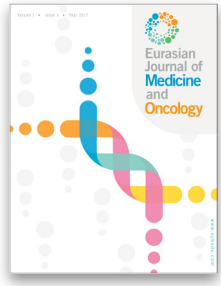
EJMO

DOI: 10.14744/ejmo.2017.77487
EJMO 2017;1(1):8–13



Research Article

^{99m}Tc-MIBI Brain SPECT Before and After Radiotherapy to Assess Survival Predictability in Glioblastoma Multiforme Patients

Huseyin Tepetam,[1] Ozlem Turkoglu,[2] Dehan Yazici[3]

[1]Department of Radiation Oncology, Kartal Dr. Lütfi Kirdar Training and Research Hospital, Istanbul, Turkey
[2]Department of Radiology, Kartal Dr. Lütfi Kirdar Training and Research Hospital, Istanbul, Turkey
[3]Department of Nuclear Medicine, Kartal Dr. Lütfi Kirdar Training and Research Hospital, Istanbul, Turkey

Abstract

Objectives: The aim of this study was to evaluate the effectiveness of technetium-99m-methoxyisobutylisonitrile (^{99m}Tc-MIBI) brain single-photon emission computed tomography (SPECT) in predicting survival in glioblastoma multiforme (GBM) patients in comparison with magnetic resonance imaging (MRI) before and after radiotherapy (RT) treatment.

Methods: A total of 25 patients with GBM were examined prospectively. The patients were evaluated according to survival, age, sex, Eastern Cooperative Oncology Group (ECOG) score, type of surgery, and tumor localization. All patients received RT. Brain MRI and ^{99m}Tc-MIBI brain SPECT were performed in all postoperative patients before RT. After RT, regular MRI was performed on all patients, while ^{99m}Tc-MIBI brain SPECT was performed on 14 patients. Tumor masses were incubated and Ki-67 proliferative index was measured. All of the patients were treated with corticosteroids. In event of recurrence, patients were treated with chemotherapy.

Results: Patient age, duration of preoperative symptoms, ECOG score, and applicability of chemotherapy after RT were statistically significant effective indicators for survival ($p<0.001$). Before RT, mean survival time measured for 4 patients without ^{99m}Tc-MIBI uptake was 17.7 months, while it was 9.58 months for 6 MRI patients. Ki-67 proliferative index was associated with survival, but there was no statistically significant correlation with ^{99m}Tc-MIBI brain uptake rate.

Conclusion: ^{99m}Tc-MIBI SPECT has a better correlation with survival than MRI. These results suggest ^{99m}Tc-MIBI brain SPECT can be used as a functional imaging method for future clinical studies.

Keywords: Brain single-photon emission computed tomography, glioblastoma multiforme, Ki-67, survival, technetium-99m-methoxyisobutylisonitrile

Cite This Article: *Tepetam H, Turkoglu O, Yazıcı D. 99mTc-MIBI Brain SPECT Before and After Radiotherapy to Assess Survival Predictability in Glioblastoma Multiforme Patients. EJMO. 2017; 1(1): 8-13*

Glioblastoma, the most common type of glioma, is associated with very poor survival; therefore, the focus is on identifying factors that can be used to improve prognosis and perhaps modified to prevent this disease. Single-photon emission computed tomography (SPECT) is widely available and routinely used, even in less developed countries. Higher tracer uptake by glioma on SPECT has been demonstrated in studies to be associated with higher grade and decreased response to chemotherapy of gliomas.[1, 2] In addition, higher technetium-99m-methoxyisobutylisonitrile (^{99m}Tc-MIBI) uptake was demonstrated to have a correlation with higher proliferative potential of gliomas and with poorer survival.[3, 4] To the best of our knowledge, previous studies employed SPECT scans only

Address for correspondence: Ozlem Turkoglu, MD. Kartal Lütfi Kirdar Egitim ve Arastirma Hastanesi, Radyoloji Klinigi, Istanbul, Turkey
Phone: +90 216 458 30 00 **E-mail:** ozlemkolcak@hotmail.com
Submitted Date: June 02, 2017 **Accepted Date:** July 30, 2017 **Available Online Date:** August 03, 2017

once during the treatment period, and currently there are no studies evaluating the association of repeated SPECT scans during perioperative periods with the prognosis of malignant glioma patients. We recently demonstrated that changes in the bulk of malignant gliomas following surgery and radiotherapy (RT) can be reliably evaluated using SPECT.[5] Analysis of such changes in the bulk of malignant glioma tissue may possibly serve as a novel prognostic marker of malignant glioma. In this study, the aim was to define the value of SPECT in the prediction of overall survival in glioblastoma multiforme (GBM) patients treated with RT and any correlation with Ki-67.

Methods

Patients and Protocol

A total of 25 patients (16 male, 9 female) who underwent resection or biopsy for histologically confirmed grade IV glioma according to the World Health Organization classification at the Dr. Lutfi Kirdar Research and Education Hospital Department of Neurosurgery in Istanbul were prospectively included in this study. Patients were grouped according to age, gender, type of surgery, location of tumor, and length of time until postoperative RT dose. We assessed patients' level of function using the Eastern Cooperative Oncology Group (ECOG) performance status score (0-4), and 2 groups were formed according to the duration of symptoms before operation. Laboratory tissues obtained were incubated with monoclonal antibody Ki-67 using the immunohistochemical method. At least 1000 cells were counted histologically for each patient. Only nuclear staining was considered positive. The Ki-67 labeling index was expressed as a percentage of positive cells. The proliferation index of pathological specimens from paraffin blocks of patients were calculated as the ratio of stained nuclei to the total number of nuclei. For statistical analysis, groups were created according to patient age (<60 or ≥60 years), ECOG score (≤1 or >1), duration of symptoms (<1 month or ≥1 month), and Ki-67 proliferative index (<30 or ≥30).

Before RT, 20 of the patients underwent surgical resection of the brain tumor. One patient required reoperation for residual tumor. All patients received standard external beam RT that consisted of a total dose of 45 to 60 Grays (Gy) (administered in 15-30 fractions of 2-3 Gy 5 times weekly). Before RT, enhanced brain MRI and ^{99m}Tc-MIBI brain SPECT were performed on all of the patients. After RT treatment, enhanced brain MRI was performed on all, but ^{99m}Tc-MIBI brain SPECT was used on only 14 patients. Patients were followed with regular enhanced brain MRI examinations at 6-month intervals. The ^{99m}Tc-MIBI uptake before and after RT was evaluated, and 2 groups were formed based on quantitative analyses: those that were <1.30 and those that were ≥1.30.

All of the patients were routinely treated with corticosteroids. In case of recurrence, patients were treated with chemotherapy. No additional surgical procedure was performed.

The study and its consent procedures were approved by the ethics committee of Dr. Lutfi Kirdar Kartal Education and Research Hospital, and were in compliance with Helsinki Declaration standards as well as the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided written, informed consent.

Imaging Protocol

Radiopharmaceutical ^{99m}Tc-MIBI (Cardiolite; Dupont Pharma, Inc., Mississauga, Canada) was used in all cases. During image acquisition, patients were placed in a supine position with an appropriate headpiece to avoid head movement and detectors were placed as close as possible to the patients' head. Images were captured 30 to 45 minutes after intravenous injection of 740 MBq (20 mCi) of ^{99m}Tc-MIBI using a Sophy (Sopha Medical Vision/GE Healthcare Inc., Chicago, IL, USA) circular, high-resolution gamma camera. The tomographic imaging parameters consisted of a 360° rotation angle and an acquisition time of 30 seconds per frame, with a zoom factor of 1.78. For image reconstruction, filtered back-projection was used and a Butterworth filter was applied with a cut-off of 1 mm in transaxial, coronal, and sagittal planes. All SPECT scan results of early and late imaging were evaluated using qualitative and quantitative methods. The region of interest (ROI) for lesions was manually located over the area corresponding to the contrast-enhanced area on the MRI. Excessive background activity was excluded from contralateral normal brain and tumor side. As a normal control, circular ROIs with a diameter of 10 mm were located within the contralateral area and within the contralateral cerebellar cortex. Mean lesion to normal (L/N) ratio was calculated using several L/N ratios obtained. Clinical signs of patients were matched with scintigrafic and MRI findings. True positivity rate of both examinations were determined during long-term clinical follow-up.

Statistical Analysis

Survival curves were calculated using Kaplan-Meier survival curve and the log-rank test. Univariate analysis of following parameters was performed: sex, preoperative duration of symptoms, ECOG status, tumoral involvement, index of Ki-67, residual mass of tumor, and ^{99m}Tc-MIBI uptake ratio before and after RT.

Factor	Univariate analysis p (log range)
Age	0.000
ECOG	0.001
Ki-67	0.032
Symptom duration	0.033

Figure 1. P value of factors evaluated in univariate analysis.

Results

Twenty-five patients were enrolled in this study. The male/female sex ratio of the patients was 1.8:1. The age of the participants ranged from 13 to 79 years. The mean age was 56.64 years and the median was 58 years. Groups were compared in terms of survival. We found that patient age, duration of preoperative symptoms, ECOG score, and Ki-67 proliferative index value were statistically significant effective indicators for survival ($p<0.01$) (Figure 1) and they each had independent prognostic value (Figure 2). We also observed that gender, tumor location, surgery type, RT dose, time interval between surgery and postoperative RT were not effective factors to predict survival.

Quantitative analyses of ^{99m}Tc-MIBI uptake before RT were divided into 2 groups: the first group had an uptake below 1.30 (9 patients), and the second group had uptake of 1.30 or above (16 patients). Median survival time of each group was 11.63 months and 5.50 months, respectively. This difference in survival time was statistically significant. There was also a statistically significant survival difference between groups after RT (Figure 3a, b).

^{99m}Tc-MIBI uptake prior to FG was observed in 21 patients. The ratio between tumoral side to normal side had a value of 1.64 [cb1]. The 4 ^{99m}Tc-MIBI uptake-negative patients had a median survival of 17.7 months (range: 6.77-21.43 months).

Six tumor-negative patients according to MRI taken before

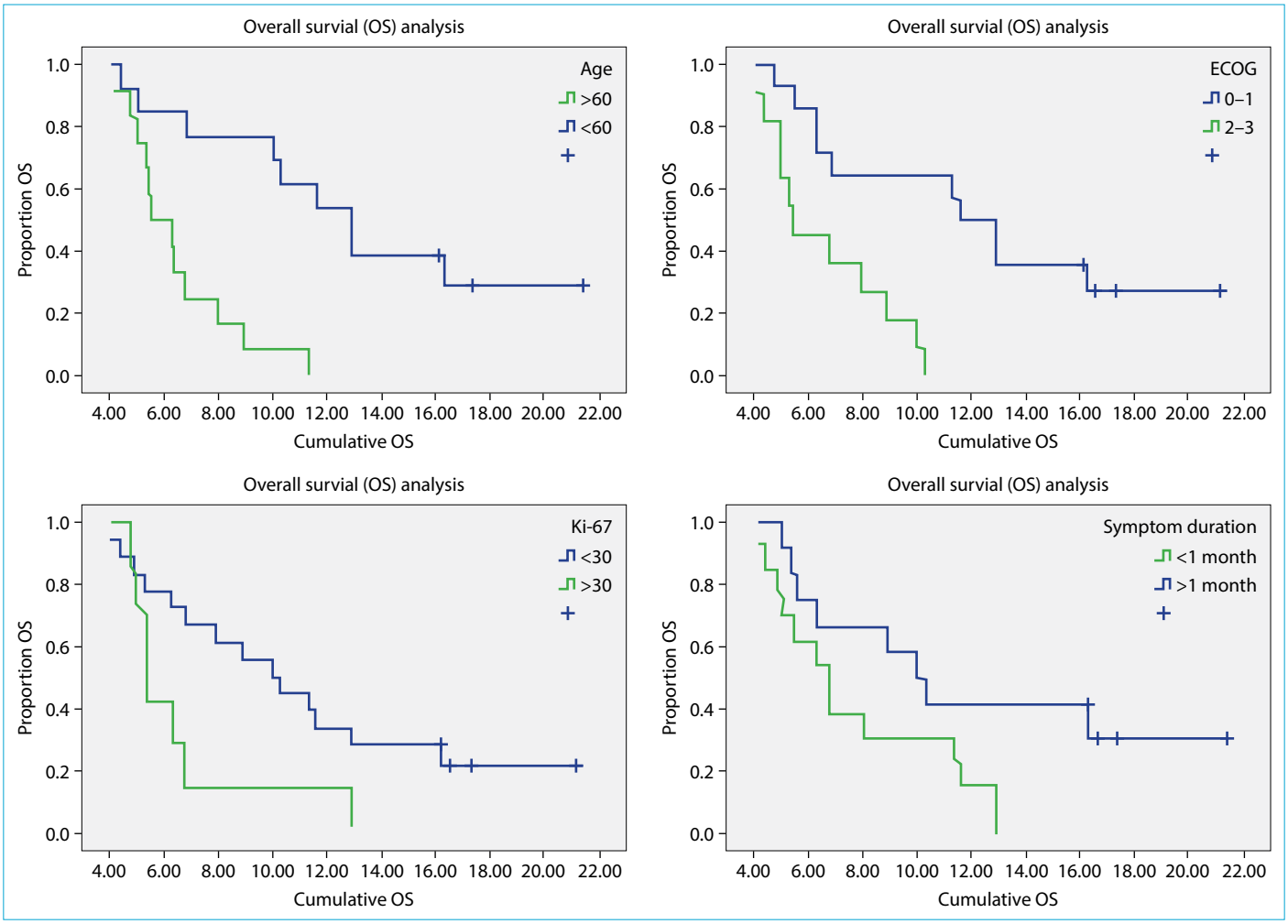


Figure 2. Graphs of overall association of age, Eastern Cooperative Oncology Group status, duration of symptoms, and Ki-67 proliferative index with survival.

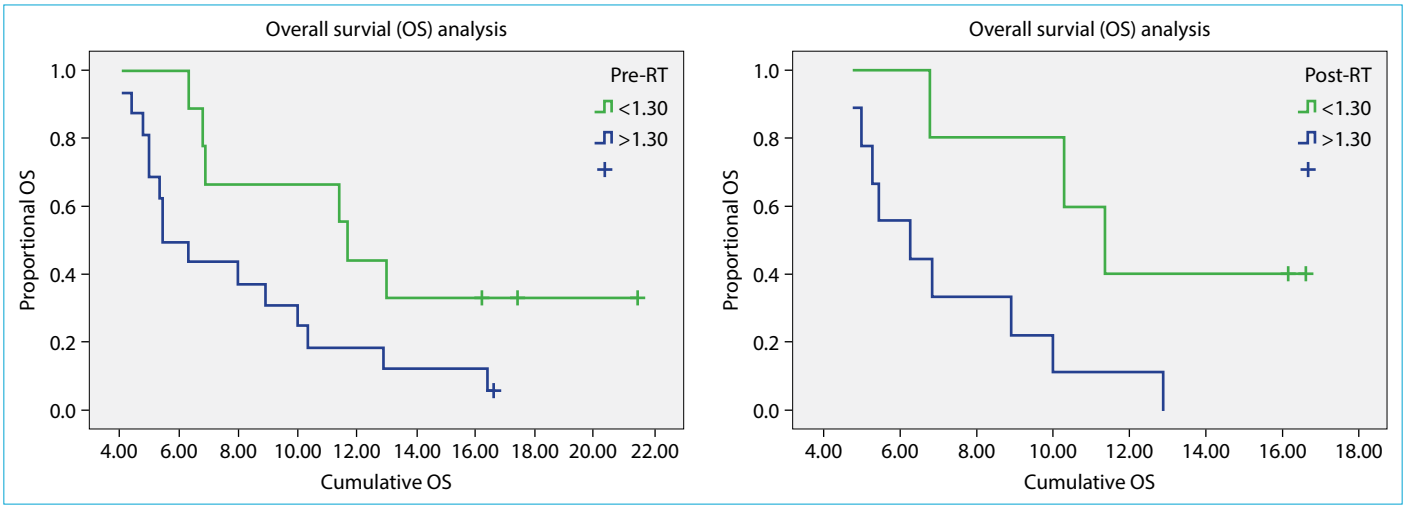


Figure 3. (a) Pre-radiotherapy (RT) uptake rate of technetium-99m-methoxyisobutylisonitrile (^{99m}Tc-MIBI) and correlation with survival, and **(b)** post-RT uptake rate of 99mTc-MIBI and correlation with survival.

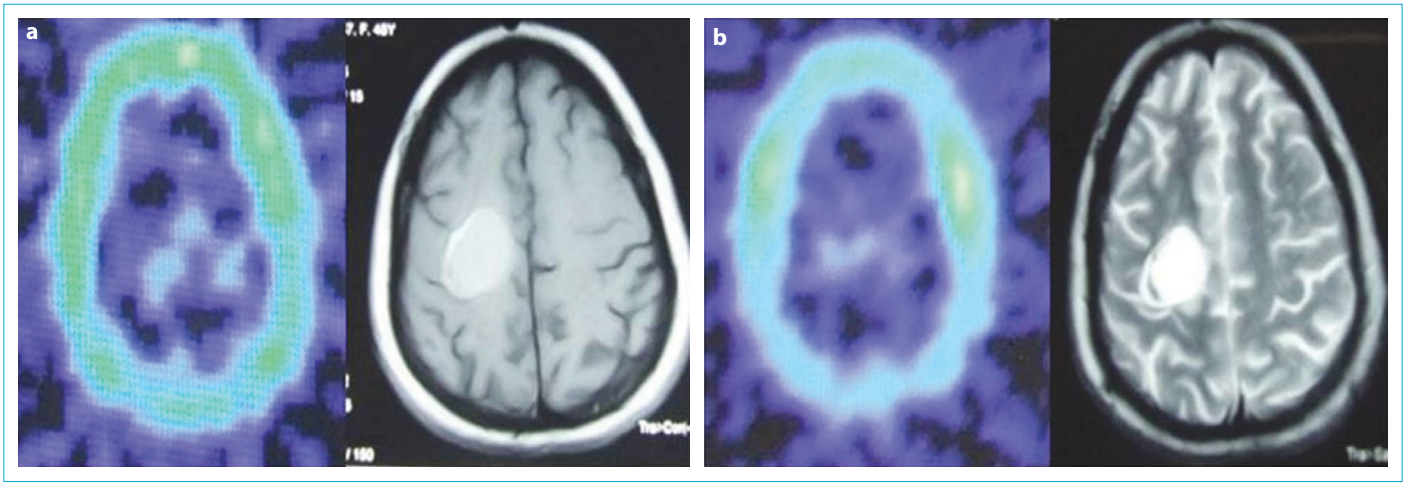


Figure 4. (a) Before radiotherapy (RT) technetium-99m-methoxyisobutylisonitrile (^{99m}Tc-MIBI) brain single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI). Residual mass was not reported with either technique. **(b)** After RT, MRI reported residual mass, but ^{99m}Tc-MIBI brain SPECT indicated no mass (quantitative analyses). Clinically, the patient was healthy and without recurrence in 6 months of follow-up.

			MIBI tumour/normal side		
Ki-67			<1.30	>1.30	Total
For 30	<30	Patient number	8	10	18
		%	32.0%	40.0%	72.0%
	≥30	Patient number	1	6	7
		%	4.0	24.0%	28.0%
		Patient number	9	16	25
		% total	36.0%	64.0%	100.0%

Figure 5. Cross table of uptake rate of technetium-99m-methoxyisobutylisonitrile and Ki-67 proliferative index.

RT had median survival time of 9.58 months (range: 6.77-17.37 months). When compared with MRI, true negativity of ^{99m}Tc-MIBI SPECT was higher (Figure 4). Statistically, there was no correlation between positive mass enhancement on MRI and ^{99m}Tc-MIBI uptake.

We found a significant survival difference between the groups based on Ki-67 proliferative index value. The group with a proliferative index <30 had a better survival rate ($p<0.01$). ^{99m}Tc-MIBI uptake and Ki-67 rates were also compared. There was no significant correlation between Ki-67 proliferative index value and ^{99m}Tc-MIBI uptake (Figure 5).

Discussion

The incidence of GBM is approximately 5 cases per 100,000 population per year.[6] Elderly GBM patients have a worse prognosis and receive various treatments.

Malignant gliomas have increased metabolic needs, increased cellular mitochondrial content, and maintain the negative mitochondrial transmembrane potential that is associated with the active diffusion of ^{99m}Tc-MIBI into the mitochondria.[7] Higher ^{99m}Tc-MIBI uptake was demonstrated to correlate with biological markers of malignancy of malignant gliomas, including aneuploidy level and percentage of cells in the S-phase fraction, and with proliferative activities of glioma as assessed using Ki-67.[8] The Ki-67 antigen has been determined to be the best marker of cellular proliferation. In this study, we found no correlation between ^{99m}Tc-MIBI and Ki-67.

MRI is significantly more sensitive to the presence of tumor, as well as its associated findings, including peritumoral edema, and is the modality of choice for the examination of a patient with suspected or confirmed GBM. MRI is also widely used in the post-treatment evaluation of tumor. After surgery, differentiating between recurrent tumor and scar tissue on the basis of MRI findings alone may be difficult. Imaging modalities used in nuclear medicine, namely positron emission tomography (PET) and SPECT have been employed to further evaluate brain tumors.[6] PET is the most effective tool in differentiating between radiation necrosis and glioma, but it is an expensive technology. Currently, there are a few studies evaluating the association between uptake of different tracers on SPECT scans and survival of glioma patients. SPECT, with the advantages of lower cost and wider availability, has been used as a method of intracranial lesion metabolic imaging.[9] Various radiotracers have been evaluated.

Treatment can involve chemotherapy, radiation, radiosurgery, corticosteroids, antiangiogenic therapy, surgery, and experimental approaches such as gene transfer. After surgery, RT is the mainstay of treatment for patients with glioblastoma. A total radiation dose of 60 to 65 Gy has been found to be optimal for treatment. In our study, radiation dose of 45 to 60 Gy was applied.

GBM is almost invariably fatal and the prognosis is extremely poor, with a median survival time of approximately 12 to 14 months. Prognostic factors that have been identified include age when diagnosed, extent of resection, and preoperative duration of symptoms.[10] But in this study, only age was found to be a statistically significant prognostic factor.

Based on our results, in a case of high grade brain tumor, the use of SPECT studies as a functional neuroimaging method could be highly beneficial for prediction of survival before and after RT. This study has several limitations. It was performed in a single institution, and the number of patients is relatively small. More studies are needed in the literature to position SPECT analysis as a reliable method in place of surgical biopsy for patients with positive contrast enhancement. ^{99m}Tc-MIBI uptake is one of the accepted parameters indicating tumor aggressiveness, but additional research that includes more homogenized GBM patient groups is required to further evaluate the usefulness of ^{99m}Tc-MIBI.

Conclusion

^{99m}Tc-MIBI brain SPECT may play a prognostic role in patients with GBM. In addition to knowledge of direct correlation between ^{99m}Tc-MIBI uptake rate and worse prognosis, the results of this study suggest there may be value in the true negativity of ^{99m}Tc-MIBI SPECT analyses for evaluating survival of GBM patients.

Disclosures

Ethics Committee Approval: The study was approved by the Local Ethics Committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

References

1. Cheng X, Li Y, Xu Z, Li D, Wang J. A meta-analysis of 99mTc-MIBI SPECT for detection of recurrent glioma after radiation therapy. J Clin Neurosci 2011;18:307–12. [CrossRef]
2. Prigent-Le Jeune F, Dubois F, Perez S, Blond S, Steinling M. Technetium-99m sestamibi brain SPECT in the follow-up of glioma for evaluation of response to chemotherapy: first results. Eur J Nucl Med Mol Imaging 2004;31:714–9. [CrossRef]
3. Alexiou GA, Tsiouris S, Kyritsis AP, Fotakopoulos G, Goussia A, Voulgaris S, et al. The value of 99mTc-tetrofosmin brain SPECT in predicting survival in patients with glioblastoma multiforme. J Nucl Med 2010;51:1923–6. [CrossRef]
4. Beauchesne P, Pedeux R, Boniol M, Soler C. 99mTc-sestamibi brain SPECT after chemoradiotherapy is prognostic of survival in patients with high-grade glioma. J Nucl Med 2004;45:409–13.
5. Deltuva VP, Jurkienė N, Kulakienė I, Bunevičius A, Matukevičius A, Tamašauskas A. Introduction of novel semiquantitative evaluation of (99m)Tc-MIBI SPECT before and after treatment of glioma. Medicina (Kaunas) 2012;48:15–21.
6. Alexiou GA, Tsiouris S, Voulgaris S, Kyritsis AP, Fotopoulos AD. Glioblastoma multiforme imaging: the role of nuclear medicine. Curr Radiopharm 2012;5:308–13. [CrossRef]
7. El Hindy N, Bachmann HS, Lambertz N, Adamzik M, Nückel H, Worm K, et al. Association of the CC genotype of the regulatory BCL2 promoter polymorphism (-938C>A) with better 2-year survival in patients with glioblastoma multiforme. J Neurosurg 2011;114:1631–9. [CrossRef]
8. Chen WS, Luker KE, Dahlheimer JL, Pica CM, Luker GD, Piwnica-Worms D. Effects of MDR1 and MDR3 P-glycoproteins,

MRP1, and BCRP/MXR/ABCP on the transport of (99m)Tc-tetrofosmin. Biochem Pharmacol 2000;60:413–26. [CrossRef]
9. Alexiou GA, Tsiouris S, Kyritsis AP, Argyropoulou MI, Voulgaris S, Fotopoulos AD. Assessment of glioma proliferation using imaging modalities. J Clin Neurosci 2010;17:1233–8. [CrossRef]
10. Weingart J, Brem H. Brain Tumors and Cancers of the Central Nervous System. Neıderhuber JE. Current Therapy. 1st ed. Mosby- Year Book Inc 1993. p. 538–46.