Central Neurocytomas:

A single institution study of

23 cases

Submitted for MCh Neurosurgery

By

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October 2008

Department of Neurosurgery
Sree Chitra Tirunal Institute for Medical Sciences & Technology
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Submitted by	**:**	**Dr. Vikas.V**
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CERTIFICATE

This is certify that the thesis entitled ***"Central Neurocytomas: A single institution study of 23 cases"*** *is a bonafide work of Dr.Vikas.V and was conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram under my guidance and supervision.*

30/9/2008

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DECLARATION

This thesis titled "***Central Neurocytomas: A single institution study of 23 cases***" is a consolidated report based on a bonafide study done by me during January 2006 to October 2008 under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

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

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Vikas.V

CONTENTS

Introduction

Central neurocytomas are low grade neuronal tumours which are usually found within the ventricular system of the brain usually within the lateral ventricles (60). They are neoplasms of neuronal origin. Surgical access to these lesions mandates transgression of normal brain tissue. Being intraventricular lesions, their presentation is usually late with minimal symptoms and non-localizing clinical signs.

Hassoun et al (31) were the first to characterize neurocytoma as a distinct pathological entity in 1982. Since then, surgeons and pathologists have well documented the clinical presentation and histology of these tumors. Central neurocytomas are commonly located in the lateral or third ventricles and usually present in the second or third decade of life with symptoms and signs related to the tumor mass or to cerebrospinal fluid outflow obstruction (115). On immunohistochemical examination, neurocytomas show expression of neuronal markers and are characterized by neuronal structures on electron microscopy.

They generally demonstrate benign biological behavior and have been shown to be amenable to surgical excision with favorable long-term outcome, and accordingly have been designated World Health Organization (WHO) Grade II (32, 83).

Rarely instances of central neurocytoma-like tumors arising outside the supratentorial ventricular system have been reported. These tumors have been designated extra-ventricular neurocytomas. A new ICD code has been used to denote extraventricular neurocytoma-9506/1.

Review of Literature

Incidence

Central neurocytomas are most commonly diagnosed in the second and third decades of life. In a retrospective review of 127 published cases, Hassoun et al (32) reported an average age at diagnosis of 29 years, but central neurocytomas may occur at any age and without sex preference. Since his first description in 1982, more than 500 cases have been reported in the literature, and it has been estimated that central neurocytomas account for 0.25 to 0.5% of all brain tumors (32, 83).

Site of Occurrence

Central neurocytomas are classically described as intraventricular tumours. The lesions usually found predominantly within the lateral ventricles. Rare presentations involving the III or IV ventricle have been described(37, 63, 118, 121). A pan-ventricular lesion with cisternal involvement has also been described (92). Rare extra-ventricular locations have been noted such as the temporal lobe (111), pineal region and in the aqueduct (28). Spinal lesions are extremely rare and literature review yielded only 9 cases (27).

fornix starts as the fimbria of the hippocampi in the medial temporal horn and runs along the thalamus in the anterior wall of the atrium. After giving off commissural fibers, it continues in the inferior medial wall of the body of the ventricle. The thalamus forms the floor of the body, interior wall of the atrium, and medial roof of the temporal horn. The choroidal fissure is defined by the groove between the thalamus and the fornix where the tela choroidea gives rise to the choroid plexus. The genu of the internal capsule lies in the lateral wall between the caudate and thalamus at the level of the foramen of Monro. The septum pellucidum is a thin wall of neural tissue, which separates the frontal horns and body in the midline. The corpus callosum bounds the ventricles superiorly. The close proximity of the optic radiation and internal capsule make operative access hazardous across them. The sole route of CSF drainage is through the foramen of Munro into the third ventricle. Thus, occlusion of the foramen of Munro even by a small lesion results in a rapid rise in intracranial pressure secondary to hydrocephalus. Conversely, any ventricular lesion is clinically silent until an extension into the foramen of Munro occurs. Slow growing lesions manifest only after a considerable size is reached, which is beyond the compensatory mechanics of the ventricles. The unique shape of the ventricles also account for the difficulty in planning surgery. It is thus suggested that the path of least damage is through the corpus callosum. The transgression of the internal capsule, caudate nucleus laterally can cause motor weakness.

The primary arteries to the choroid plexus are the anterior and posterior choroidal arteries, branches of which provide the vascular supply to tumors in this region. The anterior choroidal artery arises from the internal carotid artery, distal to the posterior communicating artery. It leaves the anterior incisural space and enters the lateral ventricle through the choroidal fissure, coursing posteriorly to lie near the lateral posterior choroidal artery. The anterior choroidal artery supplies the choroids plexus in the temporal horn and atrium. The posterior choroidal arteries are grouped into lateral and medial divisions. The lateral posterior choroidal artery is comprised of one to six branches, which arise in the ambient and quadrigeminal cisterns from the PCA. These branches then pierce the ventricle and pass around the pulvinar and through the choroidal fissure at the level of the crus of the fornix to supply the choroid plexus in the posterior temporal horn, atrium, and body of the ventricles. The medial posterior choroidal arteries arise as one to three branches from the PCA in the interpeduncular and crural cisterns. These arteries circumnavigate the midbrain and move to the pineal gland to enter the roof of the third ventricle. This vessel then passes in the velum interpositum, adjacent to the internal cerebral veins. The medial posterior choroidal arteries travel through the velum interpositum (tela choroidea), sending inconstant branches to the lateral ventricle through the choroidal fissure and foramen of Monro. The medial posterior choroidal artery supplies the choroid plexus in the roof of the third ventricle and sometimes the choroid plexus of the lateral ventricle.

Attachment of central neurocytoma

The typical location of central neurocytoma is the supratentorial ventricular system in the region of the foramen of Monro, attached most commonly to the septum pellucidum. Attachments to the walls of the lateral ventricles, the fornices, the corpus callosum, the roof of the third ventricle, or the choroid plexus are also reported (32, 119). Lobar lesions with no intraventricular extensions have been noted reported in literature (75, 96).

The neurocytoma cells are proposed to arise from remnants of the subependymal plate or from nuclei of gray matter in the septum pellucidum and lateral ventricle (19, 36, 39, 61, 91, 118). An angiographic study of lateral ventricular central neurocytomas performed by Paek et al (79) showed that in the venous phase, the ipsilateral thalamostriate vein was tortuous and enlarged, was elevated, and the internal cerebral vein was depressed. Thus, the venous angle of the ipsilateral side was found to be widened. Based on the characteristic displacement and the increased size of the associated venous system, the authors suggested that central neurocytoma might originate from a neuronal cell mass of the subependymal zone located on the floor of the lateral ventricle around the foramen of Monro rather than from the septum pellucidum

Extra-ventricular neurocytomas

Extra-ventricular locations of the lesion with typical histologic studies and immunochemistry have been documented in literature. Lenzi et al (56) have reported a child presenting with ventricular and brainstem involvement with a low

MIB-1 count with a good outcome on 3-year follow . Case reports of spinal cord involvement are also present (3, 27, 64, 99, 108). Spinal cord variant can also present in atypical form. The extraventricular neurocytomas have been documented as a distinct clinical entity

Clinical Presentation of central neurocytoma

The clinical history is usually quite short. Hassoun et al (32) reported an average of 3.2 months and some central neurocytomas have been identified incidentally (112). The usual presentation is with features of raised intracranial pressure with headache associated with vomiting and blurring of vision. The proximity of the internal capsule may be implicated in presentation with hemiparesis. Visual loss may be attributed to the associated papilledema. Rare presentations with intraventricular haemorrhage as the primary presentation have been documented (29, 40, 67, 78, 101). This propensity for hemorrhage has also been noted in an extra-ventricular lesion (90). Presentation as sudden death was noted in a patient secondary to massive intraventricular haemorrhage (6). This presentation typically occurs in adolescents and young adults. Presentation with gigantism has been noted in a septal lesion (4). The preoperative serum growth hormone level was 20.7 ng/mL, and postoperatively this fell to 0.9 ng/mL following surgical resection of the lesion. Pituitary dysfunction was noted neither before nor after surgery. Also low level of production of growth hormone releasing factor was detected on tumor cell culture.

Extra-ventricular neurocytomas

Extra-ventricular locations of central neurocytomas with typical histologic studies and immunochemistry findings have been documented in literature. Lenzi et al (56) have reported a child presenting with lesion involving the ventricles and brainstem with a low MIB-1 count. The child had a good outcome on 3-year follow-up. Case reports of spinal cord involvement are also present (3, 27, 64, 99, 108). Spinal cord variant can also present in atypical form. The extraventricular neurocytomas have been documented as a distinct clinical entity

Imaging

Computed tomographic scans usually show a well-circumscribed, isodense to hyperdense lesion with areas of calcification, which moderately and heterogeneously enhances post contrast (23, 61). Cystic components are occasionally observed.

MRI shows an intraventricular mass attached to the septum pellucidum that is isointense with cerebral cortex on T1-weighted imaging; isointense or hyperintense on T2 weighted imaging and proton-density sequences. The tumors typically display heterogenous enhancement after gadolinium injection.

Magnetic resonance spectroscopy has been utilized to charecterise central neurocytomas. The findings of increased choline, decreased creatinine, glycine and alanine have been noted in various studies.

Kim et al (46) described the characteristics of proton magnetic resonance spectroscopy in five patients with central neurocytomas. A combination of signal at 3.55 parts per million and a prominent choline peak was noted in all tumors.

Yeh et al (124) have found on MRS studies central neurocytomas have a typical appearance with a metabolite peak at 3.55 ppm due to increased Glycine.

Krishnamurthy et al (52) have also documented the presence of alanine in central neurocytomas on evaluation with MRS. The presence of alanine has also been related as a poor prognostic indicator (15). Jayasundar et al (41) have also noted the presence of N Acetyl Aspartate (NAA) and an increased glycine peak in the proton MR spectrum and claimed it to be a characteristic feature of central neurocytoma.

NAA is assumed to be a chemical seen in mature neurons and is expected to be high in this mature neuronal tumour such as central neurocytoma. The low levels noted in central neurocytoma indicate that even though the cells appear highly differentiated, they do not produce significant NAA (69).

Kawaguchi et al (43) evaluated the role of $^{(201)}$Thallium-SPECT in the diagnosis of intraventricular lesions. They demonstrated high uptake of $^{(201)}$ Thallium without washout in two cases of central neurocytoma.

Tumour Biology

The tumour is graded as a WHO grade II lesion with essentially benign behaviour. A good long-term survival has been noted in most studies. However, in recent years, numerous researchers have documented some neurocytomas that act in a malignant fashion (47, 95, 109). The realization that neurocytomas are not universally benign has prompted a great deal of interest in analyzing which tumors are prone to aggressive behavior (14, 24, 47, 95). Many studies have attempted correlation between MIB-LI staining and prognosis.

Fujimaki et al (24) measured MIB-1 staining for 10 neurocytomas and found a labeling index ranging from less than 0.1% to 5.6%. Likewise, Mackenzie (38) reviewed the histological features and MIB-1 labeling index for 14 patients with neurocytomas. Atypical features were noted on histology in three tumors. Five tumors had a labeling index of more than 2%. Four of the recurrent tumours in this series were noted to have labeling indices more than 2 %. Only one of the four patients was noted to have histologic atypia. It was concluded that proliferation potential was a better predictor of clinical outcome than histological appearance. On the contrary, Sharma et al (97) divided tumours into two groups based on the presence or absence of mitosis and necrosis. The authors reported that MIB-1 labeling was higher in the group with mitosis and necrosis. Chen et al (12, 13) have found in an analysis of 9 cases have found that GFAP positivity or MIB-1 index greater than 3% did not correlate with poor functional outcome. They also have noted that histologic features such as tumor proliferation (MIB-1 labeling index-2.0-6.8 %), vascular proliferation, and synaptophysin expression are often prominent in the recurrent tumors.

Genetic studies on central neurocytoma have showed a number of anomalies. Korshunov (51) in an analysis of genetic aberrations has found that the genes MYCN, PTEN, and OR5BF1 were strongly over expressed in the lesion, whereas the genes BIN1, SNRPN, and HRAS were found to be strongly underrepresented at the transcriptional level. The study suggested that MYCN oncogene gain/overexpression accompanied by reduced expression of BIN1 tumor suppressor may contribute to central neurocytoma tumorigenesis.

Sim et al (100) have noted that both receptors and effectors of canonical *wnt* signaling, as well as GDF8 (growth differentiation factor 8), PDGF-D, and neuregulin, were differentially over expressed by central neurocytoma, when compared to normal adult VZ (ventricular zone) and E/nestin:GFP (green fluorescent protein)-sorted native neuronal progenitors. They have suggested these overactive pathways are responsible for the pathogenesis. Fujisawa, H. et al (25) on reporting comparative genetic studies have noted allelic loss on 1p and 19q in six oligodendrogliomas (86%) and in three oligoastrocytomas (75%), but in none of the eight central neurocytomas studied by them. A similar finding was also noted by Tong, C. Y et al (110) that chromosomes 1p and 19q probably do not play an important role in the pathogenesis of central neurocytoma. N-myc and EGFR amplification are rare occurrences within the tumour

A gain of DNA sequence was detected in chromosomes 2p, 10q, and 18q by Yin, X. L et al (125). p53 mutations are charecterised by their absence (76).

Sugita, Y et al (104) have analysed neurotransmitters present within the tumour as a method to clarify tumorigenesis of central neurocytomas. They analysed tumours from four patients. Choline was found in extremely high concentration in all central neurocytomas when compared with levels in controls. In one central neurocytoma, GABA was found in extremely high concentration compared with controls. In all lesions, glutamate was found in lower or identical concentrations compared with controls. In all central neurocytomas and controls, dopamine and catecholamine concentrations were extremely low. Based on these findings, the authors have noted that the histogenesis of central neurocytomas begins with the subependymal stem cells, which have the potential to differentiate into cholinergic or GABAergic neurons.

Mena et al (66) in their study on central neurocytoma found retinal S-antigen expression in 14 of 24 cases analysed. Based on this finding, the authors have noted that the neoplastic cells can express photoreceptor differentiation thus possibly relating central neurocytomas to pineocytomas wherin such a finding has been noted.

Thus, neurocytomas, which are typical in presentation within the ventricle, have a favourable outcome in contradiction with histologically atypical, extra-ventricular, or aggressive phenotypes where recurrence is noted and the prognosis poor.

Metastasis and systemic dissemination

Though central neurocytomas are benign lesions, occasional reports of aggressive tumours are present. Takao et al (107) have reported a lesion with spinal D4 level metastasis with dissemination through the anterior wall of the lateral ventricle.

A lesion with multiple craniospinal dissemination in the middle cranial fossa and the intradural extramedullary space of the spine 15 months following surgery has been reported by Ando et al (3).

Systemic metastasis is an uncommon occurrence with a single case report of a third ventricular tumour disseminating into the peritoneum causing ascites in a six year old boy (17).

Tumour-tumour metastasis with melanoma metastasizing into the indolent central neurocytoma has been documented (11)

Histology

Cytology study of smears shows cellular tumors composed of isomorphous, round cells. The tumor cells showed ill-defined cytoplasm oval nuclei with finely granular chromatin and micronucleoli. A fibrillary matrix in the background is noted in all cases. Sugita et al (103) have commented that central neurocytomas can be diagnosed reliably using a combination of cytologic preparations and frozen sections. They based this finding after comparing the findings with postoperative H and E preparations, immunohistochemistry and electron microscopic findings.

The histological appearance of the neurocytoma closely mimics that of oligodendroglioma, and retrospective studies have demonstrated that most tumors previously diagnosed, as intraventricular oligodendrogliomas are central neurocytomas. Focal perivascular pseudorosettes observed in some neurocytomas may be reminiscent of ependymoma. Both oligodendrogliomas and neurocytomas are composed of small uniform cells with regular, rounded nuclei and scant cytoplasm, which often exhibits prominent clearing (i.e., perinuclear halos or "fried egg" artifact). Neurocytomas may also exhibit focal micro calcifications and the delicate, branching vasculature typical of oligodendrogliomas.

Mena, H et al (66) in their analysis of 33 cases have reported mineralization (20 of 33), foci of necrosis (4 of 33), chronic inflammation (4 of 33), ganglion cell differentiation (1 of 33), and lipomatous differentiation (1 of 33). None of the lesions had significant nuclear pleomorphism, mitotic activity, or vascular endothelial proliferation.

A single case of unusual pseudo papillary pattern (49) was noted in a case of neurocytoma, which was a predominant feature in the tumor and was characterized histologically by hyalinized vascular cores surrounded by a single or multilayered small round cells. The diagnosis in this case was based on immunohistochemistry.

Appearance of numerous macrophages that phagocytose hemosiderin between neoplastic cells have been reported to be characteristic of the cytomorphology of central neurocytomas (103)

Lesions mimicking Central Neurocytoma

Central neurocytomas have histological resemblance with other clear cell CNS neoplasms. Along with central neurocytomas, oligodendroglial neoplasms, clear cell ependymomas, dysembryoplastic neuroepithelial tumours (DNTs) and clear cell meningiomas histologically resemble each other (68, 81). Clear cell ependymoma (CCE) is an uncommon tumor with a predilection for the supratentorial region in children. Electron microscopy when used to analyze clear cell ependymoma show the diagnostic hallmarks of ependymoma, including complex intercellular junctions, surface microvilli and cilia, and micro rosette formation. Thus electron microscopy forms the method of choice for differentiating clear cell ependymoma from central neurocytoma. In the context of oligodendrogliomas and DNTs, OLIG2 immunohistochemistry has been found to be of importance in differentiating the same.

Pigmentation due to neuromelanin has been reported (74). Ng et al in an analysis of 3 cases (73) noted calcospherites, neuropil islands and rosette like structures.

Kordek et al (50) have documented a ventricular tumour with imaging characteristic similar to that of a neurocytoma situated within the lateral ventricle. Neurocytic component of the lesion presented strong synaptophysin immunostaining, while intermixed glial element showed GFAP-immuno positivity. The lesion was diagnosed as a papillary glioneural tumour (PGNT). PGNT is charecterised by two groups of cells; one with compact pseudopapillae composed of hyalinized vessels covered by a single layer of glial fibrillary acid protein (GFAP)-positive astrocytes and another set of synaptophysin-positive neuronal cells of varying size, including neurocytes, ganglioid cells, and ganglion cells within neuropil. Ultrastructurally, neuronal cells featured microtubule-containing processes and aberrant synaptic terminals are noted, but dense core granules were rare. Several of the older reports of GFAP positivity might come under the new classification of PGNT.

Pleomorphic astrocytoma may possess neurocytic differentiation. DNT-like neoplasm of septum pellucidum and rosetted glioneuronal tumor are other tumours, which can also cause diagnostic difficulty.

Ultrastructural studies

Ultra-structurally, central neurocytomas demonstrate features of neuronal differentiation, such as prominent mitochondria, Golgi apparatus, microtubules, thin cell processes, dense-core neurosecretory vesicles, and well-formed synapses.

Typical and Atypical Central Neurocytomas

Tumors with an atypical histology (presence of nuclear atypia, abnormal mitosis or necrosis) or an MIB-1 labeling index > 3% were defined as atypical neurocytomas by Rades and Schild (85). They used this classification to determine outcome following radiotherapy. Lenzi et al (57) have used histological atypia and MIB-1>4 as an adverse prognostic factor and have classified these lesions as atypical neurocytomas.

Immunohistochemistry

The diagnosis of Central Neurocytoma is based on immunohistochemistry-based demonstration of neuronal markers.

Immunohistochemistry becomes more important in lesions demonstrated outside of the lateral ventricle. However, it is known that focal expression of glial proteins is seen in central neurocytomas and, conversely, neuronal proteins may be seen in some oligodendrogliomas and clear cell ependymomas. In an analysis of oligodendrogliomas, Hilbig et al (34) have noted that as high as 28.5%(12 cases) of otherwise typical oligodendrogliomas were focally positive to NSE and/or synaptophysin showing neuronal differentiation. The authors concluded that though widespread staining with neuronal marker suggests central neurocytoma, the diagnosis should not be done only with a small amount of tissue. This implies that immunohistochemistry is of limited value on small tumor specimens.

Synaptophysin: Tumors with neuronal components can be identified specifically with synaptophysin. Synaptophysin is a glycoprotein component of synaptic vesicle membranes, and it plays a major role in synaptic vesicle exocytosis. Antisynaptophysin has been shown to be a good specific antibody for neuronaly-derived tumors, including ganglioglioma and neurocytoma. Because of the non-specificity of neuron-specific enolase (another neuronal marker), synaptophysin is the most specific and useful marker of neuronal differentiation available

Most neurocytomas show strong cytoplasmic immunoreactivity for synaptophysin, but results for oligodendrogliomas are negative. A tentative diagnosis of central neurocytoma may be presumed based on a clinical history of an intraventricular neoplasm in conjunction with characteristic light microscopic morphological findings, but confirmation through immuno-staining for synaptophysin is essential. In rare cases in which immunohistochemical results are inconclusive, resolution should be sought through ultrastructural examination. Recent immunohistochemical studies have revealed a subset of central neurocytomas, identifiable by a high MIB-1/Ki-67 labeling index (LI) or vascular proliferation and termed atypical central neurocytomas, which may exhibit more aggressive biological behavior and be associated with less favorable outcome (102). Neuron specific enolase has been reported to be positive in some tumours along with Synaptophysin (127).

NeuN: NeuN is considered a marker of neuronal differentiation in brain tumours. On comparing the expression of NeuN in clear cell tumours, Preusser et al (82) showed that in central neurocytoma, widespread NeuN expression had a positive predictive value of 76.9%. Lack of NeuN expression had a positive predictive value of 87.3% (76.5, 94.4) for diagnosing an oligodendroglioma. NeuN being a marker of neuronal differentiation is also suggested to have prognostic significance. On a hypothesis of NeuN positive central neurocytomas being more well differentiated, with suppression of mitosis, Englund et al (22) analysed Ki-67 expression and NeuN expression in central neurocytomas. They found that NeuN positive cells had a 15-fold lower Ki-67 labeling index, on average, than did NeuN negative cells ($p < 0.01$).

Other neuronal markers: In a series of seven neurocytomas studied (126), expression of synaptophysin was 100% , neuronal cell adhesion molecule

(NCAM) -100%, neuron specific enolase (NSE) -100%, neuronal nuclear antigen (NeuN) -100%, nestin (29%) and chromogranin A (43%), but GFAP expression was found only in one case (14%). Neurofilament expression was not found in any of the lesions. Microtubule associated protein(MAP) (59) is another protein found in neurocytomas indicating neural crest cell of origin.

In a series of 33 cases, Mena et al (66) have found expression of synaptophysin (33 of 33), neuron specific enolase (31 of 33), S-100 protein (25 of 33), retinal S-antigen (14 of 24), somatostatin (8 of 27), glial fibrillary acidic protein (4 of 33), neurofilament protein (3 of 22), and leucine enkephalin (1 of 27). Alpha synuclein positivity also has been demonstrated by Kawashima, M et al (44).

GFAP positivity along with a typical histology and synaptophysin positivity of a central neurocytoma, but suggesting glial differentiation has been noted in some cases (20, 120, 127).

Coincident Lesions

Kanamori et al (42) have reported development of anaplastic astrocytoma and anaplastic oligodendroglioma in a patient operated for central neurocytoma. The lesions developed at sites distant from the primary tumour. Bohm et al (9) have reported a patient presenting with concomitant neurocytoma of the fourth ventricle with cerebral metastasis from acute lymphatic leukemia (35). Utsunomiya et al (113) have reported a 31-year-old female who developed the anaplastic astrocytoma in the right basal ganglia and temporal lobe 8 years after partial resection and irradiation of a central neurocytoma.

Horoupian et al (36) have reported 2 cases with co-existing medulloblastoma and a lipoma respectively.

An aneurysm in a feeding lenticulostriate artery, the rupture of which caused intraventricular haemorrhage has been noted by Vates et al (116). The aneurysm was separate from the tumor but occurred on a vessel that supplied the tumor in the patient aged 35 years.

Treatment Options

Central neurocytomas have traditionally been treated by surgical excision. Other modes of treatment include radiotherapy, chemotherapy and stereotactic radiosurgery.

Surgical Approach

Removal of tumors of the lateral ventricles requires incision into the cerebral cortex or the corpus callosum, which are frequently uninvolved by the pathological process.

Walter E. Dandy described the early concepts of the interhemispheric approach for a third ventricular tumor in his classic monograph titled *Benign Tumors in the Third Ventricle of the Brain: Diagnosis and Treatment*. The interhemispheric–transcallosal access to the lateral ventricles traverses only a small area of the corpus callosum (an opening of 10–15 mm). Callosotomy except posteriorly is not associated with significant deficits thus providing a safe corridor to the ventricle

The transcortical trajectories, by definition, traverse the cortical surface and multiple layers of white matter tracts before entering the ventricular surface. Transcortical approaches through the middle frontal gyrus and combined approaches are other approaches to reach the frontal horn and the ventricular body. To reach lesions in the trigone and occipital horn, the described approaches include the transcortical-transparietal approach through the superior parietal gyrus or the parieto-occipital fissure, the interhemispheric parasplenial approach, the occipital interhemispheric trans-splenial approach, and the transcortical trans-temporal approach through the middle and inferior temporal gyri. The transoccipito-temporal gyrus approach also has been described to reach the temporal horn and trigone.

Table 1 Summary of transcortical approach to lateral ventricle (21)

Approach	Indication	Potential Complication
Middle frontal gyrus	ipsilateral frontal horn or anterior body lesions	Attention deficits in either hemisphere; speech apraxia or abulia in dominant hemisphere; subdural hygromas after removal of large lesions with hydrocephalus
middle temporal gyrus	lesions in temporal horn	language deficits in dominant hemisphere, hemiparesis; approach safer in nondominant hemisphere
lateral temporoparietal	lesions in the atrium, posterior temporal horn, for early access to posterior lateral choroidal artery; safest approach when cortex is nondominant or thin	Gerstmann syndrome in the dominant hemi sphere; neglect & visual field deficit in the nondominant hemisphere
transtemporal horn, occipito-temporal gyrus /anterior temporal lobectomy	atrium or temporal horn mass	visual field deficit in either hemisphere & language impairment in dominant hemisphere
occipital approach	posterior medial aspect of atrium, region of choroidal fissure between the crus of fornix & pulvinar, corpus callosum or occipital horn	homonymous field deficit; vascular supply is deep to tumor; risk of hemorrhage
occipital lobectomy	atrium, quadrigeminal cistern, occipital horn, ipsilateral posterior body, but not temporal & frontal horn	homonymous field deficit, Gerstmann syndrome, or alexia in dominant hemisphere
superior parietal	glomus of choroid plexus, atrium, posterior portion of body	small field deficit, vascular supply is deep to tumor; risk of haemorrhage

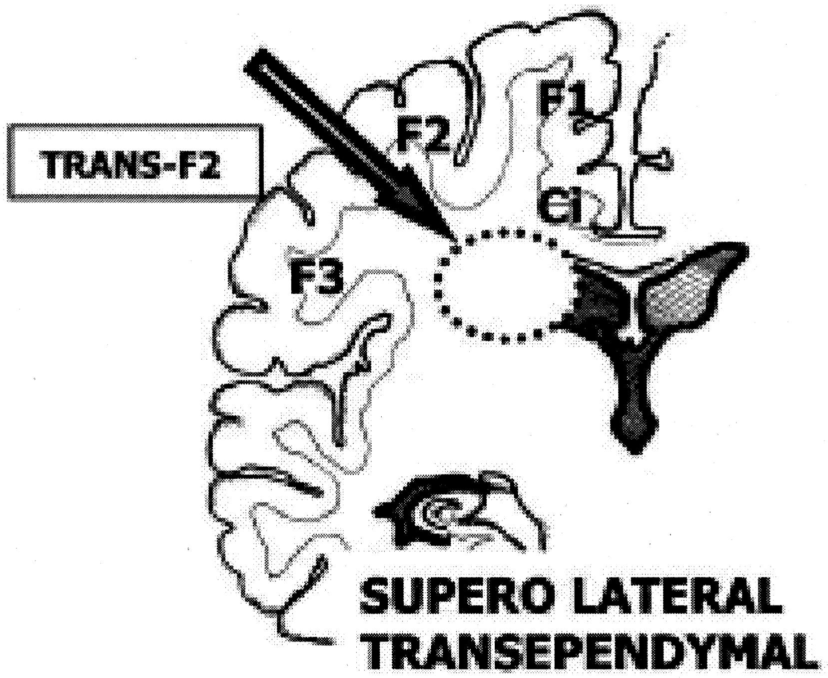


Figure 2 Transcortical approach to lesions predominantly situated in the frontal horn (18)

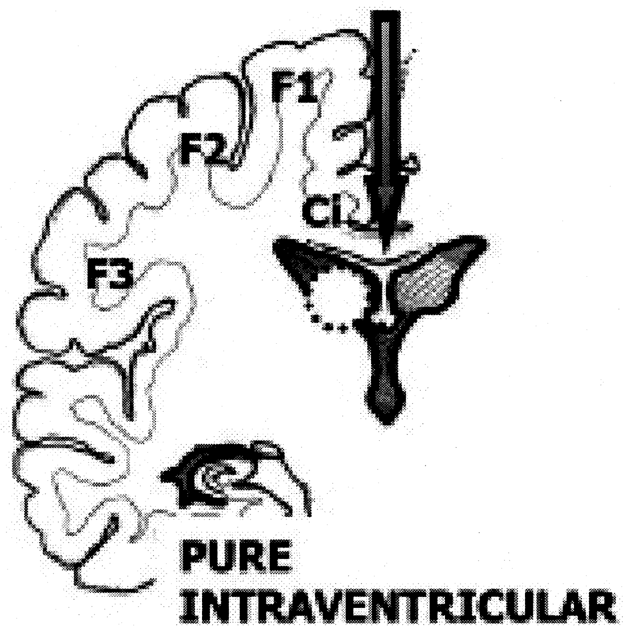


Figure 3 Interhemispheric transcallosal approach to tumours in the body (18)

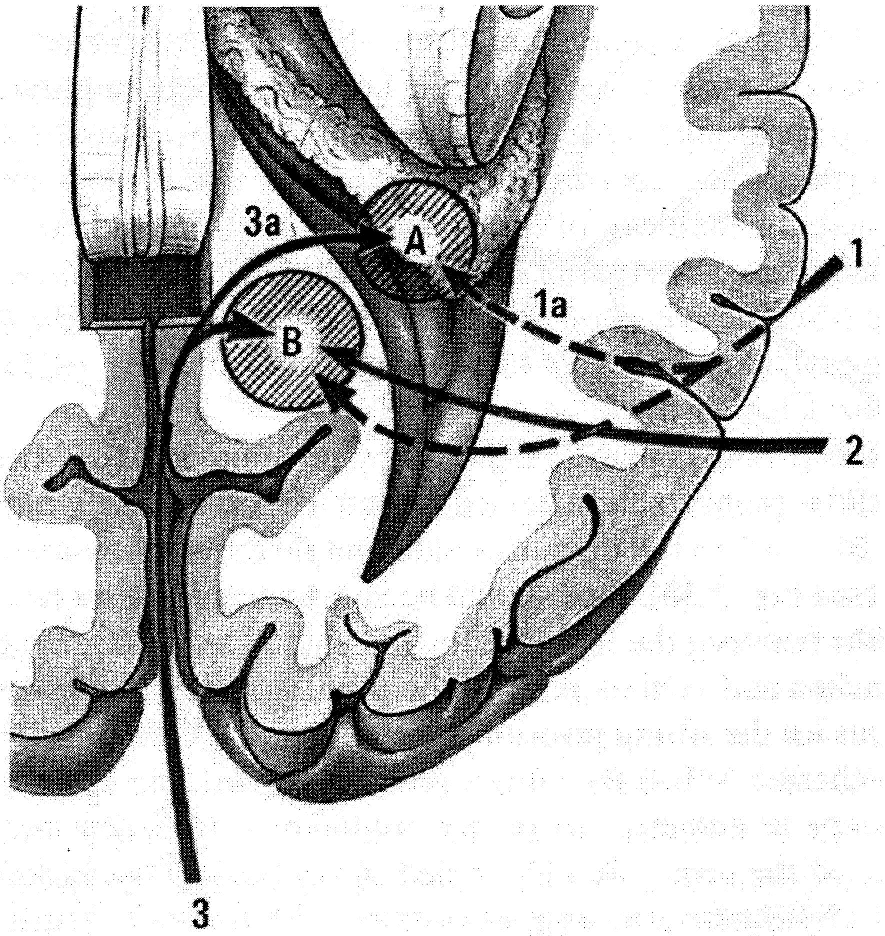


Figure 4 Approaches to lesions within the atrium

1 and 1a, subtemporal trajectories. 2, transcerebral/transparietal approach.

3 and 3a, posterior interhemispheric transprecuneus gyrus approaches.

A - represents the choroid plexus within the atrium

B - represents the precuneus gyrus at the level of the splenium (122)

Yasargil et al have recently described optimum corridors for access to tumours in the various parts of the lateral ventricle.

Table 2 Summary of optimal surgical approaches to lateral ventricle (122)

Site of tumour location	Preferred Approach
Frontal horn/body of lateral ventricle	Anterior interhemispheric transcallosal approach
Frontal horn projecting superiorly and laterally toward cortical surface	Superior frontal sulcus approach
Ventricular atrium (trigone)	Posterior parieto-occipital interhemispheric approach/precuneus trajectory
Temporal horn	Pterional-transsylvian transcisternal approach

Rather than shorter, more direct transcerebral trajectories to the ventricular region, more complex trajectories have become the surgical corridors of choice to minimize neurological morbidity (122)

Transcortical approach-related complications in the neurosurgical literature include seizures, hemiparesis, memory loss, confusion, and mutism. Transcallosal approach-related complications in the neurosurgical literature include hemiparesis, memory loss, akinetic mutism, and disconnection syndromes.

Adjuvant therapy

Adjuvant therapy in the form of radiotherapy and chemotherapy has been tried in recurrent lesions and in aggressive tumours.

Radiotherapy

The role of radiation has been questionable in view of the benign nature of the lesion. Yasargil et al have noted that advanced neuronal differentiation, low mitotic activity, absence of endothelial proliferation or necrosis suggest relative resistance to ionising radiation (123)

Rades et al (86) analyzed a series of typical neurocytoma patients who underwent incomplete resection and were subjected to conventional radiotherapy or stereotactic radiosurgery. Of 121 patients analysed, 59 underwent incomplete resection alone, 41 underwent incomplete resection with conventional radiotherapy, and 21 underwent incomplete resection and stereotactic radiotherapy. The 5-year-local control after resection alone was 51%. Local control was found to be significantly better after conventional adjuvant radiotherapy (87%, p = 0.001) and stereotactic radiosurgery (100%, p = 0.004) following incomplete resection. The difference between conventional radiotherapy and stereotactic surgery was not significant (P = 0.45). The 5-year-overall survival was 93% after incomplete resection alone, 100% after incomplete resection with radiotherapy and 100% after incomplete resection with stereotactic radiosurgery.

Rades and Schild (85) have also analysed the outcome following dose reduction from 54 Gy to 50 Gy following incomplete removal of typical central neurocytomas. They reviewed the results of 94 patients pooled from other studies. At 10 years, overall survival was found to be 100% both after < 50 Gy and after 50 Gy (p = 1.0), local control was 71% and 90%, respectively (p = 0.029) following the two doses respectively. They concluded that radiotherapy with 50 Gy (2-Gy fractions) appears sufficient in typical cases following incomplete removal.

Lenzi et al (57) in their analysis of 20 patients had subjected patients with MIB-1 index >4 with total tumour removal for radiotherapy. In subtotally removed cases, radiosurgery with LINAC was also performed (median dose 20 Gy) as well as conformational radiotherapy whenever there was a recurrence of the lesion (median dose 45 Gy). In cases in which there was only partial cytoreduction, conformational radiotherapy was administered with the adjunct of polychemotherapy if the MIB-1 was >4%. Twenty patients were surgically treated: 11 men and nine women, with an average age of 26 years (range 17 years to 42 years). Total, subtotal and partial removals were achieved in, respectively, ten, three and seven cases. At average follow-up of 7 years, 16 patients had been cured, had significantly improved or were at least stable [Karnofsky performance status score (KPS)] >70 or more)]. On the other hand, four patients had worsened; of these, two had died and two had a KPS=50 and an unfavourable prognosis.

Tumour shrinkage following gamma knife radiotherapy has also been reported by Hara et al (30) following subtotal resection of a ventricular neurocytoma in a 30 year old man.

Though good results were noted following radiation followed by stereotactic biopsy, Kulkarni et al (53) have noted a case of disseminated intracranial disease 15 months following treatment.

One case of delayed intra-tumoural haemorrhage 15 years after treatment with partial resection and radiotherapy has been documented (72). The possibility of delayed changes in vasculature causing the tumoral bleed has been noted. The authors thus caution the use of radiotherapy in these otherwise benign lesions.

Chemotherapy.

Chemotherapy has not been conventionally advocated for the treatment of central neurocytoma. However, many reports of response to chemotherapy have been documented.

A recent report highlighted the benefit of combination chemotherapy. Amini et al (1) have reported a 5 year old patient presenting with drop metastasis. They used Topotecan (0.5 mg/m^2) and carboplatin (250 mg/m^2) administered on days 1-3 and ifosfamide (1,800 mg/m^2) on days 1-5, every 21 days, for three cycles. The authors have noted a complete response without severe complications.

A report of chemotherapy with six cycles of chemotherapy including procarbazine, CCNU, and Vincristine was used to treat a young patient with multiple recurrences (117). At 16 months of follow up, minimal residual tumour was visualized on imaging.

Brandes et al (10) have used a treatment regimen comprising of etoposide, 40 mg/m(2)/day, for 4 days; cisplatin, 25 mg/m^2/day, for 4 days; and cyclophosphamide, 1,000 mg/m^2, on Day 4 with the cycle repeated every 4 weeks. With this regimen used in 3 patients with recurrence, stabilization of disease was observed in 2 patients and complete remission was observed in 1 patient for 15 months, 18 months, and 36 months, respectively.

Stereotactic Radiosurgery

Stereotactic radiosurgery has emerged as a newer treatment option for managing central neurocytomas since 1997. Kim et al (45) have analysed the results of primary and secondary (postoperative therapy) for patients with central neurocytoma. Tumors decreased in 5 (out of 6) patients who received gamma knife radiosurgery as a primary treatment. However, the tumor recurred in 2(out of 7) patients treated with a secondary gamma knife radiosurgery after surgery from the residual tumor bed that was not covered by the gamma knife radiosurgery.

Rades et al (86) have noted improved local control of typical neurocytomas with both radiotherapy and stereotactic radiosurgery following incomplete resection. Between radiotherapy and stereotactic radiosurgery, no significant difference was found in an analysis of 59 cases (P = 0.45) with 100% survival at 5 years.

Pollock and Stafford (80) have reported on a 34 month follow-up following stereotactic radiosurgery for a patient with a recurrent central neurocytoma presenting following gross total excision. There was significant decrease in size of the tumor.

Four patients with sub totally resected or recurrent central neurocytomas were retrospectively studied by Cobery et al (16). The prescription isodose was 9 to 13 Gy to the 30 to 50% peripheral isodose line. Over follow-up periods ranging from 12 to 99 months, reduction in tumor size was seen in all four patients with volume reductions ranging from 48% to 81%.

Three recurrent tumours were subjected to gamma knife radiosurgery were studied by Bertalanffy et al (7). The tumours were enclosed within the 30% to 60% isodoseline, and delivered a tumour marginal dose of 9.6 to 16 Gy. During a follow up of 1-5 years, all the patients had decrease in size of the tumour with no adverse affects due to therapy.

For a follow-up of 12 to 28 months (mean, 16.5 months) after radiosurgery for recurrent central neurocytoma, Anderson, R. C et al (2) have reported complete radiographic tumor control.

Predictors of Prognosis

Histological features in the form of nuclear pleomorphism, mitosis and markers such as MIB-1 index score have been used to evaluate prognosis of central neurocytomas. A meta-analysis performed by Rades et al (88) suggested an MIB-1 index score of >3% to be associated with a worse prognosis for local control ($p < 0.0001$) and survival ($p = 0.0004$). High levels of MIB-1 labeling has been noted to adversely affect prognosis (5) especially in recurrent lesions (14).

However, a lack of correlation between histologic atypia and MIB-1 LI was noted, with only 1 tumor having both atypia and MIB-1 LI >2% in a series of 15 cases. The tumors from all 4 patients in this series with a poor outcome had MIB-1 LI >2%, but only 1 of these had histologic atypia. Mackenzie (61) had based on these findings suggested that it would be appropriate to recognize a subgroup of central neurocytomas with elevated proliferation potential as higher grade lesions. The author suggests that the terms "atypical" and "anaplastic" are not appropriate to describe these lesions, as they imply a certain histologic appearance. The most accurate designation would be "proliferating neurocytoma."

On MRS imaging the presence of an Alanine peak has been suggested to be a marker for poor prognosis (15). Ogawa, Y et al (77) have noted progression of disease and dissemination in two patients suffering from extra-ventricular central neurocytoma both of whom underwent subtotal decompression. They attributed the bad prognosis to the presence of significant vascular proliferation, mitoses, and MIB-1 labeling index of more than 10%. Neither frequent mitosis nor necrosis was observed in both these tumours.

Lenzi et al (57) in their analysis of 20 patients had subjected patients with MIB-1 index >4 with total tumour removal for radiotherapy. The authors have noted histological atypia and MIB-1>4 as adverse prognostic factors.

MIB>5.2 has been noted by Favereaux et al (23) as an adverse prognostic factor in their series of 10 patients with atypical features on histology including high cellularity, mitotic activity and necrosis. These factors were attributed to prognosticate recurrence.

Prognosis

Tacconi (105) has reported 38 year follow up in a child operated for central neurocytoma with adjunct radiotherapy. The tumour had been diagnosed at 3 years of age and surgery was performed at 7 years. No evidence of tumour progression was noted at 38 years.

In children, central neurocytomas are extremely rare with about 60 cases being reported. Prognosis has been good with 100% at 10 years with children undergoing complete resection with or without radiotherapy and upto 93% in cases with incomplete resection (87). Extent of surgical resection appears to be the most important factor determining long term survival with incomplete resections are associated with lesser survival rates even with radiotherapy. The dose of radiotherapy of 50 Gy has also been found to be adequate.

Rades et al (84) have analysed prognosis in atypical central neurocytomas. In an analysis of 85 such cases, survival rates at 5 years and were 93% with complete resection, 90% after complete resection with radiotherapy, 65% and 43% at 3 years and 5 years respectively after incomplete resection, and 87% and 78% after incomplete resection with radiotherapy, respectively (P = 0.0076). After incomplete resection, patients appeared to benefit from radiotherapy in the study. A beneficial effect of radiotherapy after complete resection was not observed.

In a series of 18 patients with central neurocytoma followed up, 14 were alive for 8 months to 14 years and 11 months after the operation, and four died. The average survival period was 70.7 months (58).

Kulkarni et al (53) reviewed 8 patients who had undergone radiation therapy following stereotactic biopsy. 1 patient died 5 years after treatment from shunt dysfunction and 1 had disseminated intracranial disease 15 months after treatment. Six patients were symptom-free at a mean follow-up period of 78 months and had good local control as demonstrated by CT.

Soylemezoglu et al (93) in a series of 36 cases found significant correlation between MIB-1 labeling index and prognosis. Over an observation time of 150 months, there was a 22% relapse among patients with an MIB-1 LI less than 2% and a 63% chance of relapse among those with an MIB-1 LI greater than 2%. The latter cases also showed close correlation with the presence of vascular proliferation ($p = 0.0006$)

Even when the presentation is with intraventricular haemorrhage, analysis have shown a favourable outcome, when the tumour resection is complete (101).

Recurrence

Though central neurocytomas are benign lesion, recurrences have been noted even following total excision. Bertalanffy et al (8) analyzing recurrent cases have noted recurrences occurring at a median of 67 months after surgery (range, 51-79 months after surgery). The authors found no immunohistochemical or histologic feature specific for these lesions. The MIB-1 proliferation index ranged from 0.8-11% (median of 4.6%), but was reported to be 46.8% in a tumour with malignant transformation.

Aims of the study

1. To analyse the clinical presentation, imaging features, treatment options and outcome of patients treated for central neurocytoma at our center
2. To analyse the complications following surgery

Materials and Methods

In the period from January 1996 to June 2006, 95 patients were found to have primary intraventricular tumours (tumours found to arise from one or more walls of one or both lateral ventricles) and underwent surgical intervention for the same at the department of Neurosurgery Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala India. On reviewing the histological features of this cohort of intraventricular tumours, 23 were proven central neurocytomas by virtue of their distinct histological and immunohistochemical attributes. All patients included in this study were positive for synaptophysin study on their tumour during histopathologic evaluation. We excluded those tumours, which originated from adjacent structures and projected into one or both lateral ventricles.

Results

Table 3 Distribution of ventricular tumours N=95

Tumour	Number(%)
Central Neurocytoma	23(24.2)
Intraventricular meningioma	15(15.8)
Choroid plexus papilloma	6(6.3)
Choroid plexus carcinoma	6(6.3)
Subependymal Giant Cell Astrocytoma	12(12.6)
Intraventricular gliomas	20(21.1)
Septal Glioma	4(4.2)
Subependymoma	1(1.1)
Miscellaneous	8(8.4)

The medical records of these 23 patients were retrospectively analysed. We reviewed the demographic features, clinical presentation, radiological findings, operative procedures, postoperative outcome of these patients. The long-term follow-up was obtained by clinical examination and imaging studies done during follow up in the outpatient clinic.

There were 10 males and 13 females with histological and immunohistochemical features of central neurocytomas. The mean age of presentation was 27.2(20.0± 34.3) years. Twenty-two patients presented with headache and one patient presented with loss of consciousness. In patients with headache, 17 patients had associated vomiting suggestive of raised intracranial pressure. Associated visual loss was evident with headache and vomiting in 12 patients. One patient with loss of consciousness reported associated disturbances in vision without any headache or features of raised intracranial pressure.

Of the 23 patients, five patients who had raised intracranial pressure reported double vision. One patient with features of raised intracranial pressure had remote history (3 years prior to the onset of his complaints) of a single episode of epileptic seizure. Five patients had co-existent behavioural changes at the time of their presentation and these include emotional liability, impaired cognition and judgment, slowness of activity etc. Two patients each in this group had social incontinence and depressive symptoms. Four patients had limb weakness at the time of reporting to the neurosurgeon, three of them having contralateral limb weakness and one paraparesis. Four patients in this series had gait disturbances. The onset of symptoms was 3 months postpartum in one patient.

Table 4 Sex Distribution of the patients (N=23)

	Number (%)
Male	10(43.48)
Female	13(56.52)

Table 5 Presenting symptoms of the patients (N=23)

Symptom	Number of patients (%)
Raised intracranial pressure	17(73.91)
Visual loss	12(52.17)
Diplopia	5(21.74)
Behavioural changes/altered mentation	5(21.74)
Motor weakness	4(21.74)

The duration of symptoms range from 1 week to 60 months with a mean duration of 10.22 months. Three patients each had their symptoms over 2 years and 1-2 years respectively. Three other patients had complaints of 2-year duration and three had symptoms for one to two years.

The neurological examination revealed bilateral papilledema in all but one patient. Restriction in extra-ocular movements (lateral rectus paresis) was noted in the five patients. These patients had reported double vision. One patient with significant occipital lobe involvement was noted to have homonymous hemianopia. Four patients who had reported motor weakness were found to have spastic type of paralysis often, which was subtle rather than significant.

The clinical neuropsychological evaluation showed verbal memory and learning deficits in one patient; short-term memory impairment and dysphasia in two patients. Two patients had dyscalculia. One patient was drowsy on presentation.

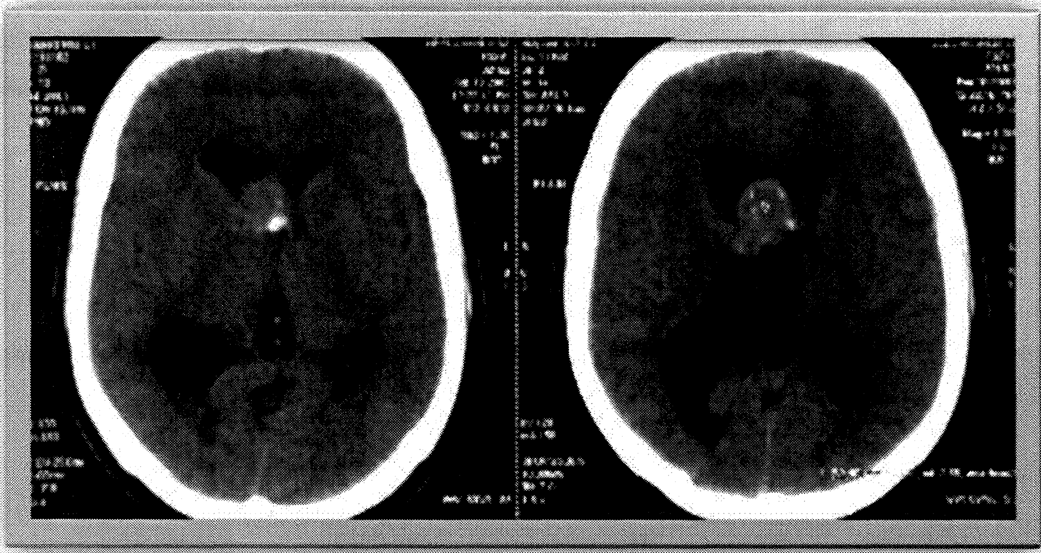


Figure 5 CT scan showing intraventricular enhancing lesion

On imaging, lesions were found to be predominantly of mixed density on CT with isodense and hyperdense areas. In 12 of the patients, the lesions were noted to have heterogenous areas of mixed density. Three patients the lesion was noted to be isodense to brain parenchyma and seven the lesion was noted to be hyperdense. Calcification was noted in 13 patients. Of the patients evaluated with a pre-op CT, contrast enhancement was noted in 21 patients; two of the lesions did not enhance on contrast. The enhancement noted on contrast, was patchy and not intense. Based on the CT scan, the primary origin and attachment could not be defined. Hydrocephalus was evident in 21 of the 23 cases predominantly involving the lateral ventricles with normal sized fourth ventricle.

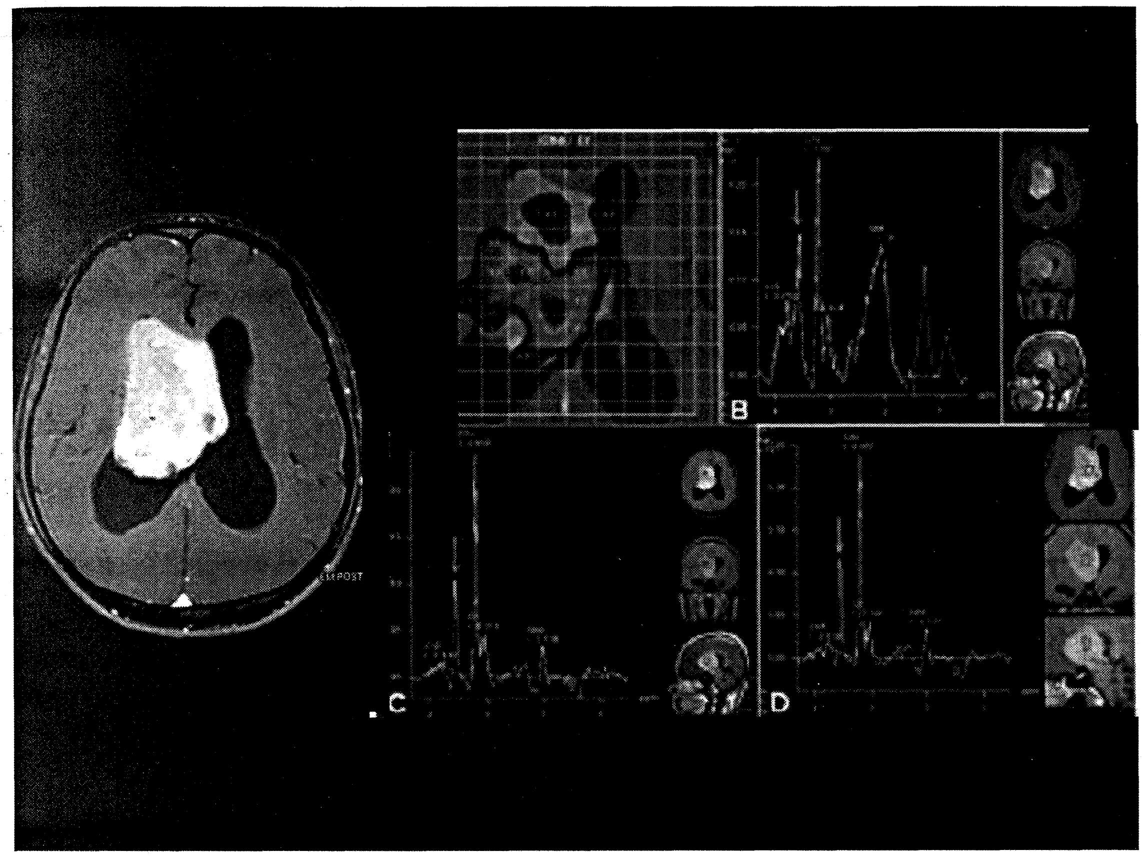


Figure 6 Imaging features showing enhancing ventricular lesion. MRS showing Glycine peak along with elevated Choline and decreased NAA

Of 14 patients who were subjected to MR imaging prior to surgery, lesions were noted to have varying intensity with 11 of the lesions appearing predominantly hypo or isointense on T1 sequence; 3 others showing patchy hyperintensity. On T2 sequences, 12 of the lesions were noted to be is or hyperintense and two noted to be hypointense. The lesions, which were hypointense on T2, were isointense on T1 sequences. All the 14 patients were subjected to contrast MR imaging which revealed patchy contrast enhancement.

Based on the imaging features(MRI and CT imaging), the size of the lesions in 21 of the 23 patients ranged from 3.5 cm to 7.2 cm in with mean maximum dimension of 4.91(SD ± 1.03)cm.

Table 6 Maximum dimensions of lesion on imaging(N=20)

Dimension(cm)	Number of patients
3-3.9	2
4-4.9	10
5-5.9	4
6-6.9	3
7-7.9	1

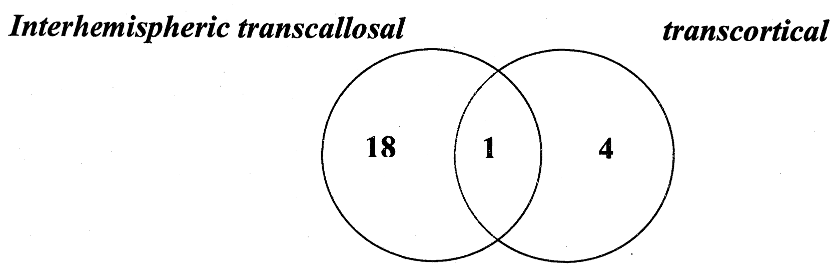
Based on imaging findings (CT and MRI), 17 of the lesions were noted to be located within the body of the ventricle predominantly arising from the septum pellucidum, 3 lesions were noted to occupy the frontal horn, 3 were noted to be predominantly located in the trigone. In 5 patients extension into the occipital horn was noted; 2 patients had extension of the lesion into the temporal horn. In 4 patients, the lesion was found to be extending into the third ventricle.

Table 7 Extension of lesion within the lateral ventricle based on imaging findings

Location within Ventricle	Number
Frontal horn	3
Body	17
Atrium	3
Occipital horn	5

A coexisting arteriovenous malformation was noted in the left cerebello-pontine angle in one patient.

Surgical Approach to the lesion



Surgery

Twenty patients underwent surgery with a pericoronal parasagittal craniotomy. Eighteen of these patients were operated utilizing the transcallosal access to the lateral ventricle. The transcallosal route was chosen when the majority of the tumour was present in the body of the lateral ventricle. One patient, who underwent transcallosal approach initially, required transfrontal cortical access to reach the tumour in the same operative sitting to access residual tumour in the posterior body of the lateral ventricle.

Four patients underwent transcortical approach- one each via a tempero-parietal craniotomy, occipital transcortical routes respectively and two via transfrontal route.

Two patients who had tumour located in the trigone were operated via the tempero-parietal transcortical approach. One patient who had a large lesion involving frontal horn and body was approached through the transcortical route. The cortical access was through the middle frontal gyrus in case of the anteriorly sited lesions and through the superior parietal lobule when the lesion was sited in the trigone or occipital horn.

The lesions were noted to have attachment to multiple walls of the lateral ventricle.

Table 8 Ventricular attachments of the lesion noted during surgery

Attachment	Number of lesions
Septum	21
Lateral wall	4
Floor	2
Roof	2

Nine of the lesions were noted to be within the left lateral ventricle, 8 lesions within the right lateral ventricle. Five lesions were noted to be biventricular. A callosotomy ranging from 1-2.5 cm in the anterior body of the corpus callosum was used to access these lesions. The callosotomy was placed anterior to the coronal suture. Fifteen of the lesions were noted to be soft and amenable to suction, whereas a firm consistency was noted in six cases. Majority of the lesions (21) were noted to be vascular whereas two lesions showed minimal vascularity during surgery.

Figure 7 Preoperative axial contrast CT showing enhancing lateral ventricular lesion

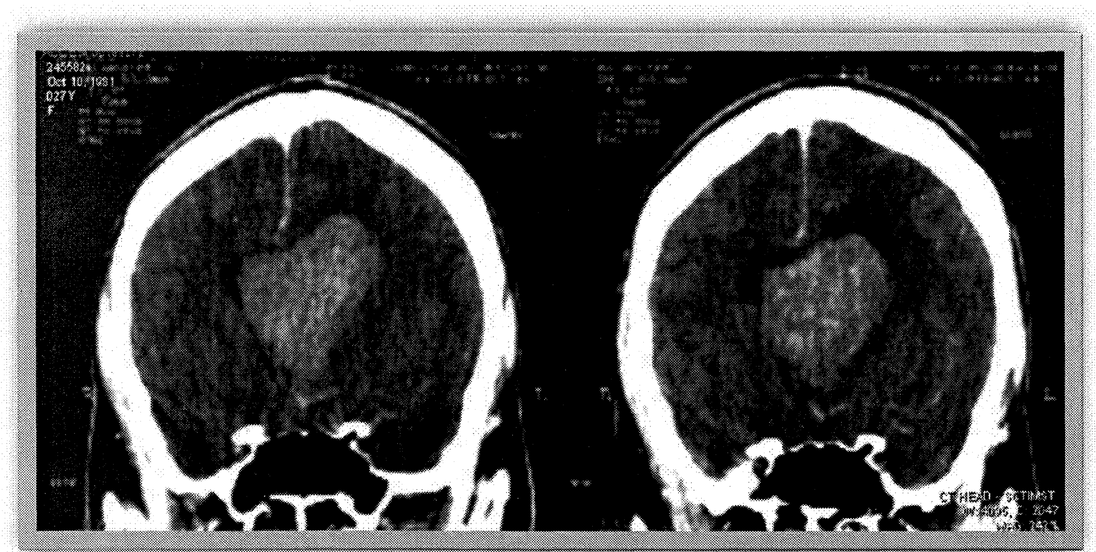


Figure 8 Coronal contrast CT images showing enhancing lesion

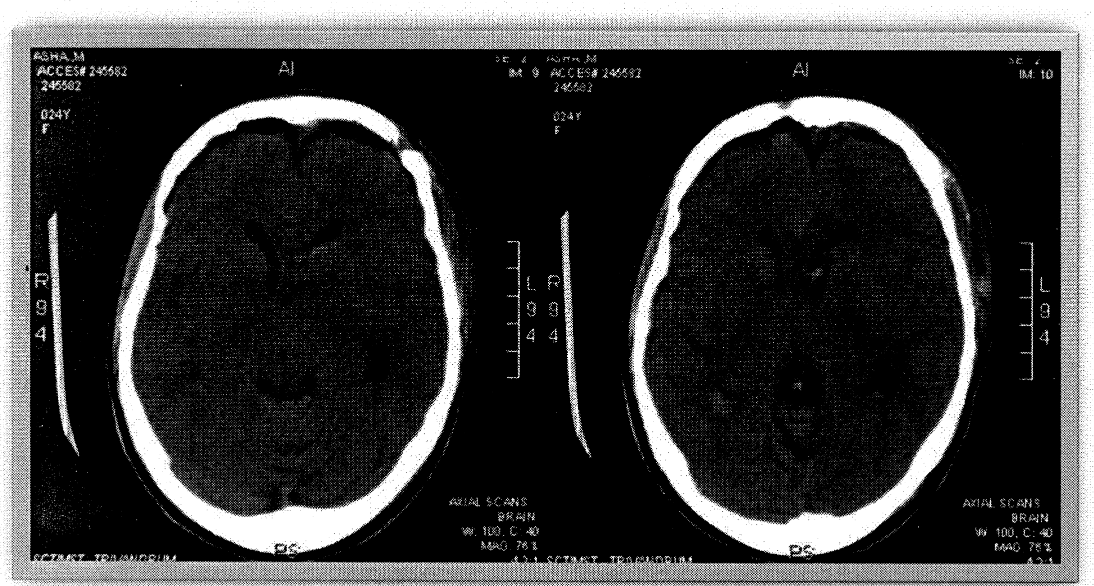


Figure 9 Immediate postop CT scan showing total resection following transcortical approach

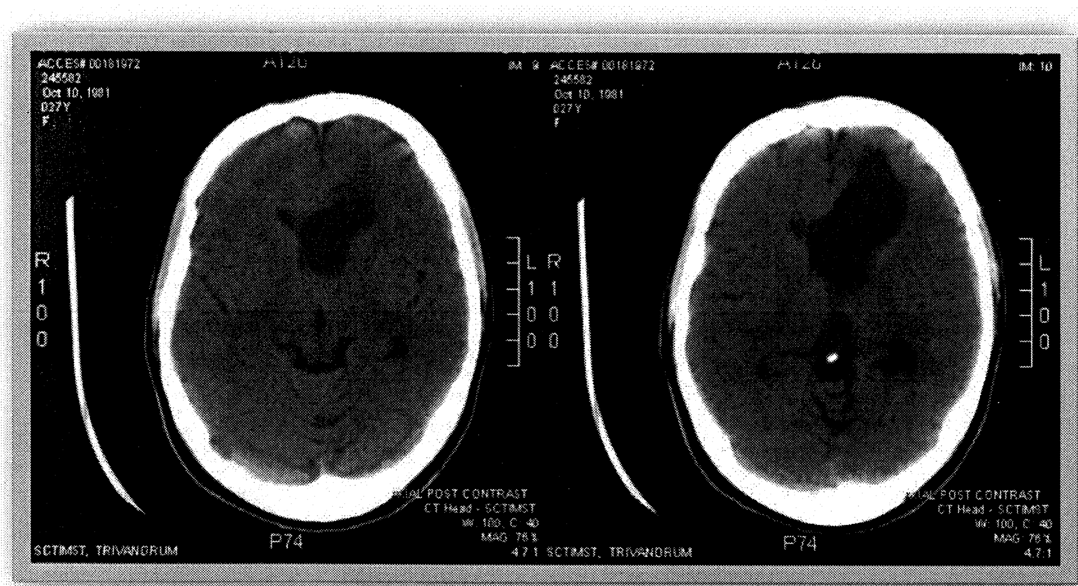


Figure 10 CT imaging obtained on 3 year follow up showing no recurrence

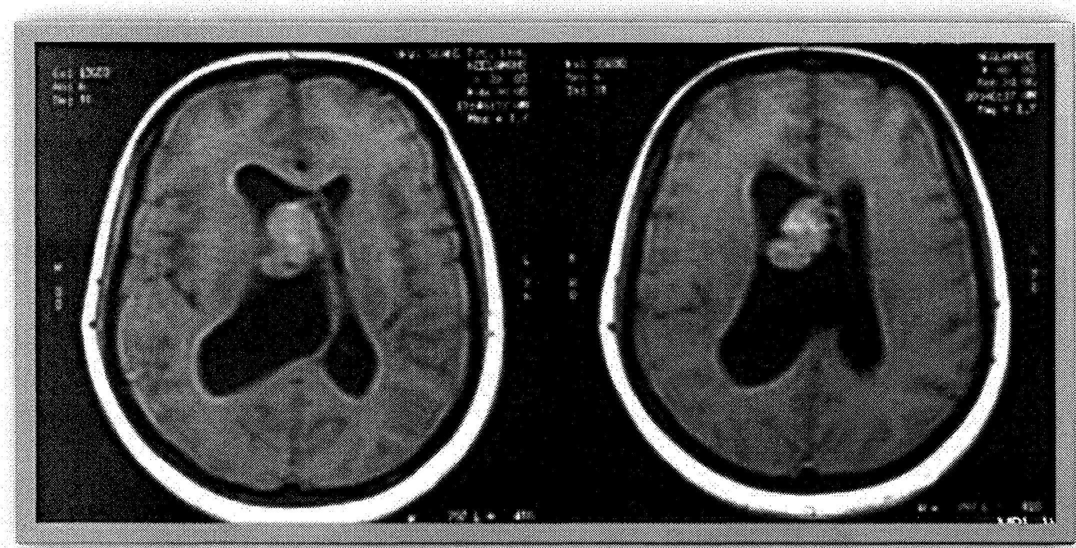


Figure 11 T1 contrast MR imaging showing enhancing ventricular lesion

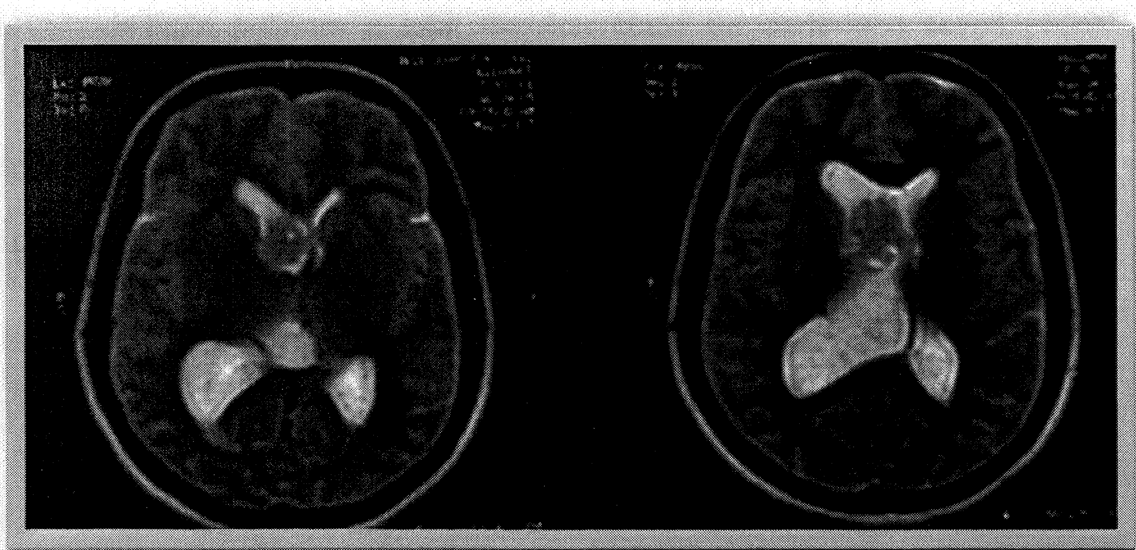


Figure 12 T2 imaging showing heterogenous intensity lesion

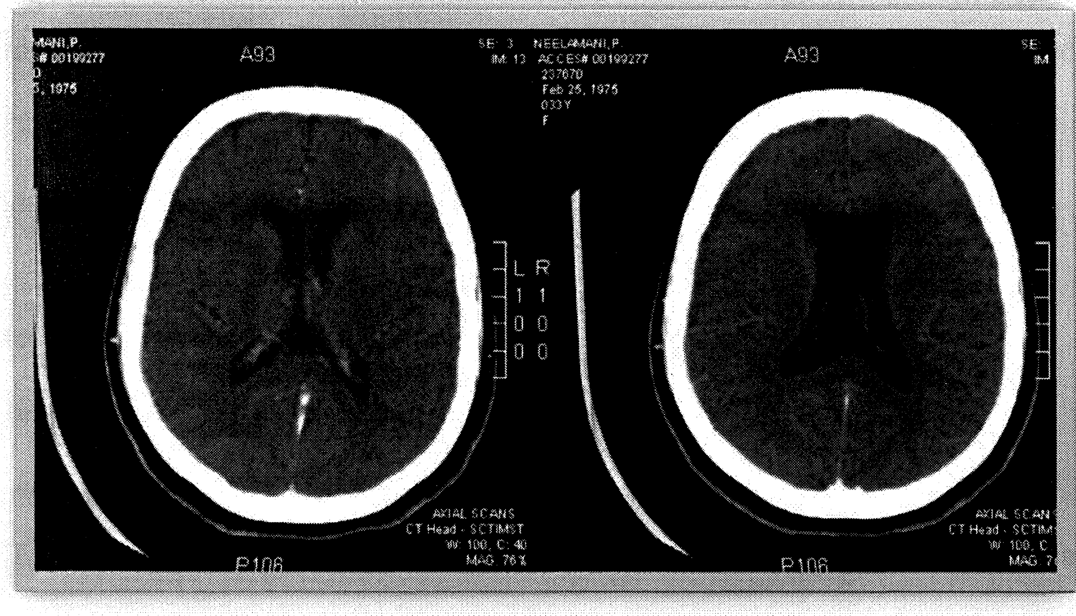


Figure 13 Follow up imaging at 3 years showing no recurrence following total excision by interhemispheric transcallosal approach

In eight patients a total excision could be performed, seven patients underwent near total excision and 8 patients underwent subtotal excision. One patient underwent occipital lobectomy subsequently due to a venous infarct detected intra-operatively.

All patients had ventricular drain in situ following surgery and this was removed only if the postoperative scan did not reveal any intraventricular haematoma or hydrocephalus.

Postop status

Nineteen of the patients had normal sensorium following surgery. Four patients had poor sensorium, which necessitated post op ventilation.

Of these nineteen patients, one patient subsequently developed facio-brachial seizures. Patient had a subsequent deterioration in sensorium following which he underwent repeat surgery. The patient had a subsequent turbulent course and died of malignant cerebral edema.

Mortality and morbidity

There were three postoperative deaths in the series.

One patient had seizures in the immediate postoperative period and her CT scan showed haemoventricle with hydrocephalus and malignant brain edema with poor sensorium. Surgical re-exploration (to evacuate the haematoma) and ventricular drainage was carried out, however there was no improvement in the clinical condition. She died in the immediate postoperative period.

A second patient who developed massive frontal venous infarct failed to recover with surgical decompression.

A third patient who was alert in the immediate postoperative period deteriorated with contralateral hemiparesis. Postop imaging showed hydrocephalus and blood at the operative site. A re-exploration was performed. Following the second surgery, patient developed hemiparesis and aphasia. Patient died on the seventh postop day with malignant cerebral edema.

Two patients were in very poor neurological status after surgery.

Both had poor sensorium in the immediate postoperative period and were ventilated. One of the patients was noted to have paraparesis. He subsequently underwent repeat surgery for decompression of residual lesion and hydrocephalus. There was no improvement noted following the second surgery. Patient had a protracted hospital stay with refractive hydrocephalus, which required management with biventricular shunts with multiple revisions. He died 6 months later.

The other patient who had residual tumour was noted to have an operated site haematoma. She underwent re-exploration and removal of residual tumour and evacuation of haematoma but failed to reverse her poor neurological status. She died 4 months later.

Of the patients who had a poor outcome (mortality/significant morbidity), all except one had poor sensorium in the immediate postoperative period. The patient with normal sensorium developed focal seizures involving the upper and lower limb and was noted to have active operative site bleeding.

Six patients suffered post op seizures. Four of them suffered from focal motor seizures and including one patient who suffered a faciobrachial seizure. Two patients suffered from generalized seizures. Four of the patients suffered only a single attack. Two patients had recurrent seizures. Of the patients who suffered recurrent seizures, one was generalized, another focal. Of the six patients who suffered seizures, four of them had a poor outcome.

Of the approaches underwent by these six patients, two had undergone a transcortical approach for decompression. Four patients had undergone transcallosal access. One of the patients had suffered a frontal venous infarct sustained probably secondary to venous injury during access along the interhemispheric corridor. One another patient with a transcallosal approach developed GTCS postoperatively. Thus, incidence of seizures in the transcallosal group is 22%, whereas that in the transcortical is 50%. In four of these patients, seizures were antecedent to deterioration and ultimately resulted in death. Seizures occurred during the first postop day.

Motor deficits were noted in eleven patients during the immediate postoperative period. Of these 11 patients, four patients had a poor outcome. In six of the patients, weakness was transient which resolved in a short time. The remaining one patient had persistent weakness at discharge, which resolved when examined at first follow up.

Operative site haematoma was noted on immediate postoperative imaging in 11 patients following surgery. Of these four patients underwent evacuation. In the remaining patients, the volume of blood was minimal and the patients with no sequlae due to the same.

Postoperative pneumocephalus was noted in five patients, however only one patient required aspiration for the same as he had deterioration in sensorium. Though five patients developed postoperative seizures, pneumocephalus was of any significance in one of them.

Though external ventricular drainage was instituted in the postoperative period, hydrocephalus was noted in 11 patients on imaging. It was of significance in all patients with poor outcome (death/severe morbidity). Among the remaining patients decrease in size was noted in all the patients. One of the patients presented 4 years after surgery and required a VP shunt placement for amelioration of symptoms.

Long term complications

Though motor deficits were noted in 11 patients in the immediate postoperative period, only one patient had persistent weakness at the time of discharge from the hospital. He had complete resolution of weakness on follow-up 6 weeks after surgery.

One patient had blindness due to progression of papilledema due to secondary optic atrophy.

Recurrence/Residual lesion

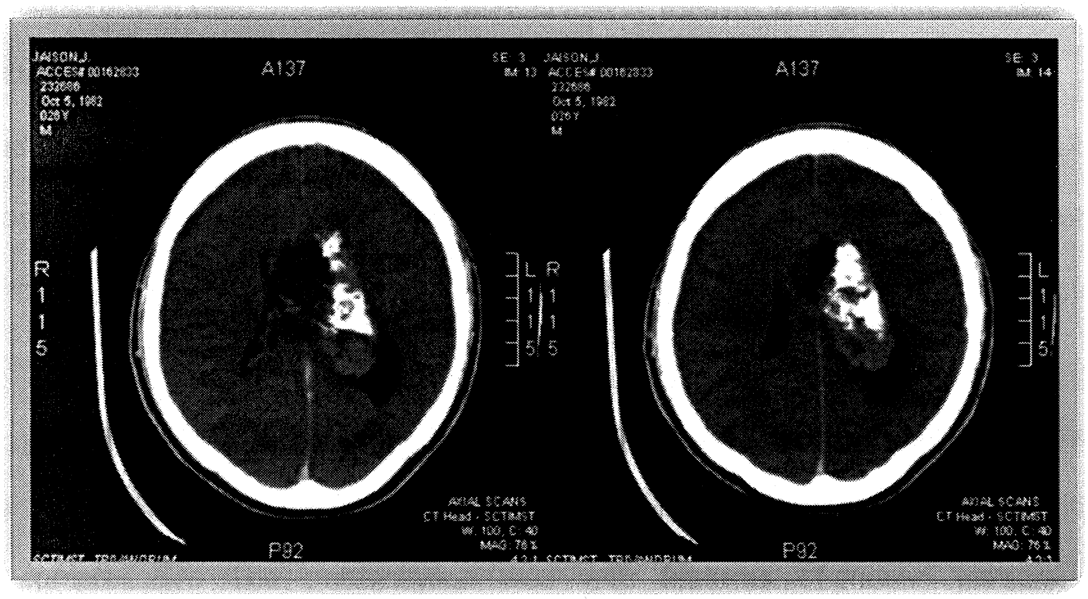


Figure 14 Recurrence 3 years after primary decompression

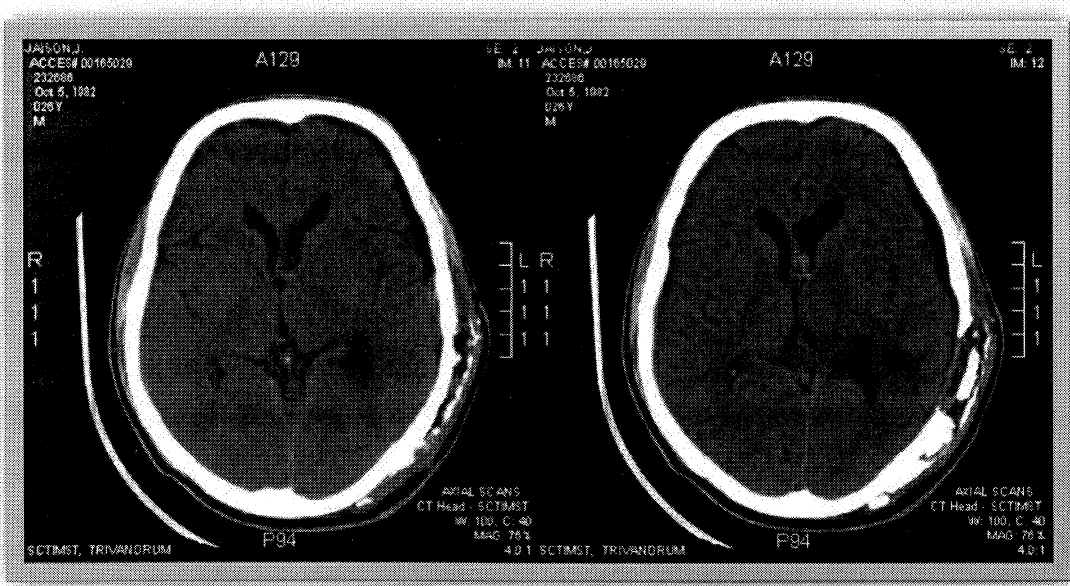


Figure 15 Near total excision after third surgery through transcortical approach

Of the 8 patients in whom only a subtotal resection was possible, 4 of the patients had a poor outcome with postoperative deaths in 2 patients and severe morbidity in 2 others. Of the remaining 4, 3 patients were subjected to radiotherapy. The remaining patient had significant residual lesion in the occipital horn and underwent repeat surgery 1 year after the first surgery with total excision through a transcortical route. The patient developed contralateral motor weakness, which gradually improved.

One of the patients, who underwent radiotherapy, developed two recurrences, which required repeat surgery, the first 3 years after the initial decompression. The presentation was with features of raised intracranial pressure. A subtotal resection could be performed. He again presented with features of raised intracranial pressure four months after the second surgery. Imaging showed increase in the size of the residual lesion. Another surgery was performed and near total excision achieved. The initial approach was interhemispheric transcallosal so was the subsequent surgery. The third surgery was through the transcortical approach with ventricular access through the superior parietal lobule. Postoperative complications included generalized seizures and contralateral hemiparesis, which resolved completely. Histopathologic evaluation of the lesion showed no atypical features.

One patient with a trigonal lesion developed recurrence following total excision. Patient underwent total excision through a transcortical approach through the superior parietal lobule. The recurrence presented 3 years following the first surgery. The lesion was decompressed completely and patient referred for radiotherapy following surgery. No atypical features were noted in both these patients on histopathologic evaluation.

Pathology

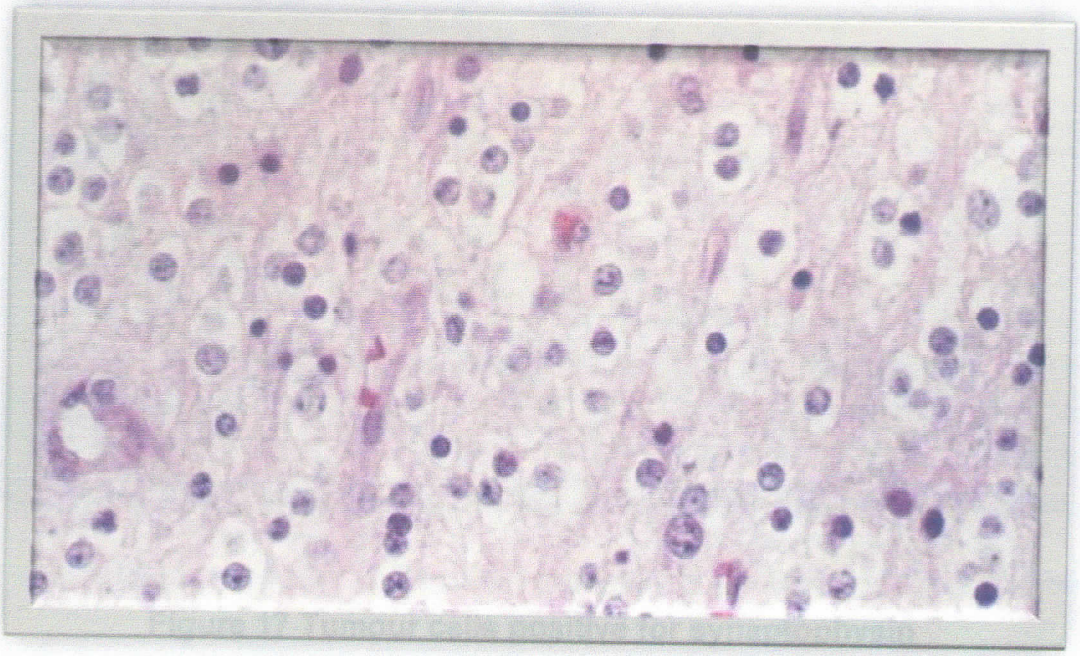


Figure 16 Haematoxylin and Eosin staining showing large vesicular cells with a clear cytoplasm

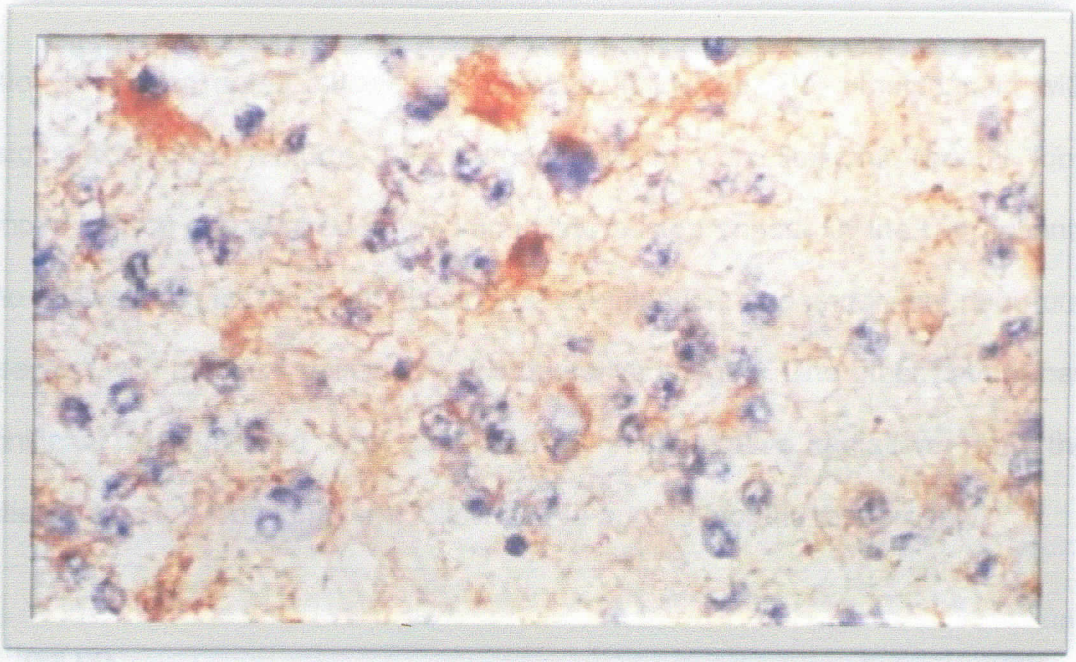


Figure 17 Tumour cells positive for synaptophysin

All the lesions were examined by haematoxylin and eosin preparations and by immunostaining for synaptophysin. All the lesions showed clear vesicular cells. Two lesions had perivascular rosette formation. Areas of haemorrhage were noted in two lesions with cells containing haemosiderin pigments. Two of the lesions showed a bimorphic picture with an additional component consisting of stellate cells. Two lesions were positive for chromogranin and one for NSE. Microscopic calcification was noted in five lesions. Atypical features in the form of nuclear atypia and necrosis were noted in two lesions. Of these two patients, one had a good outcome with no recurrence noted on follow up. This patient was not subjected to radiation in view of total surgical excision. No recurrence of the lesion has been noted following a 32-month follow up. The other patient with histologic atypical features had surgery related complications (frontal lobe venous infarct) and expired in the immediate postop period. Of the two patients who showed haemorrhage on histological examination, one underwent near total resection with mimimal residue on postoperative imaging. The other patient had significant residual and was subjected to postoperative radiation. Both the patients are stable on long term follow up (44 and 60 months respectively).

Follow up

A mean follow up of 39 months (±22months) was available for the surviving patients. Three of the patients had undergone subtotal resection and were subjected to radiotherapy. Their follow up imaging reveals stable residual tumour in one patient and one patient had resolution of the residual. The third patient required repeat surgical intervention.

Of the survivors, 10 patients showed residual lesion on postop imaging, three of who required a repeat surgery. Two of these patients showed progression of their residual tumour one of who was following postoperative radiotherapy. One patient had a repeated surgical re-exploration in view of significant residual tumour.

Regular follow up was available for 17 patients. All these patients were doing well and were independent for activities of daily living. All patients with preoperative pyramidal signs showed resolution of the same following surgery during follow up.

Discussion

We report 23 cases of central neurocytoma operated at a single centre from 1996-2006. This is one of the largest series of central neurocytomas proven by histological and immunohistochemical studies.

Central neurocytomas form about 31.5% of primary intraventricular tumours operated during the study period. In a series of intraventricular tumours, the incidence of central neurocytoma among ventricular tumours has been noted to be 1.2% (21) . An incidence of 14.2% has been noted by Morita et al (70) Our own study shows the incidence to be much higher among primary intraventricular tumours

Clinical Presentation

A male preponderance was noted by Chen et al as well as Sharma et al (13, 98). A female preponderance was noted in other studies (12, 62, 65, 94). We had a female preponderance with a male: female ratio of 1:1.3. The average age of presentation of these tumours in our series was 27.2(20.0± 34.3) years. This corroborates with the one of the first series published by Hassoun et al (33) and other series which have noted the commonest age group of involvement to be between 20 and 30 years (26, 48, 62, 71, 106, 114).

Most other series (13, 62, 70, 98, 127) document the clinical presentation with features of raised intracranial pressure. The same was noted in our series also (73.9%).

Five patients in our series had varying degrees of behavioral disturbances at the time of their clinical diagnosis. Disturbances in higher mental function had been not been documented in several other studies.

Four patients in our series had paucity in motor power. This presentation (21.7%) is much higher than quoted in literature (13, 62). We postulate that the motor deficits in central neurocytomas are attributable to mass effect on deep white matter structures especially the caudate nucleus and internal capsule that forms the lateral boundary of the body of lateral ventricle. However, these deficits were subtle.

Clinical findings were notable by their absence except for the findings of papilledema and VI nerve paresis attributable to raised intracranial pressure and mild motor deficits.

Imaging features

Analysis of the imaging features of central neurocytoma suggest the lesion to be of varying densities on CT. Calcification was noted in 56.5% of cases which is slightly higher than noted in other studies (33, 98) Three of the lesions(21.4%) showed patchy hyperintensity on T1 sequences suggesting the possibility of bleed. Lesions hypointense on T2 suggest increased cellularity, which was seen in two (14.3%) of the lesions. The mean dimension of nearly 5 cm suggests the late presentation of the lesion. A significant number of lesions were biventricular (21.4%). A similar finding(20%) had been reported by Sharma et al (98) Third ventricular spread was seen in 4 patients which has been noted in 20% of patients in the same series (98). The biventricular spread and septal origin noted can be attributed to septal origin of the lesion. Probably the lesion develops secondary attachment to the floor and lateral wall or because of secondary vascularity developing from them. The biventricular nature of the lesion can be postulated to be due to two causes.

i. The lesion may have an origin within the leaves of the septum wherin the lesion expands into both ventricles. However, in lesions with significant attachment to the septum, such a phenomenon is not seen.
ii. The lesion may have dual origin form either surfaces of the septum. These lesions may thus have a trophic factor released from the ventricles, which may be responsible for their development within the ventricular cavity.

Surgery

Majority of the lesions (18 patients-78.3 %) could be accessed by the transcallosal interhemispheric approach. Only one of the lesions, which was deemed accessible initially, required a transcortical resection for completion of the resection. The remaining five lesions (21.7%) were large and were approached through a transcortical approach. Conventionally the transcortical approach is associated with complications of seizures. The transcallosal approach is the ideal approach for accessing these lesions. Concerning the transcortical approaches, though ventricular access is easy as these patients had hydrocephalus, the advantage is minimized after the ventricle is opened. The incidence of postop seizures is about 17.4 %(4/23) in the transcallosal approach as opposed to 50%(2/4) in the transcortical. A direct causative factor was also noted in the patient who suffered a seizure following the transcallosal approach (venous infarct) which is in concordance with known literature (18, 21, 123). The reported risk of postoperative seizures after transcortical approaches ranges from 29 to 70%, whereas after transcallosal procedures, the reported risk is 0 to 10%. Seizures typically occur during the first postoperative week when the brain is still recovering form the surgical insult.

Section of the corpus callosum preserving the splenium does not result in appreciable adverse neurological deficits, but either anterior or posterior interhemispheric dissection may result in injury to the bridging veins or the posterior occipital vein. The callosotomy has been restricted to less than 1.5 cm. Three of the surviving patients with subtotal resections underwent postoperative radiation. The lesions were shown to be static or decreased in size on postoperative imaging.

Prognosis

Of the patients who underwent total resection, all had an uneventful postoperative period with no neurological deficits developing following surgery. Residual lesions were noted in patients with large lesions, which extended into the atrium causing difficulty in access due to the anterior callosotomy. These patients had a turbulent postoperative period with haemorrhage and ventricular dilatation in the immediate postoperative period. Thus the most important factor responsible for the poor outcome common to all those patients is the residual lesion. However, among patients with residue who had a good postoperative outcome, the long-term results were the same as that in those patients who underwent a total resection.

Table 9 Factors associated with poor prognosis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
30 day postop outcome	Death	Severe morbidity	Death	Death	Severe morbidity
Age	22	38	26	22	24
Sex	F	M	F	F	F
Surgical Approach	Transcallosal	Transcallosal /transcortical	Transcortical	transcallosal	Transcallosal
Cortical injury	Venous infarct	none	none	none	none
Excision	Near total	subtotal	subtotal	subtotal	Subtotal
First day postop sensorium	poor	poor	poor	poor	awake
Immediate postop seizures	Focal motor	none	Faciobrachial	GTCS	Focal
Postop Motor deficits	hemiparesis	paraparesis	hemiparesis	hemiparesis	Hemiparesis
Hydrocephalus	+	+	+	+	+
Postop haematoma	+	+	+	-	+
Pneumo-cephalus	-	-	-	+	-
Atypical histology	+	-	-	-	-

Of the eight cases presented by Yasargil et al, good outcome was noted in seven patients with one patient developing hemiparesis. There was one recurrence noted on follow-up.

In a recent series of 9 cases by Chen et al (13), good outcome was noted in 7(77.7%) patients. There was one death and 2 of the surviving patients had a KPS below 70.

Good outcome was reported in 7 (77.7%) of 9 patients operated (median follow up of 99 months), by Chen et al with 2 postoperative deaths and moderate neurologic deficits in one patient.

In a series of 5 cases presented by Maiuri et al (62), there was one postoperative death with 2 patients developing fresh postoperative neurologic deficits.

In a similar series of patients as our series, Sharma et al (98) had good outcome in 15(88%) of 20 patients operated for central neurocytoma with a mean follow up of 32 months. They reported 5 immediate postoperative deaths. All surviving patients were subjected to radiation therapy.

Central neurocytomas have traditionally been treated by surgical excision with a good resection providing long-term disease control. Leenstra et al (55) have in a study of 45 patients have documented the 10-year overall survival and local control rate as 83% and 60%, respectively. The 10-year survival and local control rate was 90% and 74% for patients with typical tumors compared with 63% ($p = 0.055$) and 46% ($p = 0.41$) for those with atypical tumors. They found that on comparing gross total resection with subtotal resection, there was no significant difference in survival or local control. Postoperative radiotherapy improved local control at 10 years (75%) with radiotherapy versus 51% without radiotherapy, ($p = 0.045$); however, this did not translate into a survival benefit. The authors have noted that the overall prognosis is quite favorable, one-third of patients experienced tumor recurrence or progression at 10 years, regardless of the extent of the initial resection.

Schild et al (94) analyzed the results of therapy for 32 patients with histologically confirmed central neurocytomas and found that patients who had subtotal resection benefit from radiotherapy. Included in this series were 15 females and 17 males with ages ranging from 4 to 57 years (median: 27 years). Gross total resections were performed in 10 patients and subtotal resections in 22 patients. Thirteen patients received postoperative radiotherapy, five after gross total resection and eight after subtotal resection. Doses of radiation ranged from 48.6 Gy to 61.2 Gy (median: 54.5 Gy) in 1.8 to 2.0 daily fractions. Follow-up ranged from 2.0 to 15.3 years (median: 4.7 years). The overall survival and local control rates at 5 year were 81% and 79% respectively. The 5-year local control rates were 70% for those having subtotal resections compared to 100% for those having gross total resections ($P=0.08$). The effect of radiotherapy was evaluated in those undergoing subtotal resection. The 5-year local control rate was 100% for those who received radiotherapy after subtotal resection compared to 50% for those with subtotal resection alone ($p = 0.02$). The 5-year survival was 88% for those having subtotal resection and radiotherapy as compared to 71% for those with subtotal resection alone ($p= 0.3$). Three patients received radiotherapy for local failure occurring after subtotal resection. All three were alive and free of disease 1 to 6 years after radiotherapy.

Landi et al (54) reviewed results of 220 published cases of central neurocytoma along with 5 of their cases. Overall, the 5-year survival and local control rates were 90% and 71%, respectively. The 5-year survival rates noted were as follows: 96% following gross total resection alone, 100% following gross total resection with radiotherapy. Survival following subtotal resection was 77% and subtotal resection with radiotherapy was 92%. Following biopsy plus radiotherapy survival was 71%. The 5-year local control rates were as follows: gross total resection, 62%; gross total resection with radiotherapy, 88%; subtotal resection, 58%; subtotal resection with radiotherapy, 77%; biopsy with radiotherapy, 60%. There was a significant difference in survival between gross total resection and subtotal resection ($p < 0.05$), subtotal resection and subtotal resection with radiotherapy ($p < 0.01$), and local control between subtotal resection and subtotal resection with radiotherapy ($p < 0.05$). There was no difference in survival comparing gross total resection with gross total resection plus radiotherapy and gross total resection with subtotal resection plus radiotherapy. There were five recurrences after gross total resection.

Conclusion

Central neurocytomas form 31.5 % of ventricular tumours in our series. They are common in the second and third decades of life with a female preponderance. They often present with features of raised intracranial pressure. The radiological features of these lesions reveal their location to be frequently in the body and frontal horn of lateral ventricle and rarely in trigone and/or occipital horn. Hydrocephalus is present involving the lateral ventricles. They have heterogenous appearance on CT and MR imaging. They enhance moderately on contrast administration.

Owing to their unique anatomical location, they are often accessed via the transcallosal route and occasionally transcortical access is required for lesions located in the trigone or isolated in the frontal horns.

Total or near total excision was possible in a majority of patients while only a subtotal excision is possible in the rest. A good surgical outcome was achieved in 78 % of patients. Rarely do they require CSF diversion in the postoperative period.

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