Introduction of Novel Semiquantitative Evaluation of ^{99m}Tc-MIBI SPECT Before and After Treatment of Glioma

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***Key words**: single-photon emission computed tomography; glioma; grade.*

***Summary.** Background and Objective. There is a need for objective semiquantitative indexes for the evaluation of results of single-photon emission tomography (SPECT) in patients with brain glioma. The aim of this study was to validate the total size index (TSI) and total intensity index (TII) based on technetium-99m-methoxyisobutylisonitrile (^{99m}Tc-MIBI) SPECT scans to discriminate the patients with high-grade glioma versus low-grade glioma and to evaluate the changes of viable glioma tissue by the means of TSI and TII after surgery and after radiation treatment.*

Material and Methods. Thirty-two patients (mean age, 55 years [SD, 18]; 20 men) underwent a ^{99m}Tc-MIBI-SPECT scan before surgery. Of these patients, 27 underwent a postoperative ^{99m}Tc-MIBI-SPECT scan and 7 patients with grade IV glioma underwent a third ^{99m}Tc-MIBI-SPECT scan after radiation treatment. TII that corresponds to the area and intensity of tracer uptake and TSI that corresponds to the area of tracer uptake were calculated before surgery, after surgery, and after radiation treatment.

Results. The TII and TSI were found to be valid in discriminating the patients with high-grade versus low-grade glioma with optimal cutoff values of 3.0 and 2.5, respectively. Glioma grade correlated with the preoperative TSI score ($r=0.76$, $P<0.001$) and preoperative TII score ($r=0.64$, $P<0.001$). There was a significant decrease in the TII and TSI after surgery in patients with grade IV glioma. After radiation treatment, there was a significant increase in the TII in patients with grade IV glioma.

Conclusions. TSI and TII were found to be reliable in discriminating the patients with high-grade versus low-grade glioma and allowed for the semiquantitative evaluation of change in viable glioma tissue after surgery and after radiation treatment in patients with grade IV glioma.

Introduction

Glioma is the most common primary brain tumor in all age groups (1, 2). Patients with grade IV gliomas or glioblastomas classified according to the World Health Organization (WHO) classification have a devastating prognosis with a median survival time of approximately 14 months even with current treatment strategy that consists of maximally safe surgical resection followed by radiotherapy plus concomitant and adjuvant temozolomide (3–7). Thus, the early identification of glioma grade and progression is essential.

High-grade gliomas can be reliably suspected using contrast-enhanced magnetic resonance imaging (MRI) that is based on proton density and relaxation times specific for different tissues and tumors. However, MRI can underestimate the true extension of high-grade gliomas and has a limited potential to differentiate treatment-induced nonmalignant changes, such as edema or radiation necrosis, from residual viable glioma tissue or recurrence of glioma (8–11).

Functional imaging methods can differentiate glioma tissue from brain tissue based on higher metabolic activity of glioma cells (9). Radiopharmaceutical technetium-99m-methoxyisobutylisonitrile (^{99m}Tc-MIBI) passively diffuses through the cell membrane, and its highest proportion is found in mitochondria (12). Single-photon emission computed tomography (SPECT) was shown to be effective in differentiating viable glioma tissue from radiation necrosis and surrounding edema (8, 13–15). Moreover, higher tracer uptake on SPECT scan was shown to be associated with higher-grade gliomas (16), decreased survival (17), and worse response to chemotherapy (18, 19).

However, the major limitation when interpreting SPECT images remains the lack of objective and quantitative indexes (19). Suspicion for glioma recurrence rests on the experience of a nuclear medicine specialist placing an emphasis on the fact whether focal tracer uptake is seen at glioma location on SPECT images. Lesion-to-normal ratio (L/N) correlates with a grade of glioma since a

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higher L/N ratio is associated with a greater malignancy of gliomas (20). In addition, a high L/N ratio was shown to be suggestive of glioma recurrence after radiation treatment; however, the clinical value of this approach was debated (20). Moreover, the L/N ratio does not include the quantitative evaluation of the total tracer uptake area, thus not allowing for quantitative follow-up of glioma burden after treatment or when disease progression is suspected.

In this study, two novel semiquantitative indexes for the evaluation of brain SPECT results are introduced: total size index (TSI) that corresponds to brain area affected by glioma and total intensity index (TII) that corresponds to glioma malignancy together with brain area affected by glioma. The aim was to evaluate the validity of preoperative TSI and preoperative TII for discrimination between patients with high-grade versus low-grade glioma and to evaluate the changes of viable glioma tissue by the means of TSI and TII after surgery and after radiation treatment.

Material and Methods

Patients. Thirty-two consecutive patients (20 men and 12 women; mean age, 55 years [SD, 18]; range, 20 to 78 years) underwent resection or biopsy for suspected glioma at the Clinic of Neurosurgery, Hospital of Lithuanian University of Health Sciences, Kaunas, Lithuania, from January 2003 until October 2003 and were included into the study.

All patients underwent preoperative ^{99m}Tc-MIBI SPECT 4 days (SD, 3) before surgery or biopsy. Diagnosis was confirmed by histological examination, and glioma grade according to the WHO classification was assigned in all the cases. Grade IV glioma was diagnosed in 20 patients (63%) (19 glioblastomas and 1 gliosarcoma); grade III glioma, in 4 patients (13%) (all anaplastic astrocytomas); grade II glioma, in 6 patients (19%) (2 low-grade astrocytomas, 3 oligodendrogliomas, and 1 oligoastrocytoma), and grade I glioma, in 2 patients (5%) (1 pilocytic astrocytoma and 1 ganglioglioma).

One patient with grade IV glioma, 2 patients with grade II glioma, and 2 patients with grade I glioma refused postoperative ^{99m}Tc-MIBI SPECT. Therefore, a subset of 27 patients underwent a postoperative ^{99m}Tc-MIBI SPECT scan 11 days (SD, 3) after surgery or biopsy. Four patients (15%) had grade II glioma, 4 patients (15%) grade III glioma, and 19 patients (70%) grade IV glioma. Glioma resection was defined as radical if more than 90% of microscopically viable glioma tissue was removed and as subtotal if less than 90% of viable glioma tissue was removed. Among patients who underwent a postoperative ^{99m}Tc-MIBI SPECT scan, resection was defined as radical in 12 patients (63%) with grade IV glioma, in 3 patients (75%) with grade III glioma, and in 1 patient (25%) with grade II glioma. Resection was defined as subtotal in 5 patients (26%) with grade IV glioma and in 1 patient (25%) with grade III glioma. Tumor biopsy was performed in 2 patients (11%) with grade IV glioma and 3 patients (75%) with grade II glioma.

A subset of 7 patients with grade IV glioma underwent a third ^{99m}Tc-MIBI SPECT scan 84 days (SD, 25) after external beam radiation treatment. Radiation treatment was started 77 days [SD, 16] after surgery and consisted of a total dose of 60 Gy that was administered in 30 fractions of 2 Gy. Twelve patients with grade IV gliomas refused another ^{99m}Tc-MIBI SPECT scan or did not receive radiation treatment or were lost to follow-up because they died, continued treatment at other institution, or were not referred to us for a SPECT scan by their oncologist.

The study and its consent procedures were approved by the Ethics Committee of the Lithuanian University of Health Sciences, Kaunas, Lithuania, and were in accordance with the Helsinki Declaration as well as the International Conference on Harmonization-Good Clinical Practice. All patients gave signed written informed consent.

Data Acquisition of ^{99m}Tc-MIBI SPECT. Radiopharmaceutical ^{99m}Tc-MIBI was used in all cases because it is intensively taken up by tumors with high mitotic activity, including high-grade gliomas, but not by low-grade gliomas, normal brain tissue, necrotic tissue, and fibrotic tissue (8, 9). ^{99m}Tc-MIBI is routinely used at our clinic for evaluation of patients with glioma before surgery and at follow-up. Image acquisition was performed using a dual-head gamma camera (Siemens, E. Cam, USA) with low-energy general-purpose collimators from 30 to 45 min after an intravenous injection of 500 MBq of ^{99m}Tc-MIBI. Patients were in the supine position with an appropriate headpiece to avoid head movement. Detectors were placed as close as possible to the patients' head. The matrix was set at 64×64 pixels because of relatively small doses of ^{99m}Tc-MIBI used in the study since the patients were exposed to repeated SPECT scans. Moreover, technical characteristics of devices prevented us from using a matrix of higher resolution. However, the chosen matrix size was sufficient to reach the aims of the study. The tomographic imaging parameters consisted of a 360° rotation angle and acquisition time of 30 s per frame with a zoom factor of 1.78. For image reconstruction, the filtered back projection was used, and the Butterworth filter was applied with the cutoff of 0.6 and with order of 7.0. The Chang's attenuation correction was applied with the attenuation coefficient of 0.12 per cm. Raw image data axial plane reconstructions of SPECT were analyzed.

Both TII and TSI were calculated by evaluating and matching SPECT and diagnostic CT images ac-

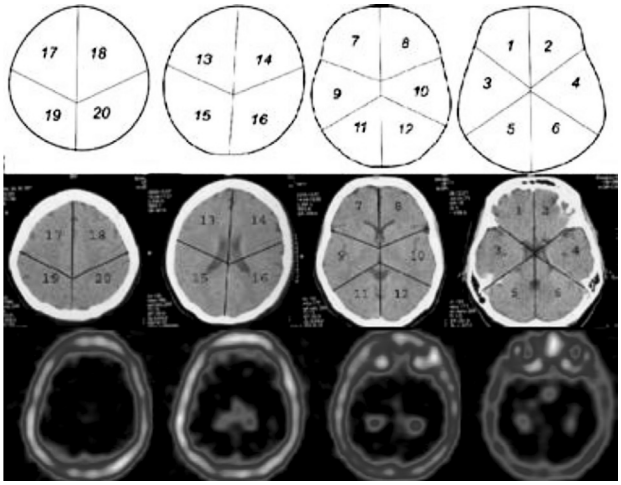

Fig. ^{99m}Tc-MIBI single-photon emission computed tomography scan images divided into 20 segments according to the anatomical landmarks seen on computed tomography and single-photon emission computed tomography scans

cording to the anatomic landmarks seen on SPECT images that included the scalp, upper parts of orbits, upper parts of frontal sinuses, and choroid plexus (Fig.). Four axial slices of each CT scan and each SPECT scan were included in the final protocol: a) at the level of the most cranial part of the choroid plexus; b) at the level of the third ventricle; c) at the level of the body of the lateral ventricles; and d) at the level of the most caudal part of the choroid plexus. The first two axial slices (a and b) of CT and SPECT images were divided into 4 segments each, and the last two axial slices (c and d) of CT and SPECT images were divided into 6 segments each. Therefore, each CT scan and each SPECT scan were divided into a total of 20 segments.

The TII was calculated by evaluating the intensity of pathologic ^{99m}Tc-MIBI uptake by glioma tissue, separately in all 20 segments of SPECT scans. Each segment of the SPECT scan was evaluated using a 4-point scale according to the intensity of tracer uptake ranging from 3 (the highest intensity of visible tracer uptake) to 0 (no visible tracer uptake). Specifically, 3, 2, and 1 points were assigned to the segment when the intensity of pathologic ^{99m}Tc-MIBI uptake in that segment was higher, equal, or lower (but higher than background) than the intensity of ^{99m}Tc-MIBI uptake in the choroid plexus, respectively. Zero was assigned to the segment when ^{99m}Tc-MIBI uptake was not evident. Calculation of the TII was performed by summing the scores of all 20 segments with a possible TII range from 0 points to 60 points.

The TSI was calculated by evaluating the area of pathologic ^{99m}Tc-MIBI uptake in all 20 segments of the SPECT scan by a 4-point scale ranging from 3 to 0. Specifically, 3, 2, and 1 points were assigned to the segment if the area of pathological accumulation of ^{99m}Tc-MIBI covered more than two-thirds of the segment, from two-thirds to one-third of the segment, less than one-third of the segment, respectively, and no points if no ^{99m}Tc-MIBI uptake was seen. The calculation of TSI was done by summing the points in all 20 segments with a possible TSI range from 0 points to 60 points.

Statistical Analysis. Data analysis was performed using the PASW Statistics for Windows 18.0 (IBM Corporation). Continuous data were presented as mean (standard deviation) and categorical data as numbers and their percentages. The level of statistical significance was defined as a probability value of less than 0.05.

First, the optimal cutoff values of TII and of TSI for discriminating between patients with high-grade glioma and patients with low-grade glioma were established. The WHO grade of gliomas was considered a gold standard. For each evaluation, the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated. Then, Pearson correlation analysis between WHO glioma grade, preoperative TSI, and preoperative TII was performed. Next, the preoperative TII and TSI with postoperative TII and TSI, respectively, were compared in all patients and patients with grade IV glioma by using the paired-sample *t* test. Finally, in patients with grade IV glioma, TII and TSI after surgery with TII and TSI after radiation treatment, respectively, were compared by applying the paired-sample *t* test.

Results

Before Surgery. The results of preoperative SPECT of all patients stratified by the WHO glioma grade are presented in Table 1. Focal tracer uptake before surgery was observed in all patients with grade IV glioma, 3 patients with grade III glioma, 2 patients with grade II glioma, and 1 patient with grade I glioma. The mean TSI and TII in patients with grade IV glioma were 6.5 (SD, 1.5) and 8.9 (SD, 2.6), respectively. The optimal cutoff values of TII and TSI for identifying the patients with high-grade glioma were 3 and 2.5, respectively, with a high sensitivity (83% and 88%, respectively) and a high specificity (88% and 88%, respectively) (Table 2). There was a positive, strong, and significant correlation between glioma grade and preoperative TSI score (r=0.76, P<0.001), glioma grade and preoperative TII score (r=0.64, P<0.001), and preoperative TSI score and preoperative TII score (r=0.85, P<0.001).

After Surgery. A significant decrease in the postoperative TSI and postoperative TII when compared with the preoperative TSI and preoperative TII, respectively, was observed in all the patients (P<0.001

Table 1. Preoperative ^{99m}Tc-MIBI SPECT Results of All Patients

	Glioma Grade by the World Health Organization				All patients (n=32)
	I (n=2)	II (n=6)	III (n=4)	IV (n=20)	
Focal tracer uptake, n Yes/no	1/1	2/4	3/1	20/0	26/6
Total size index, mean (SD) [range]	2.5 (3.5) [0–5]	0.7 (1.0) [0–2]	1.5 (1.3) [0–3]	6.5 (1.5) [3–10]	4.5 (3.0) [0–10]
Total intensity index, mean (SD) [range]	5.5 (7.8) [0–11]	0.7 (1.0) [0–2]	3.0 (4.1) [0–9]	8.9 (2.6) [4–13]	6.4 (4.5) [0–13]

Table 2. Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy of Total Size Index and Total Intensity Index at Different Cutoff Values for Discriminating Between Patients With High-Grade Versus Low-Grade Glioma

Cutoff Values	AUC	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy
Total size index						
0.5	0.93	96	63	88	83	88
1.5		92	63	88	71	84
2.5		**88**	**88**	**95**	**70**	**88**
4.0		79	88	95	58	81
5.5		67	100	100	50	75
Total intensity index						
0.5	0.86	96	63	88	83	88
1.5		92	63	88	71	84
3.0		**83**	**88**	**95**	**64**	**84**
4.5		83	88	95	64	84
5.5		79	88	95	58	81

AUC, area under the receiver operating characteristic curve; PPV, positive predictive value, NPV, negative predictive value. Optimal cutoff values in bold.

Table 3. Total Size Index and Total Intensity Index of 27 Patients Before Surgery and After Surgery

	Glioma Grade by the World Health Organization			All Patients (n=27)
	II (n=4)	III (n=4)	IV (n=19)	
Before surgery				
Focal tracer uptake, n Yes/no	0/4	3/1	19/0	22/5
TII	0	3.0 (4.1)	9.0 (2.7)	6.8 (4.4)
TSI	0	1.5 (1.3)	6.5 (1.6)	4.8 (3.1)
After surgery				
Focal tracer uptake, n Yes/no	1/3	3/1	17/2	21/6
TII	0.3 (0.5)	1.25 (0.9)	4.8 (2.5)*	3.3 (3.1)*
TSI	0.5 (1.0)	2.3 (1.5)	4.3 (3.1)*	3.8 (2.7)*

Values are mean (standard deviation) unless otherwise indicated. *P<0.05, compared with respective values before surgery. TSI, total size index; TII, total intensity index.

and P=0.016, respectively) and in a subgroup of patients with grade IV glioma (P=0.002 and P<0.001, respectively), but not in the patients with grade III and grade II glioma (Table 3).

After Radiation Treatment. In a subgroup of 7 patients with grade IV glioma, there was a significant increase in the TII and insignificant increase in the TSI after radiation treatment when compared with the postoperative TII and TSI, respectively (10.7 [SD, 3.3] and 4.3 [SD, 2.4], respectively; P=0.01, and 6.0 [SD, 4.1] and 5.1 [SD, 1.9], respectively; P=0.39).

Discussion

Both the TSI and the TII were found to be feasible indexes in selecting the patients with high-

grade glioma with optimal cutoff values of 2.5 and more and of 3 and more, respectively. Furthermore, higher preoperative TSI and TII were associated with higher grade of glioma. Previous studies have reported that ^{99m}Tc-MIBI SPECT is an accurate method in identifying the patients with high-grade glioma by the means of L/N ratio (21, 22). Thus, our results suggest that TSI and TII can be used to supplement the L/N ratio of SPECT to identify the patients with high-grade glioma when the results of contrast-enhanced MRI scan are inconclusive. Subsequently, early suspicion of high-grade glioma should be followed by expedited and more aggressive diagnostic interventions and treatment. Moreover, it should be noted that the mean preoperative TSI (2.5 [SD, 3.5]) and TII (5.5 [SD, 7.8]) were high in the patients with grade I glioma. In 1 patient with ganglioglioma, both the TSI and TII were high at the levels of 5 and 11, respectively. However, the preoperative tracer uptake was not evident in another patient with grade I glioma who was found to have pilocytic astrocytoma (both TSI and TII were 0). Two cases of gangliogliomas with very high uptake of thallium 201 (^{201}Tl) on SPECT scans were previously described (23). However, the concentrations of Ki-67, a marker of proliferation, in surgical specimens were lower than 1% in both cases of ganglioglioma, indicating low tumor growth activity; therefore, the authors suggested that high tracer uptake by gangliogliomas could be explained by metabolic characteristics other than growth activity (23).

Furthermore, our study revealed that TII and TSI could be used to evaluate the changes of viable glioma after surgery. Namely, there was a significant decrease in the postoperative TSI and TII in all the patients; however, this effect was mainly based on a decrease in the TSI and TII in the patients with grade IV glioma. A few studies have evaluated SPECT results before and after surgery. For example, postoperative ^{201}Tl SPECT showed positive results for recurrent tumor in 91% of patients with high-grade gliomas 17 days after resection (24). Other study was carried out using 3-(^{123}I) iodo-L-methyltyrosine in 71 patients from 4 to 6 weeks after the resection of low-grade and high-grade gliomas and found viable gliomas in 73% of patients (25). To our knowledge, this was the first study evaluating the use of the results of ^{99m}Tc-MIBI SPECT for the detection of viable glioma tissue before and after surgery in the same subset of patients. A discrepancy of a number of patients with detected residual glioma tissue after surgery in different studies might be attributed to different tracers used across studies and to different time intervals between surgery and SPECT. In addition, the size and location of glioma, and experience of a neurosurgeon should be taken into consideration. However, a significant decrease in the TII and TSI after surgery in patients with grade IV glioma documented in our study suggests that the main bulk of glioma was removed during surgery.

After surgery, there was a greater decrease in the TII when compared with the TSI. A more pronounced decrease in the TII can be explained that the TII corresponds to the malignancy and size of glioma, whereas the TSI corresponds to the size of glioma only. Thus, the TII is expected to be a more sensitive indicator of glioma size in patients with high-grade glioma. Indeed, the TII was more sensitive than the TSI in identifying the patients with high-grade glioma, and a decrease in the postoperative TII was higher than a decrease in the postoperative TSI in patients with grade IV glioma when compared with those who had grade III glioma. In 2 patients with grade IV glioma, there was an increase in the TSI and a decrease in the TII after surgery. Such an increase in the TSI can be explained by the increased permeability of the blood-brain barrier after surgery and by postoperative tissue shift; therefore, even a small amount of tumor left after surgery can be visualized as a large area of abnormal tracer uptake. However, postoperative accumulation of the tracer was less intensive indicating that in some cases of grade IV glioma, TII might reflect reduced tumor bulk more accurately than TSI. In addition, it is worth mentioning that new postoperative accumulation of tracer was observed in 1 patient with grade II glioma. This can be explained by the progression of glioma malignancy that can be identified in early stages by the means of SPECT. These results confirm that the total resection of glioma remains a challenge for neurosurgeons, and complete radical resection of gliomas is rarely achieved. Therefore, nowadays, multimodal treatment strategy for gliomas includes maximally safe surgical reduction of tumor bulk followed by radiotherapy with concomitant and adjuvant chemotherapy (6).

There was a significant increase in the TII after radiation treatment in patients with grade IV glioma. These findings might be explained by nonspecific local inflammatory reaction to radiation treatment and/or by disease progression after radiation therapy. Suspicion of disease progression was supported by deterioration of patients' clinical status at follow-up. Therefore, patients with an increased TII after radiation therapy should be referred for more detailed examination. In one previous study, ^{99m}Tc-MIBI SPECT was shown to be effective in identifying residual glioma at the end of radiation treatment (26). Furthermore, a recent meta-analysis has concluded that ^{99m}Tc-MIBI SPECT is highly sensitive and specific for the detection of glioma recurrence (27). Our results suggest that TSI and TII can be used to evaluate the subtle changes of viable glioma

tissue after radiation treatment. Thus, TSI and TII can supplement MRI for the detection of early recurrence of glioma after radiation treatment and for the individual assessment of response to this treatment.

This study has some limitations. Standard chemotherapy with temozolomide was not available at the time of the study in Lithuania. Therefore, the value of TSI and TII for follow-up evaluation of patients receiving combined radiotherapy and chemotherapy should be addressed in further studies. Moreover, the majority of our patients were diagnosed with grade IV gliomas, and subsamples of patients with grades I, II, and III gliomas were small. On the other hand, strengths of this study include a relatively large sample of patients who underwent ^{99m}Tc-MIBI SPECT before and after treatment. Besides, diagnosis was confirmed using histological examination, and the WHO classification for tumor grading was applied in all the cases. Furthermore, at our institution, more advanced nuclear medicine imaging modalities, such as positron emission tomography (PET) and SPECT/CT, were not used at the time of the study. On the other hand, the value of PET for the evaluation of glioma recurrence remains controversial because the studies (28, 29) were conducted in small groups of patients, and the techniques were not standardized (28–31). Several previous studies have evaluated a diagnostic value of PET for diagnosing glioma recurrence and have demonstrated that ^{18}F-FDG PET (30) and ^{11}C-methionine PET (28) were inferior techniques when compared with SPECT (30) and perfusion MRI (28), while others have showed that ^{11}C-methionine PET (31) and ^{13}N-ammonia PET (29) were valuable diagnostic modalities for the detection of glioma recurrence. However, PET remains a very expensive technique, and the use of radiopharmaceuticals other than ^{18}F-FDG is very limited and expensive. Scanning with SPECT and ^{99m}Tc-MIBI is simple, less expensive technique and can be employed even in developing countries.

Conclusions

Total size and total intensity indexes were found to be valid for identifying the patients with high-grade glioma. Moreover, these indexes allow evaluating for subtle changes after surgery, and total intensity index can detect the subtle changes of tumor bulk after radiation treatment in patients with grade IV glioma.

Statement of Conflicts of Interest

The authors state no conflict of interest.

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