Infra-Tentorial Brain Tumors – Biological Behavior during First Post-Operative Year – SKIMS, Kashmir Experience

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Research

Keywords: Biological Behavior, Infra-tentorial Tumors, First post-operative Year

Posted Date: June 25th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-35498/v1

Abstract

Background: To observe the biological behavior like residual disease, progression, recurrence, disabilities, mortality, event free survival (EFS) etc., of histologically different infra-tentorial tumors of in the first postoperative year.

Methods: The histopathological records of 410 infra-tentorial tumors out of 589 patients were compared with their clinical outcome up to first postoperative-year in a single-centre, amounting to regional epidemiological-value. In this observational study, retrospectively postoperative records of 589 infra-tentorial tumors of brain from Nov., 1990 to Dec., 2010 (20 years) were retrieved, scrutinized and compiled. The post-operative records of 410 patients with proved histopathological-examination results were included. Statistical law of Variance was applied where-ever necessary.

Results: The 63.2% of 410 operated infra-tentorial tumors were males while females predominated in meningiomas and pineoblastomas. About 31.7% infra-tentorial or posterior fossa tumours were children (below-18yrs.). About 54.1% cases were histologically malignant. The residual-tumors comprised 40.2% and symptoms of disease-progression occurred in 10.9%. The tumor recurrence occurred in 14.3% while 6.0% patients developed severe-disability. The overall mortality was 11.4% up to first post-operative year with 18.9% in malignant patients. The first-one-year event-free-survival (EFS) for all the patients was 66.0%. While the patients with malignancies had first-one-year EFS of 47.7%, the histologically benign group had 87.7%.

Conclusion: The first one-year postoperative biological behavior like EFS of histologically benign and some malignant infra-tentorial tumors both in children and adults like pilocytic astrocytomas, ependymomas and pineoblastomas was much better (87.7%) than other malignant infra-tentorial tumors.

Background

The triad of anatomically tight-spaced infra-tentorial intra-cranial-space or posterior fossa of brain, presence of biologically active tumor and obstructive hydrocephalus are the predictors of the worse outcome in the infra-tentorial space tumors. The infra-tentorial space of the cranial cavity, limited by the tentorium above, also called posterior fossa, has much smaller space than the rest of the cranial cavity. However the contents of such a comparably small space are several types of motor and sensory tracts and a number of vital nuclei and reticular formation for the systemic body functions and consciousness in the form of midbrain, pons and medulla. Also packed are cranial nerves, vascular network with large venous sinuses, changing volume of CSF in the ventricle and cisterns and prominently visible cerebellar parenchyma with nuclei and peduncles. Most of the times, the infra-tentorial space or the posterior fossa tumors present themselves as an acute emergencies following the compression of the brainstem either due to the increase in tumor size, edema, bleed or obstruction to CSF pathways and herniation. The surgical debulking, to relieve the pressure on the brainstem, though full of risks, is indispensable mode of management. However in such a small space, the intra-operative complications and postoperative disease progression owing to residual or recurrence of the lesion worsens the surgical outcome. In 1930 an account of 61 patients of infra-tentorial space tumors of brain was published by the most cherished neurosurgeon of the world, Cushing H, claiming fatal outcome in almost all [1]. The present study outlines the biological behavior of different histologically subtypes in the first postoperative year.

Materials And Methods

Literally of epidemiological value, this observational study took into account the records of those patients who were treated in the past and did not need to identify themselves to the researchers. Since the study was mainly compilation of surgical and histopathological records wherein neither IRB/Ethical approval nor patient consent was required, it provided an epidemiological data about the disease and a particular population because the population group is mainly ethnic and non-migratory. It benefited medical and community health census directly. It was conducted on all operated patients of infra-tentorial space tumors of brain admitted from Nov., 1990 to Dec., 2010 (20 years) in the division of Neurosurgery. The neurosurgical patients are managed with a standard and uniform protocol. Retrospectively records of all the 589 patients of infra-tentorial space tumors of brain were retrieved from the files in the Medical Records Department, Operation Theatre Register, Out-patient Department files, referral clinics and follow-up files of the supportive departments like medical and

radiation oncology, pathology etc., of this tertiary healthcare facility. The information about the patient's bio-data, history, examination, basic routine biochemical and hematological investigations, all the imaging (CT, MRI), surgical-procedures, intraoperative (frozen/crush) histopathological reports, final histopathological examination reports, postoperative follow-up notes and imaging records (CT, MRI) up to the first one-year of only 410 patients were available and were included and recorded. The data was analyzed, compiled and conclusions drawn. The statistical law of Variance was applied where ever necessary.

Results

Results of the study revealed a male-predominance of 63.2% (259/410) cases in overall infra-tentorial space tumors with M/F-ratio of 1.7:1.0. (Table 1). About 31.7% (130/410) of all the infra-tentorial space tumors of brain were found in the children (age=18 yrs. & below). The most commonly occurring infra-tentorial space tumors in children were medulloblastomas (Fig. 1), more of a classical variety, 84.7% (61/72). However various tumors like schwannomas 2.9% (3/102) and meningiomas 2.6% (1/38) were uncommonly found in children while metastases not at all. The results revealed that the vestibular schwannoma at the rate of 23.9% (98/410) was the most occurring individual infra-tentorial space tumor. The most common histopathology of the infra-tentorial space tumors was the malignancy occurring in 54.1% (222/410) cases (Table 1 & 2). The medulloblastoma (histologically classical) was the commonest -32.4% (72/222)- malignant infra-tentorial space tumor. The histological types of infra-tentorial space tumors and the one-year postoperative outcome showed significant relation. Comparatively, the histologically benign infra-tentorial space tumors had only 18.6% (35/188) patients left with residual lesions. The symptoms of disease progression were found in 5.1% (5/98) patients of vestibular schwannomas and 14.2% (4/28) hemangioblastomas. The EFS of hemangioblastomas was 85.7% (24/28); dermoids 100% (15/15) and it was 88.8% (8/9) for the patients of epidermoids in the first postoperative year. The postoperative residual tumor on imaging was found in 70.2% (33/47) patients of high grade astrocytomas; 66.6% (6/9) metastatic lesions (Fig. 2); 62.5% (15/24) pilocytic astrocytomas (Fig.3); 43.0% (31/72) patients with medulloblastomas and 41.8% (18/43) ependymomas (Fig. 4). The highest tumor recurrences of 100% (4/4) were noted in malignant meningiomas (anaplastic and rhabdoid variants); 56.2% (9/16) in brainstem gliomas (Fig. 5); 55.5% (5/9) in metastatic lesions; 42.8% (3/7) in pineoblastomas (Fig. 6) and 19.4% (14/72) in medulloblastomas. The severe disability was more often seen in the brainstem gliomas owing to their slow growth and long survival, decubitus ulcers and respiratory system infections. However there were no EFS in any case of malignant meningioma, which simultaneously had the highest mortality of 75.0% (3/4). The mortality in metastatic lesions was 66.6% (6/9); brainstem gliomas 43.7% (7/16) and medulloblastomas had 30.5% (22/72) mortality. There was no mortality found in pinealoblastomas and pilocytic astrocytomas, although in a postoperative-year ependymomas had a lower mortality of 6.9% (3/43) and high-grade astrocytomas 2.1% (1/47).

Discussion

The present study on the biological behavior of infra-tentorial space brain tumors in the first postoperative year observed that 31.7% patients were children (18 yrs. & below). Histopathologically, malignancy featured in most, (54.1%), of the patients while benign tumors occurred in 45.8% patients (Table1 & 2). A research study in 1997 revealed that out of the 1000 vestibular schwannoma tumors operated in 962 patients, 2.1% patients had residual tumors; 1.1% patients had severe neurological disability; 5.5% patients had caudal cranial nerve palsies and 1.1% had mortality [2]. Seol et.al, in 2006 analyzed 116 patients of vestibular schwannomas where residual tumor was seen in 77.5% and the recurrence in 17.2%. The gross total resection was the best approach to avoid the recurrence [3]. Yamakami et.al, in 2004 revealed 14% residual tumor, 4% neurodeficit and no mortality in 50 operated patients of vestibular schwannomas [4]. The present study observed 50% residual tumors in trigeminal schwannomas and 23.4% in vestibular schwannomas. About 2.9% schwannomas were found in children. Roberti et.al, 2001, wrote that a hundred and sixty one patients of infra-tentorial space meningiomas were operated over a period of 9 years with residual tumors found in 43% patients; progression of disease and recurrence in 13.7% and mortality was found in 2.5% patients [5]. The researchers in 2012 showed postoperative results of 64 patients of infra-tentorial space meningiomas, where recurrence occurred in 15.6% patients, severe neurological deficits in 33%, hydrocephalus in 43.75% patients and

mortality in 3.2% [6]. Hakuba et.al, reported 17% mortality and severe neurological deficits in 83% patients in radical excision of clival meningiomas of infra-tentorial space [7]. Couldwell et.al, studied 40 males and 69 females, a male female ratio of 1:1.7, with infra-tentorial space (petro-clival) meningiomas postoperatively in which gross total excision was achieved in 69% of the patients, 13% had recurrence or progression of disease [8]. Louis et.al, reported a 5-year progression- free survival of approximately 50% [9]. The present analysis showed almost similar results. Hemangioblastomas are uncommon highly vascular, well-circumscibed, less than 3% of all CNS tumors, mostly (7.5%) in adult cerebellum and brainstem [10]. The present study found an incidence of 6.8% for hemangioblastomas, including two sisters in a family. Research found an Event Free Survival (EFS) of 85.7% in the first-postoperative year. Dermoid cysts represent a rare clinical entity that accounts for 0.1-0.7% of all brain tumors [11]. This study observed that the dermoids comprised 3.6% of all the infra-tentorial space tumors of the brain. The EFS of dermoids was 100% in the first postoperative year. Epidermoids, also known as cholesteatomas, are pearly tumors and account for approximately 0.1% of all intracranial tumors growing by the desquamation of the cyst wall and accumulation of keratin and cholesterol [12]. Zakrzewski et.al, studied 216 children with infra-tentorial space tumors below 18th year of age, which depicted male/female ratio of 1.35:1.00. The commonest tumor was pilocytic astrocytoma - 41.5%; medulloblastoma - 34.5%; ependymomas - 13% and mixed neuronal-glial tumors - 5.5% [13]. Muzmdar D et.al, in 2011, presented 154 patients (age<18 years) of Medulloblastoma (Fig. 1) noting 92.2% (142 cases) had classical medulloblastoma, 5.1% (8 cases) had desmoplastic variant. The 5-year and 10-year progression free survival rate was 73% and 41% respectively for average risk disease while for high risk disease, it was 34% [14]. Rutka 1997 noted that medulloblastomas are intracranial childhood neoplasm, accounting for 25% of all childhood tumors [15]. Also Bloom & Bessell in 1990 showed that medulloblastomas in adults account for < 1% of all adult brain tumors [16]. Chan et.al, in 2000 found in a study that the recurrence rate for medulloblastomas in adults is approximately 50% to 60%. The median time-to-tumor progression (TTP) and recurrence is approximately 30 months after treatment [17]. In present study medulloblastomas (Fig. 4 & 5) were found in 17.5% patients mostly (84.7%) in children. The postoperative residual tumor was found in 43.0% and recurrence in 19.4%. A mortality of 30.5% occurred in the first-postoperative year. Djalilian and Hall (1998) reported that 53% patients in a study had grade IV malignant cerebellar gliomas and 47% had anaplastic grade III astrocytomas [18]. The present study observed that 11.4% infra-tentorial space tumorss had high-grade anaplastic and glioblastoma type of malignant cerebellar astrocytomas. The postoperative residual tumor was found in 70.2% and a EFS of 31.9% in first-postoperative year was observed with a mortality of 2.1%. Witt et.al, 2011 reported that the posterior fossa ependymomas comprise two distinct molecular entities, ependymoma posterior fossa A (EPN PFA) and ependymoma posterior fossa B (EPN PFB), with differentiable gene expression profiles [19]. In present study ependymoma of the 4th ventricle (Fig. 4) had residual tumors in 41.8% and recurrence in 11.6%. The EFS of 51.1% and a mortality of 6.9% were found in first postoperative-year. Desai et.al, 2001, reported that the pilocytic cerebellar astrocytomas comprise 25% of all infra-tentorial space tumors in children [20]. Following up 104 children with cerebellar juvenile pilocytic astrocytomas (Fig. 3) over a mean period of 8.3 years, Daszkiewicz et.al, 2009, found that 57.6% (60/104) patients had permanent neurological deficits while 47 had significant behavioral disorders [21]. A study by Lesniak et.al 2003 observed that among 57 patients of brainstem gliomas, 29 had a total surgical resection, 8 a near total resection (>90%), 15 a subtotal resection (50-90%) and 5 a partial resection (<50%). The progression-free survival of all patients was 71.9% at 3 years and 45.6% at 5 years [22]. Donalson et.al, 2006 reported high rate of recurrence or progression and often follow an inexorable course of progression, despite therapy [23]. All brainstem gliomas in present study had postoperative residual lesions and 37.5% had progression of disease and 56.2% recurrence. The severe disability in the brainstem gliomas, like pontine gliomas (Fig. 5), in present study, was more often linked to the long survival, motor dysfunction, decubitus ulcers and respiratory system infections caused by the early involvement of lower cranial nerves and the long tracts by these low-grade tumors. These had a mortality of 43.7% and an EFS of 31.2%. Sunderland et.al, 2016 reported that overall 80% patients underwent gross total resection (GTR), 14 % subtotal resection (STR) and 6 % underwent biopsy of metastatic infra-tentorial space contents (Fig. 1). The median overall survival (OS) was 6.00 months. The 28 day mortality was 7.6 % (n = 7) with a peri-operative morbidity of 22.8 % (n = 21) [24]. Zhang et.al, 2012 observed that the most common primary site of malignancy for brain metastasis was lung (20–40 %) followed by breast (5–17 %) and melanoma (7–11 %) with renal, colorectal and gynecological cancers making up the majority of the remaining [25]. The present series of 410 infra-tentorial space brain tumors also consisted of 2.1% patients of metastatic deposits, mostly from primaries like carcinoma lung, carcinoma breast, renal cell carcinoma and malignant melanoma. Tate et.al., in 2012 suggested an increase in survival of pineoblastomas (Fig.

6) with increasing degrees of resection by observing 5-year survival rate of 84% for patients who underwent gross total resection versus 53% for patients who underwent subtotal resection and 29% for patients who underwent debulking [26]. Pineoblastomas in this study comprised 1.7% of all infra-tentorial space tumors while 57.1% of these were children. Roberti et.al., 2001 reported 5% malignant meningiomas in a study of 161 patients [5]. However, Wang et.al. 2016, reported that about 51% patients experienced recurrences. The relapse free survival at 12 months was 84.3% and at 5 years was 57.8% [27]. Of 410 infra-tentorial space brain tumors presently, 0.97% had malignant meningiomas (WHO grade-III), mostly rhabdoid and anaplastic, which formed 10.6% of all infra-tentorial space tumors with a recurrence of 100% and mortality of 75.0%.

Conclusion

The present study of biological behavior of infra-tentorial space tumors during fist postoperative year in children and adults in an ethnic population is of the value of regional epidemiology value. Given the aggressive biological behavior, the histologically proven malignant lesions in infra-tentorial space have all the opportunities to harm the vitality of infra-tentorial space structures and lead to catastrophic outcome pre, intra and postoperatively.

Declarations

Disclosure of Funds: There is nothing to disclose about the funding. No funds used for the study.

No author of this study had any financial support from anywhere and there is no industrial affiliation of any author, no grants and no interest whatsoever.

Conflict of Interest None

Acknowledgements We thank Aisha, Huwa, Nancy, Moaji, Saimy, Roh-ul, Adam and Maqbool Kashmiri for their sincere help and sincerity

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Tables

Table 1: Biological Outcome in First Postoperative Year related to sex and age in Infra-Tentorial Space Tumors

S.No.	Histopathological Type/Site	No. of Patients	Males	Females	Children(18yrs & Below)	Postoperative		
						Residual Lesion /Dis. Prog.	Recurrence	Mortality
1.	**Schwannomas**	**102**	**63**	**39**	**03**	**25/06**	**12**	**04**
	i).Vestibular(CP Angle)	*98*	60	38	03	23/05	11	04
	ii).Trigeminal	*04*	03	01	-	02/01	01	-
2.	**Meningiomas:**	**38***	**16**	**22**	**01**	**10/03**	**05**	**03**
	i).Cerebellar Cortex & Tent.	*16*	05	11	01	-	-	-
	ii). Cerebello-pontine angle	*12*	05	07	-	05	-	-
	iii).Foramen Magnum	*07*	03	04	-	04/02	04	02
	iv).Peri-torcular	*02*	02	-	-	-	-	-
	v).Jugular Foramen	*01*	01	-	-	01/01	01	01
3.	**Hemangioblastomas**	**28**	**15**	**13**	**01**	**04/04**	**04**	**-**
4.	**Dermoids**	**15**	**09**	**06**	**04**	-	-	-
5.	**Epidermoids**	**09**	**06**	**03**	**03**	-	-	**01**
6.	**Medulloblastomas**	**72**	**53**	**19**	**61**	**31/12**	**14**	**22**
	i).Classical	*53*	42	11	51	19/07	07	15
	ii).DesmoplasticVariant	*11*	08	03	04	07/01	01	01
	iii).Anaplastic Changes	*05*	03	02	04	03/03	05	05
	iv).Glial Differentiation	*03*	01	02	02	02/01	01	01
7.	**C. Astrocytomas(HG)**	**47**	**32**	**15**	**12**	**33/01**	**02**	**01**
8.	**Ependymomas**	**43**	**29**	**14**	**09**	**18/05**	**05**	**03**
9.	**C. Pilocytic Astrocyto.**	**24**	**18**	**06**	**20**	**15**	**-**	**-**
10.	**Brainstem Gliomas:**	**16**	**11**	**05**	**12**	**16/06**	**09**	**07**
	i). J. Pilocytic Asstrocytoma	*05*	03	02	05	05/01	02	01
	ii). Glioblstoma Multiforme	*04*	03	01	01	04/03	04	04
	iii). Fibrillary Astrocytomas	*03*	01	02	03	03/01	01	-
	iv). Gangliogliomas	*02*	02	-	02	02	-	-
	v). Oligodendrogliomas	*01*	01	-	01	01	01	01
	vi). Primitive Neuroectodermal Tumor	*01*	01	-	-	01/01	01	01
11.	**Metastatic**							

	Posterior Fossa	**09**	**05**	**04**	**-**	**06/05**	**05**	**06**
	i). Carcinoma Lung	*03*	03	-	**-**	02/02	02	03
	ii). Carcinoma Breast	*03*	-	03	**-**	01/01	01	02
	iii). Renal Cell carcinoma	*02*	01	01	**-**	02/01	01	-
	iv). Malignant Melanoma	*01*	01	-	**-**	01/01	01	01
12.	**Pineoblastomas**	**07**	**02**	**05**	**04**	**07/03**	**03**	**-**
Total	**Posterior Fossa Tumors**	**410** (100%)	**259** (63.2%)	**151** (36.8%)	**130** (31.7%)	**165**(40.2%) **/45**(10.9%)	**59** (14.3%)	**47** (11.4%)

38* =4 out of 38 Meningiomas were malignant (WHO Grade-III); Postop.=Postoperative; HG=High Grade (III-anaplastic & IV-glioblastoma multiforme); C= Cerebellar; Astrocyto=Astrocytomas; J.=Juvenile; Tent.= Tentorial; Dis. Prog.=Disease Progression; CP=CerebelloPontine.

Table 2: Biological Behavior in First postoperative Year related to Histopathological Subtypes of Tumors in the Infra-tentorial Space of Cranial Cavity.

S. No.	Histological Types	No. of Patients	Postoperative Outcome					
			Residual Lesion	Symptoms of Disease Progression	Recurr.	Sev. Dis.	EFS	Mort.
Benign Lesions		**188**	**35**	**10**	**17**	**09**	**165**	**05**
1.	Vestibular (CP Angle) Schwannomas	98	23	05	11	06	85	04
2.	Trigeminal Schwannomas	04	02	01	01	0	03	0
3.	Meningiomas(Grade I,II)	34	06	0	01	03	30	0
	(i)Meningotheliomatous	*18*	*0*	*0*	*0*	*01*	*17*	*0*
	(ii)Fibrous	*6*	*1*	*0*	*0*	*0*	*06*	*0*
	(iiiTtransitional	*3*	*1*	*0*	*0*	*01*	*02*	*0*
	(iv)Psammomatous	*2*	*0*	*0*	*0*	*0*	*02*	*0*
	(v)Atypical	*2*	*2*	*0*	*01*	*01*	*00*	*0*
	(vi)Angiomatous	*1*	*1*	*0*	*0*	*0*	*01*	*0*
	(vii)Secretory	*1*	*1*	*0*	*0*	*0*	*01*	*0*
	(viii)Microcystic	*1*	*0*	*0*	*0*	*0*	*01*	*0*
4.	Hemangioblastomas	28	04	04	04	0	24	0
5.	Dermoids	15	0	0	0	0	15	0
6.	Epidermoids	09	0	0	0	0	08	01
Malignant Lesions		**222**	**130**	**35**	**42**	**16**	**106**	**42**
1.	Medulloblastomas	72	31	12	14	07	40	22
2.	C. Astrocytomas(HG)	47	33	01	02	02	15	01
3.	Ependymomas	43	18	05	05	04	22	03
4.	C. Pilocytic Astrocyto.	24	15	0	0	0	18	0
5.	Brainstem Gliomas	16	16	06	09	03	05	07
6.	Metastatic Lesions	09	06	05	05	0	02	06
7.	Pineoblastomas	07	07	03	03	0	04	0
8.	Meningiomas(Grade III)	04	04	03	04	0	0	03
	(i)Anaplastic	*03*	*03*	*03*	*03*	*0*	*0*	
	(ii)Rhabdoid	*01*	*01*	*0*	*01*	*0*	*0*	*03*
								0
Total	**Posterior Fossa Lesion**	**410**	**165**	**45**	**59**	**25**	**271**	

Recurr. =Recurrence; Sev. Dis.= Severe Disability; EFS= Event Free Survival; Mort.= Mortality;

CP= Cerebello-Pontine; C=Cerebellar; Astrocyto= Astrocytomas; HG= High Grade (III-anaplastic & IV-glioblastoma); Grade I, II, III= WHO Grades

Figures

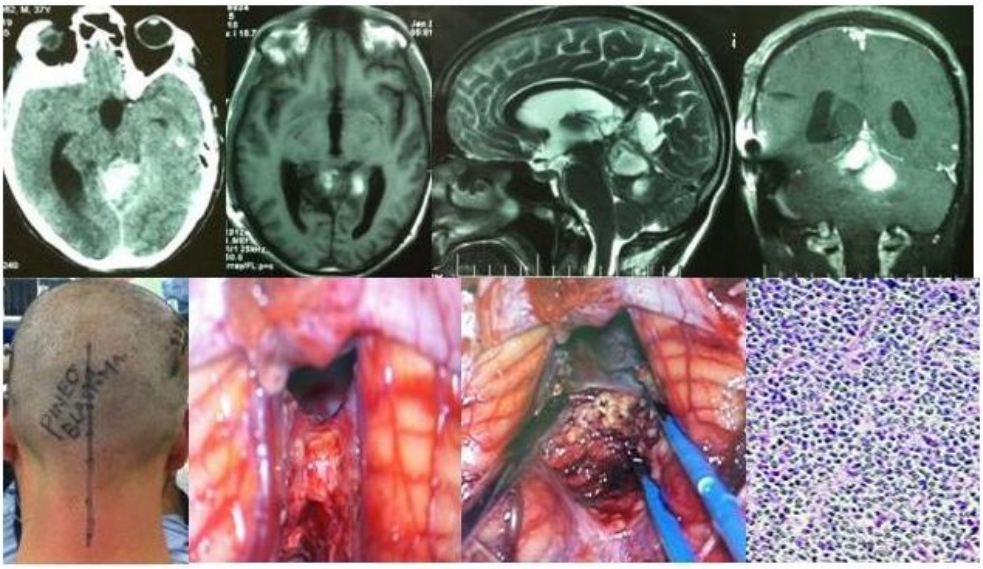

Figure 1

A case of pineoblastoma showing CT scan, MR images and intra-operative photos in sitting position. Photomicrograph reveals pineoblastoma cells on a fibrillar network (H & E Stain; 300X).

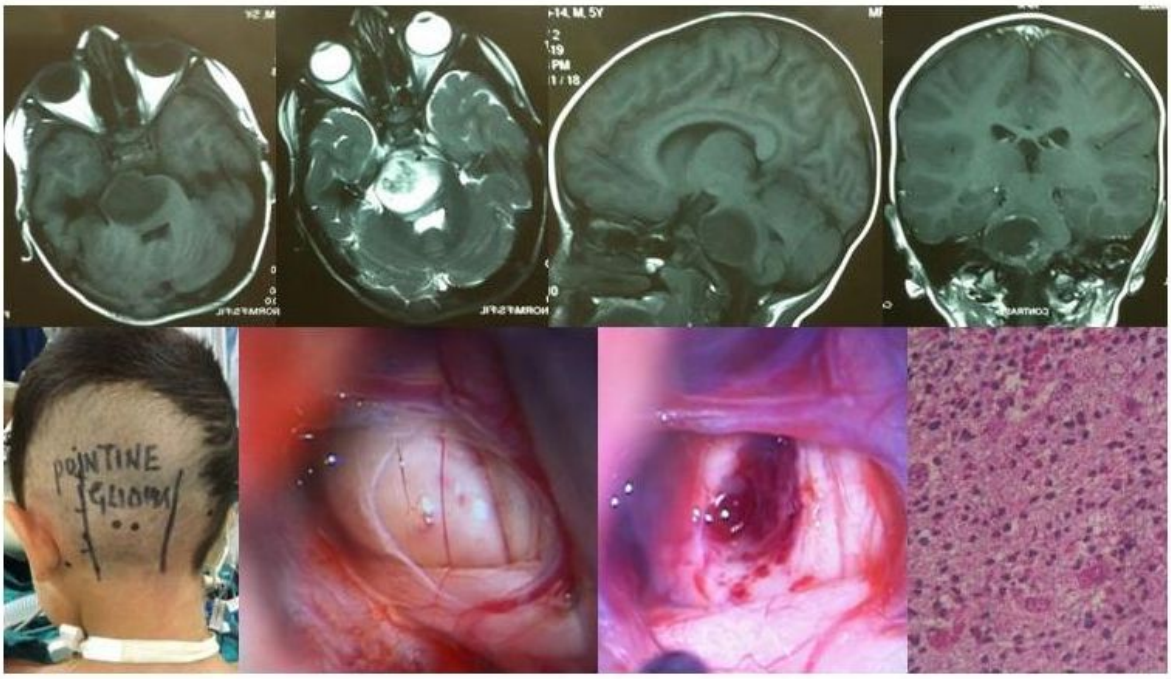

Figure 2

Pontine-Glioma Grade-III in a 5 yr. male child. MR images and intra-operative micro-photographs and clinical photo in sitting position display left retro-mastoid approach and tumor decompression. Histological micrograph (H & E Stain; X40) is seen.

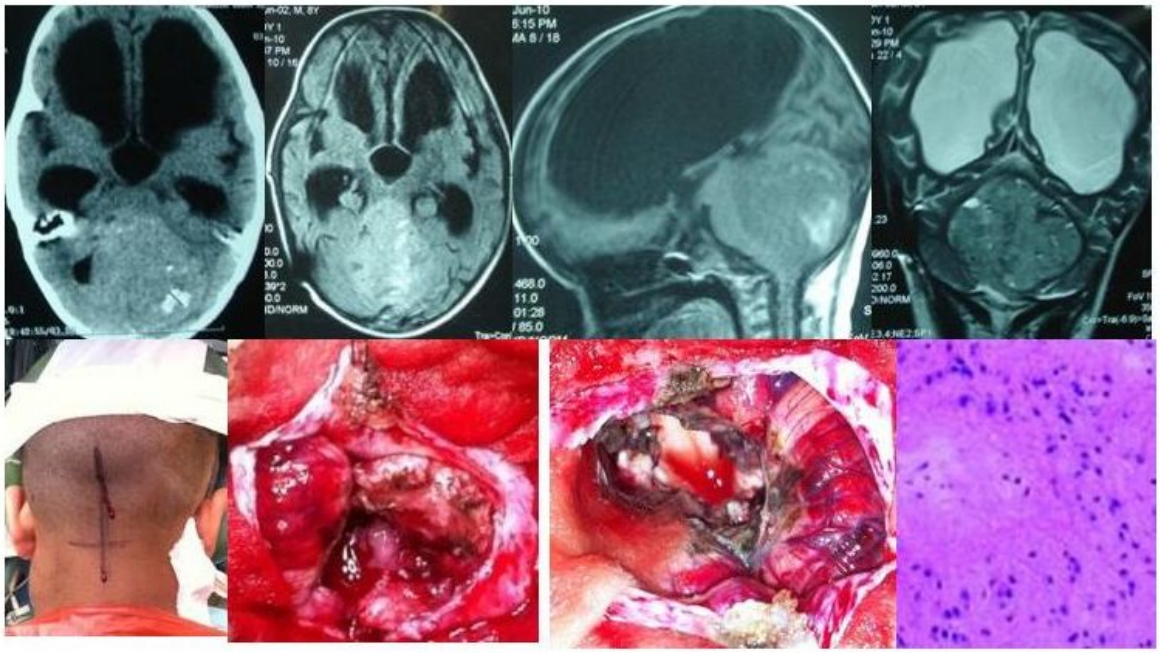

Figure 3

CT, MR and intra-operative images (sitting position) of a child with 4th Ventricular Ependymoma. CT scan depicts calcifications in the lesion. Histological micrograph shows WHO grade-II tumor (H&E; 40X).

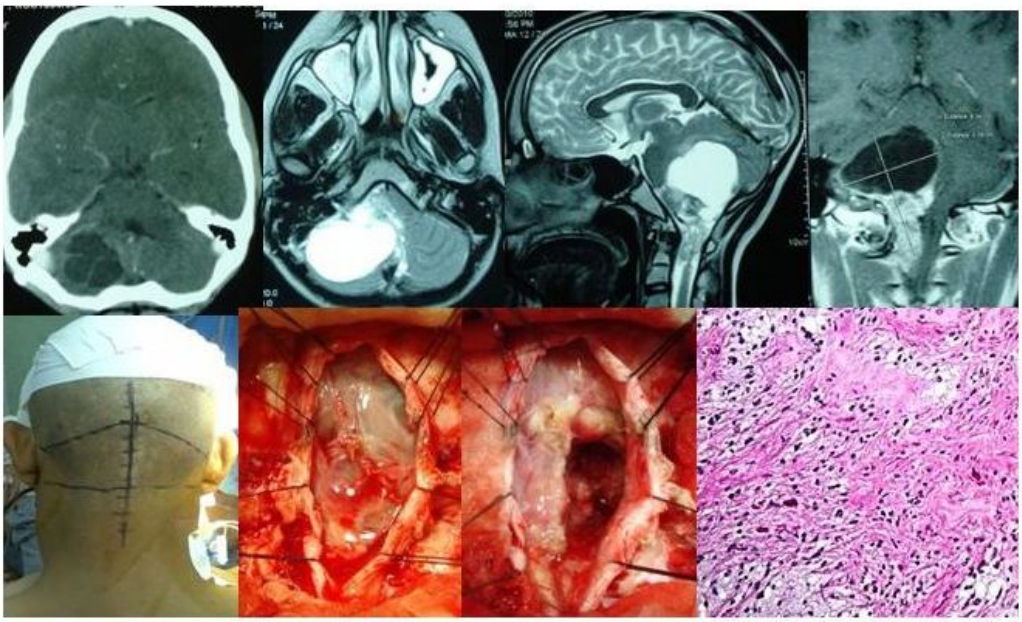

Figure 4

Pilocytic Astrocytoma Cerebellum is depicted by the CT scan, MR images and intra-operative photographs in sitting position. The histological microphotograph shows cerebellar pilocytic astrocytoma (Hematoxylin & Eosin X200).

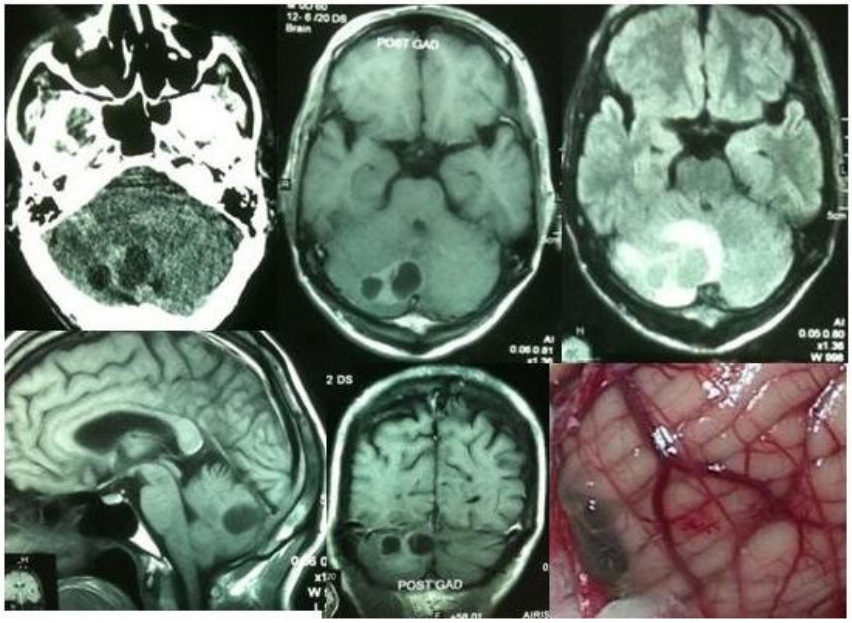

Figure 5

Metastatic lesion in right cerebellar lobe revealed on CT, MR and intra-operative images.

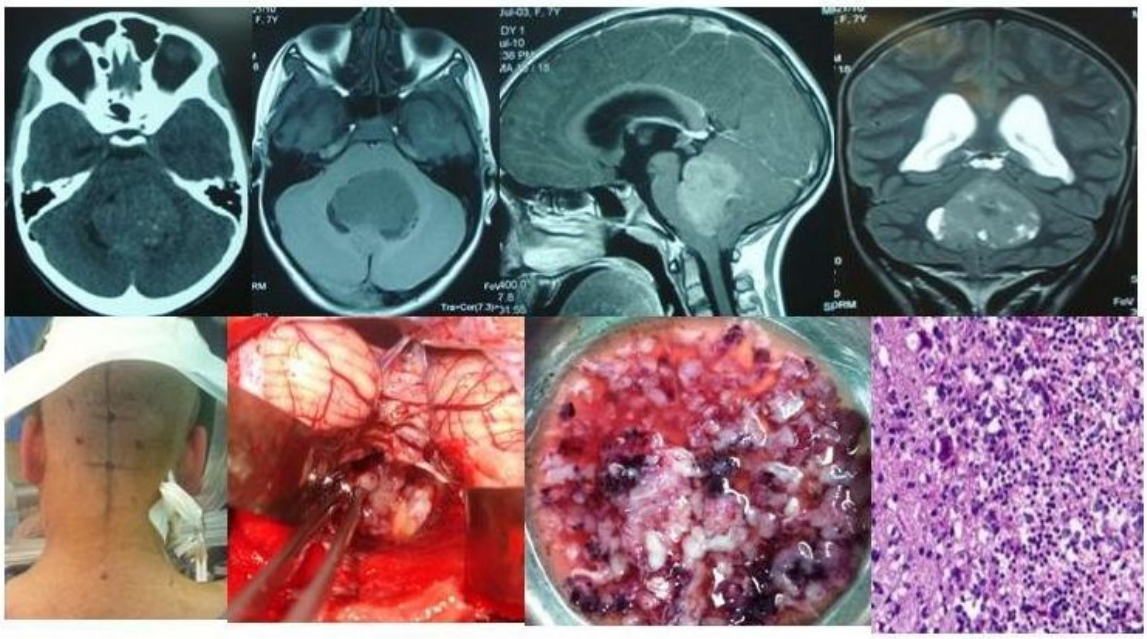

Figure 6

CT scan and MR images of Medulloblastoma in a child showing intra-operative images in sitting position. Microphotograph (H&E; 20X).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 1.FirstPageFileBiologyITST.docx