

# Role of MR Spectroscopy in Differentiating Tumor Recurrence and Post Radiation Changes in Treated Brain Tumors with Radiotherapy

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## ABSTRACT

**Introduction:** Among the space occupying lesions of brain, gliomas are the most common primary malignant brain tumor and metastases are overall most common intracranial tumors in adults. Assessing the treatment response is routinely done by contrast magnetic resonance imaging (MRI), but MRI being an anatomic imaging technique cannot be accurate in predicting the response to treatment and presents a diagnostic dilemma in assessing the changes due to tumor progression or treatment effects specifically radiation induced changes.

**Aim:** To evaluate the significance of MR Spectroscopy in differentiation between recurrent tumor and radiation necrosis in patients previously treated for brain tumor using alterations in the ratios of standard brain metabolites—Choline (Cho), Creatinine (Cr), and N-acetyl aspartate (NAA).

**Materials and Methods:** Total 37 patients with brain tumor (primary/secondary) who were treated with radiotherapy were included in this study. Plain and contrast MRI with multi-voxel MRS was performed at Kidwai Memorial Institute of Oncology, Bangalore. For MRS the volume of interest was placed over the area of signal alteration / abnormal enhancement. The spectra were analyzed for the signal intensity of Choline (Cho), Creatine (Cr), NAA,

lipids and lactate and metabolic ratios for Cho/Cr, Cho/NAA, and NAA/Cr were recorded. Categorization of the lesions into tumor recurrence and radiation necrosis was done on the basis of corresponding findings on SPECT images and clinical follow-up.

**Results:** On qualitative analysis, both tumor recurrence and radiation necrosis showed area of enhancement on post contrast T1WI. On quantitative analysis of Cho/Cr, Cho/NAA and NAA/Cr ratios, tumor recurrence showed high mean values of Cho/Cr and Cho/NAA and low mean values of NAA/Cr and vice versa. Of the three metabolic ratios Cho/NAA has proved to be the most useful ratio in discrimination between tumor recurrence and radiation necrosis. Cho/NAA of 1.87 or more was found to have a sensitivity and specificity of 95.2 % and 93.8% respectively for presence of tumor (p-value <0.05). Cho/Cr of 1.93 or more was found to have a sensitivity and specificity of 90.5 % and 87.5% respectively for presence of tumor (p value <0.05). NAA/Cr of 1.24 or less was found to have a sensitivity and specificity of 66.7 % and 67.5% respectively for presence of tumor (p-value <0.05).

**Conclusion:** Metabolic information provided by MR Spectroscopy is useful for the differentiation of tumor recurrence and radiation necrosis in post treated brain tumors after radiotherapy.

**Keywords:** Chemoradiation, Gliomas, hMRS, Metastasis, SPECT.

## INTRODUCTION

Gliomas accounts for the majority of primary malignant brain tumors [1,2] and metastasis accounts for overall most common intracranial tumors in adults [3]. In an attempt to achieve good local tumor control, overall clinical outcome and survival of patients, these brain tumors require multimodality treatment including surgery, radiotherapy, chemoradiation [3,4]. Maximum resection of the tumor with postoperative

chemoradiation is the standard therapy for these malignant tumors. Contrast magnetic resonance imaging (MRI) is routinely used to assess the treatment response. But contrast MRI being an anatomic imaging technique cannot be accurate in predicting the response to treatment and presents a diagnostic dilemma in assessing the changes due to tumor progression or treatment effects specifically radiation induced changes [5,6], Further lack of specific imaging characteristics

of brain tumors, complex tumor morphology, and their treatment protocol including chemotherapy or radiotherapy makes radiological assessment in discriminating tumor recurrence from the inflammatory or necrotic change due to treatment with radiation and/or chemotherapy. Both of these entities typically demonstrate contrast enhancement and therefore to differentiate recurrent tumor from a treatment-related changes, we often depend on the clinical course, a brain biopsy, or imaging follow-up over a period of time but not the specific imaging itself [7-10]. Magnetic resonance spectroscopy (MRS), an advanced MRI technique, a non-invasive tool can evaluate cellular metabolism and provide more information regarding response to treatment. MRS has already been shown to be capable of identifying active tumor areas, in detecting tumor recurrence before changes in contrast enhancement are evident and differentiate recurrent tumor from radiation necrosis by means of providing metabolic parameters which aids in differentiation [11-14].

Other non-invasive functional imaging methods include SPECT, PET, and DWI and perfusion weighted MRI. Of these methods, MR spectroscopy has advantages over PET and SPECT in that high-energy radiation is not used, and radio-labeled tracers are not required. As the MRS is a multi-parameter modality, it provides information about variety of metabolites within the tissue simultaneously. The invitro experiments on MRS have proved that the chemical profile of different tissue and different cell types is different. For this unique reason MRS has been used in differentiating tumor from radiation necrosis [13-22].

The purpose of this study is to further evaluate the role of proton MR spectroscopy (1HMRS) in evaluating the area of signal alteration within the irradiated volume, which include the area of contrast enhancement, aiming to differentiate recurrent/residual tumors from radiation necrosis based on correlating metabolic pattern on MRS study and patients symptoms (clinical improvement or deterioration) on clinical follow-up and complementary SPECT imaging.

## MATERIALS AND METHODS

This prospective study was conducted from November 2012 to November 2014, for a period of 2 years, at Kidwai Memorial Institute of Oncology, Bangalore in the Department of Radio-Diagnosis after Ethical committee approval. Patient consent was obtained before enrolling them for the study.

All patients underwent conventional MRI with contrast, along with MR Spectroscopy, after minimum 2 months of radiotherapy followed by correlative SPECT study. Correlation was done with SPECT which was taken as standard for categorizing the cases as tumor recurrence or radiation necrosis along with clinical history. The sample population was comprised of patients who were referred for MRI imaging

from the Department Radiotherapy who were on follow-up after a course of RT.

Total 37 treated patients of brain tumors with surgery followed by radiotherapy, between the age group of 20 to 65 years of both sexes with different varieties of brain tumors were selected for the study. Among them 30 patients were male and 7 were females.

### Inclusion Criteria

Patients who were clinically suspected tumor recurrence during their follow-up after course of radiation therapy were included in this study. Only those patients were included in study whose SPECT study was done after MRI T1+C Images shows gadolinium contrast enhancing lesion.

### Exclusion Criteria

Patients having cardiac pacemakers, MRI incompatible prosthetic heart valves, cochlear implants or any metallic implants, claustrophobic patients, dyspneic patients or who cannot lay down, pediatric / un-cooperative patients were excluded from the study.

### Protocol and Technical Details

All MRI scans were performed in 1.5 Tesla scanner (Philips Achieva MRI machine with head coil). Routine T1, T2, FLAIR images were obtained followed by Multi-planar post contrast T1 images and multi-voxel MRS. Scan parameters used were FOV of 230-300, Matrix of 384\*242, Scan time - 1.5 min, Section thickness of 1.5 mm, with intersection gap of 5 mm, Flip angle of 90° and SNR of 2-3. Two dimensional (2D) chemical shift image (CSI) of MRS was acquired using a point-resolved spectroscopy sequence (PRESS) with TR of 2000 ms, Long TE of 144 ms, Short TE of 45 ms, with variable FOV depending on lesion size and with variable Matrix.

The spectroscopic data was transferred to a separate work station and the post processing was done using machine software. The contrast enhanced region on T1 post contrast image was considered for the volume of interest (VOI). After post processing the MRS was analyzed for the signal intensity of Cho compounds at 3.2 ppm, Cr at 3.02 ppm, and NAA at 2.02 ppm. Analysis was done in both tumor and in adjacent normal brain tissue with automatic calculation of metabolite ratios for Cho/NAA, Cho/Cr, and NAA/Cr by machine software.

### STATISTICAL ANALYSIS

Statistical analysis was done using Med Calc v12.7.5.0 (freely downloadable). Independent sample t-test is used to compare metabolite ratios between recurrent tumors and radiation injury. Receiver operating characteristics (ROC) analysis was used for determining Area under curve (AUC) and cut of values. Sensitivity, specificity, positive and negative predictive

value of recurrent tumors and radiation injury parameters were calculated. For all analyses,  $p$  value  $< 0.05$  was considered statistically significant.

## RESULTS

In the present study, 32 cases out of 37 cases were primary brain malignancy and 5 cases were secondary (metastasis). In the primary malignancies all the tumors were of either astrocytic (43%) or oligodendroglial (52%) origin.

Spectroscopic data were acquired using MRS multivoxel technique with voxel being placed in the area of abnormal enhancement on T1W post Gadolinium images. The ratio of Cho/Cr, Cho/NAA and NAA/Cr were recorded. The lesions were categorized into tumor recurrence and radiation necrosis based on the cut-off values of these metabolites and is correlated with SPECT images. The cutoff values of different metabolites were based on the findings of different studies which were used to differentiate between tumor recurrence and radiation necrosis. The area of enhancement on T1+C images was anatomically matched with SPECT images to look for the region of uptake to assign them as tumor recurrence and vice versa. On this basis 21 out of 37 patients were categorized as tumor recurrence and 16 out of 37 patients were categorized as post treatment change /radiation necrosis. Both tumor recurrence and radiation necrosis shows heterogeneous enhancement on T1+ C imaging, so conventional MRI cannot be reliably used in differentiation of the same.

This study found that there is significant difference between recurrence tumors and radiation injury of two patient groups across all three metabolic ratios. Here, ROC curve (AUC) is widely recognized as the measure of a diagnostic test's discriminatory power. Using ROC curve we found sensitivity, specificity, PPV, NPV, Accuracy and LR. Likelihood Ratio test result (LR+) more than 1 show that test result associated with disease and less than 1 show that the result is associated with absence of disease. The mean  $\pm$  SD of the metabolite ratios diagnosed on MRS as recurrent/ residual tumors and radiation injury were calculated. Cho/NAA and Cho/Cr were significantly higher while NAA/Cr ratios were significantly lower in tumors than radiation injury ( $p= 0.0001$  for Cho/NAA and Cho/Cr and  $p=0.01$  for NAA/Cr).

The area under the ROC curve (AUC) is widely recognized as the measure of a diagnostic test's discriminatory power. It is drawn to identify the best metabolite ratio and to find out a

cutoff value with highest sensitivity and specificity that used to differentiate recurrent/residual tumor from radiation injury. In the present study [Table/Fig-1], Cho/Cr, Cho/NAA, NAA/Cho for predicting tumor recurrence had an area under the ROC curve of 0.982, 0.985 and 0.75 respectively, indicating excellent discrimination between tumor recurrence and radiation change with high significance and low Standard error value.

Cho/NAA ratio has the best area under the ROC curve i.e.0.985 with the highest sensitivity, specificity and accuracy as compared to the other metabolite ratios indicating excellent differentiation between tumor and radiation injury. The cut-off value greater than 1.87 for Cho/NAA ratio was considered as indicator for presence of tumor. The Cho/Cr for predicting tumor recurrence with AUC of 0.982 and  $p$  value 0.001, a ratio of 1.93 or more was found to have a sensitivity and specificity of 90.5 % and 87.5% respectively for presence of tumor. The positive predictive value and negative predictive value for Cho/Cr were 90.5% and 87.5% respectively. The likelihood ratios (LR) of Cho/Cr were 7.24.

## DISCUSSION

In current study, majority of patients were in age group of 31-50 years (57%). Mean age of patients was 42.5. In the study population, 81% were male patients and 19% were females. The current study is comparable in terms of age and sex distribution with similar studies in literature referred. Mean age of patients concurs with Schlemmer et al., [16] and Rabinov et al., [21].

In the current study, MR Spectroscopy was done on all contrast enhancing lesions detected on post gadolinium T1 Weighted images with the voxel being placed in the region of enhancement. Three metabolic ratios were obtained namely Cho/Cr, Cho/NAA and NAA/Cr within the region of enhancement using MRS multivoxel technique. Out of 37 patients, 21 patients (57%) had recurrent lesion and 16 (43%) had radiation necrosis, the categorization was on the basis of SPECT Imaging findings whereby areas of increased uptake were categorized as recurrent lesion and areas of no uptake was categorized as radiation necrosis. In the present study, the patients with tumor recurrence [Table/Fig-2,3] had shown higher mean values of Cho/Cr and Cho/NAA than those with radiation change but lower mean values of NAA/Cr which were in agreement with the other studies.

Metabolite Ratios	AUC	Cut-off Value	Sensitivity	Specificity	Accuracy	PPV	NPV	LR+
Cho / Cr	0.982	$\geq 1.93$	0.905	0.875	0.891	0.905	0.875	7.24
Cho/NAA	0.985	$\geq 1.87$	0.952	0.938	0.946	0.952	0.938	15.35
NAA / Cr	0.750	$\leq 1.24$	0.667	0.688	0.675	0.737	0.611	2.14

**[Table/Fig-1]:** Shows role Cho/Cr, Cho/NAA, NAA/Cho for predicting tumor recurrence vs radiation change.

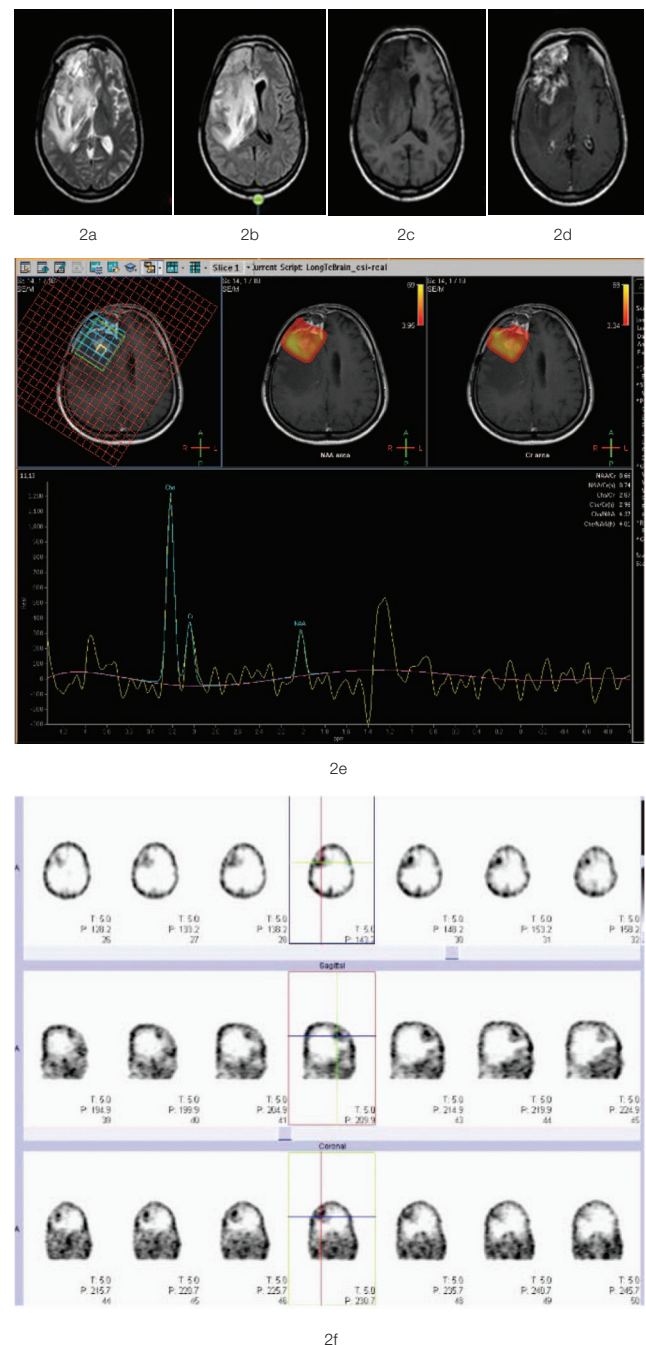
It has been shown in several studies that MR spectroscopy is an effective tool in distinguishing recurrent lesion from radiation necrosis [Table/Fig-4] in post treated brain tumors. Quantification of metabolic ratio of Cho/Cr, Cho/NAA and NAA/Cr has proved to be of significant value in the same [Table/Fig-5,6].

In the present study the patients with tumor recurrence had shown significant high values of Cho/Cr and Cho/NAA and low values of NAA/Cr. Similarly, in patients with radiation necrosis values of Cho/Cr and Cho/NAA were observed lower and value of NAA/Cr was observed to be higher. In the present study, 19 out of 21 cases of tumor recurrence showed Cho/Cr ratio greater than 1.93 and 14 out of 16 cases of radiation necrosis showed values less than 1.93 (cut off value of the same in present study). Similarly, 20 out of 21 cases of tumor recurrence showed Cho/NAA ratio greater than 1.87 and 15 out of 16 cases of radiation necrosis showed value less than 1.87 (cut off value of the same) however only 14 out of 21 cases of tumor recurrence showed NAA/Cr ratio less than 1.24 and 11 out of 16 cases of radiation necrosis showed values greater than 1.24 (cut off value of the same in present study). At above mentioned cutoff values Cho/Cr has shown a sensitivity of 90.5 specificity of 87.5 PPV of 90.5 NPV of 87.5 and accuracy of 89.1. At cut off value of 1.87 Cho/NAA has shows sensitivity of 95.2 specificity of 93.8 PPV of 95.2 NPV of 93.8 and accuracy of 94.6. Similarly, at cut off value of 1.24 NAA/Cr has show sensitivity of 66.7 specificity of 68.8 PPV of 73.7 NPV of 61.7 and accuracy of 67.5.

In the current study, although both Cho/Cr and Cho/NAA has shown to be nearly equivalent in sensitivity and specificity in differentiating Tumor recurrence from radiation necrosis, Cho/NAA has proved to be the best one.

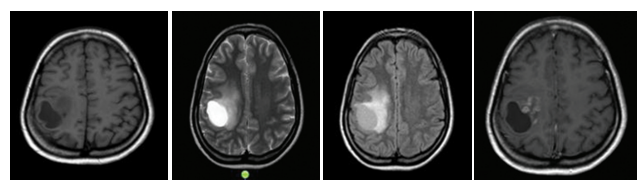
The results of the present study are nearly comparable to the other study done by Elmogy et al., [15]. According to his study Cho/NAA at cut off value of 1.8 showed sensitivity of 93 specificity of 100 PPV of 100 NPV of 93 and accuracy of 96 in differentiating recurrence from radiation necrosis. Similarly, Cho/Cr at a cut off value of 1.83 showed sensitivity of 75, specificity of 89 PPV of 87 NPV of 78 and accuracy of 82 and NAA/Cr at a cut off value of 1.1 showed sensitivity of 66 specificity of 94, PPV of 92, NPV of 73 and accuracy of 80.

Smith et al., [13] concluded that Cho/NAA had a sensitivity of 85 and specificity of 69.2 at a cut off value of 1.8 and is the best among all three in differentiating tumor recurrence from radiation necrosis which is in concur with the present study. Similar study done by Weybright et al., [14] concluded that Cho/Cr and Cho/NAA ratio greater than 1.8 categorizes the lesion as tumor recurrence however sensitivity and specificity was not available in that study.

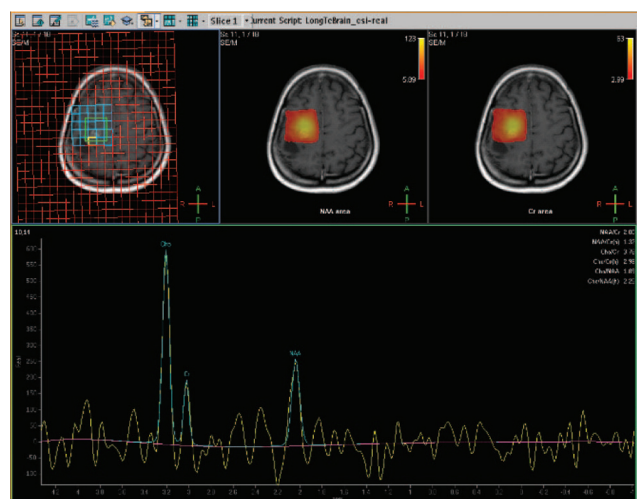


**[Table/Fig-2a-2f]:** A 53 year old male with GBM in right fronto-parietal lobe with post operative and post radiotherapy status. Present MRI with contrast, shows ill defined heterogenous lesion in the right fronto-parietal lobe with significant perilesional edema causing obliteration of right lateral ventricle on axial T2WI (2a) and FLAIR (2b) with ill defined hypointense lesion in the Pre-contrast axial T1WI (2c). On post contrast axial T1WI (2d), there is heterogenous enhancement with central necrotic areas suggesting recurrent lesion. Multi-voxel MRS (2e) shows elevated Cho/Cr of 4.28, Cho/NAA of 4.19 and NAA/Cr 1.02 confirming recurrent lesion. SPECT (2f) Shows a region of high uptake in right fronto-parietal lobe corresponding to the area of enhancement on T1+C.





3a 3b 3c 3d



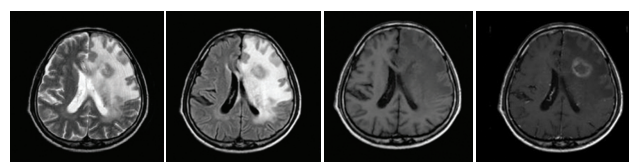
3e



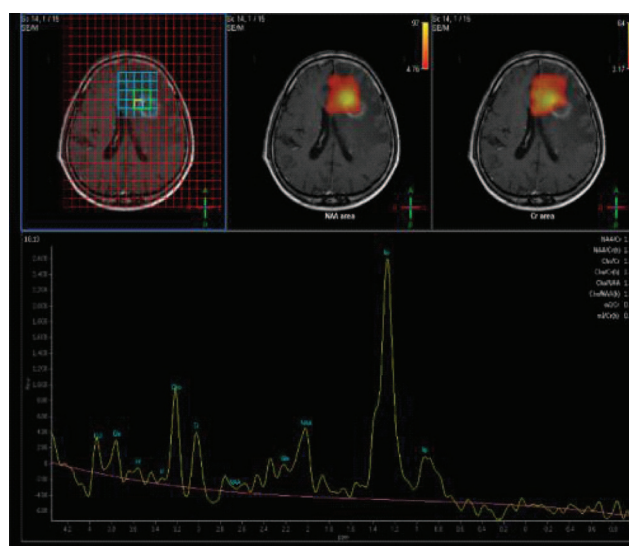
3f

**[Table/Fig-3a-3f]:** A 46 year old female with cystic lesion in right high parietal lobe with adjacent edema. On axial T1WI (3a) the cystic component appears hypointense, on axial T2WI (3b) the cyst shows hyperintense signal which is partially suppressed on axial FLAIR (3c). The adjacent edema shows hyperintensity on both axial T2WI and FLAIR. (3d) On post contrast axial T1WI there is an area of nodular enhancement. Multi-voxel MRS (3e) shows elevated Cho/Cr of 3.78, Cho/NAA of 1.89 and NAA/Cr 2 confirming recurrent lesion. SPECT (3f) Shows a region of high uptake in right parietal lobe corresponding to the area of enhancement on T1+C.

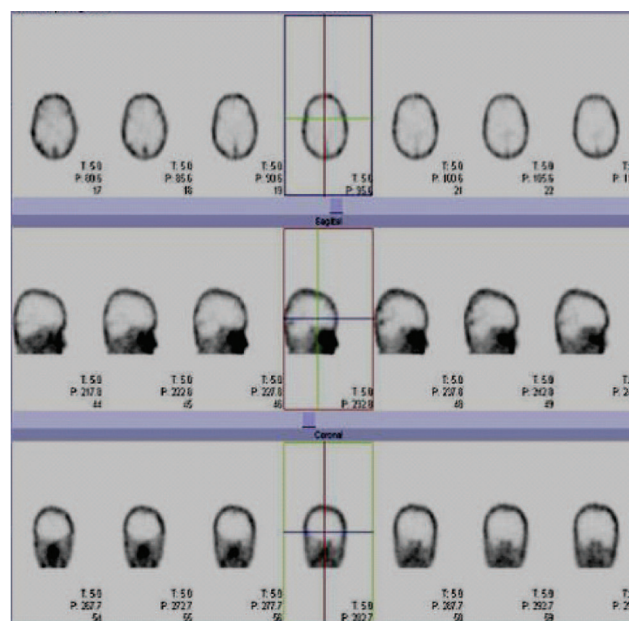
In the current study, using a cut off values of 1.93 and 1.87 for Cho/Cr and Cho/NAA respectively the contrast enhancing lesion on T1+C can be categorized into tumor recurrence and radiation necrosis based on MRS findings, further the study also highlights the importance of analyzing all the three ratios



4a 4b 4c 4d



4e



4f

**[Table/Fig-4a-4f]:** A 50 years old female with left parietal metastasis, post radiotherapy status. Axial T2WI (4a) and axial FLAIR (4b) images shows heterogenous lesion in left parietal white matter with disproportionate edema. It appears hypointense on T1WI (4c). On post contrast axial T1WI (4d), thick ring enhancing lesion noted. MRS (4e) with short TE shows Cho/Cr ratio of 1.64, Cho/NAA ratio of 1.13 and NAA/Cr ratio of 1.45 denoting radiation necrosis. Findings were confirmed on SPECT (4f), which shows no obvious uptake in left parietal lobe corresponding to the area of enhancement on T1+C.

Metabolite ratio (mean) (range)	Elmogly et al., [15]	Smith et al., [13]	Weybright et al., [14]	Current study
Cho/Cr	3.35 (1.63-6.98)	2.36 (1.3-4.26)	2.52 (1.66-4.26)	3.33 (1.73-6.43)
Cho/NAA	2.49 (1.57-4.17)	3.2 (1.3-6.47)	3.48 (1.7-6.47)	4.17 (1.54-8.77)
NAA/Cr	0.81 (0.51-1.19)	0.85 (0.47-1.23)	0.79 (0.47-1.15)	1.008 (0.29-2)

**[Table/Fig-5]:** Shows comparison of mean values of Cho/Cr, Cho/NAA and NAA/Cr between different studies with the present study in patients with tumor recurrence.

Metabolite ratio (mean) (range)	Elmogly et al., [15]	Smith et al., [13]	Weybright et al., [14]	Current study
Cho/Cr	1.39 (0.85–1.76)	1.43 (0.83–2.40)	1.57 (0.72–1.76)	1.404(0.88-2.08)
Cho/NAA	1.58 (0.81–2.00)	1.57 (0.72–2.70)	1.31 (0.83–1.78)	0.988 (0.53-2.14)
NAA/Cr	1.20 (0.83–1.65)	1.14 (0.50–1.69)	1.22 (0.94–1.69)	1.426(0.56-1.92)

**[Table/Fig-6]:** Shows comparison of mean values of Cho/Cr, Cho/NAA and NAA/Cr between different studies with the present study in patients with radiation necrosis.

before providing a conclusive diagnosis. In the current study all but one recurrent lesion showed value of Cho/NAA less than 1.87 however for the same lesion Cho/Cr and NAA/Cr ratio were higher than 1.93 and less than 1.24 respectively which were in accord with the cut off the same in the present study.

## LIMITATIONS

Even though our study results are comparable with other standard studies, our study has few limitations. The sample size was of our study is small, duration of study was short and only those patients were included in study for which prospective SPECT Imaging was available which was taken as a reference standard for categorization of cases into tumor recurrence and radiation necrosis which in turn has its own limitations. Most importantly pathological diagnosis was not available for these patients. Other MRI sequence was not incorporated into the study like DWI, MR Perfusion which if used in conjunction with MRS increases the predictive power of same.

## CONCLUSION

MRS should be incorporated regularly on conventional MRI imaging where a contrast enhancing lesion is detected in post treated cases of brain tumor. Metabolic ratios should be analyzed for assessment rather than just looking for the metabolic peaks. The results of the study substantiate significant elevations of the Cho/NAA and Cho/Cr ratios with a simultaneous reduction in the NAA/Cr ratio in contrast-enhancing lesions representing tumor recurrence compared with lesions representing post treatment change. Further, although all three metabolic ratios significantly predicted tumor when used in combination, the most significant correlation was noted with Cho/Cr and Ch/NAA ( $p < 0.001$ ).

MRS findings if correlated with other non invasive MRI imaging findings like DWI, perfusion before formulating final conclusive diagnosis results in increased accuracy.

## REFERENCES

- [1] Central Brain Tumor Registry of the United S. Statistical report: Primary brain tumors in the United States, 1998-2002. 2005. Contract No: Report.
- [2] Stupp R, Mason WP, Weller M, Fisher B et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005; 352: 987–96.
- [3] Antonadou D. Current treatment of brain metastases. Business briefing: *Eur Oncol Rev*. 2005. DOI: 10.17925/EOH.2005.0.0.1m.
- [4] Posner J. Management of central nervous system metastasis. *Semin Oncol*. 1977;4:81–91.
- [5] Steen RG, Koury BSM, Granja CI, Xiong X et al. Effect of ionizing radiation on the human brain: White matter and gray matter t1 in pediatric brain tumor patients treated with conformal radiationtherapy. *Int J Radiat Oncol Biol Phys*. 2001;49(1): 79–91.
- [6] Mullins ME, Barest GD, Schaefer PW, Hochberg FH, Gonzalez RG and Lev MH. Radiation necrosis versus glioma recurrence: Conventional MRI clues to diagnosis. *AJNR American Journal of Neuroradiology*. 2005;26(8):1967–72.
- [7] Bonavita S, Di Salle F, Tedeschi G. Proton MRS in neurological disorders. *Eur J Radiol*. 1999;30:125–31.
- [8] Vos MJ, Uitdehaag BM, Barkhof F, Heimans JJ, Baayen HC et al. Interobserver variability in the radiological assessment of response to chemotherapy in glioma. *Neurology*. 2003;60(5):826–30.
- [9] Byrne TN. Imaging of gliomas. *Semin Oncol*. 1994;21(2): 162–71.
- [10] Kaplan RS. Complexities, pitfalls, and strategies for evaluating brain tumor therapies. *Curr Opin Oncol*. 1998;10(3):175–78.
- [11] Pirzkall A, Li X, Oh J, Chang S, Berger MS, Larson DA et al. 3D MRSI for resected high-grade gliomas before Rt: Tumor extent according to metabolic activity in relation to MRI. *Int J Radiat Oncol Biol Phys*. 2004;59(1):126–37.
- [12] Graves EE, Nelson SJ, Vigneron DB, Verhey L, McDermott M et al. Serial proton MR spectroscopic imaging of recurrent malignant gliomas after gamma knife radiosurgery. *AJNR American Journal of Neuroradiology*. 2001;22(4):613–24.
- [13] Smith EA, Carlos RC, Junck LR, Tsien CI, Elias A, Sundgren PC. Developing a clinical decision model: MR spectroscopy to differentiate between recurrent tumor and radiation change in patients with new contrast-enhancing lesions. *AJR Am J Roentgenol*. 2009;192(2):W45–52.
- [14] Weybright P, Sundgren PC, Maly P, Hassan DG, Nan B, Rohrer

- S, et al. Differentiation between brain tumor recurrence and radiation injury using MR spectroscopy. *AJR Am J Roentgenol*. 2005;185(6):1471–76.
- [15] Sabry A. Elmogy AEM. MR spectroscopy in post-treatment follows up of brain tumors. *Egypt J RadiolNucl Med*. 2011;42(s 3–4):413–24.
- [16] Schlemmer HP, Bachert P, Herfarth KK, Zuna I, Debus J, van Kaick G. Proton MR spectroscopic evaluation of suspicious brain lesions after stereotactic radiotherapy. *Am J Neuroradiol*. 2001;22(7):1316–24.
- [17] Schlemmer HP, Bachert P, Henze M, Buslei R, Herfarth KK, Debus J, et al. Differentiation of radiation necrosis from tumor progression using proton magnetic resonance spectroscopy. *Neuroradiology*. 2002;44(3):216–22.
- [18] Kinoshita Y, Kajiwara H, Yokota A, Koga Y. Proton magnetic resonance spectroscopy of brain tumors: an in vitro study. *Neurosurgery*. 1994 ;35(4):606–13.
- [19] Kuesel AC, Sutherland GR, Halliday W, Smith IC. MRS of high grade astrocytomas: mobile lipid accumulation in necrotic tissue. *NMR Biomed*. 1994;7(3):149–55.
- [20] Urenjak J, Williams SR, Gadian DG, Noble M. Proton nuclear magnetic resonance spectroscopy unambiguously identifies different neural cell types. *J Neurosci Off J Soc Neurosci*. 1993;13(3):981–89.
- [21] Rabinov JD, Lee PL, Barker FG, Louis DN, Harsh GR, Cosgrove GR, et al. In vivo 3-T MR spectroscopy in the distinction of recurrent glioma versus radiation effects: initial experience. *Radiology*. 2002;225(3):871–79.
- [22] Kaminaga T, Shirai K. Radiation-induced brain metabolic changes in the acute and early delayed phase detected with quantitative proton magnetic resonance spectroscopy. *J Comput Assist Tomogr*. 2005;29(3):293–97.

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