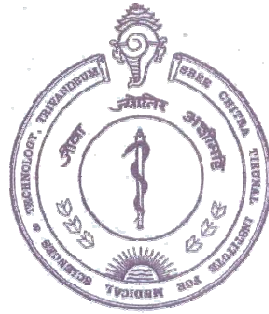


Meningeal Hemangiopericytoma, A Comprehensive
Review of Long-term Outcome, An Institutional
Experience



Submitted for MCh Neurosurgery

By

Dr. Akshay S. Patil

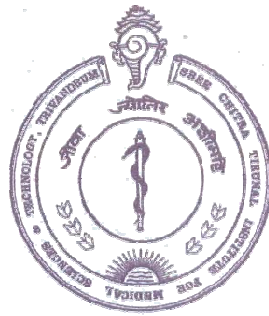
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Submitted by : Dr. Akshay S. Patil

Programme : MCh Neurosurgery

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CERTIFICATE

This is to certify that the thesis entitled “Meningeal Hemangiopericytoma; Comprehensive Review of Long-term Outcome An institutional experience” is a bonafide work of Dr.**Akshay Shrirang Patil** and was conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram (SCTIMST), under my guidance and supervision.

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DECLARATION

This thesis titled “Meningeal Hemangiopericytoma, comprehensive review of long-term outcome , an institutional experience,is a consolidated report based on a bonafide study of the period from January 2000 to May 2012, done by me under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

This thesis is submitted to SCTIMST in partial fulfillment of rules and regulations of MCh Neurosurgery examination.

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Introduction

Meningeal Hemangiopericytoma (HPC) is a malignant extra axial neoplasm that occur within Central Nervous System (CNS) and has biologic capacity to escape from CNS and metastasize widely. Their behaviour is almost like soft tissue sarcoma. Light microscopy, ultrastructural, and immunohistochemical data indicate that meningeal HPCs represent the intracranial counterpart of soft tissue HPCs. HPCs thought to arise from meningeal pericytes (Zimmerman pericytes) which are modified smooth muscle contractile cells surrounding capillary endothelium. Zimmerman pericytes are located surrounding the capillaries and postcapillary venules and are also considered as precursor cell of angioblastic variant⁴⁴ which is most commonly located in the musculoskeletal system and the skin. HPC known for their local recurrence and unknown distant metastasis. These are highly cellular and vascularised mesenchymal tumours with aggressive behaviour². It constitutes 0.4% (<1%) of the total CNS tumours and 2-4% (2.5%)^{6,1-2} of all meningeal tumour⁴⁴. They usually mimic meningioma on imaging though behaviour is different.

REVIEW OF LITERATURE:

Historical significance-

Solitary fibrous tumors (SFTs), described in the pleura by Klemperer and Rabin in 1931^{1,42}, were originally regarded as mesotheliomas⁴. *Angioblastic meningioma* was the term used by Bailey et al^{11,43} in 1928 to describe a meningeal tumor observed in three cases. In 1938, Cushing and Eisenhardt popularised 'angioblastic meningiomas' as vascular form of meningioma. He further described three variants of which first was malignant in behaviour. Retrospectively this variant further was called as HPC. In 1942, Stout and Murray described Haemangiopericytoma(HPC) as a distinctive soft tissue tumour for tumors located in the retroperitoneum, buttock, and thigh. They proposed this to be tumour was identical to angioblastic meningioma². In 1954, Begg and Garret, and Fisher in 1958¹ reported first intracranial HPC which was similar to Cushing's angioblastic meningioma. Popof et al⁴⁵ in 1974 proposed not to classify this tumour as a meningioma, because it is identical to HPCs arising in soft tissues. In 1977, Horten et al⁴⁵, after reviewing 79 cases of angioblastic meningiomas, which showed areas apparently transitional between HPC and fibrous meningiomas or hemangioblastomas, concluded that these tumours arise from multipotential behaviour cells and should be classified with the group of meningiomas. The 1979 WHO classification² still contained the 'haemangiopericytic' variant of meningioma, but it has now been long accepted that HPC and meningioma are different entities.

- 1) Morphological similarity of the tumor with the HPC in other parts of the body⁴⁷;
- 2) existence of pericytes in the blood vessel walls within the CNS;

3) fine structural differences from the arachnoid cells of meningiomas;

4) similarities found on electron microscopy .

5) Reticulin stain

demonstrates its relationship to vascular channels.

D'Amore et al.⁴⁶ comparing soft tissue and meningeal HPCs found same results as in the present series and concluded that similarities outnumber the differences and that both tumors are almost indistinguishable from one another on the basis of morphology, immunohistochemistry, and ultrastructural analysis. Also, reticulin staining demonstrates its relationship to vascular channels. The classification of the World Health Organization (WHO) 1993 has eliminated the term *angioblastic meningioma* in favour of *Meningeal HPC*. Due to its different histomorphology, immunophenotype and biological behaviour, WHO classification in 2003 recognized it as distinct entity. In the 2006 World Health Organization (WHO) fascicle of soft tissue tumors, it is stated that the histological appearances and clinical behaviour of HPC and SFT are similar⁴⁷. Accordingly, the unifying term "HPC/solitary fibrous tumor" (HPC-SFT) was proposed. In spite of this view, in the 2007 WHO study of central nervous system tumors², it was stated that HPC and SFT of meninges are histologically and clinically different entities, being HPC of meninges a frequently recurring tumor. In 2007 WHO classification², HPC groups in the category of mesenchymal non meningotheelial tumours with uncertain malignant potential and laid down clear criteria for grading HPC². The nosological position of Central Nervous System (CNS) HPC remains uncertain, but at present HPC is still recognized as clinicopathologically well-characterized malignancy distinct from meningioma (WHO and the diagnosis of primary HPC of

the CNS is histological and immunohistochemical. International classification of diseases for oncology (ICD –O) and the Systematized Nomenclature of Medicine (SNOMED) consider 9150/1 as the morphology code for HPC (behaviour is coded ‘‘/1’’ for low or uncertain malignant potential or borderline malignancy tumours) ⁴⁸.

Incidence-

The estimation of the true incidence of HPC is complex. HPC constitutes 0.4% (<1%) of all CNS tumours, while it constitutes 2-4 % of large series of meningeal tumours. About 10%, tumours occur in paediatric age group. Most of the time they are misdiagnosed as meningioma and reported as same ⁴⁴. So overall incidence of HPC constitutes 2.5% of all meningeal tumors and 1% of all intracranial tumors ⁵⁰. The majority of these tumors occurs in adults, with only 10% of cases occurring in children ⁵¹.

Age/Gender–

HPCs occur more commonly in men comprising 55–70% of patients, in contrast to meningiomas which are more common in females. Guhtrie et al ^{6,8} in his study suggested average age of presentation is between 38 and 42 years, a decade earlier than the meningioma patients. In a pathologic series of 94 CNS HPC, Mena et al ³¹ reported a mean age at presentation of 47 years among female subjects and of 41 years among male subjects. Thus different series shown HPCs usually occur during adulthood, particularly among men, and the average age at diagnosis ranges from 32 to 41 years ^{2,3,5,9,11–13}. But there are other studies which show HPC appears to occur in men and women in an almost equal ratio (55 vs 45%, respectively). According to Alen et al ⁴ in his study shows female (83.3%) predominates over male counterpart. Patient's gender has no effect on survival, and

neither does age⁵. Spinal HPC do not have gender predisposition but meningioma being common in females they were also recorded slightly higher in female. Average age of presentation was between 3rd to 4th decade i.e. 32 yrs^{52,53}. Approximately 10% of HPCs occur in children⁵¹. Infantile HPCs, those occurring within the first year of life, are even more infrequent and are associated with a more benign course. A review of the literature revealed numerous cases in adults, but only six cases of intracranial HPC have been reported in children under the age of 1 year⁵¹.

Location of tumour-

Primary HPC of the CNS are almost invariably solitary. Most common site of presentation is supratentorial location which is more commoner than infratentorial and spinal.

Location	Guthrie et al ⁶	Shiatri et al ⁵⁰	Ecker R. et al ⁵⁴	Rutkowski et al ⁵
Supratentorial	65%	69%	61%	79 %
Infratentorial	28%	19%	35%	21%
Spine	7%	12%	6%	NA

Of the supratentorial location, parasagittal and convexity region (58%) were the most common location described in literature⁵. Originating from skull base is considered to be rare. Rarely they are reported to arise from lateral ventricle (Trigone), intraparenchymal, pineal region, sellar suprasellar location and Meckel's cave as well⁵⁵.

In spine most common location is extradural (85-90%) following which are in intradural location. Most commonly Cervical spine(85-90%) is involved than thoracic and lumbar spine⁵². Intraspinal extradural HPCs and primary osseous HPCs are difficult to differentiate but are more frequent than intradural HPCs and secondary osseous HPCs. Thirty-one cases of extradural and primary osseous spinalHPC have been reported within the English literature till date. Extradural HPC generally involve mid and lower cervical spine⁵⁶.

Clinical presentation and Natural History:

Symptomatology of the tumour is mostly related to the location and size. In supratentorial location headache is most common symptom (68%), followed by Seizure (16%), and in posterior fossa location- gait unsteadiness and dysequilibrium is the most common symptom⁶. The most common type of presentation is a focal motor deficit in parasagittal or falxine tumours and visual deficit in patients with an orbital component⁴. Patient with the posterior fossa HPC sometimes presents with hearing loss as well as facial palsy, while those located along skull base present with various cranial nerve pathology and memory disturbances⁴. According to Guthrie et al⁶, the average duration for presentation was 11 months, with 8 months for supratentorial and 20 months for infratentorial in his study. However Allen et al⁴, showed the average duration at presentation was 3.1 months (range 1 week±1 year) quite early as compared to meningioma.

Spinal HPC generally presents same as space occupying lesion. The most common presenting feature of spinal HPC was pain 85%⁵³. Other presentations could be Upper Limb and Lower Limb weakness⁵⁰. The duration of symptoms varied from 1 week to 1 ½ yrs⁵³.

Both local recurrence and extraneural metastases occur late in the natural history of the HPC after prolonged disease-free intervals. The majority of patients live independently even after treatment for second and third recurrences. Thus long term follow up is essential in HPC ⁵⁰.

Age at presentation-

The mean age ranges from 38 -42 years in various studies as compared to meningioma which usually presents at 6th decade almost one decade earlier. Rutkowski et al⁵¹ in his review article suggested that, mean age of presentation of HPC was 41 years.

Imaging Characteristics-

Imaging study has revolutionised the results in intracranial pathology by locating the origin and directing the approach and helps in access for safe removal of the tumour. Imaging also categorises the prognosis of tumour.

X-ray- Skull X-ray-generally donot show any abnormality unless there is gross erosion or hyperostosis⁶. Mostly these HPC are associated with overlying bony erosion. Spinal X-ray- usually showserosion of pedicle and even vertebral body as well with widening of neural foramina if it is dumbbell shaped⁵³.

Computerised Tomogram(CT) Brain-

HPC are extra-axial dural based lesions like meningioma. Servo et al^{19,57} showed that on unenhanced CT scans, they are isodense or slightly hyperdense, well-defined, sometimes nodular masses, without calcifications, and these lesions were associated with slight perilesional edema. These HPC were typically connected to the convexity or falx with a broad base, were often bilateral, and often showed dense, ring-shaped enhancement. On contrast-enhanced CT scans they show diffuse

contrast enhancement. Overall intracranial HPC^{19,22} are heterogeneous, hyperdense, dural-based lesions that, unlike meningiomas, are not associated with calcifications or hyperostosis, and typically show heterogeneous enhancement on enhanced CT scans..

Magnetic Resonance Imaging (MRI) Brain-

Guthrie et al⁶ suggested that HPC were similar to meningioma and has T1-isointense and T2 –isointense characteristics. Intracranial HPC were heterogeneous, predominantly isointense on T1-weighted and T2- weighted MR images, showed prominent internal vessel voids, and enhanced heterogeneously on contrast-enhanced MR images with 50% having dural tail sign¹⁹. Intratumoral hemorrhage can be present on imaging. They generally have broad based dural tail, and in one third cases narrow tail which becomes important distinguishing factor. Generally they have irregular border and are lobulated in appearance with heterogeneous contrast enhancement with mushroom pattern similar to an aggressive meningioma. They are also mostly associated with peritumoral cyst (csf entrapped cyst). In contrast to malignant meningioma they have relative paucity of perifocal edema^{58-57,22}. Magnetic Resonance Spectroscopy (MRS) can be helpful as noninvasive technique⁵⁹ to differentiate from meningioma and schwannoma as it shows increase in concentration of myoinositol peak also called as spectroscopic signature of HPC^{27,59}. Other spectroscopic feature can be same as meningioma or extra axial tumour i.e.- increased concentrations of choline and occasionally lipids, while the concentrations of (N Acetyl Aspartate) NAA and PCr/Cr are decreased..

It is apparent, that MRS is a promising, noninvasive diagnostic modality which might be helpful in differentiating hemangiopericytomas from meningiomas. It requires further studies to qualify the correct diagnosis of HPC.

MRI features of Spinal HPC-

T1-isointense-hypo intense, T2 Hyperintense with heterogenous Contrast enhancement(CE).

Imaging differences of Meningioma and Hemangiopericytoma.

Imaging	Meningioma	HPC
Site	Supra>Infra> spine	same
Margins	Smooth	Lobulated and mushroom pattern
CT findings	Iso-hyper with Homo CE	Iso –hyper with hetero CE
MRI	T1/T2-iso to cortex	Almost same , T2 hetero
Dural attachment	Usually broad	Usually broad but narrow also
Internal serpentine flow void	Not significant	Significant finding
Tumour calcification	20-25%	Usually absent
Peritumoral edema	Variable	Relatively less
Enhancement	Homogenous	Heterogenous
Adjacent bone	Hyperostosis	Bone erosion is typical

Anaplastic HPC can be differentiated from HPC by MRI findings ⁶⁰–

Imaging characteristics	Anaplastic HPC(III)	HPC(II)
Tumour shape	Irregular , lobulated	Round or oval
Cross leaf growth	More common	less
Necrotic foci	Frequent	Not present
Intratumoral bleeding	Frequent	Rare
Dural tail sign	Less obvious	Usual
Intratumoral flow voids	Numerous	Less
Narrow base connected to dura	Frequent finding	Less common
Bony destruction	More common	Less common
Perilesional edema	Frequent and obvious	Not common

Differential diagnosis for intracranial HPC include –lymphoma, metastasis, sarcoidosis, solitary fibrous tumour, gliosarcoma and schwannoma.

Differential diagnosis for spinal HPC⁵³ are fibrous meningioma, fibrosarcoma, malignant fibrous histiocytoma, mets, solitary fibrous tumour, nerve sheath tumour

Positron Emission Tomography-(PET)

DiChiro et al in 1987²⁵ and Tsou et al. have reported that HPC are characterized by a significant increase in the uptake of 11C-methionine, hyperperfusion, and decreased glucose utilization ²⁷; these findings can help in distinguishing HPC from

meningiomas. HPCs demonstrate significant glucose hypometabolism relative to meningiomas on (18F) FDG-PET imaging,

(11C) methionine-PET demonstrates a 6-fold higher uptake in HPC⁴³. HPC shows hyper metabolic activity on PET and that such ``hot spots'' on the PET study have an adverse prognostic significance. However, these findings have not been replicated up to date⁴.

Cerebral Angiogram-

HPC shows characteristic angiographic features which can differentiate it from meningioma⁵⁸⁻²⁴. They are

- (1) Dual supply from the internal carotid or vertebral and external carotid arteries, with dominant supply from the internal carotid artery branches rather than a primarily external carotid supply seen with meningiomas,
- (2) A myriad of corkscrew vessels arising from a main feeder within the tumour,
- (3) A dense fluffy, long-lasting tumour stain rather than the sunburst pattern of meningiomas,
- (4) A lack of early draining veins.
- (5) Rich pial feeders.
- (6) Slow circulation and
- (7) Retarded venous drainage.

Pathology and pathogenesis-

The histogenesis of this tumor has been a matter of controversy for a long time until light microscopy, ultrastructural, and immunohistochemical data conclusively proved that HPCs represent the intracranial counterpart of soft tissue HPCs and grouped as ``mesenchymal, non-meningothelial tumours'' in the present WHO

classification 2007². HPCs are more aggressive than meningioma, and behave in a different way than meningiomas.

Macroscopy- Generally HPC are solid with well demarcated margin with mostly globoid in shape and multiple lobulations. HPC are more firm and rubbery in consistency and unencapsulated, On cut section they are fleshy, greyish to reddish-brown or frankly hemorrhagic in appearance, often with a number of visible vascular spaces either inside or outside the tumour². Sometimes they are also associated with Cystic changes . Most of the HPC are solid in nature except few case report suggestive that they are rather cystic in nature as well. Various hypothesis⁶¹ postulated that the pathogenesis behind the cystic HPC could be

- 1) Central degeneration and necrosis of the tumor due to insufficient blood flow,
- 2) Exudation of plasma components,
- 3) Intratumoral bleeding,
- 4) Reforming process of the subarachnoid spaces and
- 5) Aggregation and enlargement of microcysts.

HPC has also noted to developed from previously operated meningioma and possible mechanism stated could be tissue repair after resection of meningioma may exert different effects on local pericytes, thus inducing tumorigenesis. Long time interval between the first tumor and HPC could explain why this association is present in cases of meningioma, but not in other malignant brain tumors in which life expectancy is much shorter⁶.

Microscopy–

HPCs are highly cellular and highly vascularized mesenchymal tumors exhibiting a characteristic monotonous low-power appearance and a well-developed variably

thick-walled, branching “staghorn” vasculature. HPCs correspond histopathologically to WHO grade II, with anaplastic HPC corresponding to WHO grade III². Signs of anaplasia are high or brisk mitotic activity (> 5 mitosis per 10 High Power Field) and/or necrosis, plus at least two of the following hemorrhage, moderate to high nuclear atypia and cellularity. A rich network of reticulin fibers, typically investing individual cells, is one of the most characteristics but not invariable features of this neoplasm.

Immunohistochemistry-

HPC cells are diffusely positive for vimentin (85%) and for factor XIIIa (80–100 %) in individual scattered cells, Leu-7 (70%) and for CD34 (33–100%). The latter is usually patchy. Focal positivity for desmin, smooth muscle actin, and cytokeratin may be occasionally encountered. Tumour cells are negative for S-100 protein, classical endothelial antigens such as CD31, as well as progesterone receptor. Although the immunoreactivity pattern of HPCs is diverse and no single antibody is either 100% sensitive or specific, its immunoprofile is generally sufficiently distinctive to permit the exclusion of meningioma and solitary fibrous tumor, from the differential diagnoses⁶². HPCs are also positive for CD99, Ki-67. Vascular endothelial growth factor Vascular Endothelial Growth Factor –A (VEGF-A) is up-regulated in HPC tumour cells and the receptors VEGFR-1 and VEGFR-2 (but not VEGFR-3) in endothelial cells, suggesting a paracrine mode of interaction⁶³. Endothelial cells also express Tie-1, a tyrosine kinase receptor associated with enhanced neovascularisation expressed in HPCs. HPC cells are negative for the immunohistochemical marker factors like VIII-RA, GFAP, EMA.

HPC are genetically distinct from meningioma. Rearrangement of chromosome 12q13 are common in HPC. Several oncogene located in the region of including MDM2, CDK 4, CHOP/GADD153. NFII tumor suppressor gene (22q) associated with meningioma and not with HPC^{61,64}. Recurrent HPCs retain their histologic feature and metastatic HPC are histological identical to the primary tumor. They are histologically and biologically distinct from atypical and malignant meningioma.

The specific criteria that define malignancy for HPCs² include large

1. Tumor size (>50 mm)
2. Disseminated disease at presentation,
3. Infiltrative margins,
4. High cellularity, nuclear pleomorphism, areas of tumor necrosis, and an increased mitotic index (>4 mitoses per 10x high-powered field).

Treatment Modalities-

Various treatment modalities has been described in literature like watchful expectancy, surgery, Radiotherapy, Chemotherapy, Combined therapy and newer medicine. But HPC are histologically benign lesion with clinically aggressive course, hence watchful expectancy has not been advocated.

Surgery-

HPC are neoplasms with an aggressive natural history. HPCs have a propensity for recurring locally as well as distant site with extraneural metastatic potential. Therefore, every attempt should be made to achieve complete removal of the tumor at the time of initial surgery. The optimal method of treatment consists of GTR (Gross Total Resection) followed by postoperative radiotherapy. Surgery not only offers immediate relief of mass effect but also allows tissue confirmation of the

histopathological diagnosis to differentiate HPCs from other tumours like meningiomas. Because of the high vascularity of the lesions, preoperative embolization can sometimes be advantageous. The highly vascular nature of the lesion and the location i.e. at the skull base as well as in posterior fossa are the major hindrance to total resection and may result in operative mortality rates between 9 and 24%⁴¹. The published rates of gross-total resections for HPC in the CNS ranges from 32 to 67%^{54-10,6,65}. Due to small available patient numbers, a statistically significant benefit for GTR has never been demonstrated. Soyuer et al.^{3,5,66} reported a superior 5-year local control rate in patients treated with GTR (84%) as compared with the rate in patients treated using subtotal resection (38%). In the series of Kim et al⁶⁷, the 5-year local recurrence-free rates for patients undergoing GTR compared with those undergoing incomplete excision (STR) were 72.7% and 20.8%, respectively^{50,67}. Guthrie et al.⁶ found that the extent of surgery had a statistically significant effect on overall survival. The average survival times for patients who had complete tumor removal and those who had incomplete removal were 109 and 65 months, respectively.

The study of Marco Schiariti et al⁵⁰ further validates these results the recurrence-free interval was 63 months longer for patients undergoing GTR compared with those who did not, and the 5-year local recurrence-free interval was 77% and 36% for complete and incomplete excision, respectively. Thus wherever possible, Simpson Grade 1 and 2 resections i.e. GTR should be achieved, and is thus advocated.

Rutkowski et al^{5,67} analysed that GTR alone was associated with significantly superior survival compared with STR with or without adjuvant radiation. They also

insisted that aggressive surgical management is very important for the successful treatment of patients with recurrent HPC.

Surgical excision can be graded according to **Simpson's grading** as,

Grade	Extent of resection
I	Including dura and bone
II	Coagulation of dura
III	GTR without dural coagulation or extradural extension
IV	Partial resection
V	Biopsy

Another method of grading the excision of meningioma is as **Modified Shinshu**

/Okudesa Kobayeshi grading-

Grade I- Complete microscopic removal, dural attachment, bone

Grade II- complete microscopic with coagulation of dura.

Grade IIIa- complete microscopic intradural +extradural, without resection or coagulation of dura.

Grade IIIb- complete microscopic removal of intradural component without dural and extradural component.

Grade Iva- subtotal removal to preserve cranial nerves or blood vessel with complete microscopic removal of dural attachment.

Grade Ivb- Partial removal leaving tumour < 10% in volume.

Grade V- leaving >10%. Decompression with without biopsy.

For all purpose in literature following can be considered ,i.e.

Grade I and II- Gross Total Resection (GTR),

Grade III to V- Sub Total Resection (STR).

Surgery is the treatment of choice for HPCs and because of their propensity to recur, resection must be as radical as possible.

Embolisation-

Preoperative embolization of intracranial HPC with the purpose of limiting blood loss during surgery has been reported^{15,29,68}. But because of the frequent parasitization of cortical arteries, complete devascularization is difficult. Various case reports showed embolisation prior to surgery is useful adjunct in removing the HPC with less blood loss, though small blood supply is through pial feeders. Till date there is no report in the medical literature that therapeutic embolization without subsequent microsurgery is curative for HPC.

Radiotherapy-

The impressive recurrence rate of HPC coupled with its potential for developing extracranial metastases make clear that surgery, even if radical, cannot be considered as the optimum treatment^{7,28,32}. Several retrospective studies have shown that radiotherapy (RT) after surgery is beneficial for patients with HPC. It has been even asserted that HPC represent reasonable radiosurgical targets because of their highly vascular nature likely increases their favourable response to RT treatment. The

regression of peripheral HPC with RT is well documented in literature. The criteria for radiation therapy (RT) were not uniform. Concern about the high risk of recurrence in patients with both completely and incompletely resected tumors was the most common reason for adjuvant radiation treatment. Despite the paucity of definitive data demonstrating the survival benefit in patients who undergo adjuvant External Beam Radiotherapy (EBRT) or stereotactic radiosurgery, HPC often displayed dramatic radiographical regression and even complete elimination.

Hence HPC with the aid of adjuvant therapy i.e., RT continues to support their use in the treatment of primary as well as recurrent disease^{6,7,8,10,31,36,54,69}. In reported retrospective series, EBRT doses greater than 50 Gy have significantly lengthened the disease-free survival interval and controlled local recurrence. Guthrie et al.⁶ reported that radiotherapy significantly prolonged the disease recurrence-free interval from 34 months to 75 months. Although the difference was not statistically significant, adjuvant radiotherapy extended the survival period from 62 months to 92 months. Ecker et al and Kim et al.⁶⁷ did not find adjuvant radiotherapy to have a statistically significant effect on local control; however, Kim et al stated that the 5-year HPC recurrence-free survival rates associated with complete excision alone and complete excision with adjuvant radiotherapy were 70% and 100% respectively. Dufour et al.³⁶ also found that postoperative radiotherapy provided benefit in reducing the local disease recurrence. Dufour et al also shown that local disease recurrence rates for patients treated with surgery and adjuvant RT and patients treated with surgery alone were 12% and 88%, respectively. Although this difference was not statistically significant. Postoperative radiotherapy appear to limit the incidence of distant neural-axis metastases in the study conducted by

Dufour et al.³⁶. Marco Schiariti et al.⁵⁰ believes that RT should be given even though GTR has been achieved.

The indication for postoperative radiotherapy for spine localization is questionable because of the risk of radiation necrosis and adverse effects. The maximum tolerated dose of radiation to the spinal cord is 5000 rads⁴¹. Moreover, Mena et al.³¹ found a significant linear trend of decreasing likelihood of malignancy as the tumor site descended along the neuraxis. They found a significantly higher recurrence rate in high-grade HPC (HPC III). In series by Dufour et al.³⁶, two of four patients with spinal localization were not irradiated, and two received 4000 rads; to date, none of these patients has had a recurrence. Thus, he does not advocate postoperative radiotherapy for spinal intradural extramedullary HPC. Radiotherapy⁴¹ is under discussion for patients with a high-grade intradural extramedullary meningeal location. Despite the clear beneficial effects of radiation therapy, it should be noted that all recurrences after radiation develop within the treatment field, indicating that there is little to be gained from whole brain or spinal axis irradiation⁷³

Radiosurgery-

Radiosurgery is an effective treatment for recurrent HPCs and has been promoted as an effective means of tumor control among patients with recurrent HPC. Compared with conventional radiotherapy, radiosurgery can achieve a steep dose gradient that minimizes the radiation delivered to the surrounding areas. Consequently, it is possible to deliver a significantly larger and presumably more biologically effective dose to the tumor and minimize other undesired side effects of radiotherapy. A higher dose delivered during the initial radiosurgery seems prudent given the aggressiveness and resilience of these tumors.

Gamma Knife stereotactic radiosurgery (GK SRS)- was introduced as a treatment option for the management of intracranial HPCs recurring after surgical resection followed by RT or after GTR alone, because GK SRS provides safe delivery of a relatively high dose of radiation to a well-defined target (like HPCs), and it is not difficult to re-apply GK SRS for possible recurrence ⁷⁰. Most studies reported immediate and dramatic shrinkage of tumors after radiosurgery for HPCs, and local tumor control rates were 46–93%. Payne et al.¹⁵ emphasized that, in order to minimize GK SRS-related complications for recurrent HPCs, GK SRS should be performed at the first sign of recurrence, when the tumors are small.

Various Series of GKSRS with recurrent HPC Patients⁷⁰–

Study group	No of patients	No of tumours	Tumour volume(cm ³)	Marginal dose (Gy)	Tumour control(%)	Followup (mth)
Coffey et al	5	11	8.5	15.5	82	12.7
Galanis et al	10	20	NA	NA	90	36
Payne et al	10	12	7.6	14	75	25
Sheehan et al	14	15	8.8	15	80	31.3
Ecker et al	15	45	7.8	16	93	45.6
Sun et al	22	58	5.4	13.5	89.7	26
Kano et al	20	29	4.5	15	72.4	37.9
Olson et al	21	28	4.6	17	46.4	69
Kim et al	9	17	2.2	18.1	82.4	33.8

One of the largest study, by Sun et al⁴, which included 22 patients with 51 HPCs suggested that treatment principles for GKSRS of HPCs should be similar to those used for intracranial metastases, and that an aggressive prescription dose could achieve a reduction in the rate of local recurrence. This finding has been further supported by Sheehan et al³⁹, who recommended that a radiation dose of at least 15 Gy should be delivered to the tumor margin for successful local tumor control, and Kano et al, who reported significantly better progression-free survival in HPCs treated with high marginal dose (14 Gy)⁷⁰. Stereotactic RadioSurgery (SRS) is most effective for treating tumors < 8 cm³ (< 2 cm in diameter) in volume with radiation doses of 15 Gy or higher at the 50% isodose line. Recurrent lesions ≥ 3 cm in their greatest diameter are best treated by re-resection followed by postoperative SRS, whereas recurrent lesions < 3 cm in their greatest diameter can be successfully controlled by SRS alone³.

Complications associated with GKSRS are pronounced edema and radiation necrosis.

Chemotherapy-

The role of chemotherapy in the management of recurrent HPC is less clear. The most frequent treatment for recurrent HPC is re-resection when clinically appropriate and, increasingly, the administration of GKSRS. Chemotherapy can be considered in refractory to Surgery and RT or in moribund patient. The appropriate chemotherapy for use in recurrent HPC is problematic because the literature is very limited in this regard. Chemotherapy has tried on basis of response obtained in sarcoma patient. Recent randomized Phase III trial suggest single-agent doxorubicin is the treatment of choice of advanced soft tissue sarcomas. Chemotherapy was

associated with various toxicities .In the series reported by Galanis et al,²⁸ .1 patient of 7 showed a partial response to doxorubicin. However, isolated case reports of tumor control using a combination of ifosfamide and epirubicin have been published. But none of the studies shows significant benefit in recurrent HPC outcome. Further progress in managing recurrent surgery and radiotherapy-refractive intracranial HPC with chemotherapy will require a cooperative effort, given the rarity of these meningeal tumors and prospective Phase II clinical trials.

Other modalities-

Various case reports suggests that Interferon α (IFN α) has modest benefit in management of recurrent HPC. IFN α has anti-angiogenic activity by slowing endothelial proliferation and migration and by suppressing the production of two proangiogenic factors- interleukin- 8 and basic fibroblast growth factor (BFGF)¹⁴. Katherine Peters et al⁷¹ suggested the use of monotherapy utilizing molecularly targeted therapy to SRC-related tyrosine kinases. Dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRCfamily (SRC, LCK, YES, FYN), c-KIT, EPHA2, and Platelet Growth Derived growth Factor (PDGFR) β . Dasatinib is approved by the Federal Drug Administration(USFDA) for the treatment of chronic myelogenous leukemia or Philadelphia-chromosome positive acute lymphoblastic leukemia. HPCs often over express PDGFR as detected by immunohistochemistry. Dasatinib because of his ability to inhibit PDGFR β , showed promising result in patient with recurrent metastatic HPC.

Recurrence-

The HPC has relentless tendency to recur, even after complete surgical resection. The recurrence can be defined as progression of symptoms with radiological and operative confirmation. Otherway Local Recurrence (LR) was defined as reappearance of tumor after complete excision or intracranial growth from known residual tumor. These neoplasms are biologically aggressive and tend to recur locally and distally, frequently metastasizing to extracranial sites as well. This high propensity toward progression makes optimal primary treatment of HPC a difficult endeavour. Even after aggressive initial management combining gross total resection (GTR) with adjuvant EBRT, recurrence rates have been as high as 30%²⁸⁻¹. Median recurrence free survival ranged from 40-78 months. According to Guthrie et al⁶ Recurrence rate was 15% at 1 year, 65% at 5 year, and 85% at 15 years. JaÈaÈskelaÈinen et al⁸ reported a mean interval to recurrence of 78 months. According to Schiariti et al,⁵⁰ The recurrence rate at 1, 5, and 15 years was 3.5%, 46%, and 92%, respectively. In series of 20 or more patients, the incidence of a recurrence for HPC ranges from 50 to 80%⁵⁴. Schroder et al,⁷² in an extensive review of the literature, found a recurrence-free interval of 50 months (range 1–26 years). More recently, Alen et al.⁴ reported a 4/12 (33.4%) recurrence rate with a median recurrence-free interval of 65 months. Du et al., reported only a 4/26 (3.8%) recurrence rate, but their follow-up time was very limited (average 22 months). According to Rutowski et al⁵, time to second recurrence among irradiated patients was 10.3 years compared to 5.3 years in non-irradiated patients. Schiariti et al⁵⁰, reported an average time until second recurrence of 5.7 years in irradiated patients compared to 3 years in non-irradiated patients; although this finding was not statistically significant. It is widely accepted that, after the first recurrence, HPC

tend to recur at shorter intervals . Guthrie et al.⁶ found that the average time to second, third, and fourth operations for recurrence, was 38, 35, and 17 months, respectively which was gradually decreased with subsequent recurrence.

Metastasis-

HPCs are known for extra-cranial widespread metastasis.HPCs can metastasize to any part of body. Intracranial HPCs have the unique characteristic of giving extracranial metastases²⁷. It is well known that they can give metastases in a delayed fashion that necessitates that “disease-free” patients not to be considered as “cured”. Extraneural metastasis can occur at a different location with a different latency period which can be from months to as much as several years, even though the primary lesion has been well controlled. The most common extracranial metastatic sites in order of their decreased frequency are: bones, liver, lungs, abdominal cavity, lymph nodes,skeletal muscle, kidney, pancreas, skin and subcutaneous tissue, breast, adrenal glands, gallbladder, diaphragm, retro-peritoneum, and heart. Guthrie et al.⁶ were the first to show a significant reduction in survival following the development of metastasis.The 5-, 10- and 15-year metastasis rates reported by Guthrie et al were 13%, 33%, and 64%, respectively.The average survival period from the diagnosis found to be 24 months. Once the tumor metastasized, Overall Survival (OS) was shortened by an average of 40.5 months ($p < 0.05$). However, the mean survival period of 39 months (range 6–62 months) after metastasis detection supports the argument that treatment of these lesions should be vigorously pursued⁵⁰. The published incidence of metastatic HPC ranges from 12% to 57%. According to

Schiariti et al,⁵⁰ there was no statistical evidence that complete surgical excision or EBRT affected metastasis-free interval.

The metastases of the tumor occurred 2 to 20 years after the initial diagnosis, and the average period before metastasis varied from 63 to 99 months. Mena et al⁹ found a higher metastasis rate for undifferentiated HPCs (HPC III) or multiple metastases to the bone, lung, or liver, but rarely to the breast, thyroid, adrenal gland, kidney, lymph nodes, or pancreas.

Table showing recurrence and metastasis in various studies.

Author and year	No of patients	F/U in mth	Overall survival in mths (median)	No w/LR (%)	Period to LR in mths	No affected by mets (%)	Extraneural, mets in mths median	No w/ EBRT	No w/ GTR
Guthrie et al 1989	43	NA	84(59.4)	29(66)	51(41)	10(23)	99(115)	17 (40)	21 (49)
Dufour et al 2001	17	60	202 (223)	9(52)	73.3 (48)	3 (18)	NA	10 (59)	13 (76)
Ecker et al 2003,	20	97	NA	NA	NA	11(29)	NA	19	18
Kim et al 2003	31	77	177	12 (39)	102 (104)	4(13)	107(102)	11 (35)	24 (77)
Soyeur et al 2004	29	108	NA	17 (61)	63	16(55)	97	10 (34)	15 (52)
Schiriti et	31	123	216 (232)	28 (90)	80 (61)	10(32)	131(75)	15 (48)	15

al 2011									(48)
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Because of the absence of the intracranial lymphatic pathway, the metastasis of HPC may take the hematogenous route apart from CSF route.. Regarding to the metastatic capacity, a series of risk factors relevant to hematogenous dissemination have been postulated. They include inadequate extirpation or simple enucleation of the tumor, surgical intervention, recurrence, large tumor size, and the tumor located in proximity to venous sinuses. It is impossible to disregard the mechanical spread of tumor cells during surgery through the vascular system or vascular wall invasion. The risk factors probably play important roles in determining the development of metastases. According to Allen et al ⁴, Surgical excision of HPC is advocated in the presence of metastasis, which seems to be like the first-choice treatment..

Kruse ²³ was the first to report a metastatic HPC to the spine. Patient with weakness always suspected for HPC metastasis to spine and should be closely evaluated .

Realisation that extraneural metastasis can occur after years of apparent tumour free survival is critical for long term management of these patients. Intraaxial seeding is extremely rare. Treatment for metastasis require multimodality of tailored approach according to the location of the disease.

Survival-

Guthrie ⁶ and co-worker found that median survival after the first operation was 60 months, with actuarial 5 year, 10 year, 15 year survival rates of 67%, 40%, and 23%. Schroder et al compiled that cumulative survival rate was 65%-45%- and 15% respectively.

Rutkowski et al⁵ analysed that the median survival was 13 years, with 1-, 5-, 10-, and 20 year survival rates of 95%, 82%, 60%, and 23%, respectively. Gross-total resection (GTR) alone was associated with superior survival rates overall—with a median survival of 13 years—and 1-, 5-, 10-, and 20-year survival rates of 96%, 87%, 69%, and 26%, respectively. Subtotal resection (STR) alone resulted in a median survival of 9.75 years, with 1-, 5-, 10-, and 20-year survival rates of 100%, 87%, 44%, and 0%, respectively. GTR plus adjuvant RT resulted in a median survival of 18.6 years, with 1-, 5-, 10-, and 20-year survival rates of 90%, 77%, 68%, and 41%, respectively. STR plus adjuvant RT resulted in a median survival of 6 years, with 1- and 5-year survival rates of 83% and 17%, respectively⁵.

The average length of survival after metastasis was 24 months. Patient after first operation underwent RT experienced recurrence at average of 74 months with 5-10 yrs recurrence rate was 38%, 64% respectively.

Schiariti M et al ⁵⁰ analysed overall survival in various study reports as follows-

Author and year	No of patients	F/U in mths	Survival % 5yrs	Survival % 10yrs	Survival % 15 yrs	Survival % 20 yrs
Guthrie et al 1989	43	NA	67	40	23	NA
Ecker et al 2003	20	97	93	NA	NA	NA
Dufour et al 2001	17	60	NA	NA	NA	NA
Kim et al 2003	31	77	96.3	75.7	NA	NA
Soyuer et al 2004	29	108	85	68	43	NA
Schiariti et al 2011	31	123	93	67	45	23

AIM OF STUDY

The aim of the study is to analyse retrospectively the overall outcome and the prognostic factors directly affecting recurrence free survival (RFS) and compare with published literature.

Material and Methods-

Study involved 21 patients with Meningeal HPC who were treated atleast once at our institute(SCTIMST Trivandrum) between Jan 2000- May 2012. Patient were identified from Histo Pathology records. All imaging films and biopsy slides reviewed to confirm the diagnosis of HPC were selected for the study. Patients medical records were analysed retrospectively to collect data on Surgical treatment, adjuvant therapy, postoperative course, local or distant recurrence and follow up.

The extent of tumor resection was established from the operative notes and was defined as complete if there was no evidence of neoplasm in the tumor bed (Simpson Grade 1 or 2) and incomplete if tumor was visible macroscopically (Simpson Grades 3–5). Pathology reports were reviewed to confirm diagnosis; in addition, all specimens were graded according to WHO classification as HPC II or HPC III i.e. anaplastic HPC. Patients whose tumors were not completely removed and/or revealed anaplastic features such as necrosis, high mitotic activity, and high grade of infiltration, underwent radiation therapy. Radiation therapy consisted of EBRT to the tumor bed plus margin. Doses ranged from 50 to 60 Gy. Only 1 patient received chemotherapy following relapse (Doxorubicin, 6 cycles). One patient underwent GKS for residual tumor.

Follow-Up Data

Follow-up clinical assessment and serial imaging was performed routinely for the first 5 to 10 years to identify local recurrence and metastatic disease. Recurrence was defined as local tumor growth identified on CT/MR imaging. Local

recurrences were treated with revision surgery followed by EBRT when radical excision was not possible. Metastasis was defined as distant tumor growth identified on CT/MR imaging and confirmed by histological examination in the absence of other tumoral disease. Metastases were classified into intraneural and extraneural. Treatment modalities for metastatic disease included surgical excision and EBRT when radical excision was not possible and chemotherapy for extraneural metastasis. The patients were called for review and those not able to come contacted with telephone and the current clinical status was recorded on the Glasgow Outcome Score (GOS).

Statistical Analysis-

Epidemiological and clinical data were recorded. Recurrence free survival, survival duration following recurrence, date of revision surgery, date of diagnosis were calculated respectively. The following prognostic factors were analyzed for statistical significance – age, sex, location, extent of resection, histopathological grade and use of adjuvant RT. The overall outcome and the prognostic factors directly affecting recurrence free survival (RFS) were analyzed and compared with published literature. Windows Microsoft Excel 2007 used for statistical analysis.

Results-

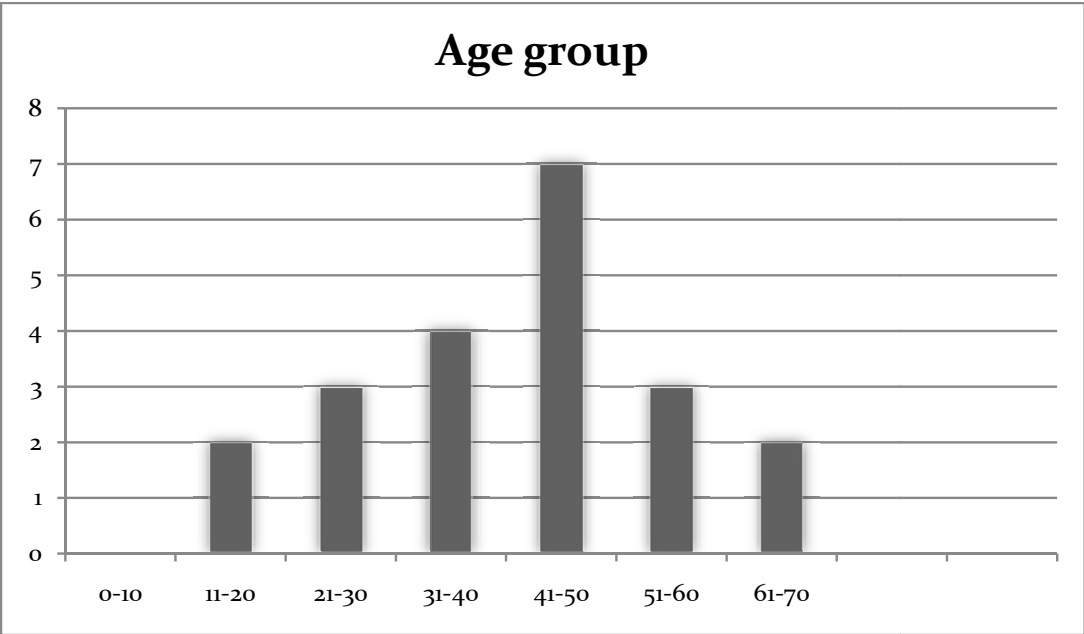
Patient profile

Our study group of 21 patients had an almost equal number of men and women (11:10). The age at diagnosis ranged from 13 years to 67 years (mean of 38.12 years). In our series HPCs were uniformly distributed through decades although a marginal predominance was seen in the fifth decade (Table 1). We also observed that HPCs were uncommon in the extremes of age.

Figure showing sex distribution –Fig-1



Age of patient at presentation-Fig-2



Tumor Location

In comparison to convexity location our series revealed a predilection for the skull base (13/21). The most common location in our series was the middle cranial fossa (4), followed by posterior fossa (3), tentorial (3), cavernous/paracavernous sinus (2), falx/parasagittal (3) sphenoid wing (3) and anterior cranial fossa (1). Two tumours were located in the spine one in the cervical region and one in the dorsal region, both in the intradural extramedullary plane (Table 1). One of our patients with a primary tentorial HPC later developed a suprasellar recurrence eleven years after surgery for the primary (Image- 4).

Location of tumour –(Table -1)

Location	No
Middle Cranial fossa	04
Posterior fossa-(3) ,Petrous	02

Cerebellar convexity	01
Sphenoid wing	03
Tentorial	03
Cavernus sinus	02
Falx/parasagittal	03
Anterior Cranial Fossa floor	01
Spine	02

Clinical Presentation

The most common presenting symptom in our series was raised intracranial pressure headache and the clinical signs were related to tumor location and the size of the tumor.(Table -2). The average duration of clinical symptoms and signs from the onset to the time of first surgery was 3.1 months (range 1 week to1 year).

Table showing clinical presentation at diagnosis-Table-2

Presentation	No of patients
Raised icp (headache)	13
Seizure	1
Facial pain ,	1
Ocular complaints	1
Tinnitus	1

Limb weakness	1
Behavioural changes	1
Neck pain	1
Back pain	1

Imaging Studies

Majority of the tumors were hyper dense on plain Computerised Tomography (CT) scans and enhanced homogeneously following intravenous contrast injection. None of the tumors had evidence of hyperostosis and eight of our patients showed erosion of the overlying bone on plain CT scan (Image 1). In the Magnetic resonance imaging (MRI) studies 12 tumours were mainly isointense with the cortical gray matter on T1-weighted images and the rest were all hypointense. On T2-weighted images nearly all the lesions were hyper intense (16/21). All tumours showed contrast enhancement, the enhancement being intense in most of the cases. Multiple flow voids and intratumoral necrosis was evident in nearly quarter (5/21) of the cases and two thirds (14/21) of the tumours showed irregular borders with significant perilesional odema (Image 2). Cerebral Angiogram was done in eighteen patients (18/21) and it revealed intense tumor blush from the meningeal branches of both external carotid artery and the internal carotid artery . Preoperative embolisation was performed in three patients .Embolisation helped in reducing the external carotid supply but was not very effective in reducing the pial supply from internal carotid artery (Image 3).

Image 1

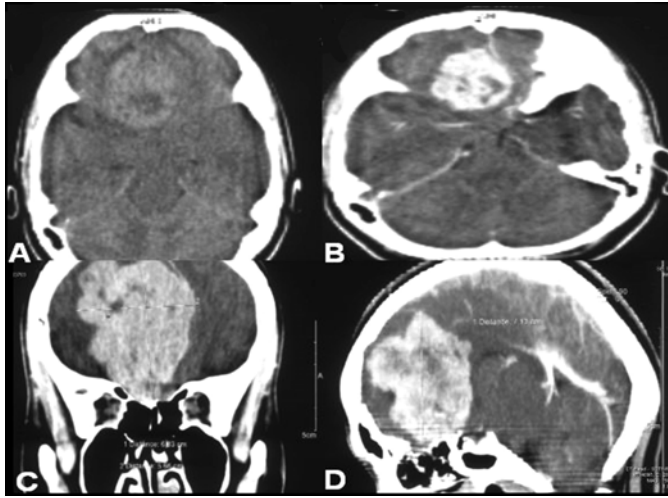


Image1. CT scan axial (A & B) images and coronal and sagittal reconstruction(C & D) images showing a anterior cranial fossa HPC . The narrow base of attachment , the mushrooming extension and the intense contrast enhancement are characteristics

Image- 2

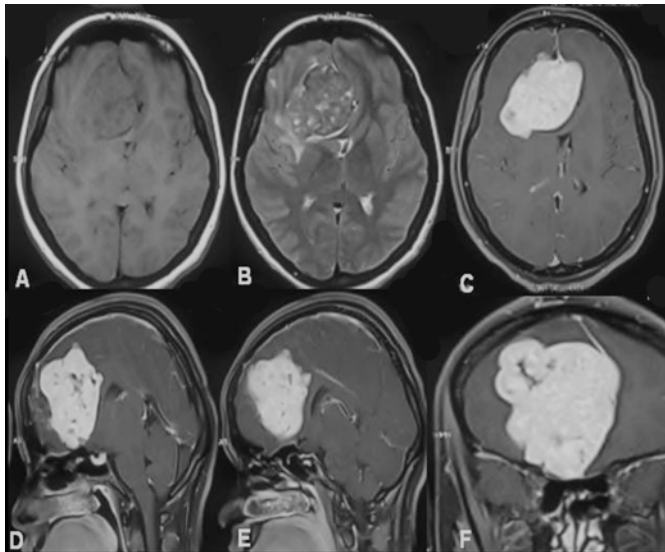


Image2. A: MRI T1 image showing an isointense lesion with areas of hypointensity. B: MRI T2 showing the same lesion with specks of hyperintensities. The surrounding odema is not pronounced. C- F Contrast images(axial, sagittal and contrast) showing marked contrast enhancement and irregular borders .

Image 3-

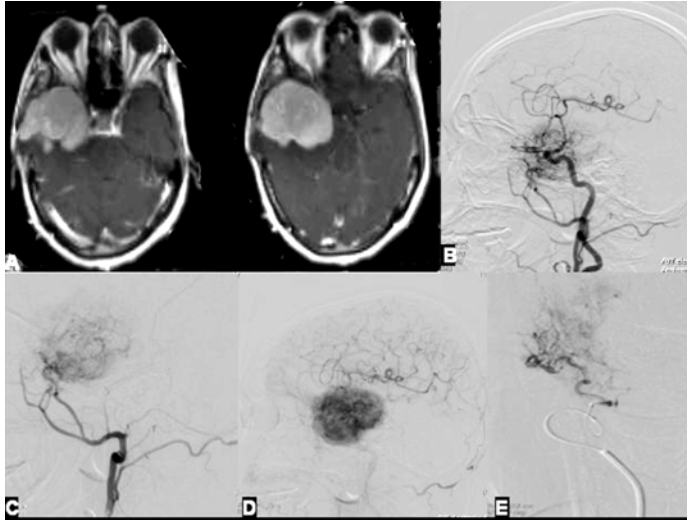


Image3. A: Axial contrast images of a sphenoid wing HPC B& C: Angiogram showing feeders from both external and internal carotid artery. D. Late capillary phase showing a persisting vascular blush. E. Post embolisation showing a partial reduction in blood supply.

Image 4

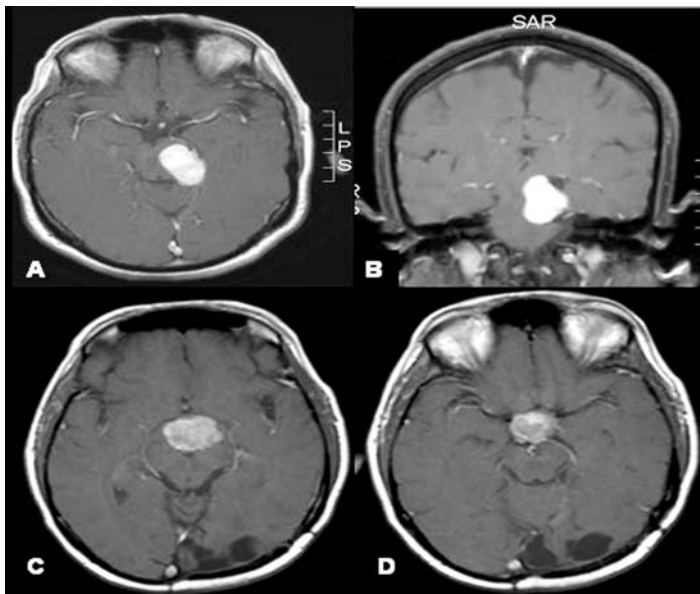


Image 4-

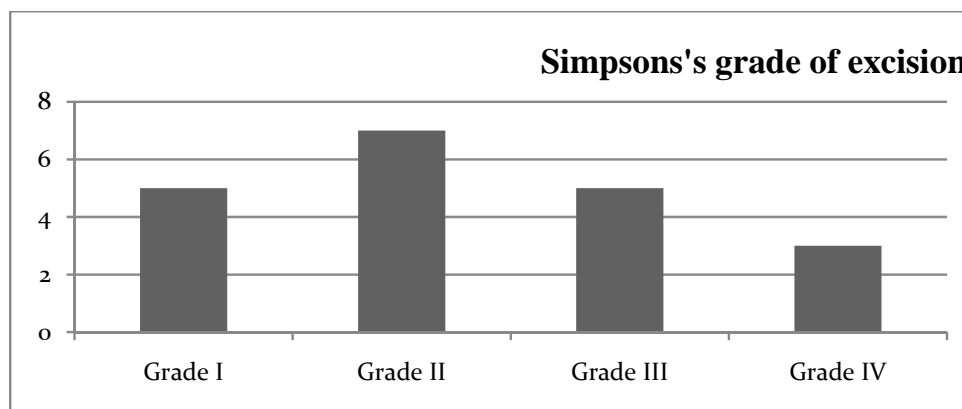
A & B: Axial and coronal MRI sections of a tentorial hemangiopericytoma operated.

C& D: Axial MRI contrast images showing a suprasellar recurrence five years later

Surgery

Intra operatively the tumors mimicked vascular meningiomas in appearance. HPCs generally have a good plane of cleavage from the surrounding brain, but tumor debulking is associated with intense bleeding. Gross total resection GTR (Simpsons Grade 1 and 2) could be achieved in 13 patients (61.90%) and the rest eight patients (38.09%) had only subtotal resection STR (Simpson's grade 3 and 4). Wide dural excision was not possible in many cases due to the base of skull location.

Grades of Excision (Figure -3)



Histopathology

Histologically, eighteen (85.7%) of our patients had differentiated HPC (Grade II) and three (14.3%) had anaplastic (Grade III) HPC.

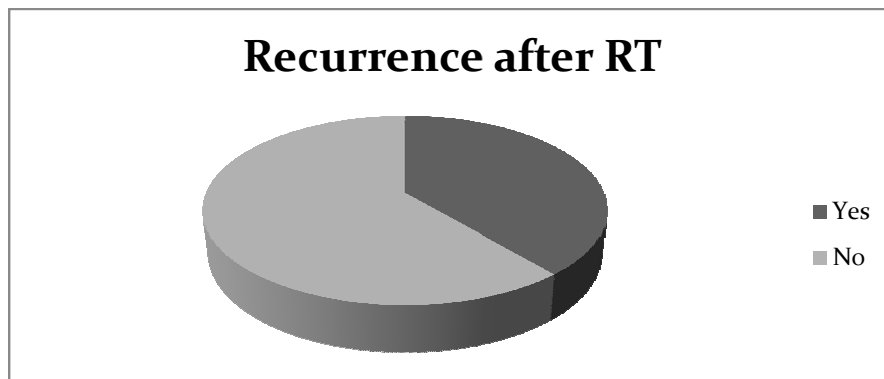
Recurrences and Metastases

Thirteen patients developed local recurrence at least once after initial surgery at an average interval of 3.36 years (range 10 months to 11 years). One young girl had multiple recurrences at 2-3 years for which she was operated thrice. Four patients had tumor recurrence twice. Of these, the first patient had the first recurrence after eleven years and the second after two years, the second patient had two recurrences at two years interval, the third patient had recurrences at 2 years and seven years interval and the fourth patient had recurrence at 7 years and four years interval. Moreover, one patient developed extra cranial metastases in his thigh muscles and upper arm and another patient developed multiple intracranial recurrences at sites distant from the first tumor. The mean follow up of patients with recurrence was 6.2 years whereas the mean follow up of recurrence free patients was 2.06 years, clearly implying a higher risk of recurrence on prolonged surveillance

Radiotherapy

We generally suggest radiotherapy for all patients with HPC independent of the completeness of resection. Eleven (52.3%) of our patients had post op adjuvant irradiation after the first surgery, six (28.5%) had radiation after surgery for recurrence and four (19.04%) refused radiation, one of them in spite of having a second surgery for recurrence. Of the seventeen irradiated patients, ten (58.82%) were free of recurrence, while seven (41.17%) had recurrence in spite of radiation. (Figure 4). Similarly of the four patients who did not undergo radiation, two (50%) had recurrences and two (50%) were free of recurrence.

Figure 4



Complications and overall outcome

There were no operative mortality but one of our patients with multiple recurrences who underwent repeated surgeries succumbed to her illness at another medical centre six months after last surgery. One patient developed hemiparesis after surgery, four patients developed persistent third nerve palsy after surgery, one of them having total ophthalmoplegia. In general, most of the patients did well with surgery and with a good Glasgow outcome score at the end of a mean follow up of 4.6 years as shown in

Table showing outcome(Table 4).

GOS(Glasgow outcome scale)	No. of patients
Expired(5)	01
Vegetative(4)	00
Severely disabled(3)	01(Hemiparetic)
Moderately disabled(2)	03(Cranial nerve palsy)
Good recovery(1)	16

Prognostic indicators:

The mean recurrence free survival (RFS) after the first surgery was 3.36 yr. Gender of the patient had no significant effect on the overall outcome and RFS (Male: 4.15 years, Female: 3.44 years). Similarly, the impact of age and location on RFS was not significant. Of the two patients with spinal HPCs, the one with cervical HPC had a recurrence requiring repeat surgery and radiation whereas the other patient with dorsal HPC was recurrence free four years post surgery. Patients with differentiated tumours (HPC II) had a better survival compared to anaplastic (HPC III) variants (RFS of 3.15 years vs 2.53 years). Gross total resection (GTR) offers the best chance for a recurrence free survival (RFS). RFS with GTR (3.95yrs) was superior to STR alone (2.4 yrs) and STR with radiotherapy (2.67 yrs). Radiotherapy alone was not seen to have a major role in preventing recurrence which was essentially related to the extent of resection. These observations did not have statistical significance mostly because of small number of cases (Table 5)

Table showing Recurrence free survival and prognostic indicators (Table-5)

Prognostic indicators	Characters	Percentage %	Recurrence free survival (RFS in yrs)
Sex	M(11)	52.38	2.95
	F(10)	47.62	3.54
Location	Skull base(13)	61.90	3.87
	Posterior fossa(3)	14.28	3
	Falx/parasagittal(3)	14.28	1.2
	Spine (2)	9.52	2.4

HPR	Grade I(18)	85.71	3.47
	Grade II(3)	15	2.53
Extent of resection	GTR (13)	61.90	3.95
	STR(8)	38.09	2.40
Radiotherapy	After first surgery(11)	52.38	2.47
	No(4)	19.04	2.5
Surgery with RT	GTR with RT(10)	47.62	3.54
	STR with RT (7)	33.33	2.67

Discussion

Hemangiopericytomas are malignant tumours which arise from Zimmerman pericytes, which are contractile spindle cells surrounding capillaries and postcapillary venules ^{3,4}. Most hemangiopericytomas (HPCs) are located in the musculoskeletal system and central nervous system HPCs are rare. Earlier grouped under angioblastic meningiomas they are now recognized as a distinct entity under the new WHO classification ². They carry a high risk of local and distant extra cranial metastasis and also have a high rate of recurrence, sometimes many years after the primary diagnosis and treatment. Gross total excision offers the best

outcome but the role of adjuvant therapy especially radiotherapy is controversial. Literature reports of large series are few and Martin et al's ⁵ recent systematic Meta analysis provides one of the most comprehensive data on this rare entity.

Incidence:

Hemangiopericytomas constitute 1-2 % of all intracranial tumours and 2-3% of all primary meningeal tumours ^{4, 6, 7}. As was seen in our series, HPCs occur most frequently in the fifth decade of life (mean 38-44 years), the average age of presentation being much lower than that of meningiomas ^{4, 6, 7, 8, 9}. Unlike in meningiomas, the sex predominance varies in different series, some being male dominant ^{6, 8, 9}, some female dominant ⁴ and others as in our series having equal incidence of male and females ⁷. Martin et al in their meta analysis of all the reported series on hemangiopericytomas observed that the patients' sex and age have no effect on survival ⁵. Our observation was similar and although females and patients in the age group 20-60 years showed a marginally better RFS, the result lacked statistical significance.

Clinical presentation:

HPCs mimic meningiomas in their presentation, which essentially depends on the size and site of the lesion. However, in view of their inherent malignant potential and faster rate of growth, the interval between initial symptoms and diagnosis is shorter with HPCs as compared to meningiomas, The median interval between initial symptoms and diagnosis is much shorter compared to meningiomas and can be as short as three months as observed in our series and by many others ^{4,6,8,9,10}. Intracerebral haemorrhage and other rare modes of presentation have also been documented in the literature ^{11,12,13,14} but was not observed in our series.

Location:

Hemangiopericytomas present as dura-based lesions often arising from the falx, tentorium, dural sinuses, and skull base. About 15% - 20 % occur in the posterior fossa¹⁵, and rare locations like the pineal, sellar and suprasellar regions and the third ventricle^{16,17,18} have also been reported by some authors. HPCs can exceptionally present as pure intraparenchymal lesions⁴. We observed a predilection for skull base in our series with thirteen (61.9%) patients having skull base tumours. We had three patients with posterior fossa lesions (14.28%), while two tumours were located in the spine, one in the cervical region and one in the dorsal region, both in the intradural extramedullary place. One of our patients with a primary tentorial meningioma developed a suprasellar recurrence eleven years after first surgery. Our study failed to observe any association between location and prognosis although some authors have reported that HPCs of the posterior fossa carry a more worse prognosis probably because of difficult surgical access, abundant cranial nerves and sinus invasion⁵.

Imaging:

HPCs are indistinguishable from meningiomas on imaging studies^{19,20,21}. Distinguishing features on CT scan are few and limited to i) narrow-based attachment ii) parenchymal invasion (mushrooming) iii) irregular or polylobulated borders iv) marked bone erosion and heterogeneous contrast enhancement^{6,19,22} v) disproportionate edema. Calcification is virtually not seen except in an odd cases^{4,5,8,23}. Erosion of the overlying bone seen on plain CT scan was a conspicuous finding in our series (8/20). On MR studies, the tumor was mainly isointense to hypo intense with the cortical gray matter on T1-weighted images and on T2-

weighted images nearly all the lesions were hyperintense . We also observed multiple flow voids and intra tumoral necrosis in nearly quarter of our cases and almost two thirds of the tumors showed irregular borders with significant perilesional edema. A higher level of myo inositol peak on MRS may help to distinguish a HPC from a meningioma. The angioarchitecture pattern in HPC is distinct from meningiomas and includes –a dual supply from the internal carotid or vertebral and external carotid arteries, with the dominant supply coming from the internal carotid artery, numerous corkscrew vessels arising from a main feeder within the tumor, a dense, fluffy, long-lasting tumor stain rather than the sunburst pattern of meningiomas, and no early draining veins ²⁴. Di Chiro et al found that HPCs may show hyper metabolic activity on positron emission tomography (PET) and that such “hot spots” on the PET study have an adverse prognostic significance, a finding not corroborated by others²⁵.

Histological Features:

The histogenesis of this tumor has been a matter of controversy for a long time until light microscopy, ultrastructural, and immunohistochemical data conclusively proved that meningeal HPCs represent the intracranial counterpart of soft tissue HPCs ²⁶ Grouped as “mesenchymal, non-meningothelial tumours” in the present WHO classification, HPCs are more aggressive than meningioma, and behave in a different way than meningiomas. Histopathologically, they are characterized by spindle cells with a rich vascular network, with large, dilated, “staghorn” vascular channels and can be graded as differentiated (WHO grade II) and anaplastic (WHO grade III) tumors. Differentiated HPCs excised completely have a good prognosis, whereas anaplastic grade III tumours which are sub totally excised carry a 20% risk

of local recurrences and a 53.3% risk of metastases respectively ²³. In our series also patients with differentiated tumours had a better survival compared to anaplastic variants (RFS of 3.15 years vs 2.53 years).

Surgery:

Surgery is the treatment of choice for HPCs and one of the most important factor for tumor control ^{4,27,28} is the completeness of surgical excision. Complete excision, however is possible in only 50- 83% of the cases⁴ in different series, a limiting factor being their vascularity, which may result in substantial intraoperative blood loss. We could achieve grade 1-2 excision in only 61.9 % of our patients. A major factor limiting radical excision including that of the surrounding dura was the base of skull location in thirteen of our cases. Preoperative embolisation to reduce intraoperative bleeding is not as effective as for some meningiomas because HPCs can parasitize leptomenigeal vasculature ²⁹. Direct percutaneous puncture and intratumoural injections of Nbutyl cyano-acrylate (NBCA) 24 to 48 hours before surgery as suggested by Casasco et al ²⁹ is another option to reduce the vascularity. We did not have any operative mortality in our series, but operative mortality for meningeal HPC can be high and ranges from 0 to 27% in different series^{6,8,30}.

Recurrence and Survival:

HPCs exhibit a relentless tendency for local recurrence and even when local control can be achieved, the risk of distant metastases remains a threat as long as the patient lives and all published series report the aggressiveness of HPCs ^{31,32,33,34}. Ours is no exception with a recurrence rate of 61.9%, increasing with each year of follow up. Five of our patients had multiple recurrences, two of them having recurrences at sites distant from the primary. In their series of 44 patients, Guthrie et al. found that

median survival after the first operation was 60 months, with actuarial survival rates of 67%, 40%, and 23% at 5, 10, and 15 years respectively, which is comparable to other series reported in literature^{4,7,28}. Guthrie et al. found a mean recurrence free interval of 47 months and calculated that the recurrence rate at 5, 10, and 15 years was 65%, 76%, and 87%, respectively while Jaakkola et al and Alan reported a mean interval to recurrence of 78 months and 65 months respectively^{4,8}. Our mean recurrence free survival (3.36years) is much shorter than those reported in literature probably due to the higher occurrence of skull base location and a lesser incidence of gross total resection. The reported observation that meningeal HPC tend to recur at shorter intervals after the first recurrence was not consistently noted in our series.

Metastases:

Meningeal HPCs are known to metastasize outside the CNS, the most common sites in descending order of frequency being bone, lungs and liver⁶. Surgical manipulation may facilitate distant metastases by disseminating cells into the circulation. The probability of developing metastases increases steadily with time, reaching 64% at 15 years⁶ and have occurred 2 to 20 years after diagnosis; the average period before metastasis being 63 to 99 months^{6,30,36}. Only one patient in our series had an extra neural metastasis, probably due to the shorter mean follow up in our study.

Radiotherapy:

Peripheral HPCs are known to respond well to radiation ³⁷, an observation not consistently observed in intracranial HPCs. For patients with meningeal hemangiopericytomas, it is thought that surgical removal followed by external radiotherapy reduces the risk of local recurrence. Postoperative radiotherapy had significantly increased disease free survival time (mean of 74 vs 29 months, $p < 0.05$) as well as a longer overall survival (92 vs 62 months) suggesting a role for RT ^{6,8,28,32,37,38}. In a recent study, EBRT after surgery decreased the local recurrence rate to 12.5%, compared with a rate of 88% after surgery alone ³⁶. These findings, however are not universally accepted, because several authors have observed no statistically significant difference in either time to recurrence or survival duration with or without radiotherapy ⁹. Radiotherapy does not seem to protect against peripheral metastasis or to increase the tumor-free interval ^{5,36}. Though most authors achieved initial tumor control in 99± 100% of the cases, regrowth occurred in 11 to 33% of the patients ¹⁵. Similarly, for recurrent tumours, it appears that radiotherapy after surgery did not prove beneficial. The recent metanalysis by Martin, does not indicate a survival benefit with the addition of post operative radiation and they do not believe that addition of radiotherapy to subtotal resection is an alternative to gross total removal ⁵. They recommend further validation that HPC require routine radiotherapy as summary of literature does not support its efficacy in extending lifespan following surgery regardless of the extent of resection. Moreover, Martin et al speculate that HPCs are relatively radio resistant and radiotherapy may be unnecessary.

Our institute policy is to advise radiotherapy for all patients with aggressive meningeal tumours. In our series radiotherapy prolonged the recurrence free survival

free period for patients with GTR compared to those with STR (3.54 years vs 2.67years). However we also observed that 41.7% (7/17) patients reported recurrence in spite of radiation. Similarly two out of the four patients who did not undergo radiation were free of recurrence.

The dosage of radiation and the role of preoperative radiotherapy are also controversial. Guthrie et al have observed a radiation dose response relationship, without local recurrences among patients receiving $> 51 \text{ Gy}^{6,36}$ and recommend doses of more than 5000 rad to protect against local recurrence. However, Martin found statistically significant relationship between radiation dose received and overall survival, with patients receiving more than 50 Gy having increased mortality compared to those receiving less than 50 Gy.

Radiosurgery offers a reasonable treatment option for recurrent HPCs after surgical resection but radiosurgical treatment of the primary neoplasm did not seem to confer protection from intra- or extra cranial metastases . Available literature suggest a 80% tumor control with a mean follow-up period of 3 years^{12, 25, 36} and a recommended tumour margin dose of 15 Gy^{39,40,41}. Sheehan et al. demonstrated in a series of 14 patients with 15 HPCs treated with radiosurgery, an 80% local control rate for recurrent intracranial HPCs using Gamma Knife surgery, with a median time to local recurrence of 21 months. They also demonstrated Kaplan-Meier survival rates of 76% and 100% 5 years after Gamma Knife surgery but reported remotemetastases in 29% of the patients, and thus concluded that local tumor control afforded by radio surgery provided seemingly little protection from distant metastases³⁹. The role of chemotherapy and other forms of adjuvant therapy is experimental and current evidence does not warrant its use²³.

Conclusion-

Hemangiopericytomas are rare tumours which mimic aggressive meningiomas clinically, but have a different histogenesis. HPCs are extremely vascular tumours and more commonly occur at skull base locations making radical removal a surgical challenge. Radical surgery is the treatment of choice and the role of adjuvant therapy as supplement to subtotal removal is yet to be established. Differentiated HPCs (HPC II) undergoing gross total resection fare better than anaplastic (III) variants with subtotal resection. Long term follow up is mandatory as HPCs have a relentless tendency for local recurrence and carry a risk of metastases outside the CNS even many years after diagnosis.

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**Sree Chitra Tirunal Institute for Medical Sciences &
Technology**

Proforma for patients with Hemangiopericytoma

A.GENERAL INFORMATION

- 1 1.1 Name
- 1.2 Age
- 1.3 Sex
- 1.4 Hospital No
- 1.5 Address
- 1.6 Phone number

1.7 Mobile

1.8 Email id

1.9 Date of admission

1.10 Date of discharge/death

1 Presentation

1.1 History of Radiation exposure

1.2 History of trauma

1.3 Headache

1.4 Raised ICT

1.5 Seizure

1.6 Focal deficit

1.7 Visual deficit

1.8 Ataxia

1.9 Incidental

2 Syndromic association

2.1 Neurofibromatosis

2.2 Gorlin syndrome

2.3 Associated tumours

3 Examination

3.1 Neurocutaneous markers

3.2 Fundus

3.3 Focal deficit

3.4 Visual deficit

4 Imaging

4.1 X-ray

4.1.1 Normal

4.1.2 Signs of raised ICT

4.1.3 Hyperostosis

4.1.4 Bone erosion

4.1.5 Calcification

4.1.6 Kyphoscoliosis

4.2 Myelography

4.3 CT scan

4.3.1 NECT

4.3.1.1 Hypodense

4.3.1.2 Isodense

4.3.1.3 Hyperdense

4.3.1.4 Calcification

4.3.2 CECT

4.3.2.1 Homogenous

4.3.2.2 Heterogenous

4.3.2.3 Non-enhancing

4.3.3 Bone changes

4.3.3.1 Hyperostosis

4.3.3.2 Bone erosion

4.4 MRI

4.4.1 T1

4.4.1.1 Hypointense

4.4.1.2 Isointense

4.4.1.3 Hyperintense

4.4.2 T2

4.4.2.1 Hypointense

4.4.2.2 Isointense

4.4.2.3 Hyperintense

4.4.3 Contrast

4.4.4 Special sequences

4.4.5 Cystic changes

4.5 MRA

4.6 DSA

5 Location

5.1 Intracranial

5.1.1 Vault

5.1.1.1 Frontal

5.1.1.2 Parietal

5.1.1.3 Temporal

5.1.1.4 Occipital

5.1.2 Base

5.1.2.1 ACF

5.1.2.2 MCF

5.1.2.3 Basisphenoid

5.1.2.4 Basiocciput

5.1.2.5 CP angle

5.2 Lateral ventricle

5.2.1.1 Frontal

5.2.1.2 Trigone

5.2.1.3 Temporal

5.2.1.4 Occipital

5.3 Third ventricle

5.4 Fourth ventricle

5.5 Multiple

5.6 Spine

5.6.1 Cervical

5.6.2 Thoracic

5.6.3 Lumbosacral

6 Surgery

6.1 Simpson's Grade of excision

6.1.1 Grade I

6.1.2 Grade II

6.1.3 Grade III

6.1.4 Grade IV

6.1.5 Grade V

7 Complications

7.1 Limb weakness

7.2 Visual deficit

7.3 Deep vein thrombosis and PTE

8 Histopathology

8.1 Specify

8.2 WHO Grade I

8.3 WHO Grade II

8.4 WHO Grade III

9 Adjuvant therapy

- 9.1 Radiotherapy
- 9.2 Chemotherapy
- 9.3 None

- 10 Followup Glasgow Outcome Scale
 - 10.1 At discharge
 - 10.2 6 weeks
 - 10.3 6 months
- 11 FurtherDuration

- 12 Mortality
 - 12.1 Operative
 - 12.2 Followup
- 13 Recurrence
 - 13.1 Yes
 - 13.2 No
- 14 Resurgery
 - 14.1 Yes
 - 14.2 No
- 15 If recurrence, use separate proforma set from page 2 for each recurrence.

ABBREVIATIONS

- 1) CNS- Central Nervous System
- 2) CT- Computerised Tomogram
- 3) CE- Contrast Enhancement
- 4) EBRT- External Beam Radiotherapy
- 5) FDG PET- Fluro dexoy Glucose positron Emission Tomogram
- 6) F/U- Follow Up.
- 7) HPC- Hemangiopericytoma
- 8) GTR- Gross Total Resection
- 9) GOS- Glassgow Outcome Scale
- 10) Gy- Gray
- 11) GKRS- Gamma Knife Stereotactic Surgery
- 12) IFN α - Interferon α
- 13) LR-Local Recurrence
- 14) MRI-Magnetic Resonance Imaging

- 15) MRS- Magnetic Resonance Spectroscopy
- 16) NBCA- N Butyl Cyanoacrylate
- 17) NAA- N Acetyl Aspartate
- 18) OS- Overall Survival
- 19) PET-Positron emission Tomogram
- 20) PDGFR-Platelet growth derived Growth Factor Receptor
- 21) RFS- Recurrence Free Survival
- 22) RT- Radiotherapy
- 23) SRS- Stereotactic radiosurgery
- 24) STR- SubTotal Resection
- 25) USFDA- United States Food Drugs Administration
- 26) VEGFR- Vascular Endothelial Growth Factor Receptor