Evaluation of Contrast-Enhanced Magnetic Resonance Imaging and Spectroscopy as Diagnostic Tests to Differentiate Tumour Progression versus Post-Treatment Changes in Adult Gliomas and Their Correlation with Single-Photon Emission Computed Tomography - A Cross-Sectional Study from a Tertiary Care Centre in Pune, India

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ABSTRACT

BACKGROUND

The differentiation of tumour progression from treatment-induced changes is critical in evaluating response to therapy among patients with gliomas. Although conventional magnetic resonance imaging (MRI) is invaluable in the overall assessment of such lesions, it is often difficult to differentiate between these two entities. We wanted to evaluate the role of contrast-enhanced MRI (CE MRI) and magnetic resonance spectroscopy (MRS) and correlation with 99 m Tc Sestamibi single-photon emission tomography (SPECT) in differentiating tumour progression from post-therapy changes in patients with glioma.

METHODS

This was a cross-sectional study. Being a rare disease, all adult patients (25 in number) with brain glioma reporting to the hospital for over a period of 12 months were included in the study. CE MRI, MRS and SPECT were performed at three months, six months and 12 months' post-surgery and radiotherapy. The ratios for choline (Cho) / N-acetyl aspartate (NAA) and choline (Cho) creatine (Cr) were obtained from the areas suspicious for tumour progression on CE MRI and were correlated with the presence or absence of uptake on SPECT. These findings were correlated with the patients' clinical course and tumour histopathology.

RESULTS

Both choline (Cho) / N-acetyl aspartate (NAA) and choline (Cho) / creatine (Cr) ratios had high detection rates for tumour progression when cut-off values of > 1.75 were used. For the Cho / NAA ratio, the sensitivity and specificity were 93.7 % and 100 %, respectively. The sensitivity and specificity for the Cho / Cr ratio were 81.3 % and 88.9 %, respectively. The sensitivity and specificity of 99 m Tc Sestamibi SPECT were 87.5 % and 100 %, respectively.

CONCLUSIONS

MRS and SPECT have high sensitivity and specificity for diagnosing tumour progression and must be used in conjunction with conventional CE MRI in the post-therapy setting.

KEYWORDS

Glioma, Progression, Post-Therapy Changes, MRI, MRS, SPECT

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BACKGROUND

The annual global age-standardized incidence of primary malignant brain tumours is ~ 3.7 per 100,000 for males and 2.6 per 100,000 for females.[1] The incidence varies with age and is 3.1 cases per 100,000 people in the age group (0 - 4 years), decreases in the age group (15 - 24 years), and again rises to 18 to 19 per 100,000 in the age group (65 - 79 years).[2] In 2016, the World Health Organization (WHO) updated the central nervous system (CNS) tumour classification system to define tumours not only based on their cellular origin (microscopic morphology) but also by molecular and genetic markers. These genetic markers are likely to help prognosticate and also guide therapy.[3,4] Tumours of glial origin are most common and mainly include astrocytoma, oligodendroglioma, ependymoma, and subependymoma. Treatment of brain gliomas depends on their location, histology, and grade of malignancy. The current treatment paradigm is a combination of surgery, radiotherapy, and chemotherapy. Radiotherapy is the primary adjuvant treatment after surgical resection for most gliomas.[5] During post-therapy imaging of patients with glioma, there often exists a dilemma between tumour progression versus post-therapy changes.[6,7,8,9,10]

Correctly classifying newly manifested lesions is the key goal in neuro-oncologic imaging for directing subsequent therapy. In areas of abnormal enhancement that are located in or near the primary tumour site and within the irradiated volume, tumour progression is difficult to distinguish from post-therapy changes as CE MRI can only recognize blood-brain barrier (BBB) disruption. In vivo proton MRS helps characterize tissue by interrogating the relative concentration of several metabolites. Various studies have shown that reliable diagnoses can be made by spectroscopy by calculating Cho / NAA, Cho / Cr, and NAA / Cr ratios.[11,12,13] 99 m Tc Sestamibi (MIBI–methoxy isobutyl isonitrile) SPECT has also been found useful in the follow-up of treated gliomas for differentiating between tumour progression and radiation necrosis.

MIBI, a tracer of cell viability, diffuses passively through the cell membrane. Approximately 95 % of intracellular MIBI is found in mitochondria with higher uptake in malignant cells. There is no uptake in normal brain parenchyma. Pathological uptake is observed when the BBB is disrupted by a metabolically active tumour.[14] While many other modalities like computerized tomography perfusion (CTP), MR perfusion (MRP), positron emission tomography (PET) (using different tracers) have been studied for this purpose, a systematic review by Furuse et al. found no single imaging modality to be the best.[9] Moreover, only a handful of studies have used histopathology as the reference standard.[9]

This study was undertaken to compare the utility of CE MRI, MRS, and 99 m Tc Sestamibi SPECT in differentiating post-therapy changes from tumour progression with histopathology as a reference standard.

METHODS

This study was a cross-sectional study conducted from Dec. 2017 to Dec. 2019 at a tertiary care oncology centre. Being a rare disease all consecutive patients with brain gliomas (confirmed on histopathology) who reported to our centre over a period of 12 months and underwent surgical resection followed by radiotherapy with or without chemotherapy were studied

The study was performed in a manner to conform with the Helsinki Declaration of 1975, as revised in 2013 concerning Human and Animal Rights and the authors followed the policy of the journal regarding informed consent.

Only those patients who had no evidence of residual disease on CE MRI performed within 48 hours after surgery were included. These patients received radiotherapy (50 - 60 Gy) at 1.8 - 2 Gy per day for 25 - 30 days. Patients with high grade glioma and some patients with low grade glioma also received chemotherapy with Temozolomide. All patients were clinically followed-up (improving, steady, or deteriorating) and underwent CE MRI, MRS, and 99mTc SPECT at three months, six months, and 12 months following completion of radiotherapy. In cases where a strong suspicion of tumour progression was present on imaging, patients underwent second surgery / biopsy or chemo radiotherapy as per the clinical status and existing recommendations.[15] The imaging features in these patients were then correlated with histopathology. Patients who were considered to be free of tumour recurrence / progression based on the results of all three modalities were kept on follow-up. Clinical stability and reduction / stability in size of any contrast-enhancing lesion if present, in patients with no evidence of recurrence on MRS and SPECT, were considered features of post-therapy changes. The sensitivity and specificity for MRS Cho / NAA and Cho / Cr ratios and SPECT were calculated with histopathology as the gold standard. The imaging parameters were as mentioned below:

MRI

1.5 Tesla system (Harmony, Siemens, Erlangen, Germany). The contrast used was gadopentetate dimeglumine (Gd - DTPA; 0.2 mmol / kg of body weight). Conventional anatomic and CE MR images were acquired adhering to the following protocol: 3-plane localizer, T1WI axial (TR / TE 500 / 7.7 ms), T2 WI axial and coronal (TR / TE, 7180 / 103 ms), fluid-attenuated inversion recovery axial (FLAIR; TR/ TE / TI, 8710 / 114 / 2500 ms), diffusion-weighted imaging (DWI) at b values of 0 - 1000 s / mm^2 and post-contrast axial and 3D T1W images.

MRS

Single voxel spectroscopy (SVS) was performed. The spectra were obtained at a TE of 135 ms for all patients. The voxels were positioned to include the enhancing lesion (and area of restricted diffusion if present) while avoiding contamination from the scalp and cerebrospinal fluid.

The voxel size was 2 x 2 x 2 cm. The spectra were analysed for concentrations of NAA, choline, creatine, lactates, and lipids. Thereafter, NAA / Cr, Cho / Cr, and Cho / NAA ratios were calculated. Metabolite ratios amongst patients with recurrent tumour and radiation injury were compared. The highest Cho / Cr and Cho / NAA ratios in one voxel were used for comparison.

SPECT

Sestamibi was labelled with 99 m Tc and a dose of 20 mCi was administered intravenously followed by acquisition after one hour. Images were acquired parallel to the orbitomeatal plane, in craniocaudal direction using a double-headed gamma camera, with a 128 x 128 matrix, zoom of 1.23, 180° rotations, and an acquisition time of 30 s per frame. Thick coronal and sagittal reconstructions were made. Positive SPECT diagnosis of tumour recurrence was defined as tracer uptake ≥ 1.5 times the uptake in the mirror area.

Statistical Analysis

Statistical analysis was performed on the software MINITAB 1513. Analysis of the data was done to determine the sensitivity, specificity, positive predictive value and negative predictive value of MRS and SPECT in detecting tumour recurrence.

RESULTS

Twenty-five consecutive patients of glioma who underwent surgery and adjuvant radiotherapy were enrolled and studied for a period of one year. Amongst the 25 patients studied, 16 were males and nine females. 21 (84 %) patients were in the age group of 31 - 65 yrs. The youngest patient was 18 years old and the oldest was 75 years old. The histological diagnoses were: grade 2 astrocytoma (17 patients), glioblastoma (grade 4) (07 patients), and anaplastic oligodendroglioma (grade 3) (01 patient) (Table 1). Two patients underwent dedifferentiation into glioblastoma and anaplastic astrocytoma, respectively on follow-up. A total of 16 patients had a recurrence. Two patients who had recurrent tumours succumbed to their disease during the study period.

The MR images were studied for the presence of restricted diffusion, contrast-enhancement, and mass effect at the primary tumour site. MRS was performed from the enhancing lesion / peri-tumoural region (and area of restricted diffusion if present) and normal contralateral brain parenchyma, and Cho / NAA, Cho / Cr and NAA / Cr ratios were calculated. For Cho / NAA and Cho / Cr, a threshold value of > 1.75 was taken to be positive for recurrence (values between 1.71 and 1.8 have been used as cut-offs for Cho / NAA and 1.5 and 2.00 for Cho / Cr, respectively in literature).[11,12,16,17]

Out of 16 patients with tumour recurrence, only one had a Cho / NAA ratio < 1.75 (false negative). Among the nine patients who had no evidence of recurrence, the Cho / NAA ratio was < 1.75 in all (true negative). Three of the 16 patients with recurrence had Cho / Cr values < 1.75 (false negative) and the remaining had values > 1.75 (true positive). One patient without recurrence had a significantly high Cho / Cr ratio (false positive). In the remaining eight patients without recurrence, the Cho / Cr values were < 1.75 (true negative).

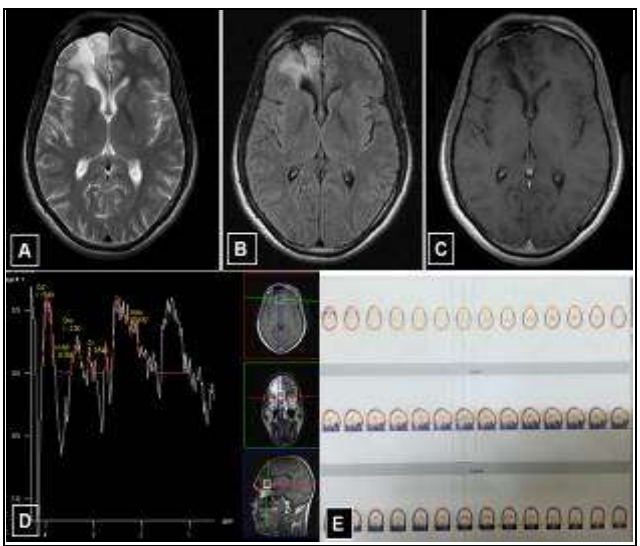

Figure 1. Panel of Axial Images: (A) T2-Weighted; (B) T1-Weighted; (C) CE MRI; (D) MRS; and (E) SPECT in a Patient with Right Frontal Grade 2 Astrocytoma, Post-Surgery, and Radiotherapy at 6 Months Follow-Up, with No Residual / Recurrent Tumour

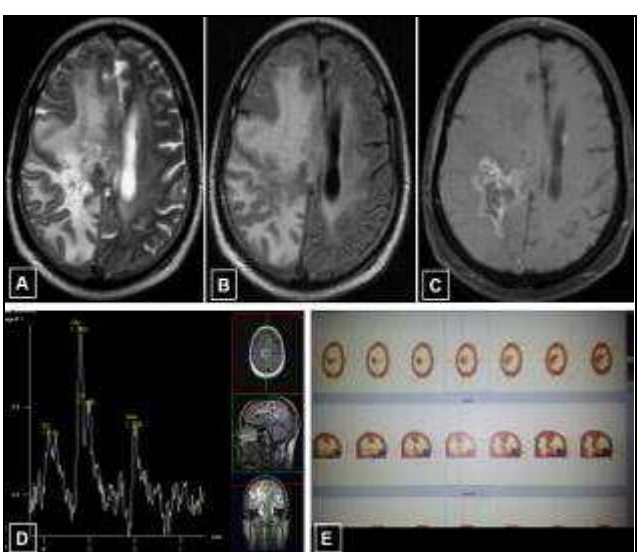

Figure 2. Panel of Axial Images: (A) T2-Weighted; (B) T1-Weighted; (C) CE MRI; (D) MRS; and (E) SPECT in a Patient with Left Fronto-Insular Glioblastoma, Post-Surgery, and Radiotherapy, with Residual / Recurrent Tumour

Sl. No.		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
	Histopathology	Diffuse astrocytoma	Diffuse astrocytoma	Diffuse astrocytoma	Diffuse astrocytoma	Diffuse astrocytoma	Diffuse astrocytoma	Glioblastoma	Glioblastoma	Diffuse astrocytoma	Diffuse astrocytoma	Diffuse astrocytoma	Glioblastoma	Diffuse astrocytoma	Diffuse astrocytoma	Glioblastoma	Diffuse astrocytoma	Anaplastic oligodendroglioma	Diffuse astrocytoma	Diffuse astrocytoma	Glioblastoma	Glioblastoma	Diffuse astrocytoma	Diffuse astrocytoma	Diffuse astrocytoma	Glioblastoma
3 Months	CEMRI	CE	CE	No CE / ME	ME	No CE / ME	ME	CE + ME	CE	CE	CE	CE + ME	CE	ME	No CE / ME	CE + ME	No CE/ME	CE + ME	CE + ME	CE	CE + ME	No CE / ME	CE	CE	CE	No CE / ME
	MRS Cho/NAA	Not done (hematoma)		0.59	1.9	1.07	2.29	3.56	0.76	2.57	2.76	3.91		34.06	0.45	1.9	2.96	3.2	1.23	3.1	8.34	5.67	1.12	1.19	1.73	0.78
	MRS Cho/Cr			4.18	1.8	1.33	1.4	2.08	1.1	2.18	2.32	6.21		7.7	0.69	1.98	1.7	5.86	1.45	2.8		3.56	1.36	1.67	1.17	0.55
	MRS NAA/Cr			7.08	0.89	1.24	0.62	0.58	1.4	0.85	0.84	1.61		0.22	1.44	0.95	1.58	0.54	1.19	0.9		1.59	1.21	1.4	0.68	0.71
	SPECT	No uptake	No uptake	No uptake	uptake	No uptake	Uptake	Uptake	No uptake	Uptake	Uptake	Uptake	No uptake	No uptake	No uptake	Uptake	No uptake	Uptake	No uptake	Uptake	9.32	Uptake	No uptake	No uptake	Uptake	No uptake
6 Months	CEMRI	No CE / ME	No CE/ME	No CE / ME	CE	No CE / ME	CE + ME	CE + ME	CE + ME	CE	CE	CE + ME	CE	ME	CE	CE + ME	NO CE / ME	CE + ME	CE + ME	CE	0.89	Ce	No CE / ME	CE	CE	No CE / ME
	MRS Cho/NAA	0.45	0.77	1.46	2	1.1	4.3	4.35	1.08	2.2	2.69	4.74	0.87	26.61	0.47	2.23	3.1	3.64	1.31	3.4	Uptake	6.12	1.31	1.23	2.33	0.71
	MRS Cho/Cr	0.59	1.25	3.9	1.89	1.22	3.07	3.7	1.21	2.04	2.39	10.3	0.96	6.92	0.67	2.14	1.44	5.12	1.42	2.9	Operated	3.07	1.65	1.56	1.54	0.65
	MRS NAA/Cr	1.3	1.62	2.7	1.94	1.1	0.71	0.85	1.12	0.93	0.89	2.1	1.1	0.26	1.42	1.04	0.37	1.4	1.08	0.85	Operated	0.5	1.26	1.28	0.66	0.88
	SPECT	No uptake	No uptake	No uptake	Uptake	No uptake	Uptake	Uptake	No uptake	Uptake	Uptake	Uptake	No uptake	No uptake	No uptake	Uptake	No uptake	Uptake	No uptake	Uptake	Operated	Uptake	No uptake	No Uptake	Uptake	No uptake
12 Months	CEMRI	No CE / ME	No CE/ME	No CE / ME	Operated	CE	Operated	Operated	CE + ME	CE	Operated	Operated	CE	Operated	No CE / ME	Operated	No CE / ME	CE + ME	Reduced CE / ME	Operated	Operated	Operated	No CE / ME	CE	Operated	No CE / ME
	MRS Cho/NAA	0.55	0.98	1.4	4.29	1.36	Operated		2.45	2.49	Operated	Operated	0.7	Operated	0.56	Operated	3.07	2.14	1.11	Operated	Operated		1.97	0.98	Operated	0.56
	MRS Cho/Cr	0.56	1.22	2	1.32	0.46			3.26	2.02		Operated	0.97		0.77		1.32	2.84	1.37				2.35	1.42		0.6
	MRS NAA/Cr	1.02	1.25	1.42	0.31	0.34			1.33	0.81			0.72		1.38		0.43	1.33	1.14				1.2	1.44		1.07
	SPECT	No uptake	No uptake	No uptake	Uptake	No uptake	Operated	Operated	Uptake	Uptake	Operated	Operated	No uptake	Operated		Operated	No uptake	Uptake	No uptake	Operated	Operated	Operated	Uptake	No uptake	Operated	No Uptake
HPE		NA	NA	NA	Residual / recurrent tumour	NA	Recurrent tumour/anaplastic astrocytoma	Residual recurrent tumour	Recurrent tumour	Residual/ recurrent tumour	Residual/ recurrent tumour	Mixed tumour and radiation necrosis	NA	Residual/ recurrent tumour	NA	Mixed tumour and radiation necrosis	Residual/ recurrent tumour	Residual/ recurrent tumour	NA	Residual / recurrent tumour, glioblastoma	Recurrent tumour	Residual/ recurrent tumour	Recurrent tumour	NA	Residual/ recurrent tumour	NA
Conclusion		No recurrence	Positive MRS & SPECT	No recurrence	Positive MRS & SPECT	No recurrence	Positive MRS & SPECT	Positive MRS & SPECT	Positive MRS & SPECT at 12 months	Positive MRS & SPECT	Positive MRS & SPECT	MRS& SPECT positive for recurrence	No recurrence	Negative SPECT for recurrence, MRS +	No recurrence	MRS & SPECT positive for recurrence	Negative SPECT for recurrence, MRS +	Positive MRS & SPECT	No recurrence	Positive MRS & SPECT	Positive MRS & SPECT	Positive MRS & SPECT	Positive MRS & SPECT	No recurrence	Negative MRS at 3 m, positive SPECT	No recurrence

Table 1. Temporal Imaging Findings in All Patients Corroborated with Histopathology

CE – Contrast enhancement; ME – Mass effect;

Diagnostic Test (MRS – Cho/NAA)	Disease / Recurrence Present	Disease / Recurrence Absent	Total
Positive test result	15	0	**15**
Negative test result	1	9	**10**
Total	**16**	**9**	

Table 2. Evaluation of MRS (Cho / NAA) as a Diagnostic Test for Recurrence, Considering Histopathology as Gold Standard. The Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value for MRS (Cho / NAA) Came Out to be 93.7 %, 100 %, 100 % and 90 %, Respectively

Diagnostic Test (MRS – Cho / Cr)	Disease / Recurrence Present	Disease / Recurrence Absent	Total
Positive test result	13	1	**14**
Negative test result	3	8	**11**
Total	**16**	**9**	

Table 3. Evaluation of MRS (Cho / Cr) as a Diagnostic Test for Recurrence, Considering Histopathology as Gold Standard. The Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value for MRS (Cho / Cr) Came Out to be 81.3 %, 88.9 %, 92.8 %, and 72.7 %, Respectively

Diagnostic Test (SPECT)	Disease / Recurrence Present	Disease / Recurrence Absent	Total
Positive test result	14	0	**14**
Negative test result	2	9	**11**
Total	**16**	**9**	

Table 4. Evaluation of SPECT as a Diagnostic Test for Recurrence, Considering Histopathology as Gold Standard. The Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value for SPECT Came Out to be 87.5 %, 100 %, 100 %, and 81.8 %, Respectively

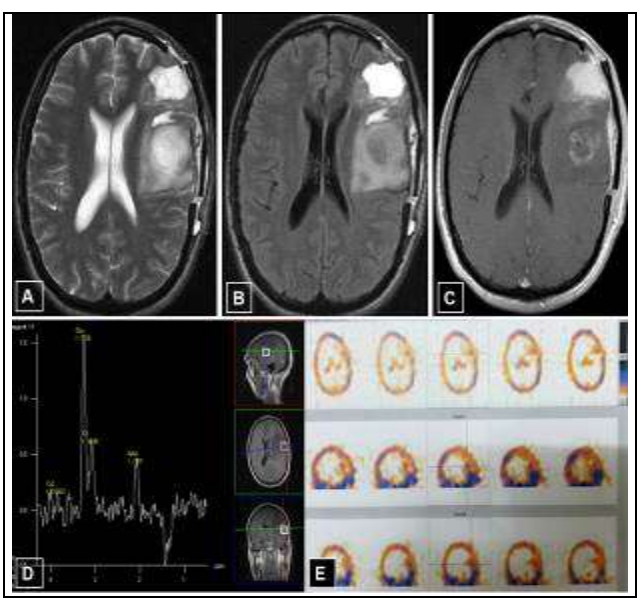

Figure 3. Panel of Axial Images: (A) T2-Weighted; (B) T1-Weighted; (C) CE MRI; (D) MRS; and (E) SPECT in a Patient with Right Frontoparietal Grade 2 Astrocytoma, Post-Surgery, and Radiotherapy at 6 Months Follow-Up, with a Swiss-Cheese Pattern of Lesion Enhancement, Raised Cho / NAA and Cho / Cr on MRS and Positive SPECT. An Impression of Mixed Radiation Necrosis (Because of Swiss Cheese Appearance) with Recurrent Tumour was Given. The Patient was Operated Upon and Recurrent Tumour with Radiation Necrosis was Confirmed on Histopathology

The sensitivity and specificity for the Cho / NAA ratio for the detection of residual / recurrent tumour was 93.7 % and 100 %, respectively. The sensitivity and specificity for the Cho / Cr ratio for detection of residual / recurrent tumour were 81.3 % and 88.9 %, respectively.

For 99 mTc Sestamibi SPECT, the presence of uptake were considered positive for recurrent / residual tumour. Two patients with recurrence did not show uptake on SPECT (false negative). No uptake was seen in patients without recurrence. The sensitivity and specificity for 99mTc Sestamibi SPECT for detection of residual / recurrent tumour was 87.5 % and 100 %, respectively.

The temporal imaging findings in all the patients, corroborated with histopathology are shown in Table. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for MRS & SPECT are depicted in Table 2, 3 and 4.

DISCUSSION

In patients with gliomas, the differentiation of tumour progression from post-therapy changes is critical in evaluating the response to therapy.

Imaging findings need to be interpreted in the appropriate clinical context like patient's clinical status, time since surgery / radiotherapy, and the type of treatment protocol (surgery and radiation with adjuvant chemotherapy / immunotherapy). In post-therapy MRI, contrast-enhancing regions on T1-weighted images may reflect either tumour progression or treatment-induced changes (pseudo progression or radiation necrosis). Also, contrast-enhancement may be seen in the early postoperative period (owing to ischemia).

Recurrent tumours usually demonstrate contrast-enhancement, mass effect, and peri-tumoural oedema. Similar findings may also be noted in pseudo progression and radiation necrosis.[18,19] Although histopathology is considered the 'gold standard', a biopsy is invasive and there may be errors owing to the heterogeneity of tumour, samples being non-representative, and admixture of tumour cells and necrosis. To resolve this clinically and therapeutically significant dilemma of differentiating recurrent tumours from the post-therapy changes that may simulate tumours, various imaging modalities besides conventional MRI have been studied.[9]

In this study, the most common post-therapy finding in the radiation field on CE MRI was demyelination. When the presence of new contrast-enhancement, restricted diffusion, and mass effect was considered together, most patients were subsequently correctly identified as having residual / recurrent tumour. The absence of new contrast-enhancement and mass effect had a high negative predictive value; most of these patients being correctly identified as having no residual / recurrent tumour on MRS and SPECT (Figure 1). Two patients who had grade 2 astrocytoma with recurrence did not show any contrast-enhancement pre-operatively or after therapy. However other morphological features (signal characteristics similar to the pre-operative lesion, mass effect) in these recurrent tumours aided their detection along with MRS. The presence of both mass effect and contrast-enhancement was present in a significantly higher number of patients with residual / recurrent tumour (Fig. 2). The presence of thick, nodular contrast-enhancement was more consistent with recurrent / residual

tumour. Most of the lesions with no recurrence had thin, peripheral enhancement on CEMRI. 'Swiss cheese' pattern of enhancement was seen in one case; however other imaging modalities suggested a recurrence and histopathology revealed a recurrent tumour with dedifferentiation into anaplastic astrocytoma (Fig 3).

Kumar et al have reported that the following imaging features favour radiation necrosis: enhancement in a pre-irradiation non-enhancing lesion, new enhancing focus within the radiation field distant from the primary tumour, enhancing or non-enhancing periventricular white matter changes, new lesions exhibiting 'soap bubble' or 'swiss-cheese' enhancement pattern.[18] Mullins et al.[19] reported that the following combination of findings favour recurrence: corpus callosal involvement with extension across the midline, multiple enhancing lesions with corpus callosal involvement, subependymal spread, and multiple enhancing lesions.

In this study, only two patients showing post-therapy contrast-enhancement and mass effect had evidence of radiation necrosis (with coexistent tumour) on histopathology, and contrast-enhancement could be attributed to both the tumour as well as necrosis. It is likely that more patients would have been detected with radiation necrosis if the study had been carried out beyond 12 months as > 70 % of cases occur between six months to two years' post-radiotherapy.[11]

MRS is used to study neuro-metabolism and has been extensively studied in detecting post-therapy recurrent / residual tumour.[9] There is a decrease in NAA in both tumour and radiation necrosis consistent with neuronal loss in both. However, choline is raised in tumour recurrence (reflecting increased cellularity and cell membrane turn-over) contrary to necrosis.

Using a threshold of 1.75 for Cho / NAA to detect recurrence, fifteen (93.75 %) out of the 16 patients who had recurrent / residual tumours were correctly identified. Only one patient during the 3rd-month scan who had recurrence had a Cho / NAA ratio of less than 1.75; however, the value for Cho / NAA was near the cut-off value (1.73). The Cho / Cr ratio for this patient was also not elevated (1.17). The patient showed uptake on SPECT. On follow-up at six months, there was an increase in the size of the contrast-enhancing lesion and the Cho / NAA ratio was 2.33 and the patient showed uptake on SPECT. The patient was operated upon shortly after this and histopathology confirmed recurrent tumour. The small size of the lesion in the initial scan and incomplete MRS sampling may have resulted in the erroneous result. Thus, in this study, the cut-off value of < 1.75 for Cho / NAA had a high positive as well as a high negative predictive value, and the sensitivity and specificity were 93.7 % and 100 %, respectively.

Using a threshold Cho / Cr > 1.75 for recurrence, three patients were incorrectly classified as having no recurrence. For one patient, both Cho / Cr and Cho / NAA values were below the cut-off value and sampling error may have been the cause for the erroneous result. For the other two, although the Cho / Cr values were low, the Cho / NAA values were raised and one patient on imaging at 6 months also showed raised Cho / Cr level. Two of these three patients showed uptake on SPECT. Therefore, in our study, the cut-off of 1.75 proved to be an optimal threshold value. There was one patient in whom the Cho / Cr value was raised significantly above the threshold value of 1.75. This patient however showed no other evidence of a recurrent/residual lesion and Cho / NAA values were not raised in this patient and there was no uptake on SPECT as well. The patient remained clinically stable on follow-up. For the Cho / Cr ratio, the sensitivity was 81.3 % and the specificity was 88.9 %. In this study, the Cho / NAA ratio had a higher detection rate as compared to Cho / Cr with only one false-negative and no false-positive patient.

In three patients MRS spectra were uninterpretable at three months because of the presence of blood degradation products at the operated site. This may be a limitation of MRS during the early post-therapeutic period.

99 m Tc Sestamibi (MIBI) SPECT has been found useful in differentiating between tumour recurrence and radiation necrosis. MIBI is a tracer of cell viability and uptake in brain parenchyma is seen in metabolically active tissues with BBB disruption. There is no uptake in normal brain parenchyma or radiation necrosis. Soler et al.[20] reported 100 % accuracy in the detection of glioma recurrence by 99 mTc-Sestamibi SPECT; however, the study lacked histological verification in all cases. Other workers have also reported high sensitivity, specificity and accuracy of SPECT in detecting tumour recurrence.[21,22,23]

In this study, 14 (87.5 %) out of the 16 patients who had residual / recurrent tumours, were correctly identified on SPECT. Two patients in whom there was residual / recurrent lesion, no uptake was found on SPECT. Both these patients had elevated Cho / NAA ratios on MRS. These tumours were grade 2 astrocytomas and both these tumours did not show enhancement on preoperative as well as postoperative, post-therapy CE MRI. The absence of uptake in these patients can be explained by the fact that there was no contrast-enhancement in these lesions suggesting an intact BBB, and uptake of MIBI requires disruption of BBB, besides the presence of metabolically active tissue. The sensitivity and specificity of SPECT for identifying residual / recurrent tumours in this study were 87.8 % and 100 %, respectively. The high specificity of 99 m Tc SPECT in agreement with other studies indicates that a positive SPECT is almost conclusive of tumour recurrence. However, SPECT is limited by poor anatomical and spatial resolution, and lesions less than 10 mm may not be picked up. Also, low-grade lesions with an intact BBB may not show uptake. Lesions that are located close to the skull or in the periventricular region may also be difficult to identify because of physiological uptake seen in the scalp and choroid plexus. SPECT is however a far better modality than FDG-PET for this purpose and also more economical.[9]

This study was limited by small sample size. Though patients were followed up clinically and on imaging beyond one-year post-therapy, the study duration was only up to one-year post-therapy, and recurrence, as well as radiation necrosis, have maximum incidence from six months to two-three years after therapy. While MRP has also been studied widely; a systematic review by Furuse et al have shown the sensitivity and specificity of this modality for detecting

recurrent tumours to be similar to MRS and SPECT.[9] Our study is strengthened by the availability of confirmatory histopathological diagnosis in all cases suspected of recurrence as very few studies have used histopathology as a reference standard.

CONCLUSIONS

No single imaging modality achieves consistently high sensitivity and specificity for distinguishing residual / recurrent tumour from post-therapy changes in patients with glioma. Multimodality imaging is essential for a confident diagnosis of tumour recurrence. Raised Cho / NAA and Cho / Cr ratios on MRS, and uptake on 99 mTc Sestamibi SPECT have high sensitivity and specificity for detecting recurrent / residual tumour in the post-therapy period, and may be used in conjunction with conventional CE MRI for this purpose.

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