, including multi-omics analysis incorporating WGS/WES, mRNA-seq, and DNA methylation profiling, offers great promise in how we diagnose, understand, and treat DIPG[17]. In non-DIPG, no tumor surgery remained the only factor that was significantly associated with worse OS after multivariate testing (HR=11.11, p=0.027)[18]. For DIPG, H3K27M mutation seems to be associated with a poor prognosis[19], and a study[5] showed that there was no survival difference between surgical resection *vs.* biopsy in DIPG.

Aside from surgical skills, neurophysiological instruments and infection prevention strategies were required for reconsideration[20]. Moreover, electrophysiological monitoring is documented as an effective approach to decrease the rate of damage and to have safe and well-oriented surgery. In this study, applying neurophysiological monitoring decreased surgical complications by about 5.0%. Therefore, with the guidance of neurophysiological monitoring, surgical treatment of brainstem tumors can acquire satisfactory postoperative results.

Limitations

Nonetheless, our study also had some limitations. Moreover, we were not able to extend the time and sample size of our study, which is an important issue when it comes to speaking about the advantages of a surgical intervention. Consequently, more randomized trials are required with larger samples in future studies.

Conclusions

In conclusion, this study showed a relatively high rate of resection in non-DIPG and that surgical intervention is remarkably efficient with relatively low complications. Both frameless stereotactic and frame-based stereotactic biopsies are safe and efficient for children. WHO grade 3-4, H3K27M mutation, and hydrocephalus indicated poor prognosis in children with brainstem tumors.

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Informed Consent

The guardians of the study participants gave written informed consent for their respective minors to participate in the study.

Ethics Approval

This research complied with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the Medical Ethics Committee of Wuhan Children's Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval No. 2022R109-E01).

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Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Authors' Contributions

H.D. and Y.-Z.H. designed the research and wrote the manuscript; Q.Z. collected and analyzed the data; W.-Y.D, Y.-Y.L, Y.-Z.H. and L.-Y.H. contributed to the analysis of the study; Y.-Y.L and Y.-Z.H. supervised the study and contributed to the writing of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interests.

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