The Value of ^{99m}Tc-Tetrofosmin Brain SPECT in Predicting Survival in Patients with Glioblastoma Multiforme

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^{99m}Tc-tetrofosmin brain SPECT has been reported as a useful tool for the evaluation of glioma proliferation. In the present study, we set out to investigate the prognostic value of ^{99m}Tc-tetrofosmin brain SPECT in patients with glioblastoma multiforme. **Methods:** We prospectively studied 18 patients (13 men, 5 women; mean age ± SD, 60.8 ± 7.79 y) who were operated on for glioblastoma multiforme. All patients underwent preoperative ^{99m}Tc-tetrofosmin brain SPECT, and surgical excision was performed within a week after SPECT. All patients received postoperative radiotherapy and chemotherapy. **Results:** By calculating the lesion-to-normal (L/N) ^{99m}Tc-tetrofosmin uptake ratio, we found that patients with an L/N ratio of more than 4.7 had significantly worse survival than did patients with an L/N ratio of 4.7 or less. Furthermore, patients with a Karnofsky Performance Score more than 90 had a significantly better survival rate. Although patients with near-total tumor resection who were younger than 60 y survived longer, the difference did not reach statistical significance. In the multivariate analysis, ^{99m}Tc-tetrofosmin uptake and Karnofsky Performance Score were identified as factors with independent prognostic power. **Conclusion:** ^{99m}Tc-tetrofosmin brain SPECT may be an independent prognostic factor in patients with glioblastoma multiforme. Further larger studies are needed to verify these results.

Key Words: ^{99m}Tc-tetrofosmin; brain SPECT; glioblastoma multiforme; survival

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Glioblastoma multiforme (GBM) is by far the most common and most malignant of the glial tumors occurring in adults. This devastating disease is usually incurable, and patients have a median survival time of approximately 1 y after diagnosis (*1*). Nevertheless, a subset of patients demonstrates long-term survival of 3 y or more (*2*). Prognostic factors that have been identified, such as age at diagnosis, Karnofsky Performance Score (KPS), and extent of resection, inadequately predict outcome (*1,3–5*). Moreover, although certain genetic factors have been associated with overall survival (OS), no sufficient, reliable, and validated biomarker has been established for clinical practice (*2,6*). The identification of prognostic variables in GBM patients is a major challenge and could increase the prognostic accuracy, identify patients who may benefit from more aggressive treatments, and allow for the selection of more homogeneous experimental populations in ongoing clinical trials.

Brain SPECT has been established as a useful tool for the evaluation of brain tumors (*7–9*). We have previously reported that ^{99m}Tc-tetrofosmin uptake correlates with glioma proliferative potential, as assessed by the Ki-67 immunohistochemical index and flow cytometry (*10,11*). Because of the established prognostic value of Ki-67 in gliomas (*12*), we set out to investigate the correlation between pretreatment ^{99m}Tc-tetrofosmin tumor uptake and OS in patients with GBM.

MATERIALS AND METHODS

We prospectively studied 18 newly diagnosed patients (13 men, 5 women; mean age ± SD, 60.8 ± 7.79 y) who were operated on for GBM in our hospital. All patients had undergone ^{99m}Tc-tetrofosmin SPECT preoperatively. Surgical excision was performed within a week after SPECT. The extent of resection was determined by comparing MRI scans obtained before surgery with those obtained within a month after resection. All patients received postoperative standard radiotherapy (6,000 rads) with temozolomide chemotherapy, followed by temozolomide therapy up to 1 y or until recurrence. Patients who had a recurrence had only supportive care, with no additional surgery or chemotherapy. All patients participating in this study gave their written informed consent; the study was approved by the Institutional Review Board and was in accordance with the Declaration of Helsinki.

^{99m}Tc-Tetrofosmin SPECT and Image Analysis

Brain SPECT was performed 30 min after an intravenous injection of 925 MBq (25 mCi) of ^{99m}Tc-tetrofosmin. The radiopharmaceutical was prepared using a domestically available powder kit (Myoview; GE Healthcare) that was reconstituted with ^{99m}Tc-pertechnetate ($^{99m}TcO_4^-$) sterile solution in the Nuclear

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Medicine Department. All studies were obtained on a dual-head γ-camera (Millennium VG3; GE Healthcare), equipped with a pair of high-resolution, parallel-hole collimators. The matrix was set at 128 × 128 pixels; the photopeak was centered at 140 keV, with a symmetric 10% window. The tomographic imaging parameters consisted of a 360° rotation angle, a 3° step-and-shoot technique, and an acquisition time of 30 s per frame. Raw imaging data were reconstructed using the Butterworth-filtered backprojection algorithm, generating tomographic views of the brain in the 3 planes (transverse, coronal, and sagittal).

Radiotracer accumulation in GBM was first assessed visually. Then a semiquantitative method of image analysis was applied, by calculating the lesion-to-normal uptake ratio (L/N): a region of interest was manually defined around the lesion on the transverse slice with the highest mean tracer uptake—with close reference to the corresponding MRI/CT slice—and a second region was drawn on the contralateral normal brain side. The L/N was calculated by dividing the mean counts in the tumor region with the mean counts in the normal region. The regions of interest were evaluated for eligibility by 2 independent experienced nuclear medicine physicians; any possible disagreements were solved by consensus.

Statistical Analysis

OS was defined as the time from surgery to death or to the last follow-up of the surviving patients. Survival curves were calculated by the Kaplan–Meier method and the log-rank test. Multivariate Cox regression analysis of the data was used to analyze possible prognostic factors. The forward-stepwise model selection procedure was used (P value of likelihood-ratio test < 0.05 as inclusion criterion and > 0.10 as exclusion criterion) to define the final model. The following variables were entered: sex, age at diagnosis, KPS, L/N, and extent of resection. With respect to L/N, receiver-operating-characteristic curve analysis was performed to determine the cutoff value for predicting survival. A 2-sided P value less than 0.05 was considered statistically significant.

RESULTS

The patients' age, sex, tumor location, KPS, extent of resection, and scintigraphic tumor characteristics are summarized in Table 1. In 8 patients, a near-total resection (>95%) was achieved, whereas in the other 10 patients, resection was subtotal (75%–95%). Tumoral tracer uptake ranged from low (Fig. 1A) to profound (Fig. 1B) (mean L/N, 9.1; range, 2.5–22.2). The OS was 12.6 mo (range, 5 to 21 mo). Receiver-operating-characteristic curve analysis gave a cutoff L/N of 4.7 as best predicting survival. Patients with an L/N exceeding 4.7 (12 patients) differed significantly from those with an L/N of 4.7 or less (6 patients) and were associated with worse survival (17.5 vs. 11 mo, respectively; $P = 0.0069$; Fig. 2). A KPS more than 90 was associated with a better outcome ($P = 0.019$). The median survival for patients with near-total resection was 14 mo, whereas for patients with subtotal resection it was 11 mo. The difference was not statistically significant. Similarly, no significant difference in survival was observed among patients older or younger than 60 y (11 vs. 14.5 mo, respectively). No significant correlation between sex and survival was observed. In multivariate analysis, the L/N and KPS were identified as factors with independent prognostic power (for L/N: $P = 0.015$, 95% confidence interval, 1.59%–72.49%; and for KPS: $P = 0.029$, 95% confidence interval, 1.21%–36.71%).

DISCUSSION

In the present study, we found that ^{99m}Tc-tetrofosmin brain SPECT may have a prognostic role in patients with GBM. To the best of our knowledge, no other study has

TABLE 1
Detailed Patient Data

Patient no.	Age (y)	Sex	Location	KPS	Resection	^{99m}Tc-tetrofosmin uptake	Survival (mo)
1	60	M	R parietal	100	STR	7.43	11
2	64	M	L temporal	80	STR	2.5	15
3	53	M	L temporal–parietal	100	STR	9.6	11
4	53	M	R temporal	100	NTR	2.5	21
5	66	M	R temporal	90	STR	20	8
6	54	F	R temporal	100	STR	3	20
7	61	M	R temporal	100	STR	10.5	15
8	58	M	R frontal	80	STR	9.5	6
9	78	F	R occipital	100	NTR	4.1	11
10	61	M	R temporal	90	NTR	5.44	10
11	59	F	R occipital	100	NTR	4.7	18
12	54	F	R temporal	100	NTR	3.2	17
13	58	M	L temporal	90	NTR	22.2	8
14	73	M	R parietal–occipital	90	STR	11.3	9*
15	70	M	R frontal	100	STR	15.9	10*
16	54	F	L frontal	100	NTR	6.57	10*
17	50	M	R temporal	100	STR	10	6
18	69	M	R frontal–parietal	80	NTR	16	5*

*Alive.
STR = subtotal resection (75%–95%); NTR = near-total resection (>95%).

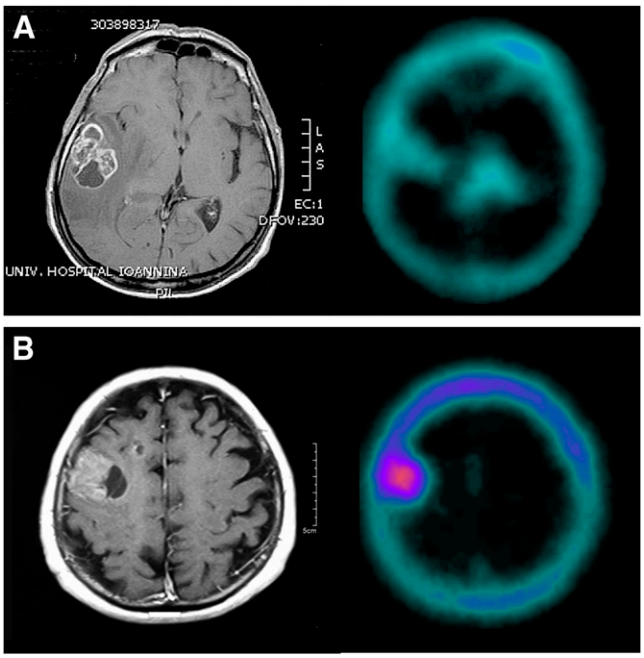

FIGURE 1. Contrast-enhanced T1-weighted MR image (left) and ^{99m}Tc-tetrofosmin SPECT image (right) in one GBM patient exhibiting low tracer uptake (A) and in another with high uptake (B) (patients 6 and 18 from Table 1, respectively).

reported a correlation between ^{99m}Tc-tetrofosmin uptake and OS in patients with GBM. Brain PET and SPECT have been used to evaluate several intracranial lesions (*9*). Di Chiro found that the regional cerebral metabolic rate of glucose, as determined by ^{18}F-FDG PET, was a better predictor of survival in patients with malignant glioma than was histologic classification (*13*). 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. Among them, ^{201}Tl

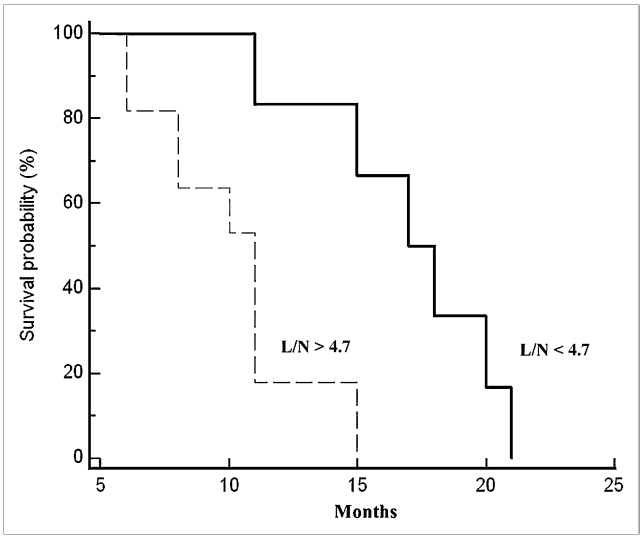

FIGURE 2. Graphs showing the relationship between ^{99m}Tc-tetrofosmin uptake (L/N cutoff, 4.7) and survival in GBM patients.

was one of the first that were widely used. Oriuchi et al. studied 28 presurgical patients with supratentorial gliomas and found that patients with a higher ^{201}Tl uptake index had a worse survival rate (*14*). Using the amino acid analog 3-^{123}I-iodo-L-methyltyrosine in patients with resected gliomas, Weber et al. reported that the intensity of tracer uptake significantly correlated with survival (*8*).

^{99m}Tc-labeled compounds have also been studied in brain tumors and were proven advantageous over ^{201}Tl (*15*). ^{99m}Tc-sestamibi has been extensively used and proved useful for metabolic characterization (*16*). ^{99m}Tc-tetrofosmin is a lipophilic diphosphine that has also proven suitable for brain tumor imaging (*10,11,17–19*). Its uptake in the healthy brain is physiologically seen in the choroid plexus and the pituitary gland but not in the normal brain parenchyma, because it does not cross the intact blood–brain barrier. We have recently shown in vivo that, in contrast to ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin is not influenced by the multidrug-resistance phenotype of gliomas and may thus be superior for brain tumor imaging (*18*). Furthermore, ^{99m}Tc-tetrofosmin can be a suitable radiotracer for the differentiation of glioma recurrence from radiation necrosis, neoplastic from nonneoplastic intracerebral hemorrhage, and benign from malignant brain space-occupying lesions and for the assessment of the proliferation potential of gliomas and meningiomas (*19–21*).

This study has several limitations. It was performed in a single institution, and the number of patients was relatively small. There is a recognized difficulty in precise region-of-interest definition on reconstructed SPECT images, particularly in cases of negligible tracer uptake or of interference between tumor uptake and physiologic tracer uptake in the choroid plexus and the pituitary. In such cases, hybrid SPECT/CT might overcome this limitation by providing better spatial tumor localization to coregister with SPECT and also by applying attenuation correction to image processing and L/N calculation.

CONCLUSION

Our results imply that ^{99m}Tc-tetrofosmin brain SPECT may hold an additional prognostic role in patients with GBM. This possible role deserves to be tested further in larger series. Overall, stratification of tumors into risk groups based on prognostic parameters has been a major component of treatment, because it may alter or intensify treatment methods to improve disease outcome. Stratification could also contribute to the development of new protocols for better management of high-risk patients.

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