"COMPARISON OF ARTERIAL SPIN LABELING TECHNIQUE WITH DYNAMIC SUSCEPTIBILITY CONTRAST TECHNIQUE OF PERFUSION MR IMAGING IN ENHANCING BRAIN TUMORS"

By

(REG NO.BS0119009)

Dissertation

Submitted to the

KLE Academy of Higher Education and Research

Belagavi, Karnataka.

In partial fulfillment of the requirements for the degree of

M.D.

IN

RADIO-DIAGNOSIS

DEPARTMENT OF RADIO-DIAGNOSIS

J. N. MEDICAL COLLEGE,

BELAGAVI -590010. KARNATAKA

APRIL 2022

KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH, BELAGAVI, KARNATAKA

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LIST OF ABBREVIATIONS

CNS	Central nervous system
CBTRUS	Central brain tumor registry of united states
WHO	World health organisation
CT	Computed tomogram
MRI	Magnetic resonance imaging
DWI	Diffusion weighted imaging
MRS	Magnetic resonance spectroscopy
DTI	Diffusion tensor imaging
DSC	Dynamic susceptibility contrast
ASL	Arterial spin labeling
DCE	Dynamic contrast enhanced
DNET	Dysembryoplastic neuroepithelial tumor
GBM	Glioblastoma multiforme
T1WI	T1 weighted image
T2WI	T2 weighted image
FLAIR	Fluid attenuation inversion recovery
GBCA	Gadolinium based contrast agents
AIF	Arterial input functioning
CBF	Cerebral blood flow
CBV	Cerebral blood volume
rCBF	Relative cerebral blood flow

rCBV	Relative cerebral blood volume
IDH	Isocitrate dehydrogenase
HGG	High grade glioma
LGG	Low grade glioma
GM	Grey matter
WM	White matter
PET	Positron emission tomography

ABSTRACT

BACKGROUND:

MR perfusion has significant role in evaluation of intracranial neoplasms which helps to estimate neo-angiogenesis of tumor for grading, guiding stereotactic biopsies, surgical planning, differentiating recurrent tumor from radiation necrosis, differentiating high grade glioma from metastases / lymphoma and therapeutic response assessment for new clinical trials on anti-angiogenic agents. Three MR perfusion techniques are currently in use: dynamic contrast-enhanced (DCE), dynamic susceptibility contrast (DSC), and arterial spin labelling (ASL).

DSC technique is most widely used and studied in literature with extensive clinical experience which requires contrast administration. Arterial spin labelling (ASL) is a novel technique which has been studied in the recent years for clinical use. It provides qualitative and quantification evaluation of CBF maps by using arterial water as an endogenous tracer by labelling blood water protons in cerebral arteries without the requirement of contrast agent.

AIM AND OBJECTIVES:

To evaluate the use of ASL as an alternative to DSC MR perfusion in imaging of brain tumors

To compare ASL derived rCBF ratios with DSC derived rCBF ratios of MR Perfusion imaging in the assessment of brain tumors (primary and metastatic).

MATERIALS AND METHODS

This is an observational study done on patients with brain tumors (primary and metastatic) who underwent MRI BRAIN PLAIN AND CONTRAST with PERFUSION IMAGING including ASL and DSC techniques using 3T MRI SCANNER ‘MAGNETOM Spectra (manufactured

by Siemens) in the department of RADIODIAGNOSIS at KLE's Dr. Prabhakar Kore Hospital & MRC, Belagavi. Image processing is done on a Siemens Multi-Modality Work station with Siemens software NUMARIS/4, version Syngo MR E11.

Perfusion image processing

For quantitative evaluation of DSC, region of interest (ROI) of 3 mm^2 will be placed in the region of tumor showing maximum perfusion value in rCBF maps avoiding the regions of necrosis, vessels, calcifications, hemorrhage and cyst. For normalization, to avoid age and patient dependent CBF variations ROI of 3 mm^2 is placed on the contralateral normal white matter (WM) and grey matter (GM). rCBF ratios are obtained by dividing rCBF value of tumor by contralateral normal white matter and grey matter. In rCBV perfusion maps, ROI of 3 mm^2 is placed in the same area and size that was used in rCBF ratio and similarly in the contralateral white matter to calculate rCBV ratios.

For quantitative evaluation on ASL, rCBF ratios are calculated in the similar way as mentioned above for DSC perfusion. rCBF values are derived from the same site and same size (ROI of 3 mm^2) which was used for DSC perfusion in lesion and contralateral health grey matter & white matter.

Statistical data analysis:

Correlation and comparison of ASL rCBF (GM) with DSC rCBF (GM) and ASL rCBF (WM) with DSC rCBF (WM) using dependent t test. Comparison of DSC rCBF (WM) and DSC rCBV (WM) ratios in low grade gliomas and high grade gliomas. Correlation and comparative analysis using scatter plot and box plot graphs and $p < 0.05$ is considered statistically significant.

RESULTS

- Our study recruited 37 cases of brain tumors (primary and secondary) who satisfied the inclusion criteria in all the age groups revealed 11 high grade gliomas, 5 low grade gliomas, 9 meningiomas, 5 metastases, 2 DNET, 1 medulloblastoma, 1 hemangioblastoma, 1 ependymoma, 1 ganglioglioma and 1 CP angle schwannoma.
- Our study showed significant correlation between ASL rCBF ratio with DSC rCBF ratio of lesion with grey matter and white matter in all the cases. Our results were consistent with the previous comparative studies between ASL and DSC techniques.
- Our study demonstrated the mean rCBV ratio of 2.5 for low grade glioma and 9.5 for high grade glioma with significant difference in rCBV ratios for low grade and high grade gliomas.
- Our data also showed significant difference in rCBF ratios for high and low grade gliomas. We obtained mean rCBF ratio (lesion and white matter) by ASL & DSC of 10.9 & 10.8 for high grade gliomas and 3.3 & 3.06 for low grade gliomas respectively.

INTERPRETATION AND CONCLUSION

- ASL is non invasive, repeatable and low cost MR perfusion technique with acceptable acquisition time in 3T MR scanner and allows to derive CBF maps comparable to DSC technique without requirement of contrast administration.
- ASL is a good alternative technique to DSC which can be used in individuals who are contraindicated to contrast agent in patients with anaphylaxis to contrast, pregnancy, lactation & renal disorders, in patients requiring repeated follow ups, pediatric imaging and also for clinical trials of new anti-angiogenic drugs.

- Perfusion imaging is valuable complementary technique in the diagnostic differentiation of high grade and low grade gliomas in the preoperative assessment. rCBV ratios and rCBF ratios can be used for histopathological grading of gliomas.

Keywords:

Brain tumors, MR perfusion, ASL, DSC, CBF, CBV.

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1: INTRODUCTION

Brain tumors are leading cause of morbidity & mortality in all age groups, globally. Posing huge social and economic burden on health care systems, mainly because of uncertain & dismal prognosis, increased treatment cost and need for frequent follow up. Proper treatment planning for neurosurgery, radiotherapy, chemotherapy and monitoring usually help in improving quality and expectancy of life in brain tumor patients.

According to Government of India 2019 data, incidence of central nervous system (CNS) tumors ranges from 5-10 per 100,000 population and is showing an increasing trend [1]. Prevalence of brain tumors in India is approximately 2% of all malignancies [2]. Peak prevalence is between 55 and 64 years of age with high incidence in men than women [3,4]. Incidence of childhood cancers is also increasing majorly due to increase in leukemia and CNS tumors [4]. According to Central Brain Tumor Registry of the United States (CBTRUS), primary CNS tumors are the most common tumors among all solid neoplasms in pediatric population and 2nd most common cause of death in individuals aged less than 20 years [4,5]. As per recent CBTRUS statistical report published in 2019, the average annual age adjusted incidence rate of malignant brain tumor was 7.08, five year survival after diagnosis of malignant brain tumors & other CNS tumors was 35.8% and average annual mortality rate is 4.4 per 100,000 [5]. In 2016, there were 3.30 lacs cases of CNS cancers, there were 2.27 lacs death globally and incidence rate of CNS cancers according to age standardization increased globally by 17.3% from 1990 to 2016 [6]. The overall survival rate of CNS tumors is 33.4% [3,7].

CNS tumors consist of brain and spinal cord tumors. Exact cause of brain tumor has not been clear but genetic factor or family history and radiation exposure are potent sources for brain tumor. The symptoms vary mainly based on location, size and type of tumor. Most common symptoms are headache, seizures, nausea, vomiting, neurocognitive symptoms and personality changes [8]. Brain tumors are classified on the basis of their location, cell of origin, level of differentiation & molecular markers; most widely used classification for CNS tumors is WHO classification, which is based on histology as well as immunohistochemistry (IHC) markers [9].

Many lesions mimic like intra-axial brain tumors on CT & MR imaging e.g. multiple sclerosis, tumor like vasculitis, intracranial tumor like hemorrhage [10]. It is essential to differentiate between tumors and tumor-like lesions for proper treatment plan, better outcome & prognosis. Misdiagnosis can lead to improper treatment of tumor like lesions and brain tumors [10].

Diagnosis of all brain tumors involves 3 steps: neurological examination, neuroimaging and tissue biopsy. Neuro-imaging includes CT, MRI and molecular imaging using positron emission tomography (PET). CT & conventional MRI are regularly used in the diagnosis of brain tumors and differentiate tumor-like lesions from true tumors. Conventional MR is used to characterize location, extent of lesion, morphology and mass effect. Stereotactic biopsy is the gold standard for brain tumor diagnosis. Biopsy is an invasive procedure and has inherent sampling bias & interobserver variability which can result in misdiagnosis or undergrading of the brain tumor. Reason for poor yield is because the stereotactic biopsies are planned based only on enhancement pattern [11] and it has been studied that highly malignant portion of tumor may not always show post contrast enhancement [12]. To establish proper diagnosis non-invasively and suggest areas with higher grade tumors more consistently for stereotactic biopsies, advanced MR imaging techniques need to be applied to the conventional MR imaging. Advanced MRI techniques include diffusion weighted imaging (DWI), MR spectroscopy (MRS), diffusion tensor imaging (DTI), and perfusion MRI, it has been possible to comment on tissue characterization, tissue cellularity, microvascular status and adjacent white matter tract status [13].

MR perfusion imaging enable to give insights on the perfusion of the tissue by blood. Techniques of MR perfusion imaging for measurement of perfusion parameters are dynamic contrast-enhanced (DCE), dynamic susceptibility contrast (DSC), and arterial spin labelling (ASL).

Need for the study

MR perfusion has significant role in evaluation of intracranial neoplasms which helps to estimate neo-angiogenesis of tumor for grading, guiding stereotactic biopsies, surgical planning, differentiating recurrent tumor from radiation necrosis and therapeutic response assessment for new clinical trials on anti-angiogenic agents [13]. DSC technique which uses contrast agent is the most superior and widely used MR perfusion technique with extensive clinical experience. ASL does not require contrast agent and is gaining its importance in recent years. The primary aim of this study is to evaluate the use of ASL as an alternative to DSC MR perfusion in brain tumors and can be used in patients with contraindication to contrast agent, requiring repeated follow ups and clinical research purposes.

2: AIM AND OBJECTIVES

Aim: To evaluate the use of ASL as an alternative to DSC technique in imaging of brain tumors.

Objective: To compare ASL derived rCBF values with DSC derived rCBF values of MR Perfusion imaging in the assessment of brain tumors (primary and metastatic).

3: REVIEW OF LITERATURE:

In the past, physicians didn't mention about brain tumors but it was seen that patients had symptoms of headache, seizures, coma which was presumed that these symptoms are due to increase in intracranial pressure and for which skull trephination was performed to relieve symptoms.

Most common intracranial tumor found in ancient history was meningioma because other tumors disappear after death due to brain lysis and these were never treated. However, evidence of meningioma remnants in ancient skulls with hyperostosis, found in Neothilic, Egyptian and South American skulls [14].

First documented, resected meningioma (an orbital one), localized by clinical palpable hyperostosis noted in Scotland, 1881. In 1885, W. Roentgen discovered X- rays. After that Edor Krause, a German neurosurgeon used skull x-ray regularly to localize brain tumor and penned a chapter in the book dedicated for this. Later with emergence of newer modality like CT, MRI and PET-CT, diagnosis of brain tumors became easy.

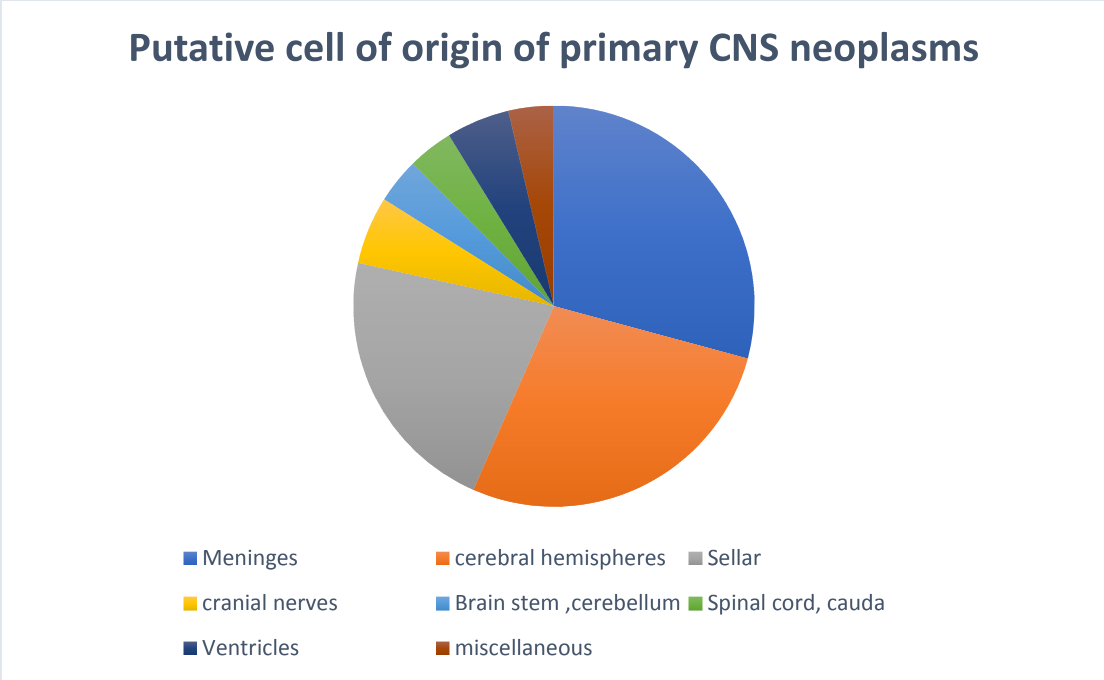
CT brain is also better modality for evaluation of intra-axial brain lesion. In CT, diagnosis is mainly based on enhancement pattern. Therefore, it is difficult to diagnose non enhancing lesions on CT neuroimaging. CT doesn't show proper micro-vasculature of brain lesion. All these difficulties were eliminated after the evolution of MR imaging as advanced MR imaging helps in better characterization of brain lesion, tumor cellularity and microvascular status of brain tumors. In study Shekhar et al (2018), showed MRI has better sensitivity than CT scan in diagnosis of brain tumors [15].

1. WHO Classification of intra-axial brain tumors

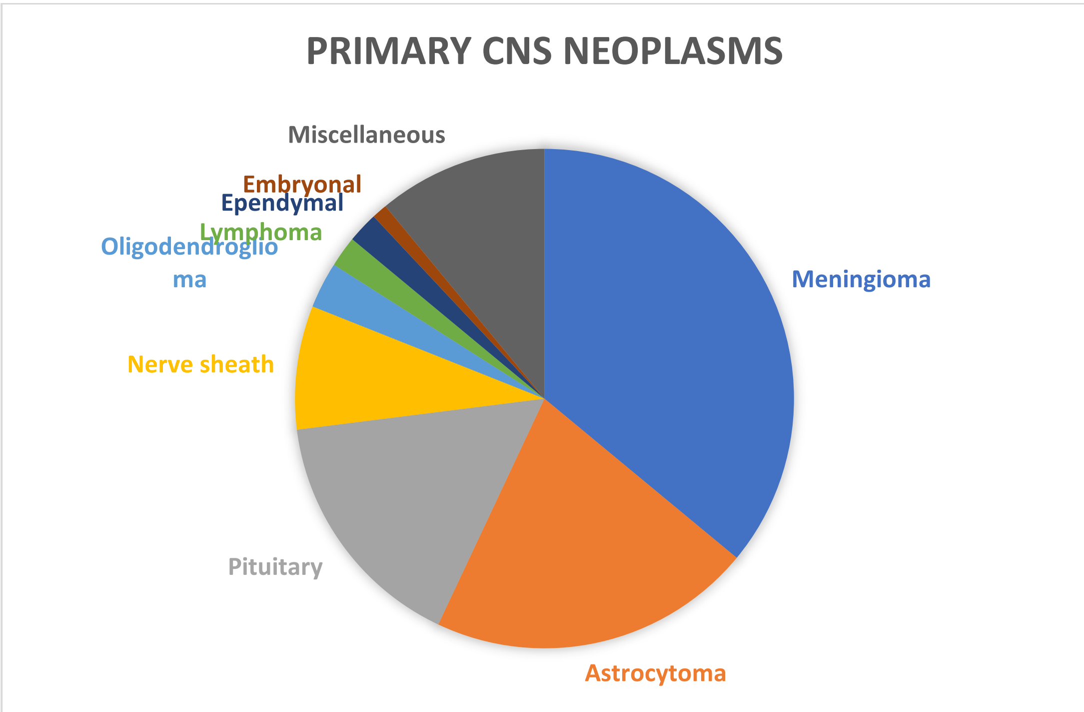
Histologically, the brain consists of neuronal and glial cells. Different types of glial brain cells are astrocytes, oligodendrocyte and microglial cells. Every cell has capacity to divide under proper conditions and according to the body's needs. Uncontrolled growth of cells leads to tumor/cancer formation. Hence primary brain tumors have their putative cell of origin e.g., glial tumors develop from glial stem cells or glial progenitor cells. Glial tumors or gliomas consist of astrocytic and non-astrocytic glioma. Out of gliomas, most common are astrocytoma and specifically glioblastoma multiforme (WHO grade IV). Other common brain tumors are meningioma and oligodendroglioma. Overall most common brain cancer in the adult and old age group is metastasis [4]. Primary brain tumors are one of the most common causes of deaths due to solid tumors in pediatric population [16]. Among all primary brain tumors in pediatric age, most common are ependymoma, medulloblastoma, low grade astrocytoma and brain stem gliomas.

CNS neoplasms can be primary arising from – meninges (36%), cerebral hemispheres (31%), sellar region (17%), cranial nerves (7%) and secondary i.e. metastases [4]. Most common tumor in adults is metastasis, its incidence increases with age. Most common primary intra-axial brain tumor is glioblastoma [4,5].

Among primary CNS tumors in adults, most common is meningioma (i.e. approximately 36% of all), followed by astrocytoma 21% and pituitary neoplasm accounting for 16% [2].



Graph 1: Pie chart diagram showing percentage of primary brain tumors based on their location.



Graph 2: Pie chart showing distribution of CNS neoplasm according to histopathology. Most common primary tumor is meningioma, followed by astrocytoma and pituitary tumors.

Brain tumors are classified on the basis of their location, cell of origin, level of differentiation and molecular markers. WHO classification is the most widely accepted system for classification of CNS tumors. In 2007, WHO Classification of Tumors of CNS grouped all the tumors according to their histology, with an astrocytic phenotype separately from those with an oligodendroglial phenotype, despite of the fact that various astrocytic tumors were clinically similar or disparate [17].

After 8 years, WHO updated classification of CNS tumors in 2016, which includes both histology as well as immunohistochemistry (IHC) markers [9]. There are total 4 grades of brain tumors i.e. Grade I-IV, based on tumor cellularity which corresponds to degree of malignancy [9]. Intra-axial brain tumors are classified as localized tumors (WHO grade I, e.g. DNET, pilocytic astrocytoma), low grade tumors (WHO grade II e.g. diffuse astrocytoma) and high grade tumors (grade III and IV e.g. anaplastic astrocytoma and GBM respectively).

In the latest 2016 WHO classification of CNS tumors, integrates molecular /genomic parameters with histopathological diagnostics. Important molecular parameters are isocitrate dehydrogenase (IDH) gene mutation, 1p19q chromosome codeletion, epidermal growth factor receptors and methyl guanine methyl transferase promoters.

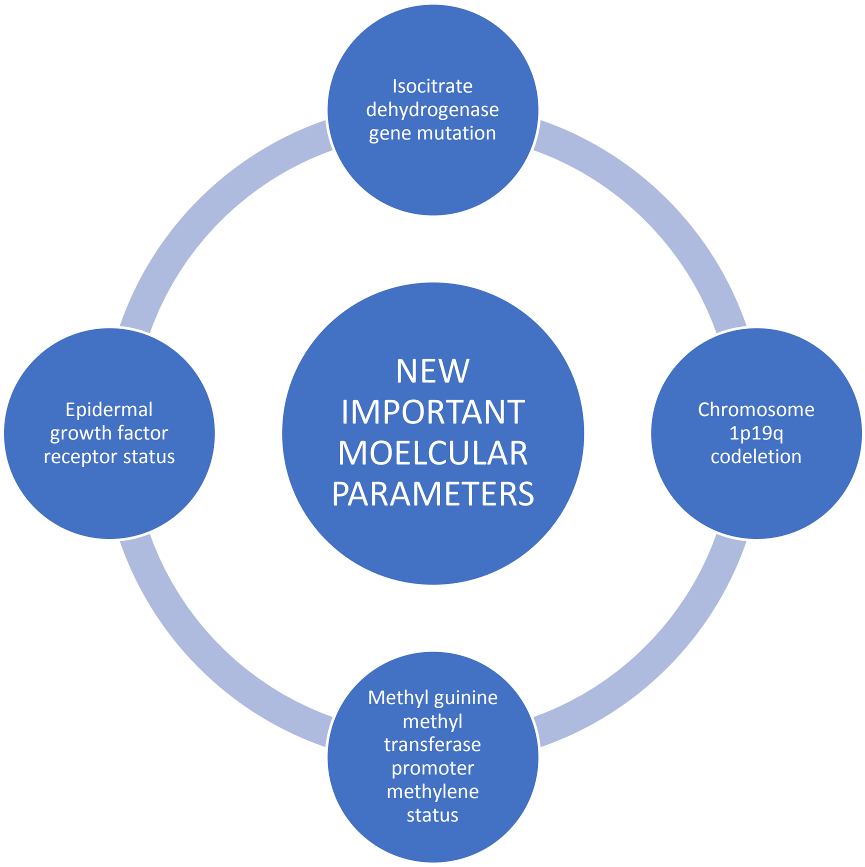


Image 1: New molecular parameters included in 2016 WHO CNS tumors classification;

It is seen that tumors which don't fit according to molecular biomarkers were categorised as not otherwise specified (NOS) group. Oligodendrogliomas are usually present with IDH mutation and 1p19q codeletion [9]. Gliomas in paediatric population behave differently from the adult population. Paediatric gliomas usually occur in the brain stem or infratentorial region while gliomas in adults predominantly occur in supratentorial location. In view of molecular status, IDH mutation and 1p19q codeletion are rare in children but more common in adult infiltrating gliomas [18].

2016 WHO classification showed some major changes in medulloblastomas, diffuse gliomas & other embryonal tumors and included new entities that are defined by both histology and immunohistochemistry including glioblastoma, IDH -wild type & glioblastoma, IDH mutant; medulloblastoma, WNT activated & SHH- activated; RELA fusion- positive ependymoma; diffuse midline gliomas- H3 K27 mutant; and embryonal tumors with multi-layered rosettes, C19 MC altered [9,4].

Layered diagnosis:

According to the new WHO 2016 classification schema with the inclusion of molecular and histological parameters, a new concept of layered diagnosis is formed for systematic reporting of CNS tumors (Table 1). It consists of 4 layers. Layer 1 depicts the final integrated diagnosis, shows sum of molecular and morphological data which best describes the tumor into a single diagnostic entity. Layer 2 is for histological classification. Layer 3 is for WHO grade, i.e. specific for each CNS tumor. Layer 4 consists of molecular and genetic features e.g. IDH mutation/ 1p19q codeletion [18].

Table 1: Layered diagnosis of CNS tumors:

The Integrated diagnosis (Layer 1) come in last, after information regarding WHO grade (Layer 3) and molecular information (Layer 4).

General Schema	**Layer 1**	**Final Integrated Diagnosis**
	Layer 2	Histologic Classification
	Layer 3	WHO Grade
	Layer 4	Molecular Information

Specific Example	**Layer 1**	**Anaplastic oligodendroglioma**
	Layer 2	Infiltrating glioma with oligodendroglial features by microscopy
	Layer 3	WHO Grade III
	Layer 4	Isocitrate dehydrogenase 1 mutation Whole-arm loss of both 1p and 19q

Table 2: Grading of selected tumors according to WHO CNS tumors classification 2016 [9]

WHO grades of select CNS tumours	
Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midline glioma, H3 K27M–mutant	IV
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion–positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypical choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic gangliocytoma of cerebellum (Lhermitte–Duclos)	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	
Pineocytoma	I
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineal region	II or III
Embryonal tumours	
Medulloblastoma (all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST)	II, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour / haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

2: Brain tumors: Etiology, Symptomatology and Tumor specific symptoms

There are different symptoms of brain tumors mainly based on location, size & type of tumor and increased pressure. Overall, most common symptoms of brain tumor are headache, seizure, vomiting and mental or behavioral changes (Table 3).

Table 3: Intra-axial brain tumor location and associated symptoms [3]

LOCATION	ASSOCIATED SYMPTOMS
Frontal lobe	Dementia, generalized focal seizures, personality changes
Temporal lobe	Generalized seizures or complex partial seizures, quadrantanopia, behavioral alterations
Parietal lobe	Sensory loss, hemianopia, spatial disorientation
Occipital lobe	Contralateral hemianopia
Thalamus	Contralateral sensory loss, language disorder, behavioral changes
Cerebellum	Nystagmus, ataxia, dysmetria
Brain stem	Ataxia, cranial nerve dysfunction, papillary abnormalities, nystagmus, hemiparesis, autonomic dysfunction

In consideration of symptoms of brain tumor separately, we can conclude that headache is mainly due to raised intracranial pressure and neurogenic inflammation as rapid increase in size of tumor is more commonly seen in posterior fossa lesions. It should be clear that all headaches are not related to brain tumors. Increased intracranial pressure or stimulation of vomiting center directly can trigger nausea or vomiting in brain cancer patients.

Seizure is also the most common brain tumor symptom. In 20-40% of patients, it presents as primary symptom and approx. 20-45% patient’s manifest seizures during their course. Of all CNS tumors, seizures are most commonly associated with glioneuronal tumors (70-80%) and especially those located in fronto-temporal region. Surgical resection of brain tumor can result in seizure free life in about 60-90 % of patients [19]. Other tumors associated with seizure are low grade glioma, high grade glioma, meningioma and metastasis [20].

3: Role of imaging in evaluation in brain tumor

After the discovery of x rays, radiology has played an essential role in diagnosis & management of intra-axial masses. With advancement in imaging i.e, CT & MRI, accurate non-invasive diagnosis and further therapeutic response became the fundamental goal of neuroimaging in brain tumor patients [13].

The gold standard diagnosis for brain tumors is by histopathological biopsy. However, biopsy is an invasive procedure and has inherent sampling bias and interobserver variability. Most of the time biopsy is inconclusive due to improper resections and intratumoral inhomogeneity. It is important to establish a proper diagnosis without biopsy in view of non-resectability of tumor and socio-economic status of patient.

Earlier CT and conventional MRI were used for diagnosis of brain tumors. Conventional MR was used to characterise morphology, extent of lesion and mass effect due to tumor lesion. After the development of advanced MR imaging like DWI, DTI, MRS and perfusion MRI; tissue characterisation, tissue cellularity, microvascular status of tumor and integrity of the adjacent white matter tracts can be assessed. Therefore, present study has evaluated added role of advanced MR Imaging techniques in characterisation of brain tumors. Shekhar et al (2018), in their study of evaluation of diagnostic efficacy of CT and MRI in detection of brain tumors showed CT & MRI are useful resource as diagnostic aids. No statistical difference was found in results between biopsy and CT scan. Sensitivity, specificity, PPV and NPV of CT scan were 82.7%, 33.3%, 94% and 14% respectively. Sensitivity, specificity, PPV and NPV of MRI scan were 92%, 33%, 94% and 28% respectively. Overall, study showed MRI is more sensitive than CT scan for diagnosing brain tumors [15].

4: Conventional MR imaging: Uses in evaluation of brain tumors and its limitations

Often radiologists are the initial one to diagnose the brain tumors, the description and differential diagnosis have profound implications for subsequent decision making. Although for brain tumors, initial investigation is computed tomography (CT), MRI play a major role in differentiating and classifying the intra-axial brain lesions.

Conventional MRI protocol includes T1WI, T2WI, FLAIR and 3-D gadolinium contrast enhanced T1 sequences [13,21]. Conventional MR helps in localization, characterization, diagnosis and therapeutic monitoring of intra-axial brain lesions. Further MR imaging helps characterization with the help of morphological features, tissue involvement, mass effect on adjacent brain tissue & ventricular system and pattern of spread [22]. T2 WI shows hyperintensity which reflects increased T2 relaxation time, related to increased water content and ultrastructure of tumor. In brain tumors, there is accumulation of Gadolinium based contrast agent in interstitium due to disruption of blood brain barrier related to neovascularization and necrosis.

Conventional imaging has limited specificity in distinguishing brain tumors from other non-neoplastic space occupying brain lesions [23]. It has been seen that all enhancing intra-axial brain lesions are not brain tumors and usually low grade astrocytoma doesn't show enhancement. However, 1/3rd of non-enhancing gliomas are malignant. Other than low grade gliomas, non-enhancing lesions also include developmental malformation e.g. focal cortical dysplasia, viral encephalitis etc. Enhancement in low grade glioma suggests malignant progression. Hence imaging appearance precedes clinical symptoms. Other features that suggest malignant transformations are ill defined border due to infiltration into adjacent brain parenchyma, increase in perilesional edema, mass effect, hemorrhage and necrosis [21]. In study Pierallini et al (1997), concluded that contrast enhancement is the best predictor of histological grade of tumors followed by presence of necrosis, signal homogeneity and border scores [24].

However, it is not sufficient to accurately characterize brain tumor or tumor-like lesion based on only conventional imaging because diagnosis of intra- axial brain lesions is not straightforward. There are different neoplastic and non-neoplastic lesions which show similar imaging findings on conventional imaging, i.e. on contrast enhanced study e.g. high grade glioma (GBM), metastasis and pyogenic abscess, all of these shows peripheral rim enhancement and central non enhancing area. It is difficult to distinguish between tumor recurrence and radiation necrosis. Most important factor to distinguish between tumor and tumor-like lesions is clinical history, then examination and for further evaluation, neuroimaging has to be done. It is important to distinguish between tumor and tumor like lesions, for therapeutic management and follow up, because most the brain lesions mimicking brain neoplasms are usually managed conservatively and misdiagnosis of lesion result in under treatment of brain tumors, which actually need aggressive treatment and surgical resection for symptom-free life after surgery [10]. Tumor like lesions includes multiple sclerosis, sarcoidosis, Bechet's disease, radiation necrosis, lesions with infective etiology e.g. tubercular, fungal, toxoplasmosis, neurocysticercosis, syphilis etc [10,25]. All these pitfalls can be fulfilled, using advanced MR imaging techniques. In study Gadia et al (2018), showed that overall diagnostic accuracy of advanced MRI using MR spectroscopy and MR perfusion, in evaluation of intra-axial brain lesions was 98.57% [26].

It is difficult to evaluate therapeutic assessment on conventional imaging i.e. to distinguish between tumor regression, tumor recurrence & radiation necrosis in post-operative cases who underwent chemotherapy or radiotherapy, as radiation necrosis showed decrease blood tumor barrier, permeability and cerebral blood volume (CBV) of that particular region [27]. Now in the era of advanced MRI, more specific findings can be evaluated about the brain tumors, i.e. biochemical characteristics, microvascular hemodynamics, tumor cellularity, integrity of nearby white matter tracts. Advanced MRI sequences comprise of: diffusion weighted imaging (DWI), diffusion tensor imaging (DTI), MR spectroscopy (MRS) and perfusion MRI [13,23,26,28,29]. When used concurrently, conventional & advanced MRI helps to differentiate between extra axial from intra axial lesions, benign from malignant, primary brain tumor from metastases, high grade from low grade neoplasms and can also suggest probable histological type in most of the cases. DWI helps in evaluation of the cellularity of the tumor, cytotoxic edema or post operative injury. MRS helps in assessing tumor biochemistry and metabolic profile. DTI helps in analyzing the direction of diffusivity and white matter tract orientation, tractography shows status of white matter tracts for surgical planning [13].

5. Perfusion MR imaging:

Perfusion weighted-MRI imaging provides information regarding cerebral physiology at capillary level [30]. It also enables qualitative & quantitative delineation of the whole tumor microvascular hemodynamics, helping in grading of tumor and targeted biopsy [31]. Three MR perfusion techniques are currently in use: dynamic contrast-enhanced (DCE), dynamic susceptibility contrast (DSC), and arterial spin labelling (ASL). Of these, DSC and DCE perfusion using intravenous contrast are most studied and widely applied techniques. As ASL doesn't need intravenous (IV) contrast, it is now being increasingly explored for clinical application specially in cerebral infarction and in cases where contrast can't be performed. In study Borja et al (2013), showed that ASL, a newer technique can be used to assess perfusion in brain tumors. Usually, ASL technique is used mainly in adults. However, its use in children is increasing due to its non-invasive imaging technique and not require contrast administration for imaging of microvascular status of brain tumors [32]. The values that can be derived from these techniques are cerebral blood flow (CBF), cerebral blood volume (CBV), time to peak (TTP), mean transit time (MTT), negative enhancement integral (NEI) and k-trans [12,50].

Basic physics of DSC perfusion:

Also recognized as bolus-tracking MRI or perfusion-weighted imaging where the first pass of bolus of Gadolinium based contrast agent (GBCA) through brain tissue is checked by series of T2* weighted imaging. With use of intravenous GBCA, there is susceptibility induced signal loss on T2* weighted sequences in vessels and surrounding tissues, when GBCA passes through these vessels [12,50]. After image acquisition it requires post processing by proper selection of arterial input functioning (AIF), time graphs with significant signal drop and advanced post processing algorithms. The signal intensity time curve is generated according to amount of signal drop, from which perfusion parameters like rCBV, rCBF and other perfusion metrices are generated [12,51,52,53].

Basic physics of ASL perfusion:

In this technique, requirement of IV administration GBCA is not required unlike in DSC and DSE techniques. It exploits the capability of MRI to magnetically label arterial blood as an endogenous tracer. The water molecules in the arterial blood are magnetically labelled or tagged using a radiofrequency pulse that saturates water protons. Subtraction between labelled or tagged and control images eliminate the static signals and the remaining signals are linear measures to the perfusion, which is proportionate to the cerebral blood flow (CBF). Few techniques have been implicated to obtain ASL perfusion, classified on the basis of magnetic labelling process, they are pulsed ASL (PASL), Continuous ASL (CASL), pseudocontinuous ASL (PCASL) and velocity-selective ASL (VS-ASL) [12,50]. Despite the various acronyms in the literature, two main types are pulsed ASL and continuous ASL. Pulsed ASL uses short radiofrequency pulse to label a thick slab of arterial blood at a single point of time and imaging is performed after a period time to allow distribution in the tissue of interest. Continuous ASL uses prolonged radiofrequency pulse that continuously labels arterial blood water below the imaging slab until a steady state of tissue magnetization transfer effect, so pulsed ASL is less technically demanding [12]. Relatively new technique known as pseudocontinuous ASL represents a compromise between pulsed ASL and continuous ASL. This technique will provide improved balance between labelling efficiency and signal-to-noise ratio (SNR). ASL data must be acquired before gadolinium administration since it causes T1 shortening leading to a decrease in the measurable signals in both the labelled and controlled images. Values that can be derived is rCBF [12].

rCBV obtained from DSC technique is important parameter which correlates with vascular status of tumor and show higher value in tumor having high rate of neoangiogenesis which correlates with high grade of tumor [33]. rCBV in brain tumors is the ratio of tumor CBV and CBV in normal white matter of contralateral hemisphere [12,34]. rCBV can be correlated with tumor grade but some low grade glioma can show elevated rCBV e.g. oligodendroglioma [35,36]. As histopathology is gold standard for diagnosis of brain tumor, biopsy is done with the help of contrast enhanced CT or MRI [11]. But a major pitfall with biopsy is that the most malignant portion of the tumor may not show contrast enhancement. In study Server et al, showed 38% of anaplastic astrocytoma were not properly enhanced and 25% of brain tumors were undergraded on histopathological evaluation [37]. In malignant neoplasms, parenchymal infiltration follows vascular channels of white matter tract [38]. This infiltration won’t be appreciated if lesion is not showing enhancement on conventional MR imaging. Hence rCBV from MR perfusion can be used to accurately characterize the highly perfused area and further biopsy can be planned [39].

Applications of MR perfusion:

Many articles in the literature stated that MR perfusion can be used to differentiate between intracranial brain tumors. Mainly this technique is used to distinguish neoplastic from non-neoplastic lesions or high-grade from low-grade glioma or high-grade glioma from metastasis or meningioma using rCBV values.

Cha S et al, 2002, in their study on MR (DSC) perfusion in intracranial mass lesion showed reduced rCBV values in lymphoma than in malignant glioma. On conventional imaging, lymphoma and high grade glioma can’t differentiate [39].

Law et al, 2002, in their study on high grade glioma and solitary metastasis: distinction using perfusion and proton spectroscopic MRI showed that rCBV in peritumoral area was significantly high in high grade glioma (1.31+/- 0.97) than metastasis (0.39+/- 0.19) [40].

Lev MH et al, 2004, in their study on Glial tumor grading and outcome prediction using DSC MR perfusion compared with conventional contrast enhanced MR: confounding effect of elevated rCBV of oligodendroglioma, showed cut off value of 1.5 for rCBV to differentiate between LGGs and HGGs with 100% PPV [41].

B Hakyemez et al, 2005, in their study on differentiation of high grade and low grade glioma using MR perfusion showed statistical difference between values of rCBV and rCBF in between low grade and high grade glioma. The cut off values for rCBV and rCBF were 1.69+/- 0.51 and 1.16 +/- 0.38 (mean+/- SD) respectively for low grade glioma and 6.50+/-4.29 and 3.32+/- 1.87 (mean+/- SD) respectively for high grade glioma.

Strong correlation between the rCBV and rCBF ratios with Pearson correlation = 0.830 and p value < 0.05 [42].

Law et al, 2008, in study of glioma for predicting time to progression or survival with cerebral blood volume measurements using DSC MR perfusion imaging showed increased predictability of high rCBV values (>1.75) for malignant transformation of LGG before the apparent contrast enhancement on post contrast T1 image [43].

B Hakyemez et al, 2010, in their study of solitary metastasis and high grade glioma: radiological differentiation by morphometric analysis and perfusion weighted MRI showed no statistical difference. Mean rCBV ratio in intratumoral areas of high grade glioma and metastasis were 5.02+/-2.47 and 4.62+/- 2.46, respectively. However in peritumoral area, significant difference was noted in rCBV ratio i.e. 0.89+/- 0.51 in high grade gliomas and 0.31+/- 0.12 in metastasis [44].

Shah et al, 2012, Imaging feature and Differentiation from Tumor Recurrence showed that diffusion restriction and increased rCBF in case of tumor recurrence than in radiation necrosis. Upper and lower cut-off values of 2.6 and 0.6 are given for recurrent tumor and radiation necrosis, respectively [45].

Akbari et al, 2014, in study of pattern analysis of DSC MR imaging demonstrates significant correlation (r= 0.46, P<0.0001) between peritumoral heterogeneity and patient survival. Further he showed discrimination between infiltrated peritumoral region and surrounding normal white matter based on DSC MR perfusion study [46].

Artzi et al, 2014, in their study of differentiation between vasogenic edema versus tumor infiltrative area in patient with GBM, showed that there are two regions surrounding GBM, tumor infiltrative region which showed higher rCBV and MRS showed higher malignant pattern, while vasogenic edema showed increased FLAIR values and reduced perfusion which suggest no evidence of tumor infiltration [47].

H cebici et al, 2014, in their study on assessment of DSC perfusion and ASL in glial tumor showed cut off for rCBV (1.80) is better parameter to grade glioma rather than cut off of rCBF (1.36). There was better correlation between CBV and rCBF- ASL rather than rCBF and rCBF-ASL [48].

In study of Kamble et al, 2015, showed that cutoff value of rCBV =1.64 to differentiate between low grade and high grade glioma on CT perfusion [49], which is near to the values shown by other studies i.e. rCBV=1.75. However, in view of radiation exposure, MR imaging is superior to CT imaging for evaluating microvascular status of intra-axial lesions [49].

Comparative studies of MR perfusion techniques:

Warmuth C et al 2003, a comparative study between ASL and DSC in brain tumors to quantify tumor blood flow showed that microvascular perfusion by ASL is a suitable method for evaluation and distinction between high- and low-grade gliomas and implemented to use ASL as routine examinations in evaluation of tumor blood flow. Glioblastoma show high perfusion values whereas low grade gliomas show low perfusion on both the perfusion techniques. There was linear correlation between ASL and DSC techniques using 36 cases of brain tumors with correlation coefficient of r=0.83 [57].

Weber MA et al, 2004, Study of brain metastases post stereotactic radiosurgery, the rCBF changes in ASL and DSC MRI perfusion techniques allow the prediction of treatment outcome, after 6 weeks follow up. Changes in the rCBF values in the follow up can predict treatment outcome [58].

H. Kimura et al, 2006, in their study on characterisation on meningioma using CASL and comparison of results with DSC and histopathologic examination showed significant correlation between CBF results derived from perfusion methods (r-0.73; p <0.001). Angiomatous meningioma showed highest perfusion values and lowest perfusion for fibrous meningioma from perfusion method [59].

Lehmann P et al, 2010, In their comparative study of perfusion measurement by ASL versus DSC MRI techniques in brain tumors at 3 Tesla MR showed that ASL is a good alternative to DSC MR perfusion based on rCBF parameters. Results of rCBF values from ASL and DSE were closely correlated (ROI A: $r = 0.69$, $p < 0.001$ and for ROI B: $r = 0.784$, $p < 0.0001$). ASL is useful when there is contraindication for contrast medium and intra venous injection is not possible [60].

Knutsson L et al, 2010, in their study on Absolute quantification of CBF: satisfactory positive linear correlation of CBF values obtained by DSC MRI and model-free ASL using 3T MRI. Average DSC-MRI estimated CBF values were 150+/-45 (ml/min 100g) (mean +/- SD) and corresponding ASL-MRI estimated CBF values were 44+/-10 (ml/min 100g) [61].

H. Järnum et al, 2010, suggested to use PCASL as an alternative to DSC-MRI and can be applied in patients with renal failure. They compared non-invasive 3D PCASL technique with clinically established DSC MR perfusion imaging in brain tumors showed good correlation between ASL nTBF and DSC nTBF with a correlation coefficient of $r=0.82$ [62].

Y. Ozsunar et al, 2010, in a pilot comparative study in distinguishing recurrent gliomas from radiation necrosis using ASL technique, DSC cerebral blood volume and PET imaging. In this study ASL technique may more precisely differentiate recurrent high-grade glioma from radiation necrosis as compared with DSC-CBV technique. Specially in the areas with necrosis, DSC-CBV technique may underestimate true blood volume due to leakage artifacts [63].

White CM et al 2014, concluded that DSC and ASL may provide regionally comparable, but spatially dissimilar measurements of CBF in the study of Regional and voxel-wise correlation of CBF between DSC and ASL MR perfusion techniques in brain tumors. Results showed a positive linear correlation of CBF values from DSC and ASL when comparing the regional values [64].

Jiang J et al 2014, analysed the difference between 3D-ASL and conventional DSC perfusion in confirmed cases of brain tumors showed closed correlation between 3D-ASL and DSC MR perfusion without significant difference between ASL nTBF and DSC nTBF when normalized to normal contralateral gray and white matter (correlation coefficient, r-0.807). The data supported that 3D-ASL is a potential noninvasive alternate to DSC MR perfusion imaging in cases of brain tumors and also helps in prognosis [65].

Ata ES et al 2016, Compared ASL technique and DSC technique in evaluating tumor perfusion in cases with brain tumor proved similar specificity and sensitivity for both ASL and DSC MR Perfusion and suggested usage of ASL perfusion in daily clinical practice. Visual inspection sensitivities and qualitative evaluation sensitivities for ASL and DSC perfusion were 88% & 94 % respectively, with 100% specificity for both [66].

Neetu soni et al 2017, in their study on comparison of ASL and DSC MR perfusion in enhancing brain tumors showed strong correlation between ASL nTBF and DSC nTBF with contralateral grey matter with values 2.9 ± 1.67 and 2.9 ± 1.43 respectively. The study also suggested use of ASL in patients requiring multiple follow ups and impaired renal functions which is a potential and non-invasive technique in the assessment of cerebral blood flow in intracranial neoplasms [67].

4: MATERIAL AND METHODS:

Source of data:

All patients with suspected brain tumors irrespective of age and sex advised for MRI BRAIN (PLAIN AND CONTRAST) TO DEPARTMENT OF RADIODIAGNOSIS AT KAHER'S DR. PRABHAKAR KORE HOSPITAL & MRC, BELAGAVI.

Method of collection of data:

Study site: In the Department of Radio-diagnosis at KAHER'S Dr. Prabhakar kore hospital & MRC, Belagavi.

Study design: Hospital based one year observational study.

Sample size: All cases with brain tumors evaluated on MRI of BRAIN (PLAIN AND CONTRAST WITH PERFUSION IMAGING) including both ASL and DSC techniques during the study duration will be the sample size.

Sampling method: Universal sampling.

Study duration: January 1st 2020 to December 31st 2020.

Inclusion criteria:

1. Patients with suspected brain tumor clinically or by MRI/CT Brain plain studies and referred to radiology department for **MRI Brain (Plain + Contrast).**

Exclusion criteria:

1. MRI study with motion artifacts and non-cooperative patients.
2. Patients having contraindications for administration of Gadolinium contrast agents i.e. chronic or acute renal failure, history of allergy to Gadolinium agents.
3. Patients having contraindications to MR examination per se i.e. metallic implants in the body, pacemakers, cochlear implant, claustrophobia.

Ethical considerations: Study was approved by the institutional human ethics committee. Informed consent from all the study participants and only those participants willing to sign the informed consent were included in the study were taken. The risks and benefits involved in the study and voluntary nature of participation were explained to the participants before obtaining consent. Strict confidentiality of the study participants was maintained.

Methodology:

1. The subjects will be enrolled in the study after they give an informed written consent for MRI brain (plain + contrast) with perfusion imaging using 3T MRI SCANNER 'MAGNETOM Spectra' (manufactured by Siemens).
2. A detailed clinical history will be taken as per the proforma.
3. After considering the inclusion and exclusion criteria, the patients will be taken up for **MRI Brain (Plain + Contrast) with perfusion imaging** including both **ASL** and **DSC techniques** which will be done as per standard imaging protocol.
4. Image processing and data analysis done on Siemens Multi-modality work station using Siemens software NUMARIS/4, version syngo MR E11.
5. Statistical analysis was done using SPSS 20.0 version.

Magnetic resonance image acquisition (protocol):

All the patients underwent MRI on 3T MRI SCANNER 'MAGNETOM Spectra' (manufactured by Siemens) present in the Department of Radiodiagnosis, KLE's Dr. Prabhakar Kore Hospital & MRC, Belagavi. Before starting the study good IV line access was obtained with no resistance to flow of saline.

The imaging sequences acquired are as follows:

1. T2W imaging in axial plane and coronal plane.

2. T1W imaging in axial plane.

3. Fluid attenuated inversion recovery sequence in axial plane.

4. DWI and ADC sequence in axial plane.

5. Gradient echo sequences in axial plane.

6. ASL perfusion imaging (3D ASL) in axial plane.

7. Pre-contrast T1W FS axial plane.

8. Dynamic susceptibility contrast (DSC) Perfusion weighted imaging in axial plane.

9. Post contrast T1W FS axial plane and coronal plane.

10. Post contrast 3D MPR T1W imaging.

11. Multivoxel MR Spectroscopy (CSI)

ASL perfusion imaging

Arterial spin labelling (Pulsed 3D ASL)

TR = 4000 ms. TE = 19.8 ms

Fov = 192 x 192 mm

Slice thickness = 3mm Distance factor = 50%

Dynamic susceptibility contrast (DSE) Perfusion weighted imaging

Concentration and quantity of contrast agent: 0.1 mmol/kg.

Rate of injection: 3-5 ml/sec.

Timing of injection: after approx 4 cycles of acquisition.

Total no of cycles in acquisition: 70

Pulse sequence T2*W (susceptibility) imaging

TR = 1470 ms TE = 30.0 ms

FoV - 220 x 220 mm.

Slice thickness = 4 mm, Distance factor = 30%

Image Post-processing.

Image processing is done on a Siemens Multi-Modality Work place (MMWP) with Siemens software NUMARIS/4, version syngo MR E11. All the sequences in the imaging protocol were evaluated for location, extensions, grading and possible WHO classification. Major sequences including were T1WI, T2WI, FLAIR, DWI & ADC, SWI, ASL perfusion, DSC perfusion, Post contrast T1W FS images and spectroscopy.

Evaluation of DSC perfusion:

On the Siemens workstation (MMWP), DSC perfusion series sequences (ep2d_perf) are loaded (Image 2). For quantitative evaluation, arterial input function (AIF) is identified and adjusted on anterior cerebral arteries or middle cerebral arteries. Best time graphs with significant signal drop were selected (3-4 graphs) (Image 3). Time ranges were set 1st at the base line, 2nd at the beginning of the drop (Gd entry) and 3rd at the peak of the recovery (Image 4). The rCBV and rCBF color images are obtained (Image 5). Region of interest (ROI) of 3 mm^2 will be placed in the region of tumor showing maximum perfusion value in rCBF maps avoiding the regions of necrosis, vessels, calcifications, hemorrhage and cyst. For normalization, to avoid age and patient dependent CBF variations ROI of 3 mm^2 is placed on the contralateral normal white matter (WM) and grey matter (GM). rCBF ratios are obtained by dividing rCBF value of tumor by rCBF values of contralateral normal white matter and grey matter. rCBF ratio of lesion & grey matter is taken as {DSC rCBF (GM)} and rCBF ratio of lesion & white matter is taken as {DSC rCBF (WM)}. In rCBV perfusion maps, ROI of 3 mm^2 is placed in the same area and size that was used in calculation of rCBF ratio, similarly in the lesion and contralateral normal white matter to calculate rCBV ratios by dividing rCBV of lesion and rCBV of contralateral normal white matter {DSC rCBV (WM)}.

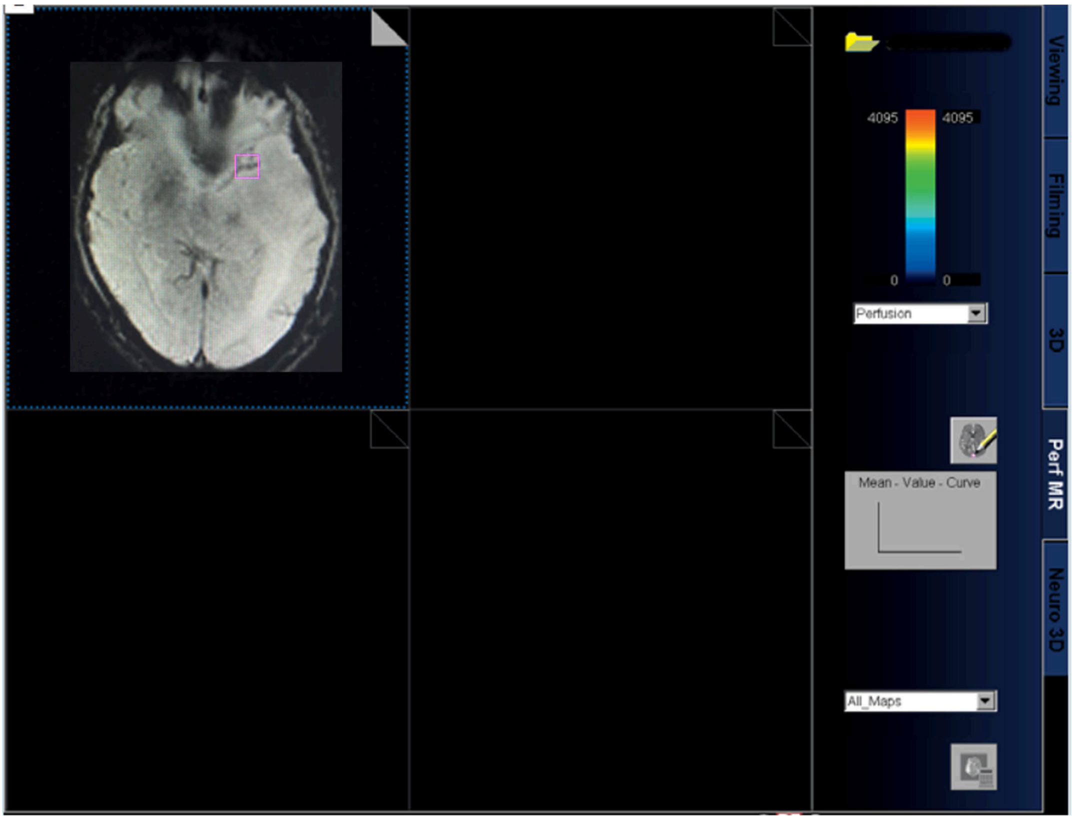


Image 2: Opening page of the perfusion application. The perfusion series has been dropped and can be seen in the first quadrant (top left).

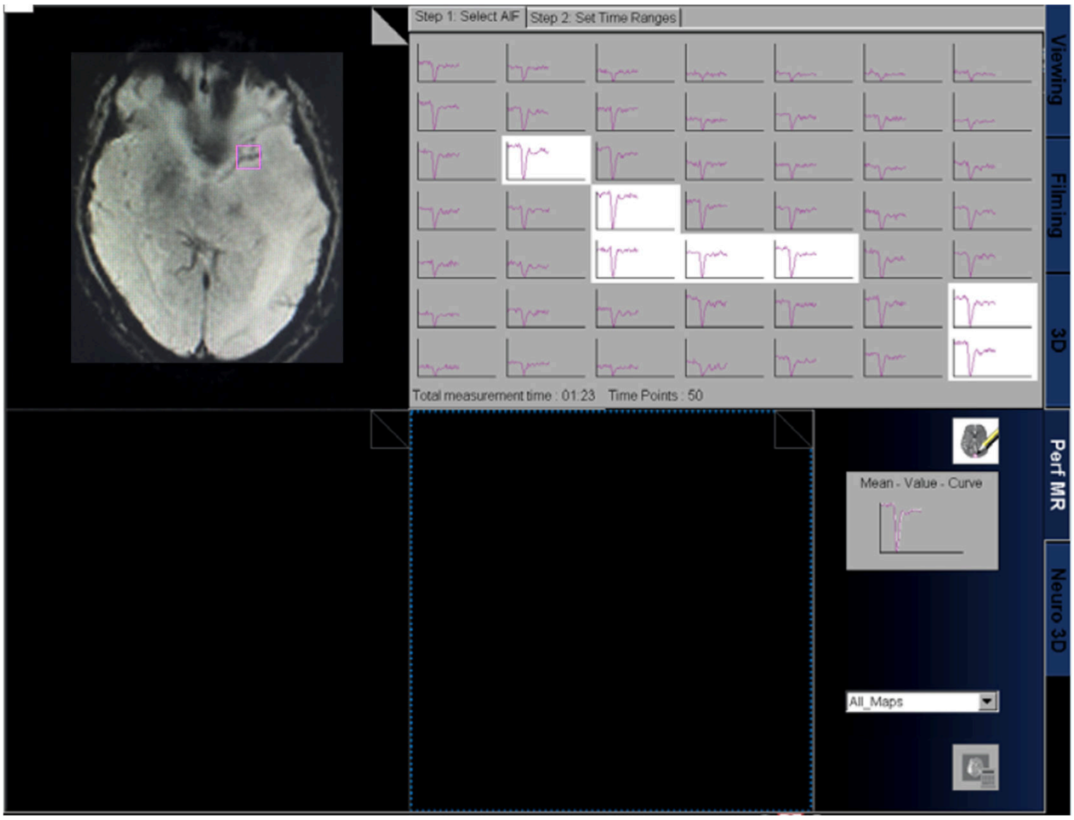


Image 3: The arterial input function (AIF) square is shown on a slice of the perfusion image data with the resulting 9x9 pixels time points on the right side. The highlighted region-of-interest (ROI) is used to calculate the AIF from.

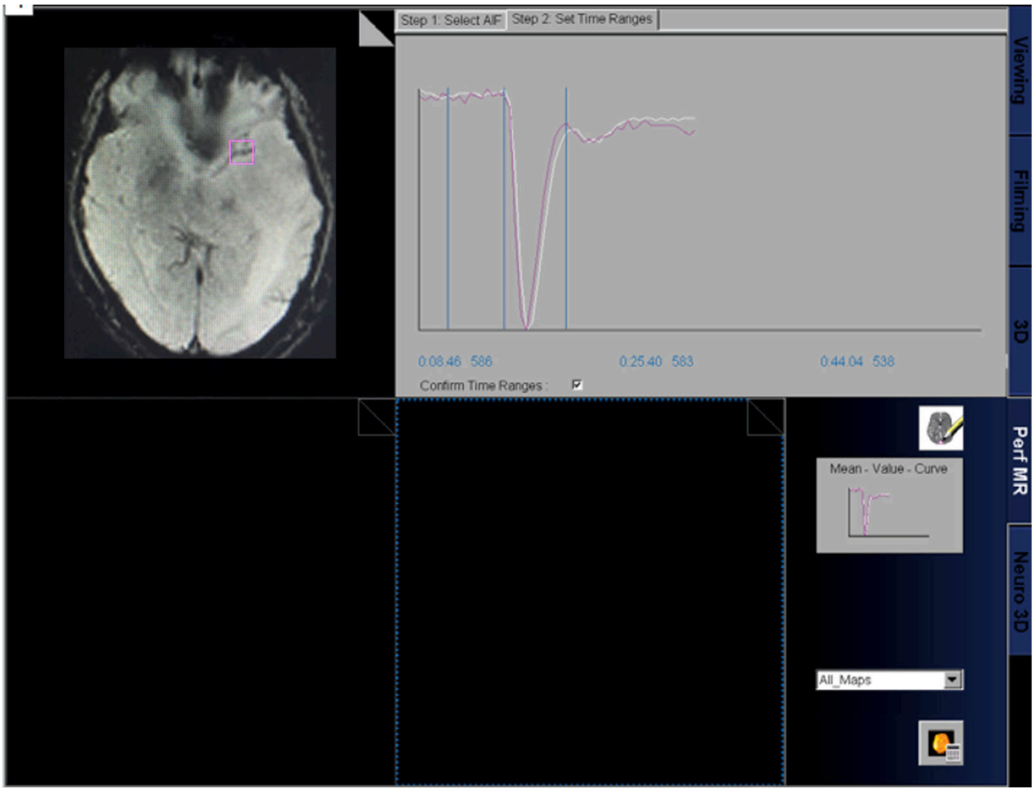


Image 4: The resulted AIF, with the three time points properly shown. The first one is at the baseline, second at the start of the drop and the third at the end of the drop (peak of recovery).

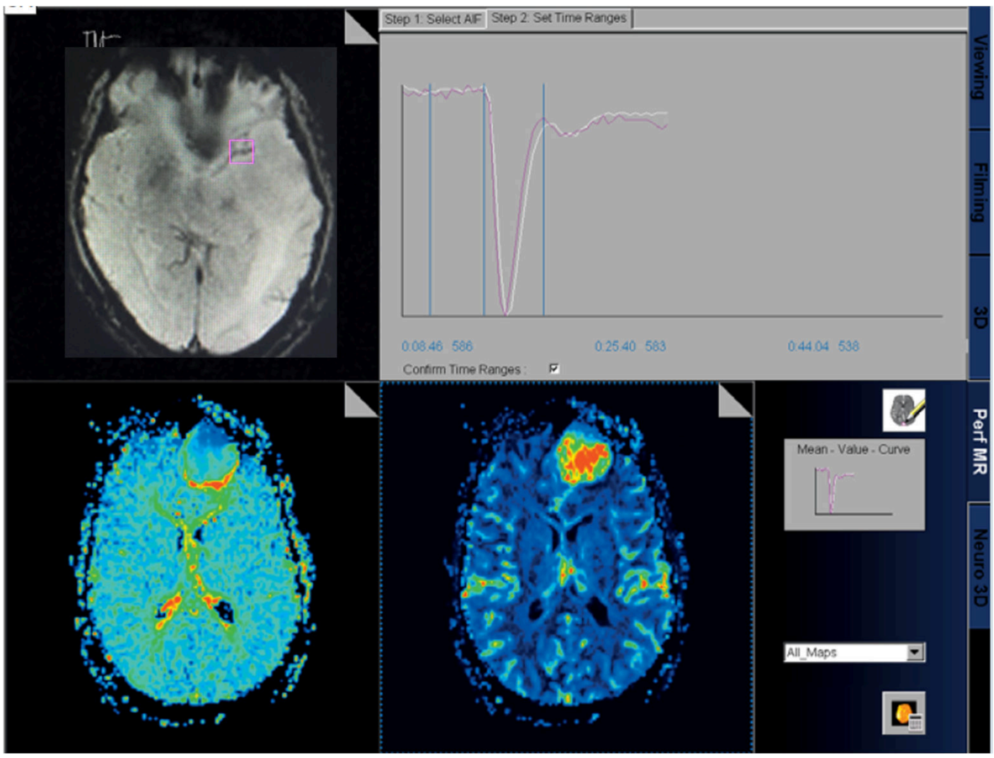


Image 5: Shows the perfusion screen, after the calculation is done. Color coded rCBF and rCBV is displayed in the fourth quadrant (lower right) and the TTP and MTT is displayed in 3rd quadrant (lower left).

Evaluation of ASL perfusion:

ASL 3D sequence (perfusion weighted imaging) is selected and split into one series to obtain color coded rCBF images (Image 6). For quantitative evaluation, rCBF ratios are calculated in the similar way as mentioned above for DSC perfusion. rCBF values are derived from the same site and same size (ROI of 3 mm^2) which was used for DSC perfusion in lesion and contralateral normal grey matter & white matter. Similarly, rCBF ratios are calculated. ASL rCBF ratio of lesion & white matter is taken as {ASL rCBF (WM)} and ASL rCBF ratio of lesion & grey matter is taken as {ASL rCBF (GM)}.

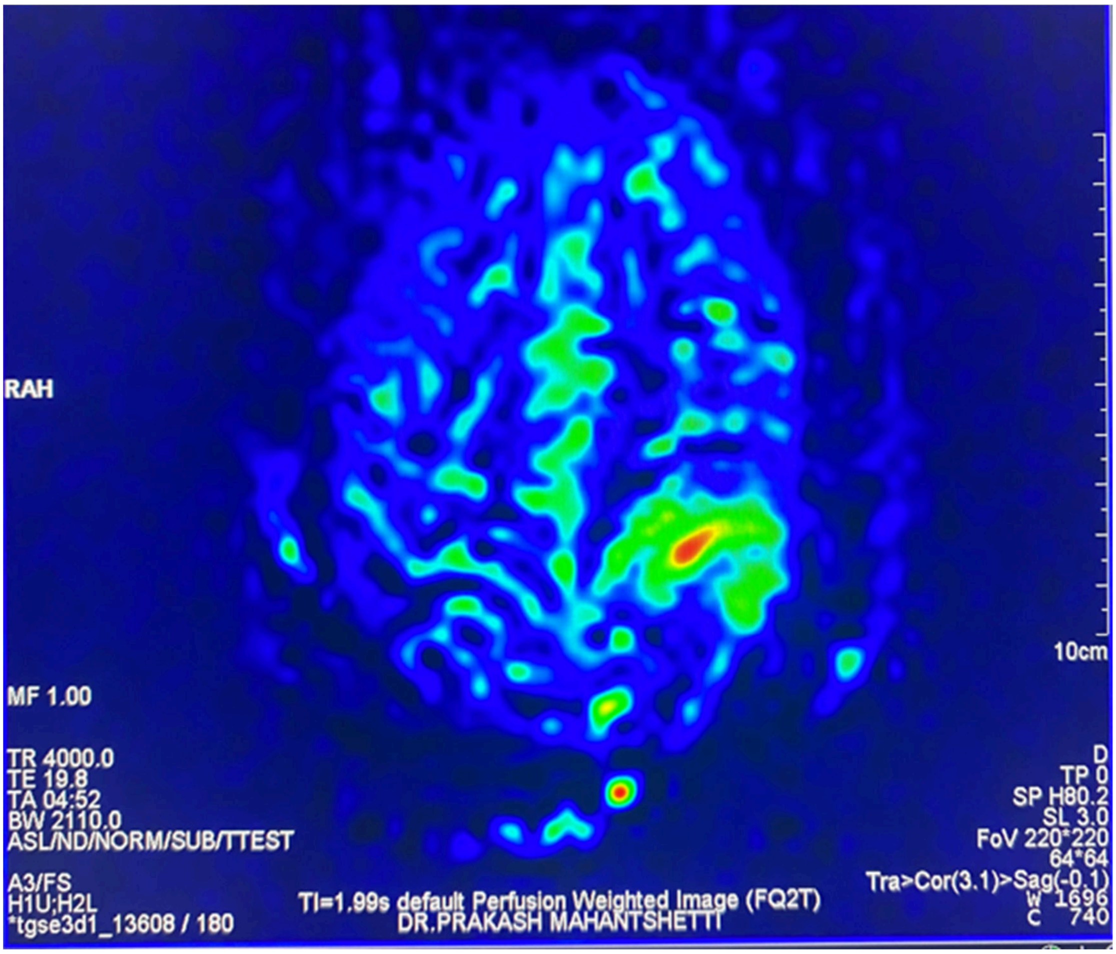


Image 6: Color coded rCBF images from ASL.

All the patients were followed up for histopathological diagnosis, grading and surgical findings.

Statistical data analysis:

Age and gender wise distribution of the cases. Distribution of cases according to classification of CNS neoplasm. Distribution of primary CNS neoplasm among the cases. Correlation and comparison of ASL rCBF (GM) with DSC rCBF (GM) and ASL rCBF (WM) with DSC rCBF (WM) using dependent t test. Correlation of DSC rCBF (WM) and DSC rCBV (WM) ratios in low grade gliomas and high grade gliomas. Correlation and comparative analysis using scatter plot and box plot graphs and $p < 0.05$ is considered statistically significant. SPSS 20.0 version is used for statistical analysis.

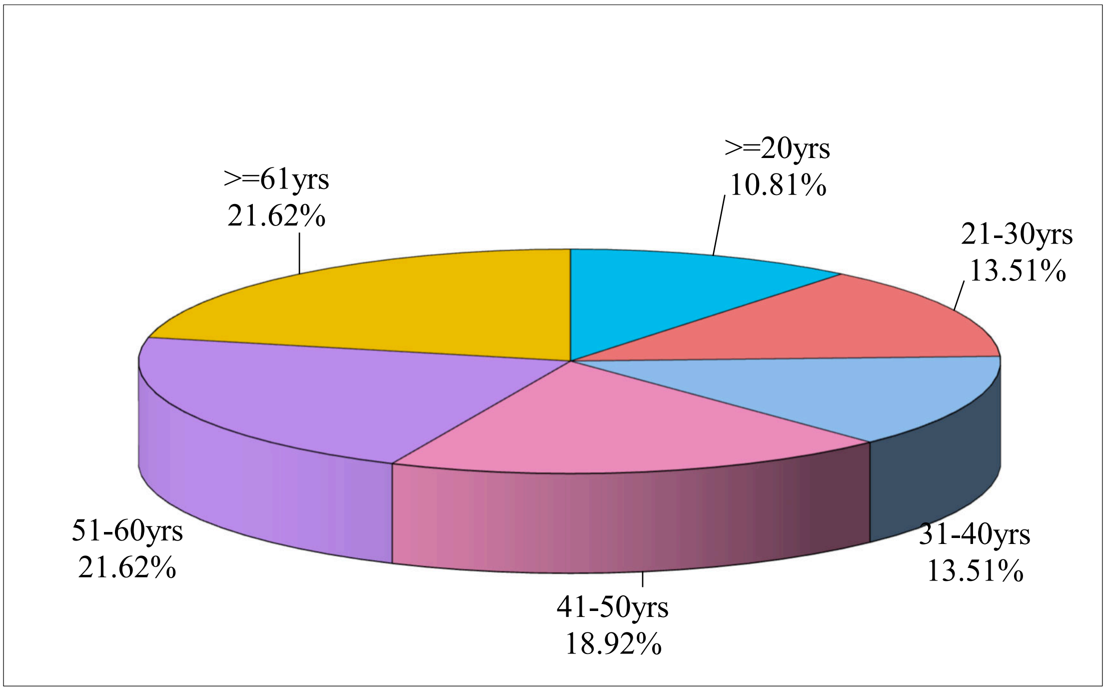
5: RESULTS

A total of 37 Patients were included in the study who underwent MRI BRAIN (PLAIN & CONTRAST with PERFUSION IMAGING) including both ASL and DSC techniques after considering the inclusion & exclusion criteria and followed up for histopathological diagnosis, grading and surgical finding revealed 11 high grade gliomas, 5 low grade gliomas, 9 meningiomas, 5 metastases, 2 DNET, 1 medulloblastoma, 1 hemangioblastoma, 1 ependymoma, 1 ganglioglioma and 1 CP angle schwannoma.

Table 4: Age wise distribution of cases among the study population.

Age groups	No of patients	% of patients
>=20yrs	4	10.81
21-30yrs	5	13.51
31-40yrs	5	13.51
41-50yrs	7	18.92
51-60yrs	8	21.62
>=61yrs	8	21.62
Total	37	100.00
Mean± age groups	45.35±18.82 years	

Graph 3: Pie chart showing age wise distribution of cases among the study population.

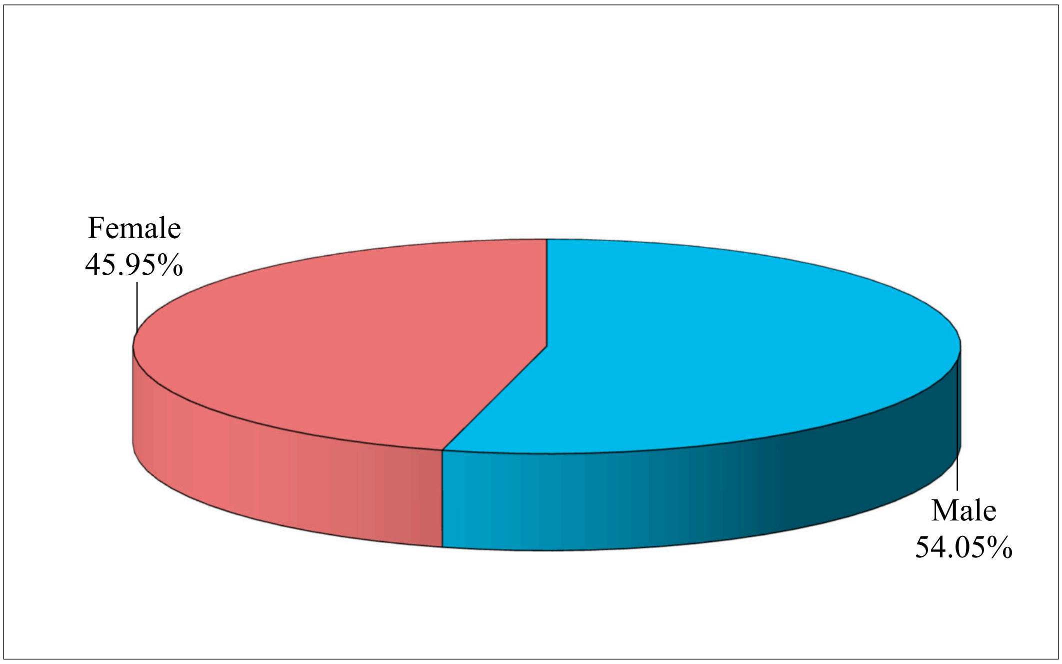


Our study showed higher incidence of CNS neoplasms above the age of 40 years predominantly between 51-60 years in 21.6 % of cases and above 60 years in 21.6 % of cases (Table 4 and Graph 3).

Table 5: Gender wise distribution of cases among the study population.

Gender	No of patients	% of patients
Male	20	54.05
Female	17	45.95
Total	37	100.00

Graph 4: Pie chart showing gender wise distribution of cases among the study population.

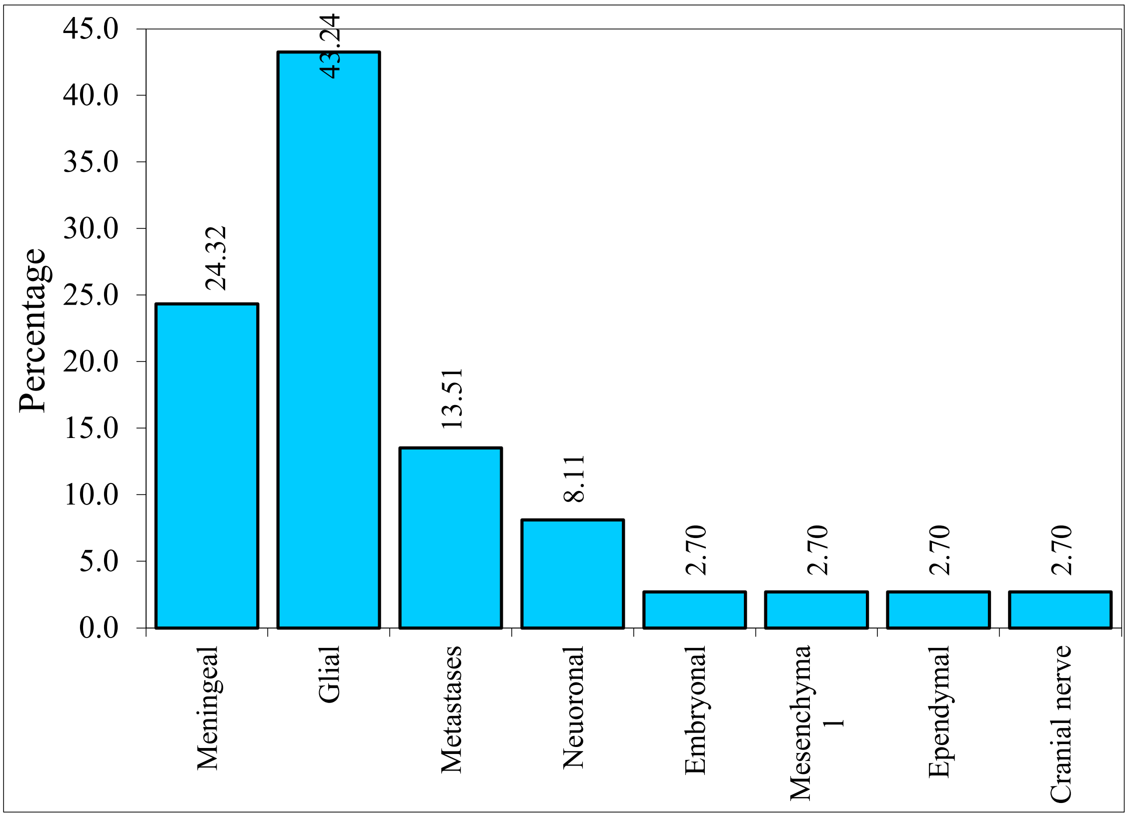


Our study showed that the brain tumors were higher in the males than in females accounting for 54.05 % and 45.95 % respectively (Table 5 and Graph 4).

Table 6: Distribution of cases according to classification of CNS neoplasm among the study population.

CNS neoplasm	No of patients	% of patients
Meningeal	9	24.32
Glial	16	43.24
Metastases	5	13.51
Neuronal	3	8.11
Embryonal	1	2.70
Mesenchymal	1	2.70
Ependymal	1	2.70
Cranial nerve	1	2.70
Total	37	100.00

Graph 5: Bar graph showing the distribution of cases according to classification of CNS neoplasm among the study population.

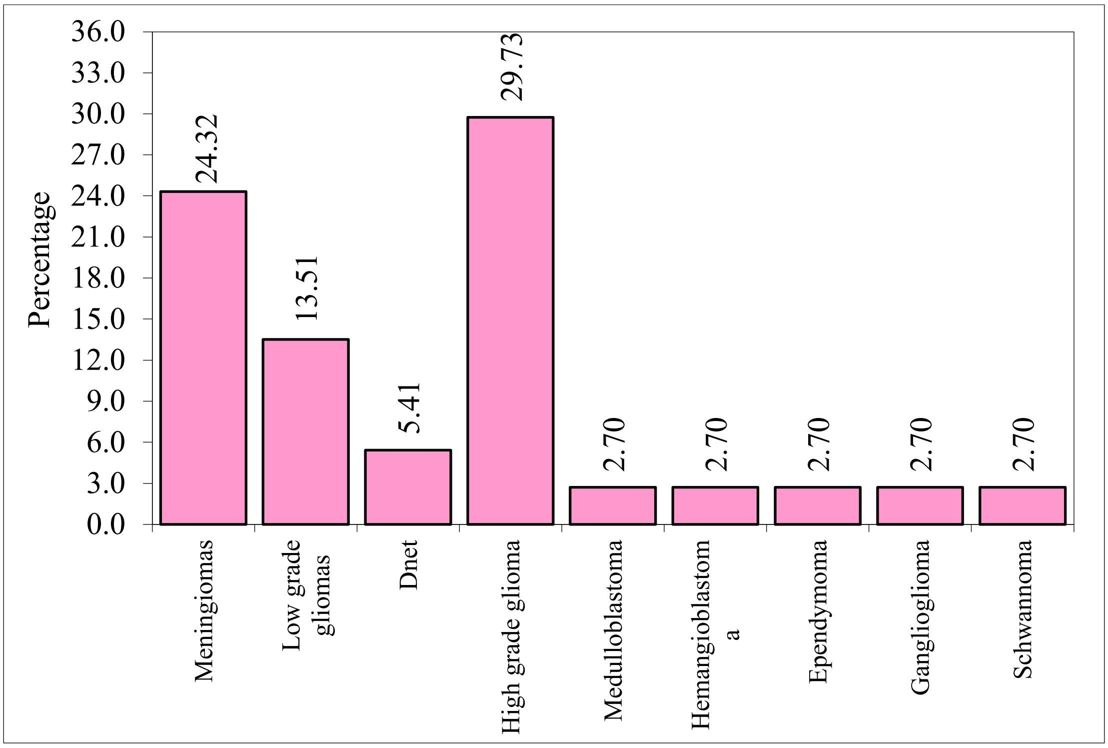


Out of 37 cases, most of the cases were glial tumors (43.24%) followed by meningiomas (24.32 %) and metastases (13.5 %) (Table 6 and Graph 5).

Table 7: Distribution of Primary CNS neoplasm among the study population.

Primary CNS neoplasm	No of patients	% of patients
Meningiomas	9	24.32
Low grade gliomas	5	13.51
Dnet	2	5.41
High grade glioma	11	29.73
Medulloblastoma	1	2.70
Hemangioblastoma	1	2.70
Ependymoma	1	2.70
Ganglioglioma	1	2.70
Schwannoma	1	2.70

Graph 6: Bar graph showing distribution of Primary CNS neoplasm among the study population.



Among the 32 primary CNS neoplasms in our study, shows highest cases were gliomas (43.4 %) predominance being for high grade gliomas (29.7 %) followed by meningioma (24.32 %) (Table 7 and Graph 6).

Table 8: Summery of rCBF values of Lesion, normal Grey matter and White matter in Arterial spin labeling.

Summery	Lesion (rCBF)	Grey matter (rCBF)	White matter (rCBF)
Min	10.20	125.30	40.50
Max	3608.10	378.10	200.00
Mean	879.19	193.65	98.50
SD	787.58	55.59	35.19
SE	21.29	1.50	0.95

Among all the cases, the mean rCBF values derived from ASL in normal grey matter and white matter were 193.6 +/-55.59 SD and 98.50 +/- 35.19 SD respectively. Mean rCBF values of all the lesions were 879.19 +/- 787.28 SD (Table 8).

Table 9: Summery of rCBF values in Lesion, normal Grey matter and White matter in Dynamic susceptibility contrast.

Summery	Lesion (rCBF)	Grey matter (rCBF)	White matter (rCBF)
Min	2.20	16.10	8.30
Max	924.80	68.30	34.90
Mean	167.15	41.26	19.96
SD	162.21	13.41	8.13
SE	4.38	0.36	0.22

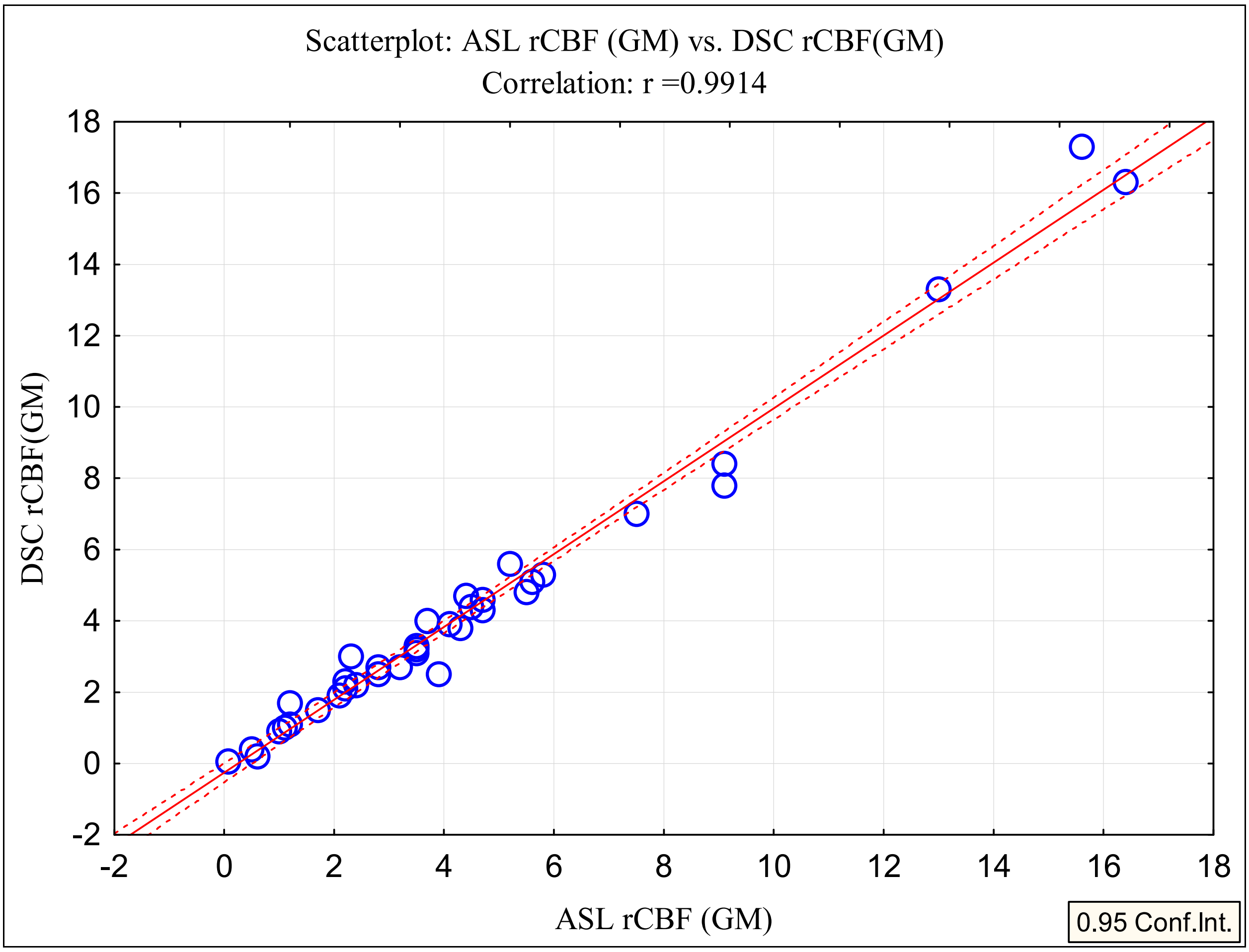
Among all the cases, the mean rCBF values derived from DSC in normal grey matter and white matter were 41.26 +/-13.4 SD and 19.9 +/- 8.13 SD. Mean rCBF values of all the lesions were 167.15 +/- 162.21 SD (Table 9).

Table 10: Correlation between ASL rCBF ratio of lesion & grey matter {ASL rCBF (GM)} and DSC rCBF ratio of lesion & grey matter {DSC rCBF (GM)}.

Variables	Correlation between ASL rCBF (GM) with		
	r-value	t-value	p-value
DSC rCBF (GM)	0.9915	44.9855	0.0001*

*p<0.05

Graph 7: Scatter plot showing the correlation between ASL rCBF ratio of lesion & grey matter {ASL rCBF (GM)} and DSC rCBF ratio of lesion & grey matter {DSC rCBF (GM)}.



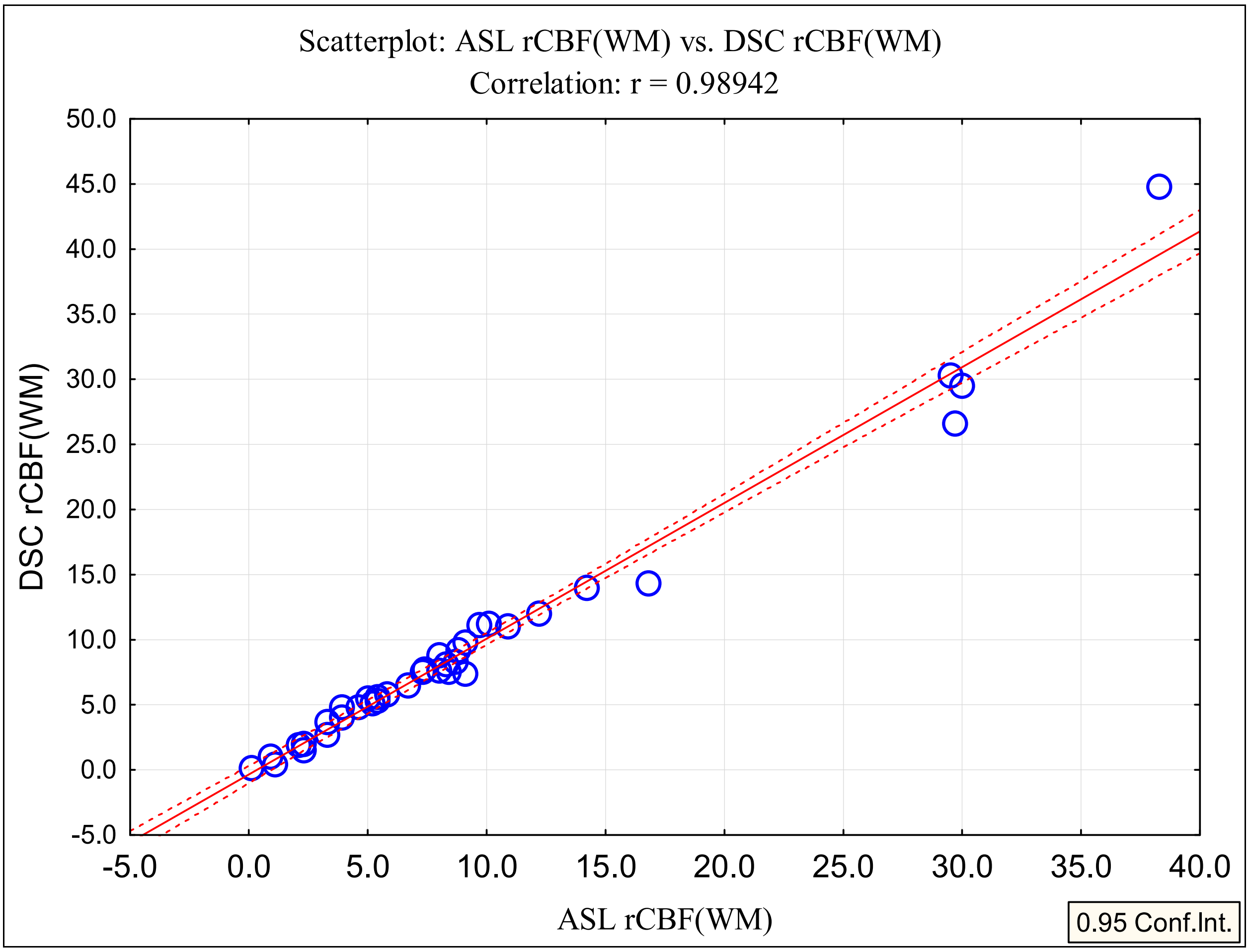
Significant correlation seen in rCBF ratios of lesion with grey matter derived from ASL & DSC techniques (p - 0.0001* and r - 0.9) (Table 10). Scatter plot diagram shows linear correlation between the rCBF ratios of lesion with grey matter from both the techniques (Graph 7).

Table 11: Correlation between ASL rCBF ratio of lesion & white matter {ASL rCBF (WM)} and DSC rCBF ratio of lesion & white matter {DSC rCBF (WM)}.

Variables	Correlation between ASL rCBF (WM) with		
	r-value	t-value	p-value
DSC rCBF (WM)	0.9894	40.3406	0.0001*

*p<0.05

Graph 8: Scatter plot showing the Correlation between ASL rCBF ratio of lesion & white matter {ASL rCBF (WM)} and DSC rCBF ratio of lesion & white matter {DSC rCBF (WM)}.

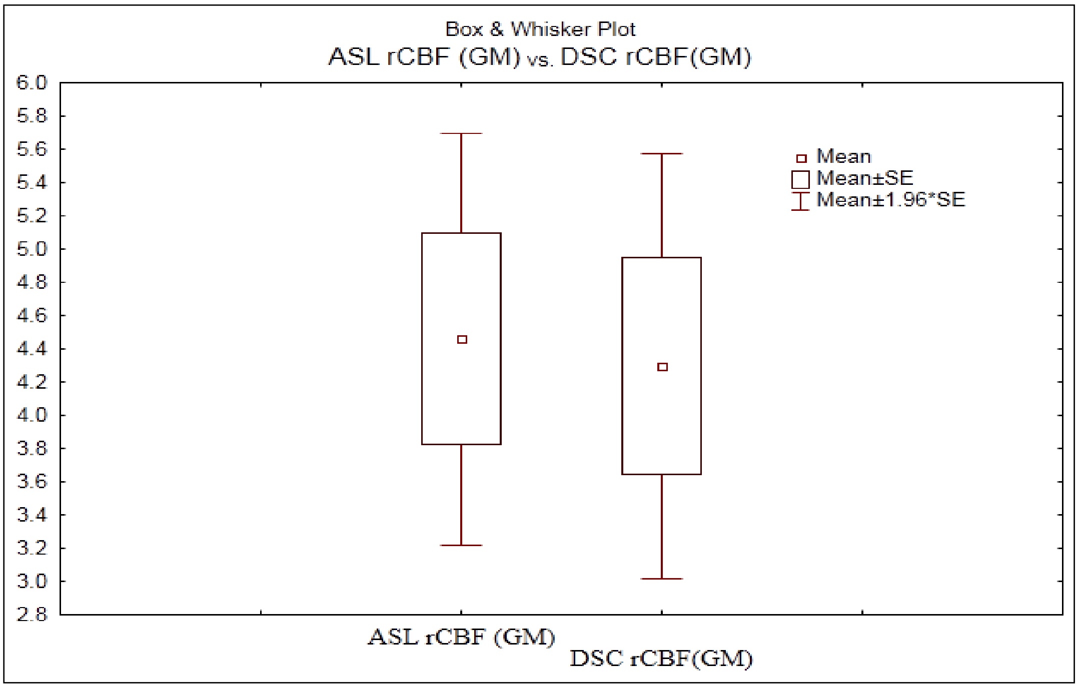


Significant correlation seen in rCBF ratios of lesion with white matter derived from ASL & DSC techniques (p - 0.0001* and r - 0.9) (Table 11). Scatter plot diagram shows linear correlation between the rCBF ratios of lesion with white matter from both the techniques (Graph 8).

Table 12: Comparison of ASL rCBF (GM) and DSC rCBF (GM) by dependent t test.

Methods	Mean	SD	Mean Diff.	SD Diff.	t-value	p-value
ASL rCBF (GM)	4.46	3.85	0.16	0.52	1.8853	0.0675
DSC rCBF(GM)	4.30	3.97				

Graph 9: Box plot showing Comparison of ASL rCBF (GM) and DSC rCBF (GM) by dependent t test.



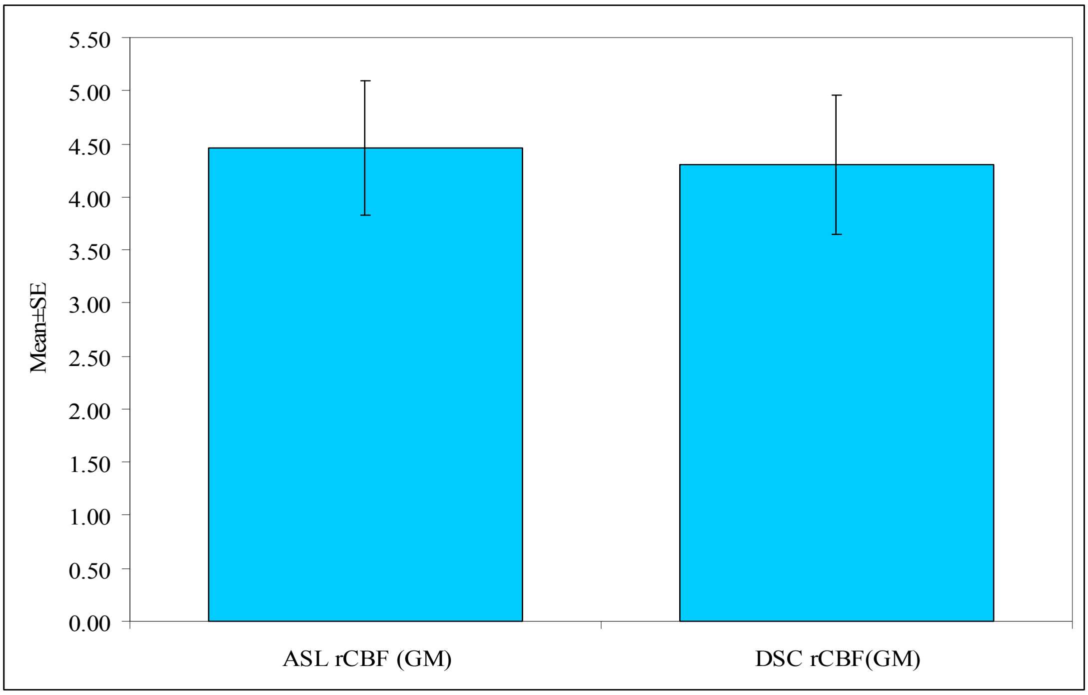
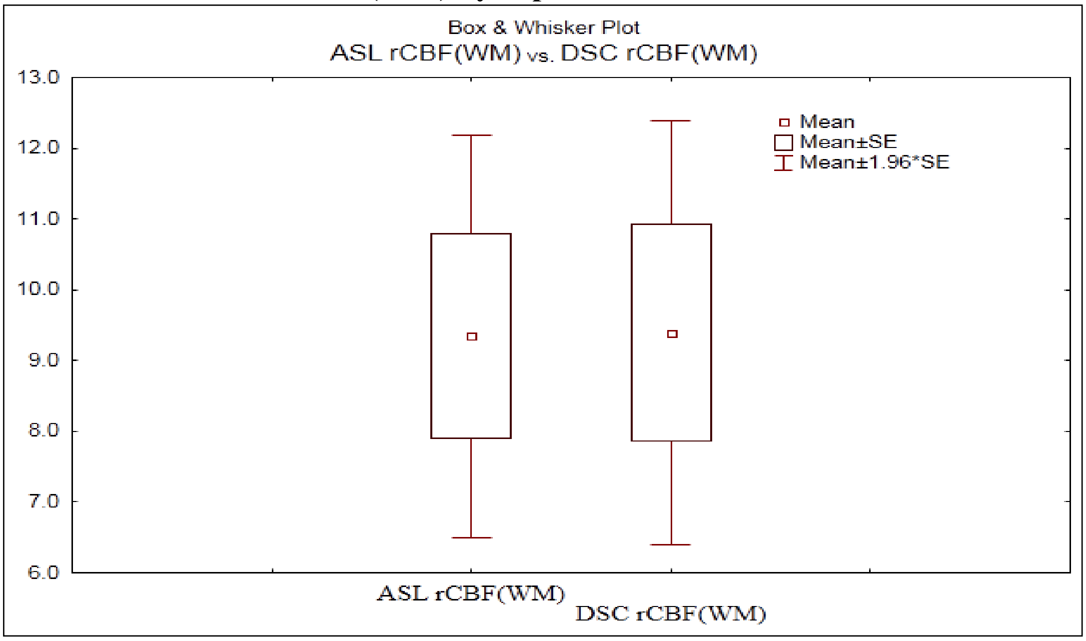


Table 13: Comparison of ASL rCBF (WM) and DSC rCBF (WM) by dependent t test.

Methods	Mean	SD	Mean Diff.	SD Diff.	t-value	p-value
ASL rCBF (WM)	9.35	8.83	-0.04	1.40	-0.1924	0.8485
DSC rCBF (WM)	9.39	9.31				

Graph 10: Box plot showing Comparison of ASL rCBF (WM) and DSC rCBF (WM) by dependent t test



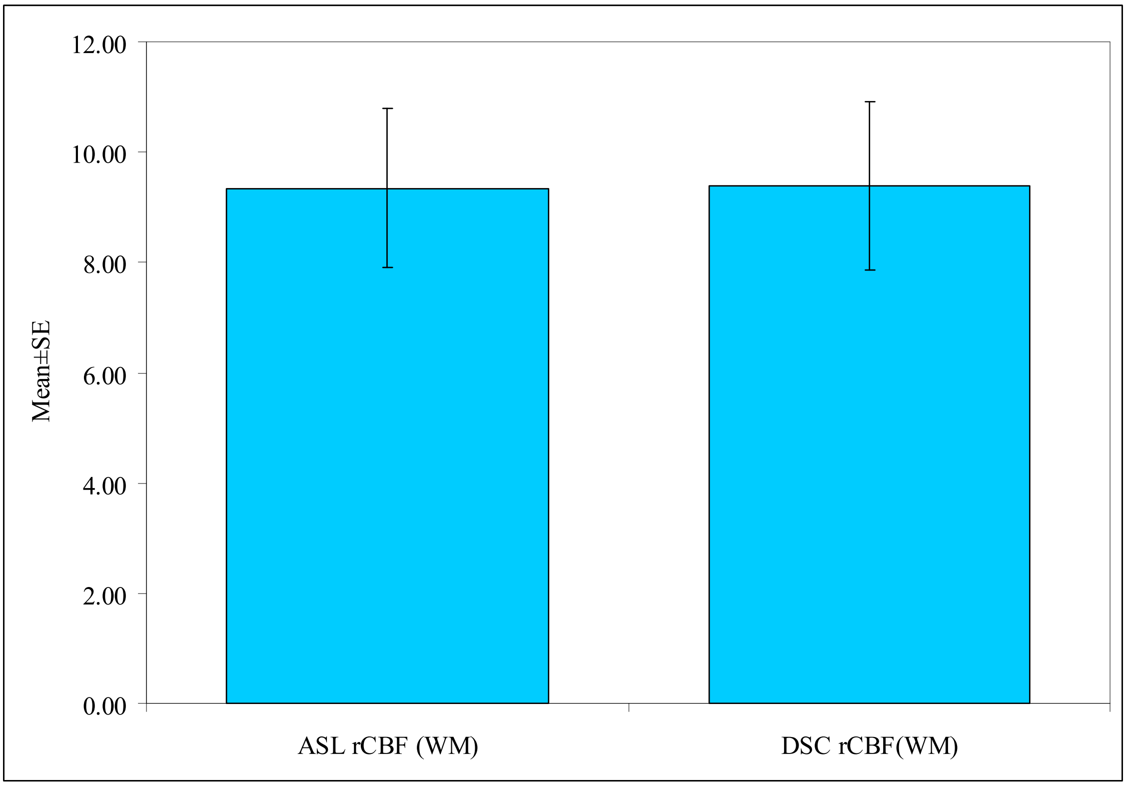


Table 14: Summery of ASL rCBF (GM), ASL rCBF (WM), DSC rCBF (GM), DSC rCBF (WM) and DSC rCBV (WM) ratios in LOW GRADE GLIOMAS.

Summery	ASL rCBF (GM)	ASL rCBF (WM)	DSC rCBF (GM)	DSC rCBF (WM)	DSC rCBV (WM)
N	5.00	5.00	5.00	5.00	5.00
Min	0.60	1.10	0.20	0.40	0.60
Max	2.80	7.30	2.50	7.50	5.90
Mean	1.36	3.34	1.28	3.06	2.58
SD	0.84	2.43	0.87	2.80	2.14
SE	0.38	1.09	0.39	1.25	0.96

Mean rCBF ratios of lesion & white matter derived from ASL and DSC MR perfusion in cases with low grade glioma measures 3.34 +/- 2.43 SD and 3.06 +/- 2.80 SD respectively. Mean rCBV ratios derived from DSC MR perfusion is 2.5 +/- 2.14 SD (Table 14).

Table 15: Summery of ASL rCBF (GM), ASL rCBF (WM), DSC rCBF (GM), DSC rCBF (WM) and DSC rCBV (WM) ratios in HIGH GRADE GLIOMAS.

Summery	ASL rCBF (GM)	ASL rCBF (WM)	DSC rCBF (GM)	DSC rCBF (WM)	DSC rCBV (WM)
N	11.00	11.00	11.00	11.00	11.00
Min	2.20	5.00	2.30	5.50	1.60
Max	9.10	29.70	8.40	26.60	17.90
Mean	5.41	10.95	5.05	10.82	9.55
SD	2.29	7.07	1.96	5.96	5.19
SE	0.69	2.13	0.59	1.80	1.56

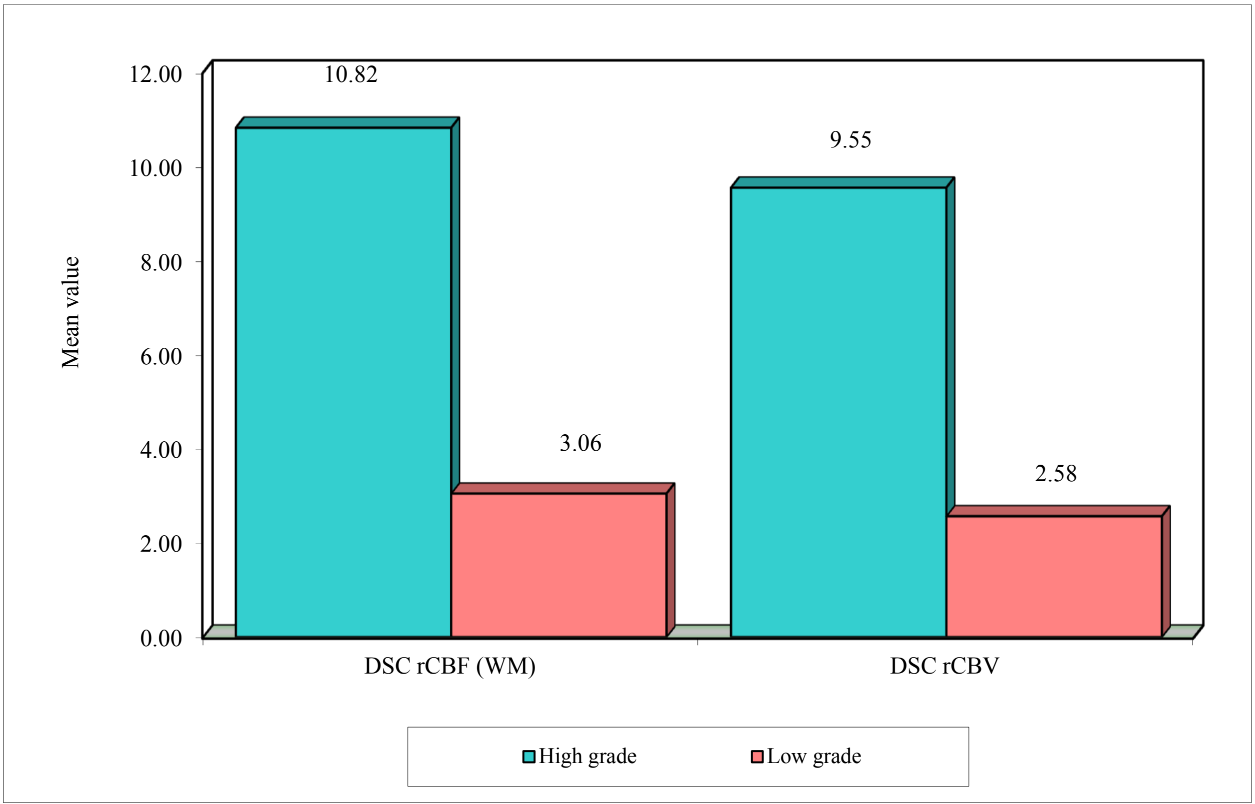
Mean rCBF ratios of lesion and white matter derived from ASL and DSC MR perfusion in cases with high grade glioma measures 10.95 +/- 7.07 SD and 10.82 +/- 5.96 SD respectively. Mean rCBV ratios derived from DSC MR perfusion is 9.55 +/- 5.19 SD (Table 15).

Table 16: Comparison of DSC rCBF (WM) and DSC rCBV (WM) ratio in Low grade and High grade Gliomas cases.

Variable	Glioma	Mean	SD	SE	t-value	P-value
DSC rCBF (WM)	High grade	10.82	5.96	1.80	2.7379	0.0160*
	Low grade	3.06	2.80	1.25		
DSC rCBV (WM)	High grade	9.55	5.19	1.56	2.8528	0.0128*
	Low grade	2.58	2.14	0.96		

*p<0.05

Graph 11: Bar graph showing the comparison of DSC rCBF (WM) and DSC rCBV (WM) in Low grade and High grade Gliomas



In 16 cases of gliomas in our study, considering DSC rCBF ratios and DSC rCBV ratios of lesion and white matter, there was significant difference found in rCBF and rCBV values for high grade and low grade gliomas.

6: DISCUSSION

In this era of advanced imaging techniques in the field of radiology, a new concept of layered diagnosis is formed for systematic reporting of CNS tumors (Table 1) [18]. Conventional imaging has limited specificity in distinguishing brain tumors from other non-neoplastic space occupying brain lesions [23]. It has been seen that all enhancing intra-axial brain lesions are not brain tumors and usually low grade astrocytoma doesn't show enhancement. However, $1/3^{rd}$ of non-enhancing gliomas are malignant. There are different neoplastic and non-neoplastic lesions which show similar imaging findings on conventional imaging, i.e. on contrast enhanced study e.g. high grade glioma (GBM), metastasis and pyogenic abscess shows peripheral rim enhancement and central non enhancing area. It is difficult to evaluate therapeutic assessment on conventional imaging i.e. to distinguish between tumor regression, tumor recurrence & radiation necrosis in post-operative cases who underwent chemotherapy or radiotherapy.

It is important to establish a proper diagnosis without biopsy for planning of treatment and prognosis in brain tumors. Biopsy is an invasive procedure, it has inherent sampling bias and interobserver variability which can result in misdiagnosis or undergrading of the brain tumor if stereotactic biopsy is planned based only on enhancement pattern [11] as highly malignant portion of tumor may not always show post contrast enhancement. To establish proper diagnosis non-invasively and also to differentiate between extra axial from intra axial lesions, benign from malignant, primary brain tumor from metastases, high grade from low grade neoplasms, assessment of therapeutic response and guiding stereotactic biopsies; Advanced MR imaging techniques need to be applied to the conventional MR imaging. Advanced MR imaging techniques such as diffusion weighted imaging (DWI), MR spectroscopy (MRS), MR perfusion and diffusion tensor imaging (DTI); tissue characterization, tissue cellularity, microvascular status of tumor and integrity of adjacent white matter tract can be assessed [13,23,26,28,29]. In study Gadia et al (2018), showed that overall diagnostic accuracy of advanced MRI using MR spectroscopy and MR perfusion, in evaluation of intra-axial brain lesions was 98.57% [26]. Gliomas being the most prevalent brain tumors, it is important in delineation of the whole tumor microvascular hemodynamics, helping in tumor grading and targeted biopsy [31,41]. On conventional imaging, lymphoma and high grade glioma cannot be differentiate, but MR perfusion shows reduced rCBV values in lymphoma compared to malignant glioma [39]. To differentiate high grade glioma and solitary metastasis, rCBV values in the peritumoral areas show higher values in high grade gliomas than in metastases [40]. To differentiate between vasogenic edema versus tumor infiltrative area in GBM, there are two regions surrounding GBM, tumor infiltrative region which shows higher rCBV and MRS with higher malignant pattern, while vasogenic edema showed increased FLAIR values and reduced perfusion which suggest no evidence of tumor infiltration [47]. To differentiate tumor recurrence and radiation necrosis, diffusion restriction in DWI and increased rCBF in perfusion is seen in tumor recurrence than in radiation necrosis [45].

Perfusion weighted-MRI imaging provides information regarding cerebral physiology at capillary level. In brain tumors it helps to distinguish neoplastic from non-neoplastic lesions, high-grade from low-grade glioma, high-grade glioma from metastasis or meningioma or lymphoma, differentiating recurrent tumor from radiation necrosis and surgical planning [13,37,42,45]. Perfusion imaging play a significant role to determine vascularization of tumor, guides stereotactic biopsy from the most appropriate area and enables detection of the grade of the tumor, thereby reducing the number of non-diagnostic biopsies [11,66]. Three MR perfusion techniques are currently in use: dynamic contrast-enhanced (DCE), dynamic susceptibility contrast (DSC), and arterial spin labelling (ASL).

Two major perfusion techniques used are DCE and DSC which require administration of IV contrast agent, where DSC technique is most widely used and studied in literature with extensive clinical experience. DSC technique is a faster dynamic echo-planar imaging scan which is based on T2* weighted imaging with parallel imaging covering the whole brain while injecting the bolus of contrast [12,13,51]. After image acquisition it requires post processing by proper selection of arterial input functioning (AIF), time graphs with significant signal drop and advanced post processing algorithms to obtain perfusion maps [52,53]. It provides qualitative and quantitative evaluation of CBV, CBF and other perfusion parameters. ASL technique does not require injection of the contrast agent and allow three-dimensional exploration of perfusion. ASL is a novel technique which has been studied in the recent years for clinical use. It provides qualitative and quantification evaluation of CBF by using arterial water as an endogenous tracer by labelling blood water protons in cerebral arteries [12,13,52,61]. CBF maps that are derived from ASL are automatically generated without complex human post-processing and acceptable acquisition time on 3T MR scanners which allows its usage in clinical and research purpose. Main objective of this study is to compare the quantitative perfusion values derived from 3D ASL with DSC MR perfusion techniques in evaluation of brain tumors with an aim of considering ASL as an alternative to DSC perfusion in clinical application and research purposes.

Our study recruited, 37 cases of brain tumors (primary and secondary) in all the age groups who underwent MRI BRAIN (PLAIN and CONTRAST with PERFUSION imaging) including both 3D ASL and DSC techniques. Most of the cases were above 40 years of age (62.16 %) (Table 4 & Graph 3) with male predominance (54.05 %) than in females (Table 5 & Graph 4) and highest cases were high grade gliomas (11) followed by meningiomas (9) then low grade gliomas (5) and metastases (5) (Table 6-7 and Graph 5-

6). All the cases underwent standard image processing protocol for both ASL and DSC. rCBF ratios were calculated using same size ROI placing at same site of the lesion and contralateral normal grey & white matter in ASL and DSC techniques for each case. Also rCBV ratios of lesion and contralateral normal white matter from DSC technique were also calculated.

Our study showed significant correlation between ASL rCBF ratio with DSC rCBF ratio of lesion with grey matter and white matter i.e, ASL rCBF (GM) with DSC rCBF (GM) and ASL rCBF (WM) with DSC rCBF (WM) with p value of 0.0001 and r value of 0.9 (Table 10-11). Our study showed evidence to demonstrate close linear correlation between rCBF ratios derived from ASL and DSC techniques (Graph 7-8). Our results were consistent to the previous studies done by Warmuth et al 2003 [57], Van westen et al 2009 [61], Jarnum et al 2009 [62], Jiang j et al 2014 [65] and Neetu soni et al 2017 [67] (Table 17). Our study showed correlation co-efficient (r value) in close approximation with the study done by Van Westen et al and Neetu Soni et al where they obtained grey matter as the reference region. We used grey matter as well as white matter as the reference regions and obtained linear correlation between ASL and DSC derived rCBF ratios with significant correlation co-efficient (r = 0.9) in both the techniques for both grey matter & white matter as the reference regions.

Table 17: Various comparative studies of ASL and DSC perfusion techniques in brain tumors using CBF values

Study	Number of cases	Correlation of ASL and DSC rCBF (correlation coefficient = r)	Reference region
Warmuth et al., 2003 [57]	36	0.8	Contralateral hemisphere
Van westen et al., 2009 [61]	11	0.9	Grey matter
Jarnum et al., 2009 [62]	28	0.8	Cerebellum
Jiang j et al., 2014 [65]	28	0.8	Mirror region
Neetu soni et al., 2017 [67]	30	0.9	Grey matter
Present study	37	0.9	Grey matter
Present study	37	0.9	White matter

Considering the reports in the literature and our study, ASL is a non-invasive repeatable technique which does not require contrast agent and complex human post processing for deriving CBF values which can be used as an alternative to DSC technique for clinical application in brain tumors for grading, guiding stereotactic biopsies, surgical planning, differentiating recurrent tumor from radiation necrosis and differentiating high grade glioma from metastases / lymphoma. ASL can be used in patients with contraindication to contrast agent (anaphylaxis to contrast, pregnancy, lactation and renal disorders), patients requiring repeated follow ups, pediatric cases and clinical trials of new anti-angiogenic drugs. In certain pathogenesis of brain tumors causes severe impairment of blood brain barrier (meningioma, GBM) causing leaky capillaries resulting in extravasation of contrast agent into extravascular area, this causes miscalculations of DSC perfusion maps [62,63]. ASL show less susceptibility to the effects of breakdown in blood brain barrier [60,68]. ASL can be repeated if the acquisition is poor due to artifacts, whereas

DSC will require another bolus of contrast agent for acquisition, as during the first passage effect of contrast agent.

Few limitations of ASL are, it provides quantification of only CBF values. ASL gives low resolution images compared to DSC and takes longer acquisition time than DSC. Our MR perfusion protocol takes 4 mins 52 sec for 3D ASL and 1 min 53 sec for DSC.

In the evaluation of the perfusion parameters in brain tumors, rCBV values is a most important parameter derived from DSC technique which helps in grading of tumor i.e high grade glioma (HGG) or low grade glioma (LGG) and indicator of increase in tumor vascularity [33,41,42,56,68]. In the literature, law et al [68] and zonari et al [56] found that rCBV is a valuable parameter in grading of glioma amongst all MR techniques. Law et al in 2003 [68] reported the mean rCBV value to be 2.14 for LGG and 5.18 for HGG. Lev MH et al (2004) showed cut off value of 1.5 for rCBV to differentiate between LGGs and HGGs with 100% PPV [41]. Hakyemez et al in 2005 reported cutoff values of 2.0 for differentiating LGG and HGG, and found mean rCBV values of 3.32 for HGG and 1.16 for LGG [42]. Emine Sevcan Ata et al in 2016 reported mean rCBV of 2.0 for benign lesions and 4.06 for malignant lesions [66]. rCBV ratios differ between various studies may be due to variations in the imaging protocol, post processing algorithm and interobserver variability. Our study demonstrated the mean rCBV ratio of 2.58 for low grade glioma and 9.55 for high grade glioma (Table 14-15) where the values are slightly higher compared to previous studies which may be because we selected region of interest (ROI) in the area of maximum perfusion values in the tumor at similar regions in view of comparing ASL and DSC techniques. However our study showed significant difference between the rCBV ratios in low grade and high grade gliomas (Graph 13 & Table 16). rCBV ratio were high for high grade gliomas with mean value of 9.5 and low for low grade gliomas with mean value of

2.5 (Table 14-15), which suggested its use in grading of brain tumors. Recently some studies have reported that CBF has diagnostic value similar to that of CBV [42,66]. Our data also showed significant difference in rCBF ratios in high grade and low grade gliomas (Graph 13 & Table 16). We obtained the mean rCBF ratio (lesion and white matter) by ASL & DSC of 10.9 & 10.8 for high grade gliomas and 3.3 & 3.06 for low grade gliomas respectively (Table 14-15). Therefore, rCBF ratios and rCBV ratio can improve diagnostic differentiation of high grade and low grade gliomas and can be used for histopathological grading.

7: CONCLUSION

- Advanced MRI techniques like diffusion weighted imaging, spectroscopy, perfusion imaging and diffusion tensor imaging improves the diagnostic ability of various brain tumors and helps in treatment planning and prognosis.
- In MR perfusion imaging, most commonly used techniques are dynamic susceptibility contrast (DSC) and dynamic contrast enhanced (DCE) which requires contrast agent. DSC technique is widely used, most studied and extensive experience in clinical application.
- ASL is non invasive, repeatable and low cost MR perfusion technique with acceptable acquisition time in 3T MR scanner and allows to derive CBF maps comparable to DSC technique without requirement of contrast administration and can be used in brain tumors for grading, guiding stereotactic biopsies, surgical planning, differentiating recurrent tumor from radiation necrosis and differentiating high grade glioma from metastases / lymphoma.
- ASL is a good alternative technique to DSC which can be used in patients with contraindication to contrast agents such as anaphylaxis to contrast, pregnancy, lactation & renal disorders, in patients requiring repeated follow ups to avoid contrast administration, pediatric neuroimaging and also for clinical trials of new anti-angiogenic drugs.
- Perfusion imaging is valuable complementary technique in the diagnostic differentiation of high grade and low grade gliomas in the preoperative assessment. rCBV ratios and rCBF ratios can be used for histopathological grading of gliomas.

8: SUMMARY

- The study was an one year observational study.
- Patients referred to the department of radiology with brain tumors either suspected clinically / found incidentally on imaging.
- All the patients underwent MRI BRAIN (PLAIN AND CONTRAST with PERFUSION IMAGING) including both 3D ASL and DSC techniques using 3T MRI SCANNER 'MAGNETOM Spectra' (manufactured by Siemens).
- 37 cases were included in the study after considering the inclusion and exclusion criteria. Image processing and data analysis done on Siemens Multi-modality work station using Siemens software NUMARIS/4, version syngo MR E11.
- Perfusion MR imaging provides information regarding cerebral physiology at capillary level. It has significant role in evaluation of intracranial neoplasms which helps to estimate neo-angiogenesis of tumor for grading, guiding stereotactic biopsies, surgical planning, differentiating recurrent tumor from radiation necrosis and differentiating high grade glioma from metastases / lymphoma.
- Three MR perfusion techniques are currently in use: dynamic contrast-enhanced (DCE), dynamic susceptibility contrast (DSC), and arterial spin labelling (ASL).
- DSC technique is most widely used and studied in literature with extensive clinical experience which requires contrast administration. ASL technique does not require injection of the contrast agent and has been studied in the recent years for clinical use.
- Purpose of this study was to compare the perfusion parameters of two perfusion techniques i.e, ASL technique with DSC technique with an aim to evaluate the use of ASL as an alternative to DSC perfusion in imaging of brain tumors.

- rCBF ratios were calculated by ASL and DSC MR perfusion techniques and the results were compared, showed linear correlation between rCBF ratios derived from both the techniques. Suggesting to use ASL as an alternative to DSC MR perfusion technique.
- ASL is non invasive, repeatable and low cost MR perfusion technique with acceptable acquisition time in 3T MR scanner and allows to derive CBF maps comparable to DSC technique without requirement of contrast administration.
- ASL is a good alternative technique to DSC which can be used in patients with contraindication to contrast agents such as anaphylaxis to contrast, pregnancy, lactation & renal disorders, in patients requiring repeated follow ups to avoid repeated contrast administration, pediatric neuroimaging and also for clinical trials of new anti-angiogenic drugs.
- Our study also showed significant difference of rCBF ratios and rCBV ratios in high grade and low grade gliomas. Perfusion imaging is valuable complementary technique in the diagnostic differentiation of high grade and low grade gliomas in the preoperative assessment. rCBV ratios and rCBF ratios can be used for histopathological grading of gliomas.

9: BIBLIOGRAPHY

1. World Brain Tumour Day2019 | National Health Portal Of India [Internet]. [cited 2020 Nov 8]. Available from: https://www.nhp.gov.in/world-brain-tumour-day2019_pg

2. Dasgupta A, Gupta T, Jalali R. Indian data on central nervous tumors: A summary of published work. South Asian J Cancer. 2016;5(3):147–53.

3. Perkins A, Liu G. Primary Brain Tumors in Adults: Diagnosis and Treatment. Am Fam Physician. 2016 Feb 1;93(3):211–7.

4. Anne G Osborn. OSBORN BRAIN IMAGING, PATHOLOGY, AND ANATOMY SECOND EDITION, chapter 16.

5. Quinn T. Ostrom. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012–2016.

6. Patel AP, Fisher JL, Nichols E, Abd-Allah F, Abdela J, Abdelalim A, et al. Global, regional, and national burden of brain and other CNS cancer, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019 Apr;18(4):376–93.

7. Lapointe S, Perry A, Butowski NA. Primary brain tumours in adults. Lancet Lond Engl. 2018 04;392(10145):432–46.

8. Chandana SR, Movva S, Arora M, Singh T. Primary brain tumors in adults. Am Fam Physician. 2008 May 15;77(10):1423–30.

9. David n louis A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol (Berl). 2016 Jun;131(6):803–20.

10. Huisman TAGM. Tumor-like lesions of the brain. Cancer Imaging. 2009 Oct 2;9(Special issue A):S10–3.

11. Kelly PJ, Daumas-Duport C, Kispert DB, Kall BA, Scheithauer BW, Illig JJ. Imaging-based stereotaxic serial biopsies in untreated intracranial glial neoplasms. J Neurosurg. 1987 Jun;66(6):865–74.

12. Essig M, Nguyen TB, Shiroishi MS, Saake M, Provenzale JM, Enterline DS, et al. Perfusion MRI: The Five Most Frequently Asked Clinical Questions. Am J Roentgenol. 2013 Sep;201(3):W495–510.

13. Villanueva-Meyer JE, Mabray MC, Cha S. Current Clinical Brain Tumor Imaging. Neurosurgery. 2017 Sep 1;81(3):397–415.

14. Mauricio Castillo. history and evolution of brain tumor imaging: insight through radiology- Mauricio Castillo, oct 2014.

15. Shekhar K. Assessment of Diagnostic Efficacy of CT Scan and MRI in Detecting Brain Tumors. :4.

16. Poussaint TY, Panigrahy A, Huisman TAGM. Pediatric brain tumors. Pediatr Radiol. 2015 Sep 1;45(3):443–53.

17. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. The 2007 WHO classification of tumors of central nervous system. 2007 Aug; 114(2): 97–109.

18. Johnson DR, Guerin JB, Giannini C, Morris JM, Eckel LJ, Kaufmann TJ. 2016 Updates to the WHO Brain Tumor Classification System: What the Radiologist Needs to Know. RadioGraphics. 2017 Oct 13;37(7):2164–80.

19. 10 Most Common Brain Tumor Symptoms: Signs of Brain Cancer [Internet]. Cytecare Hospital in Bangalore. 2019 [cited 2020 Nov 15]. Available from: https://cytecare.com/blog/brain-cancer-the-10-most-common-symptoms/

20. ENGLOT DJ, CHANG EF, VECHT CJ. Epilepsy and brain tumors. Handb Clin Neurol. 2016;134:267–85.

21. Upadhyay N, Waldman AD. Conventional MRI evaluation of gliomas. Br J Radiol. 2011 Dec;84(Spec Iss 2):S107–11.

22. Cha S. Update on brain tumor imaging. Curr Neurol Neurosci Rep. 2005 May;5(3):169–77.

23. Al-Okaili RN, Krejza J, Wang S, Woo JH, Melhem ER. Advanced MR Imaging Techniques in the Diagnosis of Intraaxial Brain Tumors in Adults. RadioGraphics. 2006 Oct;26(suppl_1):S173–89.

24. Pierallini A, Bonamini M, Bozzao A, Pantano P, Stefano DD, Ferone E, et al. Supratentorial diffuse astrocytic tumours: proposal of an MRI classification. Eur Radiol. 1997;7(3):395–9.

25. Antonio M P Omuro, CCL Karima Mokhtari, Jean-Yves Delattre. Pitfalls in the diagnosis of brain tumours. The Lancet Neurology, 5(11), 937–948 | 10.1016/s1474-4422(06)70597-x [Internet]. [cited 2020 Nov 16]. Available from: https://sci-hub.se/

26. Gadia DP, Chavda D, Sankar DL an. ROLE OF MAGNETIC RESONANCE IMAGING (MRI) IN INTRACRANIAL SPACE OCCUPYING LESIONS. Int J Sci

Res [Internet]. 2018 Apr 11 [cited 2018 Nov 25];7(2). Available from: https://wwjournals.com/index.php/ijsr/article/view/1683

27. Ostergaard L, Hochberg FH, Rabinov JD, Sorensen AG, Lev M, Kim L, et al. Early changes measured by magnetic resonance imaging in cerebral blood flow, blood volume, and blood-brain barrier permeability following dexamethasone treatment in patients with brain tumors. J Neurosurg. 1999 Feb;90(2):300–5.

28. Abdolmohammadi J, Faeghi F, Arefan D, Zali A, Haghighatkhah H, Amiri J. The Role of Single Voxel MR Spectroscopy, T2 Relaxation Time and Apparent Diffusion Coefficient in Determining the Cellularity of Brain Tumors by MATLAB Software. Asian Pac J Cancer Prev [Internet]. 2018 Oct [cited 2018 Dec 8];(10). Available from: http://journal.waocp.org/article_69129.html

29. Barajas RF, Rubenstein JL, Chang JS, Hwang J, Cha S. Diffusion-weighted MR imaging derived apparent diffusion coefficient is predictive of clinical outcome in primary central nervous system lymphoma. AJNR Am J Neuroradiol. 2010 Jan;31(1):60–6.

30. Neska-Matuszewska M, Bladowska J, Sąsiadek M, Zimny A. Differentiation of glioblastoma multiforme, metastases and primary central nervous system lymphomas using multiparametric perfusion and diffusion MR imaging of a tumor core and a peritumoral zone—Searching for a practical approach. PLoS ONE [Internet]. 2018 Jan 17 [cited 2020 Nov 19];13(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5771619/

31. Zhang J, Liu H, Tong H, Wang S, Yang Y, Liu G, et al. Clinical Applications of Contrast-Enhanced Perfusion MRI Techniques in Gliomas: Recent Advances and Current Challenges. Contrast Media Mol Imaging [Internet]. 2017 Mar 20 [cited 2018 Dec 23];2017. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5612612/

32. Borja MJ, Plaza MJ, Altman N, Saigal G. Conventional and Advanced MRI Features of Pediatric Intracranial Tumors: Supratentorial Tumors. Am J Roentgenol. 2013 Apr 25;200(5):W483–503.

33. Jain RK, di Tomaso E, Duda DG, Loeffler JS, Sorensen AG, Batchelor TT. Angiogenesis in brain tumours. Nat Rev Neurosci. 2007 Aug;8(8):610–22.

34. B R Rosen. Perfusion imaging with NMR contrast agents [Internet]. [cited 2020 Nov 19]. Available from: https://pubmed.ncbi.nlm.nih.gov/2345506/

35. Xiao H-F, Chen Z-Y, Lou X, Wang Y-L, Gui Q-P, Wang Y, et al. Astrocytic tumour grading: a comparative study of three-dimensional pseudocontinuous arterial spin labelling, dynamic susceptibility contrast-enhanced perfusion-weighted imaging, and diffusion-weighted imaging. Eur Radiol. 2015 Dec;25(12):3423–30.

36. Cha S, Tihan T, Crawford F, Fischbein NJ, Chang S, Bollen A, et al. Differentiation of low-grade oligodendrogliomas from low-grade astrocytomas by using quantitative blood-volume measurements derived from dynamic susceptibility contrast-enhanced MR imaging. AJNR Am J Neuroradiol. 2005 Feb;26(2):266–73.

37. Lev MH, Rosen BR. Clinical applications of intracranial perfusion MR imaging. Neuroimaging Clin N Am. 1999 May;9(2):309–31.

38. Kelly PJ, Daumas-Duport C, Scheithauer BW, Kall BA, Kispert DB. Stereotactic histologic correlations of computed tomography- and magnetic resonance imaging-defined abnormalities in patients with glial neoplasms. Mayo Clin Proc. 1987 Jun;62(6):450–9.

39. Cha S, Knopp EA, Johnson G, Wetzel SG, Litt AW, Zagzag D. Intracranial mass lesions: dynamic contrast-enhanced susceptibility-weighted echo-planar perfusion MR imaging. Radiology. 2002 Apr;223(1):11–29.

40. Law M, Cha S, Knopp EA, Johnson G, Arnett J, Litt AW. High-grade gliomas and solitary metastases: differentiation by using perfusion and proton spectroscopic MR imaging. Radiology. 2002 Mar;222(3):715–21.

41. Lev MH, Ozsunar Y, Henson JW, Rasheed AA, Barest GD, Harsh GR, et al. Glial Tumor Grading and Outcome Prediction Using Dynamic Spin-Echo MR Susceptibility Mapping Compared with Conventional Contrast-Enhanced MR: Confounding Effect of Elevated rCBV of Oligodendroglimoas. Am J Neuroradiol. 2004 Feb 1;25(2):214–21.

42. Hakyemez B, Erdogan C, Ercan I, Ergin N, Uysal S, Atahan S. High-grade and low-grade gliomas: differentiation by using perfusion MR imaging. Clin Radiol. 2005 Apr;60(4):493–502.

43. Law M, Young RJ, Babb JS, Peccerelli N, Chheang S, Gruber ML, et al. Gliomas: Predicting Time to Progression or Survival with Cerebral Blood Volume Measurements at Dynamic Susceptibility-weighted Contrast-enhanced Perfusion MR Imaging1. Radiology. 2008 May;247(2):490–8.

44. Hakyemez B, Erdogan C, Gokalp G, Dusak A, Parlak M. Solitary metastases and high-grade gliomas: radiological differentiation by morphometric analysis and perfusion-weighted MRI. Clin Radiol. 2010 Jan;65(1):15–20.

45. Shah R, Vattoth S, Jacob R, Manzil FFP, O'Malley JP, Borghei P, et al. Radiation necrosis in the brain: imaging features and differentiation from tumor recurrence. Radiogr Rev Publ Radiol Soc N Am Inc. 2012 Oct;32(5):1343–59.

46. Akbari H, Macyszyn L, Da X, Wolf RL, Bilello M, Verma R, et al. Pattern Analysis of Dynamic Susceptibility Contrast-enhanced MR Imaging Demonstrates Peritumoral Tissue Heterogeneity. Radiology. 2014 Nov;273(2):502–10.

47. Artzi M, Bokstein F, Blumenthal DT, Aizenstein O, Liberman G, Corn BW, et al. Differentiation between vasogenic-edema versus tumor-infiltrative area in patients with glioblastoma during bevacizumab therapy: a longitudinal MRI study. Eur J Radiol. 2014 Jul;83(7):1250–6.

48. H Cebeci a, O Aydina, E Ozturk-Isik b, C Gumus b, F Inecikli c, A Bekar d, et al. Assesment of perfusion in glial tumors with arterial spin labeling; comparison with dynamic susceptibility contrast method.Eur j radiol. 2014; 83 (10), 1914-19.

49. Kamble RB, Jayakumar PN, Shivashankar R. Role of dynamic CT perfusion study in evaluating various intracranial space-occupying lesions. Indian J Radiol Imaging. 2015;25(2):162–6.

50. Gaillard, F., Murphy, A. MR perfusion weighted imaging. Reference article, Radiopaedia.org. (accessed on 24 Oct 2021). Gaillard, F., Rock, P. Arterial spin labeling MR perfusion. Reference article, Radiopaedia.org. (accessed on 24 Oct 2021)

51 Knutsson L, Stahlberg F, Wirestam R. Aspects on the accuracy of cerebral perfusion parameters obtained by dynamic susceptibility contrast MRI: A simulation study. Magn Reson Imaging 2004;22:789‑98.

52 Petersen ET, Zimine I, Ho YC, Golay X. Non‑invasive measurement of perfusion: A critical review of arterial spin labelling techniques. Br J Radiol 2006;79:688‑701.

53 Nader Binesh, Marcel M. Maya, Helmuth Schultze-Haakh, Franklin G. Moser, Brain perfusion; how and why. Siemens Medical Solutions, Cypress, CA, USA MAGNETOM Flash 1/2012

54 J.H. Shin, H.K. Lee, B.D. Kwun, J.S. Kim, W. Kang, C.G. Choi, et al., Using relative cerebral blood flow and volume to evaluate the histopathologic grade of cerebral gliomas: preliminary results, AJR Am. J. Roentgenol. 179 (2002)783–789.

55 S. Chawla, S. Wang, R.L. Wolf, J.H. Woo, J. Wang, D.M. O'Rourke, et al.,Arterial spin-labeling and MR spectroscopy in the differentiation of gliomas, AJNR Am.J. Neuroradiol. 28 (2007) 1683–1689.

56 P. Zonari, P. Baraldi, G. Crisi, Multimodal MRI in the characterization of glial neoplasms: the combined role of single-voxel MR spectroscopy, diffusion imaging and echo-planar perfusion imaging, Neuroradiology 49 (2007)795–803.

57. Warmuth C, Gunther M, Zimmer C. Quantification of blood flow in brain tumors: Comparison of arterial spin labeling and dynamic susceptibility‑weighted contrast‑enhanced MR imaging. Radiology 2003 Aug;228 (2):523‑32.

58. Weber MA, Lichy MP, Thilmann C, Gunther M, Delorme S, Zuna I, et al. Assessment of irradiated brain metastases by means of arterial spin‑labeling and dynamic susceptibility‑weighted contrast‑enhanced perfusion MRI: Initial results. Invest Radiol 2004;39:277‑87.

59. H. Kimura, H. Takeuchi, Y. Koshimoto, H. Arishima, H. Uematsu, Y. Kawamura,et al., Perfusion imaging of meningioma by using continuous arterialspin-labeling: comparison with dynamic susceptibility-weighted contrast-enhanced MR images and histopathologic features, AJNR Am. J.Neuroradiol. 27 2006; 85–93.

60. Lehmann P, Monet P, Marco G, Saliou G, Perrin M, Stoquart‑Elsankari S, et al. A comparative study of perfusion measurement in brain tumours at 3 Tesla MR: Arterial spin labeling versus dynamic susceptibility contrast‑enhanced MRI. Eur Neurol 2010;64:21‑6.

61. Knutsson L, van Westen D, Petersen ET, Bloch KM, Holtås S, Ståhlberg F, et al. Absolute quantification of cerebral blood flow: Correlation between dynamic susceptibility contrast MRI and model‑free arterial spin labeling, Magn Reson Imaging 2010;28:1‑7.

62. H. Järnum, E.G. Steffensen, L. Knutsson, E.T. Fründ, C.W. Simonsen, S.Lundbye-Christensen, et al., Perfusion MRI of brain tumours: a comparative study of pseudo-continuous arterial spin labelling and dynamic susceptibility contrast imaging, Neuroradiology 52 2010; 307–317

63. Y. Ozsunar, M.E. Mullins, K. Kwong, F.H. Hochberg, C. Ament, P.W. Schaefer,R.G. Gonzales, M.H. Lev, Glioma recurrence versus radiation necrosis? A pilot comparison of arterial spin labeled, dynamic susceptibility contrast enhanced MRI and FDG-PET imaging, Acad. Radiol. 17 (2010) 282–290.

64. White CM, Pope WB, Zaw T, Qiao J, Naeini KM, Lai A, et al. Regional and voxel‑wise comparisons of blood flow measurements between dynamic susceptibility contrast magnetic resonance imaging (DSC‑MRI) and arterial spin labeling (ASL) in brain tumors. J. Neuroimaging 2014;24:23‑30.

65. Jiang J, Zhao L, Zhang Y, Zhang S, Yao Y, Qin Y, et al. Comparative analysis of arterial spin labeling and dynamic susceptibility contrast perfusion imaging for quantitative perfusion. Int J Clin Exp Pathol 2014;15:2790‑9.

66. Ata ES, Turgut M, Eraslan C, Dayanir YO. Comparison between dynamic susceptibility contrast magnetic resonance imaging and arterial spin labelling techniques in distinguishing malignant from benign brain tumors. Eur J Radiol 2016;85:1545‑53.

67. Neetu Soni, Devender Pal S Dhanota, Sunil Kumar1, Awadhesh K Jaiswal, Arun K Srivastava. Perfusion MR imaging of enhancing brain tumors: comparison of arterial spin labeling technique with dynamic susceptibility contrast technique. Neuroradiology india: 2017; 65; 5; 1046-1052

68 M law, S yang, H wang, JS Babb, G johnson, S cha et al.,Glioma grading: sensitivity, sepecificity and predictive values of perfusion MR imaging and proton MR spectroscopy imaging compared with conventional MR imaging, AJNR Am. J. Neuroradiol. 24 (2003) 1989-1998.

10: ANNEXURES

ANNEXURE I –CONSENT FORM

TITLE OF THE STUDY: "COMPARISON OF ARTERIAL SPIN LABELING TECHNIQUE WITH DYNAMIC SUSCEPTIBILITY CONTRAST TECHNIQUE OF PERFUSION MR IMAGING IN ENHANCING BRAIN TUMORS"

INTRODUCTION AND PURPOSE:

Brain tumors are leading cause of morbidity & mortality in all age groups, Proper treatment planning and monitoring usually help in improving quality and expectancy of life in brain tumor patients in view of neurosurgical planning, radiotherapy and chemotherapy. According to Government of India 2019 data, incidence of central nervous system (CNS) tumors ranges from 5-10 per 100,000 population and is showing an increasing trend. Prevalence of brain tumors in India is approximately 2% of all malignancies.

MR perfusion has significant role in evaluation of intracranial neoplasms which helps to estimate neo-angiogenesis of tumor for grading & extension, guiding stereotactic biopsies, and surgical planning. DSC technique which uses contrast agent, most superior and widely used MR perfusion technique with extensive clinical experience, whereas ASL is non-invasive and is gaining its importance in recent years. The primary aim of this study is to evaluate the use of ASL as an alternative to DSC MR perfusion and can be used in patients with contraindication to contrast agent, requiring repeated follow ups and clinical application.

PROCEDURE:

I request you to kindly participate in the study titled **"COMPARISON OF ARTERIAL SPIN LABELING TECHNIQUE WITH DYNAMIC SUSCEPTIBILITY CONTRAST TECHNIQUE OF PERFUSION MR IMAGING IN ENHANCING BRAIN TUMORS"** at Dr. Prabhakar Kore charitable hospital and Medical Research Centre, Belagavi" is being conducted by REG NO.BS0119009, post graduate in Radiodiagnosis at J. N. Medical College, Belagavi.

We request you to participate in this study as you are eligible to be included. During the study you will be asked questions regarding your present and past medical history and you will be required to answer to the best of your knowledge.

If you agree to participate in the study, please furnish the details pertaining to the study. Scanning equipment to be used is 3T MRI SCANNER 'MAGNETOM Spectra' (manufactured by siemens).

BENEFITS:

- ASL is non invasive, repeatable and low cost MR perfusion technique with acceptable acquisition time and allows to derive CBF maps comparable to DSC technique without requirement of contrast administration.
- Perfusion imaging is valuable complementary technique in the diagnostic differentiation of high grade and low grade gliomas in the preoperative assessment. rCBV ratios and rCBF ratios can be used for histopathological grading of gliomas.

COMPLICATIONS:

- No risk is observed with acquisition of ASL and DSC perfusion techniques.
- Acute allergic-like and physiologic reactions occur following administration of gadolinium-based contrast agents (GBCAs) for MRI examinations. These reactions are uncommon.

ALTERNATIVES:

If you are not willing to take part in the study, your treatment or any other further investigations the patient wants to undergo, in future, in KLE will not be affected by your decision.

VOLUNTARY PARTICIPATION/WITHDRAWAL:

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decides to take part, you can later change my mind and withdraw from the study. Your decision will not change the present or future health care or other services that the you would receive.

COSTS:

NIL (The study is conducted on the participants with brain tumor who are advised MRI BRAIN (P+C) as an investigation by the referring consultant and the participants will bear the charges for it).

PAYMENT FOR PARTICIPATION: No incentive will be paid to you for participating in this study.

COMPENSATION:

In the event that you become injured as a result of taking part in this study, treatment whatever available at KLE charitable hospital, Belagavi, will be offered to me. No reimbursement, compensation or free medical care is given to you.

CONFIDENTIALITY:

All information collected about you during the course of the study will be kept confidential to the extent permitted by the law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

QUESTION:

If any enquiries in the future or in case of research related injury illness, you may contact following person.

Post-Graduate, Department of Radio-Diagnosis. J.N.Medical College, Belagavi	Guide, Professor, Department of Radio-Diagnosis J.N.Medical College, Belagavi	Chairman, College Ethical Dissertation and Research Committee J.N. Medical College Institutional Ethical
		Committee for Human Subjects Research
Ph.____________, Ext. 1163	Ph. No. _________, Ext. 1163	Ph. No: Ext. 1529

CONSENT TO PARTICIPATE IN RESEARCH STUDY:

1. I understand that I am participating in the study, which includes MRI BRAIN PLAIN AND CONTRAST WITH MR PERFUSION.
2. I confirm that I have read and understood the information in the patient information sheet. Procedure is explained to me in detail along with information about the advantages and disadvantages of taking part in the study. I have been given the opportunity to discuss all aspects of the trial, to ask questions and hereby consent to participation in the trial outlined above.
3. I understand that the decision to take part in this study is completely voluntary and I am aware that I can choose to withdraw from the study at any point of time.
4. I consent to the photographing or recording of the procedure to be performed including appropriate portions of my body, for medical, scientific or educational purposes provided my identity is not revealed in the pictures or by the descriptive texts accompanying them.
5. I understand that there is no significant risk involved in the test that would be done in this study.
6. No guarantee or assurance has been given by anyone as to the results that may be obtained.
7. My signature on this form signifies that I have willingly decided to participate after understanding the above information.

Participant's Name/legally authorized representative:……………………

Signature/ Left Thumb impression :…………………………….....

Name and signature of witness:…………………………..

Date:……………………………..

Place:…………………….……….

ANNEXURE II -ETHICAL CLEARANCE LETTER

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed - to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)

JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)

Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu

Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 295 **Date: 24/12/2019**

To.
BS0119009
PG student in Radio-diagnosis,
J. N. Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"COMPARISON OF ARTERIAL SPIN LABELING TECHNIQUE WITH DYNAMIC SUSCEPTIBILITY CONTRAST TECHNIQUE OF PERFUSION MR IMAGING IN ENHANCING BRAIN TUMORS"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE III-PROFORMA

PROFORMA FOR DATA COLLECTION

1. PATIENT DATA:

IPD/OPD NO		DATE	
PATIENT NAME		MRI SCAN NO	
AGE		SEX	

2. HISTORY:

SYMPTOMS	
HEADACHE	PRESENT / ABSENT
VOMITING	PRESENT / ABSENT
SEIZURES	PRESENT / ABSENT
LOSS OF CONSCIOUSNESS	PRESENT / ABSENT
CVA	PRESENT / ABSENT

3. LABORATORY EXAMINATION:

SERUM CREATININE	

4. SYSTEMIC EXAMINATION:

CNS-FOCAL NEUROLOGICAL DEFICITS	PRESENT / ABSENT

5. EVALUATION OF LESION BY MRI SEQUENCES

T1WI	
T2WI	
FLAIR	
DWI AND ADC	
SWI	
PRECONTRAST T1 FS	
POST CONTRAST T1 FS	
OTHERS IF ANY	

6. EVALUATION OF PERFUSION SEQUENCES

ASL

Pt ID	CBF LESION	CBF WM	CBF GM

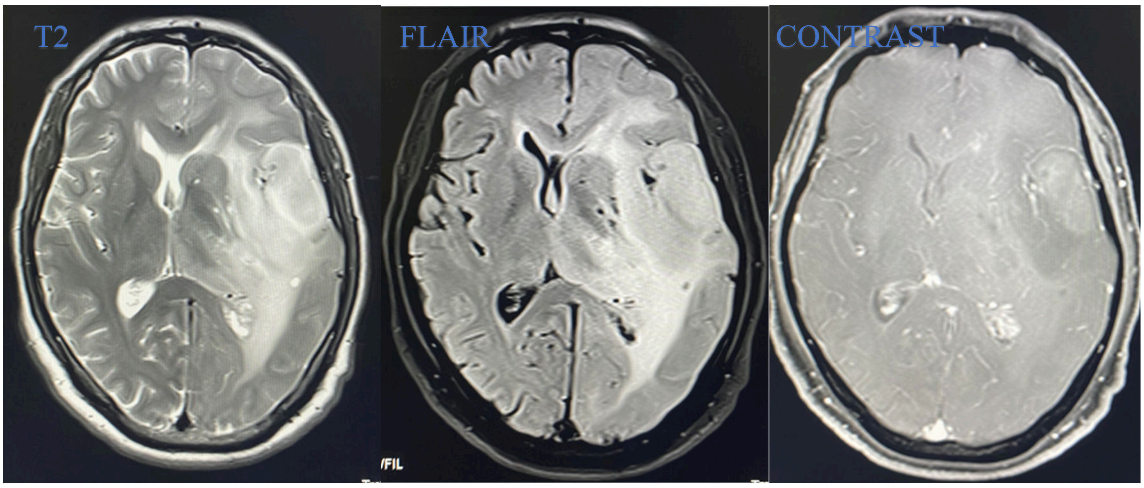
DSC

Pt ID	CBF LESION	CBF WM	CBF GM	CBV LESION	CBV WM

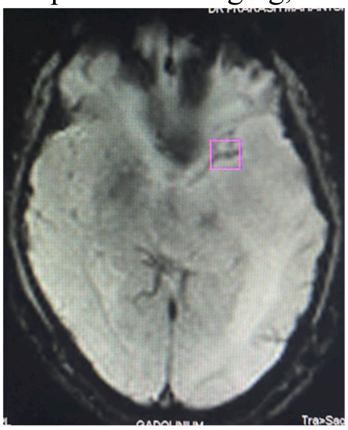
ANNEXURES IV: IMAGES

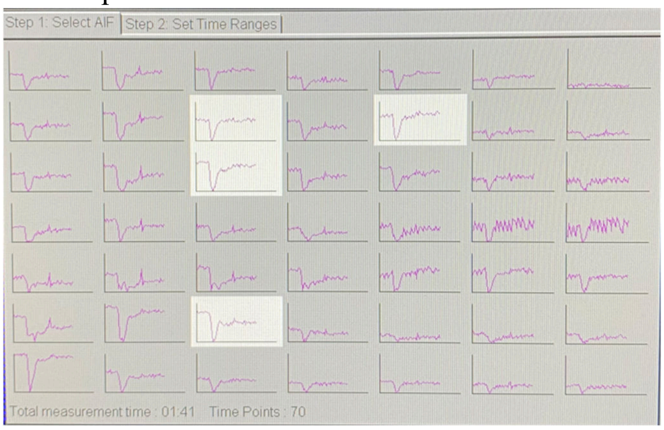
Image 7: Images and description of a case of High grade glioma

36-year male with high grade glioma (GBM). Shows ill-defined T2 and FLAIR hyperintense heterogeneously enhancing intra-axial lesion in the left fronto-temporal region with perilesional edema with mass effect and midline shift.



On perfusion imaging, in DSC technique.

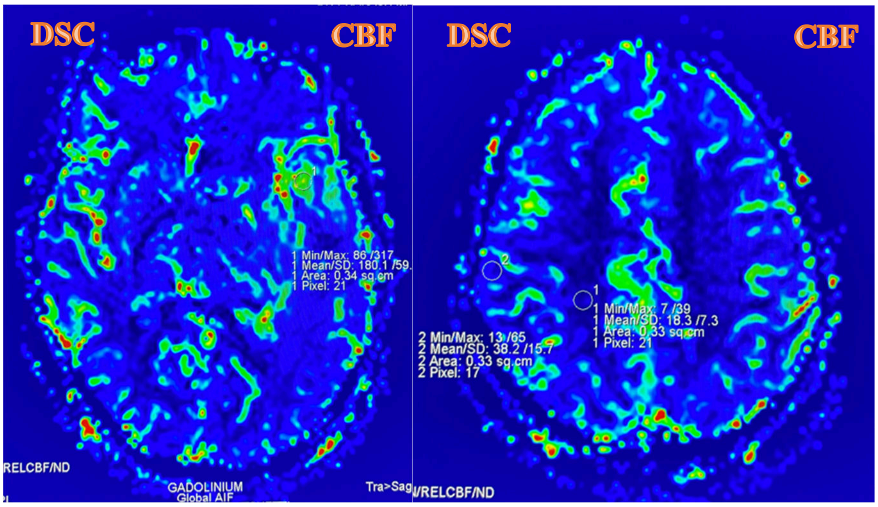




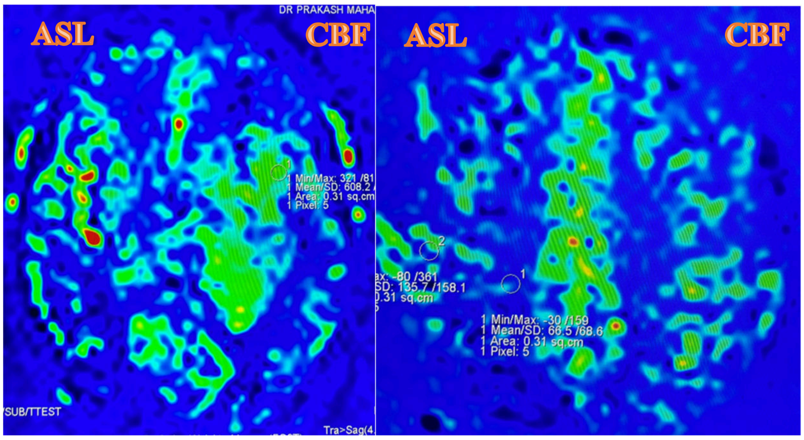
The arterial input function (AIF) square is placed on left MCA on draft images.

Best time graphs with significant signal drop were selected (4 graphs).

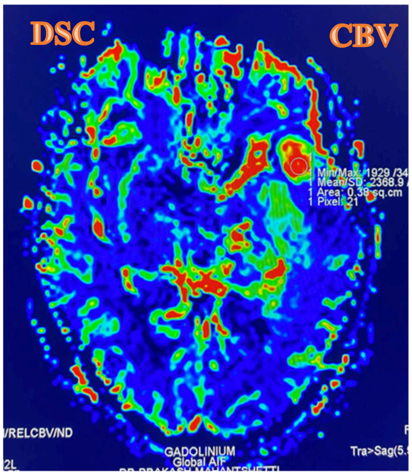
The resulted AIF, with the three time points properly shown. The first one is at the baseline, second at the start of the drop (Gd entry) and the third at the end of the drop (peak of recovery).



In DSC rCBF maps, ROI of 3 mm^2 is placed on the lesion with maximum perfusion values avoiding the region of vessels, hemorrhage, calcifications, necrosis and cysts. Similar size ROI is placed on the contralateral normal grey and white matter.



In ASL rCBF maps, ROI of similar size and site used in DSC rCBF maps were placed in the lesion, contralateral grey and white matter on ASL maps.



In DSC rCBV maps, ROI of 3 mm^2 is placed on the lesion. Similar size ROI is placed on the contralateral healthy white matter. Similar to rCBF maps.

On perfusion imaging, the lesion shows increased rCBF ratios in ASL & DSC techniques and increased rCBV ratios. ASL rCBF (GM) - 4.4, DSC rCBF (GM) - 4.7, ASL rCBF (WM) - 9.1 and DSC rCBF (WM) - 9.8 and DSC rCBV (WM)– 17.9.

Image 8: Images and description of a case of Meningioma.

45-year male with meningioma, shows a well defined T2 iso to hyper intense homogenously enhancing extra-axial lesion in the left parietal region. On perfusion imaging, similar image processing is followed and rCBF & rCBV ratios were calculated. The lesion shows significantly increased rCBF and rCBV ratios. ASL rCBF (GM)- 5.2, DSC rCBF (GM)- 5.6, ASL rCBF (WM)- 10.9 and DSC rCBF (WM)- 11 and DSC rCBV (WM) - 13.5.

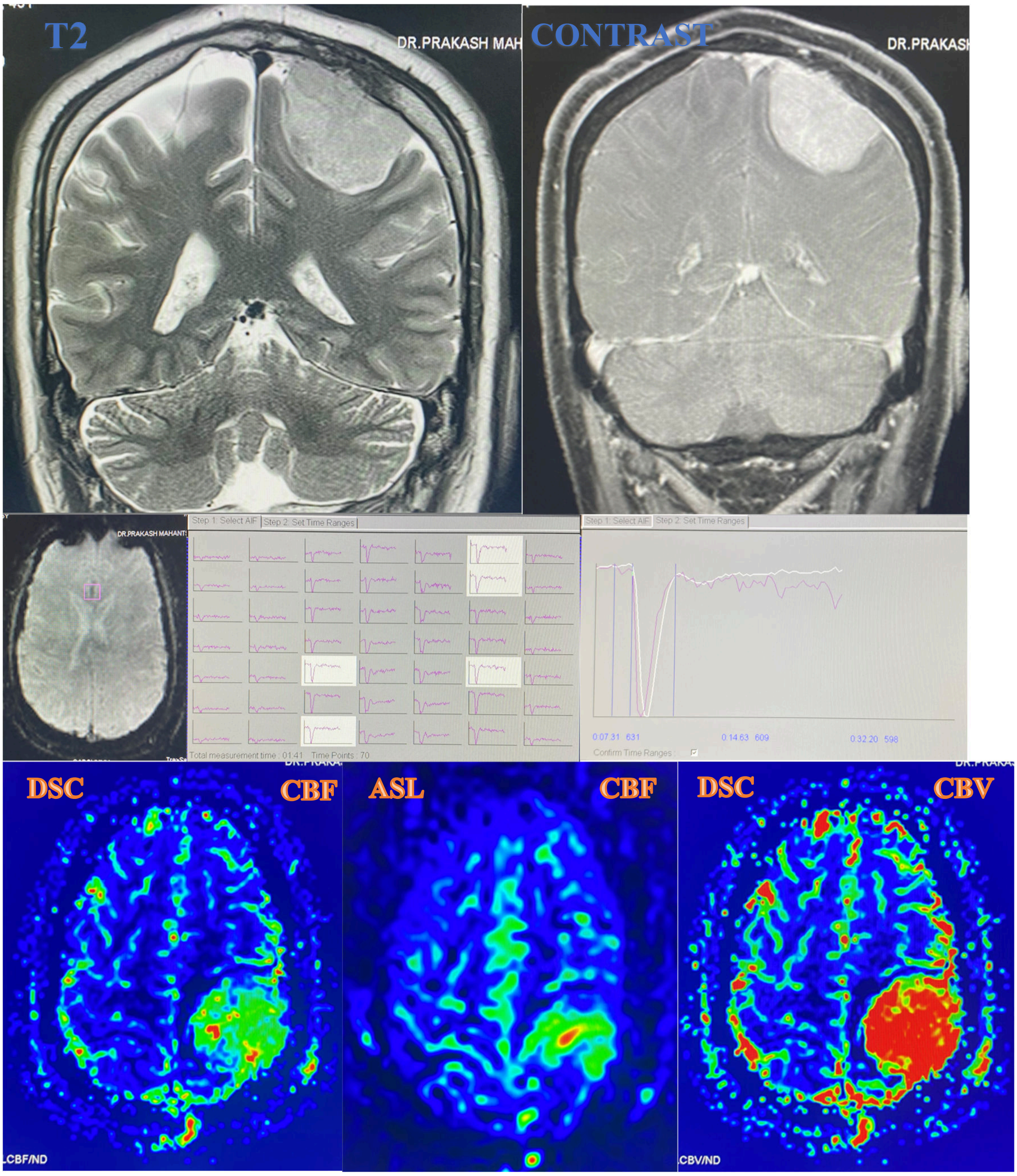


Image 9: Images and description of a case of Cerebral metastases

72-year male with cerebral metastases from carcinoma lung, shows a well-defined T2 mixed intense heterogeneously enhancing intra-axial lesion in the left temporo-parietal region with perilesional edema. On perfusion imaging, ASL rCBF (GM)- 2.8, DSC rCBF (GM)-2.7, ASL rCBF (WM)- 4.6 and DSC rCBF (WM) - 4.8 and DSC rCBV (WM) - 5.3.

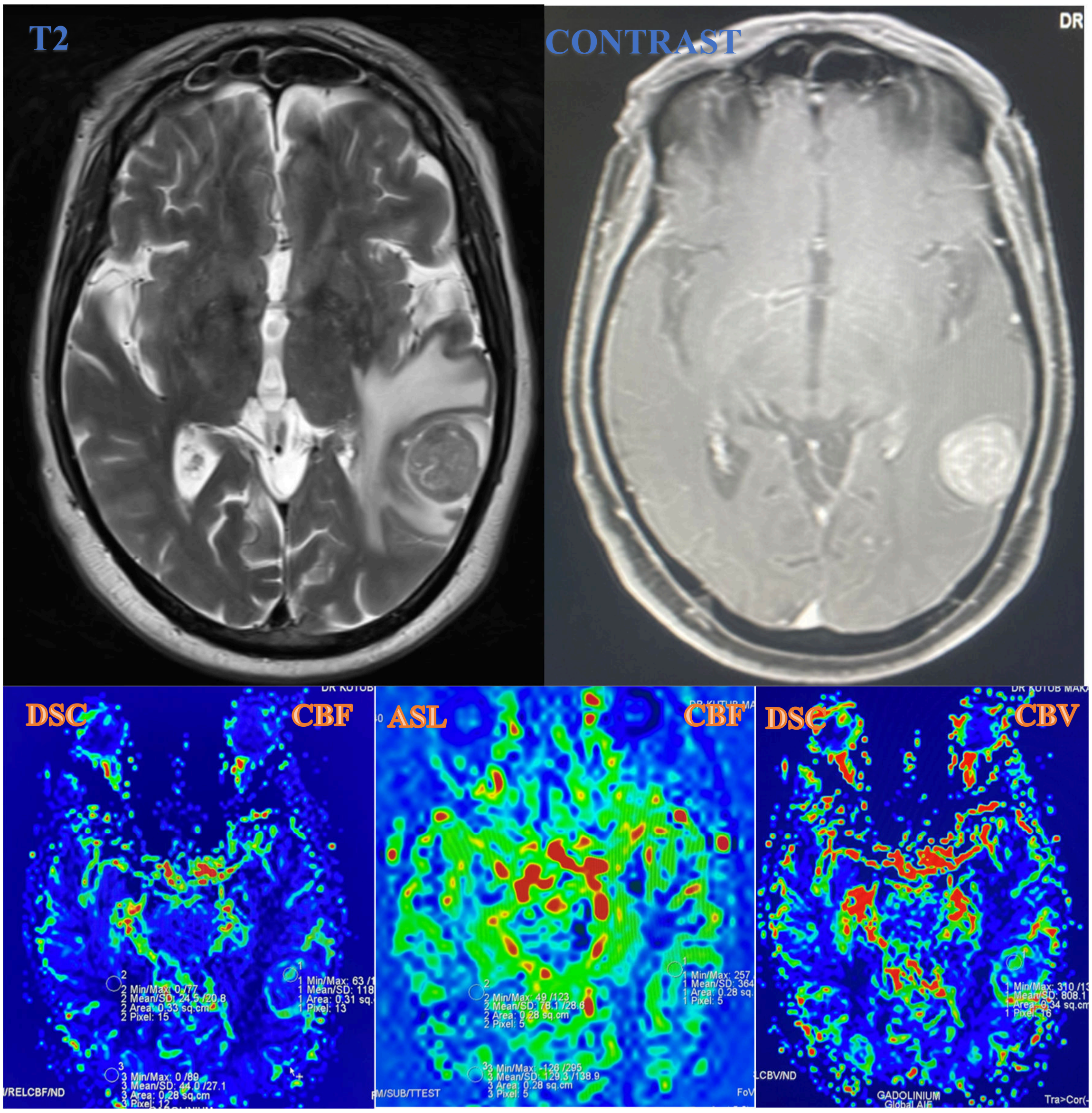


Image 10: Images and description of a case of Low grade oligodendroglioma

41-year male with low grade oligodendroglioma, shows a well defined cortical and subcortical T2 hyperintense mildly enhancing intra-axial lesion in the right fronto-temporo-parietal region. On perfusion the lesion shows mildly increased rCBF and rCBV ratios. On perfusion imaging, ASL rCBF (GM)- 2.8, DSC rCBF (GM)- 2.5, ASL rCBF (WM)- 7.3 and DSC rCBF (WM)- 7.5 and DSC rCBV (WM) - 5.9.

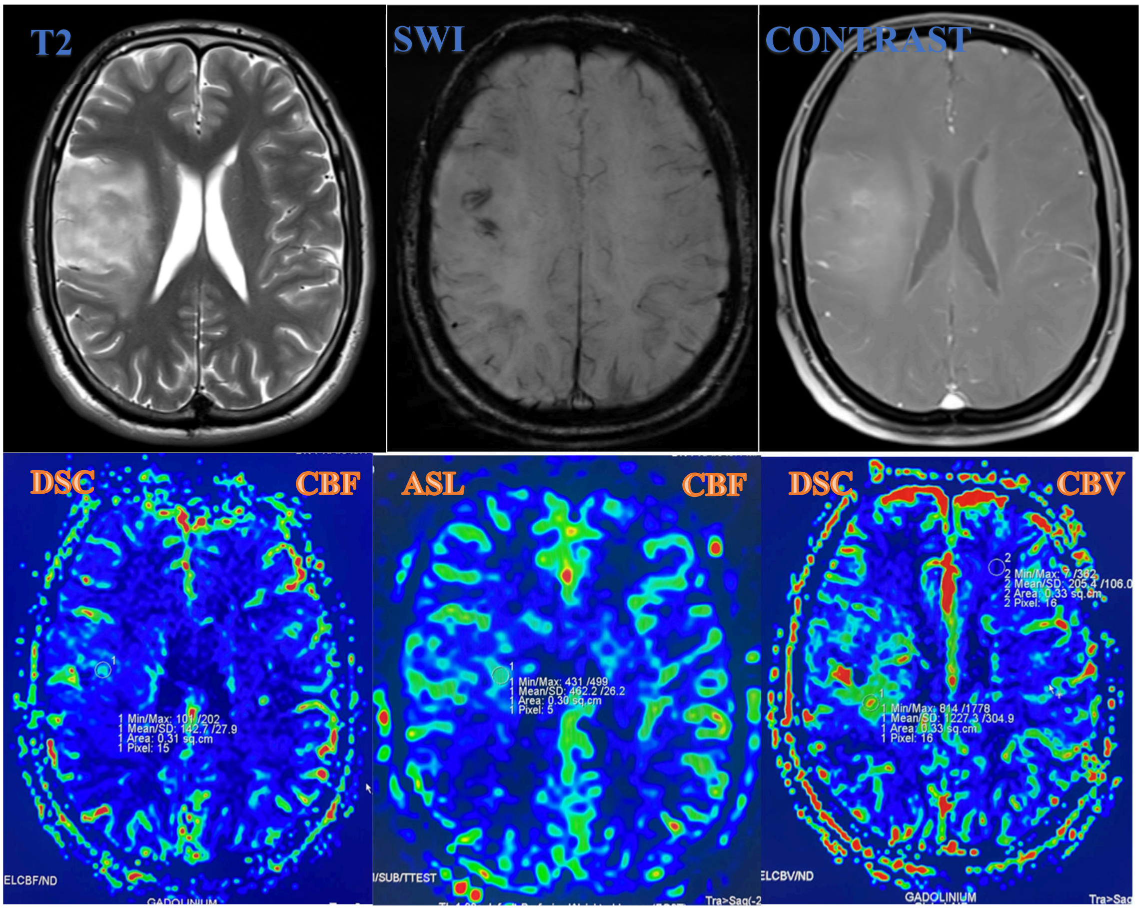


Image 11: Images and description of a case of Low grade astrocytoma

52-year female with low grade astrocytoma, shows a well defined T2 hyperintense mild heterogeneously enhancing intra-axial lesion in the left frontal region. On perfusion, the lesion shows mild increase in rCBF & rCBV ratios. ASL rCBF (GM)- 1.2, DSC rCBF (GM)-1.7, ASL rCBF (WM)- 3.9 and DSC rCBF (WM)- 4.0 and DSC rCBV (WM) -3.4.

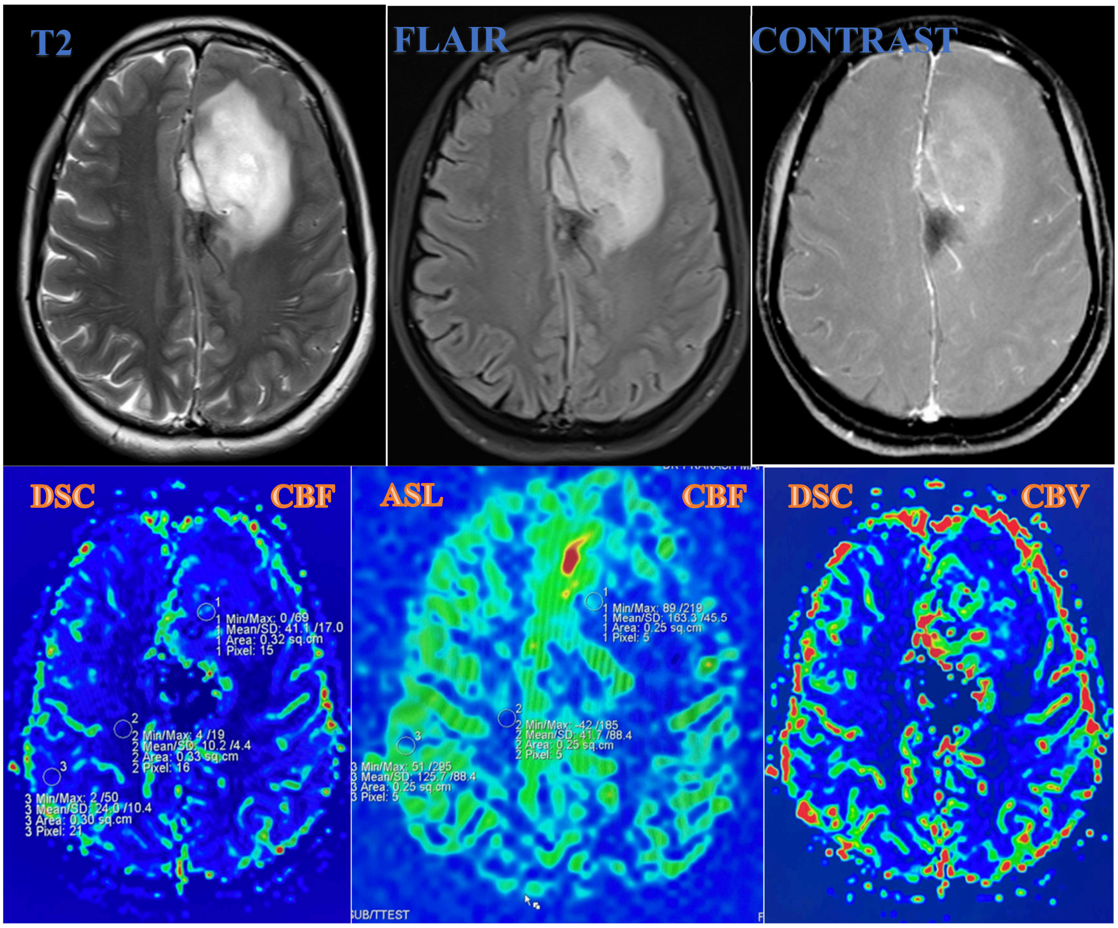


Image 12: Images and description of a case of Meningioma

50 year female with meningioma, shows a well defined T2 iso to hyperintense intense heterogeneously enhancing extra-axial lesion in the left fronto-temporo-parietal region with adjacent edema and mass effect. On perfusion imaging, the lesion shows significantly increased rCBF and rCBV ratios. ASL rCBF (GM)- 15.6, DSC rCBF (GM)- 17.3, ASL rCBF (WM)- 38.3 and DSC rCBF (WM)- 44.8 and DSC rCBV (WM) -15.8.

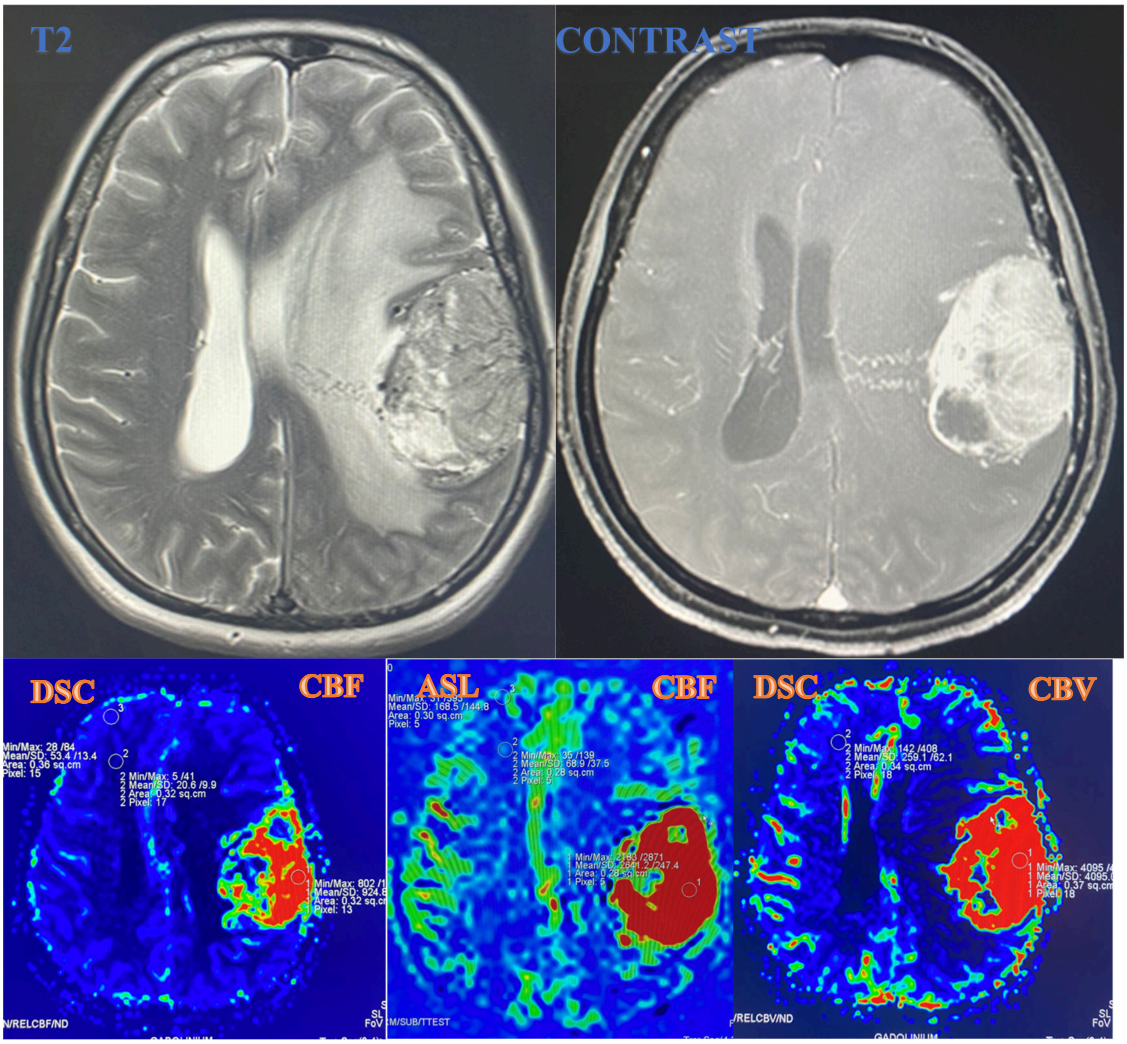


Image 13: Images and description of a case of High grade glioma

70 year male with high grade glioma, shows a well defined T2 hyperintense ring enhancing intra-axial lesion in the right parietal region with necrotic areas. On spectroscopy, the lesion shows increased choline, decreased NAA and lipid lactate. On perfusion, the lesion shows peripherally increased perfusion values with decreased perfusion in the central necrotic area. ASL rCBF (GM)- 2.2, DSC rCBF (GM)-2.3, ASL rCBF (WM)- 5.8 and DSC rCBF (WM)- 5.8 and DSC rCBV (WM) - 7.5.

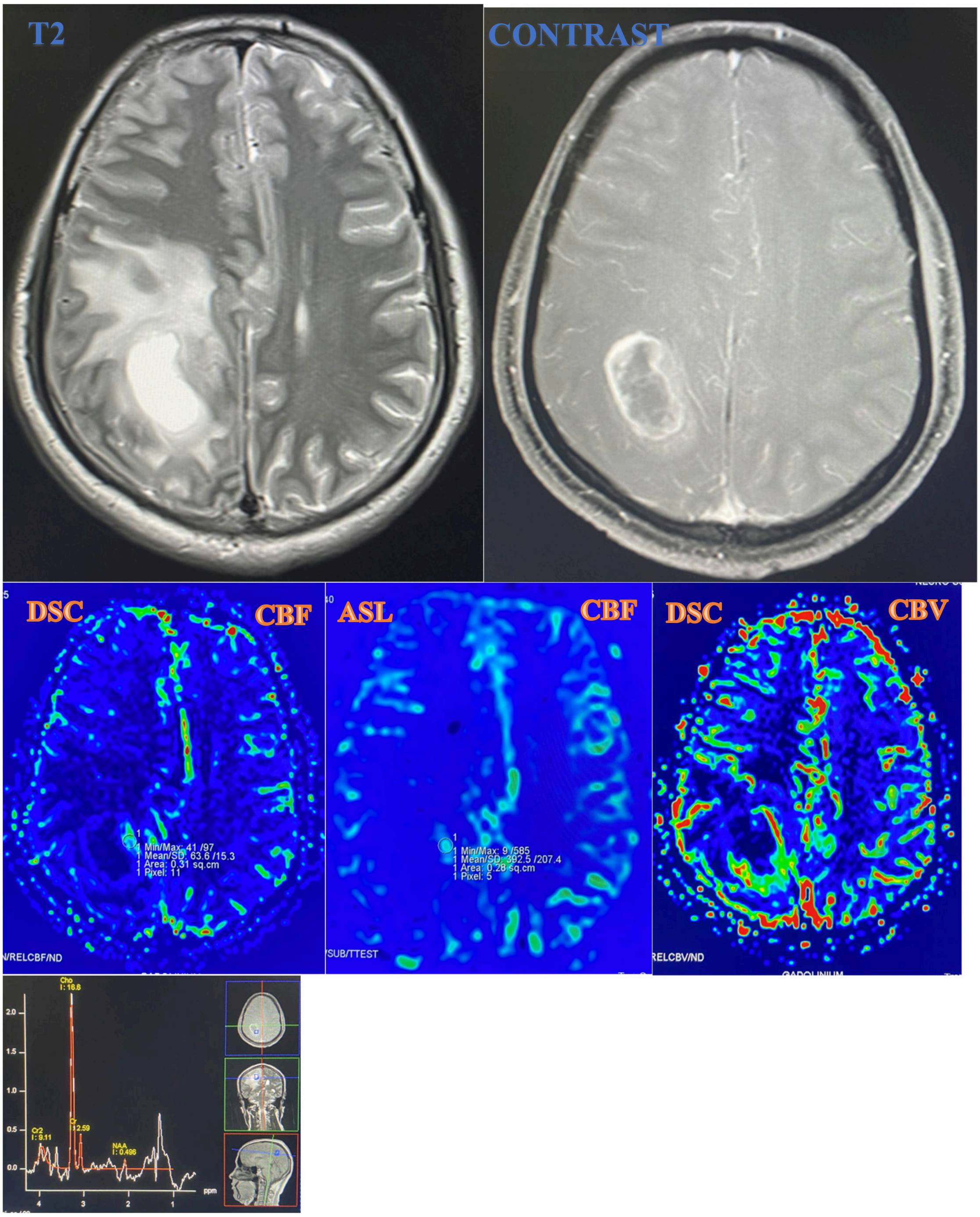


Image 14: Images and description of a case of Ependymoma

57 yead old female with ependymoma. Ill-defined T2 mixed intense heterogeneously enhancing extra-axial lesion with cystic components in the 4th ventricle. On perfusion, the lesion shows significantly increased rCBF and rCBV ratios. ASL rCBF (GM)- 16.4, DSC rCBF (GM)-16.3, ASL rCBF (WM)- 30 and DSC rCBF (WM)- 29.5 and DSC rCBV (WM) - 14.6.

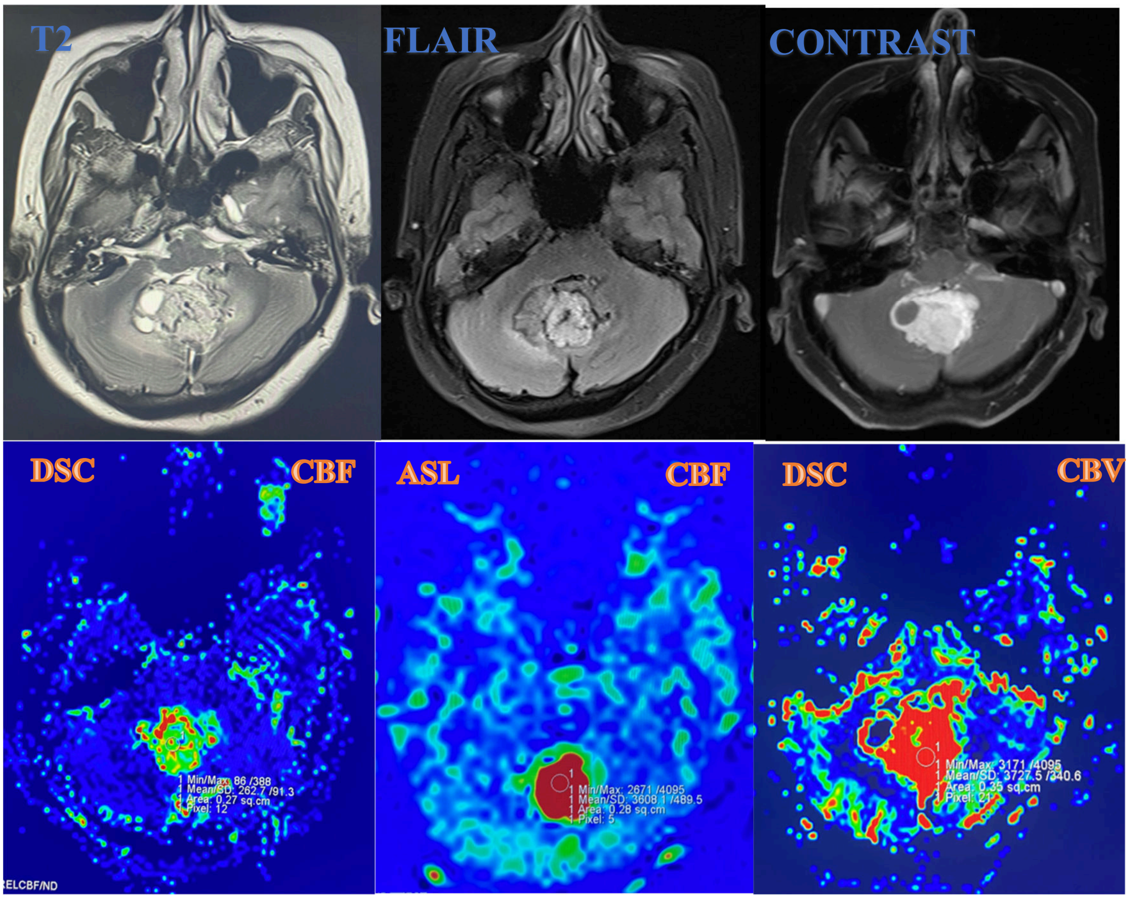


Image 15: Images and description of a case of Cerebral metastases

64 year female with cerebral metastases from carcinoma breast, shows a well defined T2 hyperintense heterogeneously enhancing intra-axial lesion in the left frontal region. On perfusion, the lesion shows increased rCBF and rCBV ratios. ASL rCBF (GM)- 3.2, DSC rCBF (GM)-2.7, ASL rCBF (WM)- 6.7 and DSC rCBF (WM)- 6.5 and DSC rCBV (WM) - 9.5.

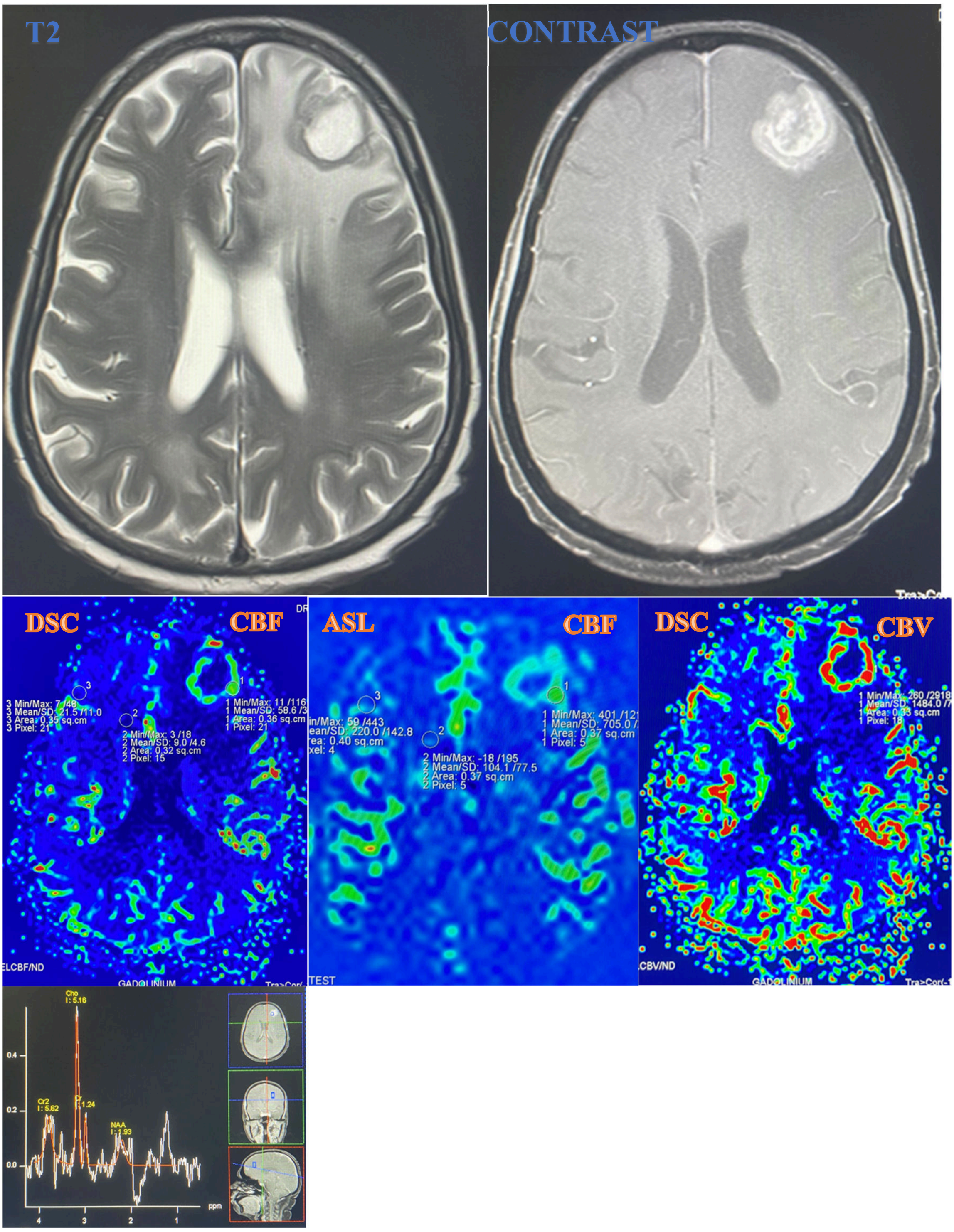


Image 16: Images and description of a case of High grade glioma

65 year old male with high grade glioma, shows a well defined T2 mixed intense peripherally enhancing intra-axial lesion in the midline arising from corpus callosum and frontal region with central necrotic areas. On perfusion imaging, the lesion shows increased peripheral rCBF and rCBV ratios. ASL rCBF (GM)- 7.5, DSC rCBF (GM)-7, ASL rCBF (WM)- 12.2 and DSC rCBF (WM)- 12 and DSC rCBV (WM) - 15.7.

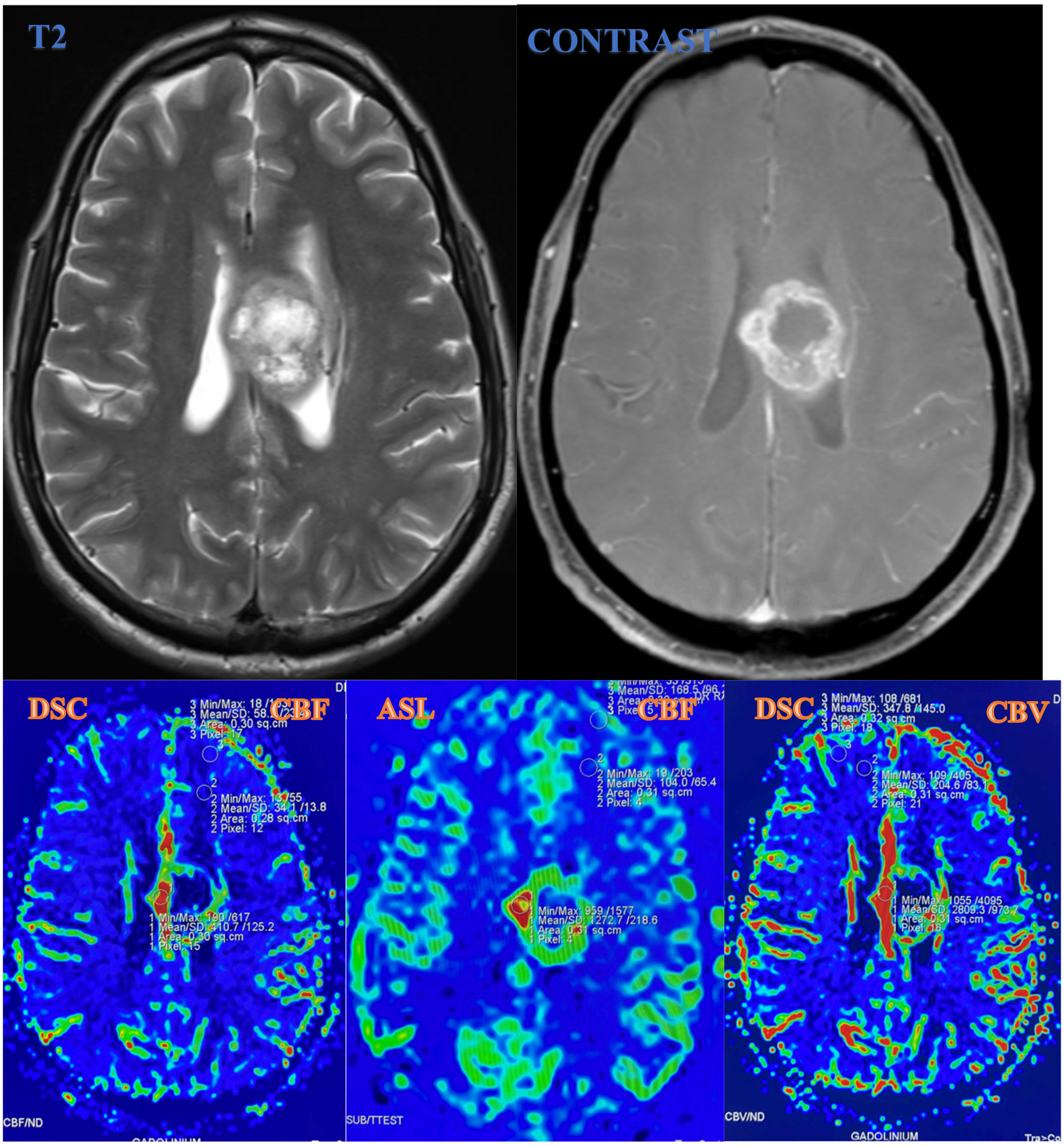


Image 17: Images and description of a case of DNET

20 year female with DNET, shows a well defined T2 hyperintense intra-axial lesion in the cortical and subcortical left frontal region. On perfusion the lesion shows decreased rCBF and rCBV ratios. ASL rCBF (GM)- 0.07, DSC rCBF (GM)-0.05, ASL rCBF (WM)- 0.1 and DSC rCBF (WM)- 0.14 and DSC rCBV ratio – 0.03.

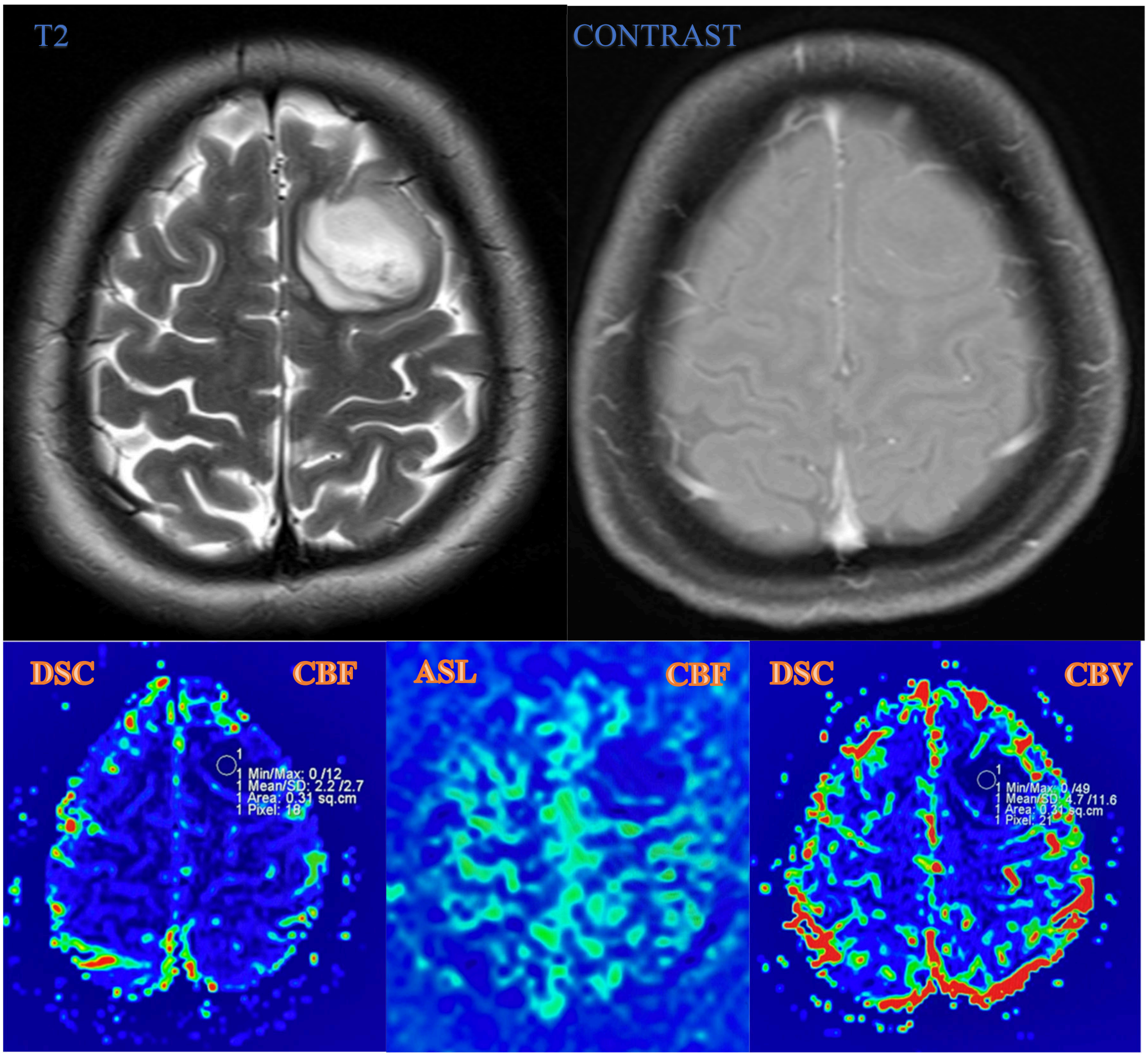


Image 18: **Images and description of a case of Meningioma**

48 year old female with meningioma, shows a well defined T2 iso to hyperintese homogeneously enhancing extra-axial lesion noted in the midline frontal region. On perfusion the lesion shows decreased rCBF and rCBV ratios. ASL rCBF (GM)- 0.5, DSC rCBF (GM)-0.4, ASL rCBF (WM)- 0.9 and DSC rCBF (WM)- 1 and DSC rCBV (WM) - 0.5.

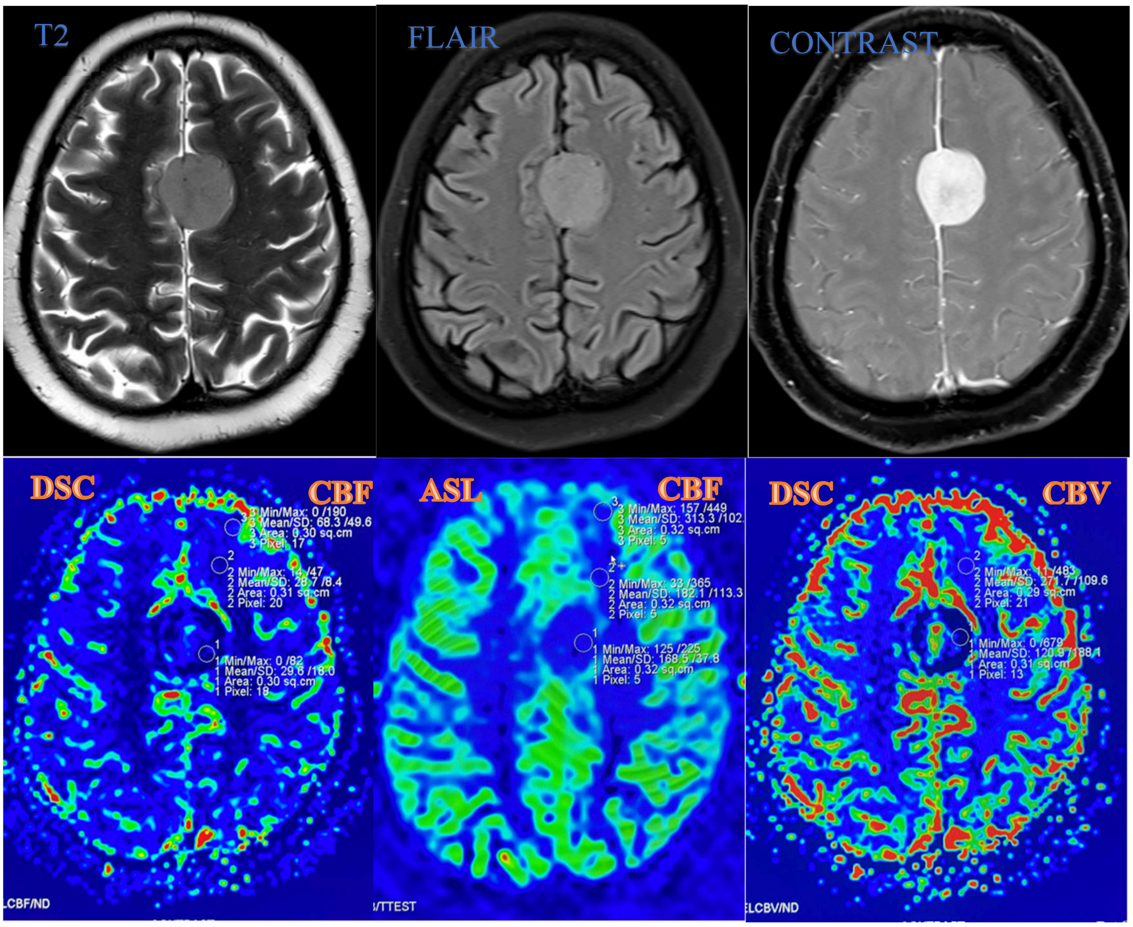
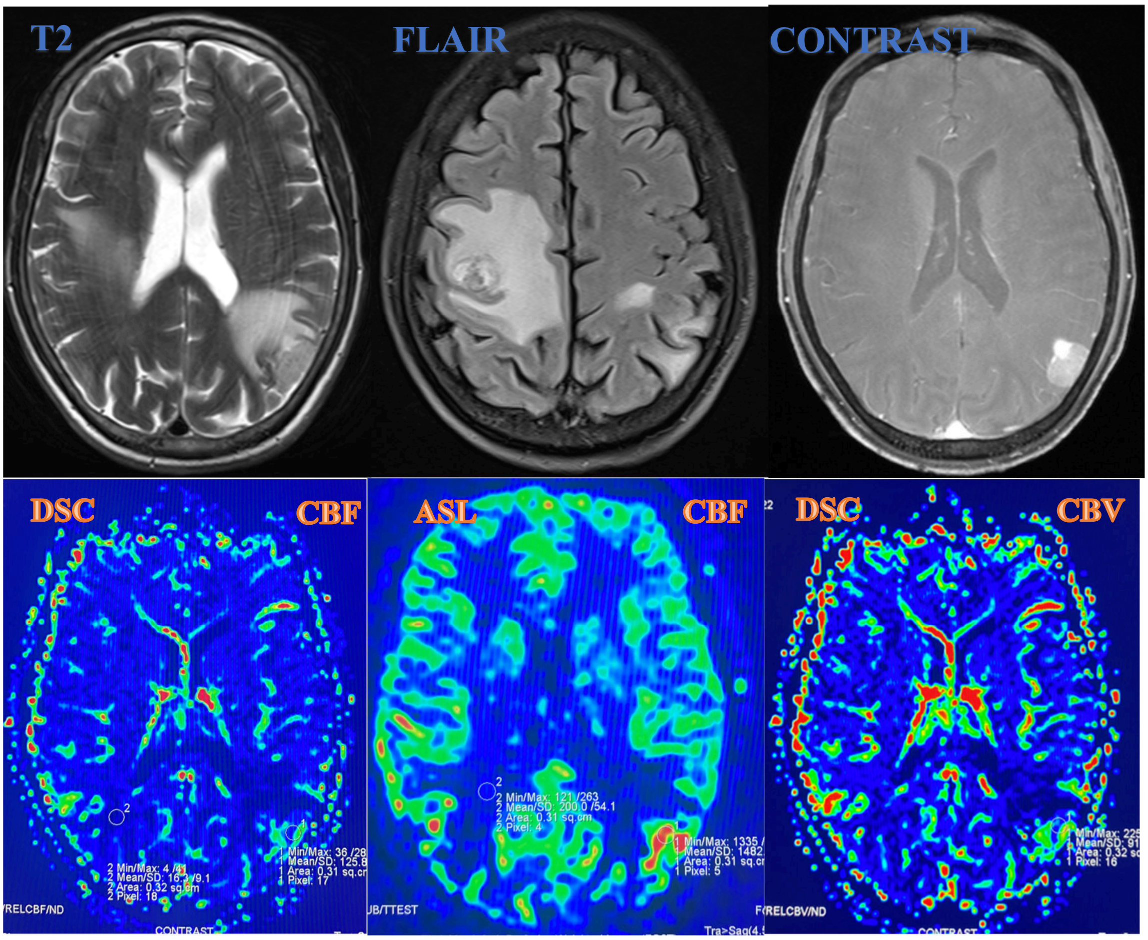


Image 19: **Images and description of a case of Cerebral metastasis**

60 year old male with cerebral metastasis from carcinoma lung, shows few well-defined T2 iso-hyperintense heterogeneously enhancing intra-axial lesions in the bilateral parietal region with perilesional edema. On perfusion imaging, the lesion shows increased rCBF and rCBV ratios. ASL rCBF (GM)- 3.9, DSC rCBF (GM)-2.5, ASL rCBF (WM)- 7.4 and DSC rCBF (WM)- 7.7 and DSC rCBV (WM) - 6.1.



ANNEXURE V: KEY TO MASTERCHART

ASL	Arterial spin labeling
CBF	Cerebral blood flow
DSC	Dynamic susceptibility contrast
rCBF	Relative cerebral blood flow
CBV	Cerebral blood volume
rCBV	Relative cerebral blood volume
GM	Grey matter
WM	White matter
M	Male
F	Female

ANNEXURE VI: MASTERCHART

				ASL rCBF			DSC rCBF			ASL rCBF ratio		DSC rCBF ratio		DSC rCBV			
SL. NO	AGE	SEX	SCAN NO	LESION	GM	WM	LESION	GM	WM	GM	WM	GM	WM	LESION	WM	rCBV ratio	DIAGNOSIS
1	15	M	M13404	2933.3	224.5	99.3	324.3	24.3	10.7	13	29.5	13.3	30.3	4095	249	16.4	MENINGIOMA
2	60	M	M13625	1482.3	378.1	200	125.8	50	16.3	3.9	7.4	2.5	7.7	912.3	148.5	6.1	METASTASES (CA LUNG)
3	20	F	M13667	10.2	133.7	62.5	2.2	43.1	15	0.07	0.1	0.05	0.14	4.7	150	0.03	DNET
4	51	M	M13718	84.3	129.5	72.5	5.8	28.5	12.5	0.6	1.1	0.2	0.4	115.5	168	0.6	LOW GRADE ASTROCYTOMA
5	50	F	M13833	2641.2	168.5	68.9	924.8	53.4	20.6	15.6	38.3	17.3	44.8	4095	259	15.8	MENINGIOMA
6	38	F	M14206	1319.9	289.3	92.5	202.8	45.5	14.4	4.5	14.2	4.4	14	2282.1	203	11.2	MENINGIOMA
7	39	M	M14240	392.5	177.7	67.6	63.6	27.5	10.9	2.2	5.8	2.3	5.8	1626.7	215.1	7.5	HIGH GRADE GLIOMA
8	57	F	M14560	3608.1	220	120	262.8	16.1	8.9	16.4	30	16.3	29.5	3727.5	254.3	14.6	EPENDYMOMA
9	47	F	M14673	440	180.9	83.3	71	31.7	13.8	2.4	5.2	2.2	5.1	388	172	2.2	MATASTASES (CA BREAST)
10	33	F	M14692	404.5	178.9	74.5	89.1	40.9	16.8	2.2	5.4	2.1	5.3	647.4	170	3.8	MENINGIOMA
11	64	F	M16385	705	220	104.1	58.6	21.5	9	3.2	6.7	2.7	6.5	1484	155	9.5	METASTASES (CA BREAST)
12	52	F	M16455	163.3	125.7	41.7	41.1	24	10.2	1.2	3.9	1.7	4	580	170	3.4	LOW GRADE ASTROCYTOMA
13	22	F	M18479	153.2	142.6	65.4	45.6	49.3	30	1	2.3	0.9	1.5	189.5	162.5	1.1	PILOCYTIC ASTROCYTOMA
14	70	M	M18562	449.8	125.3	83	90.3	26.9	16.1	3.5	5.4	3.3	5.6	308.6	189	1.6	HIGH GRADE GLIOMA
15	45	M	M18818	1193	228.1	108.9	385.5	68.3	34.9	5.2	10.9	5.6	11	2824.5	208	13.5	MENINGIOMA
16	48	M	M18991	781.8	222.9	85.7	146.2	46.4	19.6	3.5	9.1	3.1	7.4	449	152.3	2.9	MENINGIOMA
17	52	M	M20305	1645.5	179.5	97.8	309.2	39.5	21.5	9.1	16.8	7.8	14.3	2269.5	184.5	12.3	HIGH GRADE GLIOMA
18	72	M	M21119	364.5	129.3	78.1	118.9	44	24.5	2.8	4.6	2.7	4.8	808.7	152	5.3	METASTASES (CA LUNG)
19	45	M	M21125	909.8	208.9	112.9	153.1	39.6	20.1	4.3	8	3.8	7.6	1613.9	204.3	7.9	METASTASES
20	16	F	M21871	449.4	187.3	114.9	156.2	50.9	32.4	2.3	3.9	3	4.8	1276.7	145.6	8.7	GANGLIOGLIOMA
21	60	F	M21860	956.2	202.1	109.3	81.3	17.5	9.7	4.7	8.7	4.6	8.3	2435.1	196.1	12.4	HIGH GRADE GLIOMA
22	80	F	M21919	1206.2	132.1	40.5	221.3	26.3	8.3	9.1	29.7	8.4	26.6	1365.2	151.2	9	HIGH GRADE GLIOMA
23	70	M	M22493	763.8	136	78.6	125.6	24.6	11.3	5.6	9.7	5.1	11.1	945.6	143.2	6.6	HIGH GRADE GLIOMA
24	68	F	M22572	811.4	218.9	97.3	194.3	47.8	23.9	3.7	8.3	4	8.1	845	181	4.6	MENINGIOMA
25	5	M	M22659	336.5	189.5	100	78.5	50.1	28.7	1.7	3.3	1.5	2.7	259.4	191.5	1.3	MEDULLOBLASTOMA
26	52	M	M22739	869.5	149.6	85.9	197	36.8	17.5	5.8	10.1	5.3	11.2	2226.8	165.8	13.4	HIGH GRADE GLIOMA
27	27	F	M22745	1236.2	224	146.5	245.6	50.2	32.5	5.5	8.4	4.8	7.5	1946.5	246.2	7.9	HEMANGIOBLASTOMA
28	36	M	M22888	608.2	135.7	66.5	180.1	38.2	18.3	4.4	9.1	4.7	9.8	2368.9	132.3	17.9	HIGH GRADE GLIOMA
29	22	M	M23025	249.5	206.8	113.5	58.3	50.6	29.6	1.2	2.1	1.1	1.9	349.5	180.6	1.9	LOW GRADE ASTROCYTOMA
30	25	M	M23193	263.5	226.3	113.6	56.3	52.4	28	1.1	2.3	1	2	198.6	165.6	1.1	DNET
31	70	M	M23315	986.1	235.2	122.6	163.5	41.6	18.5	4.1	8	3.9	8.8	968.5	193.6	5	HIGH GRADE GLIOMA
32	57	M	M23419	328.5	156.3	98.5	85.6	43.5	22.9	2.1	3.3	1.9	3.7	317.3	156.3	2	SCHWANNOMA
33	31	F	M23792	913.8	255	180	180.8	56.5	32.4	3.5	5	3.2	5.5	798.5	212.5	3.7	HIGH GRADE GLIOMA
34	25	F	M23840	965.6	203.2	108.6	156.3	35.6	16.9	4.7	8.8	4.3	9.2	1175.5	189.6	6.2	MENINGIOMA
35	65	M	M23927	1272.7	168.5	104	410.7	58.2	34.1	7.5	12.2	7	12	2945	186.6	15.7	HIGH GRADE GLIOMA
36	48	F	M24056	168.5	313.3	182.1	29.6	68.3	28.7	0.5	0.9	0.4	1	120.9	240	0.5	MENINGIOMA
37	41	M	M24076	462.2	162	63.3	142.7	57	19	2.8	7.3	2.5	7.5	1227.3	205.4	5.9	LOW GRADE OLIGODENDROGLIOMA

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