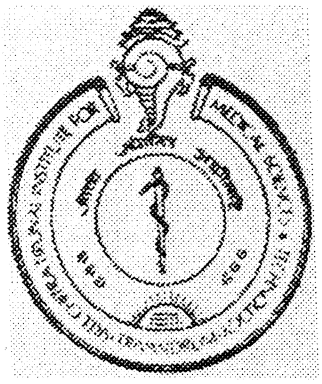
ADULT MEDULLOBLASTOMA



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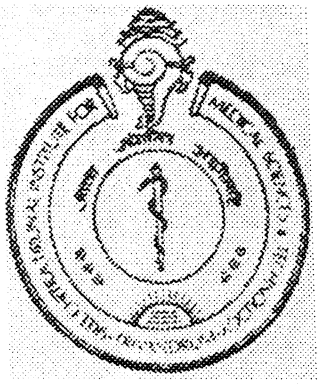

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CERTIFICATE

This is to certify that the study

*"**ADULT MEDULLOBLASTOMA**" has been carried out by*

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REVIEW OF LITERATURE

REVIEW OF LITERATURE

Medulloblastoma is the most common malignant tumor in children, accounting 4.78 % of the primary central nervous system neoplasm and approximately 30% of all posterior fossa tumors[7]. Originally classified a glioma, Medulloblastoma is referred to now as a primitive neuro-ectodermal tumor (PNET). It is a highly invasive tumor arising from the cerebellum with tendency to disseminate throughout the CNS early in its course.

Medulloblastoma is a common malignancy in the pediatric population, accounting for 25% of all childhood brain tumors[3]. The median age of diagnosis is 5 years, with 80% of cases being diagnosed in the first 15 years. Medulloblastomas, however, account for only approximately 1% of all adult brain tumors, and data for adults are relatively sparse[3].

Pathophysiology

Medulloblastoma is a cerebellar tumor arising predominantly from the cerebellar vermis. One view suggests that the cell of origin derives from the external granular layer of the cerebellum. This is supported by the finding that the proliferation of precursor neurons in this layer is controlled by sonic hedgehog gene (SHH), whose receptor is mutated in a subset of sporadic medulloblastomas[27]. Another hypothesis proposes that medulloblastomas have more than once cell of origin. This is based on studies showing differential immunoreactivity to a neuronal calcium-binding protein that is not expressed

in the external granular layer and to that beta-tubulin isotype that is expressed in the neuronal cells of the ventricular matrix and external granular layer and to a beta-tubulin isotype that is expressed in the neuronal cells of the ventricular matrix and external granular layer. Recent studies suggest that medulloblastoma expression of neurotrophin (NT3) and its cognate receptor, Trk C, may modulate the behavior of these tumors by inducing apoptosis, thereby retarding tumor progression and resulting in a more favorable prognosis.

As the tumor grows, obstruction of cerebrospinal fluid (CSF) passage through the fourth ventricle generally occurs, resulting in hydrocephalus[21]. The tumor may spread contiguously, to the cerebellar peduncle and/or the floor of the fourth ventricle; anteriorly, to the brainstem; inferiorly, to the cervical spine; or superiorly, above the tentorium. It also may spread via the CSF intracranially or to the leptomeninges and spinal cord. Of all the pediatric CNS neoplasms, medulloblastoma has the greatest propensity for extra neural spread, especially to bone and bone marrow; however, the rate of such events is less than 4%.

Incidence of medulloblastoma is 1.4-2 cases per 100,000 population, with 350 new cases in the United States each year[27]. Although the majority occur as sporadic cases, hereditary conditions have been associated with medulloblastoma, including (1) Gorlin syndrome (nevoid basal cell carcinoma syndrome), (2) blue rubber-bleb nevus syndrome, (3) Turcot syndrome (eg. glioma polyposis syndrome), and (4) Rubenstein-Taybi syndrome.

Medulloblastoma is associated with recessively inherited Turcot and ataxia-telangiectasia syndromes. As many as 5 % of patients with autosomal nevoid basal cell carcinoma (Gorlin) syndrome develop medulloblastoma.

Genetic associations: The most frequent cytogenetic abnormality in sporadic medulloblastoma is an isochromosome 17q of [i (17q)] [18]. Of tumors analyzed, 40-50% have a deletion of the short arm of chromosome 17, implicating the presence of a tumor suppressor gene that maps to 17p, which is distinct from the p53 gene.

Sex: Male: female 1.5: 1.

Many studies have shown that males have poorer prognosis[2, 3,7,14].

Age: Peak age of incidence is 3-5 years. Approximately 80% patients are diagnosed in the first 15 years of life[2, 19].

Symptoms and signs

Although 70 % of patients present with a history of headaches, emesis, and lethargy, these symptoms are generally intermittent and subtle. Duration of symptoms is usually 3 months before diagnosis[14, 21].

Early symptoms are secondary to increased ICP. The classic triad consists of morning headaches, vomiting, and lethargy. Cushing triad (i.e. hypertension, bradycardia, and hypoventilation), an uncommon finding in children with increased intracranial pressure, usually indicates impending herniation. Initial signs of increased ICP are usually subacute, nonspecific, and non-localizing. School-aged children may

complain of vague intermittent headaches and fatigue. They may demonstrate declining academic performance and personality changes. Infants may present with irritability, anorexia, and developmental delay.

The presentation of medulloblastoma in adults is different from that in children owing to the greater incidence of lateral tumors including those occurring in cerebello-pontine angle[15]. Many patients have cranial nerve palsies (mostly sixth but also fifth and seventh). Some patients have a significant reduction in conscious level; few present with convulsions.

Adult patients may develop double vision as the sixth cranial nerve becomes stretched from the hydrocephalus. Visual disturbances more commonly are a result of papilledema[15].

Cerebellar dysfunction

Most commonly found in children, the tumor involves the cerebellar vermis and causes gait ataxia more readily than unilateral symptoms[21]. Adults more commonly harbor the desmoplastic variant or medulloblastoma, which arises in the cerebellar hemisphere. These patients often have symptoms of ipsilateral dysmetria[23].

Head tilt and neck stiffness, caused by meningeal irritation, are complications of tonsillar hemiation below the foramen magnum. Alternatively, head tilt can result from trochlear nerve palsy caused by direct tumor compression.

Brain stem deficits

Tumor infiltration of the brain stem or increased ICP may result in diplopia and multiple cranial nerve findings, such as facial weakness, tinnitus, hearing loss, head tilt, and stiff neck[21].

Metastatic disease: Uncommonly, patients may present with back pain or leg weakness secondary to spinal metastasis.

The earliest signs are non-localized and caused by increased ICP. Later signs are generally due to tumor invasion of the surrounding tissue.

Examination of optic fundus shows papilledema or optic pallor in infants. Palsy of VI cranial nerve resulting in the inability to abduct one or both eyes is common. Infants may have the 'setting sun" sign[21]. This is demonstrated by impaired up gaze and seemingly forced downward deviation of the eyes. Measurement of head circumference in infants with open cranial sutures also may reveal macrocephaly. Cerebellar findings like localized deficits in truncal steadiness, upper extremely coordination, and gait are common.

Invasion into the brain stem may cause loss of conjugate gaze (gaze palsy) or the inability to adduct one eye on attempted lateral gaze. This is observed most commonly in combination with deficits of cranial nerve V, VII, and IX. Invasion into the cerebellopontine angle results in facial weakness and hearing loss, often with associated unilateral cerebellar deficits[23].

Imaging Studies:

Computerized tomography (CT): CT scan of the head with and without contrast has more than 95% sensitivity for the detection of medulloblastoma[34]. On CT, prominent hydrocephalus and a solid, homogenous, midline cerebellar mass are characteristic of (although not diagnostic of) medulloblastoma. Surrounding hypodensity is indicative of vasogenic edema. 10% show calcifications[26]. The presence of necrotic, cystic areas and hemorrhage is unusual and found in approximately 10-16% and 3% of patients, respectively.

Preoperatively, high density on CT scan can help distinguish medulloblastoma from the hypodense appearance of a cerebellar astrocytoma.

Ependymoma is another hyperdense tumor that affects the posterior fossa of children. Unlike medulloblastoma, however, it often contains calcifications. Choroid plexus papilloma usually arises in the trigone of the lateral ventricle in children; however, in adults it is most common in the fourth ventricle. Choroid plexus papilloma commonly contains calcifications.

Magnetic resonance imaging: Medulloblastomas are hypo intense to isointense on T1-weighted images. T2-weighted appearance can vary from isointense to hyper intense. Medulloblastomas classically demonstrate heterogeneous hypo intense or isointense signal. Calcifications appear as signal void on T2-weighted images. Proton density and T2-weighted imaging displays a hyper intense mass with a surrounding area of edema.

The pattern of enhancement after intravenous injection of gadolinium is similar to that after injection of iodinated contrast material on CT (CECT). However, the greater sensitivity of MRI often enables appreciation of a slightly heterogeneous enhancing pattern not as readily evident with CT[21]. Homogenous enhancement commonly occurs, whereas in adults, a more heterogeneous pattern usually is seen. MRI can be useful in such instances by better demonstrating the anatomic origin and extent of tumor.

The blurring of cerebellar folia and fissures representing tumor spread via CSF pathways (best depicted on midline sagittal images) is a helpful sign. Subarachnoid or intraventricular seeding usually demonstrates contrast enhancement.

Drop metastases appear as high signal foci on contrast-enhanced T1-weighted images in the extramedullary, intradural space and, occasionally, subpial in location.

Proton spectroscopy demonstrates nonspecific elevation of the choline peak, translating cell membrane turnover; decreased aspartate peak, translating loss of neuronal tissue; and variable lipid and lactate.

Preoperative and postoperative MRI is required for detection and measurement of residual disease following surgical resection. Postoperative MRI evaluation should be performed within 72 hours of surgery to delineate residual tumor from post surgical inflammatory changes that are visualized on MRI at this time.

MRI can help differentiate medulloblastoma from ependymoma: the latter extends further into the lateral recess of the fourth ventricle or even further into the

cerebellopontine angle. MRI can also help distinguish between medulloblastoma and exophytic brainstem glioma (the latter having a broader attachment to the floor of the fourth ventricle).

Spinal MRI is the most sensitive method available for detection of spinal cord metastasis[18,21]. Imaging of the spine is best performed prior to surgery in order to avoid postoperative artifacts, which may be interpreted as tumor metastasis. Metastasis can occur in the basal cisterns. Both recurrent lesions and metastases show sparse enhancement.

Myelography

In the past, myelography was the standard diagnostic test for medulloblastoma metastases to the spine. Today, when MRI is contraindicated, myelography is utilized, accompanied by CT scan.

Bone scan: Because medulloblastoma can metastasize outside the CNS, especially to bone, a bone scan with plain film correlation may be useful in symptomatic patients.

Lumbar puncture: CSF cytological examination is useful for the detection of microscopic leptomeningeal tumor dissemination. However, a negative CSF cytological finding does not rule out the presence of nodular spinal cord disease. As many as 50% of patients with positive spine MRI studies are asymptomatic and have negative cytological results[27].

In known cases of medulloblastoma, LP generally is deferred until 2 weeks post surgery to avoid the presence of tumor cells that have disseminated as a result of surgery. Some authors suggest obtaining CSF at the time of surgery from the cisterna magna for cytological analysis.

Bone marrow aspirate and biopsy: Medulloblastoma rarely metastasizes to the bone marrow. So bone marrow examination should be reserved for patients who demonstrate abnormal peripheral blood findings that have no clear etiology[27].

Histologic Findings

Medulloblastomas are undifferentiated embryonal neuroepihelial tumors of the cerebellum[31]. They are highly cellular, soft, and friable tumors composed of cells with deeply basophilic nuclei of variable size and shape, little discernible cytoplasm, and often abundant mitoses. These characteristics give the microscopic appearances of a small, round, blue cell tumor[18].

Homer-Wright rosettes (ring like accumulations of tumor cell nuclei around a fibrillary core) and pseudo rosettes are variably present. When involved with tumor, the surrounding subarachnoid space is opaque, with a granular appearance often referred to as "sugar coating"[21]. This condition is associated with early subarachnoid seeding along the entire neuraxis and early recurrence. These tumors express neuronal and neuroendocrine markers, including synaptophysin and neurofilament proteins.

Various degrees of glial or neuroblastic differentiation are noted, suggesting that the primitive cell of origin possesses the capacity for bipotential differentiation.

Histologic subtypes

Desmoplastic: A histologic variant with abundant stromal component. Occurs dominantly in the lateral cerebellar areas of adolescents and adults. In addition to containing all microscopic characteristics of childhood medulloblastoma, the desmoplastic type contain a dense reticulin network; cells are arranged in a biphasic pattern with areas of high and low cellularity[25].

Medullomyoblastoma: Striated and smooth muscle cells are the hallmark of medullomyoblastoma. The tumor can contain cells that show elements of neuronal and glial differentiation. If the presumptive medullomyoblastoma contain elements of ectodermal, mesodermal, and endodermal differentiation, the tumor must be considered a teratoma.

Melanotic medulloblastoma: Small, undifferentiated cells containing melanin are characteristic of the very rare melanotic medulloblastoma.

Large-cell medulloblastoma: This subtype has large vesicular nuclei with prominent nucleoli. Cells of the large-cell medulloblastoma are remarkable in their immunoreactivity for synaptophysin. This particular tumor is associated with a poorer clinical outcome.

Lipomatous: good prognosis.

Although large-cell medulloblastoma is associated with a more aggressive course, medullomyoblastoma has a clinical course similar to that of ordinary medulloblastoma. However, the desmoplastic variant has a more favorable outcome[11].

TREATMENT

Most adults with medulloblastomas are treated using the pediatric protocols, on the basis of the assumption that this disease entity behaves similarly in the adult and pediatric populations, or are treated with regimens based on individual institutional experience[3]. Although the reported survival rates for children and adults are comparable, there are some distinct differences between the two populations, and adult medulloblastomas may behave differently than do pediatric medulloblastomas.

Approximately 50% of adult medulloblastomas are laterally located, compared with less than 10% of childhood medulloblastomas. Adult medulloblastomas may, therefore, be more amenable to complete resection[3]. The desmoplastic histological variant, which has been demonstrated to be prognostic significance and which is observed in approximately 15% of pediatric cases has been demonstrated to be present in up to 50% of adult cases[25].

Current protocols use risk-adapted approaches to treat patients with medulloblastomas. The prognostic factors for pediatric medulloblastomas, which have been used to guide adjuvant treatment, are well defined which include Chang M stages, sex , the extend of surgery or post-operative residual disease of more than 1.5 cm^3 , the absence or presence of brainstem invasion, age, the histological subtype and the radiation dose to the posterior fossa[8,9,12]. Late relapse is common among adult patients

with medulloblastomas, and long-term follow-up monitoring is important[3]. Because of the high risk of systemic failure among the low-risk patients treated with radiotherapy alone, the role of chemotherapy for is not well defined as in pediatric cases. Complete resection, the absence of brainstem invasion, and overall radiotherapy duration of less 48 days are important prognostic factors.

The definition of risk factors for adult medulloblastomas, however, is controversial. The data are mainly from studies that included limited numbers of patients from several decades in which contemporary computed tomographic scanning and magnetic resonance imaging were not available and treatment methods varied with time[3].

Management

Standard therapy consists of total surgical removal of tumor followed by radiation to the entire craniospinal axis with boost to both the primary tumor size and focal CNS metastatic sites[5]. Recently, adjuvant chemotherapy also has been shown to be beneficial.

A midline suboccipital craniectomy is the usually performed mode of access to posterior fossa. Some advocate suboccipital craniotomy also as an option. Usually the tumor is soft and friable, so gentle suction is used. Micro dissection is used to remove adherent portions[18]. If the patient has not had an external ventricular drain placed preoperatively, one usually is placed at the time of surgery.

Postoperative external ventricular drainage is maintained for 3 days, after which the drain is clamped and connected to pressure monitoring. If the patient tolerates 24

hours of having the drain clamped, the ventriculostomy is removed. If repeated drainage fails to relieve symptoms, a ventriculoperitoneal shunt is placed for long-term control hydrocephalus; however, this is necessary in only approximately 15% of patients. The alternative to shunting is a third ventriculostomy[18]. This can reestablish CSF flow without the potential for peritoneal seeding of tumor.

Modern neurosurgical techniques permit complete or near complete resection with little or no significant increase in morbidity and mortality rates compared to more conservative surgery. Because surgical estimates of the extent of resection may not be reliable, postoperative MRI evaluation for residual disease is required within several days of procedure.

Postoperative Stratification of Patients into Specific Treatment Regimens

Post-surgical treatment of patients with medulloblastoma is dependent on the number of perceived patient risk factors that are known to influence survival. These risk factors include patient age, tumor size and location, extent of surgical resection, and tumor histology[9, 22].

For poorly understood reasons, children under age 3 have a significantly lower survival rate than do patients older than 3 years[18]. However, confounding the interpretation of these data are the facts that younger children tend to have disseminated tumor at the time of diagnosis, and are rarely candidates for adequate doses of radiation therapy to deal with tumor dissemination. Packer defines the age risk cut-off as 4 years; whereas Edwards et al. defines this cut-off as age 2 years[25].

Postoperative Staging

Complete postoperative staging is critical in the management of patients with medulloblastoma. Medulloblastoma has a distinct propensity to seed along the CSF pathways, and patients with such disseminated tumors are invariably associated with a poorer prognosis. In 1969, Chang et al. reported an operative staging system for medulloblastoma which they developed based on tumor size, location, and the presence or absence of CSF dissemination and metastases[10]. In this study and numerous studies subsequently, children whose tumors had metastasized into subarachnoid space had reduced recurrence-free survival. Devised in the pre-CT era, Chang's operative staging system was dependent initially on the surgeon's intra-operative impression of tumor size and extent[18].

However, neurosurgeon's assessment of the amount of residual tumor or tumor dissemination at surgery is not entirely accurate for proper staging[9]. Role of investigative studies that assess the efficacy of surgery and the extent of dissemination are now used as tools for post operative staging.

The early postoperative CT scan has been a very good guide to the presence of residual tumor. If the neurosurgeon feels that a gross total resection of the tumor has been accomplished, and the enhanced CT scan shows no enhancing tumor, then the tumor is considered totally resected. Areas on CT of contrast enhancement probably represent residual tumor[18].

Studies have shown that dissemination of medulloblastoma tumor cells occurs in approximately 30 % of patients at the time of diagnosis and a diagnostic method with significant accuracy is needed to adequately stage the patient[27]. Myelography was for

years been considered the gold standard for detecting metastases in the spinal subarachnoid space. Usually myelogram is performed 2 weeks after surgery. CT-myelogram is done if suspicion exists about small tumor nodules within the spinal canal. But a negative myelogram and CSF cytologic examination do not entirely preclude the presence of spinal metastases. Ongoing studies with gadolinium-enhanced MRI scans may render it the optimum method for detecting spinal metastases.

The **Chang operative staging system** modified in 1986 has 4 components

Tumor status (T)

T1 Tumor less than 3 cm diameter and limited to the classic midline position in the vermis, the roof of the fourth ventricle and less frequently to the cerebellar hemispheres.

T2 Tumor 3cm or greater in diameter further invading one adjacent structure or partially filling the fourth ventricle.

T3 This stage is divided in to T3A and T3B

T3A Tumor further invading two adjacent structures or completely filling the fourth ventricle with extension in to aqueduct of Sylvius, foramen of Magendie or foramen of Luschka, thus providing marked internal hydrocephalus.

T3B Tumor arising from the floor of the fourth ventricle or brainstem and filling the fourth ventricle.

T4 Tumor further spreading through the aqueduct of Sylvius to involve the third ventricle or midbrain, or tumor extending to the upper cervical cord.

Metastasis (M)

M0 No evidence of metastasis

M1 Cells present in leptomeninges or cerebrospinal fluid

M2 Nodular seeding in supratentorial compartment (CE CT scan)

M3 Nodular seeding of spinal compartment (myelogram)

M4 Combined nodular seeding of two compartments (supratentorial and / or infratentorial and / or spinal).

M5 = Evidence of systemic seeding (bone marrow, various bone and viscera scans)

Based on this classification, specific risk groups are defined as given below:

Average-risk disease : This risk group is defined as patients older than 3 years who are at stage M0 with less than 1.5 cm^3 of residual tumor postoperatively.

Poor-risk disease: This risk group is defined as patients older than 3 years who are at stage M1-M4 and/or with more than 1.5 cm^2 of residual tumor postoperatively.

Infants: This group is defined as patients younger than 3 years. This group has the worst prognosis, regardless of M stage and extent of postoperative residual disease.

In 1977, Harisiadis and Chang revised the international TNM staging for medulloblastoma. The newly devised MAPS (metastasis, age, pathology, surgery) classification system is now employed to obtain a staging value that could be statistically analysed. Chang staging system attempts to quantitate tumor size at diagnosis with survival[20].

In the MAPS system, pathological grade is incorporated relating to the benignity or malignity of tumor on microscopic examination. Postoperative residual confirmed by contrast enhanced CT scan was also incorporated to have significant correlation with prognosis[20].

Pathology (P)

P1 = Microscopic appearance – benign, classic for tumor type, well differentiated single cell line.

P2 = Microscopic appearance – anaplastic, malignant, multiple differentiated cell lines.

Surgery (S)

S0 = No tumor

S1 = Remaining tumor < 1.5 cm (largest diameter)

S2 = Remaining tumor > 1.5 cm (largest diameter)

S3 = Remaining tumor (any size) invading brainstem structures

S4 = Remaining tumor (any size) extending in to more than central nervous system compartment (supratentorial, infratentorial, spinal compartments)

Radiation Therapy

Medulloblastoma was considered a fatal disease in 1930s and 40s despite Cushing's correct notion that medulloblastomas should be irradiated. Cutler et al. demonstrated increased patient survival by increasing the radiation dose used by Cushing. However, it was not until the landmark study by Patterson and Farr in 1953 in which postoperative total neural axis radiotherapy was used in patients of medulloblastoma that significant advantages were appreciated in terms of patient survival[29, 32].

Current treatment of medulloblastoma with radiation therapy consists of a dose to the tumor bed of 5,000-5,500 cGy, with a dose of 3,500-4,000 cGy through lateral opposing ports to the whole brain, and a dose of 3,000-4,000 cGy to the spinal cord through a posterior port[8, 21]. Tomita and McClone have suggested that carefully staged, low risk patients can be equally well treated with lower dose radiation therapy to the neuraxis[36]. Because of the profound neuropsychological complications of craniospinal irradiation, attempts are now being made by the CCSG and Pediatric Oncology Group (POG) to study the efficacy of reduced craniospinal staged and relegated to low-risk group. In this study, a dose of 2340 cGy is proposed for randomized good-risk patients over 3 years of age. But preliminary results from the CCSG have warned against the reduction of dose in craniospinal radiation because of a statistically significant increase in CSF dissemination[27]. Sutton et al. have suggested reduction in craniospinal irradiation commensurate with patient age[34] (Table 2).

Age	Neuraxis dose (cGy)	Post.fossa dose (cGy)
< 18 mo	None	None
18 mo-3 yr	1,800	5,040
4-5 yr	1,800	5,580
6-10 yr	2,340	5,580
> 10 yr	3,600	5,580

Table 1. Radiation therapy doses according to patient age

Average-risk disease

Reducing the amount of craniospinal radiation in an attempt to decrease morbidity without affecting survival is adopted in this group. In a recent report by the International Society of Pediatric Oncology, children with average-risk medulloblastoma randomly received either the standard 36 Gy or a reduced dose of 24 Gy to the neuraxis. It was found that no statistical difference in progression free survival rates was demonstrated between the groups as long as the initiation of radiotherapy was not delayed by the administration of chemotherapy before radiation.

The current dose for average-risk medulloblastoma patients enrolled on Children's Cancer Group (CCG) trials is 23.4 Gy to the craniospinal axis followed

by 32.4 Gy boost directly to the primary tumor site. In both the poor-risk and average-risk groups, the total radiation dose to sites of known disease is 55.8 Gy.

Unfortunately, radiation can have a destructive influence on the developing nervous system. Complications of radiotherapy can include lowered intelligence quotient (IQ) score, small stature, endocrine dysfunction, behavioral abnormalities, and secondary neoplasms.

Poor-risk disease

The current recommendation is 36 Gy to the craniospinal axis, followed by a boost of 19.8 Gy to the primary tumor site and an additional 19.8 Gy to focal metastatic sites. The amount of boost that can be given is limited by the presence of optic nerves within the radiation field or if more than two thirds of supratentorial compartment volume is within the radiation field[18].

Spinal disease that is visible after 30.6 Gy of the prescribed 36 Gy to the craniospinal axis receives an additional boost up to a total of 45 Gy if the tumor is located above the termination of the spinal cord and up to 50.4 Gy if the tumor is located below the termination of the cord.

Infants

Radiotherapy for patients younger than 3 years, the poorest risk group, remains controversial[27]. Because the effects of radiotherapy on intellectual development are most severe in this age a group, attempts have been made to delay or omit radiation by using chemotherapy. However, in most recent CCG study, infants receiving

chemotherapy alone had a 29% 3-year progression-free survival rate for those without dissemination and only 11 % for those with metastasis. The Pediatric Oncology Group (POG) reported that, in infants with medulloblastoma treated initially with chemotherapy followed by delayed radiation, the 2-year progression-free survival rate was 34%.

Chemotherapy

Walker and Allen were among the first to show the value of the combining chemotherapy as an important adjuvant for medulloblastoma patients. They achieved partial responses from the use of cis-platin in recurrent medulloblastoma[18]. Since then, cis-platin has been used in a number of clinical trials, especially for patients with high-risk medulloblastoma[34].

The efficacy of chemotherapy in the treatment of medulloblastoma has been assessed previously in two large randomized trials conducted by the Societe Internationale d' Oncologie Pediatrique (SIOP)[18]. The SIOP study compared the results of surgery and irradiation with those of surgery, irradiation and chemotherapy using vincristine and CCNU in 287 patients. In this study, children under the age of 2 with incomplete tumor resections, and those with brainstem involvement appeared to benefit from the addition of chemotherapy consisted of vincristine, CCNU, and prednisone. Again, chemotherapy appeared to be beneficial primarily to those children in the high-risk group.

Protocols regarding treatment of medulloblastoma vary from center to center throughout the world. The Japanese consider that all patients should be regarded a high risk and therefore they treat all patients with chemotherapy[35].

Multidrug chemotherapy may be delivered using many drugs over a short interval[18]. Prior trials in laboratory and clinical settings suggested that the administration of many drugs over a short interval would be less toxic than if drugs were individually spaced over several days. In this way, the "8 in 1" regimen was conceived consisting of vincristine, CCNU, procarbazine, hydroxyurea, methylprednisolone, cisplatin, cyclophosphamide, and cytosine arabinoside for patients with medulloblastoma. Preliminary results in phase II trials have been encouraging for medulloblastoma.

Average-risk disease

The most encouraging results with adjuvant chemotherapy have been reported in children with nondisseminated medulloblastoma receiving 8 cycles of lomustine (CCNU), vincristine, and cisplatin chemotherapy for approximately 1 year following conventional dose radiotherapy and concomitant vincristine.

Latest trails indicate that children aged 3-10 years who received this regimen with reduced-dose craniospinal radiation have a superior survival rate compared to those who received standard radiation alone. The current 3-year progression-free survival rate for those receiving adjuvant chemotherapy is approximately 80 %.

Poor-risk disease

Trials regarding the use of high-dose chemotherapy (most commonly using carboplatin and thiotepa containing regimens) and autologous stem cell rescue after a course of conventional craniospinal radiotherapy and chemotherapy are on at various

centers. Chemotherapeutic agents that have been found to be most effective for this disease are cisplatin, carboplatin, cyclophosphamide, and vincristine.

Infants

In children younger than 3 years, there is evidence that some do respond at least partially to chemotherapy. In patients with minimal residual postoperative disease, this response may be long lasting. Ongoing trials are investigating high-dose chemotherapy 9carboplatin and thiotepa and stem cell rescue, following induction with chemotherapeutic agents similar to those used in the treatment of older children with poor-risk disease. Whether radiotherapy can be safely delayed or omitted altogether in certain subgroups has not yet been determined.

Post treatment imaging studies

To have an objective measurement of tumor response to therapy, MRI with contrast of the head is performed at the completion of radiotherapy, after every 2 cycles of chemotherapy, and at the end of the therapy. Unless clinically indicated, follow-up MRI scans after the completion of therapy are performed in conjuncture with the physical and neurological examination schedule[8, 18].

MRI with contrast of the spine is performed only at the completion of the therapy and annually thereafter unless there has been metastatic spinal disease, in which case more frequent evaluation may be necessary.

COMPLICATIONS OF POSTOPERATIVE TREATMENT

According to available literature as many as 40% of patients have some degree of new neurological dysfunction postoperatively. Among them an ill-defined syndrome is posterior fossa syndrome, characterized by mutism, cerebellar dysfunction supra-nuclear cranial nerve palsy, and hemiparesis that occurs 12-48 hours after surgery[28]. Resolution is expected, although is expected, although it may take several weeks.

The most common location of recurrence is at the primary tumor site in the posterior fossa[13, 30]. With the use of adjuvant chemotherapy, incidence of recurrence in the spinal canal and the supratentorial region seems to decrease. Systemic metastases, in the absence of a CSF shunting system, are also a recognized problem in 10 –20 % of patients. Bone is the most common site of systemic metastasis; regional lymph node sites follow.

The improved survival rate achieved in children with medulloblastoma has been accompanied by a growing concern of the long-term effects of radiotherapy and chemotherapy on the developing spine and brain. Cognitive function may be severely impaired by neuraxis irradiation. Duffner et al. showed a loss of at least 25 points in a full-scale intelligence quotient analysis in patients who underwent radiation therapy for medulloblastoma. Packer et al. have shown that medulloblastoma patients under 4 years of age had a median decrease in IQ of 40 points after radiation therapy, whereas those patients over 10 years of age suffered noted a high incidence of behavioral disturbance as well as low IQ scores among children treated for medulloblastoma[25].

Irradiation effects on the growing spine include axial growth retardation, scoliosis, and kyphosis. Neuhauser et al. suggested that doses in excess of 20 cGy delivered to

the spine will almost invariably cause growth retardation in children, irrespective of age. Radiation therapy may also cause endocrinologic disturbances such a growth failure due to growth hormone insufficiency, and thyroid and gonadotropin hormone deficiency.

Delayed hypopituitarism is reported in some studies in almost 18% of survivors. The important feature of hypofunction of pituitary gland from the clinical perspective is that the hormonal deficiency in patients becomes clinically evident as late as 6 years after irradiation. Other delayed complication related to radiation therapy, includes hearing impairment, convexity meningioma, radiation necrosis, and hypoplastic mandible.

In general, all chemotherapeutic agents are toxic to bone marrow. This is especially true for the nitrosoureas. Platinum analogues such as cisplatin can cause otic and renal toxicity, and severe nausea and vomiting. Otic toxicity consisting of high-tone hearing loss is also cumulative. Newer platinum analogues such as carboplatin are currently under investigation at our center and elsewhere. Carboplatin appears to be a potent as cisplatin, without its undesirable side effects and the need for large fluid volumes and diuresis (dose 560 mg/m^2). Other DNA-binding drugs such as cyclophosphamide derivatives (iphosphamide) are frequently associated with hemorrhagic cystitis[18].

Infertility in patients treated for medulloblastoma could arise for three reasons

(i) Inadequate gonadotropin production following raised intracranial pressure or hypothalamic-pituitary irradiation (40 Gy in most patients)

(ii) Scattered irradiation to the ovaries from spinal irradiation and

(iii) Ovarian failure or impaired spermatogenesis following chemotherapy.

Long-term effects

In spite of successful treatment, a significant number of patients have neurocognitive and endocrinologic deficits. Although most long-term survivors have normal intelligence, many subsequently develop learning difficulties that require individualized educational programs. Biochemical growth deficiency is observed in 70 – 80% of patients, and some degree of growth impairment is present in well over half of patients after treatment. Thyroid and gonadotropin hormonal deficiency also may occur. Cranio spinal radiation, a mainstay treatment, has been implicated as a major cause of these deficits.

Because of the immunosuppressive effects of chemotherapy, trimethoprim sulfamethoxazole and nystatin are commonly prescribed for prophylaxis against Pneumocystis carinii pneumonia and mucocutaneous candidiasis, respectively, for the duration of treatment.

Granulocyte colony stimulating factor (GCSF) following chemotherapy may be used in treatment regimens expected to cause marked neutropenia. Childhood immunizations should be deferred for up to 1 year from completion of therapy. Patients are at risk of acquired infection from attenuated live-virus preparations (measles, mumps, and rubella [MMR]; oral polio; varicella). Inactivated injectable polio (IPV) and remaining immunizations may be given; however, they may not provide adequate protection because of immunosuppression.

To avoid varicella infection, varicella-zoster immunoglobulin (VZIG) should be given within 72 hours of exposure to all patients with no prior varicella immunization or infection.

PROGNOSIS

Medulloblastoma is a very aggressive tumor. Even after a good response to surgery and radiation, recurrence is common; most recurrence occur within 2 years after treatment.

Radical tumor resection is directly related to longer patient survival than is partial resection or biopsy - 5-year survival of 59% for patients with radically excised tumor, 49% for subtotal excision, and 30% for partial excision or biopsy[1].

Patients who had their tumors completely or sub-totally resected survived significantly longer than those who had only a partial removal or biopsy[15]. In the latter group all deaths occurred within the first 4-5 years: the 22% 5-year survival rate, or 78% mortality, was maintained at 10 and also 15 years. In contrast, only 24% of deaths in a group of patients having complete or sub-total excision died within 5 years: however, several late recurrences occurred in this group[15].

As far as tumor histology is concerned, opinions differ as to whether the desmoplastic medulloblastoma is associated with a more favorable prognosis[12]. Packer et al. have reported that medulloblastomas that show differentiation along glial, neuronal, or ependymal cell lines had a 32 % 4-year survival compared with a 72 % survival for medulloblastomas that were undifferentiated[25]. Children with undifferentiated

medulloblastomas did better because they were considered to have more radiation-sensitive tumors than children with differentiated tumors.

The Collin law, first hypothesized for Wilm's tumor holds for medulloblastoma. It states that if a tumor has not recurred in a period of time equal to age of patient plus 9 months then patient can be considered to be cured. However several late recurrences have been reported[3].

The recognition of relative risk factors has allowed for the identification of two groups of children with medulloblastoma who can be stratified into different treatment regimens (Table 2).

First, a low-risk group is comprised of those patients over 3 years of age with small tumors confined to the posterior fossa that have been successfully resected to a volume of residual tumor <1.5 mm^3.

Second, a high-risk group includes those patients under age 3 with large tumors incompletely resected to a volume of residual tumor > 1.5 cm^3 with leptomeningeal or metastasis spread. Patients in the low risk group are treated with radiation in full dose to the posterior fossa and reduced doses to the whole brain and spinal cord. They are not treated with chemotherapy.

In contrast, patients in the high-risk group are treated with pre- and post irradiation chemotherapy, as well a full-dose radiation therapy to the posterior fossa and neuraxis[18].

	Low risk	High risk
Age (yr)	>3	<3
Tumor size (cm)	<5	>5
Amount of residual tumor (cc)	<1.5	>1.5
CSF dissemination or metastases	No	Yes

Table 2. Risk factors influencing prognosis in medulloblastoma

Prognosis depends on 3 principal features age; extend of postoperative residual disease, and the metastasis.

Average-risk disease are patients older than 3 years who are at stage **M0** with less than 1.5 cm^3 of residual tumor postoperatively. The 5-year survival rate for this group is currently 78%[18, 21].

Poor-risk disease are patients older than 3 years who are at stage M1-M4 and/or with more than 1.5 cm^3 of residual tumor postoperatively. The 5-year rate for this group is currently 30 - 55%.

Infants: This group is defined as patients younger than 3 years. This group has the worst prognosis, regardless of M stage and extent of postoperative residual disease. The 5-year survival rate is approximately 30%; however, patients with metastatic disease do considerably worse.

Prognosis of adult medulloblastoma

Compared with pediatric medulloblastomas, the desmoplastic histological variant and laterally located tumors are more common in adults[8,11,18]. Late relapse, which is uncommon among pediatric patients, occurs much more frequently among adult patients with medulloblastomas[3]. Long term follow-up monitoring is important for adult medulloblastomas. Complete resection should be performed if possible and that radiotherapy be completed as soon as possible. Because of the high risk of systemic failure for the low-risk patients treat with radiotherapy alone, the role of chemotherapy needs to be further investigated[3].

None of the therapeutic regimen available can achieve complete cure in recurrent medulloblastoma. But, some partial responses to combination therapies have been reported, and a significant percentage of patients are clinically well enough to tolerate further treatment options[18].

The most frequent site of tumor recurrence remains the posterior fossa, with leptomeningeal or systemic disease occurring less frequently. If patient is well without evidence of metastatic disease and negative CSF and myelography, the re-operation may be considered. Occasionally, late recurrences in the posterior fossa may exhibit peculiar and totally different histological patterns suggestive of a radiation-induced malignancy such as a gilosarcoma or malignant astrocytoma[18].

Re-irradiation of the posterior fossa has been considered an option for some patients with relapsed medulloblastoma. While some patients will respond to a second course of radiation therapy, the actual sustained response is short lived and briefer than the initial response to radiation. The main hazard of administering a second course of

radiation therapy is the significant risk of radiation toxicity. Approximately 21% of patients in the study by Wara et al. developed radiation toxicity after a focal boost dose of 30 cGy and two patients died due to brain necrosis[6,18].

A number of groups have now reported modest results with various chemotherapeutic agents in patients who have relapsed with medulloblastoma. Allen and Helson described a 100% response in eight patients with high-dose cyclophosphamide for a median time of 6 months. Walker and Allen reported a 75% response rate to cis-platin (120 mg/m^2) for 8 months. Drug combination chemotherapy appears to be more effective than single-agent chemotherapy for relapsed medulloblastoma[6,18].

Detection of recurrence at early stages may sometimes be difficult and CSF polyamine levels help to predict medulloblastoma recurrence after surgery. Often, the CSF putrescine level may be elevated above the postoperative baseline before clinically or radiologically proven tumor recurrence [18].

Long term survival is possible in adults treated for medulloblastoma. All modern adult series show an approximate 50 to 60 % 5 year survival rate. More important is the fact that among those adults who survived, their quality of life

Authors	Year of publication	No. of patients	5-year survival rate
Spitz et al.	1947	30	24%
Bloom et al.	1969	16	38%
Miles and Bhandari.	1970	18	22%
Noel et al.	1970	5	60%
Chatty and Earle.	1971	38	26%
Bloom and Walsh.	1975	19	42%
Quest et al.	1978	28	38%
Bouchard.	1980	20	40%
Kopelson et al.	1982	17	46%
Hughes.	1984	15	66%
Lepage et al.	1986	19	58%
Skloyszewski and Glinski.	1987	13	62%

Table 3 : Results of treatment of medulloblastoma in adults[19]

EXPERIMENTAL STUDIES IN MEDULLOBALSTOMA

Paucity of well-characterized medulloblastoma cell lines, the lack of medulloblastoma-specific antibodies and rarity of tumor in adults has made Medulloblastoma an enigmatic tumor to investigate. After a relatively long, scientifically fallow period, progress in medulloblastoma research appears to be advancing in strides[18].

There are four well-characterized, permanent medulloblastoma cell lines[18]. This represents a small number of cell lines when one considers the number of times medulloblastoma has been placed into culture systems. The inability to maintain a medulloblastoma in culture is difficult to understand, especially since the tumor in vivo is rapidly growing and invasive. From in vitro clonogenic stem cell assays and the growth of these cell lines in athymic mice, the growth kinetics and response to chemotherapeutic agents of these four cell lines are derived. However, because of the apparent heterogeneity of these medulloblastoma cell lines, clearly more cell lines must be established and analyzed[18].

Chromosomal Changes in Medulloblastoma

Most of the knowledge of the cytogenetic changes within human medulloblastoma is derived from detailed analyses of the established medulloblastoma cell lines. Since the discovery of visible chromosomal alterations within a variety of cancers, it is now generally accepted that somatic genetic changes are important in carcinogenesis. (Table 4). To date, there are only a few reports on the cytogenetics of

primary medulloblastoma cells. Trisomy for 1q and 17q, and monosomy for 17p were the most consistent features seen for the six medulloblastoma with abnormal cytogenetics in Bigner's study[35].

Double minutes (DMs) are spherical, usually paired chromosome like structures that lack a centromere and may contain circular DNA in chromatin form. They are thought to provide cytological evidence of DNA sequence amplification. Bigner et al. estimate that approximately 10-20% of medulloblastomas may demonstrate DMs.

Chromosome				
Cell line	Stemline karyotype	Additions or deletions	Marker chromosomes	Others
TE 671	47 XX[a]	+1, +2, +8, +13, +16 –14, -21, -X	4q +, 9q +, 17p+, Gq-	
Daoy	Near tetraploid	+10, -22	1q-, pq+	Double minutes
D283 Med	47 XY	+11	8q +, 17p+ , 20q +	
D 341 Med	47 XY	+8, -22	1p-, 17p-	Double minutes

Table 4 : Cytogenetic comparison of medulloblastoma cell lines.

Oncogenes and Tumor Suppressor Genes in Human Medulloblastoma

Due to chromosomal aberrations (Table 4) altered gene sequences and expression may be involved in the pathogenesis of the medulloblastoma[18]. Proto-oncogenes encode for proteins that appear to play a major role in the normal growth and development of the organism. Proto-oncogenes can be altered by point mutations, chromosomal translocations, deletions, or amplifications. The altered proto-oncogene is called an oncogene and can lead to abnormal cellular proliferation and tumor formation. Many groups are now using molecular probes to determine if medulloblastomas preferentially express one or more of the oncogenes.

Friedman et al. reported that D341 med showed a 20-fold amplification of the c-*myc* oncogene. Fults et al. have shown that the N-*ras* oncogene is activated in TE-671 by a mutation at the third position of codon 61 . A recent report by Wasson et al. showed that none of 20 primary medulloblastomas had amplification of any of 11 known oncogenes including N-*myc* and c-*myc* with the exception of one tumor, which showed amplification of the erB1 oncogene[18].

The nuclear protein p53 is thought to represent a tumor suppressor gene and has been mapped to the short arm of chromosome 17. Recently, Raffle et al. have shown that medulloblastomas have p53 mutations as identified by cDNA sequencing, suggesting inactivation or faulty transcription of the active protein encoded for by p53. These p53 mutations may be important in the pathogenesis of human medulloblastoma[18,35].

Difficulty was encountered in developing experimental model systems for the medulloblastoma and lack of adequate in vitro or in vivo models have seriously affected the time course of medulloblastoma research. More research efforts are directed at working with the original tumor material and analyzing tumor tissue for various oncogenes, growth factor, and growth factor receptor expression. Once a larger sample of tumors has been analyzed, a consistent pattern may emerge which will eventually have clinical utility. There are a number of phase I and II trials currently under investigation using novel forms of therapy for children with medulloblastoma. The bone marrow toxicity of the chemotherapeutic agents used for medulloblastoma is now countered by recombinant human granulocytic colony stimulating factor in clinical trials in Japan so that higher doses of chemotherapy can be used. Immunotherapy is being tested using tumor-specific monoclonal antibodies tagged with radioisotope or toxins to kill residual tumor cells. The selection of medulloblastoma-specific antibody has remained fairly elusive. A number of groups are now investigating the efficacy of biological response modifiers such as the interferon, and interleukins in clinical trials. Interleukin 2 has been especially promising in activating autologous lymphocytes to form lymphokine activated killer (LAK) cells, which are being tested for their tumoricidal activity. The difficulty with LAK-cell therapy so far has been delivery of the primed lymphocytes to the residual tumor mass.

AIMS AND OBJECTIVES

Aims and objectives

The goal of this retrospective study is to

1. Study the various clinical and radiological features of adult medulloblastoma
2. To compare the various clinical and radiological features with pediatric medulloblastoma and assess the differences in outcome.
3. Outline the complications.
4. Assess overall outcome of adult medulloblastomas with regard to clinical status.
5. Identify predictors of poor outcome.
6. Assess patterns of relapse.

MATERIALS AND METHODS

Materials and methods

During the period from January 1990 to December 1999, a total of 89 patients underwent surgery for medulloblastoma. There were 18 adults in this study (age 16 years and above).

The present study was conducted retrospectively by analyzing the clinicoradiological data of these patients, which included the age at identification, sex, the clinical presentation, radiological data and clinical as well as radiological outcome in the post operative period as well as during the follow up period.

All patients were evaluated preoperatively with either CT or MRI scans / both. Post operative radiological evaluation was done in most patients. All patients were evaluated by oncologist and underwent adjuvant therapy. The various modalities of adjuvant therapy were analyzed. All patients were called to outpatient department and detailed neurological examination done on review. Letters regarding status of patient were obtained from relatives in cases who could not report for review

RESULTS

&

ANALYSIS

Results

There were 18 adults in the study. 9 were males and 9 were females. Age range was 16 to 47 years with mean age of 31.5 years. The average duration of symptoms were 0-2 months in 22.22%, 4-6 months in 11.11%, 6-8 months in 5.55%, 8- 1 year in 22.22% and 1year above in 11.11%.

Headache was the predominant symptom in all patients. Vomiting was present in 17 (94.4%) cases. 9 (50%) had visual blurring and 6 (33.3%) presented with diplopia. Cerebellar symptoms in the form of gait unsteadiness were present in 14 (77.7%). 4 patients had seizures. Loss of consciousness was present in 4 (22.2%) of cases and history of weight loss was seen in 1 patient.

4 patients (22.2%) presented in altered sensorium. Papilledema was present in 15 (83.3%) on admission to hospital. 12 patients (66.62%) had nystagmus . III cranial nerve palsy was observed in 6 (33.3%) patients. VI cranial nerve palsy was seen in 9 (50%) cases preoperatively. 2 patients (11.1%) had lower cranial nerve palsy. 1 patient presented with hemiparesis. Cerebellar signs were observed in 11 (61.1%) patients.

All patients underwent CT scan of head for evaluation and 15 patients underwent pre-operative MRI scan of head. The tumor was located in vermis in 12 patients (66.6%) while 3 lesions (16.6%) were in right cerebellar hemisphere and 2 lesions (11.1%) were located in left cerebellar hemisphere. Lesions were isodense to grey matter in 6 cases (33.3%), hypodense in 3 (16.6%) and hyperdense in 7 (38.8%) cases. Calcification was observed in 2 cases (11.1%). CT head showed hydrocephalus in 6 cases (33.3%) and

IV ventricle could be visualized only in 6 cases (33.3%). MRI evidence of brainstem infiltration was present in 3 cases (16.6%).

All patients underwent surgical excision of lesion. The policy adopted in this center was to avoid placement of a ventriculoperitoneal shunt pre-operatively as far as possible.

In patients who presented with raised intra-cranial pressure symptoms , endoscopic third ventriculostomy was kept as a treatment option in case they showed any sign of deterioration in the evaluation period from September 1999 onwards. Total excision was performed in 13 cases (72.2%), near total excision in 4 cases (22.2%) and subtotal excision in 1 case.

External ventricular drain was placed in 9 (50%) cases and in the immediate post-operative period, it was released prophylactically in 10 patients (55.5%). 3 patients (16.6%) in whom raised intracranial pressure was present in post-operative period underwent VP shunt placement. Per-operatively CSF pathway could be established in 16 (88%) cases.

Histopathological examination showed classical medulloblastoma in 3 cases (16.6%) while desmoplastic variant was observed in 6 (33.3%) cases. 8 patients (44.4%) had medulloblastoma with glial differentiation. 1 case was reported as medulloblastoma with neuronal differentiation. Histopathological evidence of calcification was present in 7 (38.8%) cases. Fresh cranial nerve deficits were seen as complication in 4 (22.2%) cases. 1 patient developed hemiparesis and gait unsteadiness appeared in 3 cases (16.6%) post-operatively. 1 patient had mutism in the post-op period and 2 developed meningitis.

All patients underwent adjuvant radiotherapy in the form of craniospinal irradiation with posterior fossa booster radiation.

On follow-up, 11 patients (61.1%) were observed to have recurrence in follow-up CT head scans and were located in the posterior fossa. All 11 of them subsequently were subjected to chemotherapy. 2 patients had to undergo re-surgery due to residual/recurrent lesion causing raised intracranial symptoms.

Follow up data in 2004 May showed that 10 patients (55.5%) were alive and 5 patients (27.7%) died in the follow up period. 3 (16.6%) were lost in follow up.

71 patients were in the pediatric age group (15 years or less) in this study. 39 were males and 32 were females. The average duration of symptoms were 0-2 months in 43.66%, 4-6 months in 25.35%, 6-8 months in 15.49%, 8- 1 year in 11.26% and 1year above in 2.81%.

Headache was the predominant symptom in 63 (88%) patients. Vomiting was present in 65 (91.5%) cases. 34 (47%) had visual blurring and 15(21.1%) presented with diplopia. Cerebellar symptoms in the form of gait unsteadiness were present in 49 (69%). 7 (9.8%) patients had seizures. Loss of consciousness was present in 10 (14%) of cases and history of weight loss was seen in 3 (4.22%) patients.

10 patients (14%) presented in altered sensorium. Papilledema was present in 57 (80.2%) on admission to hospital. 31 patients (43.6%) had nystagmus . III cranial nerve palsy was observed in 3 (4.22%) patients. VI cranial nerve palsy was seen in 12(16.9%) cases preoperatively. 8 patients (11.26%) had lower cranial nerve palsy. 4 patients

(5.6%) presented with hemiparesis. Cerebellar signs were observed in 44 (61.97%) patients.

All patients underwent CT scan of head for evaluation and 64 patients underwent pre-operative MRI scan of head. The tumor was located in vermis in 64 patients (90.1%) while 2 lesions (2.81%) were in right cerebellar hemisphere and 4 lesions (5.63%) were located in left cerebellar hemisphere. Lesions were isodense to grey matter in 16 cases (22.5%), hypodense in 5 (7%) and hyperdense in 48 (67.6%) cases. Calcification was observed in 13 cases (18.3%). CT head showed hydrocephalus in 62 cases (87%) and IV ventricle could be visualized only in 16 cases (22.5%). MRI evidence of brainstem infiltration was present in 6 cases (8.4%).

All patients underwent surgical excision of lesion. Total excision was performed in 23 cases (32.2%), near total excision in 28 cases (39.4%) and subtotal excision in 18 (12.7%) cases. In 2 cases only partial excision could be performed.

External ventricular drain was placed in 56 (78.8%) cases. 20 patients (28.16%) in whom raised intracranial pressure was present in post-operative period underwent VP shunt . Per-operatively CSF pathway could be established in 51 (71.8%) cases.

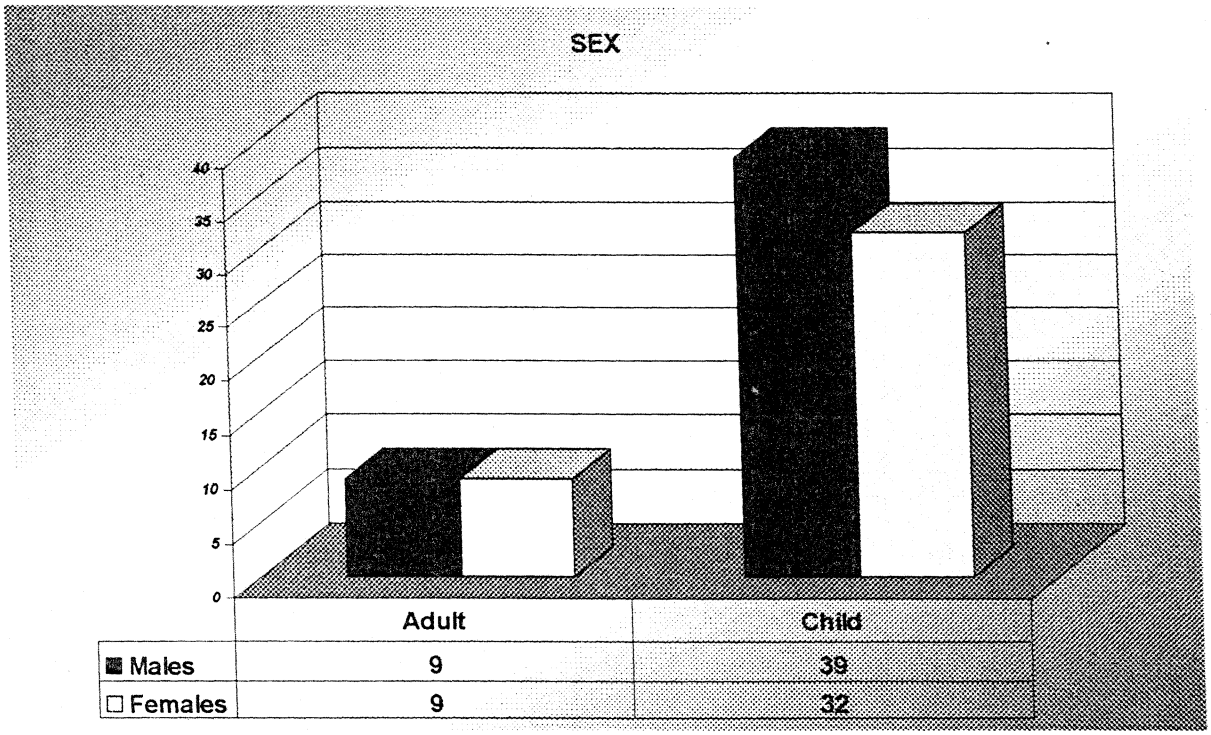
Histopathological examination showed classical medulloblastoma in 44 cases (62 %) while desmoplastic variant was observed in 9 (12.6 %) cases. 18 patients (12.7 %) had medulloblastoma with glial differentiation. Histopathological evidence of calcification was present in 14 (19.7%) cases.

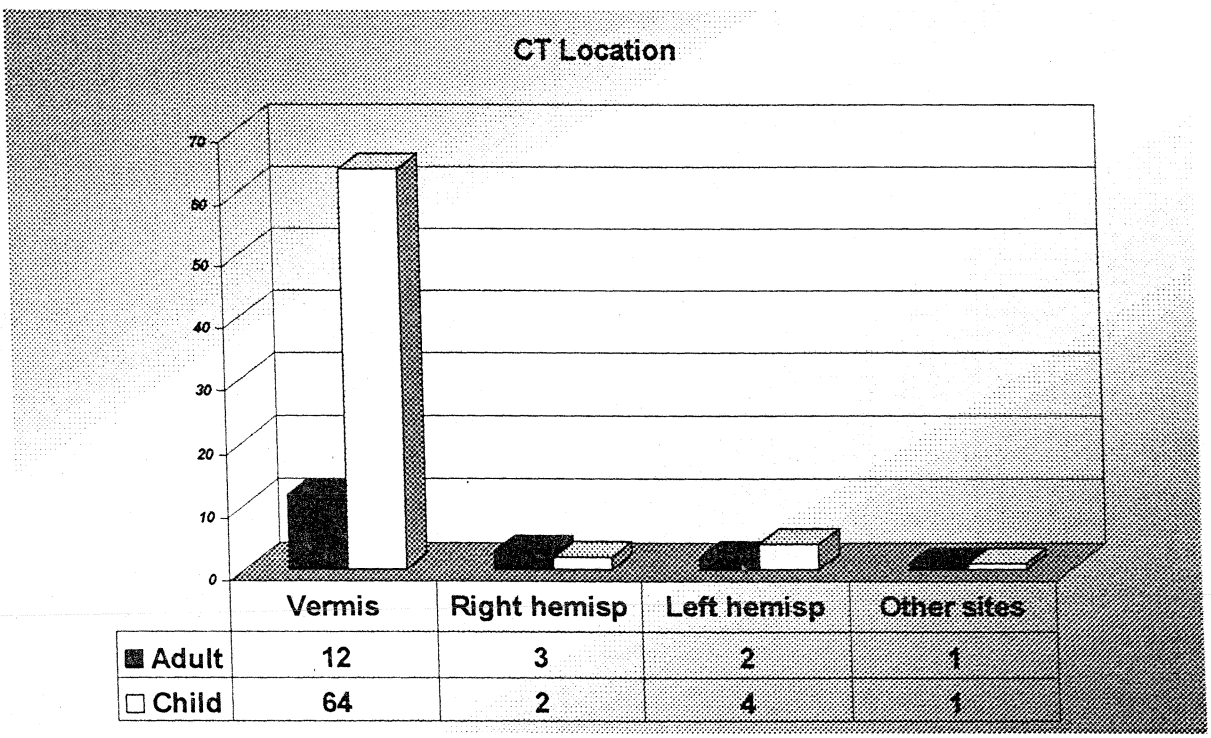
Fresh cranial nerve deficits were seen as complication in 7 (9.86 %) cases. 2 patients developed hemiparesis and gait unsteadiness appeared in 13 cases (18.3%) post-

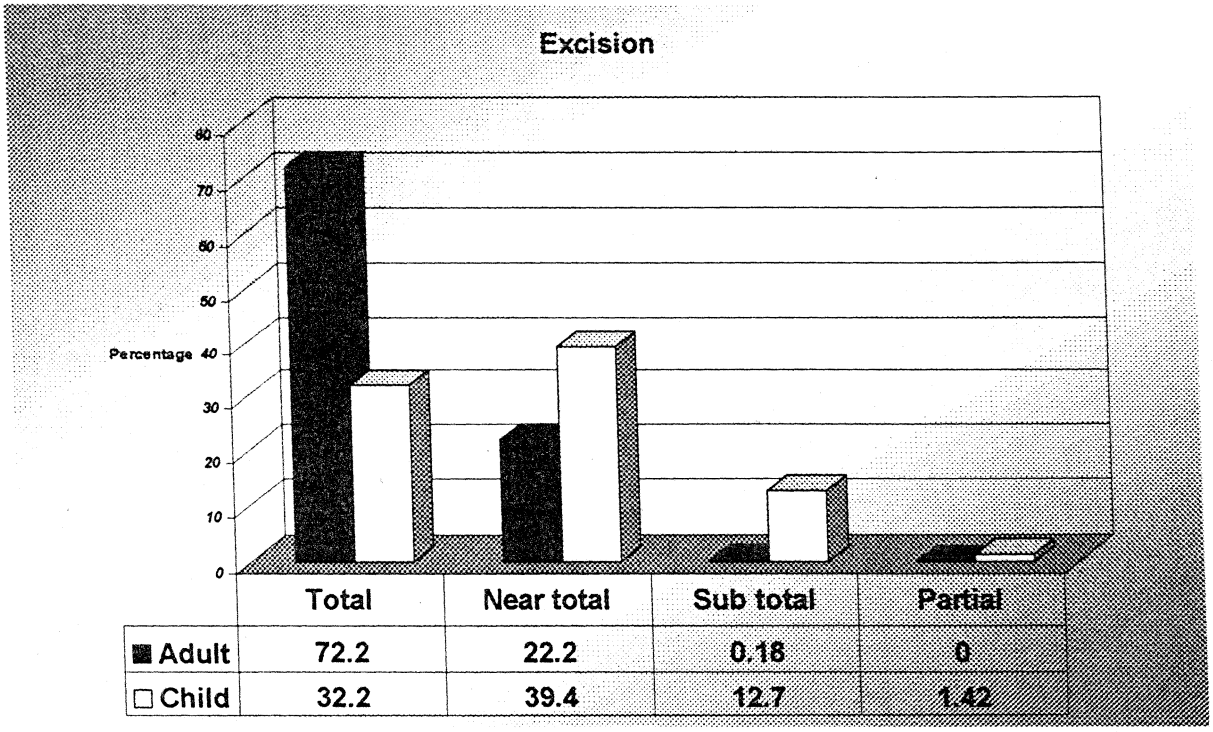
operatively. 14 patients had mutism in the post-op period and 6 patients (8.45%) developed meningitis .

All patients underwent adjuvant radiotherapy in the form of craniospinal irradiation with posterior fossa booster radiation. On follow-up, 31 patients (43.6 %) were observed to have recurrence in posterior fossa in follow-up CT head scans. 17 (12%) patients were detected in follow-up MRI to have spinal metastasis. Supratentorial metastasis occurred in follow-up in 15 (10.65%) patients. After detection of supratentorial / spinal metastasis, patients subsequently were subjected to chemotherapy. 3 (4.2%) patients had to undergo re-surgery due to residual/recurrent lesion causing raised intracranial symptoms.

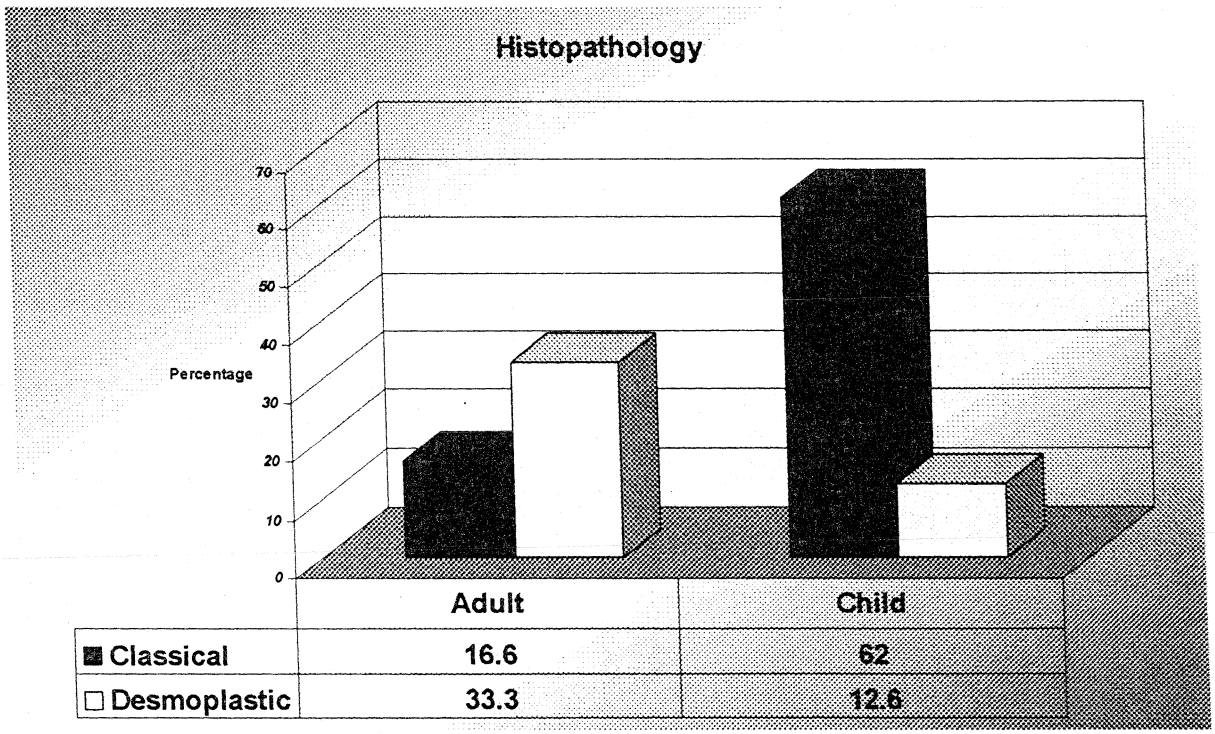
18 patients (12.7 %) could be followed up for more than 5 years. Follow up data in 2004 May showed that 16 patients (11.36 %) were alive and 20 patients (14.2 %) died in the follow up period. 35 patients (49.2%) were lost in follow up. Of them, 27 (19.1% of total study group) were referred to local hospital for terminal and palliative care from oncology center due to poor general physical condition.


SEX
40
35
30
25
20
15
10
5
0
Adult
Child
Males 9 39
Females 9 32


CT Location
70
60
50
40
30
20
10
0
Vermis
Right hemisp
Left hemisp
Other sites
Adult 12 3 2 1
Child 64 2 4 1



	Total	Near total	Sub total	Partial
Adult	72.2	22.2	0.18	0
Child	32.2	39.4	12.7	1.42



	Adult	Child
Classical	16.6	62
Desmoplastic	33.3	12.6

Analysis

The following variables were assessed by bivariate analysis for adult and pediatric study groups:

1. Age
2. VI cranial nerve palsy
3. CT location of lesion
4. Hydrocephalus
5. Brainstem invasion
6. Total excision of tumor
7. Histological subtype

Statistical tests for relevance performed include Pearson Chi-square test, Fisher's exact test and T – test.

Poor outcome was observed in the pediatric population with age below 7 years and better outcome for those above age 9 years.

Bivariate analysis showed influence of CT location of tumor with outcome in adult medulloblastoma – vermian location carrying better prognosis than other locations.

Significant association was observed between radiological evidence of brainstem involvement and outcome in cases of adult medulloblastoma.

Desmoplastic variant of medulloblastoma was observed to be a significant prognostic factor in pediatric group.

Crosstab

			FUMORTAL		Total
			0	1	
CTLOCAT	0	Count	9	1	10
		% within CTLOCAT	90.0%	10.0%	100.0%
	1	Count	1	1	2
		% within CTLOCAT	50.0%	50.0%	100.0%
	2	Count		2	2
		% within CTLOCAT		100.0%	100.0%
	3	Count		1	1
		% within CTLOCAT		100.0%	100.0%
Total		Count	10	5	15
		% within CTLOCAT	66.7%	33.3%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	8.700[a]	3	.034
Likelihood Ratio	9.821	3	.020
Linear-by-Linear Association	7.721	1	.005
N of Valid Cases	15		

a. 7 cells (87.5%) have expected count less than 5. The minimum expected count is .33.

Table 5 : Analysis of influence of CT location of lesion in adults with outcome
Location 0 = vermis, 1 = right hemisp; 2= left hemisp ; 3 = other sites.
Follow-up 0 = Alive ; 1= Expired.

Crosstab

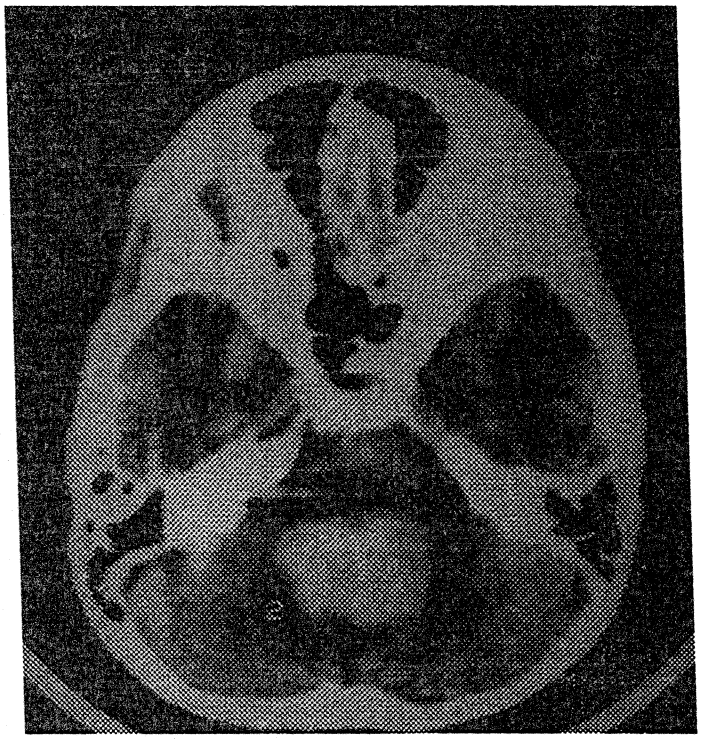
			FUMORTAL		Total
			0	1	
HISTOPAT	0	Count	12	11	23
		% within HISTOPAT	52.2%	47.8%	100.0%
	1	Count	3	1	4
		% within HISTOPAT	75.0%	25.0%	100.0%
	2	Count	1	8	9
		% within HISTOPAT	11.1%	88.9%	100.0%
Total		Count	16	20	36
		% within HISTOPAT	44.4%	55.6%	100.0%

Chi-Square Tests

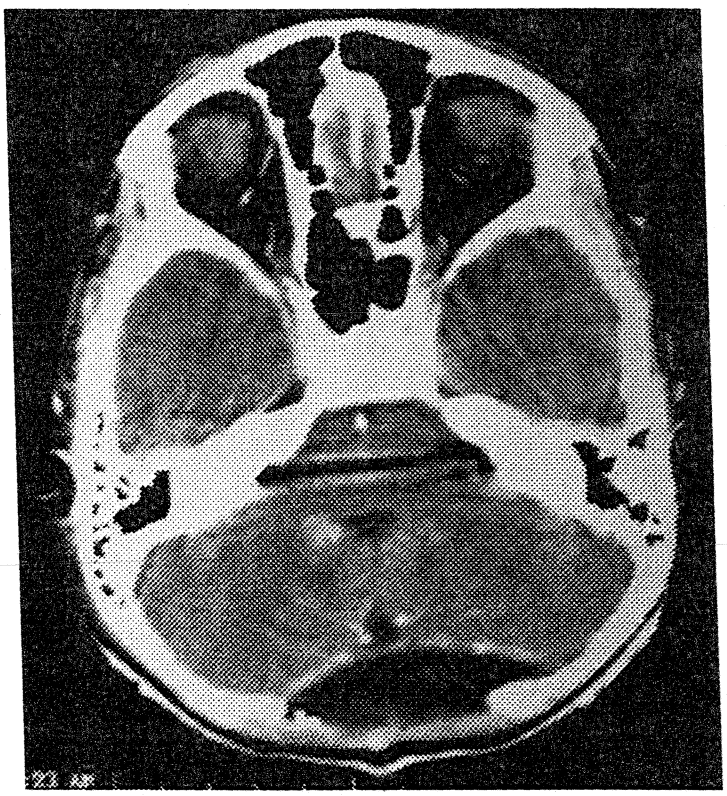
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	6.119[a]	2	.047
Likelihood Ratio	6.842	2	.033
Linear-by-Linear Association	3.385	1	.066
N of Valid Cases	36		

a. 3 cells (50.0%) have expected count less than 5. The minimum expected count is 1.78.

Table 6 : Analysis of influence of Histopathology of lesion in children with outcome
0 = classical, 1 = desmoplastic; 2= others
Follow-up 0 = Alive ; 1= Expired.



Pre operative and follow up CT scan of a patient with desmoplastic variant



DISCUSSION

Discussion

Symptoms due to raised intra-cranial pressure were common in both adult and pediatric populations in this study. This correlates well with other studies in literature. Incidence of episodes of loss of consciousness, seizures, cranial nerve palsies were definitely more in adult population. H J G Bloom et al noted that the difference in presentation of medulloblastoma in adults was due to greater incidence of lateral tumors[15]. Cerebellar symptoms were distributed equally in both the reference populations.

Radiological evaluation in the present study showed predominant vermian location of tumor in the pediatric population while more incidence of non-vermian / hemispheric location was seen in adults when compared to children. Bourgouin et al noted that 50 – 60 % adult medulloblastomas were non-vermian in location[3]. The therapeutic implication of this finding is that non-vermian locations enabled total resection of tumor resulting in improved long-term survival.

Incidence of tumor calcification was less in pediatric population and so was contrast enhancement. Tomita et all also noted that calcification is rare in pediatric medulloblastomas[35].

Incidence of hydrocephalus was less in adult population (33.3%) as opposed to pediatric patients where 87% had hydrocephalus. This could be attributable to the more-lateral location of the tumour. Tomita et all also had 85 – 90% patients in the pediatric age group with hydrocephalus in the pre-operative CT scans[35].

In our series adult population had more evidence of brainstem infiltration. Park et all found 36% of patients with radiological evidence of brainstem infiltration[26].

Total excision of lesion could be performed in significant number of adults (72.2%) where as majority of pediatric population (39.4%) underwent near total excision. Establishment of CSF pathway was more achieved in adult population when compared to pediatric population.

Histopathological examination of tumor in the present study showed clear predominance of desmoplastic variant of medulloblastoma in adult population whereas classical medulloblastoma was predominant in children. This is concordance with available literature reviews. Bloom et al, Carrie et al and Haie C have observed in their studies up to 50% cases showing desmoplastic variant[7, 9]. Adult medulloblastomas

showed more evidence of tumor calcification also. Tomita et al have noted that tumor calcification is rare in pediatric age group[36].

Incidence of post operative complications like mutism and gait unsteadiness were less in adult population. Tomita et al reported up to 10% of cases with post operative mutism in the pediatric age group, which improved in 6 months follow-up[35].

Follow-up data in 2004 may show better prognosis in the form of overall survival for adult medulloblastoma. More than half of operated cases were alive while only less than 23% of patients were alive in the pediatric population in long-term follow-up. Similar observations were made by Berry et al who noted 50 – 60% survival for pediatric age group at end of 5 years of treatment while 46-78% 5-year survival for adult age group[6].

Desmoplastic medulloblastoma was found to have a better prognosis in pediatric patients in this study. Annie W Chan et al and Bloom & Bessel et al in their analyses of adult medulloblastoma have also found that desmoplastic variant though common in adult population bears no importance in outcome[3, 7]. Only the 1971 study by Chatty EM et al suggested a favorable prognosis for desmoplastic variant of medulloblastoma in adult population[11].

Conclusions

1. Desmoplastic medulloblastoma was found to have a better prognosis in pediatric patients
2. Location of tumor in adults had influence in outcome – vermian location had a better outcome.
3. Radiological evidence of brain stem invasion in MRI was associated with poor outcome in adults
4. Classical outcome determinants like age, extent of excision and residual tumor did not show any statistically significant association with outcome probably because a large number of patients were excluded because of lack of follow-up in nearly 50% of the pediatric patients.

BIBLIOGRAPHY

Bibliography

1. Albright AL, Wisoff JH, Zeltzer PM: Effects of medulloblastoma resections on outcome in children: a report from the Children's Cancer Group . Neurosurgery 1996 Feb; 38(2): 265-71

2. Allen JC, Epstein F: Medulloblastoma and other primary malignant neuroectodermal tumors of the CNS. The effect of patients' age and extent of disease on prognosis. J Neurosurg 1982 Oct; 57(4): 446-51

3. Annie W Chan, Peter Mcl Black : Adult medulloblastoma ; prognostic factors and patterns of relapse. Neurosurgery, 47 (3), sept 2000.

4. Aragones MP, Magallon R, Piqueras C, Ley L, Vaquero J, Bravo G: Medulloblastoma in adulthood: Prognostic factors influencing survival and recurrence. Acta Nurochir (wien) 127:65-68, 1994.

5. Balter-Seri J, Mor C, Shuper A: Cure of recurrent medulloblastoma: the contribution of surgical resection at relapse. Cancer 1997 Mar 15; 79(6): 1241-7

6. Berry MP, Jenkin RD, Keen CW, Nair BD, Simpson WJ: Radiation treatment for medulloblastoma: A 21-year review. J Neurosurg 55:43-51, 1981.

7. Bloom HJ, Glees J, Bell J, et al: The treatment and long-term prognosis of children with intracranial tumors: a study of 610 cases, 1950-1981. Int J Radiat Oncol Biol Phys 1990 Apr; 18(4): 723-45

8. Caputy AJ, McCullough DC, Manz HJ, Patterson K, Hammock MK. A review of the factors influencing the prognosis of medulloblastoma. J. Neurosurg 1987;66:80-7.

9. Carrie C, Lasset C, Alapetite C, Haie-Meder C, Hoffstetter S, Demaille MC, Kerr C, Wagner JP, Lagrange JL, Maire JP, Seng S, Man YO, Murraciole X: Multivariate analysis of prognostic factors in adult patients with medulloblastoma: Retrospective study of 156 patients. Cancer 74: 2352-2360, 1994.

10. Chang CH, Houspian EM, Herbert C. An operative staging system and a megavoltage radiotherapeutic technique for cerebellar medulloblastoma. Radiology 1969; 93: 1351.

11. Chatty FM, Earle KM. Medulloblastoma. A report of 201 cases with emphasis on the relationship of histologic variant to survival. Cancer 1971;28:977-83.

12. David KM, Casey ATH, Hayward RD, et al. : Medulloblastoma; is the five-year survival rate improving? A review of 80 cases from a single institution. J Neurosurg 86:13-21, 1997.

13. Friedberg MH, David O, Adelman LS: Recurrence of medulloblastoma: violation of Collins' law after two decades. Surg Neurol 1997 Jun; 47(6): 571-4

14. Frost PJ, Laperriere NJ, Wong CS, Milosevic MF, Simpson WJ, Pintilie M: medulloblastoma in adults. Int. J Radiat Oncol Biol. Phys 32:951-957, 1995.

15. H. J. G. Bloom; E. M. Bessell. Medulloblastoma in adults: A review of 47 patients treated between 1952 and 1981. Int. J. Radiation Oncology Biol. Phys.; Vol. 18 .763-772; 1990.

16. Hubbard JL, Scheithauer BW, Kispert DB, Carpenter SM, Wicklogical, Radiographic, and clinical disease spectrum. J. Neurosurg 1989; 70: 536-44.

17. Hughes PG. cerebellar medulloblastoma in adults. J Neurosurg 1984; 60: 994-997.

18. James T R, Harold Hoffman. A critical review of medulloblastoma : from a difficult past to a promising future ; Neurosurgery quarterly (1) 54-78, 1991

19. Jan Skolyszewski, Bogdan Glinski. Results of postoperative irradiation of medulloblastoma in adults. Int. J. Radiation Oncology Biol. Phys. Vol. 16, pp. 479-482: 1989.

20. Laurent J, Chang C H, Michael E C ; Classification for Medulloblastoma of posterior fossa . Cancer 56: 1807-09, 1985

21. Luis Schut, Derek A Bruce, Leslie N Sutton : Medulloblastomas . In Robert H Wilkins, Setti S Rengachary , ed. Neurosurgery 1996 ; 2 :1177-1181

22. Mark B. Hazuka; Jeannie J. Kinzie. Survival results in adult patients treated for medulloblastoma. Cancer April 15, 1992, Volume 69, No.8.

23. Miles J, Bhandari YS. Cerebellar medulloblastoma in adults review of 18 cases. J. Neurol Neurosurg Psychiatr 1970;33:208-11.

24. Norris DG, Bruce DA, Byrd RI, et al. Improved relapse-free survival in medulloblastoma utilizing modern techniques. Neurosurgery 1981; 9:661.

25. Packer RJ, Sutton LN, Rorker LB. Prognostic importance of cellular differentiation in medulloblastoma of childhood. J Neurosurg 1984; 61: 296-301.

26. Park TS, Hoffman HJ, Hedrick EB, et al. Medulloblastoma; clinical presentation and management. J Neurosurg 1983; 58:543-52.

27. Perez A, Brady L W ; Medulloblastoma. In: Principles and practice of Radiation oncology ; 4th edition 2004.

28. Pollack IF, Polinko P, Albright AL: Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: incidence and pathophysiology Neurosurgery 1995 Nov; 37(5): 885-93

29. Prados MD, Warnick RE, Wara WM, Larson DA, Lamborn K, Wilson CB: Medulloblastoma in adults. Int. J Radiat Oncol Biol Phys 32:1145-1152, 1995.

30. Quest, D. O.; Brisman, R.; Antunes, J. L.; Housepian, E.M. Period of risk for recurrence in medulloblastoma. J. Neurosurg. 48:159-163; 1978.

31. Rorke LB: The cerebellar medulloblastoma and its relationship to primitive neuroectodermal tumors. J Neuropathol Exp Neurol 1983 Jan; 42(1): 1-15

32. Silverman, C. L.; Simpson, J. R. Cerebellar medulloblastoma: The importance of posterior fossa dose to survival and patterns of failure. Int. J. Radiant. Oncol. Biol. Phys. 8:1869-1876; 1982.

33. Skolyszewski J, Glinski B. Results of postoperative irradiation of medulloblastoma in adults. J Radiat Oncol Biol. Phys. 1988; 16:479-482.

34. Sutton LN, Packer RJ, Schut L. Medulloblastomas. Neurosurg Clin North Am 1990; 1: 97-111.

35. Tomita T: Medulloblastomas. In: Youmans JR, ed. Neurological Surgery. 1996; 4: 2570-92.

36. Tomita, C.; McLone, D. G. Medulloblastoma in childhood results of radical resection and low-dose neuraxis radiation therapy. J. Neurosurg. 64:238-242; 1986.

37. William F. Hartsell; Anthony G. Montag; Jean Lydon; Dennis L. Galinsky; Pramilla Sarin: Treatment of medulloblastoma in adults. Am. J.Clin Oncol 15(3): 207-211; 1992.