ORIGINAL RESEARCH ARTICLE

Utility of Magnetic Resonance Spectroscopy and Perfusion Studies in Characterization of Intracranial Space Occupying Lesions

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A B S T R A C T

Introduction: The advancement in surgical treatment and chemotherapy options imaging modalities also need to incorporate advanced neuroimaging modalities for more accurate diagnosis and grading of intracranial masses. This prospective study aimed at characterization of intracranial space occupying lesions using dynamic susceptibility magnetic resonance perfusion and multi voxel spectroscopy techniques. It also attempts to distinguish between high and low grade lesions and gliomas from metastasis and other infective morphologically similar pathologies.

Method and Materials: Subjects of all age groups with intra and extra axial lesions diagnosed on conventional imaging were subjected to perfusion and/or multi voxel spectroscopy on 1.5T Magnetom Siemens Avanto system. Histopathology was gold standard. Data was analysed using statistical package SPSS version 17 and cut off values for rCBV, Cho/NAA and Cho/Cr were obtained. Data analysis was done by using correlation coefficient and diagnostic tests (sensitivity, specificity, positive predictive value and negative predictive value).

Results: By means of this study it was concluded that an intracranial lesion could be said to be high grade if rCBV value was greater than or equal to 2.5(sensitivity- 85%, specificity- 88%) while cut off value for Cho/NAA was 2.5 for high grade gliomas (sensitivity 91%, specificity 87%) and similarly cut off value using Cho/Cr was obtained as 1.7 for high grade gliomas (sensitivity 75%, specificity 62%). These also aided in solving dilemma faced in distinguishing post treatment changes from residual/recurrence.

Conclusion: MR perfusion and spectroscopy if used wisely can improve diagnostic performance especially where conventional MRI is doubtful.

Key words: Conventional, Gliomas, Neuroimaging, Recurrence, Residual

INTRODUCTION

The conventional MR (magnetic resonance) imaging methods do not have a high sensitivity and specificity and insufficient to precisely diagnose and grade intracranial space occupying lesions. Sensitivity and PPV for the overall population have been reported as 72.0-90.7% and 91.9-95.4% respectively.[1]

Hence such drawbacks have led to further exploration and discovery of newer neuroimaging techniques, some of which have found a place in day to day clinical practice while some are still in the research phase.

Brain lesions have many mimickers like granulomas, abscesses, demyelinating lesions and solitary metastasis. Contrast MR imaging can be misleading as it shows enhancement in any lesion associated with disruption of the blood-brain barrier. It is not the true representative of tumour perfusion and does not show physiological or biochemical changes. [2]

So the need for other imaging techniques was realised, for example MR spectroscopy and perfusion MR, which could solve the common dilemma in characterization of intracranial lesions. Further detailed investigation is needed in this direction as there is inadequate data to enable us to incorporate these methods into regular MRI protocol. [2]

The last modality in cross sectional imaging often sought to is MRI as it can give detailed structural information and now we can gain information on tumour metabolism (MR spectroscopy) and perfusion at a cellular level (perfusion-weighted imaging). Despite such advantages confusion and debate occur when it comes to grading, confirming invasion into peritumoural area, distinguishing post treatment changes from residual/ recurrence lesion. [3]

More studies are needed to quantify these limitations and also to prove use of such newer modalities as complementary diagnostic tools and able to improve preoperative diagnostic accuracy or even obviate stereotactic biopsy.

Current study aimed to study the utility of advanced MR imaging characteristics in enabling more accurate diagnosis and grading of intracranial space occupying lesions.

To understand the applications of MR perfusion and MR

spectroscopy in firstly grading of intracranial lesions into high grade and low grade lesions, secondly differentiating lesions mimicking infective/demyelinating lesions and thirdly, differentiating high grade lesions versus metastatic lesions.

MATERIALS AND METHODS

A total of 150 patients (95% confidence level and 85% power and with reference to sensitivity of 70% ad specificity of 80%) with intracranial space occupying lesion detected or followed up in a time period of July 2014-July 2016 at KMC, Mangalore were included in the study and subjected to contrast enhanced perfusion-weighted and proton spectroscopic MR imaging.

Formula used for calculating size of prospective study was: $n = Z_{\alpha}^{2} \times S_n \times (1 - S_n) / L^2 \times P$

(Where $Z_{\alpha} = 1\text{-}96$, 95% confidence level, S_n = Sensitivity, L= Absolute precision(10%)

P= Prevalence).

A 1.5 T MRI System was used – (Magnetom Siemens Avanto) and gold standard set as Histopathology/based on clinical response if biopsy was not performed.

Composite case definition: Histopathology report to be obtained wherever possible and for all those cases it will be taken as gold standard. However, for cases not undergoing biopsy (such as inflammatory lesions thought to be malignant initially, tuberculoma resolved on treatment etc.) clinical response shall be considered instead of histopathological correlation.

Inclusion Criteria

Patients of all age groups with space occupying lesion in cranium (intra-axial and extra-axial) detected by conventional CT and MR imaging. Patients on follow up i.e. post-operative or on chemotherapy were also included.

Exclusion Criteria

Patients with intracranial aneurysm clips, intra-orbital metal fragments or any electrically, magnetically or mechanically activated implants (including cardiac pacemakers, biostimulators, neurostimulators, cochlear implants, and hearing aids).Patients having claustrophobia and those with preexisting renal disease / raised creatinine levels were similarly excluded.

Cases where multi-voxel spectroscopy could not be performed (three such cases in study) due to proximity to calvarium were subjected to single-voxel spectroscopy. Purely cystic lesions were excluded.

Any losses to observation such as patients whose treatment could not be followed up were excluded from the study.

Method of collection of data

For the 150 patients undergoing conventional MR imaging, the intracranial lesions were grouped into intra-axial and extra-axial, as judged with MR imaging.

They were subjected to volume selective spectroscopy using stimulated echo acquisition mode and spin echo sequences using multi axial and single voxel technique.

For perfusion studies CBV, CBF and MTT will be calculated for all lesions. For spectroscopy, Cho: NAA and Cho: Cr will be calculated. More than two standard deviations from mean value were considered abnormal.

Protocol used for dynamic susceptibility based perfusion imaging consisted following parameters: TR/TE 1710/30, Flip angle – 90 degree, Matrix – 128x128 with section thickness- 5mm and section gap- 1.5mm. 10 ml contrast at the rate of 5ml/s NS 10 ml was injected at the rate of 5ml/s and 50 acquisitions 20-22 images upto 5 minutes of contrast dose were acquired. Region of interest (ROI) for perfusion was 60/100 mm^2. ROIs were placed within the enhancing portion of the tumour, peritumoural region and contralateral normal white matter.

STATISTICAL ANALYSIS

Data analysis was done by using correlation coefficient and diagnostic tests (sensitivity, specificity, positive predictive value and negative predictive value).A statistical package SPSS version 17 was used.

Comparison of CBV, CBF, MTT between different intracranial lesions and correlation with Histo-Pathological Examination (HPE) was carried out. (CBV – Cerebral Blood Volume; CBF – Cerebral Blood Flow; MTT – Mean Transit Time). For spectroscopy comparison of NAA, Cho, Cr and any other special metabolite among different lesions was performed.(NAA – Acetyl Aspartate, Cho –Choline, Cr-Creatine)

RESULTS

The study group included a mixed population (Males- 80, Females- 70, and median age 45.5 years).

First comparing MR perfusion and spectroscopy for characterization of high grade and low grade gliomas, perfusion showed higher specificity (Sensitivity- 83.3%,

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		t value	p
					Lower Bound	Upper Bound		
Cho/Naa	Low	16	2.11	.62	1.78	2.44	5.868	.000
	High	24	5.34	2.14	4.44	6.24		HS
	Total	40	4.05	2.33	3.30	4.79		
Cho/Cr	Low	16	1.44	.59	1.13	1.75	3.530	.001
	High	24	2.48	1.07	2.03	2.93		HS
	Total	40	2.06	1.04	1.73	2.39		

Table 1 - Comparison of spectroscopy ratios for low and high grade tumours, Source- Original

	N	Mean	Std. Deviation	Median	95% Confidence Interval for Mean		Mannwhit ney test Z	p
					Lower Bound	Upper Bound		
High	20	4.20	2.01	4.00	3.26	5.14	4.313	.000
Low	17	1.06	1.24	.00	.42	1.69		HS
Total	37	2.76	2.31	3.00	1.99	3.53		

Table 2 rCBV for High grade and Low grade gliomas, Source- Original

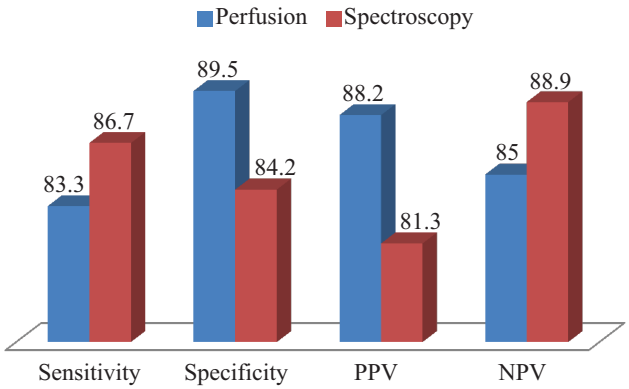
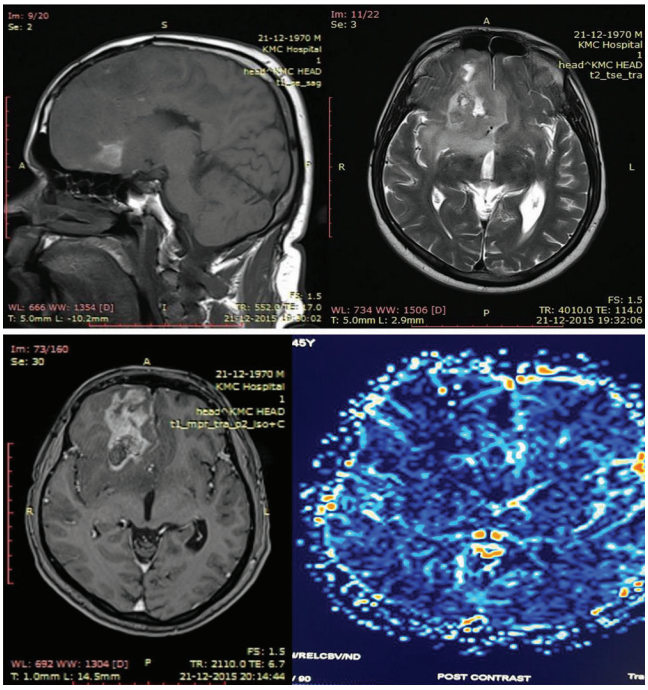
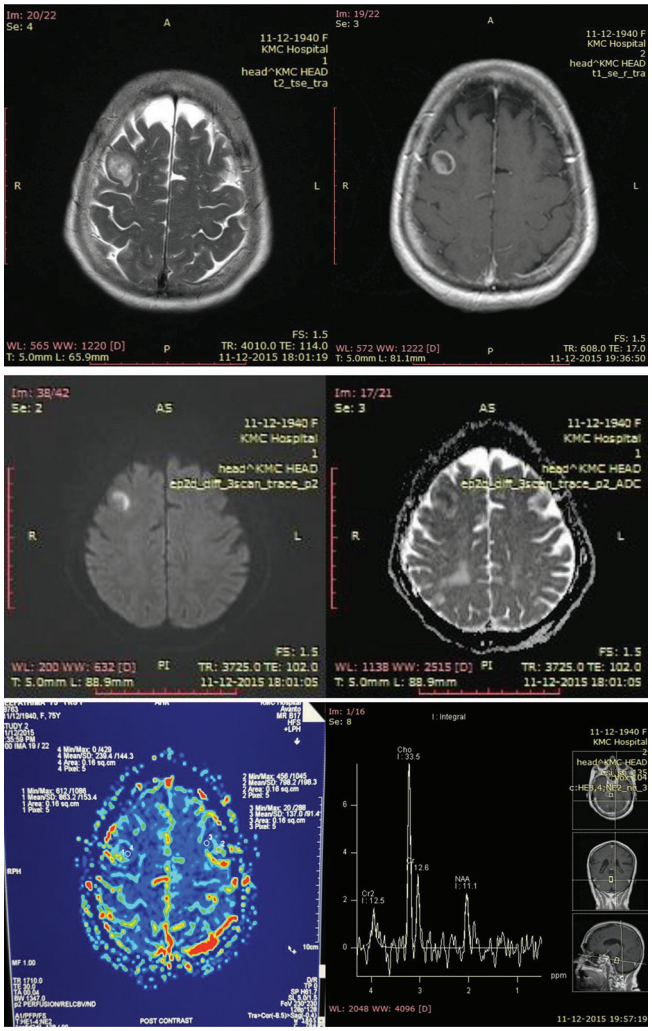


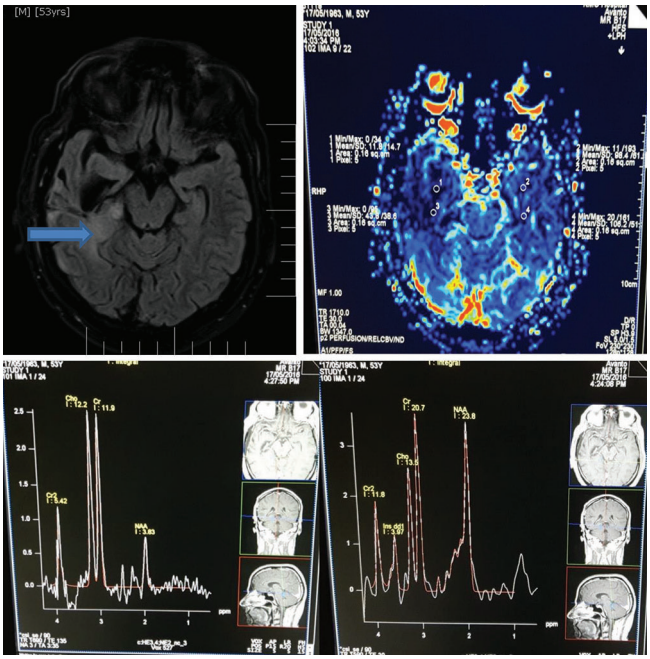
Table-3: Comparison of gliomas by both the methods.



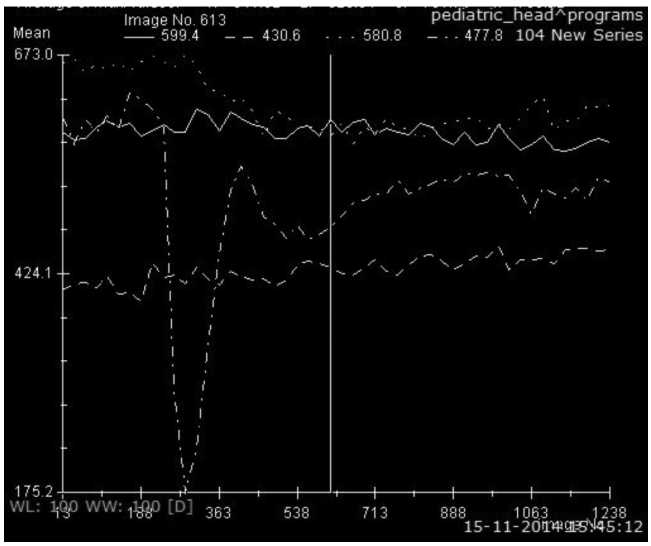
Case-1: Above images represent case of post op grade II Oligodendroglioma (no known treatment details) suspected with conversion to high grade which was ruled out after MRI. Perfusion was helpful despite suspicion of high grade due to haemorrhagic foci and mass effect. Patient was stable on follow up. **(a, b)** T1 sagittal and T2 axial sections showing heterogeneous ill-defined lesion with T1 hyperintense areas – s/o haemorrhagic foci involving right frontal and right anterior temporal lobe, corpus callosum with minimal midline shift. **(c, d)** Minimal enhancement on post contrast while perfusion (rCBV colour map) showed no significant increase in perfusion. (There was patchy diffusion restriction, no dip in perfusion curve; increased choline was seen on spectroscopy)



Case-2: Elderly female with multiple peripherally enhancing lesions in bilateral cerebral and cerebellar hemispheres. No h/o fever, weight loss or systemic complaints. Diagnosis of metastasis was given in view of multiplicity, thick irregular enhancement, perfusion and spectroscopy findings. Same was proved on biopsy. **(a)** Axial T2 images showing one of the multiple intra axial lesions (heterogeneously hyperintense) in this patient. **(b)** Post contrast T1 images show thick peripheral enhancement in all lesions. **(c, d)** Peripheral diffusion restriction is noted in one of the multiple lesions in brain. **(e, f)** Perfusion images (rCBV) shows significantly raised rCBV in periphery of the lesion. Spectroscopy showed elevated choline only in enhancing area and no significantly raised Cho/NAA in peritumoural region.



Case-3: Known case of diffuse astrocytoma post excision post radiotherapy on follow up. Pre-treatment films and reports were not available for comparison. **(a)** Axial FLAIR image showing ill-defined hyperintensity in right temporal white matter with dilated temporal horn of right lateral ventricle. No diffusion restriction or enhancement was present. **(b)** No increased perfusion seen in right temporal lobe compared to normal contralateral white matter. **(c, d)** Spectroscopy at high and low TE showing no significant elevation in choline. (Cho/NAA- 1.9 and Cho/Cr- 0.6).Small lipid lactate peak at low TE.



T2/FLAIR hyperintensity was thus thought to be due to post radiation changes rather than residual or recurrent tumour. Perfusion was helpful in other cases where even the exact primary diagnosis was unknown. Low grade astrocytomas may not show significant enhancement, thus post contrast images are not enough for confident diagnosis.

In certain cases dynamic perfusion curves in addition to colour maps were beneficial. Example above:

Dynamic perfusion curve - Significant dip (Dash and dots) in perfusion curve with slow return towards baseline is seen in a heterogeneous temporal lesion in an eleven year old child. Other two curves represent normal white matter for comparison, and perilesional white matter. The lesion was proven to be an Ependymoma on biopsy.

specificity- 89.5%, PPV- 88.2% and NPV- 85%) versus (Sensitivity- 86.7%, specificity- 84.2%, PPV- 81.3% and NPV- 88.9%) for spectroscopy. Accuracy among the two methods was similar (86.5% for perfusion and 85.3% for spectroscopy).

Comparing the two ratios studied in MR spectroscopy method Cho/NAA proved far more beneficial than Cho/Cr in grading of gliomas. (Fig1, table1) The cut off value for Cho/NAA was 2.5 for high grade gliomas (sensitivity 91%, specificity 87%) and similarly cut off value using Cho/Cr was 1.7 for high grade gliomas (sensitivity 75%, specificity 62%) when values were taken compared with contralateral normal white matter.

An intracranial lesion could be said to be high grade if rCBV value was greater than or equal to 2.5(sensitivity- 85%, specificity- 88%).The utility of perfusion in this regard is depicted in Table/Fig2.

For the follow up cases with known histopathology which were followed up at 6 month interval, perfusion was superior compared to spectroscopy (Sensitivity- 84.2%, specificity- 100%, PPV- 100% and NPV- 78.6% for perfusion versus Sensitivity- 81.8%, specificity- 100%, PPV- 94.7% and NPV- 50% for spectroscopy).Post-operative cases were subjected to MRI after 3 months from surgery.

Accuracy of perfusion was 90% compared to 84.6% by spectroscopy in diagnosing residual/recurrent lesion. It solved the dilemma of post-contrast enhancement in treated/irradiated subjects and thus prevented false diagnosis of recurrence. All metabolite peaks were supressed in two cases of post radiation lesion necrosis when compared with recurrence.

In differentiating metastasis from other lesions especially solitary metastasis from glioma or more rarely granulomas, perfusion had a better sensitivity and accuracy (75%) compared to spectroscopy (64.3%).

Spectroscopy however had better accuracy of 88.4% in differentiating tuberculomas from toxoplasmosis or neurocysticercosis as compared to MR perfusion whose accuracy was only 60.9%.

DISCUSSION

In this prospective study of 150 patients comprising various types of intracranial lesions, it is clear that MR perfusion and spectroscopy have a reasonably good sensitivity, specificity and efficacy in characterization of lesions as well as their follow up. As Aprile and his colleagues mentioned in 2012, the basic MR sequences themselves with or without contrast can help to accomplish diagnosis or probable grading in obvious case such as advanced GBM [4]. Thus by this analysis, the best use of these newer methods could be distinguishing among less obvious cases and predicting residual/recurrent disease where post radiation and chemotherapy could produce confusion. The physiological and biochemical behaviour of lesions thus illustrated, proved that these methods are value additions

to baseline images when read along with conventional sequences.

Perfusion yielded better results when compared to use of spectroscopy particularly in lesions with known histopathology on reimaging after treatment and assessment of progression versus pseudo-response. Superiority of perfusion is clear by the comparative analysis of follow up cases depicted in Table/Fig 3.

Early detection of metastasis can enable early screening and change the patient's course of management. Importance of studying peritumoural infiltration (88% of studied cases in study) was realised on biopsy correlation as assessing abnormal perfusion and spectroscopy parameters helped differentiate metastasis from gliomas. Also in few cases infiltration could be detected in the area beyond the enhancing portion showing superiority of these techniques. This can aid in more accurate grading and radiation/resection planning.

It is crucial to distinguish tumour recurrence from pseudo-progression as the latter shows spontaneous resolution. The addition of immunotherapy and newer drugs are making such diagnosis more challenging. Perfusion proved more sensitive and specific than spectroscopy in this study.

When past treatment details are not available, as often in clinical practice, perfusion characteristics can help. In one of the cases of low grade oligodendroglioma (Case 1), type of treatment received was unknown and conversion to high grade was suspected. Despite presence of small haemorrhagic areas and diffusion restriction there was no increase in rCBV within the lesion. It was later confirmed on biopsy as low grade with no higher conversion.

In developing countries like ours, ring enhancing lesions due to infective aetiology like tuberculomas still have to be ruled out prior to considering more sinister causes. This remains challenging due to the varied presentations and "tumour mimics". A case of fungal granulomas was successfully differentiated from haemorrhagic metastasis by lower perfusion parameters. In our study granulomas were differentiated from pyogenic abscesses, metastasis and multi-centric gliomas in >85% of the cases. The differentiation between tuberculomas and toxoplasmosis however was sometimes difficult due to overlapping imaging features.

The large overlap in enhancement and diffusion patterns of neoplasms (ex. Solitary metastasis versus GBM) inspires development of more problem solving tools. Application of rCBV values (cut off of 2.5 derived from this study by Mann Whitney test; $p<0.001$) and measurements and Cho/Cr and Cho/NAA ratios (cut off of 1.7 and 2.5 respectively for high grade lesions) increased the sensitivity of preoperative glioma grading and can potentially help in mapping more aggressive site for biopsy.

Cho/NAA proved to be a more reliable marker in grading lesions compared to Cho/Cr. The lower specificity of Cho/Cr can be attributed to high level of choline in some low grade gliomas as also mentioned in literature previously. Characteristic peaks like amino acids, glutamate and glutamine in spectroscopy and characteristic dynamic perfusion curves such as in lymphoma or high grade transformation of low grade neoplasms can be very helpful. Myoinositol when present in this study group signified low grade lesions (four cases in this study). Few cases of tuberculomas presenting as ring enhancing lesions were differentiated from neurocysticercosis by a higher Cho/Cr >1.

Lactate was seen in low as well as high grade neoplasms as well as in the core of necrotic abscesses and tuberculomas. Similarly it was present in both tumour recurrence and radiation necrosis. Hence it is a nonspecific metabolite and cannot be interpreted in isolation. Similarly necrosis in high grade lesions can cause lower choline levels. Gross haemorrhage within a mass lesion can lead to erroneous spectroscopy curve as encountered in few cases which were excluded from the study.

CONCLUSION

The true utility of newer MR methods lies not in further description of obvious cases detected by conventional sequences like advanced gliomas but to narrow down differentials in cases like necrotic mass versus pyogenic abscess, demyelinating lesions and hypo vascular metastasis. A limitation of this study was reliance on previously reported threshold values for metabolite ratios. The cut offs derived were within the range reviewed in literature. Uniform criteria and standardization however need to be established so that these evolving methods can be incorporated in routine MR protocols, beyond confines of academic interest and to save the radiologist in diagnostic dilemmas.

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