

# Giant pediatric intracranial tumor: Size feature and surgical strategy

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## Research Article

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# Abstract

**Purpose:** To quantify the size of the giant pediatric intracranial tumor (GPIT), analyze the character of GPIT and optimize the management of GPIT.

**Materials and methods:** This study analyzes the clinical data of 36 cases of GPIT at a center from January 2015 to August 2020. The volume of GPITs were measured by 3D slicer software based on preoperative magnetic resonance imaging (MRI).

**Result:** The mean volume of GPITs is 110.7ml, with the maximum volume 619.8ml and the minimum volume 27.3ml. Hemisphere held the largest mean volume of GPIT among all locations, including 7 cases whose volume is over 100ml. There is no statistical difference in volume of GPIT between sex. The most common sites of GPITs are hemisphere and cerebellum. Other locations include ventricle, sellar-parasellar region and cerebropontine angle. Medulloblastoma is the most common postoperative histopathological type, other types contain ependymoma, pilocytic astrocytoma, atypical teratoid rhabdoid tumor (AT/RT), choroid plexus carcinoma (CPC), choroid plexus papilloma (CPP), oligodendroglioma, primitive neuroectoderm tumor (PNET), immature teratoma and yolk sac tumor. 28 cases achieved total resections while 4 cases only achieved subtotal resections. The patient with giant immature teratoma died during the operation because of bleeding. High-grade malignant tumors indicate poorer prognosis.

**Conclusion:** GPIT is a common disease in children with unfavorable prognosis, especially in high-grade malignant tumors like CPC, PNET and AR/RT. Volume measurement based on MRI is an effective approach to access and compare the sizes of GPITs. Operation can extend the survival periods of the patients. Surgical strategies should be chosen according to the location and pathological feature of the tumors.

## 1. Introduction

Pediatric brain tumor is the most common disease in children aged less than 14 years in the United States from 2012 to 2016, with occurrence rate of 5.55–5.83 cases per 100,000 person years[1]. Surgical resection is the traditional treatment, usually combined with radiotherapy and chemotherapy. Among them, the giant pediatric intracranial tumor (GPIT), defined as the diameter of tumor is longer than 5cm in any direction, is still a challenging type with high morbidity and mortality[2].

Pediatric brain tumors are often overlooked in early period of disease for the absence of expression in children especially in the infants, which result in the delay of diagnosis of tumor[3]. Besides, the treatment of pediatric is also a challenge because of children's rapid-growth bodies and immature mental development. However, there were few studies completely describe the early diagnosis and treatment of GPIT. Furthermore, the size of GPITs cannot be obtain from previous reports. This study is concentrated on the diagnosis, treatment and management of GIPT. We also calculate the volume of the tumor based on MRI to describe the tumor size and improve the understanding of GPIT.

## 2. Materials And Methods

This study was approved by the Ethics Committee of the hospital.

### 2.1 Patient

We retrospectively analyzed the clinical data of 158 cases of pediatric intracranial tumor at the Department of Neurosurgery of the Second Affiliated Hospital of Wenzhou Medical University, between January 2015 and August 2020. 36 cases were proved to be GPIT (See Table.1). 32 cases received surgical treatment and 4 cases didn't received the surgery.

We sorted out GPITs according to following criteria: (1) the largest diameter of pediatric intracranial tumors is  $\geq 5$ cm on preoperative magnetic resonance (MR) image, including intracranial cystic tumors. (2) The operations were performed at our neurosurgery department, or patients didn't receive the surgeries but the MRI was conducted and the diagnosis was clear. (3) no history of intracranial surgeries.

### 2.2 Clinical data

The clinical data were collected from the medical record system of hospital, including the patient's basic characteristics, MR or CT image, operation record and pathology report. The follow-up was conducted regularly after surgery, including MR image and a neurology examination, whose period ranged from 2 to 58 months, and the mean period is 21 months. For patients received operations, we conducted follow-up at least 6 months.

### 2.3 The volume of tumor

The volume of the tumor is calculated through 3D slicer software (version 4.10.2, <https://www.slicer.org/>). Firstly, we used segmentations module to create a segment in axial, sagittal and coronal T1-weighted image of MR, choosing the tumor area which shows high signal with threshold tool. Then we modified the edge and fill the unselected space inside the tumor with pencil and erase tools to improve the precision of the segment. Eventually, we reconstructed and exported 3D model of tumor based on this segment. Thus, the volume of the tumor can be read from the information panel of this 3D model.

### 2.4 Surgical procedure

Surgical procedures were designed differently according to size, location and type of tumor, as well as the personal conditions of the patients. The suboccipital craniotomy is the most common surgical approach in this series which is for posterior fossa tumors. Other surgical approaches include lateral suboccipital craniotomy, transcallosal-interforniceal approach, pterional approach, parietal approach, frontal approach, etc. Neuroendoscopy and microsurgical techniques were applied in some cases to cope with deep focus. In patients with severe obstructive hydrocephalus, we implant Ommaya reservoir or use external ventricular drainage (EVD) to drain the fluid out and lower intracranial pressure before tumor

resection. The aim to achieve gross total resection (GTR) in most of tumors. However, in tumors with abundant blood supply such as AT/RT, only subtotal resection (STR) can be performed.

## 2.5 Statistical analysis

SPSS 25.0 (IBM Corp., Armonk NY, USA) was used for data analysis. Since the data doesn't conform to normality, nonparametric tests were employed in this study. Two-sample independent Mann-Whitney U test was used to compare tumor volume between boys and girls, infant group and non-infant group. Multiple-sample independent Kruskal-Wallis H test was for comparison of tumor volume in different age groups and different locations. The data were considered statistically significant when  $P < 0.05$ .

## 3. Result

The age group with the largest proportion is one to five years, including 20 cases (55.6%). The most common sites of tumor are hemisphere and cerebellum, other locations include ventricle, sellar region and cerebropontine angle. The mean volume of GPIT is 107.5ml and the median is 68.6 ml, with the maximum is 632.8ml (102mmx124mmx98mm) and the minimum is 27.3ml (67mmx40mmx20mm). The frequency histogram of tumor volume was shown in Fig. 1. Above half of the tumors' volume ranges in 40-80ml, 9 cases' volume is over 100ml and only 2 cases' volume surpass 300ml. There is no statistical difference in volume of GPIT between sex. Mean tumor volume in infants is bigger than older children though no statistical significance was found. Hemisphere held the largest mean volume of GPIT among all locations, including 7 cases whose volume is over 100ml. The common symptoms of GPIT are vomiting, headache and gait disorder. Muscle weakness, fever, sleepiness and convulsion is also connected with GPIT.

The surgical group includes 23 boys and 9 girls. 28 cases received total resection and 4 cases only achieved subtotal resection. Medulloblastoma is the most common postoperative histopathological type, other types contain ependymoma, pilocytic astrocytoma, AT/RT, CPC, CPP, oligodendroglioma, PNET, craniopharyngioma, immature teratoma and yolk sac tumor (See Table.2).

The patient with giant immature teratoma died during operation because of massive bleeding. Postoperative complications occurred in 8 cases, including subcutaneous effusion in 5 cases, pulmonary infection in 1 case, intracranial infection with pneumocrania in 1 case and mild dyskinesia in 1 case. Most of patients got improvement after the surgeries. However, patients with CPC and AT/RT recurred and died in 1 year.

Table 1  
Baseline characteristics of 36 cases of GPIT

Variable	Cases(percentage)	Volumes(ml)	P value
Age groups			
Normal			0.392
<1 year	4(11.1%)	234.2 (59.5-632.8)	
1–5 year	20(55.5%)	94.2 (33.2-317.3)	
6–10 year	9(25%)	94.2 (49.0-255.8)	
11–14 year	3(8.3%)	67.7 (27.3-116.2)	
Infant or not			0.288
<3year	19(52.8%)	126.0 (42.6-632.8)	
4-14year	17(47.2%)	86.9 (27.3-255.8)	
Sex			0.920
Males	24(66.6%)	106.7 (27.3-632.8)	
Females	12(33.3%)	109.2 (33.2-317.3)	
Sizes(mm)			
Minimum	67 x 40 x 20	27.3	
Maximum	102 x 124 x 98	632.8	
Average		107.5	
Locations*			0.154
Supratentorial–hemisphere	11(30.6%)	192.6(27.3.8-632.8)	
Cerebellum	12(33.3%)	66.8(48.4-116.2)	
Sellar region and third ventricular	5(13.9%)	89.8(40.1-230.4)	
Cerebropontine angle	1(2.8%)	79.7	
Lateral ventricular	1(2.8%)	70.4	
Fourth ventricular	3(8.3%)	43.3/45.7/68.9	
Mixed	2(5.6%)	77.1/83.9	
Symptoms			

\*The P value of the mean volume of “Supratentorial (hemisphere) tumors” and “infratentorial tumors” is 0.015.

<b>Variable</b>	<b>Cases(percentage)</b>	<b>Volumes(ml)</b>	<b>P value</b>
Vomiting	24(66.7%)		
Headache	16(44.4%)		
Gait disorder	14(38.9%)		
muscle weakness	9(25.0%)		
hypersomnia	4(11.1%)		
fever	3(8.3%)		
convulsion	1(2.8%)		
*The P value of the mean volume of "Supratentorial (hemisphere) tumors" and "infratentorial tumors" is 0.015.			

Table 2  
Surgical outcomes of 32 cases of GPIT

Variable	Cases(percentage)
Age groups	
<1 year	3(9.4%)
1–5 year	18(56.3%)
5–10 year	9(28.1%)
10–15 year	2(6.3%)
Sex	
Males	23(71.9%)
Females	9(28.1%)
Preoperative Hydrocephalus	
With	28(87.5%)
Without	4(12.5%)
Histological features	
Medulloblastoma(WHO I)	12(37.5%)
Ependymoma(WHO II-IV)	6(18.8%)
Pilocytic astrocytoma (WHO I)	5(15.6%)
Atypical teratoid rhabdoid tumor (WHO IV)	2(6.3%)
Choroid plexus carcinoma (WHO III)	1(3.1%)
Choroid plexus papilloma (WHO I)	1(3.1%)
Oligodendroglioma (WHO II-III)	1(3.1%)
Primitive neuroectoderm tumor (WHO IV)*	1(3.1%)
Craniopharyngioma (WHO I)	1(3.1%)
Immature teratoma	1(3.1%)
Yolk sac tumor	1(3.1%)
Surgical condition	
Gross Total resection	28(87.5%)

\*. This case was before WHO removed the “Primitive neuroectoderm tumor” in new classification system in 2017.

Variable	Cases(percentage)
Subtotal resection	4(12.5%)
Complication	
Subcutaneous effusion	5(15.6%)
Infection	2(6.3%)
Pneumocrania	1(3.1%)
Mild dyskinesia	1(3.1%)
Prognosis in 6 month	
Improvement	27(84.3%)
Recurrence	9(28.1%)
*. This case was before WHO removed the “Primitive neuroectoderm tumor” in new classification system in 2017.	

## 4. Discussion

Recently, intracranial tumors have overtaken leukemia as the most common cancer in children aged over 14 years old[1]. GPIT is a challenging type of pediatric intracranial tumors with pessimistic prognosis, which puts forward a higher requirement in management. Previously, a study analyzed pathological features and outcomes of GPIT, and found that microsurgery is an effective way to treat GPIT[2]. Another study shared their management strategies of giant supratentorial tumors in children[4]. However, we cannot acquire the size feature of GPIT in previous researches and there is still a lack in the systematic study of GPITs. As far as we know, this study is the first one to measure and analyze the volume of GPITs, with the experience sharing of the GPIT management including diagnosis, operative strategy and postoperative treatment.

In the past literature, measurements such as length, width and height were often used to describe the size of tumors[5]. However, intracranial tumors from different locations vary dramatically in shape and volume. Thus, it was difficult to compare the sizes of tumors directly. Recently, a prospective study used quantitative sodium MR imaging to calculate cell volume fraction and volume of glioblastoma[6]. Another research got figures of brain tumor volume in rats with multimodal MRI[7]. Our study is retrospective, so we measured the volume of GPITs in this series according to preoperative MR image with 3D model reconstruction in 3D slicer software. With the accurate value of tumor volume, the sizes of GPITs could be described and compared directly. The frequency histogram of tumor volume was shown in Fig. 1. Over time, we found some characters and the connections between the size and the location of GPITs. The average volume of GPITs in this study is 107.5ml, but the majority (22/36, 61.1%) is between 40-80ml. Tumors with volume over 100ml are rare, with only 9 cases (25%), of which 7 cases occurred in cerebral hemispheres, accounting for 58.3% of GPITs in the supratentorial–hemisphere. Other two cases

occurred in suprasellar region and cerebellum. The supratentorial–hemisphere and cerebellum were the most common sites of GPIT, but GPIT in the supratentorial–hemisphere was generally larger in volume than other locations. One possible reason is that the hemisphere has more space for tumor to grow, which may reduce the severity of symptoms and cause delay of diagnosis. Supratentorial tumors also have better prognosis than infratentorial tumors, which may be associated with derivation and pathologic types of tumors. However, because of the deficiency in number of cases, we did not find an exact relationship between tumor volume and histopathology, as well as the tumor volume and prognosis. Further research depends on the establishment of a database of pediatric intracranial tumor with detailed dates including tumor volume.

In histopathology outcomes, medulloblastoma, ependymoma and pilocytic astrocytoma are the most common types in this series, which was similar to the Guo et al.'s research on GPIT's clinicopathological features[2]. However, among statistic researches of pediatric intracranial tumor, the most common ones are pilocytic astrocytoma, glioma malignant (NOS) and embryonal tumors (including medulloblastoma), while ependymal tumors are relatively rare[1, 8, 9]. In GPITs, ependymoma seems to occur more frequently, but high-grade glioma was not seen in this study and Guo et al. 's. This indicates that GPITs have certain particularity in histopathology. Different types of tumors show diverse biological characteristics in the origin location, growth speed and metastasis, leading to the difference in the size of tumors at the time of diagnosis. In high-grade malignant pathological types like AT/RT, CPC and PENT in GPIT, tumors grow and transfer rapidly, their rich blood supply and unclear boundaries also create huge obstacle for surgical treatment, which results in poor prognosis.

The most common symptoms in GPITs of this series are vomiting, headache, gait disorders, muscle weakness and hypersomnia, which are similar to intracranial tumors. However, since infants' ability to express feelings is not fully developed, the early symptoms are difficult to be noticed by their guardians or might be misdiagnosed as other diseases in primary medical and health care institutions. Consequently, GPITs are diagnosed only after tumors grow further and symptoms aggravate. This may also be the reason why over half of patients in this study are infants under 3 years old. (19 /36, 55.9%) Most intracranial tumors lack blood biomarkers, imaging examination is the basis of diagnosis. Pediatricians should consider central nervous system diseases and perform CT or MR examination for symptoms such as unreasonable crying and vomiting when other diseases were excluded. Besides, economic and social factors are also important factors for the occurrence of GPIT. In this study, 70.6% (24/34) of patients were from rural areas. The relatively lower education level of guardians and weaker medical services delayed the discovery of tumors, and some patients even gave up surgical treatment in this series. Interestingly, the male-to-female ratio is 2:1 in our study, the number of boys dramatically surpass girls. However, though boys have a higher incidence in embryonal tumors[10], the sex difference of the incidence of pediatric brain tumors is not that obvious in other researches[2, 9, 11]. This phenomenon may attribute to "son preference" thought in economic undeveloped regions of China, some parents of GPIT girls in rural areas might have refused further treatment in upper-level hospital.

We adopted different treatment strategies according to the concrete situation of each patient and have achieved a low-mortality rate during the perioperative stage. Hydrocephalus is common in pediatric brain tumors, approximately 70–90% of posterior fossa tumors present with preoperative hydrocephalus[12, 13]. GPIT patients are more likely to have preoperative hydrocephalus because giant tumor blocks the circulation of cerebrospinal fluid. We chose Ommaya reservoir or EVD to manage obstructive hydrocephalus before the surgery for their convenience, high efficiency and low infection rate. Massive bleeding is a cardinal factor in surgery that decides the quality of the operation. Coagulation test would be done before the surgery and we estimate blood loss to prepare for blood transfusion. Researches show that GTR indicates better prognosis with the higher survival rate and lower recurrences rate[14, 15]. However, some GPITs are only feasible to STR on account of restriction of surgical space or adherence to the surrounding structure. We applied microsurgical approach in most of the cases to identify and resect deep tumors. Nevertheless, in a case of pilocytic astrocytoma in suprasellar region, we only achieved STR for unclear border between tumor and brain stem tissue, further resection may be life-threatening or cause nerve dysfunction. Besides, encasement of neurovascular structures in tumors and extensive bleeding in operation is also the significant obstacle preventing GTR. This situation occurred frequently in highly malignant tumors like CPC and AT/RT[16]. A 7-years-old boy was considered to have a choroid plexus tumor in lateral ventricles on MR image (Fig. 2). However, we underestimated the blood supply of tumor and failed to resect whole tumor due to severe bleeding in practice. Relatively small bone windows craniotomy also restricted our operation space. From then on, we enhanced the preoperative evaluation of tumor blood vessels. An 8-years-old girl had a giant ependymoma in left frontal lobe with hemorrhage necrosis and significant calcification, and the tumor volume was 255.8 cm<sup>3</sup> (Fig. 3). We performed CT angiography before the surgery to confirm the blood supply of tumor. In surgery, we cut off the main blood vessels of the tumor and successfully removed the entire tumor with minimal blood loss. With continuous efforts and improvement of surgical skills, we achieved GTR in 87.5% (28/32) of patients in this series.

Surgical treatment for infants under 3 years old is the most difficult part in GPITs. Owing to their weak physical function and immature immune system, the surgery itself was a challenge for them, the probability of postoperative infection is also significantly higher than that of older children. Besides, radiation therapy is the contraindication for infants. Our strategy is that complete resect the tumor as far as possible and combine it with postoperative chemotherapy. In this series, 18 infants received the surgery, 72.2% (13/18) got improvement in 6 months. Unfortunately, the case of immature teratoma, which is also the biggest tumor in this study, died of excessive bleeding in the surgery. 4 cases recurred and 2 cases including CPC and AT/RT therein died in one year. The prognosis of the high-grade malignant tumors is poor, but to some extent, surgical treatment can extend survival time and strive time for the following treatment. Some surgeons remove some GPITs in twice with different craniotomy approaches[17], yet we assumed that a staged operation may increase the risk of operation-related complication and it might be meaningless in highly malignant tumors. New experimental treatment including molecular targeted therapy, gene therapy, autologous stem cell transplantation combined with

chemotherapy and so on have shown certain benefit on highly malignant tumors in recent research[18–20], which forebode a bright future.

## 5. Conclusion

Volume measurement based on MR is a novel and effective approach to access and compare size of GPITs for retrospective study. Medulloblastoma is the most common GPITs in our study and supratentorial–hemisphere held the biggest mean volume of GPITs. Surgical resection could evidently improve the prognosis of benign and low-grade GPITs, though its effect is still insufficient in high-grade malignant GPITs including CPC, PNET and AT/RT.

## Declarations

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### Data Availability Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

### Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

### Author Contribution

All authors contributed to the study conception and design. Material preparation and data collection were performed by Zhongding Zhang, Huangyi Fang, Chen Pang and Yue Yang. Date analysis were performed by Zhongding Zhang, Xiepan Jing, Lingli Zhou and Guanghui Bai. The first draft of the manuscript was written by Zhongding Zhang and Hansong Sheng. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

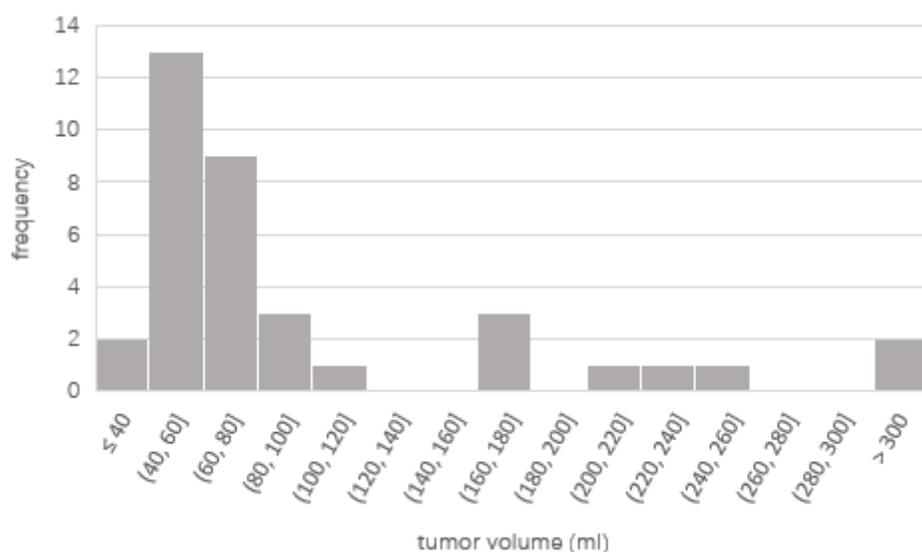
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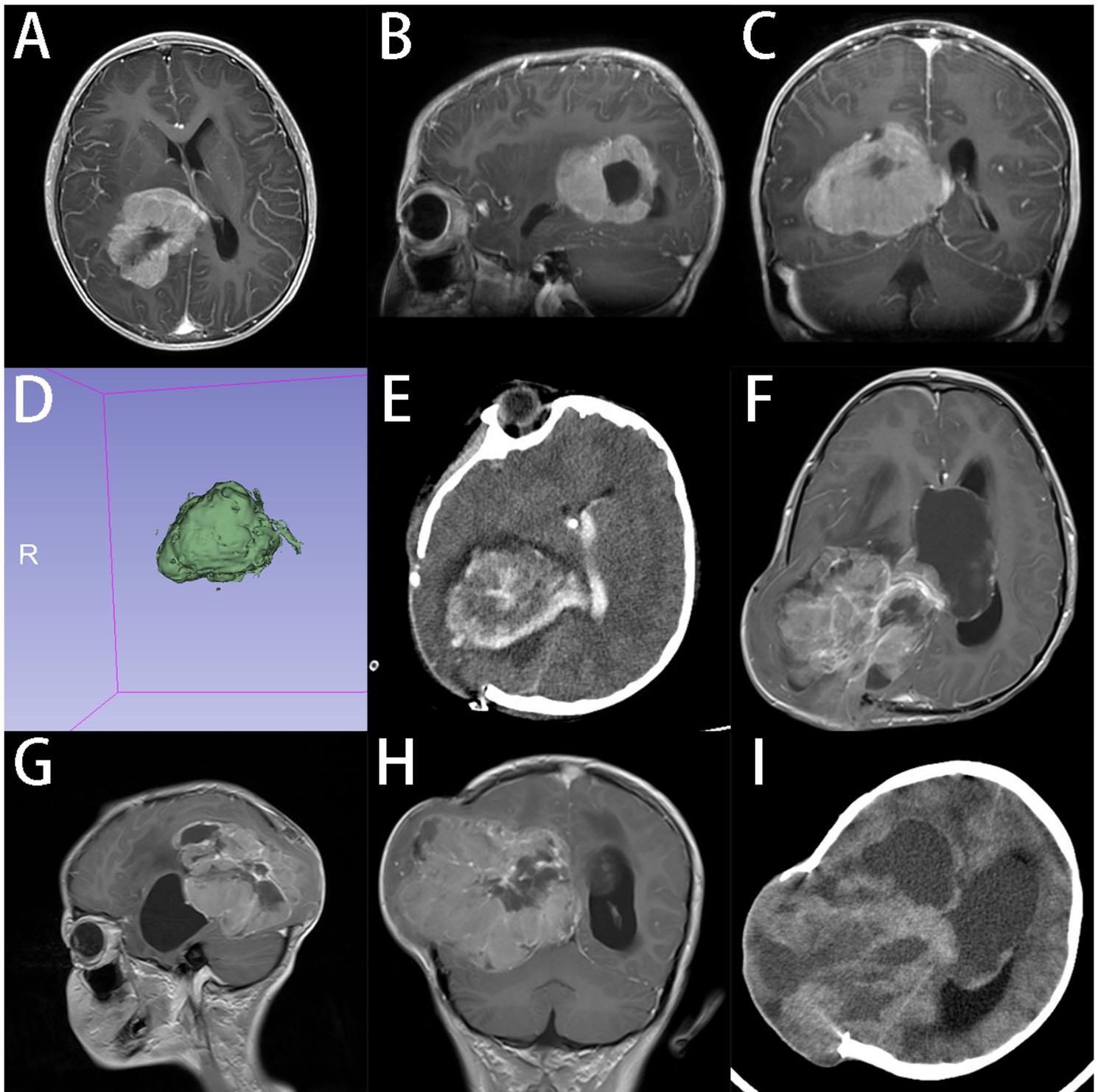
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## Figures



**Figure 1**

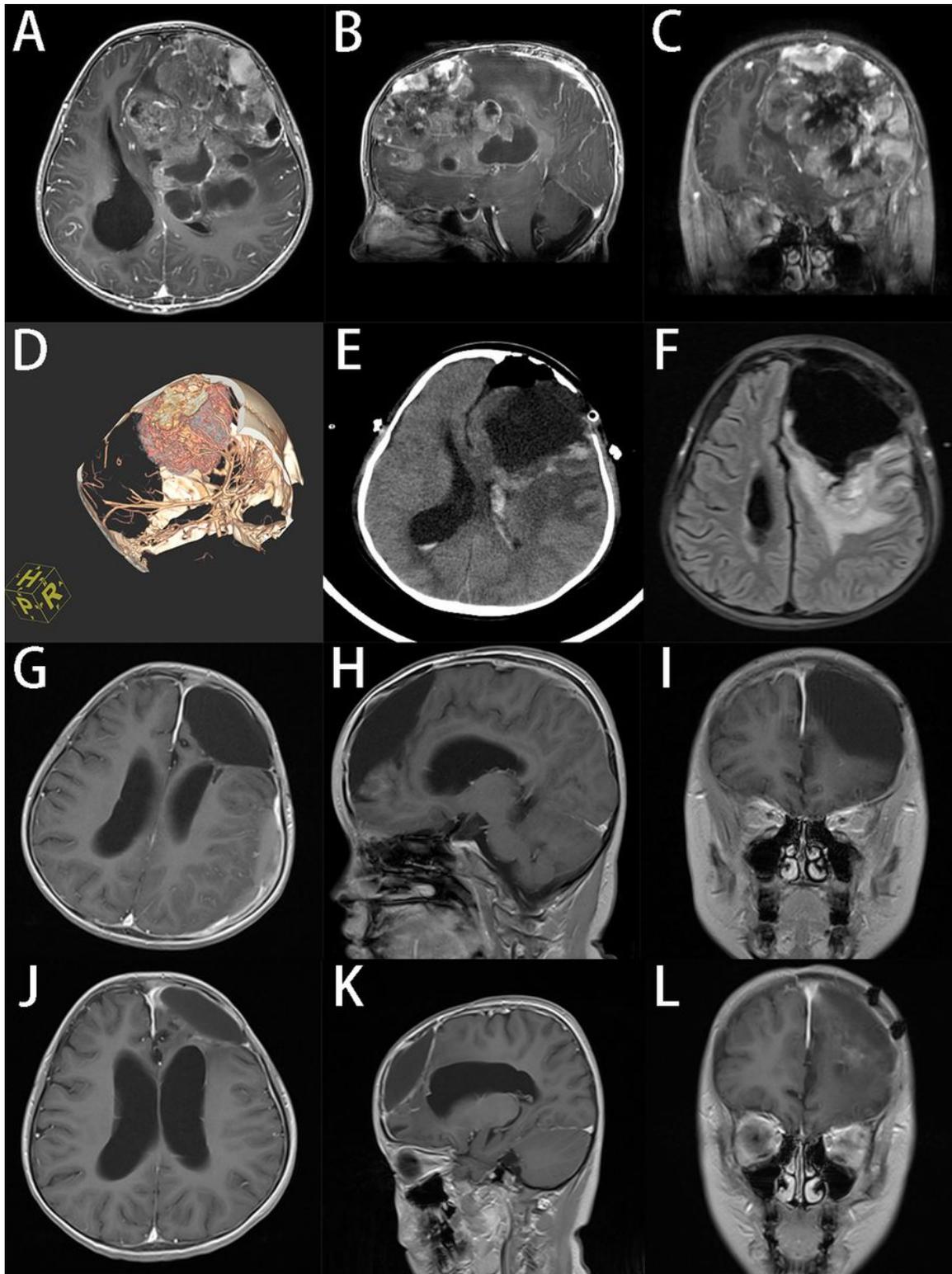
The frequency histogram of tumor volume



**Figure 2**

A 7-years-old boy with CPC in lateral ventricles a-c. preoperative axial, sagittal and coronal gadolinium-enhanced T1-weighted MRI scan shows an inhomogeneous tumor with partial cystic changes in right lateral ventricle. d. 3D model reconstruction of the tumor, the volume of tumor is 70.4 cm<sup>3</sup> e. CT shows that tumor was partially removed at 24 h after operation. Guardians reject the advice of secondary surgery after radiation and chemotherapy. f-h. axial, sagittal and coronal enhanced T1-weighted MRI scan

indicates that tumor recurred at 3 months after operation. i. CT at 4 months after operation, tumor grew further and the condition of patient got worse. Patient died at 5 months after operation.



**Figure 3**

An 8-years-old girl with a giant ependymoma in left frontal lobe a-c. preoperative axial, sagittal and coronal gadolinium-enhanced T1-weighted MRI scan shows an inhomogeneous enhanced tumor with hemorrhage necrosis and calcification. d. 3D reconstruction of CT angiography. e. Postoperative CT in

24h after operation f. Axial MR at 7d after operation g-i. axial, sagittal and coronal T1-weighted MRI scan indicates that the tumor was totally removed at 3 months after operation. j-l. axial, sagittal and coronal T1-weighted MRI scan at 6 months after operation, the residual cavity of tumor reduced.