

## Outcome of Adult and Pediatric Posterior Fossa Tumors Linked with Histopathological subtypes - Observations of Two Decades

Abdul Rashid Bhat<sup>1\*</sup>, Muhammed Afzal Wani<sup>2</sup> and Altaf Rehman Kirmani<sup>1</sup>

<sup>1</sup>Professor, Department of Neurosurgery, SKIMS Srinagar, Kashmir, India

<sup>2</sup>Professor and Head, Department of Neurosurgery, SKIMS Srinagar, Kashmir, India

**\*Corresponding Author:** Abdul Rashid Bhat, Professor and Unit Head, Department of Neurosurgery, SKIMS Srinagar, Kashmir, India.

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### Abstract

**Objectives:** To analyze the link between histopathological-type of posterior fossa tumors (PFTs) and the outcome in children and adults. The postoperative quality and span-of-life in these tumors is complicated by the residual disease, progression, recurrence, disabilities and mortality.

**Materials and Methods:** The histopathological records of 410 PFTs 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 PFTs from November 1990 to December 2010 (20 years) were retrieved, scrutinized and compiled. The post-operative records of 410 patients with proved histopathological-examination results were included. The statistical law of Variance was applied where-ever necessary.

**Results:** The 63.2% of 410 operated PFTs were males while females predominated in meningiomas and pineoblastomas. About 31.7% PFTs 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 EFS of histologically benign and some malignant PFTs both in children and adults like pilocytic astrocytomas, ependymomas and pineoblastomas was much better (87.7%) than other malignant PFTs.

**Keywords:** Outcome; Posterior Fossa Tumours; Histopathological Subtypes; Children-adults

### Introduction

The triad of anatomically tight-spaced posterior fossa, presence of biologically active tumor and obstructive hydrocephalus are the predictors of the worse outcome in PFTs. The posterior fossa of the cranial cavity, limited by the tentorium above, also called

infra-tentorial space, 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 func-

tions 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 posterior fossa tumors (PFTs) 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 posterior fossa tumors was published by the most cherished neurosurgeon of the world, Cushing H, claiming fatal outcome in almost all [1]. The present study emphasizes the significance of histological identification to the surgical outcome.

## 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 mountain locked, ethnic, non-migratory. It benefited medical and community health census directly. It was conducted on all operated patients of PFTs admitted from November, 1990 to December, 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 PFTs 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 included and recorded. The data was analyzed, com-

pared and conclusions drawn. The statistical law of Variance was applied wherever necessary.

## Results

Results of the study revealed a male-predominance of 63.2% (259/410) cases in overall posterior fossa tumors with M/F-ratio of 1.7:1.0. (Table 1). About 31.7% (130/410) of all the PFTs were found in the children (age = 18 yrs and below). The most commonly occurring PFTs in children were medulloblastomas (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 (Figure 1) at the rate of 23.9% (98/410) was the most occurring individual posterior fossa tumor (PFT). The most common histopathology of the posterior fossa tumors was the malignancy occurring in 54.1% (222/410) cases (Table 1 and 2). The medulloblastoma (histologically classical) was the commonest -32.4% (72/222)-malignant posterior fossa tumor. The histological types of PFTs and the one-year postoperative outcome showed significant relation. Comparatively, the histologically benign PFTs 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 (Figure 2). 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 (Figure 3) 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; 62.5% (15/24) pilocytic astrocytomas; 43.0% (31/72) patients with medulloblastomas (Figure 4 and 5) and 41.8% (18/43) ependymomas (Figure 6). The highest tumor recurrences of 100% (4/4) were noted in malignant meningiomas (anaplastic and rhabdoid variants); 56.2% (9/16) in brainstem gliomas; 55.5% (5/9) in metastatic lesions; 42.8% (3/7) in pineoblastomas and 19.4% (14/72) in medulloblastomas. The severe disability was more often seen in the brainstem gliomas owing to their 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).

**Figure 1:** A patient of left cerebello-pontine angle vestibular schwannoma; Intra-operative photos in sitting position and post-operative axial MRI with histopathological photograph (H & E; 400X).

## Discussion

The present study observed 31.7% patients were children (18 yrs and below). Histopathologically malignancy featured in most, (54.1%), of the patients while benign tumors occurred in 45.8% patients (Table 1 and 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 161 patients of posterior fossa meningiomas were operated over a period of 9 years with residual tumors found

S. No.	Histopathological Type/Site	No. of Patients	Males	Females	Children (18yrs and 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 and 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 Astrocytoma	05	03	02	05	05/01	02	01
	ii). Glioblastoma 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%)

**Table 1:** Histopathology, sex, and postoperative outcome in posterior fossa tumors.

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

S. No.	Histological Types	No. of Patients	Postoperative Outcome					
			Residual Lesion	Symptoms of Disease Pro-gression	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
	(iii) Ttransitional	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	03
	(ii) Rhabdoid	01	01	0	01	0	0	0
Total	Posterior Fossa Lesion	410	165	45	59	25	271	47

**Table 2:** Surgical outcome related to histopathological types of tumors in posterior fossa.

Recurr. = Recurrence; Sev. Dis.= Severe Disability; EFS= Event Free Survival; Mort.= Mortality; CP= Cerebello-Pontine; C=Cerebellar; Astrocyto= Astrocytomas; HG= High Grade (III-anaplastic and IV-glioblastoma); Grade I, II, III= WHO Grades.

**Figure 2:** Two (Sibling) patients of hemangioblastomas; shows Imaging, resected specimen and histological photograph (H & E Stained; 400X). The large serpentine vessel supplying the intra-mural nodule as viewed on MR images, in the lower row, is seen on intra-operative photograph.

**Figure 5:** Adult Medulloblastoma; depicts CT and MR images, intra-operative photographs in sitting position and post-operative CT scan at day fourth. The histopathological micrograph shows moderate anaplasia (H & E Stain; 100X).

**Figure 3:** CT scan, MR images, intra-operative photographs in sitting position and tumor specimen of a cerebello-pontine angle Epidermoid with histopathological microphotograph.

**Figure 6:** MR images and intra-operative photographs of an Ependymoma of 4<sup>th</sup> ventricle (WHO Grade II). The Aqueduct of Sylvius is seen opening inside the fourth ventricle. Low power microphotograph shows the histopathological view of the tumor.

**Figure 4:** An 8 year male Child with Medulloblastoma shows radio-imaging and intra-operative pictures. Histopathological images show infiltrating tumor cells invading cerebellar cortex (Hematoxylin and Eosin Stain; 200X).

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 posterior fossa 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 posterior fossa [7]. Couldwell, *et al.* studied 40 males and 69 females, a male female ratio of 1:1.7, with posterior fossa (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-circumscribed, 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 (Figure 2), 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 posterior fossa tumors. 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 PFTs below 18<sup>th</sup> 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 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 and 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 (Figure 4 and 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. The SEER (Surveillance, Epidemiology, and End Results) which is one of the large population database study about the information on cancer incidence, prognostic factors and survival in the US has analyzed the adult medulloblastoma. Multivariate prognostic factors like year of admission of patients, age, sex, skin-colour, education, family income, marital status, tumor size, extent of surgical

resection, histopathology etc. have been included. However, SEER does not provide detail information on treatment regimens [18]. There were 454 cases retrieved from SEER registries database between 1973 and 2004. The 5-year observed and relative survival was 64% and 64.9%, and the 10-year observed and relative survival was 50.4% and 52.1%, respectively. However, the data for patients diagnosed from 2001 - 2004 was grouped together with those from 1991 - 2000 because there was inadequate follow-up time for those diagnosed in the current decade (data censored in November 2006). The median survival for those diagnosed before or during 1980 was 39 months (3.3 years) and during 1981 - 1990 was 127 months (10.6 years) while the median survival for those diagnosed from 1991 - 2000 and after 2000 has not been reached. The prognostication for the age in this study showed that those who were diagnosed at 18 - 20 years of age the median survival has not been reached. In contrast, the median survival of those between 21 - 40 was 116 months and older than 40 year of age had worse prognosis with median survival at 92 month. The average age of this cohort was 33 years. The majority of patients were white (87.9%), and almost 60% of them were men. Almost 50% (one-half) of patients had gross total resection, but precise information on the degree of resection was missing for approximately 24% of them. The histological types were 87.44% classical medulloblastoma, 11.45% desmoplastic nodular type, 0.66% large cell variant and 0.44% were medulloblastoma. The information on the extent of disease was missing in 22% patients at the time of diagnosis [17]. In comparison the present study had a total of 72 cases of medulloblastoma over a period of 20 years from 1990 to 2010 consecutively. The 12 months observed survival was 55.5%. The age mostly involved was 18 years and below making it 84.7% of all the cases and were mostly males 73.6%. The histological tumor types in this study were 73.6% classical medulloblastoma, 15.2% desmoplastic variant type, 6.9% with anaplastic changes and 4.1% were medulloblastoma with glial differentiation [19].

Djalilian and Hall (1998) reported that 53% patients in a study had grade IV malignant cerebellar gliomas and 47% had anaplastic grade III astrocytomas [20]. The present study observed that 11.4% PFTs 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 dis-



tinct molecular entities, ependymoma posterior fossa A (EPN PFA) and ependymoma posterior fossa B (EPN PFB), with differentiable gene expression profiles [21]. In present study ependymoma (Figure 6) 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 posterior fossa tumors in children [22]. Following up 104 children with cerebellar juvenile pilocytic astrocytomas 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 [23]. 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 [24]. Donalson, *et al.* 2006 reported high rate of recurrence or progression and often follow an inexorable course of progression, despite therapy [25]. 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, 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 posterior fossa. 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) [26]. 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 [27]. The present series of 410 PFTs 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 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 [28]. Pineoblastomas in this study comprised 1.7% of all

PFTs 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% [29]. Of 410 PFTs presently, 0.97% had malignant meningiomas (WHO grade-III), mostly rhabdoid and anaplastic, which formed 10.6% of all PFTs with a recurrence of 100% and mortality of 75.0%.

## Conclusion

The present study of posterior fossa tumors in children and adults, of an ethnic non-migratory Himalayan-population of India, is of regional epidemiological value. Given the aggressive biological behaviour, the histologically proven malignant lesions in posterior fossa have all the opportunities to harm the vitality of posterior fossa structures and lead to catastrophic outcome pre, intra and postoperatively.

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