Imaging Characteristics of Primary CNS Lymphomas and its significance in preoperative diagnosis:

A retrospective analysis

Submitted for MCh Neurosurgery

By

Dr. Adam Kamrudeen

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Department of Neurosurgery

Sree Chitra Tirunal Institute for Medical Sciences & Technology

Thiruvananthapuram – 695011

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Submitted by : **Dr. Adam Kamrudeen**

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DECLARATION

This thesis titled **"Imaging Characteristics of Primary CNS Lymphomas and its significance in preoperative diagnosis: A retrospective analysis;** is a consolidated report based on a bonafide study of the period from January 2013 to June 2015, done by me under the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

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

Dr. Adam Kamrudeen
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

CERTIFICATE

This is to certify that the thesis entitled "Imaging Characteristics of Primary CNS Lymphomas and its significance in preoperative diagnosis: A retrospective analysis"; is a bonafide work of **Dr. Adam Kamrudeen** and was conducted in the Department of Neurosurgery, Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram (SCTIMST), under my guidance and supervision.

Prof. Suresh Nair N.
Professor and Head
Department of Neurosurgery
SCTIMST, Thiruvananthapuram

Dated: 5/10/15

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1 Introduction

Primary central nervous system lymphomas (PCNSL) historically have accounted for approximately 2% of primary brain tumors. The review of literature regarding PCNSL strongly supports a protocol for stereotactic biopsy to establish diagnosis. Also it should be noted that administration of steroids for intracranial malignancy which is a common place in today's practice, and affects the biopsy report adversely. Hence it is necessary to improvise existing practice of find alternative ways to diagnose or aid in diagnosis and management. Recently many investigators have showed interest in MRI diffusion characteristics and perfusion curve for aiding in diagnosis and stratify prognosis. This study focusses on finding any relation between the imaging characteristics of the lesion and patient characteristics like nature of surgery, presentation, post-surgery outcome and preoperative diagnosis.

Pre-operative early diagnosis of PCNSL offers a possibility of early effective primary therapy that is chemo radiotherapy and avoids the cost, effort and morbidity of a major surgical effort. Hence and effort to use imaging protocols to establish a pre-operative diagnosis of PCNSL could preclude the need for a biopsy and offer potential management benefits. However surgery cannot be avoided for PCNSL in the event of progressive raised intracranial pressure and progressive neurological deterioration.

2 Review of literature

2.1 Epidemiology

Primary central nervous system lymphoma (PCNSL) is a rare disorder involving the intracranial structures, spinal cord and eye. Intracranial structures involved could be both brain and the leptomeninges. It is extra nodal form of non- Hodgkin's lymphoma mainly of B-cell type. The incidence of PCNSL ranges between 3-5% affecting age group with more predilection towards the fifth decades in non AIDS cases[1]. The typical age of presentation is 60 years for immunocompetent individuals and 30-35 yrs for immunodeficient individuals[2]. Mainly seen in immunocompetent individuals, but its incidence is increasing in parallel to the incidence of AIDS[3]. There is 3000 fold higher risk of developing PCNSL in patients with AIDS than general public[4]. The increase in incidence is not solely because of AIDS, but also attributed to increase in life expectancy, better diagnostic methods and immunosuppressive therapy[5]. But such an increased incidence of PNCSL is not seen in Indian setting. Lanjewar et al[6] in his autopsy series did not find a single PCNSL cases. Another study by Satishchandra et al[7] showed 100 cases of AIDS with multiple neurological conditions but not PCNSL. Such contradictory incidence is attributed to early death of Indian patients due to opportunistic infection. A multicentric Indian study encompassing AIIMS and NIMHANS to study the incidence of PCNSL in north India and south Indian population was conducted in 2005. The period was from 1980 to 2003. Their study revealed no change in the incidence between the two groups. They also showed that the Indian patients were 10 years younger as compared to west and more was commonly seen in immunocompetent patients[8]. In recent times the incidence of AIDS related PCNSL is decreasing because of effective antiretroviral therapy. Also to mention, there are reports of increasing incidence of the disease in normal individuals independent of the overall trend of the brain malignancy[9]. This could be due to some environmental factors rather than purely because of more awareness and diagnostic accuracy. There are many studies evaluating the association of PCNSL and infectious agent especially EBV, but data is primitive to comment on. Bashir et al[10] found EBV in most of the AIDS related PCNSL but none in immunocompetent PCNSL cases. Other organisms to name which are seen in lymphoma cells are human herpes virus-8, Toxoplasma gondii[11,12].

2.2 Clinical features

Clinical features depend on the location of tumor and the signs and symptoms may vary. It can range from mild headache to raised ICP type headache, seizure, focal neurological deficit, behavioral abnormalities and cognitive decline. Feurerhake F et[13] in their series found focal sensorimotor deficit by far the most common presentation. Eichler FA[14] et al also noticed similar finding re enforcing the fact that seizure as a primary presentation is very rare. Lobar involvement is more common followed by other periventricular sites like thalamus, basal ganglia and corpus callosum. Lobar involvement[15] is in the following order: frontal lobe (20.2%), parietal lobe (17.6%), temporal lobe (15.2%), and occipital lobe (4%). Lymphocytic infiltration of meninges, ventricular lining epithelium and roots are also reported[16].

2.3 Diagnosis

The clinical presentation of the PCNSL is so vague and varied that its diagnosis purely on clinical history and examination is difficult. Baseline evaluation consist of eye examination, CSF analysis, HIV status and serum LDH level. Physical examination for lymph node enlargement, testicular enlargement should be done. Imaging with CT and MRI helps to narrow down the differential diagnosis and also helps to rule out secondary lymphomas. A lookout for secondary lymphoma/occult lymphoma is very important, as subgroup of patients with PCNSL may have systemic involvement. Five to twenty percent of ocular lymphoma are seen in PCNSL and present with visual blurring and floaters. Ocular presentation precedes brain lesion in 95% of cases[17].

Advance sequence MRI like diffusion and perfusion curve are being studied in detail in its accuracy of diagnosis of PCNSL, but still brain biopsy remains the gold standard. Most of them are isodense to hyperdense on plane CT scan with variable enhancement on contrast. On MRI, they are hypointense on T1W images and hyperintense on T2W images. Though classically described as periventricular lesion, kuker et al reported cortical location with meningeal enhancement in 50% cases[18]. Enhancement is moderate to marked[3]. Enhancement trailing the Virchow robin space is very specific[19]. T2W hyperintensity around the lesion which is suppressed on flair can be seen suggesting perilesional edema. Most of the lesion are hyperintense on Diffusion weighted imaging because of restriction of water molecule within it. This characteristic is also seen in high grade glioma, stroke and abscess. Bleed, calcification and necrosis are rare. About 8% of PCNSL cases have systemic involvement. Detailed examination of abdomen, chest, testes and bone marrow is recommended[20]. In another series 7% of systemic involvement was detected using FDG PET[21].

Brain biopsy is mandatory for diagnosis. Total or subtotal resection is only indicated when the lesion size is the cause of worsening sensorium or poor neurological status. Sometimes if biopsy not amenable, CSF cytology, PET scan and positivity for EBV can be taken as indirect evidence[22]. Brain biopsy remains the gold standard with only one drawback i.e. false negative result[9]. This is because of the steroid induced transient remission as a result of apoptosis which is usually given to almost every patient with a mass lesion and perilesional edema. Such tumor also surprisingly "vanish" on imaging but only to recur. This initial response to steroid have shown to be of favorable prognosticate value with survival of 9.75 years vs < 1 year[23]. This fact was challenged by Porter et al [24], who elaborated that false negative biopsy was almost same in both groups i.e. those treated with steroids vs no treatment(12% vs 13%). Also not all vanishing tumors are lymphoma, it could be MS and other inflammatory conditions like sarcoidosis. According to Ann Arbor staging system PCNSL is classified as stage IE. Ann Arbor staging system does not have prognostic value. Factors as reported by international extra nodal lymphoma study group of poor prognosis are age >60, poor performance scale, high serum lactate dehydrogenase, elevated CSF protein and deep location of tumor[25].

According to WHO classification, 95% are B cell lymphoma are evident by surface marker B 19 and B20. Only 4% are T cell lymphoma. Though T cell lymphoma are clinically more benign, the prognosis and outcome of various therapy did not show any difference statistically from B cell lymphoma[26]. CSF examination has inconsistently been used for diagnostic purpose but has not attained clinical relevance. CSF is examined for CSF cell morphology, biochemical profile, beta macroglobulin, IgH (immunoglobulin heavy chain) and immunohistochemistry. Tumor markers like LDH isoenzymes, Beta glucoronidase and Beta microgloblin may provide indirect evidence of leptomeningeal spread. Fischer[27] et al in his study of 117 patients, CSF analysis showed positive lymphoma cells in 18%. Immunohistochemical studies for clonal proliferation of B cells was not specific but specificity could be improved with PCR amplification[28]. Most of the B cell lymphoma have germinal center origin. Most of the diffuse B cell lymphoma are high grade tumors except for few low grade tumors with atypical presentation which are mainly seen in spine. These low grade tumors include immunocytoma and MALT. Diffuse B cell lymphoma are positive for CD20 and negative for CD138 (also usually negative for EBV). Proto oncogenes mutations seen are Pim-I, RhoH/TTF and c-MYC[29]. Immunohistochemical study revealed expression of MUM-1 (marker of activated b cell) and BCL-6 (marker of germinal center). BCL-6 expression is generally associated with poorer outcome[30]. Some rare types of CNS lymphomas[31] which can be encountered in clinical practice are intravascular large B cell lymphoma presenting with lacunar stroke and has a poor prognosis. And marginal zone B cell lymphoma of dura mimicking meningioma with favorable prognosis. Histiocytic sarcoma is another extremely rare and very aggressive variant of PCNSL.

2.4 Treatment

The role of surgery is limited only to biopsy as gross total excision is associated with poor prognosis and carries a risk of neurological deficits without a definite survival advantage. However surgery cannot be avoided for PCNSL in the event of progressive raised intracranial pressure and progressive neurological deterioration.

There are studies to the contrary like Murray et al[32] who suggested radical excision of solitary lesion actually improves survival. He reported 55 months vs 12 months in surgical decompression plus radiation and radiation alone respectively. Interestingly in sonstein[33] et al series, 60% of survivors were those who underwent resection of solitary lesion. Another skeptical example was given by Davies et al[34] where he reported survival of a patient with PCNSL for over 20 years without any recurrence following surgery. But there are multiple literature publications which proves beyond doubt that surgery is not indicated in PCNSL cases and has no survival benefit. In a study by Bellinzona et al [35], a total of 30 patients were analyzed retrospectively who underwent surgery for multiple reasons like raised ICP and neurological decline. They found no statistically significant benefit in surgical group.

PCNSL is highly radiosensitive tumor. Radiotherapy has a survival advantage. According to RTOG a dose of 40Gy to whole brain followed by boost of 20Gy to tumor bed to be given and spinal radiation is warranted only when spinal dissemination is documented[36]. Radiotherapy in the form whole brain radiation has been replaced by combination of chemo radiation. A retrospective analysis of 300 patients was done by Ferreri[37] et al comparing chemotherapy with radiotherapy and radiotherapy alone. He found favorable outcome in chemo radiation group. In trans-tasman radiation group, methotrexate was given at 1gm/m^2 over 6 hours on day 1 and 8 followed by RT of 45Gy and 5Gy boost to tumor bed in 1.8 fractions after day 15. Total 45 patients were studied, complete response in 80% and partial response in 13% with overall survival of 33 months at 2 yr follow up was seen[38]. Chemotherapeutic drugs used are methotrexate, steroid, vincristine and cyclophosphamide. Methotrexate if given iv, needs to be given in high doses >1gm/m^2 in order to attain therapeutic level in brain and CSF. There were multiple trial to explore the possibility of using chemotherapy as a standalone treatment in PCNSL. The German phase 2 trial (NOA-03-trial) [39] investigated the efficacy of high dose methotrexate (as high as 8gm/m^2 every 14 days for 6 cycles) but the study was prematurely terminated because of poor response rate. Another study with similar protocol was conducted by Batchelor et al [40], who showed 54% complete remission rate but the progression free survival was only 12 months. Also the efficacy of polychemotherapy was studied by multiple authors. A prospective multicentric phase 1 and 2 trial enrolling 65 patients were subjected to methotrexate, cyatarabine, vinka alkaloids in combination with intraventricular prednisolone, methotrexate and cyt-C. Complete response rate was as high as 61% and partial response in 10% with progression free

survival in 21% and overall survival at 50 months. The response was better in patients under 60 yrs and those aged >60 years the overall survival was only 30 months[41]. The EORTC trial (2003)[42] studied 52 patients aged 60 or more with KPS 50(median) with iv methotrexate, procarbazine, methylprednisolone with intrathecal methotrexate and ara-C. In patients with some degree of response on imaging were subjected to maintenance dose of iv methotrexate. Overall response rate of 48%, overall survival 14 months and PFS at 1 year 40% was noted. In another French study combination of methotrexate and temozolamide was given to 23 patients with median event free survival of 32 weeks and overall survival 30 months[43]. The use of intrathecal chemotherapy is not well substantiated. Methotrexate, cyatarabine and prednisolone have been tried with varying success. Both lumbar and intraventricular route can be used, but intraventricular route dictates lower dose for same CSF level of drug. The indirect evidence of usefulness intrathecal chemotherapy comes from the fact that omission of intrathecal therapy form pels et al previous protocol (2003)[41] led to worse prognosis. The attendant risk of ventriculitis and leucoencephlomalacia needs to be entertained when assessing the benefit risk ratio. Liang et al[44] in 1993` have shown beyond doubt the survival advantage after intrathecal methotrexate in conjunction with radiotherapy. However, all the studies where intrathecal therapy was used, also had WBRT in conjunction and hence statement "the additive response is due to intrathecal therapy may be an over assumption"[20]. Methotrexate has also been used in high dose myeloablative chemotherapy with stem cell transplant rescue. Illerhaus et al[45] studied high dose chemotherapy and WBRT according to chemotherapy response has resulted in 69% 5 yr survival rate. Initial monocentric trials have shown some positive results. Future multicentric trials are required to recommend such treatment. Soussaain et al[46] states that in PCNSL recurrence high dose methotrexate with stem cell transplant may be a viable option for younger patients.

The dose intensity with which chemotherapy and radiotherapy are instituted have a positive correlation with the outcome. But the limiting factor is long term neurotoxicity. Abrey et al[47] did a single center evaluation of long term deleterious effects of the treatment and found that 100% of patients over 60 yrs developed some form of cognitive decline. Affected individuals showed brain atrophy and leukoencephalomalacia rendering them bed ridden and dependent on others with a poor of quality of life. Most of the neurotoxicity is attributed to radiotherapy. Hence the treatment needs to be modified on individual basis taking into account the age of the patient and pre-treatment cognition.

The prognosis of HIV infected patients with PCNSL was very grim. About 1/3 die while taking treatment. But now the scenario has changed with introduction of HAART. With the introduction of HAART, 1) the incidence of the AIDS has reduced and, 2) the response to chemotherapy when their viral load is less is good. In a multicentric trial by Hoffman et al (2001)[48]reported very good outcome

in AIDS patients treated with HAART and chemoradiotherpay. He reported median survival rate of 39 months in HAART group, 4.71 months in only chemo radiation group and 1 month in no treatment group.

Even with the best of treatment the prognosis of PCNSL is worse and almost all the patients have recurrence.

2.5 Recent trends

Most of PCNSL express CD20 antigen on their surface. So theoretically antibodies against CD20 might work in most. Rituximab, an anti-CD20 antibody which have been tried in refractory cases of PCNSL. Rituximab does not achieve necessary concentration in brain when BBB is intact. Hence its use limited to intrathecal administration. Rubenstein et al[49] have showed the ability of Rituximab to clear tumor cell from CSF if given intrathecal. He also studied the maximum dose tolerated and pharmacokinetics of the drug. He used escalating doses and found that 10mg and 25 mg dose was well tolerated as compared to 50mg dose which produced side effect in virtually all subjects. But limited publications backs it up for use in intraparenchymal PCNSL except for few scattered single case use. Shah et al[50] treated a subset of patients with standard protocol chemotherapy and radiotherapy, and additionally gave iv rituximab 500mg/m2. Though he reported good tolerance to the regime and a good 2 yr survival rate, he was not convinced to commit that the favorable response was due to rituximab.

Continued research in the development of effective chemotherapy with minimal toxicity is underway. One of the major difficulty encountered is the drug resistance. A multicenter trial comparing multiple genes in PCNSL and systemic lymphoma was done. There were over 100 genes expressed in high frequency in PCNSL and some others in systemic lymphoma. Among those who were expressed in high frequency in PCNSL were X-box binding protein-1(XBP-1), Pim-1, c-MYC. Also there is higher concentration of interleukins as well as activated Stat-6[51]. Another study searched for any protein marker which can be linked to prognostication. They found a surface expressed protein antithrombin-III which is associated with poor prognosis and DAP-1(death associated protein) which was associated with favorable response when patient was subjected to MTX and rituximab[52].

Though biopsy is mandatory and gold standard for diagnosis, protein biomarkers are looked for in CSF which can act as substitute to biopsy in patients who are not fit for any surgical procedures. Such biomarkers may also help in detection of recurrent disease, response to treatment and aid in prognostication. In this context, Roy et al studied CSF of patient with PCNSL and other benign conditions in 2 separate set of patients 1 year apart. He found over 80 protein markers were consistently elevated in PCNSL cases with high degree of statistical significance[53]. Most of the elevated protein subgroups were serine proteases, protease inhibitors, complement mediators, glycoproteins

and lipoproteins. Proteins which were reduced in concentration are normal brain components like neuropeptides and neurotransmitter. Antithrombin -3 is one of such protein marker (also confirmed by gene analysis) whose concentration is markedly elevated in cancers patients with 75% sensitivity and 98% specificity when the level was 1.2ng/ml. This marker though elevated in PCNSL can also be seen in glioblastomas. Retrospective analysis of prognosis of PCNSL cases with high level of antithrombin-3 was generally poor.

Gene expression analysis and CSF protein marker holds a promising future to change the way we diagnose and treat PCNSL, but much work is required to achieve such optimistic goals.

Can imaging replace biopsy??? This question could be solved in time to come. DWI sequence of MRI has potential to diagnose PCNSL without the need of biopsy. Many studies have even reported specific diffusion restriction level above which, diagnosis of PCNSL can be made. Also the response to chemotherapy and radiotherapy can be predicted on the basis of diffusion characteristics of the tumor. Such a unique potential of DWI if tapped, can be very usefull in early management of PCNSL when its most required.

3 Aim of the study

To analyze diagnostic characteristics of Primary CNS lymphomas with reference to imaging features namely CT, MRI diffusion and perfusion characteristics with an attempt to establish a pre-operative diagnosis.

4 Materials and Methods

All patients with tissue diagnosis of Primary CNS lymphoma (treated at our institute from 2005 -2014) were included in the study. This is a retrospective study. Including all the cases, who underwent biopsy/surgery with a tissue diagnosis of lymphoma and these were selected from the medical records data base. Those patients who had shown evidence of secondary lymphoma were excluded. Medical records, imaging data and charts were reviewed to obtain study variables like preoperative diagnosis and focal deficit (pre and post-surgery). Available information from medical records were analyzed and additional information was derived via questionnaires sent to patients or in person interview.

Imaging sequences used:

CT scan Philips ICT scanner 256 slice was used for both plain and contrast scan. Non contrast scan was taken at 120KV and 350mAs with 5mm slice thickness covering from skull base to vertex with contiguous axial slices parallel to the inferior orbit meatal line. With similar specification contrast scan was taken after injecting 40 ml of Iohexol dye.

Diffusion Imaging acquired using single-shot echo-planar imaging (EPI) sequence with diffusion gradients along 30 noncollinear directions of about 20 slices of 5 mm thickness with TR 3,500 ms, TE 105 ms, field of view 230 x 230, matrix size 192 x 192, b values of 0 and 1,000 mm^2/s in three orthogonal directions. Calculation of different Diffusion Tensor Metrics p, q, and L and FA and its linear, planar, and spherical components, designated CL, CP, and CS respectively will be done and later analysed with Siemens Software

Accordingly For DSC Perfusion Imaging, T2* weighted gradient EPI sequence (TR 1,800 ms, TE 43 ms, 16 slices with 5 mm slice thickness; interslice gap of 6.5 mm; matrix 128 x128; and 1 average). About 50 dynamic scans with a time resolution of 1.0 s per image performed after intravenous bolus injection of 15 ml Gd- DTPA (Omniscan; GE Healthcare) with an MR-compatible power injector at a flow rate of 5 ml/s and a 20 ml saline flush. DSC perfusion imaging was performed using the same section orientations and coverage as those used for conventional MRI.

All the analysis and post processing will be performed on a separate workstation (Leonardo; Siemens, Erlangen, Germany). Perfusion parametric maps will be obtained by using a dedicated software package. After eliminating recirculation and leakage of contrast agent, the relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF) and time intensity curve are computed

- All images will be interpreted separately by two radiologists, who will be blinded to clinical data.

5 Statistical analysis

SPSS.4 windows version 21 was used to analyse the results. To test the significance of data student t test and ANOVA was used.

6 Results

Total number of patients studied was 34 with sex distribution of 23 (67.6%) male and 11 (32.4%) female. Mean age of presentation was 47 years.

Table 1: Gender distribution

Sex	n	Percent
Female	11	32.4
Male	23	67.6
Total	34	100.0

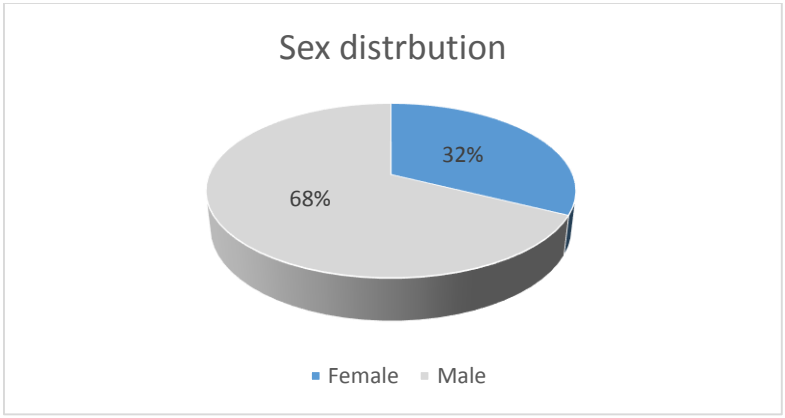
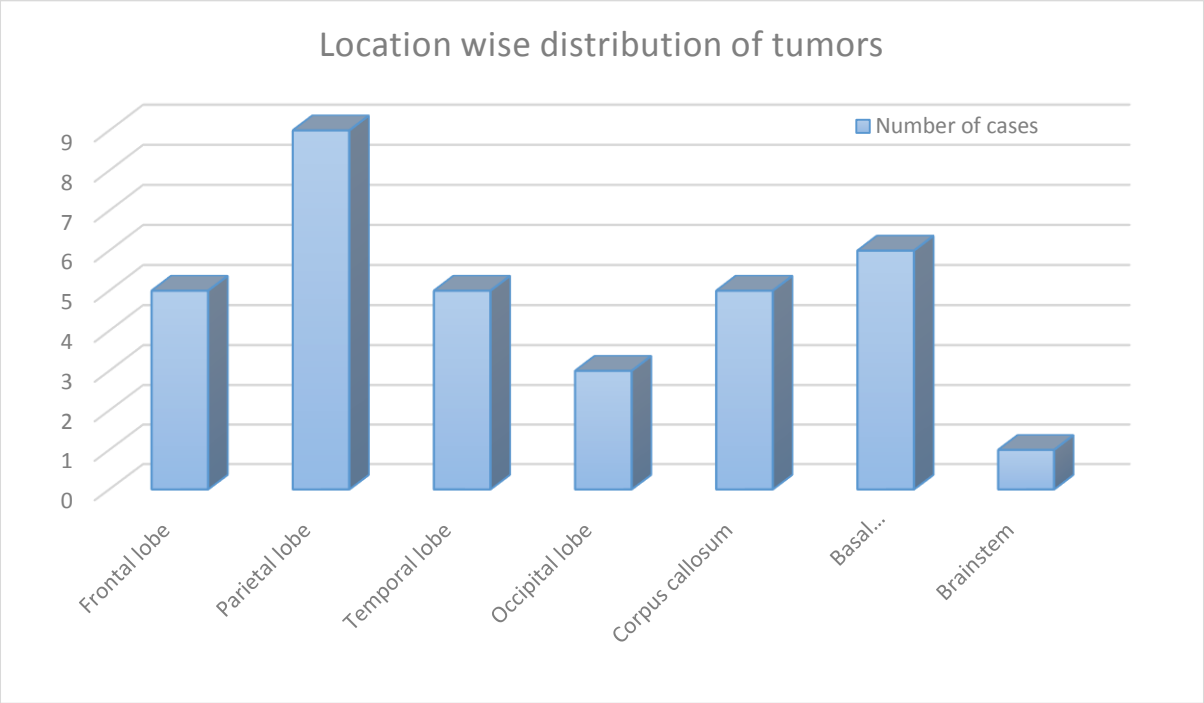


Table 2: Location wise distribution of tumors

Sr no	Location	Number of cases	Percentage
1	Frontal lobe	5	14.7%
2	Parietal lobe	9	26.4%
3	Temporal lobe	5	14.7%
4	Occipital lobe	3	8.8%
5	Corpus callosum	5	14.7%
6	Basal ganglia/Thalamus	6	17.6%
7	Brainstem	1	2%
	Total	34	100%



Of the total 34 cases, the most common location was parietal lobe and least was in the occipital lobe. Most of the lesion were in supratentorial compartment except for one which was involving the brainstem. Total number of cases in frontal lobe was 5 (14.7%), parietal lobe was 9 (26.4%), temporal lobe was 5 (14.7%), occipital lobe was 3 (8.8%), corpus callosum was 5 (14.7%) and basal ganglia/Thalamus was 6 cases (17.6%). Size of the lesions varied form minimum of 2cm to maximum of 5cm.

Of the total 34 patients, 21 patients (61%) presented to outpatient's department with CT scan. Out of these 21 patients, 13 (61%) had hypodense lesion on CT scan as compared to 1 patient (4.8%) isodense and 7 patients (33%) with hyperdense lesion. None of the lesion showed calcification or bleed. Contrast enhancement was uniformly present in all cases except for 2 cases (9.5%). Of the total contrast enhancing lesion 14 (41%) showed homogeneous enhancement and 6 (17.6%) showed heterogenous enhancement.

Table 3: CT Plain

Nature of lesion		N	% (Total)	% (CT group)
	Hypodense	13	38.2	61.9
	Isodense	1	2.9	4.8
	Hyperdense	7	20.6	33.3
	Total	21	61.8	100.0
Missing	Data	13	38.2	
Total		34	100.0	

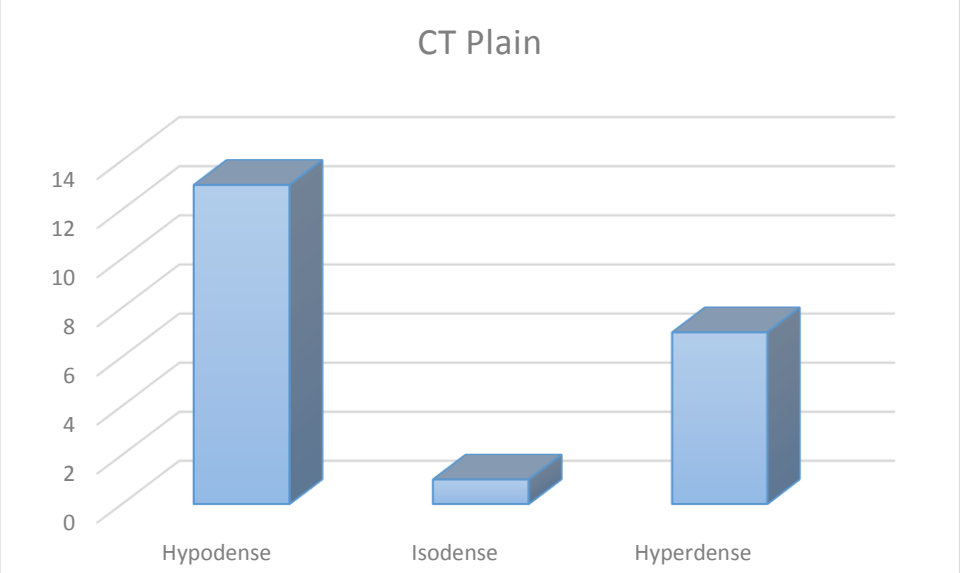
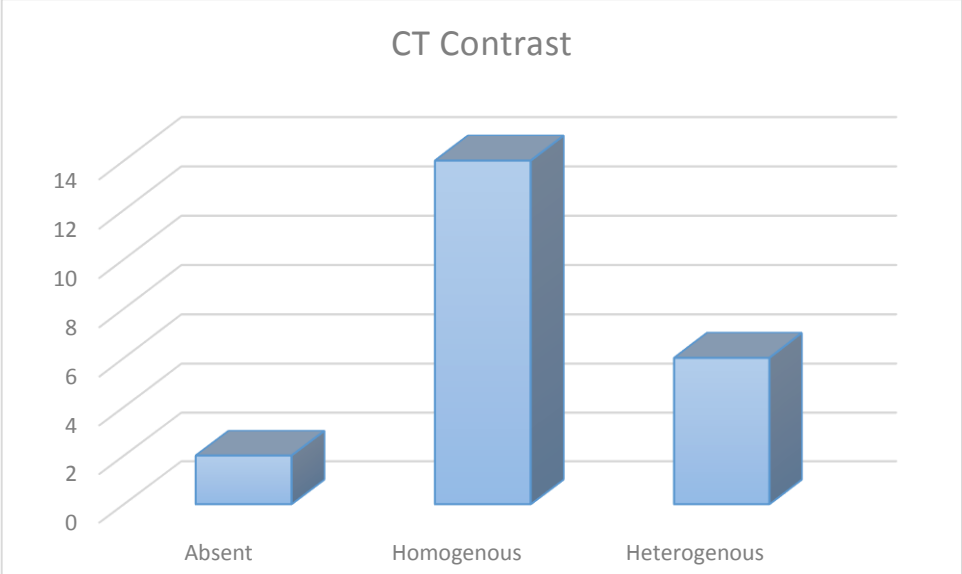


Table 4: CT Contrast

Nature of lesion		N	% (Total)	% (CT group)	
	Absent	2	5.9	9.1	
	Homogenous	14	41.2	63.6	
	Heterogenous	6	17.6	27.3	
	Total	22	64.7	100.0	
Missing	Data	12	35.3		
Total		34	100.0		



MRI data was available for 28 patients. On T1 weighted images 16 cases (57.15) were hypodense and 12(42.9%) was hyperdense. The same lesion on T2 weighted images showed 1(3.6%) hypointense lesion, 2 (7.1%) isointense and 25 (89.3%) hyperintense lesion. Twenty one cases (75%) showed homogenous contrast enhancement and 7 (25%) showed heterogeneous contrast enhancement. Diffusion characteristics could be recorded for 26 cases.

Table 5: MRI T1W

Nature of lesion		**N**	**% (total)**	**% (MRI group)**	
	hypodense	16	47.1	57.1	
	Isodense hyperdense	12 0	35.3 0	42.9 0	
	Total	28	82.4	100.0	
Missing	data	6	17.6		
Total		34	100.0		

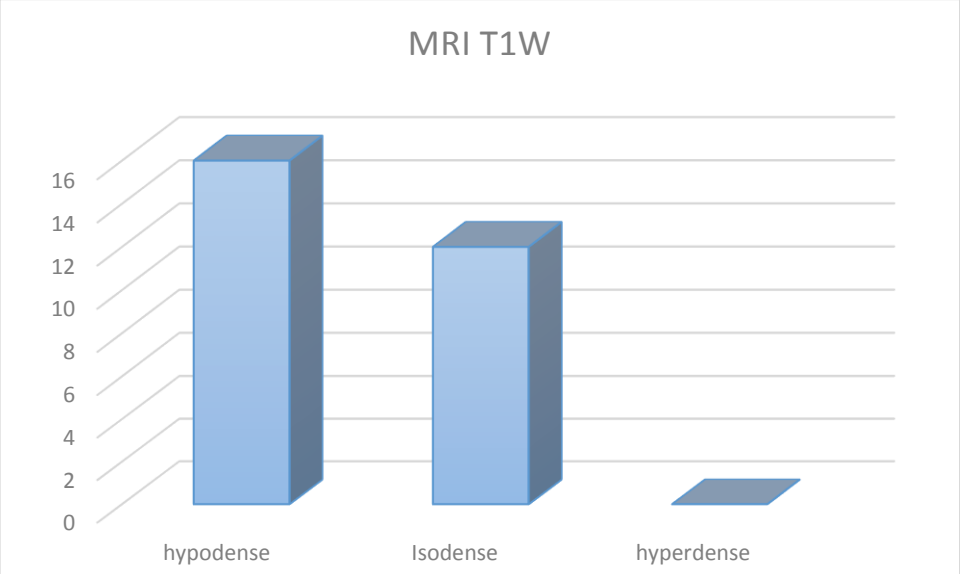


Table 6: MRI T2W

Nature of lesion		N	% (total)	% (MRI group)	
	Hypodense	1	2.9	3.6	
	Isodense	2	5.9	7.1	
	Hyperdense	25	73.5	89.3	
	Total	28	82.4	100.0	
Missing	Data	6	17.6		
Total		34	100.0		

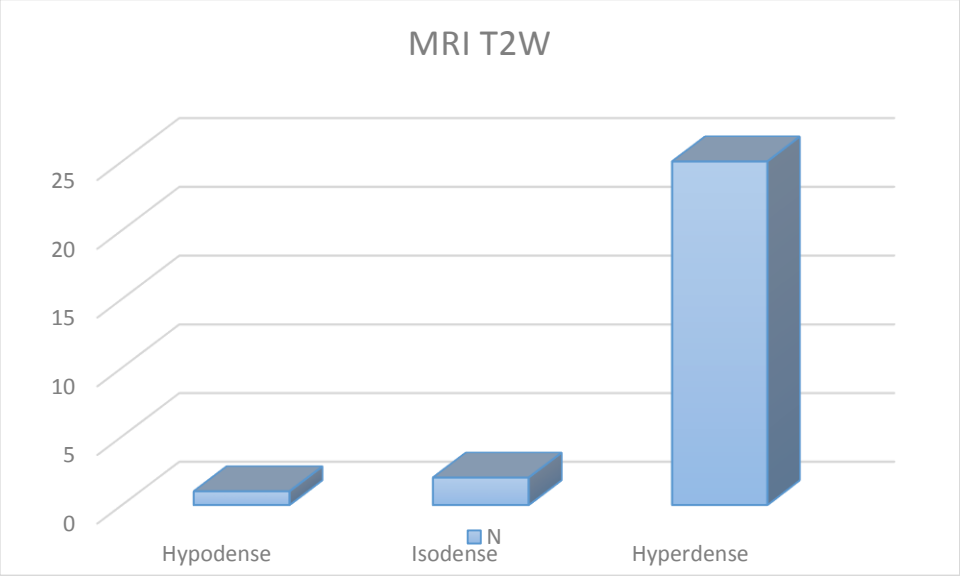
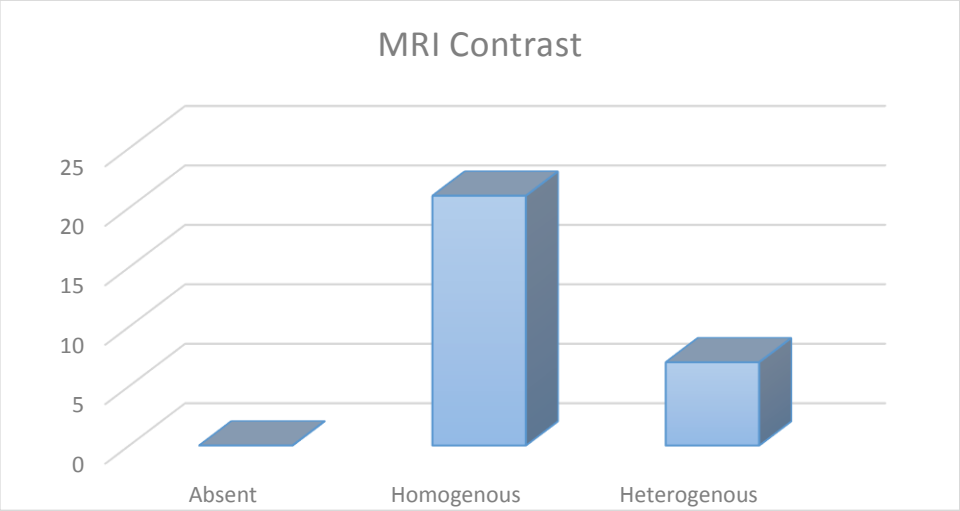


Table 7: MRI Contrast

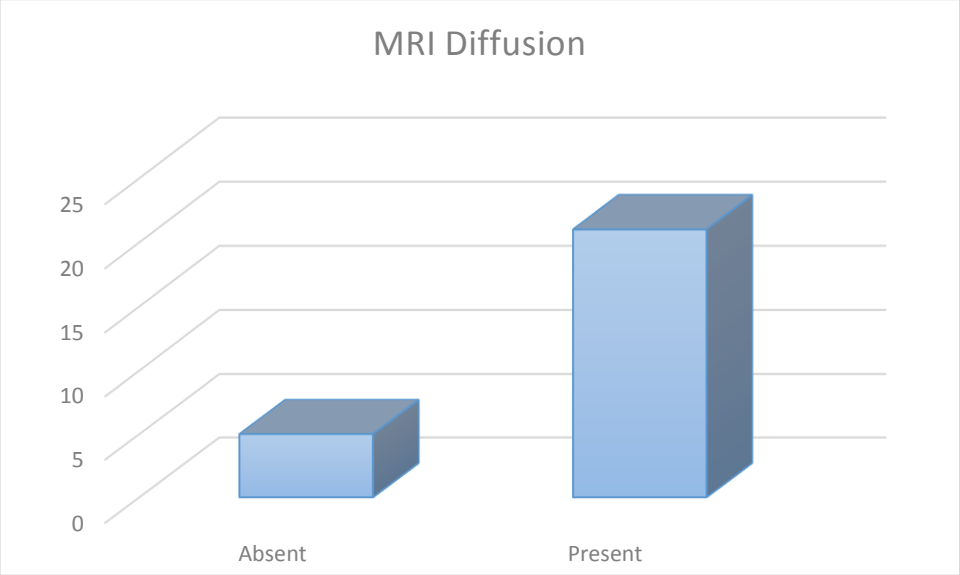
Nature of lesion		N	%	%(MRI group)	
	Absent	0	0	0	
	Homogenous	21	61.8	75.0	
	Heterogenous	7	20.6	25.0	
	Total	28	82.4	100.0	
Missing	Data	6	17.6		
Total		34	100.0		



Five cases (19.2%) had no diffusion restriction and 21 (80.8%) had diffusion restriction. The absolute value of ADC (minimum and mean) was noted in 12 cases. The ADC (min) ranged from 31-982 s/mm^2 with a mean of 381 s/mm^2. ADC (mean) ranged from 464 -1198 s/mm^2 with a mean of 514 s/mm^2. The relation of this ADC value to pre-operative diagnosis and post-operative deficit after surgical intervention will be discussed below.

Table 8: MRI diffusion

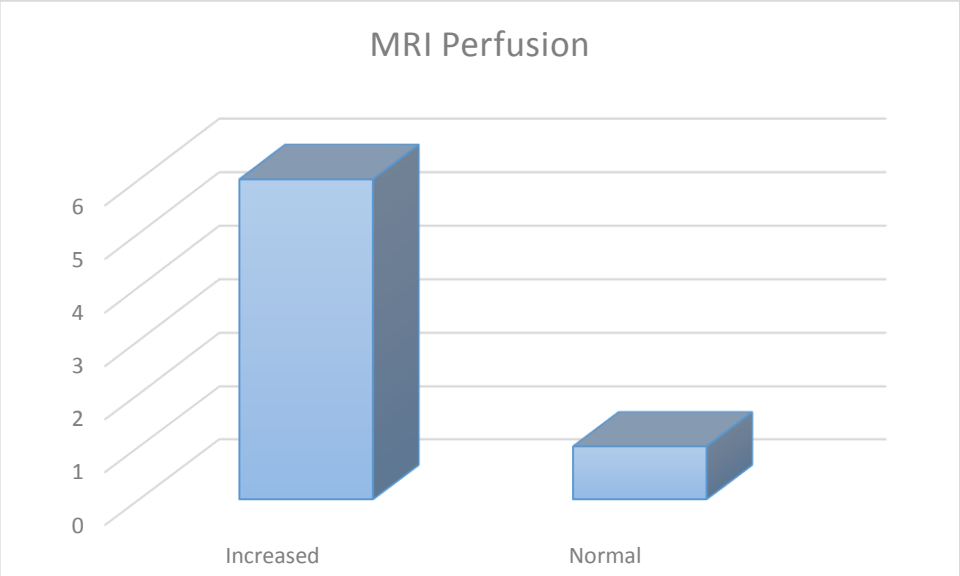
Diffusion restriction		N	%	% (MRI group)	
	Absent	5	14.7	19.2	
	Present	21	61.8	80.8	
	Total	26	76.5	100.0	
Missing	Data	8	23.5		
Total		34	100.0		



Perfusion characteristics details could be obtained only for 7 patients out of which 6 showed raised perfusion. The cerebral blood volume (CBV) in the tumour and representative areas of normal hemisphere were also calculated. CBV_{min} average at 0.75 (range 0.001 to 2.3). Similarly CBV_{mean} ratio was 1.61 (range 0.52 to 3.2).

Table 9: MRI Perfusion

Perfusion		N	%	%(MRI group)	
	Increased	6	17.6	85.7	
	Normal	1	2.9	14.3	
	Total	7	20.6	100.0	
Missing	Data	27	79.4		
Total		34	100.0		



The presenting symptoms encountered in this study are motor deficit, seizures and headache. Focal neurological deficit was present in 13 (38%) of cases while headache in 27 (79%) and seizure in 7 (20.4%). Documented focal neurological deficit was evident in 16 cases (48.5%).

Table 10: Presentation

Presentation		N	%
		1	2.9
	Deficit	2	5.9
	Deficit and seizure	1	2.9
	Headache	15	44.1
	Headache and deficit	9	26.5
	Headache and seizure	3	8.8
	Seizure	3	8.8
	Total	34	100.0

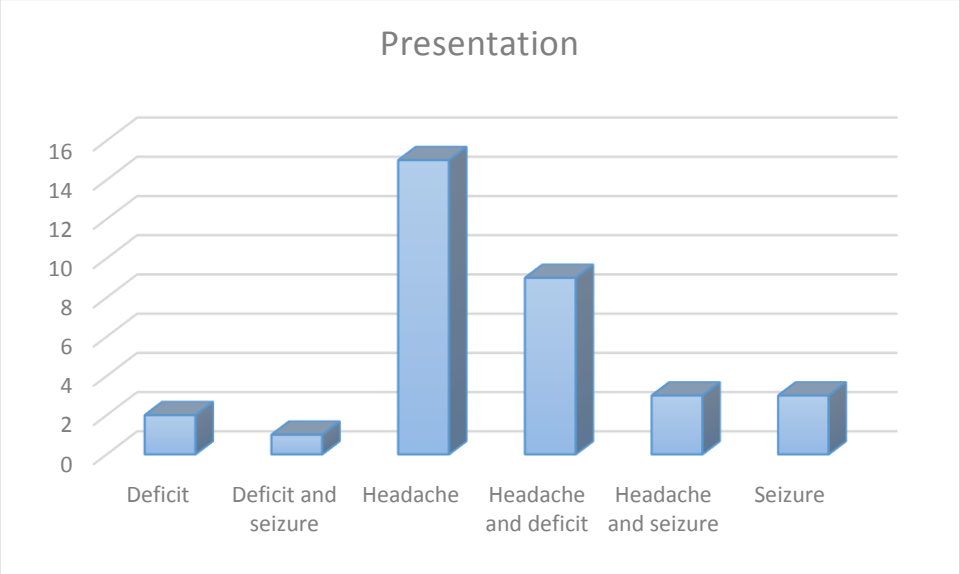
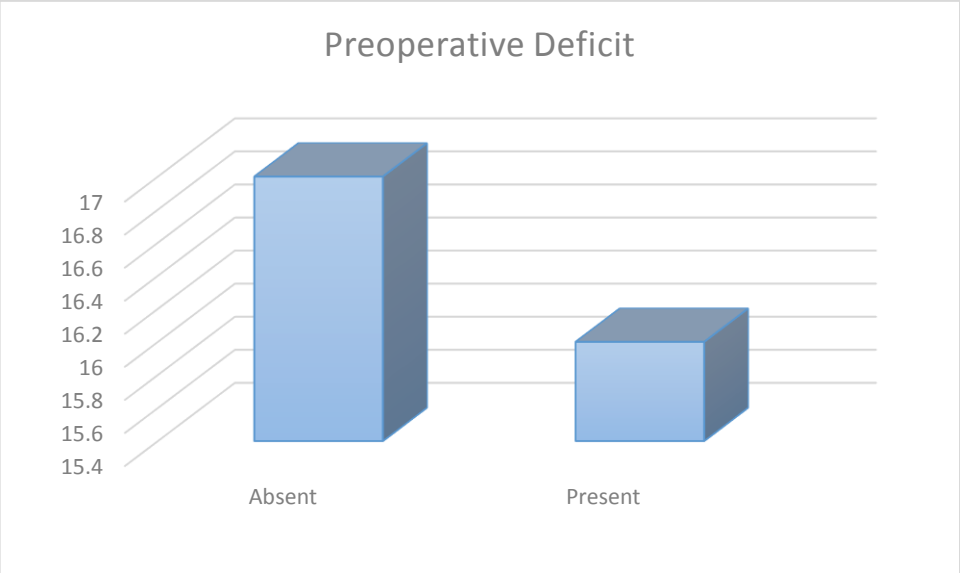


Table 11: Preoperative deficit

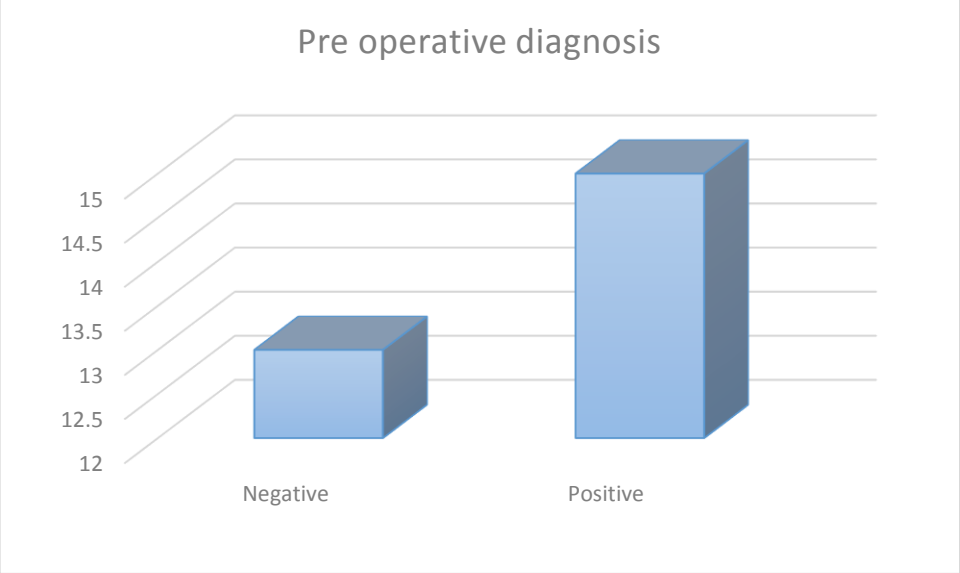
Focal deficit		Frequency	%	% (within group)
	Absent	17	50.0	51.5
	Present	16	47.1	48.5
	Total	33	97.1	100.0
Missing	Data	1	2.9	
Total		34	100.0	



Detailed assessment of the medical records had shed light on the number of cases where preoperative diagnosis and diagnosis of PCNSL was made. Of the total 28 medical records available, 13 cases (46.4%) did not have a working provisional diagnosis of PCNSL while 15 cases (53.6%) had a working diagnosis of PCNSL.

Table 12: Preoperative diagnosis

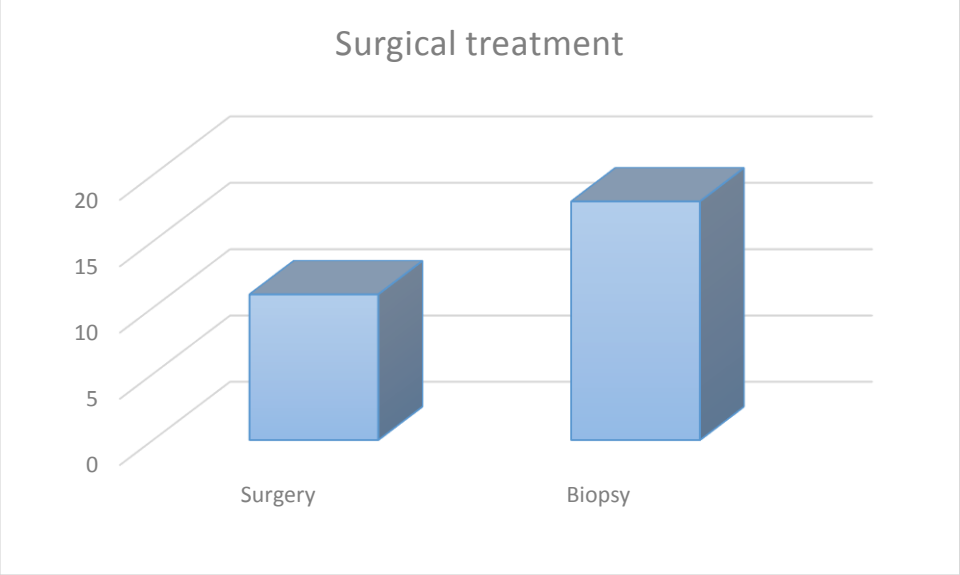
		N	%	% (within group)	
	Negative	13	38.2	46.4	
	Positive	15	44.1	53.6	
	Total	28	82.4	100.0	
Missing	Data	6	17.6		
Total		34	100.0		



Almost all the cases underwent some form of surgical treatment, be it biopsy or decompression. Records were available for 29 cases. Eleven (37.9%) underwent surgical decompression due to multiple reason i.e. mass effect, non eloquent area, worsening sensorium etc. The other 18 cases (62.1%) for tissue diagnosis.

Table 13: Surgical treatment

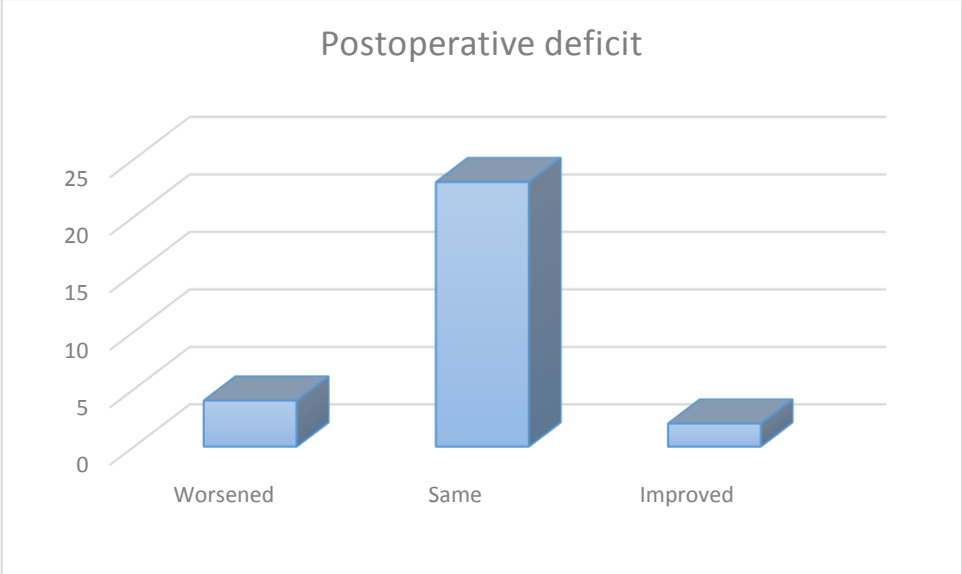
Treatment		N	%	% (within group)
	Surgery	11	32.4	37.9
	Biopsy	18	52.9	62.1
	Total	29	85.3	100.0
Missing	Data	5	14.7	
Total		34	100.0	



After surgery around 23 (79%) did not have any change in their neurological status. Two (6.8%) showed worsening of neurological status but in contrast 4 (13.7%) showed improvement.

Table 14: Postoperative deficit

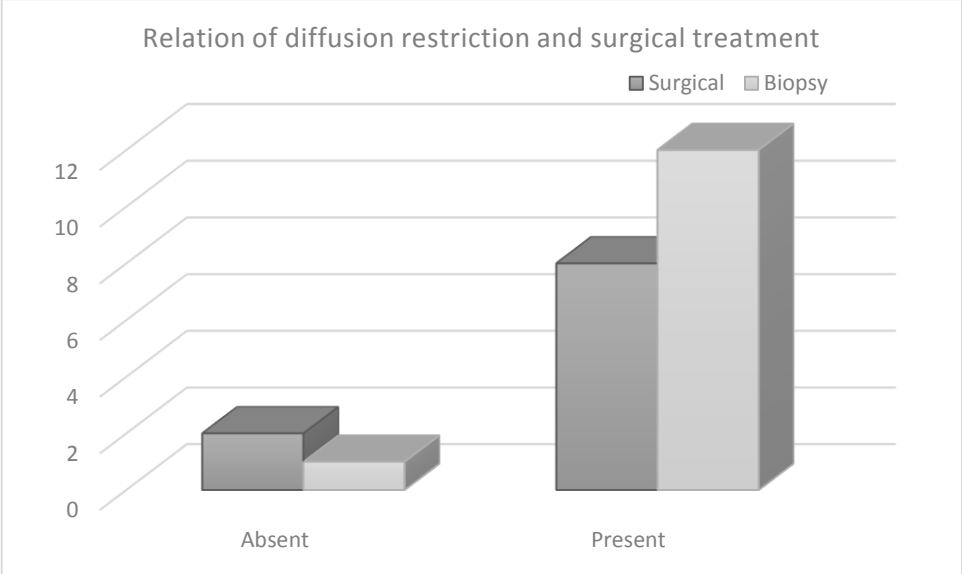
Focal deficit		N	%	% (within group)
	Worsened	4	11.8	13.7
	Same	23	67.7	79.3
	Improved	2	5.9	6.8
	Total	29	85.2	100.0
Missing	Data	5	14	
Total		34	100.0	



There was no significant correlation between the treatment group and diffusion restriction on MRI (p= 0.56). Out of the total 23 patients for whom diffusion characteristics and medical record regarding surgical procedure was present, 10 underwent surgery and of these 2 (20%) had no diffusion restriction and 8(10%) had diffusion restriction. Similarly, 3 (13%) who underwent biopsy had no diffusion restriction and 20 (87%) had diffusion restriction.

Table 15: Relation of diffusion restriction and surgical treatment

			Treatment		Total
			Surgery	Biopsy	
MRI_DR	Absent	Count	2	1	3
		% within MRI_DR	66.7%	33.3%	100.0%
		% within Treatment	20.0%	7.7%	13.0%
	Present	Count	8	12	20
		% within MRI_DR	40.0%	60.0%	100.0%
		% within Treatment	80.0%	92.3%	87.0%
Total		Count	10	13	23
		% within MRI_DR	43.5%	56.5%	100.0%
		% within Treatment	100.0%	100.0%	100.0%



Of the total 29 patients with surgical intervention details, 7 patients (63%) remained neurologically same, 3 (27.2%) worsened and 1(9%) improved in surgery group. Sixteen patients (88.8%) remained neurologically same, 1(5.5%) worsened and 1(5.5%) improved in biopsy group. (p=1.0)

Table 16: Relationship of preoperative diagnosis with treatment

			Treatment		Total
			Surgery	Biopsy	
Preoperative diagnosis	Yes	Count	5	10	15
		% within yes group	33%	66%	100%
		% within preoperative diagnosis group	38%	35%	53%
	No	Count	5	8	13
		% within no group	39%	61%	100%
		% within preoperative diagnosis group	17.8%	28.5%	46.4%
Total		Count	10	18	28
		% within preoperative diagnosis group	35.7%	64.2%	100%

Of the total 15 patients who had a preoperative diagnosis of PCNSL, 5(33%) underwent surgical decompression and 10(66%) underwent biopsy. Similarly in those patients who were not suspected to have PCNSL, 5(39%) underwent surgical decompression and 8(61%) underwent biopsy.

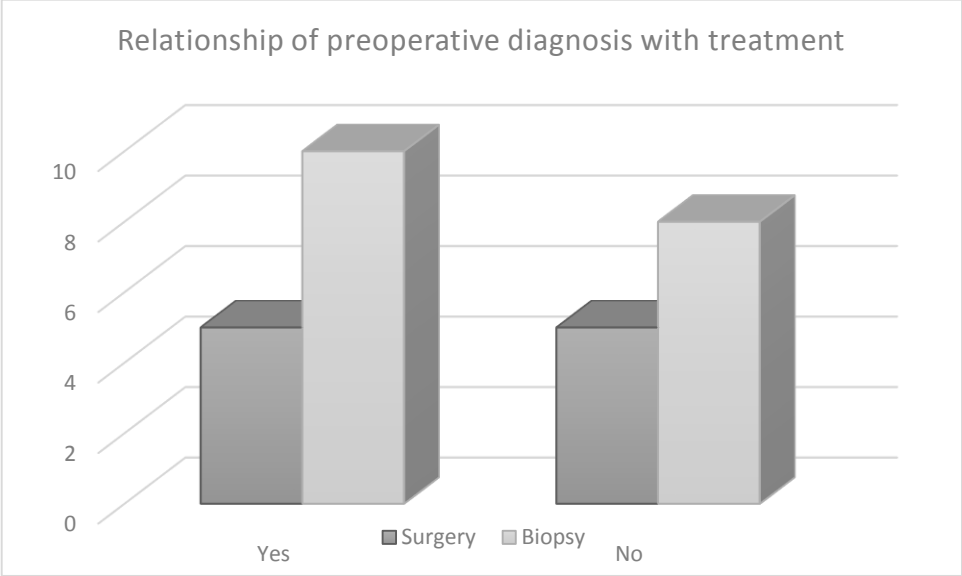
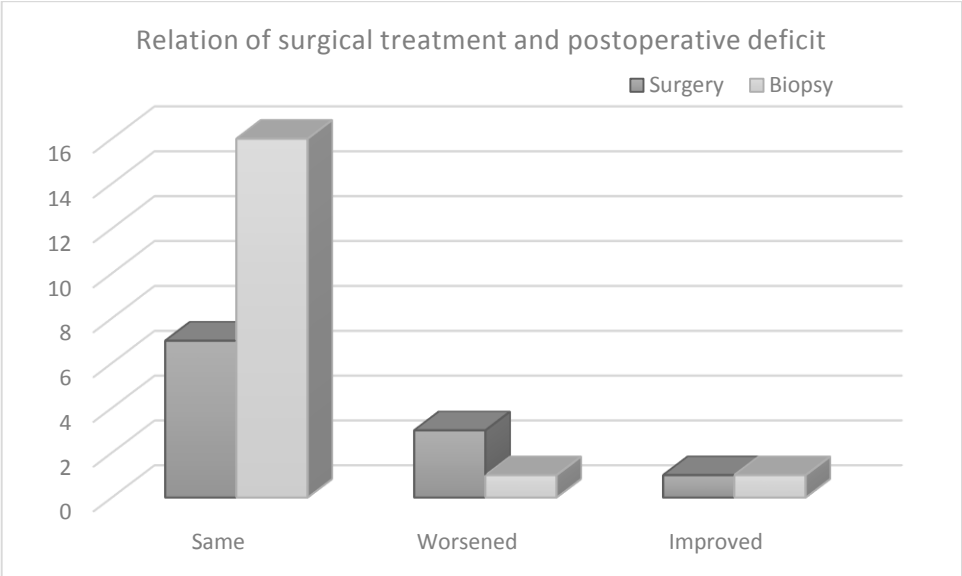


Table 17: Neurological outcome of surgical treatment

				Postoperative deficit		Total
			Same	worsened	Improved	
Treatment	**Surgery**	Count	7	3	1	11
		% within Treatment	63.3%	27.2	9%	100.0 %
	Biopsy	Count	16	1	1	18
		% within Treatment	88.8%	5.5%	5.5%	100.0 %
Total		Count	23	4	2	29
		% within Treatment	79.3%	13.7	6.8%	100.0 %



The following chart compares the absolute value of ADC and CBV with respect to preoperative diagnosis and postoperative deficit

While comparing the ADC value in preoperative diagnosis group, we found that the ADC_{min} = 2.67(SD=1.15), ADC_{mean} =633.3(SD=87.01), CBV_{mean} = 0.99 (SD=0.042), CBV_{min}= 0.56(0.44) in the group where preoperative diagnosis was not there. In the group where preoperative suspicion was there, ADC_{min}= 6.25(SD=2.37), ADC_{mean}= 486.58 (SD=479.26), CBV_{mean}= 1.95 (SD=1.04) and CBV_{min}= 0.93(SD=0.99).

Table 18: Chart for statistical significance between preoperative diagnosis vs ADC and CBV

Preoperative diagnosis		ADC_Min	ADC_Mean	CBV_Mean	CBC_Min
Negative	Mean	2.67	633.33	.9900	.5950
	N	3	3	2	2
	Std. Deviation	1.155	87.008	.04243	.44548
Positive	Mean	6.25	486.58	1.9567	.9333
	N	8	8	6	6
	Std. Deviation	2.375	479.260	1.03842	.98926
P value					
		0.037*	**0.622**	**0.258**	**0.669**

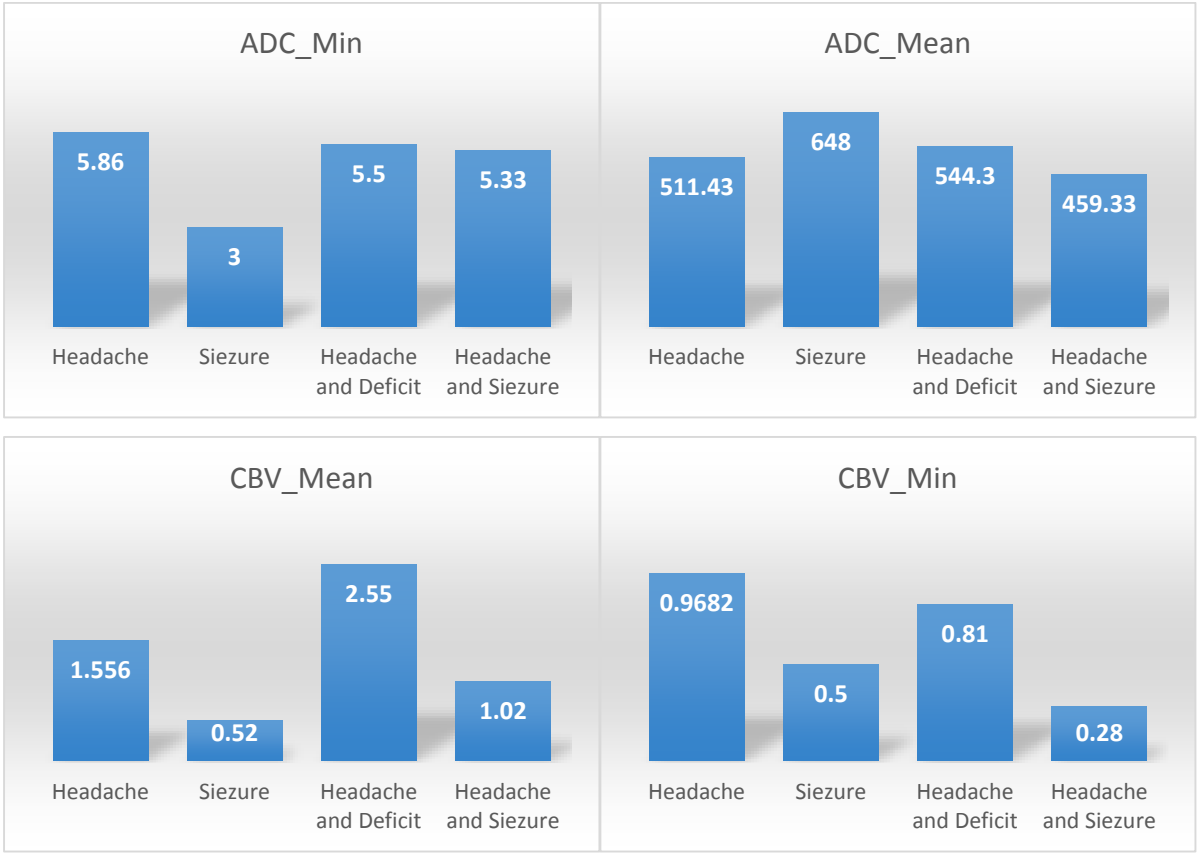
Chart for Preoperative Diagnosis vs ADC and CBV

Clinical presentation in the study group varied from headache, motor deficit and seizure. The ADC value and CBV in different presentation group with their p value is shown in the following table. None of them were clinically significant.

Table 19: Chart showing symptom correlation with ADC and CBV

Presentation		ADC_Min	ADC_Mean	CBV_Mean	CBC_Min
HEADACHE	Mean	5.86	511.43	1.5560	.9682
	N	7	7	5	5
	Std. Deviation	2.410	453.672	.94185	.96150
SIEZURE	Mean	3.00	648.00	.5200	.0500
	N	1	1	1	1
	Std. Deviation	.	.	.	.
HEADACHE AND DEFICIT	Mean	5.50	544.30	2.5500	.8100
	N	2	2	2	2
	Std. Deviation	3.536	703.854	.91924	1.11723
HEADACHE AND SIEZURE	Mean	5.33	459.33	1.0200	.2800
	N	3	3	1	1
	Std. Deviation	3.055	329.370	.	.
P value					
		0.806	**0.987**	**0.382**	**0.810**

Chart for Presentation vs ADC and CBV



Initial presentation of patient with deficit and occurrence of new deficit or worsening of existing deficit was related to the ADC and CBV values. As shown in the following charts we can see that none of ADC or CBV value had any bearing on the preoperative or postoperative deficit.

Table 20: Chart for statistical significance between preoperative deficit vs ADC and CBV

Preoperative deficit		**ADC_Min**	**ADC_Mean**	**CBV_Mean**	**CBC_Min**
Absent	Mean	5.78	480.33	1.3833	.8152
	N	9	9	6	6
	Std. Deviation	2.438	421.051	.94263	.93814
Present	Mean	4.75	592.90	2.0400	.6333
	N	4	4	3	3
	Std. Deviation	2.754	417.420	1.09672	.84719
P value					
		0.513	**0.664**	**0.379**	**0.786**

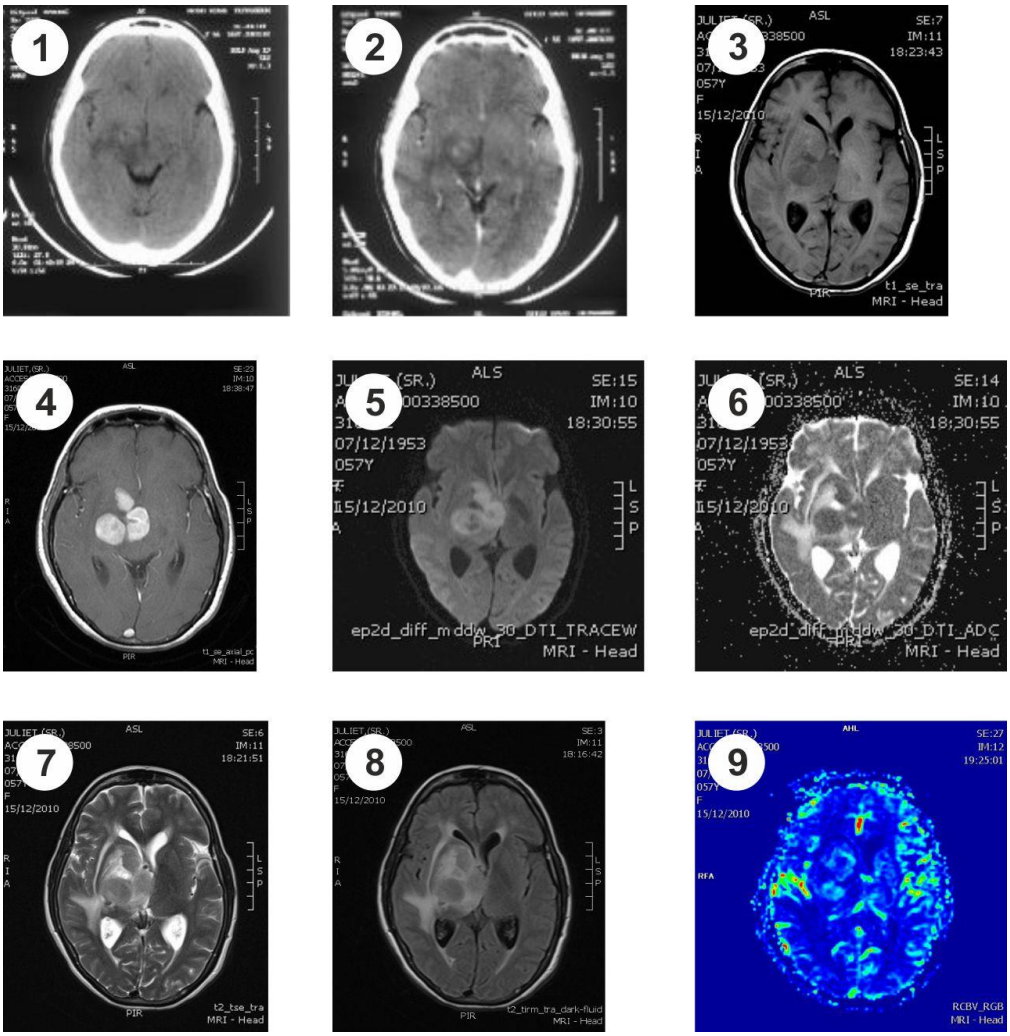
Chart for Preoperative Deficit vs ADC and CBV

Table 21: Chart for statistical significance between postoperative deficit vs ADC and CBV

Postoperative deficit		ADC_Min	ADC_Mean	CBV_Mean	CBC_Min
Worsened	Mean	2.00	632.00	.9600	.9100
	N	1	1	1	1
	Std. Deviation	.	.	.	.
Same	Mean	6.10	477.96	1.7771	.8001
	N	10	10	7	7
	Std. Deviation	2.234	459.324	1.06028	.96938
Improved	Mean	4.00	641.50	1.0200	.2800
	N	2	2	1	1
	Std. Deviation	2.828	133.643	.	.
P value					
		0.197	**0.858**	**0.669**	**0.872**

Chart for Postoperative deficit vs ADC and CBV

7 Representative images of PCNSL



FIGURES: **Image 1**- Plain CT scan showing heterohypodense lesion. **Image 2**- CT Contrast scan showing heterogenous contrast enhancement. **Image 3**- MRI T1 showing hypointense lesion**. Image 4**- MRI T1 contrast showing homogenous contrast enhancement. **Image 5 and 6**- Diffusion restriction with corresponding ADC. **Image 7 and 8-** MRI T2 and Flair showing hyperintense lesion. **Image 9**- CBV sequence for persion shows marginally elevated perfusion.

8 Discussion

8.1 Standard of care:

PCNSL is a very rare but aggressive tumour with a high mortality rate. The standard of care is chemo radiation after tissue diagnosis. Therapy ranges from single drug regime, multidrug regime to WBRT. Methotrexate is the preferred drug at dose 3.5mg/m^2. Other drugs used are vincristine, procarbazine, temozolamide, rituximab and dexamethasone. These drugs are used alone or with WBRT. The response rate to single drug regime using MTX is 52-88%, to multiple drug regime combining MTX and other chemotherapeutic drugs is 70-94%, and to WBRT is ~90%. The two-year survival rate of the patients who received single and multiple drug MTX therapy combined with WBRT was 58-72% and 43-73%, respectively[54]. The total radiation dose under WBRT is 45Gy. Such high dose comes with the cost of neurocognitive decline. But before any treatment protocol is personalised for the patient, tissue diagnosis is mandatory.

8.2 Role of imaging in preoperative diagnosis

There are no definite diagnostic imaging technique for diagnosis and physicians heavily rely on surgical biopsy. This time to biopsy and delay in management has a negative impact on outcome. Formulating a diagnostic protocol which would make use of only imaging without the need of biopsy will be very useful as treatment can be started immediately, economically efficient especially in resource challenged country like ours. Studies are now targeting MRS, PWI and DWI for diagnosis and predictors of response to treatment and overall outcome[67]. This study focuses on the use of imaging for diagnosis and assessment perioperative morbidity.

The mean age of presentation in this study was 47 years which is concordant with other published case series[,55,56,57]. Our series showed male preponderance (male:23 vs female:11) as shown similarly by other series series[54,55,56,57,58]. It can be seen both supratentorial and infratentorial. We found most of the lesion were supratentorial with majority involving the parietal lobe. Kuker et al in his 2006 paper demonstrated the supratentorial distribution of the lesion mainly in the cerebral hemisphere[59]. Brainstem, spinal cord and cerebellar involvement is rare which was the case in our observation also[60]. Bleed and calcification was conspicuously absent in PCNSL[61]. We observed that none of our cases demonstrated haemorrhage or calcification. But sometimes calcification may be seen in patients who have undergone radiotherapy or chemotherapy[62]. PCNSL is described as very hypercellular tumour and hence it is expected to be hyperdense on plain CT. But we found only 33% hyperdense and around 68% hypodense. Contrast enhancement is a hallmark feature of PCNSL which was seen in approx. 90% of cases in our study on CT scan similar to other published series[63,64]. A negative findings on contrast CT scan cannot rule out lymphoma, because false negative results have

also been reported[65,66]. Similarly on contrast MRI 100% showed enhancement. This was concordant with Mansour et al[67] who demonstrated>80% contrast enhancement. But it not a rule and lymphoma cases with flair hyperintensity with non contrast enhancing lesion can be seen in the literature[65]. It is also stated that contrast enhancement most of time is homogenous except in immunocompromised cases where central necrosis can be seen[59]. In our case 63% was homogenous on CT and 75% on MRI. Because of hypercelluarity of the PCNSL they are normally isodense on T1 and T2 weighted images[67]. In our series most of the lesion were equally distributed between hypointense and isointense on T1 weighted images. On T2 weighted images 75% was hyperintense.

Table 22: Typical imaging features of primary and secondary CNS lymphoma

	Primary CNS lymphoma	**Secondary CNS Lymphoma**
Primary site of CNS involvement	Brain parenchyma, -100%	Brain parenchyma. -1/3; leptomeninges. -2/3
Typical location CT findings	Parenchymal CNS lymphoma Periventricular and superficial brain regions lso- or hypodense lesions with marked CE	Leptomeningeal CNS lymphoma leptomeninges leptomeningeal, subependymal. dural. or cranial nerve CE; superficial cerebral lesion; communicating hydrocephalus
MRI findings	Tl: hypo- or isointense lesions, moderate-marked CE T2: iso- or hyperintense lesions; often hypointense to gray matter	leptomeningeal, subependymal, dural, or cranial nerve CE; superficial cerebral lesion; communicating hydrocephalus
Enhancement pattern	Non-AIDS patients: homogeneous CE, -90%; ring-CE, -0%-13% AIDS patients: i rregular CE common; rrng-CE. -75%	leptomeningeal, subependymal, dural, or cranial nerve CE

Though PCNSL have very definite appearances on CT and MRI, none of them are characteristic enough to make diagnosis with doubt. Many lesion like GBM, metastases, meningioma, abscess, stroke, multiple sclerosis and toxoplasmosis share the imaging findings[65,68,69]. As we know that PCNSL is a hypercellular tumor and increased cellularity dictates diffusion restriction[70]. Eighty percent of lesion in this study showed diffusion restriction. This feature as mentioned above is shared with GBM, abscess and ischemic stroke. But higher restriction and lower ADC values are seen in PCNSL than in other causes[71,72,73]. Many studies have come up recently comparing the ADC value of contrast enhancing area and prognosis.

Table 23: Advanced imaging techniques in CNS lymphoma

Imaging Method	**Findings in CNS Lymphoma**	**Potential Value as Diagnostic Tool in CNS Lymphoma**
MRI/CT Diffusion MRI/diffusion tensor imaging	Restricted diffusion in lesions (hyperintense on DWI and hypointense on ADC maps) Decreased FA values in lesions	Differentiation of CNS lymphoma and malignant glioma/ metastases
Perfusion MRI/perfusion CTI permeability MRI	Low maximum CBV Characteristic intensity time curve related to leakage of contrast into the interstitial space	Differentiation of CNS lymphoma and malignant glioma/ metastases Assessment of microvascular tumor permeability relevant for diagnosis prognostication and therapy
MR spectroscopy	Elevated lipid peaks and high Cho/Cr ratios	Differentiation of CNS lymphoma and some gliomas and CNS lymphomas and toxoplasmosis/PML in AIDS patients
High-resolution SWI MRI with new contrast agents	Blood products and calcifications are rare findings MRI with iron oxide nanoparticles: lesions enhance less than with gadolinium	Differentiation of CNS lymphoma and high-grade gliomas Differentiation of CNS lymphoma and MS
Metabolic imaging PET	FOG PET methionine PET: hypermetabolrc lesions with increased uptake of FOG or methionine	Differentiation of CNS lymphoma and gliomas / metastases / meningiomas Early evaluation of therapeutic response
SPECT/SPET	Hypermetabolic lesions with high N isopropyl iodoamphetamine or thallium-201 uptake	Differentiation of AIDS-related CNS lymphoma and infectious intracranial lesions

Lower ADC value was directly proportional to overall survival and inversely proportional to tumor cellularity. It was also showed that the tumor ADC value falls after treatment, thereby investigating the potential of diffusion imaging on surveillance[74]. We tried to deduce importance of the ADC value with respect to the preoperative and postoperative focal neurological deficit. We did not find any correlation between the two groups. The preoperative diagnosis of PCNSL based on history and examination was higher in diffusion restricted group and this was statistical significant (p=0.03). The presentation and type of surgical treatment instituted was also not significantly related to ADC.

Sr no.	Study	Number of cases	Conclusion
1	Blake Johnson et al(1997)[76]	23	They found statistically significant correlation between a higher degree of necrosis histologically and hyperintensity on T2-weighted MR images
2	R F Barajas Jr et al(2010)[74]	18	ADC value is inversely proportional to cellularity of tumor and directly proportional to progression free survival and overall survival.
3	Mansour et al[67]	21	In the proper clinical and radiological setting, suggesting the diagnosis of PCNSL can help institute proper treatment in a timely fashion and avoid unnecessary attempts at surgical resection and the associated morbidity
4	Our study	34	Preoperative diagnosis can be made to some extent with the help of diffusion restriction on MRI imaging

Tumor growth is directly proportional to angiogenesis. These developing vessels are immature and they confide different characteristic to the tumor tissue. In case of PCNSL, it imparts brilliant contrast enhancement and because of the immature leaky vessels there is massive leak of contrast into the interstitial space which is shown in the perfusion curve as rapid return to below baseline and then normalization. The relative CBV in lymphoma cases are low as compared to GBM. Our study also found a low CBV ratio (6 out of 7 had normal perfusion). CBV did not have any correlation with type of surgical treatment, preoperative deficit and postoperative deficit.

The most common presentation in my cohort was headache followed by headache with focal neurological deficit. Batchelor et al has found in their series of PCNSL cases, 70% presented with focal neurological deficit[63].

According to the literature, the only surgical treatment required is biopsy. Surgical intervention is some time indicated. Surgery has limited role in the management because of diffuse infiltrative nature of disease, response of disease to steroid and radiation and poor overall outcome. In our study total 29 patients underwent surgical intervention of which 11 underwent surgery and 18 underwent biopsy. The post-operative complication like new/worsening of focal deficit was not clinically different in both the groups. Similar results were published by Tomlinson et al where out of 89 cases of PCNSL, 42 underwent and craniotomy and decompression and survival was not significantly different between the groups[75].

Table 24: Craniotomy for PCNSL

				Extent of Reseclion			Postop Survival	
Author, Yr	No. of Patients	Study Type	Cranio -torny	Subtotal	Gross Total	Unknown	Craniotomy	Biopsy
Murray et al., 1986	693	lit rev	398				median = l mo for 85 pts w/out adj ther	NA
Murray et al., 1986	11	retr chart rev	7	3	4		53 mos for pts w/ gross-total resection	15 mos
Davies et al.,1994	1	retr chart rev	1	0	1	0	13 mos for pts w/ subtotal resection	NA
Tomlinson et al., 1995	89	retr chart rev	42				240 mos	24.5 mos
Sonstein et al., 1998	1	retr chart rev	1	0	1	0	60 mos	NA
Bataille et al., 2000	248	retr chart rev	116	45	66	5	56.6% of pts alive at 12 mos	48.6% of pts alive at 12 mos
Bellinzona et al., 2005	32	retr chart rev	25	10	15	0	NA	NA

There is also trend in transition from open surgical biopsy to endoscopic biopsy with comparable results. Piero Andera et al published his experience with 60 patients who underwent endoscopic biopsy and recommended to consider endoscopic biopsies as an alternative to open surgical biopsy.

All said and discussed, the final prognosis of the patient depends on the chemotherapy and radiotherapy one takes after making the diagnosis. Though these treatment modalities have some initial response, the final outcome of the disease is poor.

Merits of study

This study of imaging correlation with preoperative diagnosis will act a pilot study for future large prospective study for formulating a diagnostic criteria using MRI advanced sequences which can reduce the waiting period for patients before they take the definitive treatment. This would be of great help to developing countries like India.

Limitations of our study

Relatively small cohort of patients with limited “survival” follow up and hence not adequately powered to reach definitive statistical conclusions. However the study is one of its kind in an Indian cohort of patients and in a “resource challenged nation “avoiding a biopsy for diagnosing PCNSL so as to initiate early primary chemo radiotherapy can be of great significance. Thus, the study introduces and explores an important concept to use imaging parameters to establish preoperative diagnosis of PCNSL precluding a biopsy. However, it needs further validation by a larger cohort of patients and a suitably designed randomized control study including survival data in two groups of patients, one with upfront primary chemo radiotherapy based on imaging diagnosis of PCNSL compared with those who received therapy subsequent to histological diagnosis.

9 Conclusion

We conclude that MRI and CT characteristics alone could not be used as "stand alone "means to establish a preoperative diagnosis of primary CNS lymphoma without a histological diagnosis to initiate primary chemo radiotherapy which is the current standard of care in PCNSL. However certain MRI features like ADC_{min} were significant in our study in establishing a pre-operative diagnosis in comparison to other parameters like cerebral blood flow. CT characteristics were not useful in establishing a pre-operative diagnosis of PCNSL.

Our study introduces and explores an important concept of utilizing imaging parameters to establish preoperative diagnosis of PCNSL precluding a biopsy. However, it needs further validation by a larger cohort of patients and a suitably designed randomized control study including survival data in two groups of patients, one with upfront primary chemo radiotherapy based on imaging diagnosis of PCNSL compared with those who received therapy after histological diagnosis.

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11 Appendix

Sr. No	Name	Age	Sex	Hosp No	LOCATION	SIZE cm	CT Nature	CT bleed	CT calcifi-cation	CT contrast	MRI T1	MRI T2	MRI PER	MRI DR	MRI CE	Treat-ment	Preop Suspi-cion	Present -ation	per op deficit	post of deficit	ADC MIN	ADC MEA N	CBV MEA N	CBC MIN
1	Haneef	55	m	286687	LEFT PARIETO OCCIPITAL	5.9X4. 1	1	0	0	2						1	0	1	1	-1				
2	Selvarani	26	f	291027	Left parietal	4x3x4	1	0	0	2	2	2		1	1	1	0	1,3	1	1	284	547	1.02	0.28
3	Elsby Baby	47	f	294300	rt basal ganglia	3x2x1	3	0	0	2	2	3		1	1	1	0	1,3	1	0				
4	Mohd Basheer	45	m	298574	rt parieto temporal	4x2x3	3	0	0	1	1	2	1	1	1	1	0	1	0	0	471	721		
5	Sreekumar	39	m	300696	left temporo pareital	4x3.6	1	0	0	1	1	1	1	1	1	2	1	1	0	0	86	68	3.1	2.3
6	Prema	30	f	307982	rt fronto parietal	3x2x1	1	0	0	0	2	3			2	2	0	1,2	1	0				
7	sumangala	62	f	309665	rt cingulate		1	0	0	1	1	3		1	2	2	1	1,2	1	0	868	1042	3.2	1.6
8	juiet	57	f	316092	rt basal ganglia						1	3	1	1	1	2	0	1	0	-1	298	632	0.96	0.91
9	jerome fernandes	43	m	324453	LEFT PARIETO OCCIPITAL						1	3	1	1	1	2	1	1	0	0	982	1198	1.32	0.13
10	surendran	42	m	331574	splenial	5x4x2	1	0	0	1	1	3		1	1	2	1	1	0	0				
11	lalgi george	36	m	335078	left frontal						1	3	1	0	1	1	0	2	1	0				
12	sukumaran nair	52	m	340277	brainstem						1	3	1	0	1	1		1	0	0	729	836		
13	papaye	55	f	253977	rt thalamic		1	0	0	1														
14	khunt anghita	13	f	254632	rt thalamic						2	3		1	1			1	1	0				
15	ramesh nair	36	m	362900	rt temporal	3x3	1			1	1	3	3	1	1	1	1	1	0	0				
16	pradeep Kumar	30	m	249630	rt thalamic					1	1	3		1	1	1	1	3	0	0	368	648	0.52	0.05
17	Manikantan nair	47	m	314284	left temporal						1	3		1	1	1	1	3	0	0				
18	Bala subramaniam	42	m	315653	left occipital		1	0	0	1						2	1	1,2	1	0				
19	victor andrew	40	m	321179	left temporal						2	3		1	1	2	1	1,3	1	1	645	736		
20	devasi	76	f	9906169	rt frontal		3	0	0	1	1	3			1			1,2	1	-1				
21	thankaman	52	f	217286	b/l frontal		1	0	0	1						2	0	1,2	1	0				
22	saada ibrahim	31	m	216957	rt parieto temporal	3x2x4					2	3		1	2	2	0	3	0	0				
23	muthaiah	63	m	219179	rt occipital		1	0	0	2						2	0	1	0	0				
24	gopinathan nair	62	m	224966	rt parieto occipital		1			2						2	0	1,2	0	0				

Sr. No	Name	Age	Sex	Hosp No	LOCATION	SIZE cm	CT Nature	CT bleed	CT calcifi-cation	CT contrast	MRI T1	MRI T2	MRI PER	MRI DR	MRI CE	Treat-ment	Preop diagnosis	Present -ation	per op deficit	post of deficit	ADC MIN	ADC MEAN	CBV MEAN	CBC MIN
25	sudharshan nair	64	m	229197	corpus callosum						1	3		0	1			1	1	0				
26	rameshan	45	m	238423	temporal		1	0	0	1	1	3		1	2	1	1	1,3	0	0	82	95		
27	rajendran	37	m	249124	LEFT PARIETO OCCIPITAL		3			2	2	3		1	1	2	1	1	0	0	52	59	1.7	1.5
28	rajam	46	m	258485	b/l frontal	4x4	2	0	0	0	2	3		1	2	2	1	1	0	0				
29	kutubdeen	61	m	259141	splenial		3			1	2	3		1	1	2	1	2	1	0				
30	dominic	52	m	260497	corpus callosum						1	3		1	1	2	1	1,2	1	-1				
31	ramadevi	54	f	264675	rt pareital	5x3x4					1	3		1	2	1	1	1,2	1	0	36	46.6	1.9	0.02
32	sosamma	60	f	265548							2	3		0	1			1	0	0	61	66	0.7	0.001
33	abraham	50	m	267854	LEFT PARIETO OCCIPITAL	2x3	3	0	0	1	2	3		0	1	2	0	1	0	0				
34	mohanlal	35	m	277311	rt thalamic	5x3x2.5	3	0	0	1	2	3		1	2	2	0	1,2	1	0				

Legends:

CT scan nature: 0=hypodense, 1= isodense, 2=hyperdense CT scan bleed: 0=absent, 1=present CT calcification: 0=absent, 1=present CT contrast: 0=absent, 1=homogenous, 2=heterogeneous MRI-T1: 0=hypointense, 1= isointense, 2=hyperintense MRI-T2: 0=hypointense, 1= isointense, 2=hyperintense MRI-Contrast: 0=absent, 1=homogenous, 2=heterogeneous MRI diffusion: Ratio of diffusion values and ADC MRI perfusion: absolute values indicated	Treatment: 1= surgery, 2 = biopsy Preoperative diagnosis: 0= NO, 1= YES Preoperative deficit: 0= absent, 1= present Postoperative deficit: 0 = worsened, 1= same, 2= improved.

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