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[^{99m}Tc]-Bis-Methionine-DTPA Single-Photon Emission Computed Tomography Impacting Glioma Management: A Sensitive Indicator for Postsurgical/ Chemoradiotherapy Response Assessment

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Abstract

Background: The present study evaluated the prognostic value of [^{99m}Tc]MDM (bis-methionine-DTPA) follow-up single-photon emission computed tomography (SPECT) imaging for response assessment to chemoradiotherapy in glioma postoperatively.

Materials and Methods: One hundred fourteen glioma patients (80 M:34 F) were followed postoperatively by sequential [^{99m}Tc]MDM SPECT, dynamic susceptibility contrast-enhanced (DSCE)-MRI, and magnetic resonance spectroscopy (MRS) at baseline, 6, 12, and 22.5 months postchemoradiotherapy. The quantitative imaging results and the clinical outcome were used for response assessment and for the final diagnosis. The quantitative parameter of [^{99m}Tc]MDM SPECT were also used for survival analysis.

Results: A significantly ($p=0.001$) lower target to nontarget (T/NT) ratio was observed in responders than in nonresponders. The sensitivity and specificity of [^{99m}Tc]MDM-SPECT for identifying tumor recurrence from radiation necrosis at a cutoff ratio of 1.90 were estimated at 97.9% and 92%. Whereas, the sensitivity and specificity of DSCE-MRI with the normalized cerebral blood volume (nCBV) cutoff of 3.32 for this differentiation was found to be 84.6% and 93.0%. MRS intensity ratios of Cho/NAA and Cho/Cr provided comparatively lower sensitivity of 81.0% and 85.3% and specificity of 73.0% and 73.7%. T/NT ratios correlated with nCBV ($r=0.775$, $p<0.001$) and to a moderate extent with Cho/NAA ratios ($r=0.467$, $p=0.001$). [^{99m}Tc]MDM SPECT and DSCE-MRI provided comparable results for predicting response assessment to chemoradiotherapy. There was a final diagnosis in 72 patients, of which 47 cases were tumor recurrence and 25 were radiation necrosis. The Kaplan–Meier analysis indicated that patients with T/NT ratio <1.9 showed prolonged survival (53.8 months) as compared (37.2 months) with those who demonstrated T/NT ratio >1.9 ($p=0.0001$).

Conclusion: Thus, this low-cost SPECT technique in combination with DSCE-MRI can be used accurately for mapping the disease activity, response assessment, and survival in glioma. [^{99m}Tc]MDM SPECT and DSCE-MRI had the same diagnostic efficacy to detect recurrent/residual tumor and radiation necrosis while MRS was inferior to both the techniques.

Keywords: glioma, chemoradiotherapy, response assessment, [99mTc]-methionine SPECT

Introduction

GLIOMAS ARE THE MOST COMMON PRIMARY TUMORS of the central nervous system with a reported annual incidence of 20.5/100,000.[1] The prognosis in high-grade glioma (HGG) remains challenging with the median survival of 15.0 months and 5-year survival of $\sim$10%.[2] An accurate treatment response assessment by accurate and noninvasive techniques is important as the disease recurrence warrants a change in treatment, whereas a finding of

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radiation necrosis will call for continuation of the standard treatment.[3–5]

The conventional magnetic resonance imaging (MRI) is the standard modality of choice both in the initial diagnosis and postsurgery/chemoradiotherapy response assessment. Conventional MRI has suboptimal specificity due to its ''inherent limitation'' in differentiating pseudoprogression/radiation necrosis from tumor recurrence.[6] However, with the advanced MRI techniques, such as magnetic resonance spectroscopy (MRS) and dynamic susceptibility contrast-enhanced (DSCE)-MRI, it is possible to characterize tumors at the levels of various metabolites and microvascular density.[7–9]

In particular, recent joint recommendations of the Response Assessment in Neuro-Oncology working group and the European Association for Neuro-Oncology have considered positron emission tomography (PET) imaging with radiolabeled amino acids as a clinically promising tool and suggested its use for the management of patients with glioma as complementary to MRI.[10] Over the past few decades, different amino acid-based PET tracers, such as 18F-fluoro-ethyl-tyrosine ([^{18}F]FET), ^{18}F-fluoro-choline ([^{18}F]FCH), and ^{11}C-methionine ([^{11}C]MET) PET have been used in therapy planning and to evaluate the treatment response.[11] Among these tracers, [^{11}C]MET is one of the most extensively investigated PET tracers in the diagnostic workup of glioma. [^{11}C]MET accumulates extensively in proliferating tumors by the mechanism of increased amino acid transport through system L-transporters-1 (LAT1) and greater rates of protein synthesis relative to normal brain.[12] Additionally, it has been reported in various studies that target to nontarget (T/NT) ratio on [^{11}C]MET PET may be used for predicting prognosis of glioma.[13]

Therefore, it would be a good idea to note that the PET methods, especially [^{11}C]MET, require on-site cyclotron facility, employed in only a few research centers, and often cost prohibitive, so there is motivation to identify an appropriate single-photon emission computed tomography (SPECT) tracer as a feasible imaging alternative for imaging glioma. In a preliminary analysis in a small cohort of 28 patients with brain gliomas, the authors reported the evaluation of [^{99m}Tc]-bis-methionine-DTPA ([^{99m}Tc]MDM)-SPECT and observed comparable diagnostic utility with DSCE-MRI to identify recurrent/residual tumors.[14] However, the small sample size may be underpowered in disseminating the usefulness of [^{99m}Tc]MDM SPECT for response assessment post-chemoradiotherapy and demonstrating its prognostic ability. In this prospective study, the authors therefore propose, the sequential change in [^{99m}Tc]MDM uptake, as a noninvasive and early indicator of disease progression in glioma and compared its diagnostic performance with DSCE-MRI and MRS for identifying post-treatment response assessment and survival.

Materials and Methods

Patients

One hundred fourteen (80 M:34 F) patients (mean age 42.11 ± 12.0 years; range 18–71 years) with histopathologically proven glioma and planned for chemoradiotherapy were recruited prospectively (Table S1). Among 114 patients, 55 patients were glioblastoma multiforme (GBM) (G-IV), 27 were G-III (16 anaplastic astrocytoma; 1 oligoastrocytoma; 10 oligodendroglioma), and 32 were G-II glioma (20 astrocytoma; 2 oligoastrocytoma; 10 oligodendroglioma). All the patients in the study were treated radically by radiotherapy with or without chemotherapy. HGG (GBM, anaplastic astrocytoma, anaplastic oligodendroglioma) received a total 60.0 Gy in 30 fractions over 6 weeks with concurrent daily oral chemotherapy with cap Temozolomide at a dose of 75.0 mg/m^2. This was followed by six cycles of adjuvant chemotherapy with cap Temozolomide 150–200 mg/m^2 on days 1–5 at 4 weekly intervals. Low-grade glioma (LGG) (astrocytoma, oligodendroglioma WHO Grade II) received radiotherapy alone, 54.0 Gy in 27 fractions over 5 weeks.

Ninety-two patients were enrolled before radiotherapy (postsurgery) that is, in the initial diagnostic phase and 22 were enrolled in the recurrent disease phase. All the patients underwent [^{99m}Tc]MDM SPECT and contrast-enhanced MRI (ceMRI). The SPECT and MR procedures were undertaken at around the same time. Repeat [^{99m}Tc]MDM SPECT (a total of 198 scans) and ceMRI were performed in 92 patients, whereas a single time point imaging was carried out in 22 patients. Among the 92 patients, 50 (50/92) patients underwent sequential SPECT and MRI at baseline (within 1 or 2 weeks before the initiation of radiation therapy) and then at 6 months posttreatment follow-up. Twenty-six (26/50) patients underwent additional follow-up imaging at 12 months post-treatment. Furthermore, 8 (8/26) patients underwent fourth SPECT and MRI at the median follow-up period of 22.5 months (range 18–24 months). Additionally, 47/114 patients underwent DSCE-MRI and MR spectroscopy (79 procedures). At the end of the follow-up, the quantitative scan findings and clinical assessment were used to classify the patients retrospectively at each time point as responders or nonresponders (Figure S1).

The final diagnosis of recurrent/residual tumor or radiation-induced necrosis could be made in 72 patients for which the cutoff values of the quantitative parameters of 6-months time point SPECT and MR techniques were used to differentiate these two disease entities. A written and informed consent was obtained from each patient. The study protocol was approved by the Institutional Ethics Committee.

[^{99m}Tc]MDM brain SPECT/CT imaging

In this study, ready to label (with 99mTc), single vial ''lyophilized'' cold kit preparations of bis-methionine DTPA developed by INMAS, DRDO, Delhi, India were used. The details of the development of the formulation, radiolabeling procedure, its preclinical validation, and prior clinical use have been reported previously.[14–16] Briefly, 555.0–740 MBq radioactivity of [^{99m}Tc]MDM was injected intravenously in each patient and SPECT (Symbia-T16; Siemens, Erlangen, Germany) acquisition was started at 2 h after injection and data acquired over 360°—degree rotation (circular orbit) in 128 projections (20 s/projection) in 128×128 matrix with a zoom factor of 1.5. The acquired [^{99m}Tc]MDM SPECT data were reconstructed and analyzed as described previously.[14] The reconstructed SPECT (axial images) data were interpreted visually and also subjected to a semiquantitative analysis to calculate the T/NT ratio of the radiotracer over the identifiable lesions.

Dynamic susceptibility contrast-enhanced MRI

MRI was performed by using two whole body 3.0 Tesla MR Units (Siemens, Verio or Discovery™ MR750w GEM–

GE Healthcare, Germany). Two MRI datasets were acquired before and after intravenous administration of Gadopentetate dimeglumine contrast (0.15 mmol/kg @ flow rate of 3.0–5.0 mL/min). The image acquisition sequences for Siemens MR Unit included T1-axial (TR/TE: 1800/3.8), T2-axial (TR/TE: 6000/96), T2-coronal (TR/TE: 9000/94), FLAIR (TR/TE: 9000/94), and DSCE (TR/TE: 1610/30). Whereas, the image acquisition sequences for GE MR Unit included Axial FLAIR T2 imaging (TR/TE: 11,000/100), Axial T2 PROPELLER (periodically rotated overlapping parallel lines with enhanced reconstruction) (TR/TE: 4800/114), SAG FSPGR BRAVO (Fast spoiled grass sequence) (TR/TE: 8.4/3.2), and DSCE (TR/TE: 2000/21). The MR data were analyzed by using a comprehensive neuroimaging software (nordicBrainEx; Nordic Neuro Lab, Norway) and evaluated as described previously.[14]

MRS imaging

Multi or single voxel (2D-CSI; SV) MRS on tumoral/peritumoral regions (large/small lesions) to evaluate the pattern for N-acetyl-aspartate (NAA), Choline (Cho), Creatine (Cr), Lipid-Lactate (LL) metabolites was performed. The FLAIR (TR/TE: 9000/94) or contrast-enhanced transverse T1-weighted images (TR/TE: 1800/3.8) were used to localize the volume of interest. Multivoxel and single-voxel sequence acquisition parameters for GE Healthcare scanner were of TR/TE: 1000/135 and TR/TE: 1000/30, respectively. These values for 3T Siemens scanner were TR/TE: 1700/135 and TR/TE: 2000/30, respectively.

Siemens and GE healthcare inbuilt software packages were used for processing the MRS data. MRS raw data were transferred to the workstation (Syngo MR Workstation, Siemens containing B 17 version of the software or GE Healthcare workstation) for postprocessing. The relative metabolite concentration ratios of Cho/NAA, Cho/Cr, Cr/NAA, Cr/Cho, and Cho/LL on the tumors were estimated.

SPECT/MR image fusion

The multimodality image fusion software (Multimodality Oasis Server version 1.9.4.3; Segami Corp., Houston) was used to fuse the corresponding SPECT and MR reconstructed images to match the abnormal brain foci seen on both the imaging modalities.

Statistical analysis

The statistical analysis (using the Statistical Package for Social Sciences; IBM SPSS statistics -21) included Wilcoxon signed-rank test, the receiver operating characteristic (ROC) analysis, Pearson correlation, Kaplan–Meier curves, and log-rank analysis. All statistical tests were two-sided and were performed at a significance level of $p \leq 0.05$.

Results

The radiolabeled product remained stable for up to 24 h. The radiolabeling efficiency for the final product of [^{99m}Tc]MDM was evaluated for each kit and the mean value was estimated to be 97.0% ± 1.5%. No adverse effects were observed in any of the patients after the radiotracer administration.

Postsurgery follow-up image findings (n = 92)

Imaging results at preradiotherapy. The mean (baseline) T/NT ratio in HGG patients (2.79 ± 1.34, $n = 70$) was significantly higher ($p = 0.002$) than in LGG patients (1.90 ± 1.02, $n = 22$). Fifty (50/92) patients underwent serial follow-up imaging and at the end of follow-up, the patients were classified as responders and nonresponders. This analysis showed (Table 1) that at preradiotherapy stage, only the T/NT ratio differed significantly ($p = 0.0001$) between the responders (2.11 ± 1.23, $n = 36$) and the nonresponders (3.51 ± 1.80, $n = 14$) and this difference in T/NT ratio persisted until the end of follow-up. No significant difference in any of the MRI parameters was observed at this time point.

Imaging results at 6-months postradiotherapy follow-up. No tracer avid lesions were seen in 29 (29/50) patients, 7 (7/50) patients showed diffuse uptake, and the remaining 14 (14/50) patients demonstrated focal tumor uptake. Nine (9/14) patients showed an increase in T/NT ratio in comparison with the reference baseline values. In responders, the T/NT ratio decreased (1.62 ± 0.70) significantly ($p = 0.04$) at 6 months as compared with the baseline 2.11 ± 1.23 value. The corresponding value in the nonresponders increased but

Table 1. The Quantitative Results of Different Quantitative Parameters in Responder and Nonresponder Patients During Follow-Up at Preradiotherapy, 6 and 12 Months Postradiotherapy

	Responders mean ± SD	*Nonresponders mean ± SD*	p
Preradiotherapy			
T/NT	2.11 ± 1.23 ($n = 36$)	3.51 ± 1.80 ($n = 14$)	0.0001*
nCBV	3.63 ± 3.43 ($n = 12$)	3.54 ± 0.7 ($n = 5$)	0.79
Cho/NAA	3.72 ± 2.87	2.1 ± 0.51	0.29
Cho/Cr	1.71 ± 1.13	1.76 ± 1.18	0.94
Cr/NAA	1.82 ± 1.88	1.68 ± 0.90	0.88
Cr/Cho	0.61 ± 0.30	0.92 ± 0.77	0.26
Postradiotherapy 6 months			
T/NT	1.62 ± 0.70 ($n = 36$)	4.65 ± 2.23 ($n = 14$)	0.0001*
nCBV	2.48 ± 2.39 ($n = 22$)	5.65 ± 2.09 ($n = 9$)	0.002*
Cho/NAA	2.5 ± 1.6	2.76 ± 2.19	0.73
Cho/Cr	1.77 ± 0.96	3.11 ± 1.97	0.01*
Cr/NAA	1.22 ± 0.67	1.48 ± 1.93	0.57
Cr/Cho	0.79 ± 0.46	0.55 ± 0.43	0.20
Postradiotherapy 12 months			
T/NT	1.81 ± .78 ($n = 19$)	5.49 ± 1.53 ($n = 7$)	0.0001*
nCBV	1.96 ± .97 ($n = 9$)	5.41 ± 3.23 ($n = 5$)	0.01*
Cho/NAA	1.99 ± 1.22	3.22 ± 1.89	0.16
Cho/Cr	2.41 ± 1.52	3.18 ± 2.73	0.50
Cr/NAA	0.82 ± 0.43	1.55 ± 1.14	0.10
Cr/Cho	0.59 ± 0.40	0.48 ± 0.28	0.63

*$p < 0.05$.

nCBV, normalized cerebral blood volume; T/NT, target to nontarget.

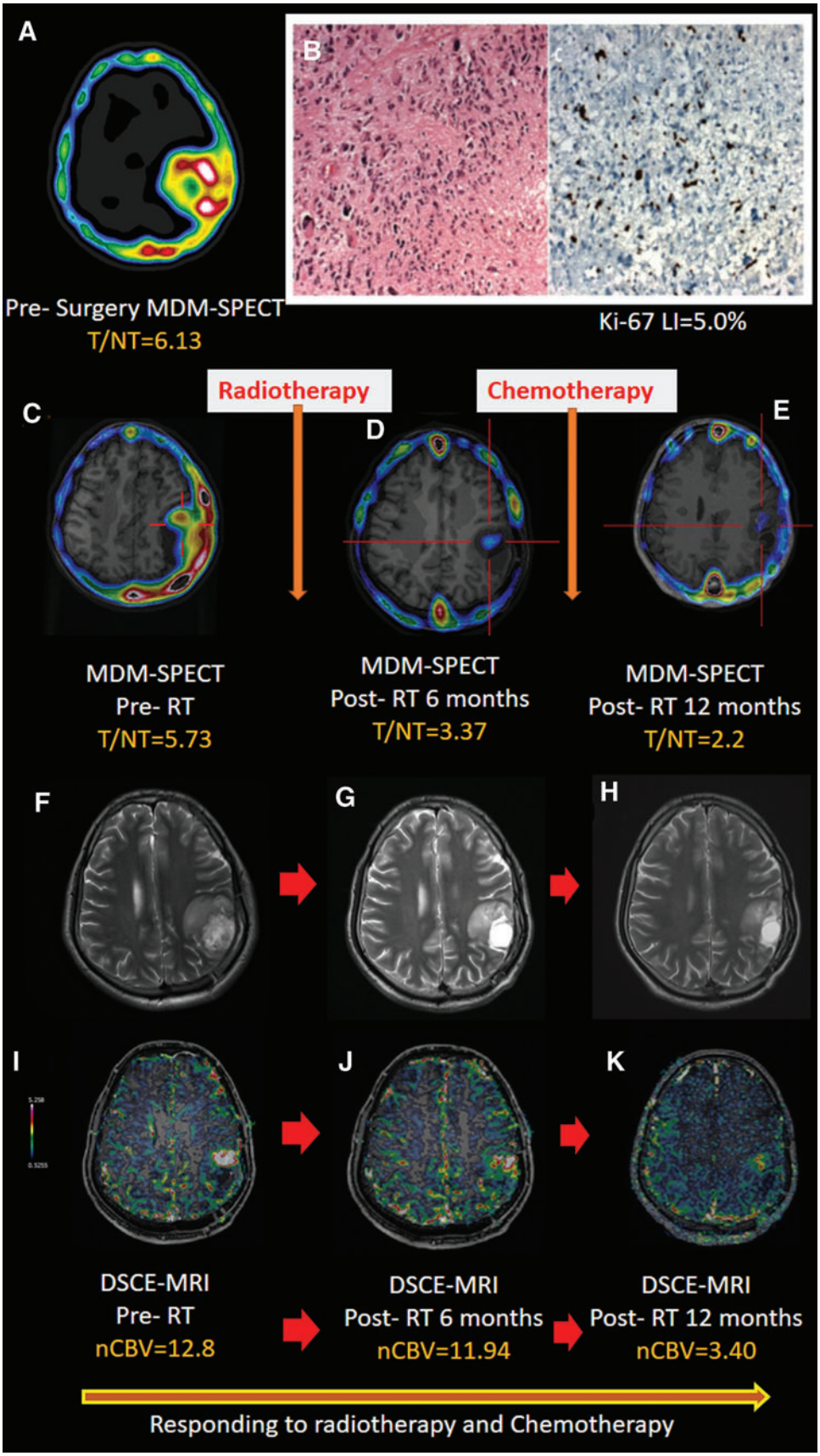


FIG. 1. Presurgery [^{99m}Tc]MDM SPECT imaging **(A)** in a 28-year-old male patient with GBM (G-IV) showing an increased tracer uptake (6.13) in the left parietal lobe with histology (H & E staining, 400×) shows **(B**, *left panel*) a moderate cellular and nuclear pleomorphism, numerous mitosis with regions of palisading necrosis and lower proliferation index of Ki-67 LI = 5.0% **(B**, *right panel*). Serial axial T2-weighted MR images **(F, G, H)** presenting no conclusive enhancement on tumor bed in the follow-up scans. Follow-up SPECT/MRI demonstrated that the baseline pre-radiotherapy **(C)** tracer uptake (5.73) and **(I)** nCBV (12.8) decreased **(D, J)** at 6 months (T/NT = 3.36, nCBV = 11.94) and at 12 months **(E, K)** (T/NT = 2.3, nCBV = 3.40) indicating a significant treatment response (Responder). GBM, glioblastoma multiforme; nCBV, normalized cerebral blood volume; SPECT, single-photon emission computed tomography; T/NT, target to nontarget. Color images are available online.

not to a significant extent. However, the mean value in responders ($n=36$) was significantly lower ($p=0.0001$) than in nonresponders ($n=14$) at the 6-month follow-up period.

Likewise, the mean normalized cerebral blood volume (nCBV) ratio at 6 months in responders was lower, whereas in nonresponders the value was significantly higher than the baseline value. Overall, the mean nCBV ratio differed significantly ($p=0.002$) between the responders and nonresponders at 6 months. On the other hand, among the various MRS parameters, a significant difference ($p=0.01$) between responders and nonresponders was found only for Cho/Cr ratio at 6 months.

Imaging results at 12 months (and beyond) postradiotherapy follow-up. Twenty-six (26/50) patients underwent follow-up imaging at 12 months. SPECT findings were negative for evidence of the disease recurrence in 11 (11/26) patients, which was in agreement with the clinical observations of improved symptoms in those patients. Six patients showed diffuse uptake pattern, whereas, 9 (9/26) patients demonstrated intense tracer uptake and was interpreted as having active disease/recurrence. The T/NT ratio at 12 months in responders did not differ significantly from the corresponding value seen at 6 months. Overall, the mean T/NT ratio (1.81 ± 0.78) in responders was significantly ($p=0.0001$) lower than (5.49 ± 1.53) that observed in nonresponders. The nCBV ratio in responders was significantly lower (1.96 ± 0.97) than in nonresponders (5.41 ± 3.23). None of the MRS parameters was found to be significantly different between responders and nonresponders.

[^{99m}Tc]MDM-SPECT imaging at ≥1.5 years postradiotherapy follow-up. Among these 26 patients, 8 (3 G-II; 5 G-IV) patients also underwent quantitative [^{99m}Tc]MDM-SPECT at a median follow-up time period of 22.5 months (18–24 months). At the end of this follow-up, 5 (5/8) patients were clinically stable (mean T/NT ratio $=1.45\pm0.86$; range 0.68–2.92). The remaining 3 (G-IV) patients who eventually succumbed to recurrent disease had significantly ($p=0.005$) higher mean (5.67 ± 2.0; range 3.40–7.20) ratio of the radiotracer. Representative and comprehensive [^{99m}Tc]MDM SPECT, MR, and DSCE-MRI images of baseline and follow-up imaging in a responder is presented in Figure 1.

[^{99m}Tc]MDM-SPECT imaging in patients with recurrent glioma (n = 22)

The SPECT findings in all the 22 patients of this group were positive for the disease recurrence and the mean T/NT ratio was estimated to be 5.54 ± 2.14 (range 2.51–12.0). However, these ratios differed significantly between patients of G-II versus G-III ($p=0.01$) and of G-II versus G-IV ($p=0.03$).

Final diagnosis of recurrent/residual tumor versus radiation necrosis (based upon the multimodality imaging and clinical follow-up)

The final diagnosis could be established in 72 patients, where 47 patients had recurrent/residual disease and 25 patients had radiation-induced necrosis. The detailed analysis of the quantitative parameters of SPECT and MRI is presented in Table 2. However, subgrouping the patients with tumor recurrence into HGG and LGG, the mean T/NT ratio was significantly higher in HGG (5.56 ± 2.38, $n=31$) than in LGG (3.95 ± 1.48, $n=16$).

However, these values in radiation-induced necrosis had no significant difference in HGG (1.37 ± 0.59, $n=16$) and LGG (1.59 ± 1.24, $n=9$). The mean nCBV values were significantly higher in HGG (6.15 ± 3.15, $n=21$) than in LGG (4.32 ± 0.67, $n=5$), whereas, no difference in the mean nCBV values (HGG vs. LGG) was found in patients with necrosis. Any of the MRS parameters either in HGG or in LGG did not differ significantly between radiation necrosis and tumor recurrence/residual disease, respectively.

The ROC curve analysis estimated the T/NT cutoff of 1.90, which offered sensitivity of 97.9% and specificity of 92.0% to differentiate tumor recurrence from necrosis (Fig. 2A). A similar analysis for nCBV provided a cutoff value of 3.32, which calculated the sensitivity of 84.6% and specificity of 93.0%, respectively, for this differentiation (Fig. 2B). Similarly, the cutoff values for various MRS parameters were estimated (Table 2). The estimated cutoff value of greater than 1.57 for Cho/NAA provided a sensitivity of 81% and specificity of 73% (Fig. 2C) to identify recurrent/residual tumor. The other MRS parameters presented lower sensitivity and specificity and the results are presented in Figure 2D. A representative and comprehensive [^{99m}Tc]MDM SPECT, DSCE-MRI, and MRS images are presented in Figure 3. T/NT ratio showed a strongest linear

Table. 2. The Quantitative Ratios/Values of Different Single-Photon Emission Computed Tomography/Magnetic Resonance Imaging Parameters in Patients with Glioma Disease Recurrence and Radiation Necrosis

Final disease status (diagnosis)						
Quantitative values of SPECT/MR parameters	*Recurrence/ residual tumor Mean ± SD (no. of patients)*	*Necrosis Mean ± SD (no. of patients)*	*Statistical difference* (p)	*Cutoff*	*Sensitivity (%)*	*Specificity (%)*
T/NT ratio	5.01 ± 2.23 (47)	1.45 ± 0.87 (25)	0.00001	>1.90	97.9	92.0
nCBV value	5.8 ± 2.92 (26)	1.84 ± 0.96 (13)	0.00003	>3.32	84.6	93.0
Cho/NAA ratio	3.07 ± 1.75 (21)	1.8 ± 1.48 (11)	0.05	>1.57	81.0	73.0
Cho/Cr ratio	2.48 ± 1.65 (21)	1.47 ± 0.94 (11)	0.01	>1.64	85.7	73.7
Cr/NAA ratio	1.36 ± 1.15 (21)	1.01 ± 0.56 (11)	0.37	>1.06	57.1	63.3
Cr/Cho ratio	0.47 ± 0.24 (21)	0.93 ± 0.54 (11)	0.003	<0.60	72.2	81.0
Cho/LL ratio	3.90 ± 3.06 (14)	1.87 ± 1.65 (11)	0.05	>0.90	71.4	50.0

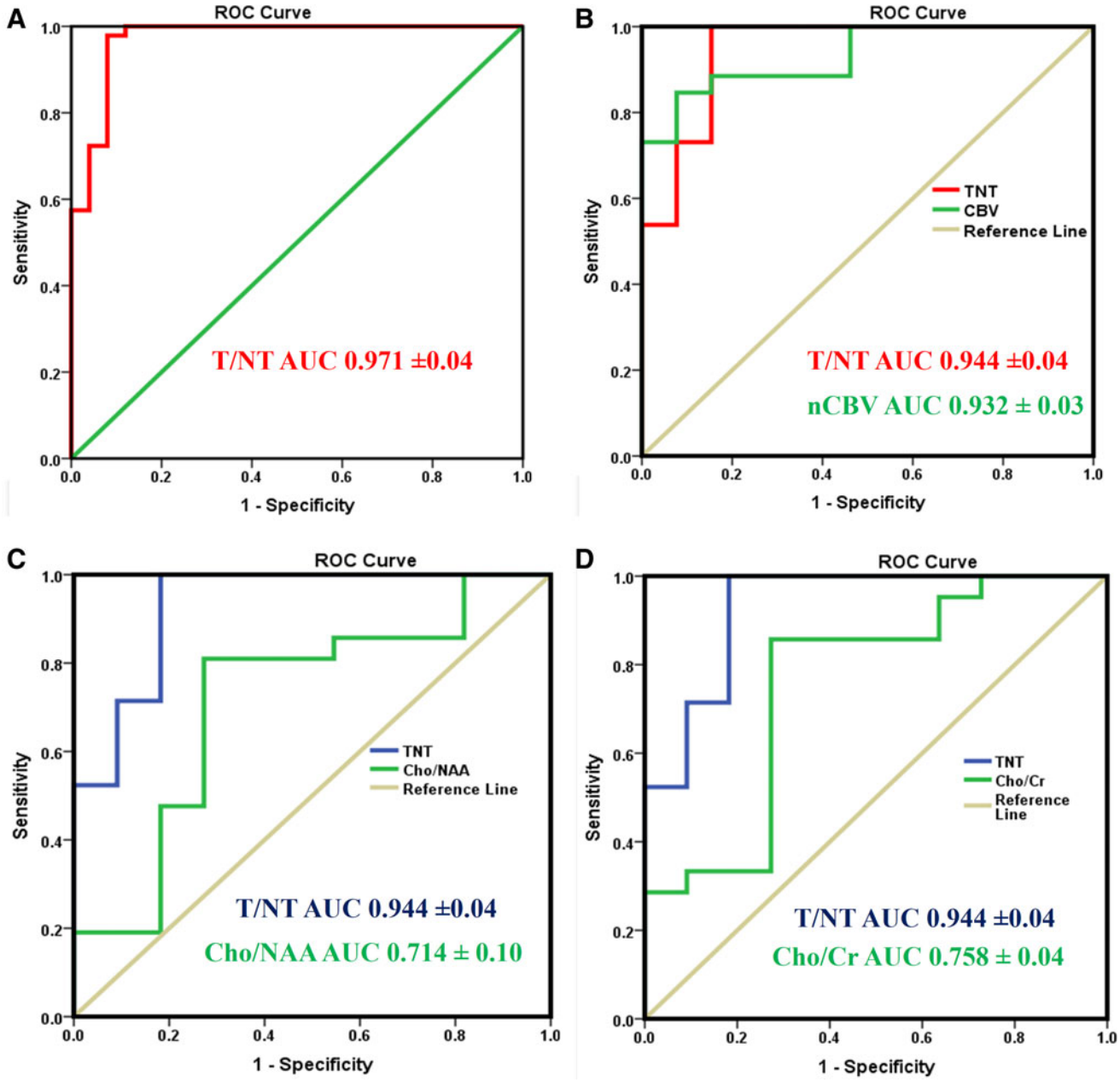


FIG. 2. The ROC curve analysis estimating the cutoff of [^{99m}Tc]MDM uptake (T/NT) **(A)**, comparative T/NT versus nCBV **(B)**, T/NT versus Cho/NAA **(C)**, and T/NT versus Cho/Cr **(D)** differentiating recurrent disease and radiation-induced necrosis in glioma. ROC, receiver operating characteristic. Color images are available online.

correlation with nCBV ($r=0.775$, $p<0.00001$) ratio. On the other hand, the association of T/NT ratio with MRS parameters that is, Cho/NAA, Cho/Cr, and Cho/LL was weaker and the values were $r=0.467$, $p=0.007$; $r=0.368$, $p<0.03$; and $r=0.443$, $p<0.03$, respectively.

[^{99m}Tc]MDM uptake (T/NT ratio) association with survival in gliomas

The cutoff value of 1.9 of T/NT ratio was used to discriminate tumor recurrence from radiation necrosis, and the same was also used for survival analysis in 50 patients who were followed-up with serial imaging. Using this T/NT cutoff, 25 patients with stable or declining ratio were diagnosed as having radiation necrosis and the remaining 25 patients who showed ratio above this cutoff were diagnosed to have tumor recurrence.

All the patients (irrespective of the histological grade) with T/NT ratio <1.9 had a significantly ($p=0.0001$, log-rank) longer survival (53.8 months) than (37.2 months) in patients with T/NT ratio >1.9. Therefore, statistically, the T/NT cutoff value of 1.9 accurately predicted the survival benefits in glioma patients. Among the 25 patients having recurrent disease, 21 patients were of HGG and the remaining 4 were of LGG. The Kaplan–Meier analysis indicated that among LGG and HGG groups having T/NT ratio

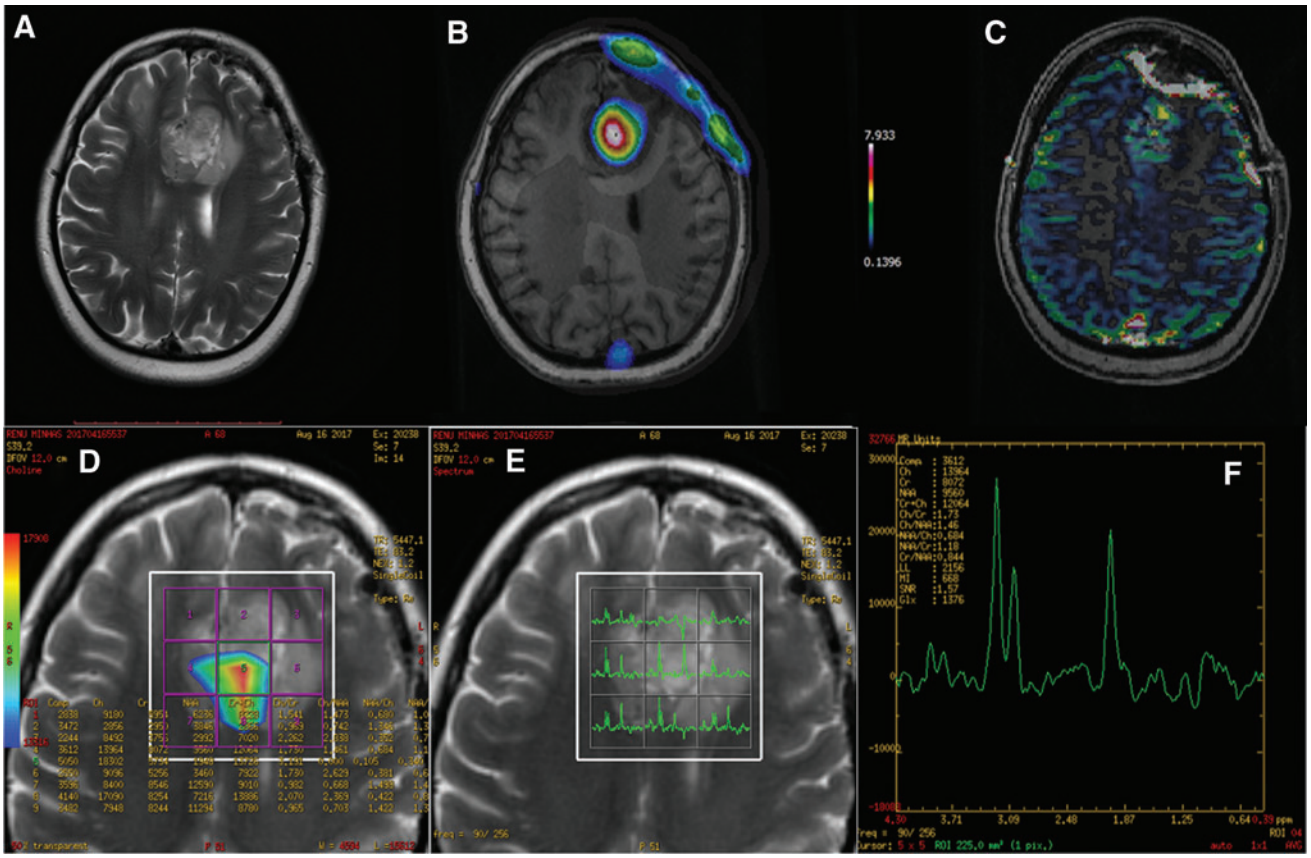


FIG. 3. A 37-year-old female patient with recurrent tumor in corpus callosum left frontal lobe with astrocytoma grade II. At *top*, T1-weighted contrast-enhanced MR image **(A)**, increased [^{99m}Tc]MDM **(B)** tracer uptake (T/NT ratio = 5.77) and **(C)** elevated perfusion (nCBV = 5.1) in the same area. At *bottom*, MR metabolite map of Cho **(D)** with increased Cho signals in the central area, multivoxel spectra **(E)** from area with highest choline elevation signal **(F)** indicating recurrent tumor. Color images are available online.

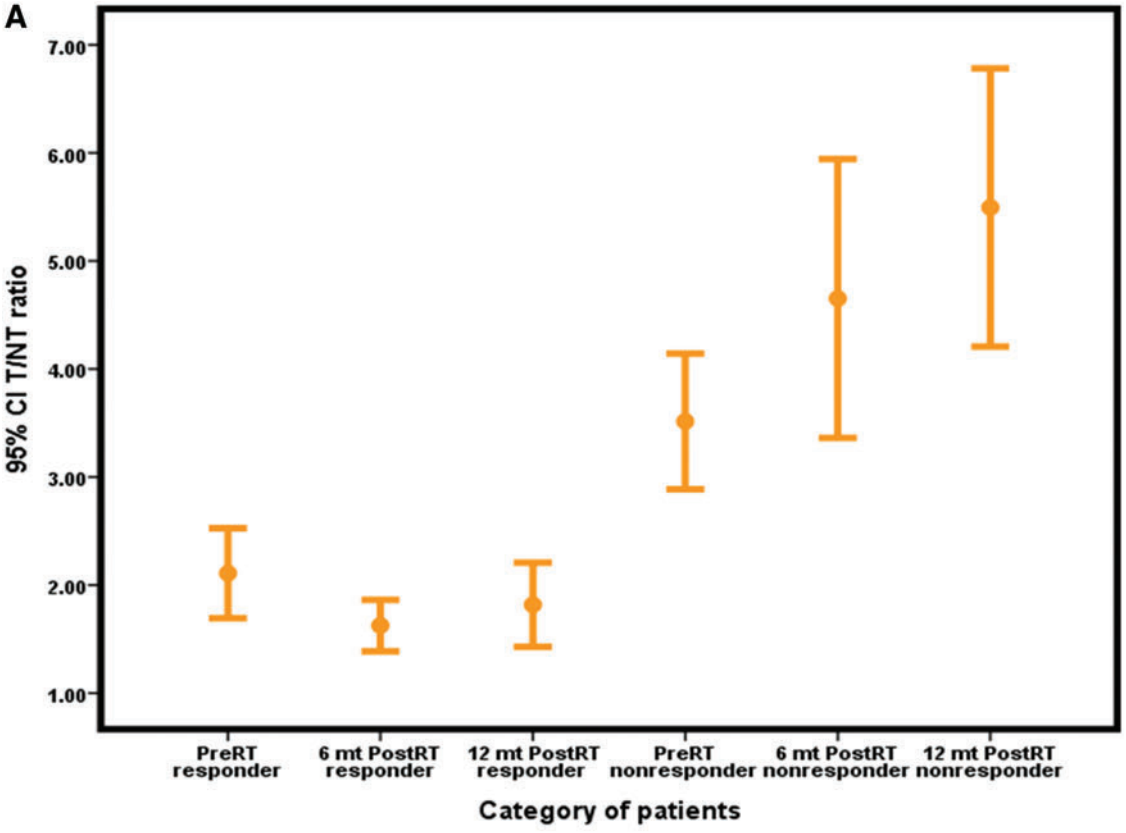
higher than 1.9, the time for the onset of disease progression was longer (median survival = 86.62 months) in low-grade than (median survival = 29.2 months) in HGG ($p = 0.001$, log-rank test).

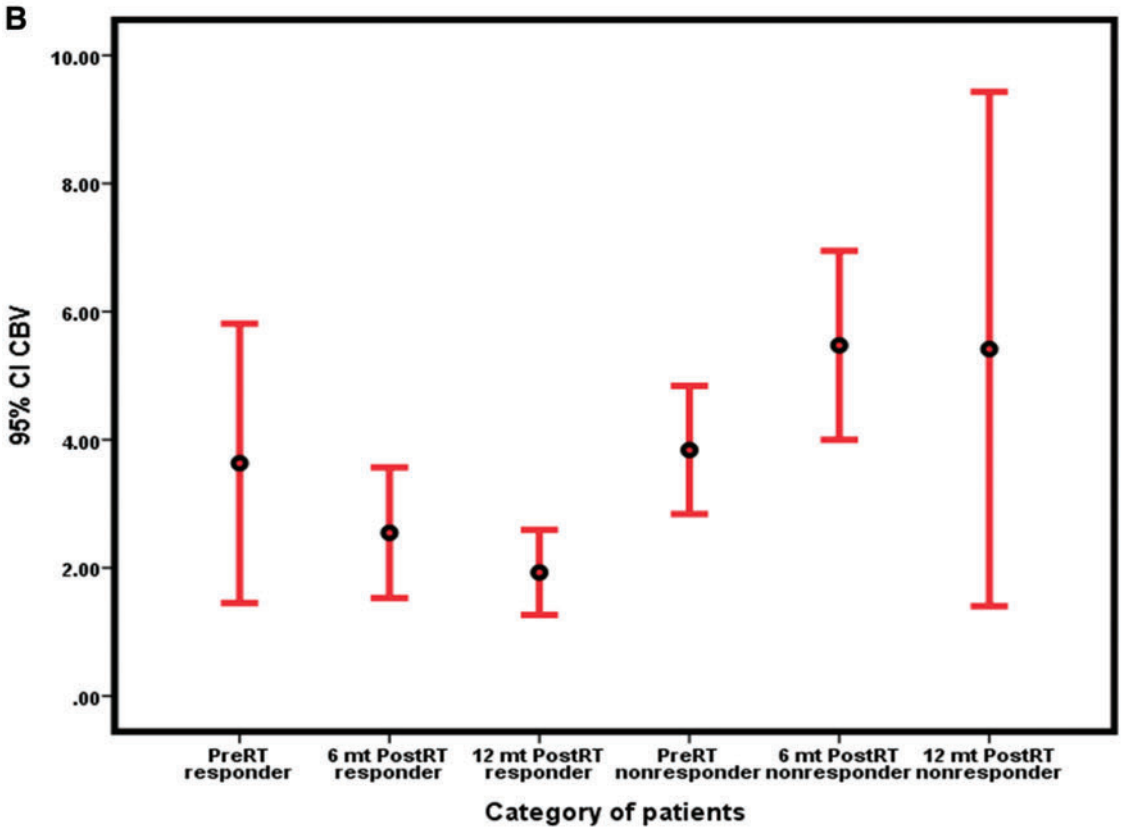
Among the 25 patients having radiation necrosis or stable disease, 16 patients were of HGG and the remaining 9 were of LGG. In this group of patients (all having T/NT ratio <1.9), the Kaplan–Meier analysis indicated that the duration of the progression-free survival was higher (55.5 months) in LGG than (37.8 months) in HGG ($p = 0.001$, log-rank test). The results of this statistical analysis are presented in Figure 4.

Discussion

This is the first clinical follow-up study providing evidence that the observed difference in baseline [^{99m}Tc]MDM uptake in responders and nonresponders can serve as a promising imaging biomarker for predicting treatment response in gliomas at an early stage. The use of amino acid PET in monitoring the response to radiochemotherapy and management of glioma patients has been advocated in several studies.[17–19] Wyss et al. observed that an increase in [^{18}F]FET uptake of more than 14.0% during the course of radiotherapy/chemotherapy predicted malignant transformation to glioma with the sensitivity and specificity of 92% and 92.3%, respectively.[17] On the other hand, a decrease of >10.0% in the metabolic tumor volume was considered as a sensitive indicator of an early response to radiotherapy/chemotherapy. In this context, it had been reported that the significance of [^{18}F]FET in identifying responders versus nonresponders was highest when TBR_{max} was used for this analysis.[20] The findings from this study with [^{99m}Tc]MDM SPECT imaging also suggested that the T/NT ratio emerged as a sensitive parameter to measure treatment response in follow-up imaging as the mean T/NT ratio was significantly

FIG. 4. The bar graphs demonstrating comparatively higher T/NT ratio **(A)** and nCBV **(B)** in nonresponders than in responders and the values for all these parameters increased consistently in nonresponders. **(C)** Kaplan–Meier curves demonstrating overall survival (in months) (at the end of follow-up) in patients (all grades of glioma) having cutoff T/NT ratios of <1.9 (*green curve*) versus >1.9 (*blue curve*) presenting higher survival in the former. **(D)** Kaplan–Meier curves demonstrating proportional survival (in months) (at the end of follow-up) in patients with T/NT ratio >1.9 (LGG, *green*; HGG, *purple*) and T/NT ratio <1.9 (LGG, *red*; HGG, *blue*). LGG, low-grade glioma; HGG, high-grade glioma. Color images are available online.





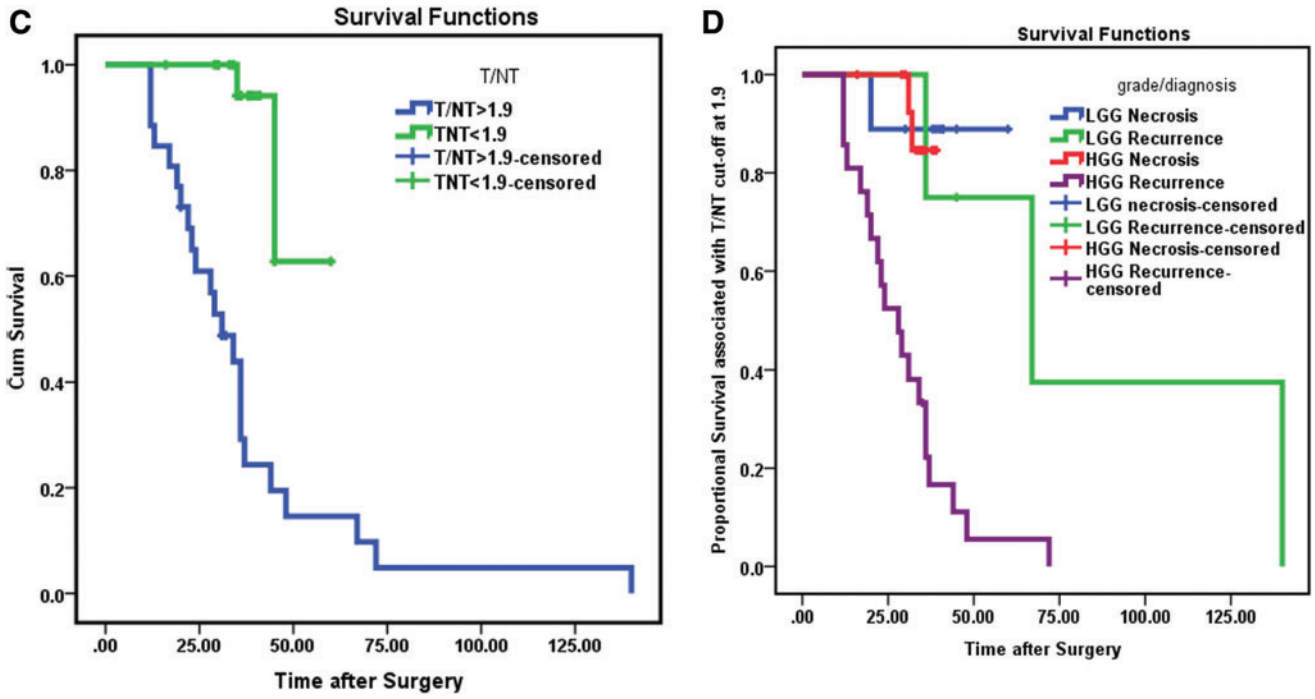


FIG. 4. (Continued).

($p = 0.0001$) higher in nonresponders than in responders at preradiotherapy as well as postradiotherapy at 6 months.

Similarly, the use of DSCE-MRI for serial assessment of glioma has also been recommended to detect malignant transformation and to identify therapy effects such as pseudoprogression or radiation necrosis from tumor progression.[21,22] Cao et al. suggested that during radiotherapy treatment, early change in the relative cerebral blood volume can indicate response to therapy and correlates with the survival outcome.[22] In the present study, DSCE-MRI results also demonstrated that a change in nCBV ratio was a sensitive indicator for the detection of disease recurrence or radiation necrosis and exhibited excellent prognostic utility. However, the MRI-calculated tumor volume did not yield similar results for response assessment, whereas, the change in the peak metabolic activity in the residual tumor after chemoradiotherapy treatment has a higher prognostic impact on the overall survival. On the other hand, MRS-derived quantitative parameters were inferior to [^{99m}Tc]MDM SPECT and DSCE-MRI parameters to predict therapy response. The latter two techniques have equal diagnostic utility for prediction of therapy response. In this context, recently Thust et al. observed that MRS is recommended in glioma imaging as an optional modality for specific indications and should be considered on an individual case basis, whereby caution is advised regarding its use in isolation and strongly recommended its use only in combination with other imaging modalities.[23] An earlier study, comparing [^{123}I]Iodomethyltyrosine (IMT) SPECT and MRS in gliomas have also reported that [^{123}I] IMT SPECT had higher accuracy than MRS for distinguishing tumor recurrence from the therapy response.[24]

In the present study, T/NT ratios of [^{99m}Tc]MDM in tumor recurrence were higher than in necrosis and cutoff ratio of 1.90 provided sensitivity and specificity of 97.9% and 92.0%, respectively, for differentiating recurrence from necrosis. In disease recurrence, the increased uptake of the radiotracer is probably attributed to the high density and activity of amino acid transporters.[16]

The diagnosis of radiation necrosis was based on the consistent findings, from this study, of either decreasing or stable quantitative parameters on follow-up SPECT and MRI as well as on patients' survival/clinical outcomes. Therefore, the observed variability in methionine uptake in the two pathologic entities and the clinical outcome could be considered convincingly (in the absence of histopathological confirmation) as a sensitive marker of distinguishing disease recurrence from radiation necrosis.

It has been reported that quantitative analysis of [^{11}C]MET PET is helpful in the differentiation of disease recurrence from radiation necrosis.[25–27] This study showed comparable sensitivity (97.9%) and specificity (97%) for [^{99m}Tc]MDM SPECT with the standard [^{11}C]MET PET imaging. Therefore, the wider availability of SPECT as a low-cost imaging procedure holds great promise for the accurate characterization and treatment response assessment in the postoperative glioma management. Various SPECT tracers have been investigated mainly for the identification of tumor recurrence from radiation necrosis. [^{99m}Tc]Sestamibi and [^{99m}Tc]Tetrofosmin have been found to be the promising tracers for the detection of recurrent tumors.[7,28] Furthermore, ^{201}Thallium and Pentavalent technetium-99m dimercaptosuccinic acid [^{99m}Tc]-(V)DMSA] SPECT have also been used to evaluate the response to therapy in HGG.[29,30] Furthermore, [^{99m}Tc]Tetrofosmin was reported to have similar accuracy with perfusion MRI to detect tumor recurrence following glioma treatment.[7] In a previous study that evaluated the diagnostic ability of [^{99m}Tc]MDM SPECT in 44 patients with suspected glioma recurrence, similar diagnostic values of [^{99m}Tc]MDM SPECT with [^{18}F]FDG PET and higher than ceMRI were reported.[31]

However, all these SPECT tracers have demonstrated differing results and none of these target the LAT1 receptors and thus do not offer comparability with [^{11}C]MET PET.

The fusion of SPECT and MR images using appropriate software resulted in better image contrast and accuracy for the detection of residual/recurrent glioma. It has been reported that the tumor boundaries are better delineated on [^{11}C]MET PET and the image fusion (PET/MR) can be used more accurately for targeted treatment planning compared with CT or MR-based planning alone.[32–34] The authors found similar AUC for [^{99m}Tc]MDM SPECT (0.971 ± 0.02) and DSC-MRI (0.932 ± 0.03), respectively, which suggests that both the techniques have similar sensitivity and specificity for the detection of glioma recurrence and necrosis. However, previous studies demonstrated mixed results for the superiority of [^{11}C]MET PET and perfusion MRI in detecting tumor recurrence.[35,36] MRS parameters showed lower sensitivity and specificity than [^{99m}Tc]MDM SPECT and DSCE-MRI to distinguish tumor recurrence.

These findings are in agreement with a previous study which performed [^{18}F]FET and 1H-MRS in 15 glioma patients and demonstrated a significant correlation between increased amino acid uptake and elevated Cho/NAA ratios.[37] Furthermore, Morana et al. also reported a significant positive correlation between [^{18}F]DOPA parameters and 1H-MRS data.[38] However, these findings are in contrast to a recent study by Mauler et al. which reported a limited spatial congruence between [^{18}F]FET uptake and elevation in Cho/NAA ratios.[39]

A few more studies with [^{11}C]MET PET have indicated that the intensity of methionine uptake reflects patients' prognosis.[13,40] Takano et al. demonstrated significantly ($p = 0.004$) higher (64.2 ± 7.2 months) median progression-free survival in patients with methionine uptake ratio of <2.0 compared with 18.6 ± 6.9 months seen in patients with T/NT ratio of >2.0.[41]

Our findings of significantly ($p = 0.0001$, log-rank) prolonged survival in patients (irrespective of any histological type/grade) having T/NT ratio <1.9 than in patients with T/NT ratio >1.9 are thus in agreement with the previous studies and reflects prognostic value of this novel radiopharmaceutical in gliomas.

The authors further found that LGG patients, despite presenting with the disease recurrence, had longer progression-free survival (55.5 months) than in HGG patients (37.8 months; $p = 0.001$, log-rank test). Additionally, another study using [^{18}F]FET PET reported that in intracranial gliomas, the T/NR cutoff of 1.88 accurately predicted the overall survival in these patients.[42]

Conclusion

[^{99m}Tc]MDM SPECT and DSCE-MRI provide similar diagnostic efficacy and thus can be used interchangeably for glioma characterization and response assessment depending upon the availability. However, when both are available in a given clinical setting, they can be potentially combined together for a comprehensive *in vivo* disease mapping and response assessment in glioma. Therefore linear combinations of the results of both of these techniques could give better prognostic information. MRS also showed promise for specific indications, but was inferior to both [^{99m}Tc]MDM SPECT and DSCE-MRI in postchemoradiotherapy response assessment.

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Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Figure S1
Supplementary Table S1

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