Paediatric supratentorial high grade lesions- Outcome analysis

Submitted for MCh Neurosurgery

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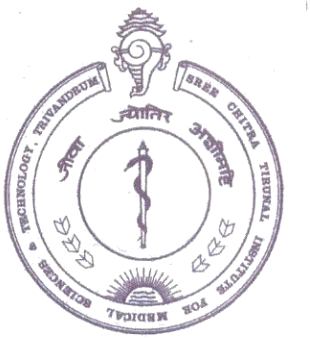

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DECLARATION

This thesis titled **Paediatric supratentorial high grade lesions-Outcome analysis**; is a consolidated report based on a bonafide study of the period from January 2013 to June 2015, 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 fulfilment of rules and regulations of MCh Neurosurgery examination.

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CERTIFICATE

This is to certify that the thesis entitled **Paediatric supratentorial high grade lesions- Outcome analysis;** is a bonafide work of **Dr. Chandra Sekhar Tavisetty** and was conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram (SCTIMST), under my guidance and supervision.

5/11/18

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INTRODUCTION

In children, the majority of primary supratentorial hemispheric tumors are gliomas. In contrast to adults, high-grade lesions are significantly less common than low-grade lesions, comprising only 20% of all hemispheric lesions in pediatric series. Overall, malignant gliomas represent approximately 6.5% of all newly diagnosed childhood intracranial neoplasms; this comes to an incidence of approximately two cases per million children annually. We have ample studies to understand adult high grade lesions over many years. By contrast, high-grade lesions in children and adolescents have remained a relatively under-investigated disease. Unlike the adult counterparts, paediatric high-grade lesions are not only distinct in their cytogenetic and molecular alterations. They will also show distinct type of lesion and difference in their distribution. Treatment and outcome also varies when compared to adult tumors. Here is an attempt to summarize and evaluate the epidemiology, clinical presentation, histopathological features, treatment, and outcome of pediatric high grade lesions

Review Of Literature:

Malignant brain tumors are the leading cause of cancer-related death and account for 20% to 30% of all childhood malignancy. The annual incidence of brain tumors has been rising, because of newer diagnostic modalities. There is slight male dominance, so many studies consistently showing a male/female ratio of about 1.5. More favourable histological subgroups have been found to occur in adolescents, whereas higher grade lesions, unfavourable sites, and poorer prognosis generally reported in children below 3 years[1].

The brain tumors occurrence in childhood and adulthood differs not only in histology but also in location[2]. Most of the childhood CNS tumors are infratentorial[3], in contrast to adults. In most of the studies reported supratentorial tumors are most common in below 6 months of age; however, location reverses after 2 years of age[3].

Age is also plays an important role in prognosis for children with brain tumors in general. Data analysis on survival rates shows survival is longer in age group10- to 15-years than those who are younger than 2 years. The overall survival rate of childhood brain tumors has improved considerably over the past several years can be attributable to earlier diagnosis and availability of better therapies[4]

Classification of tumors allows physician to make accurate prediction regarding the natural course of the disease. Response to certain treatment and prognosis can also be derived from a classification[5]. CNS tumors classified primarily based on cell of origin[2,6] and sub classified on the basis of existence of specific cell type as well. However such tumors can differ in their histologic, cytologic, and behavioural characteristics[2,5]. CNS tumors more broadly categorized by occurrence of age group and location.

The nervous system composed of nerve cells and supporting cells called *neuroglial.* Glial cells include astrocytes, oligodendrocytes, ependymal and microglia which outnumber the nerve cells by approximately 3 times more.

Neuroepithelial	**Non neuroepithelial**
Astrocytoma 50% [1,6,7]	Germ cell tumors (2.5%)
Oligodendroglioma	AT/RT(1.3%),
Ependymoma 10%	Choroid plexus tumor (0.9%),
Microglioma	Craniopharyngioma (5.5%)
PNET 1.9%;	
Mixed tumors	

Overall, the most common brain tumors seen in children are astrocytomas, ependymomas, and germ cell tumors. The incidence of these tumors, however, varies within age groups, and certain lesions tend to occur in particular age during life. Before two years of age choroid plexus tumors, desmoplastic

infantile astrocytomas, teratomas, and neuroembryonal tumor are most frequent. Between 3 to 11 years of age astrocytomas and craniopharyngiomas predominate. After 12 years, germ cell tumors are most frequently encountered and after 15 years the incidence high grade astrocytomas become more common.

ONCOGENIC FACTORS

Population studies proposed that several syndromes and genetic markers have been associated with brain tumor occurence.The disorders associated with specific chromosomal abnormalities; leads to alteration in genes, which typically regulate normal cell growth but, when altered, lead to tumor genesis.

Syndrome	Genetic abnormality	Brain tumor association
NF1	chromosome 17	optic glioma , malignant nerve sheath tumor.[2,6]
NF2	chromosome 22	Meningiomas and vestibular schwannomas.[6]
Tuberous sclerosis	chromosome 9	Astrocytomas.
VHL syndrome	chromosome 3	Cerebellar hemangioblastomas.

Several common brain cancers are linked to certain genetic tumor markers that are prognostic indicators. Examples include over expression of the oncogene *p53* in childhood gliomas. *p53* mutations seen in approximately 40% of malignant childhood gliomas after 3 years age[2,6] and associated with a poor prognosis independent of both the clinical and histology[8]. Interestingly, choroid plexus tumors are intraventricular epithelial tumors, stain for the *INI1* gene.

CLINICAL FEATURES

It is imperative to the physician be able to recognize the signs and symptoms of brain tumors in children at initial encounter which are almost accounts for one fourth.[9] The signs and symptoms like raised intracranial pressure (ICP), focal neurological deficits, at diagnosis are typically dependent on tumor location. The signs and symptoms may be progressive and can delay in making diagnosis by doing lengthy investigations. Brain tumors should be a part of differential diagnosis in a child presented with the aforementioned symptoms, because early diagnosis plays role not only in treatment and also in prognosis[10]

Raised intracranial pressure (ICP):

Approximately 40% of childhood intracranial neoplasm's presents with raised ICP feature. The symptoms of elevated ICP are morning headache, nausea, and projectile vomiting and generalised weakness.[2,3,11] Less commonly enlarged head and a prominent fontanelle can be seen in infants.[11]

Hydrocephalus is most commonly seen with infratentorial tumors when compared with supratentorial tumors.

Seizures

Seizures usually seen with supratentorial lesions, increases with age and may also be a sole sign.[6]

Focal neurologic deficit:

Focal neurological deficits frequently seen in supratentorial tumors; either because of the local mass effect or infiltration; the deficits vary according to location[2]. Paralysis of up gaze, paresis of accommodation and convergence nystagmus occurs due to compression of midbrain tectum and collectively called as Parinaud's syndrome.

Others:

Weight loss or gain, growth retardation, precocious or delayed puberty, and excessive thirst and urination are more commonly associated with tumors located near the pituitary gland and hypothalamus.

DIAGNOSTIC EVALUATION

Neuro-imaging plays critical role in the evaluation of a patient with a suspected brain lesion. The introduction of computed tomography (CT) and MRI revolutionized the management of brain tumors. CT and MRI now become the mainstay not only in diagnosis, also in surgical planning and treatment.

Contrast administration in these studies essential in identifying subtle lesions, as well as to demarcate the margins. However enhancement is not useful for paediatric gliomas in predicting a cancer phenotype. Some childhood gliomas like pilocytic astrocytomas, often show diffuse contrast uptake despite being lower grade.

Newer developments in CT and MRI have led the lesion further distinguish abnormal tissue. These imaging modalities are not only useful in pre op diagnosis but also in postoperative period for surveillance of tumor to identify residual or recurrent, secondary malignancies, or secondary effects of therapy such as radiation-induced necrosis. Fluid-attenuated inversion recovery (FLAIR) MRI images are better in differentiating the tumor from adjacent normal parenchyma by blunting the hyper intense signal produced by cerebrospinal fluid on T2-sequences.[12] In addition, spectroscopy (MRS) provides the metabolic biochemical components of cells.[2,12,13] Especially, MRS provides information about peaks of the neuronal membrane turnover marker like *N*-acetylaspartate, choline, as well metabolic marker like as lactate and creatinine [2,8,13] Not only the level of markers, their ratios can also help to delineate brain tumors, and also to differentiate neoplasia from radiation necrosis.[8,13] However, MRS should be used with caution, because alike patterns can also be found in non neoplastic masses like abscesses and within different tumor types and it is more appropriate for long-term follow-up.

Recent imaging modalities that can be used to detect CNS abnormalities are Positron emission tomography (PET) and single-photon emission computed tomography (SPECT). PET- FDG assesses uptake of the radioactive metabolite, isotope 18F-fluorodeoxyglucose (FDG), which provides an objective measurement of tissue metabolism. Higher the metabolically active more the FDG uptake and usually seen in high grade lesions such as malignant tumors. SPECT is capable of measuring the distribution of blood flow by detecting the radioactive tracer technetium 99m (99mTc).[12,1] there by increased levels of 99mTc uptake occur in metabolically active areas as well. 99mTc-SPECT as well as PET help to delineate high grade areas within heterogeneous lesions and differentiate between necrosis and recurrence.[7,12,15].

However the diagnosis of some brain malignancies, does not end with standard imaging, may require imaging of entire neuraxis. Some tumors like medulloblastomas, germ cell tumors, ependymomas, and PNETs have a tendency for dissemination within the nervous system.[2,11] If these are the lesions for evaluation, imaging must include the entire nervous system to look for small metastases preferably prior to surgery. Spinal imaging must be performed preferably after 2 weeks following surgery, is necessary to avoid blood product artefacts. In addition, CSF analysis also has a role to assignment the treatment categories in patients with image negative drop metastasis.[2] Germ cell tumors can produce several proteins, can be detected in body fluids. Such markers include beta- hCG, alpha fetoprotein, and placental alkaline phosphatase, whose levels can help to establish the diagnosis;[2] these markers

can also be assessed by immunohistochemistry of tumor tissue after biopsy or resection.

TREATMENT:

Includes surgery followed by adjuvant therapy, surgery being the mainstay[2,3]. Prognosis of brain tumors is mainly related to the order of surgical decompression without significant neurological impairment. [2,9]. However, there are exceptions to this rule ex:- Germinomas are known to be extremely sensitive to radiation, with a long-term survival rate greater than 89% with neuraxis irradiation alone.[16] If preoperative markers and biopsy; consistent with germinoma surgical decompression not warranted and should proceed with neoadjuvant therapy unless otherwise patient had hydrocephalus; it must be treated first.[11] Endoscopic third ventriculostomy (ETV) is the treatment of choice.[11] Frequently, after ETV persistently elevated ICP, warrants permanent CSF drainage like shunt.[16] Additionally, tumors located in eloquent areas and diagnosis is doubtful on imaging the role of surgery limited to biopsy only .[11]

Radiation therapy is avoided in young children especially below 3years of age, due to its deleterious effects on neuraxis[2]. The choice field of radiotherapy to be given is determined by the size, location and tumor tendency to spread in subarachnoid space.[3]

Several studies reported that paediatric brain tumors are more responsive and well tolerated to chemotherapy than adult counterpart. Various drug regimens have been used in combination to increase efficacy and responsiveness. More investigational therapies are under the focus and being developed in the hope of improving drug delivery by the use of immunotherapy.[2,4,8, 17]

GLIOMAS

Brain tumors can be classified depending on cell of origin: glial, neuronal, mixed glial and neuronal, and primitive neuroectodermal. These can be differentiated by using clinical history, physical examination and advanced imaging technique. These tumors are unique in their molecular genetics. Management options and prognoses of these tumors are entirely different from such lesions in adults.

EPIDEMIOLOGY

Hemispheric tumors account for <26% of all primary brain tumors in children beyond infancy.[18] Supratentorial low- and high-grade gliomas each occur annually in less than 1 per 100,000 individuals younger than 20 years, with low-grade being more common.[19] Second most common tumor is Supratentorial primitive neuroectodermal tumors (SPNETs) and more frequently reported in less than 10 years.[20] Male dominance reported only in oligodendrogliomas[18,21]

Familial genetic syndromes associated with likelihood for the development of primary intracranial tumors. Other risk factors are history of previous nervous system mass lesion, cranial irradiation or systemic malignancies, reported to be increased risk for the development of secondary brain neoplasm.[22] Broniscer et.al reported cranial irradiation is dose dependent predisposing factor for development of secondary neoplasm. [23]

GLIAL TUMORS

Imaging

Imaging features that help in predicting the biologic behaviour of hemispheric tumors is 1.Density of cells 2.excertion of mass effect on surrounding tissue, 3. Cortical tumor 4. Overlying bone changes. Symptomatic child suspected to have brain lesion evaluation, begins with computed tomography (CT).

Differential findings on CT brain:

Low grade	High grade
Hypo-dense	Hyper-dense with surrounding hypo-dense regions
Calcification [24]	
Remodelling of the inner table of the skull	
Cavitations' is contrasted with the well-circumscribed ring of enhancement	Cavitations' surrounded by contrast heterogeneity

MRI

Recent day's magnetic resonance imaging (MRI) has become the standard imaging modality of choice in evaluation of brain tumors. High-grade gliomas have mixed signal intensity, with predominant hypo intensity on T1-weighted and hyper intensity on T2-weighted images.[24] A broad region of T2 or FLAIR hyper intensity surrounding the tumor represents the highly infiltrative growth characteristic and surrounding edema frequently seen in these aggressive tumors. Regions of hypercellularity within the heterogenous lesion may reflect as bright signal on diffusion-weighted imaging. Magnetic resonance

spectroscopy depicts the elevated levels of choline, *N*-acetylaspartate, and lactate and a rise in the choline-to-creatine ratio. [25]

Pathology:

Glial tumors classified on their cellular composition. Histopathologic examination is essential to differentiate high grade from low-grade lesions. Grade III and IV are the World Health Organization (WHO) high grade lesions.

Grade III tumors display cellular pleomorphism, frequent mitoses, and the hypercellularity lacking in grade II lesions. Presence of necrosis changes the tumor grade to IV. Both AA and glioblastoma, demonstrate immunohistochemistry positive for GFAP. A high index of proliferation confers worsened prognosis.[26]

Treatment

Surgery:

Gross total resection is the primary goal of surgery in hemispheric tumors. Biopsy never been recommended unless the tumor is located in such an area that limit the ability to perform extensive resection. From an oncologic point of view, extensive resection improves local tumor control as well as extent of life irrespective of pathology.

Unlike adult counterparts, 5-year survival rate < 50% in paediatric high grade gliomas [27,28,29,30] Debulking of tumor more than 90% has been associated with better outcomes in both AA and glioblastoma. [27, 31-35]. The value of total resection first has been instrumented in CCG studies 943 and 945.

five year event survival rate reported in CCG 945 trial	GBM	Anaplastic astrocytoma
Resection 90% or more	35%	44%
subtotal resection	17%	22%

Differences in survival were statistically significant[35].The role of a second resection in improving survival has yet to be well defined.

Aggressive tumor removal not advisable in tumors that infiltrate vital anatomic compartments ex:- the primary motor cortex, descending corticospinal tracts, dominant language centers, diencephalic or mesencephalic compartments, or both hemispheres.

Goal of maximal tumor removal is also enhanced through the incorporation of several operative adjuncts ex: integration of high-resolution MRI with triplanar navigation intra operative modalities like ultrasound and MRI. Some reports regarding resection under fluorescence has suggested improvement in order of mass decompression. [36]

Intraoperative brain mapping is an important safety mechanism for lesions located around eloquent areas. Immaturity of brain in younger children may render the direct stimulation ineffectual; detection of the phase reversal potential is useful in these patients [37]. Cortical localization of primary language area is difficult in children younger than 10years, because it requires co operation[38] and this can be overcome by functional MRI.[39]

Adjuvant therapy:

Radiotherapy

Noteworthy studies on adjuvant therapy evaluation for paediatric high-grade gliomas, have included cranial irradiation as initial management in appropriate children[27,35,40]. Data from recent studies suggest that role stereotactic radio surgery, limited to patients, who are not a candidates for surgery. [41]

Radiation therapy is classically reserved for children older than 3 years due to its well established cognitive risk.[42],[43] . Reported secondary neoplasm following radiation is significant, but it typically outweighed by the survival benefit in patients with malignant lesions.[44]

Chemotherapy:

It has become standard adjuvant for paediatric high grade gliomas following CCG 943 publication in 1989. The 5-year event-free survival rate in chemo-radiotherapy was 46% when compared with radiotherapy alone 18%.

Chemotherapy is an even more important tool for children too young to undergo irradiation. For high-grade glioma, the North American Paediatric Oncology Group reported a 3-year event-free survival rate of 43% only with adjuvant chemotherapy [31, 42] In another recent trail under the French BBSFOP protocol reported a <40% five-year event-free survival rate for chemotherapy alone following decompression of tumor.[32] Despite being safe in long term measures chemotherapy in younger children, risk of myelosupression, and rate of opportunistic infection is not negligible and must be recommended in poor KPS score patients. Secondary malignant gliomas survival results are found to be in dismal. [43]

PRIMITIVE NEUROECTODERMAL TUMORS

Hemispheric SPNETs included in neuroectodermal tumor group. Histologically they are composed of hyper cellular blue cells that have scant nuclei and frequent mitoses[44]. PNET have tendency to disseminate along the neuraxis.

PNETs exhibit heterogeneous contrast enhancement with edema[45] and better demarcated from normal brain parenchyma when compared with high grade gliomas. Calcification and intratumoral haemorrhage can be seen

PNETs are treated with multimodal therapy consists of surgery, irradiation, and chemotherapy.

Role of surgery in PNET:

Aggressive resection has been shown to improve survival in children with SPNETs. Reported 4-year survival rate and 5-year event free survival is better in patients who had post operative residue less than a 1.5-cm2 in series by Albright's Pittsburgh. [20, 46,47].

Role of RT in PNET

HIT TRIAL	63children	Post surgical RT only significant predictor for PFS
Mc Bride [48]	15 patients with RT+CT or CT only	Patients who has received radiation therapy remained recurrence free

Primitive neuroectodermal tumor (PNET) has higher likelihood of dissemination along the neuraxis unlike gliomas, favours craniospinal radiation along with booster dose to the primary**.** [49]

Chemotherapy has become the standard of management over the past 20 years in the initial management of PNETs at large institutions.[20, 45, 46] The Prospective Trials by German Brain Tumor administered chemotherapy before and after irradiation and reported a 49.3% 3-year progression-free survival rate with optimal surgery followed by chemoradiation.[32] Even though the efficacy of "8-in-1" regimen in the treatment of high-grade glioma is demonstrable but failed in childhood PNETs. [50] The significance of temozolomide in PNET treatment yet to be proved.

Unlike SPNET, reported 3year event free survival rates as high as 60% with multimodal therapy in pineoblastoma,[51,52] probably due to these tumors are amenable to complete resection and chemotherapy accounts for this survival advantage, although there is no definitive evidence from literature..

Tumor genetics

Even though paediatric HGG histologically identical, they differ in occurrence of genetic alterations when compared with adult lesions.

EGFR[53]

EGFR	Amplification	Over expression
Adult HGG	+	
Paediatric HGG	<5%	+

However, there is no clear evidence that neither *EGFR* gene amplification nor over-expression has effect in terms of prognosis.[54,55,56]

The *TP53* is perhaps the most frequently reported genetic alteration in childhood malignant lesions. CCG 945 study, reported that 33% lesions harboured *TP53* mutations.[57,58] Sung and colleagues studied the molecular genetics of 29 paediatric high-grade gliomas and found all but 1 to demonstrate preferential inactivation of the p53.[55] In childhood tumors over expression of p53 is an indicator of poor prognosis.[59] However, there is no definitive evidence

of prognostic correlation in adults [60]. The PDGF receptor has also been found to be over expressed. [61]

Investigation of medulloblastoma genetics, which may abide relevance in understanding the molecular pathology in PNETs, have revealed abnormalities in activation of the Wnt, Hedgehog, and Notch pathways.[62,63]

EXPERIMENTAL THERAPY

High-dose chemotherapy with autologous stem cell rescue for PNETs has been shown to be of greater benefit and provide the potential for complete response in children with recurrent disease.[64]

BBB prevents the medications to achieve therapeutic concentrations in brain tumors. Children's Oncology Group conducted phase I and II trial to know the effect of imatinib on recurrent tumors and role of lobradimil in combination with carboplatin respectively. These trial concluded that there was no role of lobradimil to increase the level of carboplatin in nervous system.[65,66]

However, in nervous system greatest concentration can be achieved by interstitial infusion; where by small catheters are used as a vehicle for direct delivery of agents to the parenchyma[66-70]. In adults, phase I and II as well as a phase III trial on recurrent malignant gliomas used these technique to deliver the recombinant immunotoxin interleukin-13-PE38 [71,72].

Ependymomas:

Tumors arising from the ependymal lining of ventricle are the third most frequent paediatric brain tumor. These tumors are surgically curable and surgeon has a crucial role in the management. The current management protocol childhood ependymoma is maximum safe resection followed by tumor bed radiotherapy; chemotherapy is indicated in recurrent tumors not being used as part of standard management protocol.

Overview

Ependymomas are <11% of paediatric brain tumors and the mean age of presentation is around 5 years.[73,74,75,76] Approximately 4.5% of ependymoma patients shows evidence of leptomeningeal dissemination at the time of diagnosis[77] Different trial reported 5-year survival between 50% to 64%; and progression free survival between 23% to 45%.[73,73,78,79,80] Recurs of tumor typically seen at the site of the original tumor, but approximately in 18% of cases there distant metastasis.

Intracranial 90%	1/3 supratentorial	58% in lateral ventricle or third ventricle 42% away from ventricle
	2/3 infratentorial	Fourth ventricular floor (58%) Lateral aspect (33%) Roof of fourth ventricle (9%)

Prognostic factors

Extent of disease and amount of tumor decompressed at surgery are considered to be the determining factors in prognosis of central nervous system ependymomal tumors.

Extent of resection

The order of decompression is a single most important determinant of outcome in ependymomas.

Resection order [73-76, 78-89]	Five year survival	Five year event free survival
More than 90%	65-78%	50-74%
Less than 90%	22% to 47%	<25%

Repeated resection has been advocated by many authors in case of residual tumor found on immediate postoperative imaging. [83, 90, 91]

Grade of tumor on histopathology

The role of histologic grading of ependymoma in determining the prognosis of patients is controversial.[75,80,84,86,87,92-95] In a 50 patient co hart of contemporary ependymomas from St. Jude children hospital, reported 2year event free survival in classic ependymoma significantly better than anaplastic ependymoma and grade of the tumor only significant following irradiation in terms of survival.

Age at presentation

Patients younger than 3 years of age at the time of presentation have a poorer prognosis than older ones. Reported five-year survival rate of 61% for children aged 2 to 3 years, significantly better than children aged below two years in which five year survival only 26%.

Pathology

Ependymomas can be diagnosed straight forwardly by histopathologic examination and immunohistochemical stain. Ependymomas exhibit moderate cellularity with monomorphic nuclei; contain perivascular pseudorosettes, less commonly true rosettes, rarely demonstrate endothelial proliferation, and they are usually positive GFAP stain.

Grade-ii	Grade iii
Nodules with increased cellularity and mitotic activity. [96]	Brisk mitotic activity, vascular proliferation, pseudopalisading necrosis, clears ependymal differentiation, perivascular pseudorosettes, cytologic atypia, and microvascular atypia. [96]

Poor prognostic histopathologic features
Absent true ependymal rosettes or perivascular pseudorosettes. Presence of necrosis, endothelial proliferation, and a mitotic index greater than 5

Role of mitotic activity in prognostification significant only in supratentorial ependymomas as observed by some authors [97]

Hereditary tumor syndromes

There is well documented association of ependymomas with hereditary syndromes; however the majority are sporadic. Even though there is well known association of NF2 with intramedullary spinal ependymoma, the probability of increased risk of developing brain ependymomas is unclear. There is no reported mutation of the *NF2* gene in intracranial ependymomas, myxopapillary ependymomas, or tanycytic ependymomas. [98] The *NF2* gene is located on chromosome 22q and loss of genetic material on same is well known in intracranial ependymomas, but they do not harbour *NF2* mutations. This supports an existence of another distinct ependymoma tumor suppressor gene in this region of the genome.

Ependymoma has also been reported in patients with the Li- Fraumeni and Turcot's syndrome (due to a mutation in the *p53*, mutation of in the *APC* gene on chromosome 5 and an overactive Wnt signalling pathway respectively). [99, 100] . However, in sporadic ependymomas somatic mutations of *p53* are not commonly found and likely do not play a role in their pathogenesis.[101, 102]. And the *APC* gene and Wnt signalling role in sporadic ependymomas has not been elucidated. Some of the unrecognised familial syndromes have also been reported with an increased occurrence of ependymoma.[103-105]

Cancer genetics

On G-banding karyotyping of ependymomas, there is frequent deletion of genes on chr 22q, 6q, 9q, 17p, and 11q and addition of genes on 11q [98, 100, 106-111]. LOH of chromosome 22q is more common seen in adult ependymomas.[100.]

Neuroimaging

MRI is the cornerstone imaging modality in ependymoma evaluation. Children diagnosed with brain ependymomas should undergo pre-operative imaging of spine also. Postoperative imaging should be done before 3days of surgery or couple of weeks later; in between this period difficult to interpret the extent of resection probably post surgical artifacts. Leaving haemostats in the wound is strongly discouraged; these can interfere with the interpretation of postoperative imaging.

Ependymomas are notorious to spread to adjacent areas through existing natural foramen. A careful and detailed inspection of all images is necessary for accurate determination of the extent of the tumor, which will helpful in preoperative planning treatment. Interpretation of ependymoma images can pose a difficulty, because of its heterogenous enhancement pattern. Supratentorial ependymomas have a distinct margin from the surrounding normal tissue; hence their surgical management is straight forward

Keen observation of preoperative images is crucial for complete resection at the time of surgery, to avoid probability of leaving the non enhancing part of

tumor. Most of the recurrence or tumor progression has been reported between one to two years after the initiation of therapy. Earlier the detection of recurrence on surveillance imaging increases the chance for alternative therapies and better outcome in asymptomatic patients rather than in symptomatic patients, however there is no definitive proof.[112, 113]

Preoperative spinal imaging useful to detect leptomeningeal spread, in about 5% of newly diagnosed ependymomas at the time of presentation. Evaluation of spine with imaging should be delayed at least 7 to 10 days after any invasive procedure on nervous system.

Only partial response has been reported with chemo radiotherapy. Even though ependymomas appears to be decreased in size, contrast enhancement may take approximately 1 year to disappear owing to disappearance of vascularity. After full course of radiation therapy, recurrence rate found to be rare in first year. Effect of chemo regimes on ependymomas may take six months to become evident.

Initial surgery

Extent of resection has the greatest impact not only on the extent of life of patient and also improves wellness of patient's further life. Childhood ependymomas are most often locally invasive disease at the time of diagnosis. Recurrence has been noted most often at the resection margin, but these tumors are known to spread across the subarachnoid space and increase the

mortality. Only in 42-62% of patient with ependymomas could achieve complete resection, which has paramount importance in patient survival.[74,76,79,87] Most of the retrospective reviews and few of prospective trials have reported that gross total resection has been overrated in ependymoma management.[73-76, 78-80, 84,87, 114] Complete resection is possible only in tumors that are supratentorial and those originating from the roof of the fourth ventricle.

Resection order	No.of patients	>90%	<90%
Sutton and colleagues [76] 5year overall survival	45	60%	21%
Pollack and associates [79] 5year overall survival		80%	22%
Perilongo and co-workers [75] 10year overall survival 10 event free survival	92	70% 57%	32% 11%
Robertson and colleagues [80] Prospective trial	35	66%	11%

There is overwhelming evidence that cytoreductive surgery is beneficial to children with ependymoma and supports maximal safe resection to lessen the tumor burden to improve the chance of long-term survival.

Some studies have reported that surgery alone as a sole therapeutic option for children with supratentorial localised ependymoma particularly in the absence of high grade features on histopathology examination and when one can able to remove a rim of normal parenchyma matter around the tumor margin. Resection margin biopsies had been suggested if surgery alone used as the therapeutic option.

Role of surgery in residual or recurrence

Repeat surgery has been advocated in patients who have not received near total decompression, to reduce tumor load, except in those cases in which resection may injure critical structures. Chemotherapy may delay the surgery if given before second surgery owing to decrease in the vascularity of the tumor and provides an opportunity for children to develop physically as well as mentally. [91, 115]

Redo decompression has been advised for ependymoma without any deleterious effect on morbidity [91,115]. From a 40 paediatric ependymoma cohort from St. Jude children hospital, 90% of patients received >90% decompression and reported successful resection in the order more than ninety percent even at immediate second surgery may provide the opportunity to lower the dose of

radiation and increases survival time. There was a lower complication rate and improved performance, if second look surgery performed before 30days. Local recurrence that is amenable for surgical resection is an ideal condition for cytoreduction thereby reduces the burden of tumor.

Surgical technique

Generous craniotomy may enhance the tumor margin visibility clearly, removal of a thin rim of normal tissue advised in tumor at noneloquent areas. Pure ventricular ependymomas are rare in supratentorial compartment. Preoperative MRI is helpful in identifying the predominant feeding artery of the tumor.

Radiation therapy

Radiation following surgery has become a part of the standard of care for ependymoma patients. Mork and Loken [116] reported survival rate of 17% for patients who underwent surgery only and 40% for those who had received radiation following resection. In a classic ependymoma withhold of radiation after gross total resection with adequate margin is acceptable, but not in anaplastic ependymoma. [85, 117]

One year and two year delay in radiotherapy following surgery has worsened the overall survival from 88% to 38% in a series of Paediatric Oncology Group study. [114] Ependymoma shows leptomeningeal dissemination in less than 5% of newly diagnosed patients. Reported risk factors for metastasis are young age, decompression less than 90%, high grade and high proliferative index on

histology.[118] Most of the recurrence do so at the primary site, regardless of the location of the primary and or its histopathology grade.[73,75,76] There is no role of prophylactic craniospinal irradiation in localised ependymomas as suggested by multiple retrospective trials.[74, 90,119, 120]The current recommendation craniospinal irradiation only limited in patients with leptomeningeal spread.

Review of various studies had shown dose response rage for ependymal tumor is between54-60 Gy, however the optimal radiation dose is still uncertain.[121,122] Conformal radiation therapy (CRT) limits the radiation dose highest at the primary site, their by decreases the exposure dose of surrounding normal parenchyma [83]. In St.jude trial in 88 patient co-hart children reported progression free survival of 74□□5% at 3years and less cognitive affect in children who has treated with CRT following gross total resection. This study included 54% of children, whose age was less than 3years during radiation therapy.

Radio surgery use in ependymal tumor has been reported good local control and no significant deleterious effect on brain[123-125]. Patients at high risk for anaesthesia and very small tumors in eloquent area can be appropriately managed by Stereotactic radio surgery. Role of repeat radiation following surgery in recurrent ependymoma after maximal safe surgical resection of the recurrence, in the form of fractionated external beam radiation has been reported in some series.[126]

CHEMOTHERAPY

Chemotherapy is not a part of standard treatment, its role in the management of childhood ependymal tumors still unclear. Reported response rate of ependymal tumor to a sole agent is approximately 10%, and complete response is less than 5%.[127] Cisplatin seems to be the most effective agent, among the tried chemotherapeutic agents; however there is no survival benefit in children who had shown response to chemotherapy. Cytotoxic Chemotherapeutic agents did not show benefit in newly diagnosed ependymomas. [73-76, 79, 119, 121]. Randomised control study conducted by Children's Cancer Group and Paediatric Oncology Group did not show any survival extension in additional chemotherapy received group. A Societé Internationale d'Oncologie Paediatric study reported 33% and 22% of progression free at 2year and 4year survival following maximal resection in a co-hart of 73 patients treated with chemotherapy for maximum of 18 months without radiotherapy [128]. These results are significantly worse than historical controls treated with radiotherapy following surgery. Inspite of maximum efforts by paediatric oncology community, the role chemotherapy in the treatment of children with localized ependymoma could not be concluded.

A prospective trial conducted by United Kingdom reported adjuvant chemo may play a role in delay in start of radiation without affecting survival in children less than three year age group with intracranial ependymal tumors. [129] Some authors suggested chemotherapy may also have a role before second surgery for better tumor border delineation and easier dissection.

INTRACRANIAL GERM CELL TUMORS

CLASSIFICATION AND EPIDEMIOLOGY

Germ cell tumors can be classified according to histological picture, location of the lesion, and the presence or absence of CSF dissemination. The WHO histological classification describes six types, but from a treatment point of view classifying them as germinomas, nongerminomatous germ cell tumors (NGGCTs), and teratomas is more helpful.

Distribution of tumors [130-135]

Germinomatous	50%
Non germinomatous	
Embryonal carcinoma	5-10%
Endodermal sinus (yolk sac) tumor	5-10%
Choriocarcinoma	5-10%
Mixed tumors	10-20%
Teratomas	10-20%

Teilum has demonstrated that the every subtype of germ cell tumor is either embryonic like germinoma, teratoma or extra embryonic like NGGCT).[136] Presence of nongerminomatous component is shown to affect outcome in a unfavourable manner, therefore sufficient tissue sampling for histologic analysis and detailed evaluation of tumor markers are essential in directing the required

therapy. Germ cell tumors can also be classified according the location of tumor viz. suprasellar and pineal region (because most of the intracranial germ cell tumors occur in these region).[132, 137, 138] Pineal region tumors being more common as compared to the suprasellar located tumors represented by 2 : 1 ratio. [130,137] Age and sex affect the distribution of germ cell tumor, with female preponderance in suprasellar tumors and male preponderance in pineal region tumor.[135,137] All germ cell tumor taken together present during puberty. Tumors with non germinomatous elements present early in life during childhood. [131] Occurrence of tumor in both location i.e. Pineal and suprasellar location is around 10%.[130,137] The reason behind this bifocal origin is still debated but most accepted explanation is metastatic spread form one site to other rather than separate origin of tumor at both locations. This former theory was supported by presence of metastatic deposit on endoscopy..[139] This metastatic deposit can also explain the occurrence of tumor at atypical locations like basal ganglia and posterior fossa. [137, 138]

Clinical features

The clinical signs and symptoms depend largely on the location of the lesion and few by tumour histology and patient age. Pineal region tumor was characterised by perinaud's syndrome or syndrome of aqueduct which encompasses impairment of both up gaze and pupillary constriction to light, retraction nystagmus on attempted convergence. They can also present with raised ICT. Whereas suprasellar lesions typically cause disturbances of hypothalamic pituitary axis[130,134,137,138] Most common hormonal disturbance

seen is diabetes insipidus, which is almost a rule. Visual blurring and field cuts are also more common in suprasellar location of tumor.[137,140] Diabetes insipidus can also be seen in few subset of patients with purely pineal tumor, which could be explained by the metastatic potential of such tumor to hypothalamus and 3rd ventricle floor.[130,137,139] Similarly, precocious puberty is mainly seen in both genders if tumor is suprasellar location and only in males if the tumor is present in pineal location. Precocious puberty is because of direct effect on hypothalamus or by over expression of human chorionic gonadotropin by the tumor.

NGGCTs are diagnosed earlier than germinomas. NGGCT's are more aggressive as compared to germinomas and hence diagnosed early. Germinomas, normally present only features diabetes insipidus which is usually undetected for many years before they seek medical attention.[130,137,140,141] Germinomas originating in ectopic locations like the basal ganglia or thalamus have shown to present late with seizures, focal deficits, and cognitive dysfunction before diagnosis.[142] Among the non germinatous tumors, choriocarcinomas has tendency to present acutely because of accelerated growth of tumor and propensity for bleed.[131,137] Germ cell tumors infancy present mainly with raised ICP features macrocephaly, widely placed sutures, and a tense fontanelle. [130,134,137] Sometimes the presentation can be very vague like failure to thrive and regression of developmental milestones making diagnosis more difficult. Most of the time tumors in such cases are very large[143]

DIAGNOSTIC EVALUATION

Teratoma by definition has components of all cell lineage, and has heterogenous appearance on imaging. Presence of fat and bone which are easily seen on imaging help in diagnosis of teratoma.[144] . Same is not true with other germ cell tumors which can mimic pineal parenchymal tumors and suprasellar cystic lesion and difficult to identify on imaging. In the past such limitations were overcome by using a indirect diagnosis of germ cell tumor was giving test dose radiation which literally melts away the tumor and confirming the same. Biopsy was reserved for non responder's only.[145] But now the protocol does not allow test dose radiation to be used for diagnosis instead many CSF and blood tumor markers and advanced sequence MRI are being increasingly used for this purpose. Tumor markers used are alpha-fetoprotein (AFP) and beta-hCG, PLAP. AFP is elevated in yolk sac tumor, and beta-hCG is elevated in choriocarcinomas. Placental alkaline phosphatase has been shown to be specific for germinoma. If these tumor markers does not help in making diagnosis then histologic diagnosis is warranted130,131,134,137,138.

AFP and beta-hCG	High level	Low level	Absent
NGGCT	Present	Germinoma with syncytiotrophoblastic cells [146]	Biopsy

Another germinoma marker i.e. soluble c-kit present in CSF though has fairly good [148] sensitivity and specificity, but the results have not be validated by clinical series.

High propensity of CSF spread dictates evaluation of spine for metastasis. CSF cytomorphology and contrast MRI are used for this purpose. Dissemination is commonly seen in tandem germ cell tumors are around 10% of solitary either pineal or suprasellar tumors.[135, 149]

Surgical management

In the management of germ cell tumors, role of surgery is primarily depends on the histology and location. Tumors of the pineal region usually presents with obstructive hydrocephalus, which warrants some form diversion. Ventriculoperitoneal shunt was the modality of diversion procedure, which not only allows immediate relief of symptoms but also provides CSF for examination. Shunt poses risk of shunt-related metastases [132, 134, 150]

Most popular alternative for CSF diversion is endoscopic third ventriculostomy, except in patient with suprasellar lesion where in Shunt remains a valuable option. It allows internal CSF diversion, tissue for histopathological examination, provide CSF for cytological and biochemical examination. Another option is to do temporary diversion like EVD till the tumor is dealt with. Like radiation therapy for germinoma which will melt the tumor and relive hydrocephalus.

The next step after dealing with raised ICP symptoms is to get a tissue diagnosis which can be accomplished, either by stereotactic or endoscopic technique. Some surgeons prefer open biopsy, in view of risk of haemorrhage associated with these approaches. [144] A third aspect is tumor debulking, which has some therapeutic benefit in selected situations. Ex: teratoma requires surgical removal, because these lesions respond poorly to adjuvant therapy.

Role of surgery in germinoma is limited to tissue diagnosis only as they are very sensitive to radiotherapy and chemotherapy [151]. But NGGCTs has different scenario, which contain many radioresistent teratomas, mixed germ cell tumors. Most of the recent trials suggest initial adjuvant therapy to eradicate the malignant component and remnant teratoma can be managed with additional intervention like biopsy or decompression. [130,137,138, 152-157] Management of residual / recurrent is controversial and the benefit of second time surgery remains questionable. [155]

ADJUVANT THERAPIES AND PROGNOSIS

One of the most important predictor of outcome in CNS germ cell tumor is histology. Germinoma having a better prognosis compared to non germinomatous tumors. Germinomas are very sensitive and amenable to both radiation therapy and chemotherapy. Long-term survival and overall survival is better in germinomas as compared to nongerminomatous. [134,137, 158] Presence of metastasis and high levels of □-hCG (a marker of syncytiotrophoblastic elements) are poor prognostic factors. [158-160] However these factors do not

preclude good survival rates, unless the therapy is appropriately personalised.[146, 161].

Germinomas

Radiotherapy has been the mainstay of treatment for patients with germinomas. The choice of application of radiation viz. teletherapy or brachytherapy is controversial. Also the ideal dose that should be administered to the tumor bed is variable.[137, 162-164]

The multi center Maligue Keimzelltümoren (MAKEI) series of prospective studies demonstrated PFS rates > 90% with cranio spinal radiation doses of 3000 cGy supplemented with a booster dose of 1500 cGy to the tumor bed[164] which provided a strong rationale for using these lower doses as opposed to higher doses in previous studies. Reports in literature show that patients with no distant spread respond better as compared to those who have dessimination.[165-167]Some studies have demonstrated an higher failure rate with local field therapy.[168] Around 96% PFS can be achieved with cranio spinal radiation even in the presence of metastasis, therefore radiation is still the treatment of choice.

Chemotherapy has shown some effectiveness in recurrent CNS germinomas. Making use of this data, prior to giving radiotherapy, drugs were tried with the intention of reducing the dose of radiation. **[168-170]**. Allen et al reduced the dose of radiation in patients who had complete response with cyclophosphamide and

Cisplatin from 50 to 30 Gy for those with localized disease and the craniospinal dose from 36 to 21 cGy for those with disseminated disease. [171] Sawamura and co-authors also reported good response rates with 24Gy to the localised germinoma, following preirradiation therapy with Cisplatin and etoposide. [152] Similarly, a phase II study by the Paediatric Oncology Group subjected patients to Cisplatin and etoposide regime and depending the response were subjected to variable dose of radiation. They observe 95% response rate. Patients with complete response were given 30Gy and those with incomplete response were given 54Gy. With this regime they obtained 100% survival rate. Those with multicentric disease received standard craniospinal radiation. [172]

Such impressive chemotherapy results prompted researchers to harvest the potential of only chemotherapy regime if any for the treatment of germinoma. In a cohort of 45 patient exclusively treated with chemotherapy alone initial response was excellent, relapse occurred in 48.8%. those who relapsed were successfully treated with high dose chemotherapy and/or craniospinal radiation.[173] They used agents like carboplatin, etoposide and bleomycin, given in four cycles.[154] The reported mortality rate was 10% with treatment itself. Mortality due to the side effects of chemotherapy has nullified the favourable response attained with only chemotherapy regime. It can be safely commented and followed that chemotherapy can only helpful in reduction of radiation dose and fields, but not for elimination of radiotherapy.

SFOP	preirradiation chemotherapy with etoposide and carboplatin, alternating with etoposide and ifosfamide, was followed by local radiation doses of 4000 cGy with 2-cm margins	96.4% at 3 year event free survival 83% at 8-year event-free survival
Japanese study	treatment with etoposide and either carboplatin or cisplatin followed by 2400-cGy local irradiation to the tumour plus a 1-cm margin	28% recurrence rate in irradiation 0% in whole-brain irradiation 6% in extended field radiotherapy

These results concur with smaller series from west demonstrating a higher incidence of ventricular relapses in patients receiving focal radiation.[174]

In some series of endoscopy microscopic tumor nodule were seen which were not seen on pre operative contrast MRI raising the question false negative results on MRI. There for tumor burden or diagnosis to tumor may be underestimated in MRI.

Nongerminomatous Germ Cell Tumors

In contrast to starkling response of germinoma to radiation, similar effect is not seen with non germinomatous tumors.(survival rates<40%.)[130,134,137,138, 158, 175] Multiple radiation regime with varying doses have been tried with nihilistic response. As mentioned above MAKEI series showed very poor disease control rate with standard regime in NGGCT.[164] However, different histologic subtypes of NGGCTs have variable sensitivity to radiation. A review by Matsutani and associates studied the histological type with response to radiation. They found around 30% response rate in embryonal tumors, endodermal sinus tumors and choriocarcinoma. Outcome was more grave in teratomas. But NGGCT with some germinomatous component conferred little survival advantage. Thus optimal management of NGGCT's area personalised treatment depending on histology. [134]

The overall outcome of NGGCTs is worse when compared to germinomas. Because of poor response to radiation, multiple chemotherapeutic agents like carboplatin, cisplatin, etoposide, cyclophosphamide, ifosfamide, and bleomycin are being tried with varying success.[177-185] Robertson et al. reported favourable outcome with pre and post radiation chemotherapy with cisplatin and etoposide. [183] MAKEI study demonstrated 80% 5 yr survival rate with such chemo radiation regime. They use cisplatin and etoposide before and ifosfamide and cisplatin after radiation. Likewise, in the Paediatric Oncology Group implanting similar regime obtained PFS of 60 months(n=14).[172]

Use of chemotherapy in germinoma raised the hope of replacing the radiation, but such optimistic results were not seen with NGGCT. NGGCT continually needs both chemotherapy and radiotherapy for adequate control of diseas.[154, 186] In the First International Central Nervous System Germ Cell Tumor Study Group trial, 26 subjects were administered 4 cycles of carboplatin, etoposide, and bleomycin. Those with response received extra dose of chemotherapy and those with partial response received radiation. Though initial response was favourable in 80% of cases, 50% relapsed and 10% died because of chemotherapy.[154] In continuation the second trial came which added Cisplatin and cyclophosphamide but the results were not fruitful, 36% PFS at 5 yrs[186]. Similarly, Calaminus et al did a meta analysis of multiple European series and reported that 80% of cases treated with cisplatin alone without radiation died, whereas 74% in one series were disease free even at 4 yrs after receiving both chemotherapy and radiotherapy. [187]

Whether addition of chemotherapy for NGGCT's reduces the need or dose of radiotherapy is not established. NGGCT's itself dictates craniospinal radiation but it is more so if metastasis is detected. The recent SFOP[185] studies noted favourable results with induction chemotherapy and 5500-cGy focal radiotherapy but with same dosage Robertson[183] et al reported 35% relapse around the radiated field..[185].

In summary, the highest PFS CNS NGGCTs are reported in trials with multidrug platinum chemotherapy and cranio spinal radiation. Children's Oncology Group multi centre study was designed to strengthen the above stated results with platinum bases chemotherapy. For residual or recurrent tumors on imaging, the recommendation is to go for surgery in order to confirm the histology of the enhancing part viz. fibrosis vs. tumor. The growing teratoma syndrome is a well known fact and they are subjected to surgery not only for histological confirmation but also benefit from debulking. If the histology comes out to fibrosis or mature teratoma with falling tumor markers, it can be safely said that patient has attained complete remission. Patients with more than 50% decrease in tumor volume with normal tumor maker are also considered in complete remission. And those with <50% reduction in tumor volume are considered to have residual lesion.

Myeloablative high dose chemotherapy with stem cell rescue has been successfully tried in extra cranial NGGCT's. This approach was tried in non

responders in cranial NGGCT's. the rationale of using this approached was re enforced by the favourable response obtained in SFOP pilot study.[187-190] [191] and in several other published reports, [173, 192-194].

The study ACNS0122 will test the efficacy of a strategical treatment protocol to improve outcomes in children with newly diagnosed intracranial NGGCTs. This study has 100 patients dividing into groups based on serum markers and response to therapy to understand the stratification technique for future usage. At present the consensus is that there are some NGGCT which respond well to standard treatment and some who require aggressive therapy.

Choroid Plexus Tumors

Choroid plexus tumors can pose great challenge to treat. Surgical risk increased by their significant vascularity, location, and the common occurrence in young children. Low grade choroid plexus lesions are curable with surgical resection alone, where the malignant forms shows long-term survival even with multimodality therapy.

CP tumors representing less than 1% of all CNS tumors.[195-197] However, they represent a significant percentage of the tumors in infants. [198] CP tumors arise from the specialized neuroepithelial cells in the ventricles. These tumors have similar structural appearance and function of normal choroid plexus, results in excessive secretion of CSF and lead to HCP. Pure ventricular mass either in child or adult must suspect CP tumors in the differential diagnosis.

History

The first description of a choroid plexus tumor by Guerard in 1832, in three year girl autopsy. [199] The initial surgical resection and long term survival was reported in year 1906 and 1919 respectively. [200,201] Till 1930s, research has limited to rarity of these lesions and their association with HCP[202-206]. Van Wagenen [206] reported good outcome following resection of ventricle tumor in an infant in 1930. Various approaches like transcallosal approach by Dandy, transfrontal approach by Masson to remove the third ventricular choroid plexus tumor

Incidence

CP lesions represent only 0.5% to 0.6% of all intracranial tumors and reported to occur in all age groups. [196, 197, 207] They represent up to 2.9% of all paediatric brain tumors, but reported highest in infants between 10% and 20%.[198, 208] Choroid plexus tumors known to occur in children 70% when compared to adults and 50% in child less than two years.[208-213] Congenital tumors have been reported [207, 214-217] Some reports have noted a slight male predominance, whereas others have seen an equal distribution.[195, 208,212, 218-220] Malignant form of CP tumors have a significant tendency to metastasize through CSF. [221] Metastasis not only limited to carcinomatous one, the property also reported in benign one also.

Histologic classification:-

CP papilloma	
Anaplastic papilloma	
Choroid plexus carcinoma	15% to 20% - 80% are found in children.

Presentation:

The presenting features are varies with age of presentation and most of the patients presents with features HCP[207, 209, 213, 220]. HCP in CP tumors is due to excessive secretion of CSF and outlet obstruction [209, 210,213, 222-228.] The excessive production of CSF is also supported frequent resolution of HCP after tumor resection and ascites following shunt but before tumor surgery. [229]

However, increased rate of CSF production has been actually shown in only a few patients. [223,224, 227, 228]

Reported rate of non responsiveness of HCP following tumor removal 45%, and this could relate to surgery-induced haemorrhage or inflammation[208, 213, 220, 227.] Various endocrine disturbances and diencephalic dysfunction may be a manifestation of tumors in the third ventricle .[205, 231].

Location

Choroid plexus tumors location—[206, 208, 212, 213, 227, 229, 232-235]

Lateral ventricle	40% to 50%,
Third ventricle	4.5% to 10%
Fourth ventricle	40.3%
more than one ventricle	5.5%.

Pure extraventricular locations reported are CP angle and spinal subarachnoid space[236,237]. Bilateral tumors also been reported in literature.[210, 229, 233]

Atrium is the most frequent location for CP tumors, although they can be seen at foramen of Monro anteriorly and also in temporal horn, even though not consistently reported they have predilection to occur on the left side. Metastases look like normal choroid on histopathology and assumed to be “drop” lesions. [238] There has been report of pulmonary metastasis in one case[239].

Arterial supply of tumors

anterior choroidal artery[240,241]	primarily in the atrium and temporal horn
lateral posterior choroidal artery[240,241]	the temporal horn, atrium, and body of the lateral ventricle
medial posterior choroidal artery[240,241]	roof of the third ventricle
posterior inferior cerebellar and the superior cerebellar arteries	fourth ventricle

The blood supply to the intraventricular tumors is the same as for normal choroid plexus in that ventricle. Vascular supply and anatomic relationships are important for planning the surgical approach.

DIAGNOSIS

Imaging

Plain radiography are historical can show nonspecific calcium deposit in tumor and widely spaced sutures.[195, 233, 242,243] Raimondi and Gutierrez [244] provide excellent angiographic features in the diagnosis. However, currently angiography has been replaced by MRA.

CP tumors on CT will show a variable density[209, 213] usually well demarcated and calcification occurs in about 10% and rather has brilliant enhancement[213.] Malignancy suggested by cystic degeneration of tumor. [209] In MRI CP tumors

are variable in intensity on T2-weighted images show an intermediate to high signal intensity, and the irregular flow void[221, 245]. On MRS myoinositol and choline peak reported in papilloma and carcinoma respectively[246, 247]. This could helpful in the management of carcinoma whether to embolization or chemotherapy[246]

PATHOLOGY

Choroid Plexus Papilloma

Choroid plexus papillomas correlate with World Health Organization (WHO) grade I classification.[248] On histopathology papillomas resembles the structure of normal choroid plexus [249, 250] and differs in cellularity and nuclear pleomorphism.[236] The main histology distinguish feature is fibrillary neuroglial stroma. A variant of papillomas undergoing malignant transformation, can show brain invasion called atypical choroid plexus papilloma.[251-254]

Choroid Plexus Carcinoma

Malignant were included in grade III.[243] Cells in malignant form are tightly packed, exhibit high proliferation and morphology variability in nucleus[249, 255]. The malignant features in the carcinoma are usually prominent. Anaplasia, absence of central stroma, high proliferative activity and necrosis, and giant cell formation are the features of malignancy. [208,221] The presence of brain invasion suggests malignancy[256] however, there can be tumors with benign histologic features shows some brain invasion.[208, 257]

Metastatic carcinoma in adults or neuroepithelial embryonal tumors in children form a differential in the evaluation of choroid plexus tumors.[236] A combination of cytologic, ultrastructural, and immunohistochemical evaluations can be used to differentiate choroid plexus carcinomas from atypical teratoid/rhabdoid tumors (AT/RT). [258]

Atypical Choroid Plexus Papillomas

Demonstration of more than two mitoses figures per ten high-power fields on histopathology [232] and categorised under WHO grade II.[248]

Choroid Villous Hypertrophy

In 1924 Davis [202] described this as a bilateral entity. Excision by resection or destruction by endoscopic coagulation of this plexus has resulted in the resolution of symptom[227, 259, 260].

Immunohistochemistry and Molecular Biology

Choroid plexus tumors can stain for both epithelial and glial antigens. GFAP and cytokeratin are positive in both papilloma and carcinoma but can also be seen in normal choroid plexus.[249, 261]. The cell proliferation markers (Ki-67, MIB-1) are consistently low in papillomas where as high in Carcinomas. [262,263]

	Papilloma	Carcinoma	
S-100 [249, 252]	55% to 90%	variable	Benign histology (□50% of cells)
GFAP	25% to 55%	20%	
CEA [249]	29%	100%	More aggressive

Chromosomal sequencing of Choroid plexus tumor demonstrate multitude of chromosomal genetic aberrations.[264]

SURGICAL TREATMENT AND COMPLICATIONS

Review of literature shows high operative mortality and morbidity rates (26% to 64%)[195, 209, 243] in previous decades but recent results are favourable however the perioperative death still happening. [208, 220, 244]

The primary goal of CP tumor surgery is to achieve a gross total resection and to alleviate any hydrocephalus (temporarily or permanently). The tumor location necessitates an approach through normal neuron parenchyma, except in some fourth ventricular lesions. [240,241]

The standard surgical technique of internal debulking lead to massive bleeding and endangerous the life of patients, hence early “vascular pedicle control” has been strongly recommended.[213, 243] But early vascular pedicle control is difficult in some tumors, this has led to recommendations for embolization of tumor before surgery. [213] However, the option for embolization may be limited due to inability to get vascular access in small children age less than one year.[213] The

best approach depends on tumor location within the lateral ventricle. While taking decision on surgical approach consideration must be given to shortest way to reach tumor and to the vascular supply

Tumor location	Surgical apparoach	
Frontal horn	Middle frontal gyrus	
Trigone	Superior parietal lobule	dominant hemisphere has inherent risks
Temporal horn	Middle temporal gyrus	Limited exposure of the vascular pedicle

Persistence of hydrocephalus is treated with CSF diversion procedure like shunt. Occurrence of significant subdural fluid collection following surgical resection of these tumors has been reported and these can be prevented by use of a modified “brain patch” technique. [212, 213, 265]

OUTCOME

Surgical resection remains the most important factor in determining long-term survival in patients with tumors of the choroid plexus. [208, 209, 213, 234, 266-269] Role of adjuvant therapy not only limited to leptomeningeal spread, also used for malignant tumors. Radiation plays a reasonable role in adults and older children, but it has no demonstrable role in young children.

Reported long term survival in papilloma is 90% to 100% only after gross-total resection[208, 213, 234]. Malignant choroid plexus lesions treated only with surgery had a very poor outcome [208, 256, 270,271] and combination chemotherapy after surgery reported betterment in survival rate to 26% to 50% at 5 years. [208, 253, 266,267, 271-273]

Aggressive resection and chemotherapy on malignant ones the reported maximum long-term survival rate is70%.[213, 256, 274,275] Initial biopsy to confirm the diagnosis, followed by chemotherapy to reduce the bulk of tumor and a second surgery to attempt complete excision has becoming the standard of management.

The key in prolonging the life of a patient with choroid plexus carcinoma is to achieve gross total resection, even with multiple surgeries if required. [208, 213, 266, 274] Recurrences tend to manifest early. [232] Role of chemotherapy following gross total resection is controversial, but chemotherapy in incomplete resection results in poor long term outcome.

Materials and method

103 supratentorial high grade consecutive cases were diagnosed in patients aged less than 19years between January 2000 and December 2010. Their hospital records reviewed retrospectively including follow-up notes and imaging studies.

Pre operative workup included a detailed neurologic examination and imaging studies either CT or MRI depending on what was available. Extent of resection determined by post operative CT scan in most of the cases which were performed within 24hrs following surgery and grade of the tumor confirmed by neuropathologist.

The patients underwent regular follow-up and clinical examination at each visit. The follow-up period was defined as the period extending from surgery to the most recent clinical visit or death. Patients did not turned up following discharge and visit less than three months were considered as lost to follow up. Recurrent tumor was judged according to findings on imaging studies, which were either taken at regular interval or appearance of symptoms.

The outcome was analysed with respect to the following variables: age, gender, extent of resection, tumour location, the histopathological variant, time of first recurrence and survival. Data was analyzed using student t test, ANOVA and chi square test.

Inclusion criteria:

- Patients age less than 19yeras
- Histopathology diagnosis of high grade lesion.
- Supratentorial located tumors

Exclusion criteria:

- Patients age more than 19yeras
- Histopathology diagnosis of low grade lesions
- Infra tutorial tumors
- Patients available follow-up less than 3months

Order of resection of tumor

Gross total resection- G 99%

Near total resection- N more than 99%

Subtotal resection- S more than 50% but less than 90%

Biopsy- B less than 50%

Results

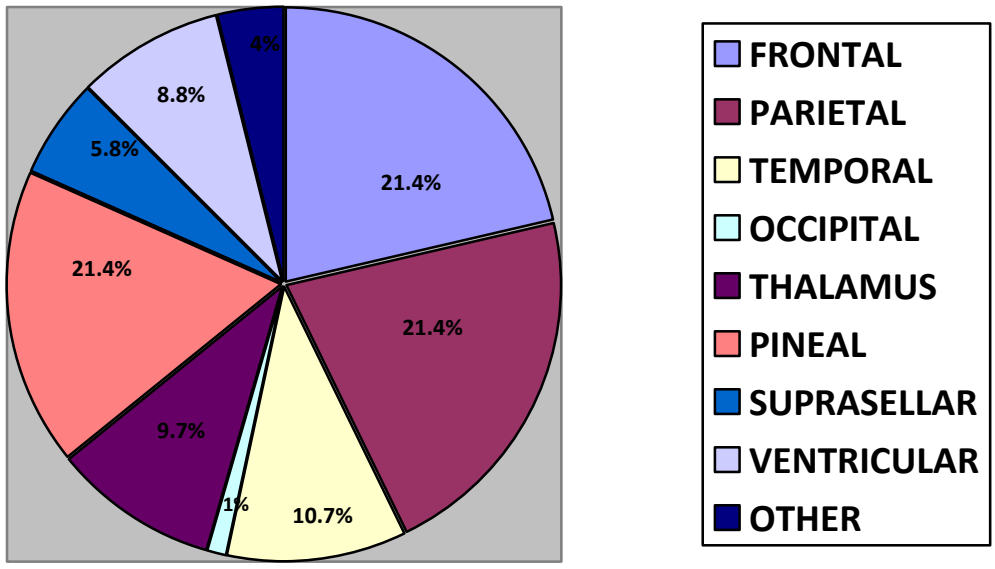
In this present study there were a total of 103 patients identified to have supratentorial high grade lesions between January 2000 to December 2010. A total of 137 surgeries performed on 103 patients. Out of these 137 surgeries, 122 were surgeries related to tumors including biopsy, subtotal, near total or gross total decompression. The remaining 15 other surgeries included CSF diversion in 14 patients and one patient who underwent evacuation of post operative sub dural hematoma. Out of 103 patients six patients never turned back following surgery, seven had less than 3moths follow up and two patients had expired during hospital stay. Follow-up of more than 36months in present study is highest in grade III gliomas 62.9%(17), followed by pineal region tumor 58.8%(10), PNET 57.1%(12), 43.7%(7) in grade IV gliomas in 42% (3) in CPC.

Tabulation of follow-up

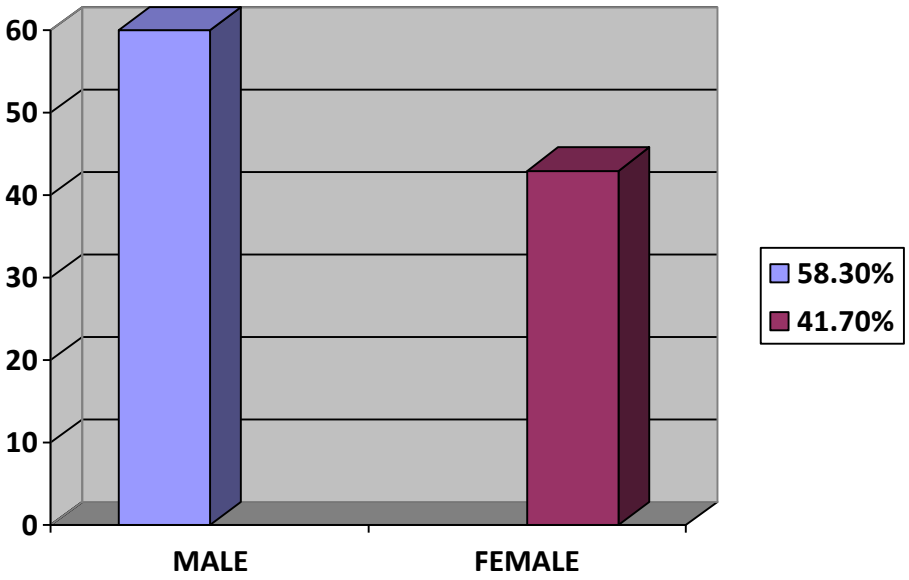
	<6 months	6-12mon	12-24mon	24-36mon	36-60mon	60-120mon	>120mon	Total
III	3	4	3	1	4	9	3	27
IV	3	2	4	5	2	0	0	16
PNET	1	3	5	2	3	5	2	21
PINEAL	3	1	3	2	1	6	1	17
CPC	2	1	1	1	0	2	0	7
Total	12	11	16	11	10	22	6	88

Follow up in percentages

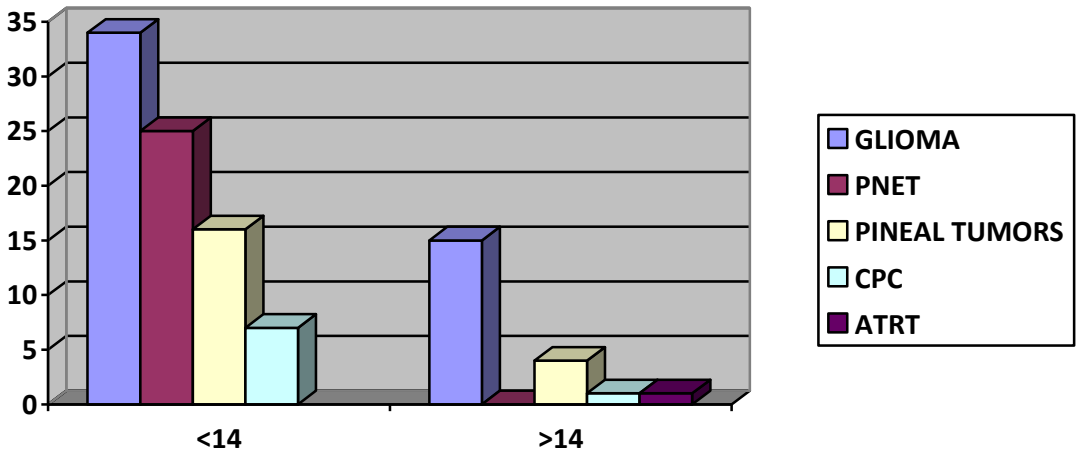
	3-6 months	6-12mon	12-24mon	24-36mon	36-60mon	60-120mon	>120mon	Total
III	100%(27)	88.8% (24)	74%(20)	62.9%(17)	59.2%(16)	44.4%(12)	11%(3)	27
IV	100%(16)	81.2%(13)	68.5%(11)	43.7%(7)	12.5%(2)	0	0	16
PNET	100%(21)	95%(20)	809%(17)	57.1%(12)	47.6%(10)	33.3%(7)	9.5%(2)	21
PINEAL	100%(17)	82.3%(14)	76.4%(13)	58.8%(10)	47%(8)	41.1%(7)	5.8%(1)	17
CPC	100%(7)	71.4%(5)	57%(4)	42%(3)	28%(2)	28%(2)	0	7
Total	100% (88)	86.36%(76)	73.86(65)	55.68%(49)	43.1%(38)	31.81%(28)	6.8%(6)	88



Distribution of high grade lesions in various lobes in supratentorial region



Male and female ratio of supratentorial high grade lesions



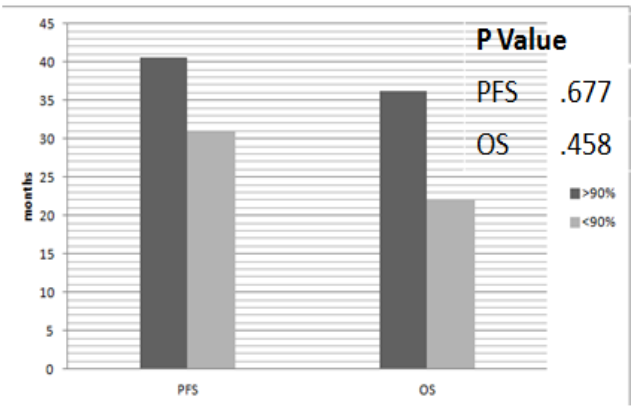
Age distribution of supratentorial high grade lesions

Astrocytomas grade (III>IV) were the most commonly found tumors flowed by PNET, pineal region tumors and Choroid Plexus Carcinomas**.**

Out of 103 high grade lesions that were operated grade-III tumors accounted for 28.1%.There was a slight male preponderance with the sex ratio in grade III tumor being 1.4:1 (Male: Female).The hemispheric distribution was observed almost equally with 13 patients having a left hemispheric lesion and 14 on the right side also . Pineal and CC lesions were found in single patients respectively. It was observed that Parietal lobe 37.9% (11) was the most commonly involved lobe, followed by frontal(27.6%), temporal(13.8%), thalamus(10.3%) and occipital lobes (3.4%). Observational analysis regarding presenting symptoms revealed raised ICP features in 19 patients, followed by seizures in five, focal neurologic deficits in 4 and diplopia in one patient. Regarding tumoral size at presentation, it was seen that tumors more than >6cm were found in 48.3% patients. Out of a total of twenty nine patients, 55.1% underwent gross or near total decompression. Postoperatively 75.9% (22) received radiothepray and 24.1%(7) received combined chemo radiotherapy. The two year progression free survival was 23.8% while 5 year PFS 10.2%.

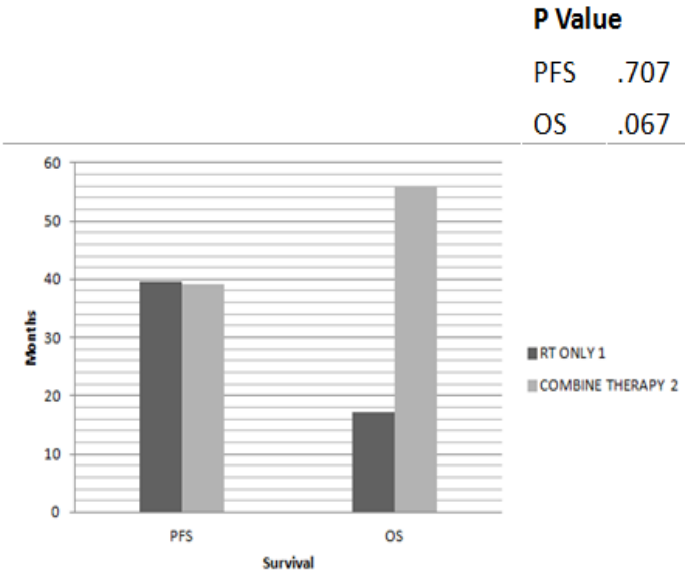
Pathology1 = III

		N	Mean	Std. Deviation
PFS	G or N	8	40.63	47.910
	B or S	8	31.13	41.201
	Total	16	35.88	43.445
OS	G or N	5	36.200	40.9658
	B or S	7	22.000	22.9565
	Total	12	27.917	30.8411



Pathology1 = III

		N	Mean	Std. Deviation
PFS	Neither	2	10.50	3.536
	RT only	10	39.60	52.190
	Both	4	39.25	27.765
	Total	16	35.88	43.445
OS	Neither	4	10.750	16.9189
	RT only	4	17.250	13.5247
	Both	4	55.750	37.9594
	Total	12	27.917	30.8411



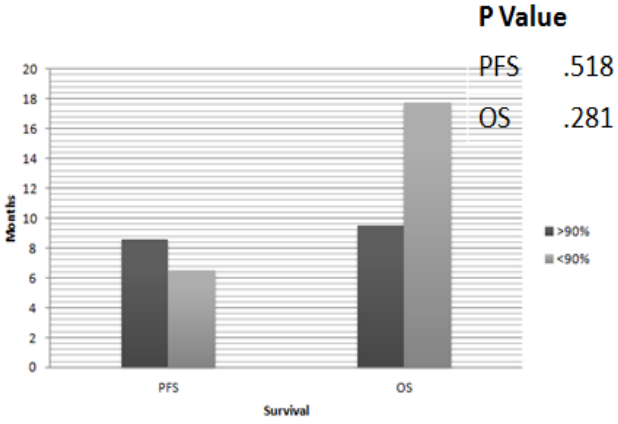
The mean progression free survival in months was 40.63 (SD of 47.10) months in patients who underwent gross or near total decompression (8) and 31.3 with SD of 41 in patients who had undergone biopsy or subtotal resection (8) which was not statically significant p value-0.677. The overall survival was 22 (SD22.95) months in patients who underwent biopsy or subtotal decompression and 36.2(SD 40.96) months in the gross or near total surgical group with a p value of 0.458. The mean progression free survival in patients who received radiotherapy was 39.6 (SD of 52.19) months, in patients who received both

chemotherapy and radiotherapy the mean survival was 39.25 (SD 27.76) months. The p value was 0.76 which was not significant. When coming to overall survival RT group survival was (4)17.25(SD 13.52) months, in the combined group it was (4) 55.75(SD 37.95) months with p value of 0.067.

Out of 103 high grade lesions grade-IV tumors were present in 19.4%. The sex ratio in grade IV tumor is 1.8:1 (M:F) again with a male preponderance with 40% in left hemisphere while 60% were present in right hemisphere involvement. Frontal and thalamus equally involved 6 (30%) in each, followed by parietal lobe (4)20%, temporal lobe (3) 15% and ventricular (1) 5%. Presenting features were raised ICP symptoms in (15) 75%, followed by seizures were in (4) 20% and focal neurologic deficit in(1) 5%.Tumoral size at the time of presentation in most of the patients was 3-6cm (14) 70%. 65% of children underwent gross total and near total decompression and postoperatively 75%(15) received RT, 25%(5) of them had taken combined therapy. The observed one year progression free survival was 15%.

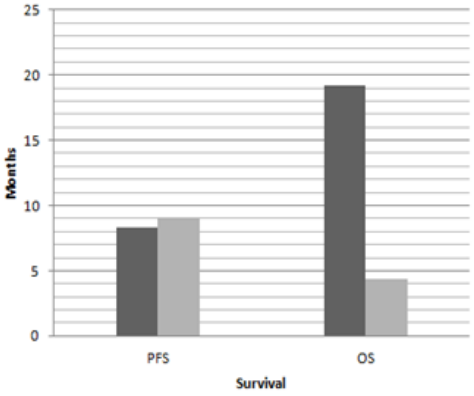
Pathology1 = IV

		N	Mean	Std. Deviation
PFS	G or N	7	8.57	4.315
	B or S	4	6.50	5.916
	Total	11	7.82	4.771
OS	G or N	6	9.500	10.5214
	B or S	4	17.750	11.8989
	Total	10	12.800	11.2625



Pathology1 = IV

		N	Mean	Std. Deviation
PFS	Neither	2	5.00	1.414
	RT only	7	8.29	4.716
	Both	2	9.00	8.485
	Total	11	7.82	4.771
OS	Neither	3	3.667	4.0415
	RT only	5	19.200	11.8195
	Both	2	10.500	9.1924
	Total	10	12.800	11.2625



P Value

PFS .689

OS .160

The mean progression free survival was 8.57 (SD of 4.3) months in patients who underwent gross or near total decompression (7).and 6.50 (SD of 5.92) in patients who had undergone biopsy or subtotal resection (4) which was not statically significant p value-0.518. The overall survival was 17.75(SD of 11.9) months in 4 patients who underwent biopsy or subtotal decompression and 9.5 (SD of 10.52) months in the gross or near total surgical group (6) with a p value of 0.281. The mean progression free survival in seven patients who received radiotherapy was 8.29 (4.71) months, in patients who received both chemotherapy and radiotherapy the mean survival was 9 (SD 8.5) months. The p value was 0.68 which was not significant. When coming to overall survival RT group survival was (5 patients) 19.2 (SD of 11.8) months, in the combined group it was(2 patients) 10.5 (SD of 9.2) months with p value of 0.16.

Out of 103 high grade lesions PNET tumors are 24.3%. Observed sex ration in PNET is 0.9:1 (M: F), 28% in left hemisphere, 52% in right hemisphere, and

20% at pineal region. Found lobe distribution 32% in frontal lobe followed by 28% in parietal lobe, temporal(8%), thalamus and intraventricular one in each (8%), Presented with raised ICP features(44%), followed by focal neurologic deficit(32%), seizures (16%) irritability and diplopia 4% each. Size of the tumor at the time of presentation is >6cm in 36% patients. In 68% of children underwent gross total and near total decompression and postoperatively 44%(11) received RT, 68%(17) taken chemotherapy. One and two year progression free survival is 50% and 25% respectively.

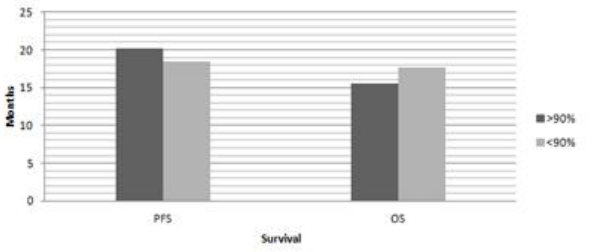
Pathology1 = PNET

		N	Mean	Std. Deviation
PFS	G or N	4	20.25	23.042
	B or S	4	18.75	11.701
	Total	8	19.50	16.937
OS	G or N	4	15.500	3.6968
	B or S	4	17.750	8.6554
	Total	8	16.625	6.2778

P Value

PFS .911

OS .649



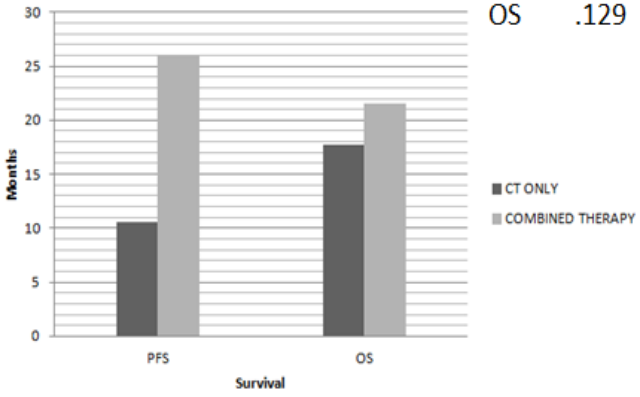
Pathology1 = PNET

		N	Mean	Std. Deviation
PFS	Neither	1	36.00	.
	CT only	4	10.50	5.972
	Both	3	26.00	24.269
	Total	8	19.50	16.937
OS	Neither	2	9.500	4.9497
	CT only	4	17.750	4.3493
	Both	2	21.500	6.3640
	Total	8	16.625	6.2778

P Value

PFS .328

OS .129



The mean progression free survival was 20.5 (SD of 23.04) months in patients who underwent gross or near total decompression (4) and 18.75 (SD of 11.70) in patients who had undergone biopsy or subtotal resection (4) which was not statically significant p value-0.911. The overall survival was 17.75 (SD of 8.65) months in 4 patients who underwent biopsy or subtotal decompression and 15.5 (SD of 3.69) months in the gross or near total surgical group (6) with a p value of 0.65. The mean progression free survival in patients who received chemotherapy was 10.50 (SD of 6) months (SD of 4), in patients who received both chemotherapy and radiotherapy the mean survival was 26 (SD of 24.3) months. The p value was 0.328 which was not significant. When coming to overall survival Chemotherapy group (4) survival was 17.7(SD 4.34) months, in the combined group(2) it was 21.5(SD of 6.4) months with p value of 1.3.

In supratentorial high grade tumors, 7.8% consisted of choroid plexus carcinomas. The sex ratio in CPC is 1.6:1 (M:F) which showed a male preponderance, 25% in left hemispheric distribution while 62.5% were in right hemisphere, and 12.5% in 3rd ventricle, Presenting features included , raised ICP in (62.5%), followed by seizures 25% and focal neurologic deficit (12.5%). Size of the tumor at the time of presentation was >6cm in 25% and 3-6cm in 75% of patients. All of the patients underwent gross total decompression and postoperatively 37.5% (3) received RT, 25%(2) taken chemotherapy. One year progression free survival is 12.5%.

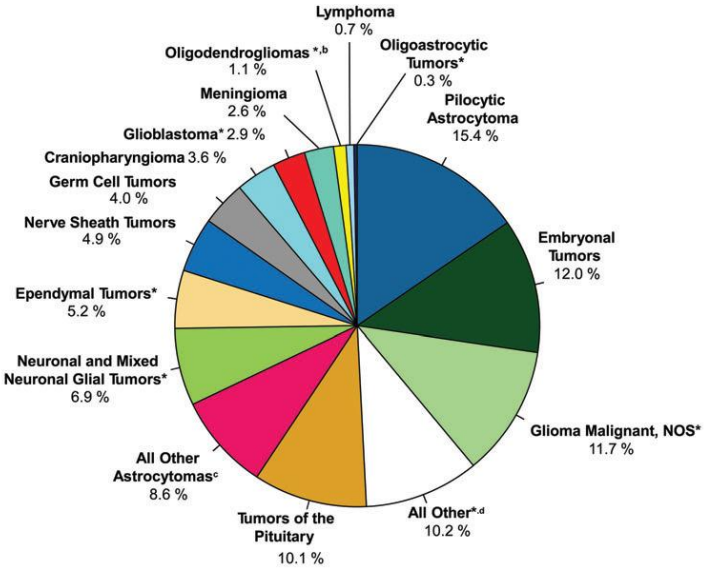
Lastly, 19.4% of supratentorial high grade tumor consisted of pineal region tumors. In which males (65%) were most frequently affected and presenting features included raised ICP .Out of all pineal tumors, 61.8% patients underwent gross or near total decompression and 39.2% and 65.2% received radiotherapy and chemotherapy respectively. The mean survival was 9 months in this group.

Discussion

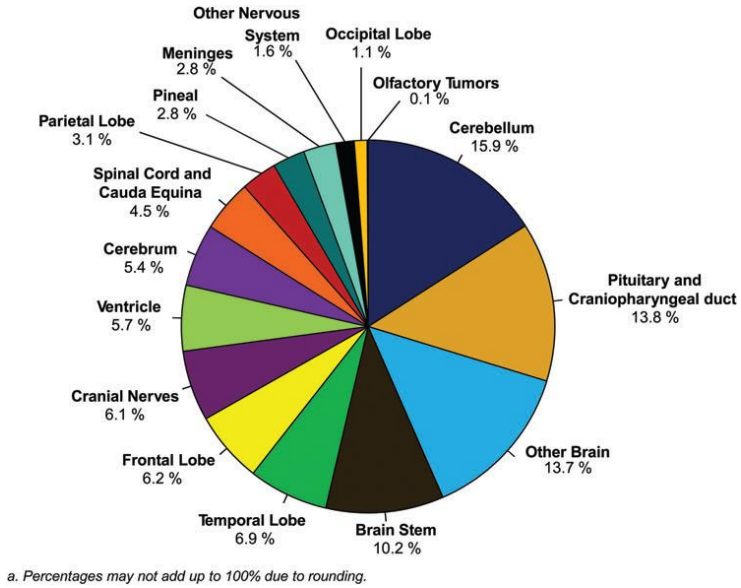
Malignant brain tumors are the leading cause of cancer-related death and account for 20% to 30% of all childhood cancers. CNS tumors are the most common neoplasm among those 0–19 years old, with an average annual age-adjusted incidence rate of 5.42 per 100,000. Overall, approximately 42% of all tumors occurred in males where as 58% in females, but malignant ones were more common in males 55% when compared to females 45%[18]. In this present study we have observed that malignant tumors are predominant in males (59%). Gliomas may occur at any age, but most commonly encountered in adults and old age. Review of the current literature indicates an overall pediatric CNS glioma incidence 20-30% of all pediatric cancers. There is slight male predominance with female/male ratio is 1:1.5[18, 20, 21]. We observed that there is slight male predominance in gliomas that is 1:1.3. Tumors with higher grade, more unfavorable locations, and poorer prognosis have generally occurred in younger than 3years. Overall, the most common CNS tumors seen in childhood are astrocytomas, ependymomas, and germ cell tumors. Gliomas accounts for 50-60%% [1,4,11] and PNET 1.9%; We also have found that gliomas being the more common tumor followed in decreasing order PNET, pineal region tumors and Choroid Plexus Carcinomas

Childhood pediatric high grade lesions are characteristically known to have nonspecific symptomatology. The elasticity of skull and non cooperation makes diagnosis difficult. Quite often a local swelling of cranial vault may be the first

sign in many children. Common clinical manifestations of pediatric high grade lesions include signs of increased ICP, focal



Distribution in Children and Adolescents (Ages 0–19) of Primary Brain and CNS Tumors by CBTRUS Histology Groupings and Histology (N= 22,535), CBTRUS Statistical Report: NPCR and SEER, 2007–2011



a. Percentages may not add up to 100% due to rounding.

Distribution in Children and Adolescents (Ages 0–19) of Primary Brain and CNS Tumors by Site (N= 22,535), CBTRUS Statistical Report: NPCR and SEER, 2007–2011.

neurological deficits, seizures and other rare symptoms and signs based on their location [9,10]. We also observed raised ICP being the predominant presenting symptoms followed by seizures and focal deficits in decreasing order. A substantial proportion of our patients had visual symptoms also.

Overall, frontal lobe is the frequently affected (8.6%) followed by temporal (6.4%), parietal (4.0%), and occipital lobes (1.1%) account for 20.1% of all tumors. For malignant tumors, frontal (23.2%) lobe was most commonly involved cerebral lobe followed by temporal (17.0%), parietal (10.9%), and occipital (2.9%) account for 54.0% of tumors[18]. In our series the most frequently affected lobes are frontal and parietal with a combined frequency of 42.8%, followed by pineal region 21.4%.

Gliomas represents approximately 28% of all tumors and 80% of malignant forms where approximately 47.9% of tumors in less than 19 years of age patients. There is a decline in incidence rates of gliomas and embryonal tumor type between age groups 0–19. There is substantial increase in incidence of tumors of the pituitary between 10 –19, whereas incidence of PNET is highest in the 0–4 age group[18]. We have observed that all PNETs before 14yeras of age, gliomas incidence has been found decreased from 68.7% in below 14years of age to 31.3% between 14-19 years of age. However in both age groups glioma was the most common high grade CNS tumor

Glioblastoma is the second most frequently reported histology and the most common malignant tumor. Glioblastoma accounts for 15.4% of all primary brain

tumors and 45.6% of primary malignant brain tumors. Glioblastoma is more common in older adults and is less common in children; these tumors comprise approximately 3% of all CNS tumors reported among 0–19 year old[1,18]. Glioblastoma has been found that 19.4% among high grade lesions and is 1.6 times more frequent in males. Relative survival estimates for glioblastoma are quite low; 5.0% of patients survived five years post diagnosis[18]. Most of the studies on high grade gliomas reported 5year event free survival 46% with combined chemo-radiotherapy and 18% when treated with radiotherapy alone. [27-30.] One year progression free survival of glioblastoma is 15% in this present series and two year progression free survival 23.8% and 5year PFS 10.2% in grade iii.

Embryonal tumors are the most frequently reported tumor type in children ages 0–4, and the second most common tumor type overall in children and adolescents ages 0–19.

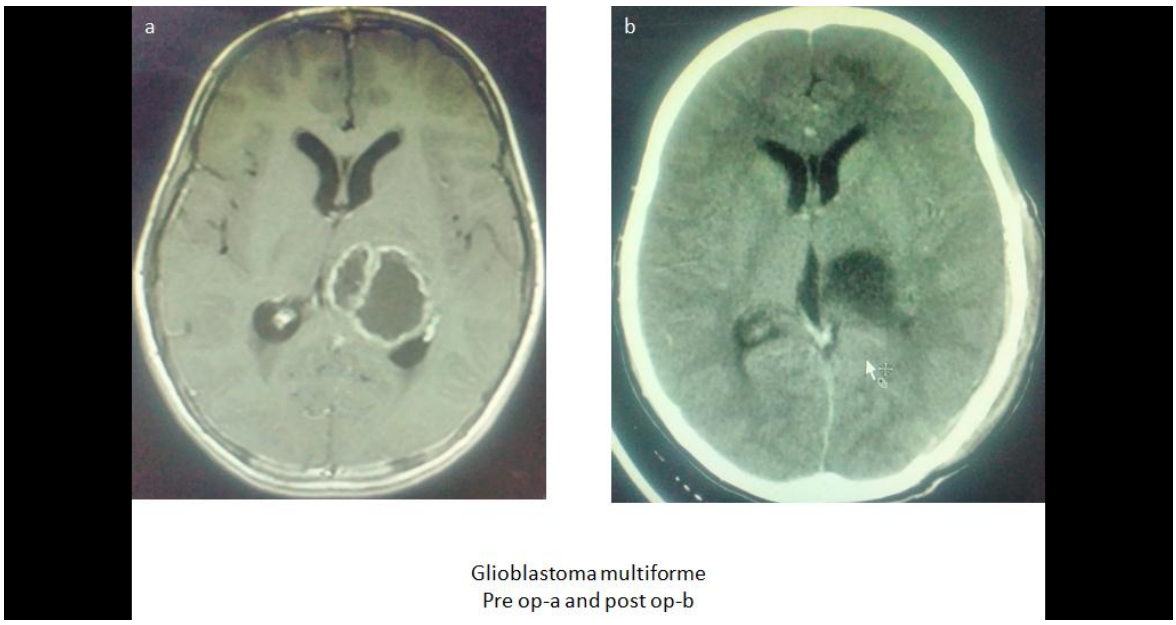
Relative survival estimates for embryonal tumors are low but vary significantly by histology. Reviews of literature reveals that 10-year survival is 42.6% for PNET[20, 46,47,51,52] and 25.9% for ATRT where as in our observation PNET being second most frequent tumor, one and two year progression free survival is 50 and 25% respectively. In present study, there was no significant benefit either CT or CT and RT in overall survival except in added 3months longevity by giving RT in PNET. A 16months progression free survival by adding RT, however this is not statistically significant. One and two year progression free survival is 50 and 25% respectively**.**

CONCLUSION

Childhood supratentorial high grade lesions are uncommon but not rare Overall survival and progression free survival didn't differ significantly in groups' gross total versus subtotal decompression and radiotherapy versus combined therapy. Absence of large series precludes any definite conclusions on survival outcome.

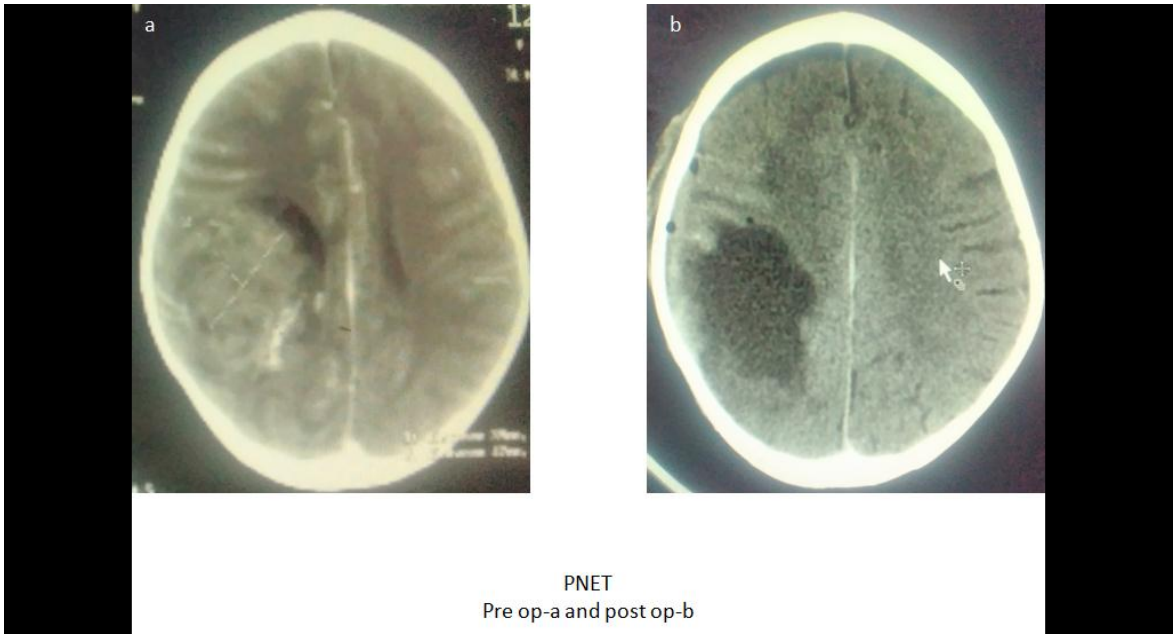
Illustrative images

Fig:1



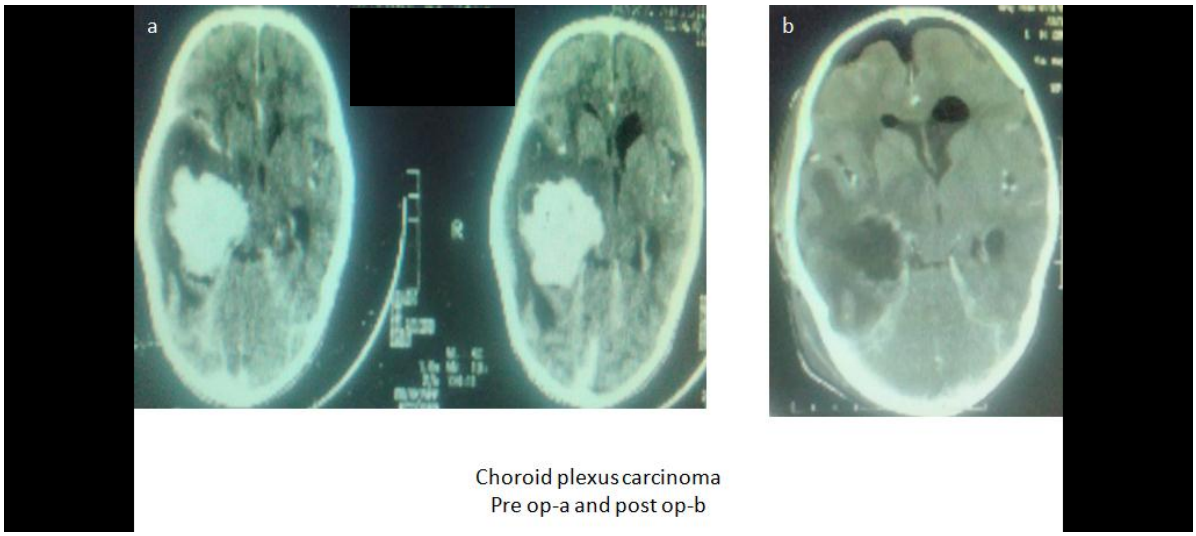
Glioblastoma multiforme
Pre op-a and post op-b

Fig:2



PNET
Pre op-a and post op-b

Fig:3



Choroid plexus carcinoma
Pre op-a and post op-b

Bibliography

1. **Rickert CH, Paulus W**: Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. *Childs Nerv Syst.* 17:503-511 2001
2. **Ullrich NJ, Pomeroy SL**: Pediatric brain tumors. *Neurol Clin North Am.* 21:897-913 2003
3. **Duffner PK, Cohen ME, Freeman AI**: Pediatric brain tumors: an overview. *Cancer J Clinicians.* 35:287-301 1985
4. **Khatua S, Jalali R**: Recent advances in the treatment of childhood brain tumors. *Pediatr Hematol Oncol.* 22:361-371 2005
5. **Lim M, Harsh GR**: Neuro-oncology:An overview. **Rengachary SSEllenbogen RG** *Principles of Neurosurgery.* 2005 CV MosbyEdinburgh 429-449
6. **Baldwin RT, Preston-Martin S**: Epidemiology of brain tumors in childhood—a review. *Toxicol Appl Pharmacol.* 199:118-131 2004
7. **Rutka JT, Kuo JS**: Pediatric surgical neuro-oncology: current best care practices and strategies. *J Neurooncol.* 69:139-150 2004
8. **Robertson RL**: Advances in treatment of pediatric brain tumors. *J Am Soc Exp Neurotherapeutics.* 3:276-291 2006
9. **Wilne S, Collier J, Kennedy C, et al.**: Presentation of childhood CNS tumours: a systemic review and meta-analysis. *Lancet Oncol.*8:685-695 2007
10. **Reulecke BC, Erker CG, Fiedler BJ, et al.**: Brain tumors in children: initial symptoms and their influence on the time span between symptom onset and diagnosis. *J Child Neurol.* 23:178-1832008
11. **Maher CO, Raffel C**: Neurosurgical treatment of brain tumors in children. *Pediatr Clin North Am.* 51:327-357 2004
12. **Vezina G, Booth TN**: Neuroradiology. **Keating RF Goodrich JTPacker RJ** *Tumors of the Pediatric Central Nervous System.* 2001Thieme New York 27-43
13. **Warren KE**: NMR Spectroscopy and pediatric brain tumors.*Oncologist.* 9:312-318 2004

14. **Spencer SS, Theodore WH, Berkovic SF**: Clinical applications: MRI, SPECT, and PET. *Magn Reson Imaging.* 13:1119-1124 1995
15. **Pirotte B, Acerbi F, Lubansu A, et al.**: PET imaging in the surgical management of pediatric brain tumors. *Childs Nervous System.*23:739-751 2007
16. **Shono T, Natori Y, Morioka T, et al.**: Results of a long term follow-up after neuroendoscopic biopsy procedure and third ventriculostomy in patients with intracranial germinomas. *J Neurosurg.* 107:193-198 2007
17. **Tamber JS, Bansal K, Liang ML, et al.**: Current concepts in the molecular genetics of pediatric brain tumors: implications for emerging therapies. *Childs Nervous System.* 22:1379-1394 2006.
18. **CBTRUS** Statistical Report: Primary Brain Tumors in the United States, 2007-20011. 2014 Central Brain Tumor Registry of the United States
19. **Pollack IF**: Brain tumors in children. *N Engl J Med.* 331:1500-1507 1994
20. **Albright AL, Wisoff JH, Zeltzer P, et al.**: Prognostic factors in children with supratentorial (nonpineal) primitive neuroectodermal tumors. A neurosurgical perspective from the Children's Cancer Group. *Pediatr Neurosurg.* 22:1-7 1995
21. **Favier J, Pizzolato GP, Berney J**: Oligodendroglial tumors in childhood. *Childs Nerv Syst.* 1:33-38 1985
22. **Romeike BF, Kim YJ, Steudel WI, et al.**: Diffuse high-grade gliomas as second malignant neoplasms after radio-chemotherapy for pediatric malignancies.*Childs Nerv Syst.* 23:185-193 2007
23. **Broniscer A, Ke W, Fuller CE, et al.**: Second neoplasms in pediatric patients with primary central nervous system tumors: the St. Jude Children's Research Hospital experience. *Cancer.* 100:2246-2252 2004
24. **Osborn A**: Diagnostic Imaging: Brain. 2004 Amirsys Salt Lake City, UT
25. **Girard N, Wang ZJ, Erbetta A, et al.**: Prognostic value of proton MR spectroscopy of cerebral hemisphere tumors in children. *Neuroradiology.*40:121-125 1998
26. **Pollack IF, Hamilton RL, Burnham J, et al.**: Impact of proliferation index on outcome in childhood malignant gliomas: results in a multi-institutional cohort.*Neurosurgery.* 50:1238-1244 2002

27. **Campbell JW, Pollack IF, Martinez AJ, et al.**: High-grade astrocytomas in children: radiologically complete resection is associated with an excellent long-term prognosis. *Neurosurgery.* 38:258-264 1996
28. **Broniscer A, Gajjar A**: Supratentorial high-grade astrocytoma and diffuse brainstem glioma: two challenges for the pediatric oncologist. *Oncologist.* 9:197-206 2004
29. **Finlay JL, Boyett JM, Yates AJ, et al.**: Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen. Children's Cancer Group. *J Clin Oncol.* 13:112-123 1995
30. **Stupp R, Mason WP, van den Bent MJ, et al.**: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 352:987-996 2005
31. **Duffner PK, Horowitz ME, Krischer JP, et al.**: The treatment of malignant brain tumors in infants and very young children: an update of the Pediatric Oncology Group experience. *Neuro Oncol.* 1:152-161 1999
32. **Dufour C, Grill J, Lellouch-Tubiana A, et al.**: High-grade glioma in children under 5 years of age: a chemotherapy only approach with the BBSFOP protocol.*Eur J Cancer.* 42:2939-2945 2006
33. **Sposto R, Ertel IJ, Jenkin RD, et al.**: The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: results of a randomized trial. A report from the Children's Cancer Study Group. *J Neurooncol.* 7:165-177 1989
34. **Wagner S, Reinert C, Schmid HJ, et al.**: High-dose methotrexate prior to simultaneous radiochemotherapy in children with malignant high-grade gliomas. *Anticancer Res.* 25:2583-2587 2005
35. **Wisoff JH, Boyett JM, Berger MS, et al.**: Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: a report of the Children's Cancer Group trial no. CCG-945. *J Neurosurg.* 89:52-59 1998
36. **Stummer W, Pichlmeier U, Meinel T, et al.**: Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol.* 7:392-401 2006

37. **Chitoku S, Otsubo H, Harada Y, et al.**: Extraoperative cortical stimulation of motor function in children. *Pediatr Neurol.* 24:344-350 2001
38. **Gupta N, Berger MS**: Brain mapping for hemispheric tumors in children.*Pediatr Neurosurg.* 38:302-306 2003
39. **Souweidane MM, Kim KH, McDowall R, et al.**: Brain mapping in sedated infants and young children with passive-functional magnetic resonance imaging.*Pediatr Neurosurg.* 30:86-92 1999
40. **Fouladi M, Hunt DL, Pollack IF, et al.**: Outcome of children with centrally reviewed low-grade gliomas treated with chemotherapy with or without radiotherapy on Children's Cancer Group high-grade glioma study CCG-945.*Cancer.* 98:1243-1252 2003
41. **Hodgson DC, Goumnerova LC, Loeffler JS, et al.**: Radiosurgery in the management of pediatric brain tumors. *Int J Radiat Oncol Biol Phys.* 50:929-9352001
42. **Duffner PK, Horowitz ME, Krischer JP, et al.**: Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. *N Engl J Med.* 328:1725-1731 1993

43. **Carret AS, Tabori U, Crooks B, et al.**: Outcome of secondary high-grade glioma in children previously treated for a malignant condition: a study of the Canadian Pediatric Brain Tumour Consortium. *Radiother Oncol.* 81:33-38 2006

44. **Gold DG, Neglia JP, Dusenbery KE**: Second neoplasms after megavoltage radiation for pediatric tumors. *Cancer.* 97:2588-2596 2003
45. **Cohen BH, Zeltzer PM, Boyett JM, et al.**: Prognostic factors and treatment results for supratentorial primitive neuroectodermal tumors in children using radiation and chemotherapy: a Children's Cancer Group randomized trial. *J Clin Oncol.* 13:1687-1696 1995
46. **Reddy AT, Janss AJ, Phillips PC, et al.**: Outcome for children with supratentorial primitive neuroectodermal tumors treated with surgery, radiation, and chemotherapy. *Cancer.* 88:2189-2193 2000

47. **Tomita T, McLone DG, Yasue M**: Cerebral primitive neuroectodermal tumors in childhood. *J Neurooncol.* 6:233-243 1988
48. **McBride S, Daganzo S, Banerjee A, et al.**: Radiation is an important component of multimodality therapy for pediatric non-pineal supratentorial primitive neuroectodermal tumors. *Int J Radiat Oncol Biol Phys.* 72:1319-1323 2008
49. **Timmermann B, Kortmann RD, Kuhl J, et al.**: Role of radiotherapy in supratentorial primitive neuroectodermal tumor in young children: results of the German HIT-SKK87 and HIT-SKK92 trials. *J Clin Oncol.* 24:1554-1560 2006
50. **Geyer JR, Zeltzer PM, Boyett JM, et al.**: Survival of infants with primitive neuroectodermal tumors or malignant ependymomas of the CNS treated with eight drugs in 1 day: a report from the Children's Cancer Group. *J Clin Oncol.*12:1607-1615 1994
51. **Gilheeney SW, Saad A, Chi S, et al.**: Outcome of pediatric pineoblastoma after surgery, radiation and chemotherapy. *J Neurooncol.* 89:89-95 2008
52. **Jakacki RI, Zeltzer PM, Boyett JM, et al.**: Survival and prognostic factors following radiation and/or chemotherapy for primitive neuroectodermal tumors of the pineal region in infants and children: a report of the Children's Cancer Group. *J Clin Oncol.* 13:1377-1383 1995
53. **Liang ML, Ma J, Ho M, et al.**: Tyrosine kinase expression in pediatric high grade astrocytoma. *J Neurooncol.* 87:247-253 2008
54. **Bredel M, Pollack IF, Hamilton RL, et al.**: Epidermal growth factor receptor expression and gene amplification in high-grade non-brainstem gliomas of childhood. *Clin Cancer Res.* 5:1786-1792 1999
55. **Sung T, Miller DC, Hayes RL, et al.**: Preferential inactivation of the p53 tumor suppressor pathway and lack of EGFR amplification distinguish de novo high grade pediatric astrocytomas from de novo adult astrocytomas. *Brain Pathol.*10:249-259 2000
56. **Zhou YH, Tan F, Hess KR, et al.**: The expression of PAX6, PTEN, vascular endothelial growth factor, and epidermal growth factor receptor in gliomas: relationship to tumor grade and survival. *Clin Cancer Res.* 9:3369-3375 2003

57. **Pollack IF, Finkelstein SD, Burnham J, et al.**: Age and TP53 mutation frequency in childhood malignant gliomas: results in a multi-institutional cohort. *Cancer Res.* 61:7404-7407 2001
58. **Pollack IF, Finkelstein SD, Woods J, et al.**: Expression of p53 and prognosis in children with malignant gliomas. *N Engl J Med.* 346:420-427 2002
59. **Raffel C, Frederick L, O'Fallon JR, et al.**: Analysis of oncogene and tumor suppressor gene alterations in pediatric malignant astrocytomas reveals reduced survival for patients with PTEN mutations. *Clin Cancer Res.* 5:4085-4090 1999
60. **Shiraishi S, Tada K, Nakamura H, et al.**: Influence of p53 mutations on prognosis of patients with glioblastoma. *Cancer.* 95:249-257 2002
61. **Rood BR, MacDonald TJ**: Pediatric high-grade glioma: molecular genetic clues for innovative therapeutic approaches. *J Neurooncol.* 75:267-272 2005
62. **Clifford SC, Lusher ME, Lindsey JC, et al.**: Wnt/Wingless pathway activation and chromosome 6 loss characterize a distinct molecular sub-group of medulloblastomas associated with a favorable prognosis. *Cell Cycle.* 5:2666-2670 2006
63. **Thompson MC, Fuller C, Hogg TL, et al.**: Genomics identifies medulloblastoma subgroups that are enriched for specific genetic alterations. *J Clin Oncol.*24:1924-1931 2006
64. **Shih CS, Hale GA, Gronewold L, et al.**: High-dose chemotherapy with autologous stem cell rescue for children with recurrent malignant brain tumors.*Cancer.* 112:1345-1353 2008
65. **Warren K, Jakacki R, Widemann B, et al.**: Phase II trial of intravenous lobradimil and carboplatin in childhood brain tumors: a report from the Children's Oncology Group. *Cancer Chemother Pharmacol.* 58:343-347 2006
66. **Pollack IF, Jakacki RI, Blaney SM, et al.**: Phase I trial of imatinib in children with newly diagnosed brainstem and recurrent malignant gliomas: a Pediatric Brain Tumor Consortium report. *Neuro Oncol.* 9:145-160 2007
67. **Luther N, Cheung NK, Dunkel IJ, et al.**: Intraparenchymal and intratumoral interstitial infusion of anti-glioma monoclonal antibody 8H9. *Neurosurgery.*63:1166-1174 2008

68. **Bobo RH, Laske DW, Akbasak A, et al.**: Convection-enhanced delivery to macromolecules in the brain. *Proc Nat Acad Sci U S A.* 91:2076-2080 1994
69. **Sampson JH, Akabani G, Friedman AH, et al.**: Comparison of intratumoral bolus injection and convection-enhanced delivery of radiolabeled antitenascin monoclonal antibodies. *Neurosurg Focus.* 20 (4):E14 2006
70. **Sandberg DI, Edgar MA, Souweidane MM**: Convection-enhanced delivery into the rat brain stem. *J Neurosurg.* 96:885-891 2002
71. **Kunwar S, Prados MD, Chang SM, et al.**: Direct intracerebral delivery of cintredekin besudotox (IL13-PE38QQR) in recurrent malignant glioma: a report by the Cintredekin Besudotox Intraparenchymal Study Group. *J Clin Oncol.*25:837-844 2007
72. **Lidar Z, Mardor Y, Jonas T, et al.**: Convection-enhanced delivery of paclitaxel for the treatment of recurrent malignant glioma: a phase I/II clinical study. *J Neurosurg.* 100:472-479 2004
73. **Foreman NK, Love S, Thorne R**: Intracranial ependymomas: analysis of prognostic factors in a population-based series. *Pediatr Neurosurg.* 24:119-1251996
74. **Horn B, Heideman R, Geyer R, et al.**: A multi-institutional retrospective study of intracranial ependymoma in children: identification of risk factors. *J Pediatr Hematol Oncol.* 21:203-211 1999
75. **Perilongo G, Massimino M, Sotti G, et al.**: Analyses of prognostic factors in a retrospective review of 92 children with ependymoma: Italian Pediatric Neuro-oncology Group. *Med Pediatr Oncol.* 29:79-85 1997
76. **Sutton LN, Goldwein J, Perilongo G, et al.**: Prognostic factors in childhood ependymomas. *Pediatr Neurosurg.* 16:57-65 1990
77. **Gajjar A, Fouladi M, Walter AW, et al.**: Comparison of lumbar and shunt cerebrospinal fluid specimens for cytologic detection of leptomeningeal disease in pediatric patients with brain tumors. *J Clin Oncol.* 17:1825-1828 1999
78. **Needle MN, Goldwein JW, Grass J, et al.**: Adjuvant chemotherapy for the treatment of intracranial ependymoma of childhood. *Cancer.* 80:341-347 1997

79. **Pollack IF, Gerszten PC, Martinez AJ, et al.**: Intracranial ependymomas of childhood: long-term outcome and prognostic factors. *Neurosurgery.* 37:655-666 1995
80. **Robertson PL, Zeltzer PM, Boyett JM, et al.**: Survival and prognostic factors following radiation therapy and chemotherapy for ependymomas in children: a report of the Children's Cancer Group. *J Neurosurg.* 88:695-703 1998
81. **Figarella-Branger D, Civatte M, Bouvier-Labit C, et al.**: Prognostic factors in intracranial ependymomas in children. *J Neurosurg.* 93:605-613 2000
82. **Healey EA, Barnes PD, Kupsky WJ, et al.**: The prognostic significance of postoperative residual tumor in ependymoma. *Neurosurgery.* 28:666-671 1991
83. **Merchant TE, Mulhern RK, Krasin MJ, et al.**: Preliminary results from a phase II trial of conformal radiation therapy and evaluation of radiation-related CNS effects for pediatric patients with localized ependymoma. *J Clin Oncol.* 22:3156-3162 2004
84. **Nazar GB, Hoffman HJ, Becker LE, et al.**: Infratentorial ependymomas in childhood: prognostic factors and treatment. *J Neurosurg.* 72:408-417 1990
85. **Palma L, Celli P, Mariottini A, et al.**: The importance of surgery in supratentorial ependymomas. Long-term survival in a series of 23 cases. *Childs Nerv Syst.* 16:170-175 2000
86. **Paulino AC, Wen BC, Buatti JM, et al.**: Intracranial ependymomas: an analysis of prognostic factors and patterns of failure. *Am J Clin Oncol.* 25:117-122 2002
87. **Rousseau P, Habrand JL, Sarrazin D, et al.**: Treatment of intracranial ependymomas of children: review of a 15-year experience. *Int J Radiat Oncol Biol Phys.* 28:381-386 1994
88. **van Veelen-Vincent ML, Pierre-Kahn A, Kalifa C, et al.**: Ependymoma in childhood: prognostic factors, extent of surgery, and adjuvant therapy. *J Neurosurg.* 97:827-835 2002
89. **Zamecnik J, Snuderl M, Eckschlager T, et al.**: Pediatric intracranial ependymomas: prognostic relevance of histological, immunohistochemical, and flow cytometric factors. *Mod Pathol.* 16:980-991 2003
90. **Sanford RA, Gajjar A**: Ependymomas. *Clin Neurosurg.* 44:559-570 1997

91. **Foreman NK, Love S, Gill SS, et al.**: Second-look surgery for incompletely resected fourth ventricle ependymomas: technical case report. *Neurosurgery.*40:856-860 1997
92. **Kovalic JJ, Flaris N, Grigsby PW, et al.**: Intracranial ependymoma long term outcome, patterns of failure. *J Neurooncol.* 15:125-131 1993
93. **Pierre-Kahn A, Hirsch JF, Roux FX, et al.**: Intracranial ependymomas in childhood. Survival and functional results of 47 cases. *Childs Brain.* 10:145-1561983
94. **Shaw EG, Evans RG, Scheithauer BW, et al.**: Postoperative radiotherapy of intracranial ependymoma in pediatric and adult patients. *Int J Radiat Oncol Biol Phys.* 13:1457-1462 1987
95. **Timmermann B, Kortmann RD, Kuhl J, et al.**: Combined postoperative irradiation and chemotherapy for anaplastic ependymomas in childhood: results of the German prospective trials HIT 88/89 and HIT 91. *Int J Radiat Oncol Biol Phys.* 46:287-295 2000
96. **Kleihues P, Sobin LH**: World Health Organization classification of tumors.*Cancer.* 88:2887 2000
97. **Schiffer D, Chio A, Giordana MT, et al.**: Histologic prognostic factors in ependymoma. *Childs Nerv Syst.* 7:177-182 1991
98. **Lamszus K, Lachenmayer L, Heinemann U, et al.**: Molecular genetic alterations on chromosomes 11 and 22 in ependymomas. *Int J Cancer.* 91:803-808 2001
99. **Metzger AK, Sheffield VC, Duyk G, et al.**: Identification of a germ-line mutation in the p53 gene in a patient with an intracranial ependymoma. *Proc Natl Acad Sci U S A.* 88:7825-7829 1991
100. **von Haken MS, White EC, Daneshvar-Shyesther L, et al.**: Molecular genetic analysis of chromosome arm 17p and chromosome arm 22q DNA sequences in sporadic pediatric ependymomas. *Genes Chromosomes Cancer.* 17:37-44 1996
101. **Fink KL, Rushing EJ, Schold SC Jr, et al.**: Infrequency of p53 gene mutations in ependymomas. *J Neurooncol.* 27:111-115 1996
102. **Tong CY, Ng HK, Pang JC, et al.**: Molecular genetic analysis of non-astrocytic gliomas. *Histopathology.* 34:331-341 1999

103. **Nijssen PC, Deprez RH, Tijssen CC, et al.**: Familial anaplastic ependymoma: evidence of loss of chromosome 22 in tumour cells. *J Neurol Neurosurg Psychiatry.* 57:1245-1248 1994

104. **Savard ML, Gilchrist DM**: Ependymomas in two sisters and a maternal male cousin with mosaicism with monosomy 22 in tumour. *Pediatr Neurosci.* 15:80-84 1989

105. **Yokota T, Tachizawa T, Fukino K, et al.**: A family with spinal anaplastic ependymoma: evidence of loss of chromosome 22q in tumor. *J Hum Genet.*48:598-602 2003

106. **Granzow M, Popp S, Weber S, et al.**: Isochromosome 1q as an early genetic event in a child with intracranial ependymoma characterized by molecular cytogenetics. *Cancer Genet Cytogenet.* 130:79-83 2001

107. **Huang B, Starostik P, Schraut H, et al.**: Human ependymomas reveal frequent deletions on chromosomes 6 and 9. *Acta Neuropathol.* 106:357-362 2003

108. **Kramer DL, Parmiter AH, Rorke LB, et al.**: Molecular cytogenetic studies of pediatric ependymomas. *J Neurooncol.* 37:25-33 1998

109. **Mazewski C, Soukup S, Ballard E, et al.**: Karyotype studies in 18 ependymomas with literature review of 107 cases. *Cancer Genet Cytogenet.* 113:1-8 1999

110. **Vagner-Capodano AM, Zattara-Cannoni H, Gambarelli D, et al.**: Cytogenetic study of 33 ependymomas. *Cancer Genet Cytogenet.* 115:96-99 1999

111. **Wernicke C, Thiel G, Lozanova T, et al.**: Involvement of chromosome 22 in ependymomas. *Cancer Genet Cytogenet.* 79:173-176 1995

112. 64**Good CD, Wade AM, Hayward RD, et al.**: Surveillance neuroimaging in childhood intracranial ependymoma: how effective, how often, and for how long?. *J Neurosurg.* 94:27-32 2001

113. **Steinbok P, Hentschel S, Cochrane DD, et al.**: Value of postoperative surveillance imaging in the management of children with some common brain tumors. *J Neurosurg.* 84:726-732 1996

114. **Duffner PK, Krischer JP, Sanford RA, et al.**: Prognostic factors in infants and very young children with intracranial ependymomas. *Pediatr Neurosurg.*28:215-222 1998

115. **Khan RB, Sanford RA, Kun LE, et al.**: Morbidity of second-look surgery in pediatric central nervous system tumors. *Pediatr Neurosurg.* 35:225-229 2001

116. **Mork SJ, Loken AC**: Ependymoma: a follow-up study of 101 cases. *Cancer.*40:907-915 1977

117. **Hukin J, Epstein F, Lefton D, et al.**: Treatment of intracranial ependymoma by surgery alone. *Pediatr Neurosurg.* 29:40-45 1998

118. **Rezai AR, Woo HH, Lee M, et al.**: Disseminated ependymomas of the central nervous system. *J Neurosurg.* 85:618-624 1996

119. **Merchant TE, Haida T, Wang MH, et al.**: Anaplastic ependymoma: treatment of pediatric patients with or without craniospinal radiation therapy. *J Neurosurg.*86:943-949 1997

120. **Vanuytsel LJ, Bessell EM, Ashley SE, et al.**: Intracranial ependymoma: long-term results of a policy of surgery and radiotherapy. *Int J Radiat Oncol Biol Phys.* 23:313-319 1992

121. **Chiu JK, Woo SY, Ater J, et al.**: Intracranial ependymoma in children: analysis of prognostic factors. *J Neurooncol.* 13:283-290 1992

122. **Goldwein JW, Leahy JM, Packer RJ, et al.**: Intracranial ependymomas in children. *Int J Radiat Oncol Biol Phys.* 19:1497-1502 1990

123. **Aggarwal R, Yeung D, Kumar P, et al.**: Efficacy and feasibility of stereotactic radiosurgery in the primary management of unfavorable pediatric ependymoma. *Radiother Oncol.* 43:269-273 1997

124. **Hodgson DC, Goumnerova LC, Loeffler JS, et al.**: Radiosurgery in the management of pediatric brain tumors. *Int J Radiat Oncol Biol Phys.* 50:929-9352001

125. **Jawahar A, Kondziolka D, Flickinger JC, et al.**: Adjuvant stereotactic radiosurgery for anaplastic ependymoma. *Stereotact Funct Neurosurg.* 73:23-301999

126. **Merchant TE, Boop FA, Kun LE, et al.**: A retrospective study of surgery and reirradiation for recurrent ependymoma. *Int J Radiat Oncol Biol Phys.* 71:87-972008

127. **Bouffet E, Foreman N**: Chemotherapy for intracranial ependymomas. *Childs Nerv Syst.* 15:563-570 1999

128. **Grill J, Le Deley MC, Gambarelli D, et al.**: Postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age: a multicenter trial of the French Society of Pediatric Oncology. *J Clin Oncol.* 19:1288-1296 2001

129. **Grundy RG, Wilne SA, Weston CL, et al.**: Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study. *Lancet Oncol.* 8:696-705 2007 .

130. **Jennings MT, Gelman R, Hochberg F**: Intracranial germ-cell tumors: Natural history and pathogenesis. *J Neurosurg.* 63:155-167 1985

131. **Sano K**: Pathogenesis of intracranial germ cell tumors reconsidered. *J Neurosurg.* 90:258-264 1999

132. **Hoffman HJ, Yoshida M, Becker LE, et al.**: Pineal region tumors in childhood: experience at the Hospital for Sick Children, 1983. *Pediatr Neurosurg.* 21:91-1031994

133. **Horowitz MB, Hall WA**: Central nervous system germinomas: a review. *Arch Neurol.* 48:652-657 1991

134. **Matsutani M, Sano K, Takakura K, et al.**: Primary intracranial germ cell tumors: a clinical analysis of 153 histologically verified cases. *J Neurosurg.* 86:446-4551997

135. **Keene D, Johnston D, Strother D, et al.**: Epidemiological survey of central nervous system germ cell tumors in Canadian children. *J Neurooncol.* 82:289-295 2007

136. **Teilum G**: Special Tumors of the Ovary and Testis and Related Extragonadal Lesions. 1976 JB Lippincott Philadelphia

137. **Packer RJ, Cohen BH, Coney K**: Intracranial germ cell tumors. *Oncologist.* 5:312-320 2000

138. **Jubran RF, Finlay J**: Central nervous system germ cell tumors: controversies in diagnosis and treatment. *Oncology.* 19:705-711 2005

139. **Wellons JC 3rd, Reddy AT, Tubbs RS, et al.**: Neuroendoscopic findings in patients with intracranial germinomas correlating with diabetes insipidus. *J Neurosurg Pediatr.* 100:430-436 2004

140. **Kretschmar CS**: Germ cell tumors of the brain in children: a review of current literature and new advances in therapy. *Cancer Invest.* 15:187-198 1997

141. **Maghnie M, Cosi G, Genovese E, et al.**: Central diabetes insipidus in children and young adults. *N Eng J Med.* 343:998-1007 2000

142. **Ozelame RV, Shroff M, Wood B, et al.**: Basal ganglia germinoma in children with associated ipsilateral cerebral and brain stem hemiatrophy. *Pediatr Radiol.*36:325-330 2006

143. **Souweidane MM**: Brain tumors in the first two years of life. **Albright AL PollackIF Adelson PD** *Principles and Practice of Pediatric Neurosurgery.* 2008 ThiemeNew York 489-510

144. **Tomita T**: Pineal region tumors. **Albright AL Pollack IF Adelson PD** *Principles and Practice of Pediatric Neurosurgery.* 2008 Thieme New York 585-605

145. **Nakagawa K, Yukimasa A, Akanuma A, et al.**: Radiation therapy of intracranial germ-cell tumors with radiosensitivity assessment. *Radiat Med.* 10:55-61 1992

146. **Shibamoto Y, Takahashi M, Sasai K**: Prognosis of intracranial germinoma with syncytiotrophoblastic giant cells treated with radiation therapy. *Int J Radiat Oncol Biol Phys.* 37:505-510 1997

147. **Shinoda J, Yamada H, Sakai N, et al.**: Placental alkaline phosphatase as a tumor marker for primary intracranial germinoma. *J Neurosurg.* 68:710-720 1988

148. **Miyanohara O, Takeshima H, Kaji M, et al.**: Diagnostic significance of soluble c-kit in the cerebrospinal fluid of patients with germ cell tumors. *J Neurosurg.*97:177-183 2002

149. **Shibamoto Y, Oda Y, Yamashita J, et al.**: The role of cerebrospinal fluid cytology in radiotherapy planning for intracranial germinoma. *Int J Radiat Oncol Biol Phys.* 27:1089-1094 1994

150. **Rickert CH**: Abdominal metastases of pediatric brain tumors via ventriculoperitoneal shunts. *Childs Nerv Syst.* 14:10-14 1998

151. **Sawamura Y, de Tribolet N, Ishii N, et al.**: Management of primary intracranial germinomas: diagnostic surgery or radical resection?. *J Neurosurg.* 87:262-2661997

152. **Sawamura Y, Shirato H, Ikeda J, et al.**: Induction chemotherapy followed by reduced-volume radiation therapy for newly diagnosed central nervous system germinoma. *J Neurosurg.* 88:66-72 1998

153. **Baranzelli MC, Patte C, Bouffet E, et al.**: Carboplatin-based chemotherapy (CT) and focal irradiation (RT) in primary cerebral germ cell tumors (GCT): A French Society of Pediatric Oncology (SFOP) experience. *Proc Am Soc Clin Oncol.*18:140A 1999

154. **Balmaceda C, Heller G, Rosenblum M, et al.**: Chemotherapy without irradiation—a novel approach for newly diagnosed CNS germ cell tumors: results of an international cooperative trial. The First International Central Nervous System Germ Cell Tumor Study. *J Clin Oncol.* 14:2908-2915 1996

155. **Weiner HL, Lichtenbaum RA, Wisoff JH, et al.**: Delayed surgical resection of central nervous system germ cell tumors. *Neurosurgery.* 50:727-734 2002

156. **Sawamura Y, Kato T, Ikeda J, et al.**: Teratomas of the central nervous system: treatment considerations based on 34 cases. *J Neurosurg.* 89:728-737 1998

157. **Baranzelli MC, Patte C, Bouffet E, et al.**: Non-metastatic intracranial germinomas. The experience of the French Society of Pediatric Oncology.*Cancer.* 80:1792-1797 1997

158. **Sawamura Y, Ikeda J, Shirato H, et al.**: Germ cell tumours of the central nervous system: treatment consideration based on 111 cases and their long-term outcomes. *Eur J Cancer.* 34:104-110 1998

159. **Inamura T, Nishio S, Ikezaki K, et al.**: Human chorionic gonadotropin in CSF, not serum, predicts outcome in germinoma. *J Neurol Neurosurg Psychiatry.*66:654-657 1999

160. **Aoyama H, Shirato H, Ikeda J, et al.**: Induction chemotherapy followed by low-dose involved-field radiotherapy for intracranial germ cell tumors. *J Clin Oncol.*20:857-865 2002

161. **Bouffet E, Baranzelli MC, Patte C, et al.**: Combined treatment modality for intracranial germinomas: results of a multicentre SFOP experience. *Br J Cancer.*79:1199-1204 1999

162. **Hardenbergh PH, Golden J, Billet A, et al.**: Intracranial germinoma: the case for lower dose radiation therapy. *Int J Radiat Oncol Biol Phys.* 39:419-426 1997

163. **Wolden SL, Wara WM, Larson DA, et al.**: Radiation therapy for primary intracranial germ-cell tumors. *Int J Radiat Oncol Biol Phys.* 32:943-949 1995

164. **Bamberg M, Kortman RD, Calaminus G, et al.**: Radiation therapy for intracranial germinoma: results of the German cooperative prospective trials MAKEI 83/86/89. *J Clin Oncol.* 17:2585-2592 1999

165. **Shibamoto Y, Abe M, Yamashita J, et al.**: Treatment results of intracranial germinoma as a function of the irradiated volume. *Int J Radiat Oncol Biol Phys.*15:285-290 1988

166. **Linstadt D, Wara WM, Edwards MS, et al.**: Radiotherapy of primary intracranial germinomas: the case against routine craniospinal irradiation. *Int J Radiat Oncol Biol Phys.* 15:291-297 1988

167. **Chao CK, Lee ST, Lin FJ, et al.**: A multivariate analysis of prognostic factors in management of pineal tumor. *Int J Radiat Oncol Biol Phys.* 27:1185-1191 1993

168. **Haddock MG, Schild SE, Scheithauer BW, et al.**: Radiation therapy for histologically confirmed primary central nervous system germinoma. *Int J Radiat Oncol Biol Phys.* 38:915-923 1997

169. **Allen JC, Bosl G, Walker R**: Chemotherapy trials in recurrent primary intracranial germ cell tumors. *J Neurooncol.* 3:147-152 1985

170. **Allen J, Siffert J, Velasquez L, et al.**: Review of contemporary North American clinical trials in primary CNS germinoma. *Neuro Oncol.* 7:517-518 2005

171. **Allen JC, DaRosso RC, Donahue B, et al.**: A phase II trial of preirradiation carboplatin in newly diagnosed germinoma of the central nervous system.*Cancer.* 74:940-944 1994

172. **Kretschmar C, Kleinberg L, Greenberg M, et al.**: Pre-radiation chemotherapy with response-based radiation therapy in children with central nervous system germ cell tumors: a report from the Children's Oncology Group. *Pediatr Blood Cancer.* 48:285-291 2006

173. **Merchant TE, Davis BJ, Sheldon JM, et al.**: Radiation therapy for relapsed CNS germinoma after primary chemotherapy. *J Clin Oncol.* 16:204-209 1998

174. **Douglas JG, Rockhill JK, Olson JM, et al.**: Cisplatin-based chemotherapy followed by focal reduced dose irradiation for pediatric primary central nervous system germinomas. *J Pediatr Hematol Oncol.* 28:36-39 2006

175. **Fuller BG, Kapp DS, Cox R**: Radiation therapy of pineal region tumors: 25 new cases and a review of 208 previously reported cases. *Int J Radiat Oncol Biol Phys.* 28:229-245 1994

176. **Borg M**: Germ cell tumors of the central nervous system in children: controversies in radiotherapy. *Med Pediatr Oncol.* 40:367-374 2003

177. **Kida Y, Kobayashi T, Yoshida J, et al.**: Chemotherapy with cisplatin for AFP secreting germ-cell tumor of the central nervous system. *J Neurosurg.* 65:470-475 1986

178. **Itoyama Y, Kochi M, Kuratsu J, et al.**: Treatment of intracranial nongerminomatous malignant germ cell tumors producing alpha fetoprotein.*Neurosurgery.* 36:459-464 1995

179. **Patel SR, Buckner JC, Smithson WA, et al.**: Cisplatin-based chemotherapy in primary central nervous system germ cell tumors. *J Neurooncol.* 12:47-52 1992

180. **Chang TK, Wong TT, Hwang B**: Combination chemotherapy with vinblastine, bleomycin, cisplatin, and etoposide (VBPE) in children with primary intracranial germ cell tumors. *Med Pediatr Oncol.* 24:358-372 1995

181. **Kobayashi T, Yoshida J, Ishiyama J, et al.**: Combination chemotherapy with cisplatin and etoposide for malignant intracranial germ cell tumors. An experimental and clinical study. *J Neurosurg.* 70:676-681 1989

182. **Yoshida J, Sugita K, Kobayashi T, et al.**: Prognosis of intracranial germ cell tumors: effectiveness of chemotherapy with cisplatin and etoposide (CDDP and VP-16). *Acta Neurochir (Wein).* 120:111-117 1993

183. **Robertson PL, DaRosso RC, Allen JC**: Improved prognosis of intracranial non-germinoma germ cell tumors with multimodality therapy. *J Neurooncol.* 32:71-80 1997

184. **Calaminus G, Koch S, Frappaz D, et al.**: Markers in serum/cerebrospinal fluid (CSF) in non-germinomatous CNS germ cell tumors (GCT): implication of site and dissemination. *Pediatr Blood Cancer.* 45:469 2005

185. **Baranzelli MC, Patte C, Bouffet E, et al.**: An attempt to treat pediatric intracranial α FP and β HCG-secreting germ cell tumors with chemotherapy alone. SFOP experience with 18 cases. Society Francaise d-Oncologie Pediatrique. *J Neurooncol.* 37:229-239 1998

186. **Kellie SJ, Boyce H, Dunkel IJ, et al.**: Primary chemotherapy for intracranial nongerminomatous germ cell tumors: results of the Second International CNS Germ Cell Study Group protocol. *J Clin Oncol.* 22:846-853 2004

187. **Calaminus G, Bamberg M, Baranzelli MC, et al.**: Intracranial germ cell tumors: a comprehensive update of the European data. *Neuropediatrics.* 25:26-31 1994

188. **Seigert W, Beyer J, Strohscheer I, et al.**: High-dose treatment with carboplatin etoposide and ifosfamide followed by autologous stem cell transplantation in refractory germ cell cancer—a phase I/II study. *J Clin Oncol.* 12:1223-1231 1994

189. **Beyer J, Kramar R, Mandanas W, et al.**: High-dose chemotherapy as salvage treatment in germ cell tumors: a multivariate analysis of prognostic variables. *J Clin Oncol.* 14:2638-2645 1996

190. **Motzer RJ, Mazumdar M, Bosl GJ, et al.**: High-dose carboplatin, etoposide and cyclophosphamide with autologous bone marrow transplantation in first-line therapy for patients with poor-risk germ cell tumors. *J Clin Oncol.* 15:2546-25521997

191. Bouffet B, Baranzelli C, Patte D, et al. High dose etoposide and thiotepa for refractory and recurrent malignant intracranial germ cell tumors. No. 38, 9th International Symposium in Pediatric Neuro-Oncology, June 11-14, 2000, San Francisco.

192. **Modak S, Gardner S, Dunkel I, et al.**: Thiotepa-based high-dose chemotherapy with autologous stem cell rescue in patients with recurrent or progressive CNS germ cell tumors. *J Clin Oncol.* 22:1934-1943 2004

193. **Mahoney DH Jr, Strother D, Camitta B, et al.**: High-dose melphalan and cyclophosphamide with autologous bone marrow rescue for recurrent/progressive malignant brain tumors in children: a pilot Pediatric Oncology Group study. *J Clin Oncol.* 14:382-388 1996

194. **Kadota RP, Mahoney DH, Doyle J, et al.**: Cyclophosphamide (CPM) and melphalan (MEL) for recurrent medulloblastoma (MB) and intracranial germinoma (GCT): a Children's Oncology Group study. *Pediatr Blood Cancer*.49:422 2007

195. **Matson D**: Tumors of the choroid plexus. **Matson DD** *Neurosurgery of Infancy and Childhood.* 2nd ed 1969 Charles C Thomas Springfield IL 581-595

196. **Cushing H**: Intracranial Tumors. 1932 Charles C Thomas Springfield IL

197. **Zulch K**: Biologie und pathologie der hirngeschwulste. **Olvecrona H Tonnis W***Handbuch der Neruochirurgie.* Vol 3 1956 Springer-Verlag Berlin

198. **Laurence KM**: The biology of choroid plexus papilloma in infancy and childhood. *Acta Neurochir.* 50:79-90 1979

199. **Guerard M**: Tumeur Fongeuse dans le ventricle droit du cerveau chez une petite fille de trois ans. *Anat Paris.* 8:211-214 1832

200. **Bielschowsky M, Unger E**: Kenntnis der primaren Epithelgeschwulste der Adergeflechte des Gehirns. *Arch Klin Chir.* 81:61-82 1906

201. **Perthes G**: Entfernung eines Tumors des Plexus Choriodeus an dem Seitenventrikel des Cerebrums. *Munch Med Wschr.* 66:677-678 1919

202. **Davis L**: A physiopathological study of the choroid plexus with the report of a case of villous hypertrophy. *Med Res.* 44:521-534 1924

203. **Rand C, Reeves D**: Choroid plexus tumors in infancy and childhood: report of four cases. *Bull L A Neurol Soc.* 5:405-410 1940

204. **Slaymaker S, Elias F**: Papilloma of the choroid plexus with hydrocephalus: report of a case. *Arch Intern Med.* 3:289-294 1909

205. **Turner O, Simon M**: Malignant papillomas of the choroid plexus: report of two cases with review of the literature. *Am J Cancer.* 30:289-297 1937

206. **Van Wagenen WP**: Papillomas of the choroid plexus: report of two cases, one with removal of tumor at operation and one with "seeding" of the tumor in the ventricular system. *Arch Surg.* 20:199-231 1930

207. **Strojan P, Popovic M, Surlan K, et al.**: Choroid plexus tumors: a review of 28-year experience. *Neoplasma.* 51:306-312 2004

208. **Ellenbogen RG, Winston KR, Kupsky WJ**: Tumors of the choroid plexus in children. *Neurosurgery.* 25:327-335 1989

209. **Johnson DL**: Management of choroid plexus tumors in children. *Pediatr Neurosci.* 15:195-206 1989

210. **Pascual-Castroviejo I, Villarejo F, Perez-Higueras A**: Childhood choroid plexus neoplasms: a study of 14 cases less than 2 years old. *Eur Pediatr.* 140:51-56 1983

211. **Allen J, Wisoff J, Helson L, et al.**: Choroid plexus carcinoma: responses to chemotherapy alone in newly diagnosed young children. *J Neurooncol.* 12:69-74 1992

212. **Boyd M, Steinbok M**: Choroid plexus tumors: problems in diagnosis and management. *J Neurosurg.* 66:800-805 1987

213. **Pencalet P, Sainte-Rose C, Lellouch-Tubiana A, et al.**: Papillomas and carcinomas of the choroid plexus in children. *J Neurosurg.* 88:521-528 1998

214. **Drucker GA**: Papillary tumor of the choroid plexus in a newborn infant. *Arch Pathol.* 28:390-395 1939

215. **Braunstein H, Martin F Jr**: Congenital papilloma of choroid plexus: report of a case, with observations on pathogenesis of associated hydrocephalus. *AMA Arch Neurol Psychiatry.* 68:475-480 1952

216. **Matson DD**: Hydrocephalus in a premature infant caused by papilloma of the choroid plexus with report of surgical treatment. *J Neurosurg.* 10:416-420 1953

217. **Body G, Darnis E, Pourcelot D**: Choroid plexus tumors: antenatal diagnosis and follow-up. *J Clin Ultrasound.* 18:575-578 1990

218. **Kahn E, Luros J**: Hydrocephalus from overproduction of cerebrospinal fluid (and experiences with other papilloma of the choroid plexus). *J Neurosurg.*9:59-67 1952

219. **Knierim DS**: Choroid plexus tumors in infants. *Pediatr Neurosurg.* 16:276-2801990

220. **Tomita T, McLone DG, Flannery AM**: Choroid plexus papillomas of neonates, infants and children. *Pediatr Neurosci.* 14:23-30 1988

221. **Meyers SP, Khademian ZP, Chuang SH, et al.**: Choroid plexus carcinomas in children: MRI features and patient outcomes. *Neuroradiology.* 46:770-7802004

222. **Ray BS, Peck FC Jr**: Papilloma of the choroid plexus of the lateral ventricles causing hydrocephalus in an infant. *J Neurosurg.* 13:405-410 1956

223. **Milhorat T, Hammock M, Davis D, et al.**: Choroid plexus papilloma: proof of cerebrospinal overproduction. *Childs Brain.* 2:273-289 1976

224. **Eisenberg H, McComb G, Lorenzo A**: Cerebrospinal fluid overproduction and hydrocephalus associated with choroid plexus papilloma. *J Neurosurg.* 40:380-385 1974

225. **Portnoy H, Croissant P**: A practical method of measuring hydrodynamics of cerebrospinal fluid. *Surg Neurol.* 5:173-177 1976

226. **Sahar A, Feinsod M, Beller A**: Choroid plexus papilloma: hydrocephalus and cerebrospinal fluid dynamics. *Surg Neurol.* 13:476-478 1980

227. **Welch K, Strand R, Bresnan M, et al.**: Congenital hydrocephalus due to villous hypertrophy of the telencephalic choroid plexuses: case report. *J Neurosurg.*59:172-175 1983

228. **Gudeman S, Sullivan H, Rosner M, et al.**: Surgical removal of bilateral papillomas of the choroid plexus of the lateral ventricles with resolution of hydrocephalus. *J Neurosurg.* 50:677-681 1979

229. **Schijman E, Monges J, Raimondi A, et al.**: Choroid plexus papillomas of the III ventricle in childhood. *Childs Nerv Syst.* 6:331-334 1990

230. **McDonald J**: Persistent hydrocephalus following the removal of papillomas of the choroid plexus of the lateral ventricles. *J Neurosurg.* 30:736-740 1969

231. **Pollack IF, Schor NF, Martinez AJ, et al.**: Bobble-head doll syndrome and drop attacks in a child with a cystic choroid plexus papilloma of the third ventricle. Case report. *J Neurosurg.* 83:729-732 1995

232. **Jeibmann A, Hasselblatt M, Gerss J, et al.**: Prognostic implications of atypical histologic features in choroid plexus papilloma. *J Neuropathol Exp Neurol.*65:1069-1073 2006

233. **Rovit RL, Schechter MM, Chodroff P**: Choroid plexus papillomas: observations on radiographic diagnosis. *AJR Am J Roentgenol.* 110:608-617 1970

234. **McGirr SJ, Ebersold MJ, Scheithauer BW, et al.**: Choroid plexus papillomas: long-term follow-up results in a surgically treated series. *J Neurosurg.* 69:843-849 1988

235. **Jooma R, Grant D**: Third ventricle choroid plexus papillomas. *Childs Brain.*10:242-250 1983

236. **Burger PC, Scheithauer BW**: Tumors of neuroglia and choroid plexus epithelium. **Burger PC Scheithauer BW** *Tumors of the Central Nervous System.*1994 Armed Forces Institute of Pathology Washington DC 136-161

237. **Kimura M, Takayasu M, Suzuki Y, et al.**: Primary choroid plexus papilloma located in the suprasellar region: case report. *Neurosurgery.* 31:563-566 1992

238. **Leblanc R, Bekhor S, Melanson D, et al.**: Diffuse craniospinal seeding from a benign fourth ventricle choroid plexus papilloma: case report. *J Neurosurg.*88:757-760 1998

239. **Vraa-Jensen G**: Papilloma of the choroid plexus with pulmonary metastases.*Acta Psychiatr (Koln).* 25:299-306 1950

240. **Rhoton AL Jr**: Microsurgical anatomy of the lateral ventricles. **Wilkins RHRengachary SS** *Neurosurgery Update I. Diagnosis, Operative Technique, and Neuro-Oncology.* 1990 McGraw-Hill New York 354-368

241. **Timurkaynak E, Rhoton A, Barry M**: Microsurgical anatomy and approaches to the lateral ventricles. *Neurosurgery.* 19:685-723 1986

242. **Crofton F, Matson D**: Roentgenologic study of choroid plexus papillomas in children. *AJR Am J Roentgenol.* 84:273-311 1950

243. **Hawkins JCI**: Treatment of choroid plexus papillomas in children: a brief analysis of twenty years' experience. *Neurosurgery.* 6:380-384 1980

244. **Raimondi AJ, Gutierrez FA**: Diagnosis and surgical treatment of choroid plexus papillomas. *Childs Brain.* 1:81-115 1975

245. **Coates TL, Hinshaw DB Jr, Peckman N, et al.**: Pediatric choroid plexus neoplasms: MR, CT, and pathologic correlation. *Radiology.* 173:81-88 1989

246. **Krieger MD, Panigraphy A, McComb JG, et al.**: Differentiation of choroid plexus tumors by advanced magnetic resonance spectroscopy. *Neurosurg Focus.* 18:E42005

247. **Horska A, Ulug AM, Melhem ER, et al.**: Proton magnetic resonance spectroscopy of choroid plexus tumors in children. *J Magn Reson Imag.* 14:78-82 2001

248. **Paulus W, Brandner S**: Choroid plexus tumors. **Louis DN Ohgaki H Wiestler ODCavenee WK** *WHO Classification of Tumors of the Central Nervous System.* 2007IARC Press Lyon, France 82-85

249. **Coffin CC, Wick MR, Braun JT, et al.**: Choroid plexus neoplasms: clinicopathologic and immunohistochemical studies. *Am J Surg Pathol.* 10:394-404 1986

250. **Russell DS, Rubinstein LJ**: Pathology of Tumors of the Nervous System. 5th ed1989 Williams & Wilkins Baltimore

251. **Chow E, Jenkins JJ, Burger PC, et al.**: Malignant evolution of choroid plexus papilloma. *Pediatr Neurosurg.* 31:127-130 1999

252. **Paulus W, Janisch W**: Clinicopathologic correlations in epithelial choroid plexus neoplasms: a study of 52 cases. *Acta Neuropathol.* 80:635-641 1990

253. **Chow E, Reardon DA, Shah AB, et al.**: Pediatric choroid plexus neoplasms. *Int J Radiat Oncol Biol Phys.* 44:249-254 1999

254. **Jeibmann A, Wrede B, Peters O, et al.**: Malignant progression in choroid plexus papillomas. *J Neurosurg.* 107 (3 suppl):199-202 2007

255. **Newbould MJ, Kelsey AM, Arango JC, et al.**: The choroid plexus carcinomas of childhood: histopathology, immunocytochemistry and clinicopathological correlations. *Histopathology.* 26:137-143 1995

256. **St. Clair SK, Humphreys RP, Pillay PK, et al.**: Current management of choroid plexus carcinoma. *Pediatr Neurosurg.* 17:225-233 1991

257. **Ausman J, Shrontz C, Chason J, et al.**: Aggressive choroid plexus papilloma.*Surg Neurol.* 22:472-476 1984

258. **Tena-Suck ML, Gomez-Amador JL, Ortiz-Plata A, et al.**: Rhabdoid choroid plexus carcinoma. *Arq Neuropsiquiatr.* 65:705-709 2007

259. **Philips M, Shanno G, Duahime A**: Treatment of villous hypertrophy of the choroid plexus by endoscopic contact coagulation. *Pediatr Neurosurg.* 28:252-256 1998

260. **Hirano H, Hirahara K, Tetsuhiko A, et al.**: Hydrocephalus due to villous hypertrophy of the choroid plexus in the lateral ventricles. *J Neurosurg.* 80:321-323 1994

261. **Cruz-Sanchez F, Rossi M, Hughes J, et al.**: Choroid plexus papillomas: an immunohistological study of 16 cases. *Histopathology.* 15:61-69 1989

262. **Vajtai I, Varga Z, Aguzzi A**: MIB-1 immunoreactivity reveals different labelling in low grade and malignant epithelial neoplasms of the choroid plexus.*Histopathology.* 29:147-151 1996

263. **Wyatt-Ashmead J, Kleinschmidt-DeMasters B, Mierau GW, et al.**: Choroid plexus carcinomas and rhabdoid tumors: phenotypic and genotypic overlap.*Pediatr Dev Pathol.* 4:545-549 2001

264. **Rickert CH, Wiestler OD, Paulus W**: Chromosomal imbalances in choroid plexus tumors. *Am J Pathol.* 160:1105-1113 2002

265. **Hirsch JF, Sante-Rose C**: A new surgical approach to subcortical lesions: balloon inflation and cortical gluing. *J Neurosurg.* 74:1014-1017 1991

266. **Berger C, Thiesse P, Lellouch-Tubiana A**: Choroid plexus carcinomas in childhood: clinical features and prognostic factors. *Neurosurgery.* 42:470-4751998

267. **Packer R, Perilongo G, Johnson D, et al.**: Choroid plexus carcinoma of childhood. *Cancer.* 69:580-585 1992

268. **Pierga J, Kalifa C, Terrier-Lacombe MJ, et al.**: Carcinoma of the choroid plexus: a pediatric experience. *Med Pediatr Oncol.* 21:480-487 1993

269. **Sharma R, Rout D, Gupta A, et al.**: Choroid plexus papillomas. *Br J Neurosurg.*8:169-177 1994

270. **Humphreys R, Nemoto S, Hendrick EB, et al.**: Childhood choroid plexus tumors. *Concepts Pediatr Neurosurg.* 7:1-18 1987

271. **Carpenter D, Michelsen W, Hays A**: Carcinoma of the choroid plexus. *J Neurosurg.* 56:722-777 1982

272. **Lena G, Genitori L, Molina J, et al.**: Choroid plexus tumors in children: review of 24 cases. *Acta Neurochir (Wein).* 106:68-72 1990

273. **Wrede B, Liu P, Wolff JE**: Chemotherapy improves the survival of patients with choroid plexus carcinoma: a meta-analysis of individual cases with choroid plexus tumors. *J Neurooncol.* 85:345-351 2007

274. **Duffner PK, Kun LE, Burger PC, et al.**: Postoperative chemotherapy and delayed radiation in infants and very young children with choroid plexus carcinomas. *Pediatr Neurosurg.* 22:189-196 1995

275. **Souweidane M, Johnson JJ, Lis E**: Volumetric reduction of a choroid plexus carcinoma using preoperative chemotherapy. *J Neurooncol.* 43:167-171 1999

AGE	SEX	SIDE	LOCATION	PATHOLOGY	PRESENTATION	SIZE	CT					MRI					SURGERY	COMPLICATIONS	RT	CT	PFS	OS	ALIVE	LFU WITH RECURRENCE	LFU WITHOUT RECURRENCE	TUMOR RELATED SURGERY	OTHER SURGERIES
							CE	CYST	HAEMORRHAGE	CA	DENSITY	T1	T2	CE	CYST	HAEMORRHAGE											
12	F	LEFT	P	AE-III	SEIZURES	2	0	0	0	0	0	2	1	1	0	0	G		1		142		166				1
4	M	LEFT	F	OA-III	SEIZURES	3	1	1	0	0	0	0	0	0	0	0	S		1	1	35-13	67		60			2
13	M	RIGHT	F	G-IV	ICP		1		1								G	csf rhinorrhea				0					
18	M	RIGHT	T	IV	SEIZURES	2	1										S	meningitis	1	1	3	4			3	1	
6	M	LEFT	P	ODG-III	ICP	3											G		1				108				SHUNT, SDH
10	M	LEFT	T	AA-III	ICP	3											G				13			18			1 TP
16	M	RIGHT	F	AA-III	ICP	3											G	hemiparesi	1	1	79-23	104					2
6	F	LEFT	F	AA-III	SEIZURES	1											G		1						64		
17	M	LEFT	F	G-IV	ICP	2											G		1	T	9			11			1
14	M	RIGHT	F	O-IV	ICP	2											N		1	1	15	17					1
9	M	LEFT	TH	O-IV	ICP	2	1	1				2	3	1	0	0	S	hemiparesi	1			25			4		
10	M	RIGHT	P	G-IV	ICP	3											G		1	T					50		
6	F	RIGHT	F	IV	SEIZURES	1											G		1						40		
15	M	RIGHT	P	O-IV	SEIZURES	3											N	hemiparesi	1		6	27			6		
12	M	LEFT	P	AA-III	ICP	3	1		1								S		1		15	15		15			
16	F	RIGHT	P	AA-III	ICP	2	1	1		0		1	3	1	1		S		1		129			129			
15	M	CC		AA-III	ICP	2			1			4	3	1	1	1	N		1		7	8		7			
15	M	LEFT	T	AA-III	DIPLOPIA	3							3				S					3					
18	F	LEFT	O	OA-III	ICP	2						2	3		1		G		1	T	6			6			
5	F	RIGHT	F	S-IV	ICP	2			1			2	3				G				6				14	1	
6	F	LEFT	F	ODG-III	ICP	3	1	1	0	1		2	3	1			G		1		42			42			SDH
14	F	RIGHT	T	IV	ICP	2		1				2	4		1		G		1		6			26			
7	M	LEFT	V	IV	ICP	2	1										G		1			2			2		SHUNT
13	M	RIGHT	F	AA-III	FND	3				1		2	3	1		1	N					0					
7	M	RIGHT	T	OA-III	FND	2						2	3	1		1	S										
7	F	RIGHT	P	ODG-III	FND	2		1		0	1			6			G		1	1					71		
18	M	LEFT	T	2-IV	ICP	1	1	1									G				4	8		4			
3	F	LEFT	P	OA-III	ICP	3		1		1							S		1		5--20-10			80			2
17	M	LEFT	TH	AA-III	ICP	2		1				2	1		1		S		1		10			10			
18	M	LEFT	P	IV	ICP	3						2	2	0			G					3					
5	F	RIGHT	T	AA-III	ICP	2						1	3	1			G						ALIVE74				
12	M		PINEAL	AA-III	ICP	2						4	4	4	1		S		1	1	15	19			17		
6	M	RIGHT	P	AE-III	ICP	3		1		1		1	1				G		1	1	28	33					
16	F	LEFT	TH	OA-III	ICP	2		1				1	1	1			S		1			9			2		
17	F	RIGHT	TH	IV	ICP	2											B		1		6	30					1
11	F	RIGHT	P	AE-III	ICP	2		1									S		1		6		ALIVE 53				
10	M	LEFT	P	OA-III	ICP	3		1		0							S		1		34	37		36			1
12	M	RIGHT	F	AA-III	SEIZURES	3	0			0							G	meningitis			8	36					
11	M	RIGHT	P	AE-III	ICP	1	1	1									S		1				ALIVE112				
7	M	RIGHT	TH	O-IV	ICP	2	1	1	1								S		1		2						
13	M	LEFT	TH	IV	ICP	2	1			1			3				S		1		15			15			
9	F	LEFT	TH	IV	ICP	2	1	1	1								S		1								
7	F	RIGHT	TH	AA-III	FND	3		1				2	4	1			B					4			1		
14	F	RIGHT	T	PNET	FND	0	1	1	1								S		7-Jan		36			38			
10	M	RIGHT	T	PNET	SEIZURES	0											G										
0.8	M	RIGHT	F	PNET	FND	0		1	1								G			1				17			
12	F	RIGHT	P	PNET	ICP	2		1	1	1							G	meningitis	1				ALIVE150				
0.15	M	LEFT		PNET	ICP	3					3	3	3				B					6					
1.5	F	RIGHT	F	PNET	FND	2				1	1						N		1	1	54			54			1
5	F	RIGHT	P	OA-III	ICP	0						2	3	1	1		N		1	1					137		
1.25	F	RIGHT	TH	S-IV	SEIZURES	2	1		1								G			1					45		
2.5	F	RIGHT	F	PNET	SEIZURES	0		1		1							G	meningitis		1			ALIVE66				
3	F	LEFT	TH	PNET	IRRITABILIT	0											B			1	12				3		
9	F	RIGHT	F	PNET	DIPLOPIA	3	1					1	1	1			S			1	16	17		16			
12	F	LEFT	F	PNET	FND	2	1				2						B		1	1	11			60			
2	F	RIGHT	F	PNET	SEIZURES	1	1			1	1						N			1	2			2			
5.5	M	LEFT	P	PNET	FND	3						2	3				G	meningitis	1	1					94		
3	M	LEFT	P	PNET	FND	3											N								12		
13	M	RIGHT	F	AE-III	SEIZURES	3	1	1		1	3	1	2	1	1		G		1						95		
8	M	RIGHT	F	PNET	ICP	2						1	1	1			G			1	12	20					
0.4	M	LEFT	P	PNET	ICP	3	1			1		1					B										

3	M	RIGHT	P	PNET	FND	3	1	1		1						1	1	G	meningitis								2				
3	F	RIGHT	P	PNET	ICP	3												G		1	1	13	17				16	1			
8	F	RIGHT	V	PNET	SEIZURES	1												B		1	1		26				12		SHUNT		
1.4	M		3RD	CPC	ICP	2						1	1	1				G		1		24	35				32	1			
0.93	M		PINEAL	PNET	ICP	0					2	1	1	1				G			1		12				6		SHUNT		
2	F		PINEAL	PNET	ICP	2	1			1								B		2	1		22				6		ETV		
6	F		PINEAL	PNET	ICP	2	1			1	1							N		1	1						126				
14	M		PINEAL	PNET	ICP	2	1				3	1	1					G		1	1						74		SHUNT		
0.41	F	LEFT	P	PNET	ICP	3	1	1										G	meningitis		1						63		SDH		
17	F	LEFT	V	CPC	FND	3					3							G				5				6					
2.25	M	RIGHT	V	CPC	ICP	3												G	DVT								2				
1.3	M	RIGHT	V	CPC	ICP	2					3							G	meningitis		1	7					14	1	SHUNT		
0.91	F	RIGHT	V	CPC	ICP	2		1			3							G				4				4			SHUNT		
11	M		PINEAL	PB	ICP	2	1				3							B		1	1	20				20			SHUNT		
10	F		PINEAL	PB	ICP	2	1		1									G		1	1	13	17						SHUNT		
5	M		PINEAL	PNET	ICP	2						1	2	1	1			N		1	1						84				
1.7	M	RIGHT	T	CPC	SEIZURES	2									1			G				3					68	1			
12	M		PINEAL	PB	ICP	3	1					2	1	1				B	meningitis	1	1						11		SHUNT		
1.7	M		PINEAL	PB	IRRITABILIT	2	1				3							B			1						5				
2.5	M	LEFT	V	CPC	ICP	2	1				3	1	3	1				G	UTI	1	1	9									
3	F	RIGHT	V	CPC	SEIZURES	2	1			1	3	1	2	1				G		1							62				
2	M		PINEAL	PB	ICP	1						1	1	1				B			1		6								
11	M		PINEAL	GER	V	0				1	3							B													
16	F		SS	GER	AME	0						3	3	1				B		1				130							
13	M		PINEAL	GER	ICP	0												B									70				
13	F		SS	GER	DI	1						1	2	1				N		1	1						64				
14	M		SS	GER	DI	1												G													
13	F		SS	GER	DI	1												B													
7	F		SS	MIXGER	DI	2		1		1								G					2								
16	M		MULTIPLE	GER	VISION LOS	0	1											B		1			95A								
14	F		SS	GER	DI	1	1											G		1	1		109A								
18	M		PINEAL	GER		1	1					1	1	1				S		1			71A								
10	M		PINEAL	GER	ICP	2				1		3	3					B		1	1										
16	M		PINEAL-SS	GER	ICP	1		1		1		1	2	1				B		1			24								
17	F	LEFT	F	IV	FND	2						1	3	1				G		1		14				14					
5	M	RIGHT	P	O-IV	ICP	2												S		1			12								
3	M	RIGHT	F	PNET	FND	3												N					13								
18	F	RIGHT	T	ATRT	SEIZURES	2												G		1											
7	M		PINEAL	TERA	ICP	2						3	1				1	G			1		8								
5	F		PINEAL	TERA	ICP	1												G		1	1										
9	M		PINEAL	TERA	ICP	1												G									61				
15	M	RIGHT	F	AA-III	ICP	1	1											G		1							14		SHUNT		

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