Clinical Application of ^{201}Tl SPECT Imaging of Brain Tumors

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This study investigated the clinical usefulness of evaluating the histologic grade of brain tumors by ^{201}Tl SPECT brain imaging. **Methods:** Early and delayed SPECT brain images were obtained about 10 min and 3 h, respectively, after intravenous injection of 111MBq (3 mCi) ^{201}Tl in 9 healthy subjects (control subjects), 3 patients with brain hematomas, and 41 patients with brain tumors. Semiquantitative data were obtained for early and delayed ^{201}Tl uptake indices and ^{201}Tl retained index in all patients and healthy subjects. **Results:** In 9 healthy subjects, there was little radioactivity in brain substance. In all patients with brain hematomas or tumors, a high tracer uptake was visible in lesions on early images, but the radioactivity in lesions varied with the histologic nature of the lesion on delayed images. The radioactivity decreased remarkably in brain hematomas (average retained index, 0.61 ± 0.04). The radioactivity was stable or decreased slightly in benign or low-grade tumors (average retained index, 0.96 ± 0.24). The radioactivity was increased in high-grade or metastatic tumors (average retained index, 1.26 ± 0.28). **Conclusion:** This study indicates that ^{201}Tl brain SPECT early and delayed imaging is very useful in brain tumor localization, in distinguishing low-grade from high-grade brain tumors, in predicting histologic grades of brain tumors, and in detecting residual or recurrence of brain tumors postoperatively. ^{201}Tl brain SPECT may also offer the most accurate assessment of response to therapy.

Key Words: ^{201}Tl SPECT; brain tumor; ^{201}Tl retained index

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A myocardial imaging agent in common use is ^{201}Tl, which was incidentally noted to show uptake in lung carcinoma. ^{201}Tl is considered to be an excellent radiopharmaceutical for tumor localization and has been used extensively in the study of various tumors, including lung, thyroid, liver, and esophageal cancer (*1,2*). Further observations suggested its usefulness in the diagnosis of cerebral lesions (*3,4*). A substantial uptake occurs in primary and metastatic cerebral tumors, with little uptake in normal brain (*2–4*). We performed ^{201}Tl brain SPECT studies on patients with brain tumors to determine the value of ^{201}Tl SPECT in distinguishing and evaluating the histologic grade of brain tumors.

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MATERIALS AND METHODS

Subjects

The study group consisted of 9 healthy subjects (7 men, 2 women; median age, 60.6 y; range, 33–72 y) who served as the control group, 3 patients with brain hematomas (1 man, 2 women; ages 48, 18, and 40 y), and 41 patients with brain tumors (26 males, 15 females; median age, 40.4 y; range, 15–65 y). Brain tumors or hematomas were diagnosed in 44 patients by preoperative brain CT or MRI and postoperative histopathologic examination. The 41 patients with brain tumors were divided into two subgroups according to postoperative pathologic diagnosis. Low-grade or benign tumors (n = 26) included meningioma, primary astrocytoma (grades I–II), oligodendroglioma (grades I–II), teratoma, and neurilemoma. High-grade or metastatic lesions (n = 15) included primary astrocytoma (grades III–IV), glioblastoma multiforme, medulloblastoma, and metastatic tumors. The brain histologic grade classification is according to the method of Kernohan et al. (*5*).

^{201}Tl SPECT

^{201}Tl brain SPECT was performed 1–5 d preoperatively. Each patient was injected with 111 MBq (3 mCi) ^{201}Tl in isotonic sodium chloride. SPECT images were obtained about 10 min (early imaging) and 3 h (delayed imaging) after injection using a single-head rotating camera (Elscint APEX 609 RG; Elscint Ltd., Haifa, Israel) equipped with a low-energy, high-resolution collimator and connected to a dedicated Elscint 8086 computer. Data were collected from 60 projections in the 69-keV photopeak (15% window) over 360° in a 64 × 64 matrix with an acquisition time of 25–30 s/view. A zoom factor of 2 was used. Image reconstruction and analysis were performed using the computer system with iterative backprojection, reconstruction, and attenuation correction. The acquisition data were corrected for nonuniformity; orthogonal transverse, coronal, and sagittal planes were generated, followed by orbitomeatal line (OML) reorientation of the reconstructed volume. The final dataset used for visual interpretation consisted of 2-pixel-thick (0.4552 cm/pixel) OML level, transverse, coronal, and sagittal slices.

Abnormal ^{201}Tl Imaging

In healthy subjects, ^{201}Tl cannot normally diffuse into brain tissue, and there is little radioactivity in the brain substance (*4,6*). Brain tissue is defined as abnormal if there is more radioactive accumulation in brain tissue and the radioactive concentration in brain tissue is close to or greater than the radioactive concentration in the bilateral temporal scalp.

Semiquantitative Analysis

For investigating further the relation between ^{201}Tl uptake in brain tumor and the tumor histology, three indices (early ^{201}Tl uptake index, delayed ^{201}Tl uptake index, and ^{201}Tl retained index)

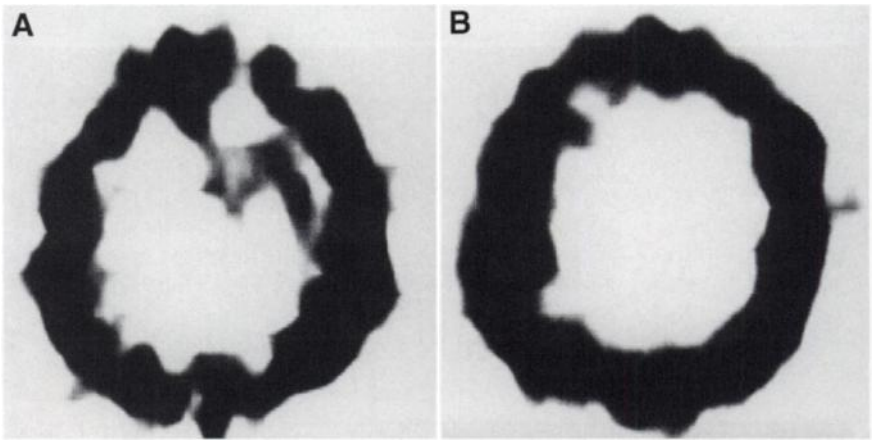

FIGURE 1. Healthy subject (55-y-old man) with brain SPECT associated with heart imaging. (A) Early SPECT brain image. (B) Delayed SPECT brain image. There is no radioactivity in brain tissue.

were calculated for all healthy subjects and patients with brain hematomas and brain tumors. The uptake index is based on the ratio of ^{201}Tl uptake in the tumor to that in the area of contralateral scalp adjacent to the temporal fossa. The retained index is based on the ratio of delayed ^{201}Tl index to early ^{201}Tl index. For this purpose, an OML level slice was selected. The greatest activity in the tumor could be seen in this slice. Preoperative CT or MRI scans were used as anatomic guides. Operator-defined regions of interest (ROIs) were drawn on the radioactive accumulation area of tumor in the slice. Each ROI is square (4 × 4 pixels). Using the system's ROI program, the same ROI could be easily moved to the area of contralateral scalp adjacent to the temporal fossa that showed the greatest activity. The indices were recalculated from counts/pixel of the individual ROI for semiquantitative analysis as follows: early or delayed ^{201}Tl uptake index = (average ROI counts/tumor)/(average ROI counts/pixel in area of contralateral temporal scalp). ^{201}Tl retained index = delayed ^{201}Tl uptake index/early ^{201}Tl uptake index.

Statistical Analysis

The semiquantitative analysis data were expressed as mean ± SD. Paired Student *t* tests were performed to test for differences between the means.

RESULTS

Healthy Subjects

^{201}Tl cannot normally diffuse into brain tissue because of the blood–brain barrier (BBB), so no radioactivity is seen in the brain substance. On ^{201}Tl brain SPECT images of 9 healthy subjects, high radioactivity was seen in the orbits, the base of the skull, and the nasopharyngeal region. A ringlike zone of radioactive accumulation around the scalp included the scalp adjacent to the temporal fossa. Only a small amount of scattered radioactivity was seen in the brain substance. The radioactivity in the brain substance was remarkably lower than that in the bilateral temporal scalp (Fig. 1). There was no significant difference between early and delayed ^{201}Tl images. The average value of the early and delayed ^{201}Tl uptake index for healthy subjects was 0.65 ± 0.11 (Table 1).

Brain Hematomas

On early ^{201}Tl images of 3 patients with brain hematomas, abnormal accumulations of radioactivity were seen in the hematoma sites, but the radioactivity was decreased on delayed ^{201}Tl images (Fig. 2). For brain hematoma, the average values of the early and delayed ^{201}Tl indices were 1.04 and 0.63, respectively, and the retained index was 0.61 ± 0.04 (Table 1).

Brain Tumors

Visual Assessments. The SPECT images of all patients with brain tumors clearly showed abnormal ^{201}Tl accumulation in the brain substance. The location of the abnormal area

TABLE 1
Results of Semiquantitative Analysis in Four Groups

Group	No. of patients	Uptake index		Retained index
		Early	Delayed	
Brain tumor				
High-grade	15	1.56 ± 0.23 (0.32)*	1.92 ± 0.38 (3.95)†	1.26 ± 0.28 (3.56)†
Low-grade	26	1.59 ± 0.32	1.50 ± 0.33	0.96 ± 0.24
Brain hematoma	3	1.04 ± 0.13	0.63 ± 0.13	0.61 ± 0.04
Healthy subjects	9	0.65 ± 0.11‡		

*$P > 0.05$ in comparison with low-grade tumor group.
†$P < 0.001$ in comparison with low-grade tumor group.
‡Average value of early and delayed ^{201}Tl uptake index.
Data are expressed as mean ± SD. *t* values are given in parentheses.

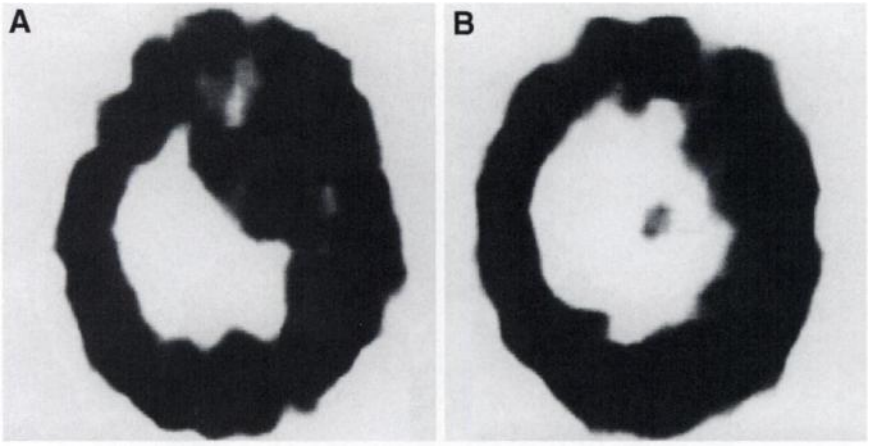

FIGURE 2. Brain hematoma patient (40-y-old woman) 3 d after traffic accident. CT scan revealed hematoma in left frontal area. (A) Early SPECT brain image shows high uptake of radioactivity in left frontal area. (B) Delayed SPECT brain image shows lower uptake of radioactivity in same area as in (A). Retained index = 0.60.

was coincident with the brain tumor site seen on CT or MRI scans. The size of the abnormal area on ^{201}Tl images was slightly bigger than that seen on CT or MRI scans. In 41 patients with brain tumors, delayed ^{201}Tl images of each patient were visually compared with the respective early ^{201}Tl images. The radioactivity in the location of the tumor on delayed ^{201}Tl images increased in 9 of 41 patients, and 8 of the tumors (88.9%) were shown to be high-grade or metastatic lesions on postoperative histologic examination (Fig. 3).The radioactivity increased slightly on delayed images in 11 of 41 patients, and about half of the tumors were shown to be high-grade or benign lesions. Decreased or unchanged radioactivity was observed on delayed images in 21 of 41 patients, and 20 of the tumors (95.2%) were shown to be low-grade or benign lesions (Fig. 4). Table 2 gives the results of the visual assessments.

Semiquantitative Analysis. The results of semiquantitative analysis indicated that in early ^{201}Tl indices, no discrepancies were evident between patients with low-grade and high-grade tumors ($P > 0.05$); however, in delayed ^{201}Tl indices and retained indices, discrepancies were obvious between patients with low-grade or benign tumors and patients with high-grade or metastatic lesions ($P < 0.001$). Positive relations were evident between the retained index and the histology of the tumor (Fig. 5). Tables 1 and 3 give the results of semiquantitative analysis.

Residual or Recurrent Tumors. Twelve of 41 patients with various grades of brain tumors were restudied using ^{201}Tl 6–30 d postoperatively. In 9 of the tumors, increased radioactivity was still seen in the original tumor site on early and delayed ^{201}Tl brain SPECT images. According to two reports (*3,4*), radioactive accumulation was seen on early ^{201}Tl images in the areas of BBB breakdown and inflammation and in the operative site, but the radioactivity was decreased markedly on delayed images. The 9 patients in this study were considered to have residual tumor, which was confirmed during follow-up. For example, a 34-y-old man had ^{201}Tl brain SPECT imaging before surgery that showed an abnormally high accumulation of radioactivity in the left frontotemporal region. Postoperative histologic examination indicated an astrocytoma (grade III). Repeated ^{201}Tl imaging was performed 8 d postoperatively and showed a small area of accumulation of radioactivity in the original tumor site. The retained index was 1.15, which indicated a residual tumor. Over the intervening 2 mo, increasing symptoms of headaches and dizziness developed in the patient. Further ^{20}Tl imaging 2 mo after surgery showed tumor recurrence in the same location. The area of abnormal accumulation of radioactivity was larger than that seen on the ^{201}Tl images before surgery, and the retained index had increased to 1.18. The tumor recurrence was also revealed on further CT.

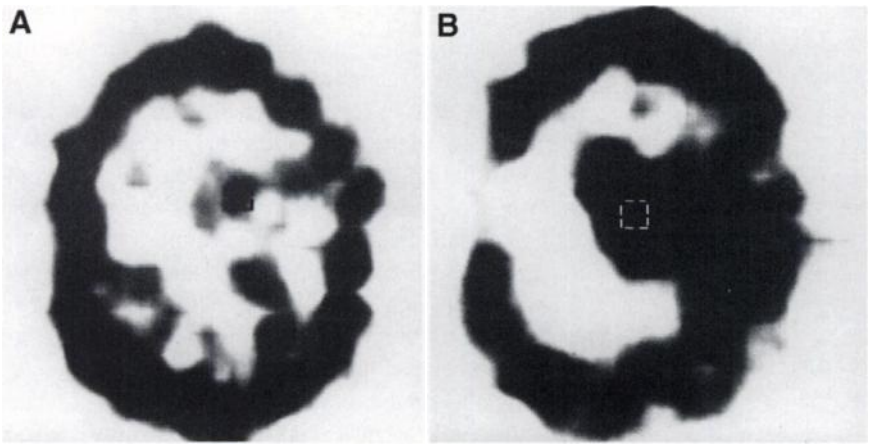

FIGURE 3. High-grade tumor patient (39-y-old woman) with headache for one-half month. CT scan showed tumor in left temporal region. (A) Early SPECT brain image shows high uptake of radioactivity in right frontal area (uptake index = 1.38). (B) Delayed SPECT brain image shows higher uptake of radioactivity in same area as in (A) (uptake index = 2.30). Retained index = 1.67. Pathologic examination of surgical specimen revealed astrocytoma (grades III–IV).

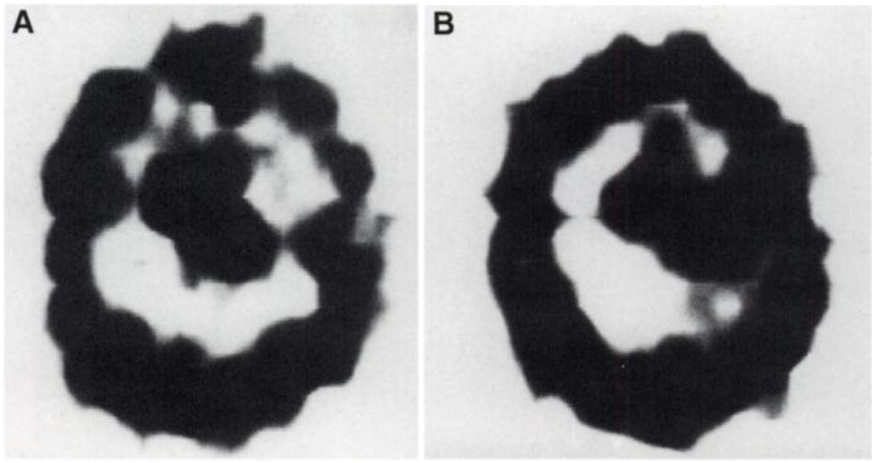

FIGURE 4. Low-grade tumor patient (22-y-old woman) with headache and dimness of vision for 2 mo. CT scan showed glioma in left ventricle of brain. (A) Early SPECT brain image shows high uptake of radioactivity (uptake index = 2.11). (B) Delayed SPECT brain image (uptake index = 1.26) shows lower uptake of radioactivity in same area as in (A). Retained index = 0.84. Pathologic examination revealed astrocytoma (grade II).

Brain CT or MRI

The results of brain CT or MRI in 41 patients with brain tumors are given in Table 4. Brain CT or MRI can locate the tumor well anatomically and confirm the tumor. The conformable rate of diagnosing the lesion as tumor on CT or MRI was 92.7% (38/41). However, the conformable rate in brain tumor histologic classification was low, i.e., 51.2% (21/41). The size of brain tumor seen on CT or MRI was accordant with that seen during surgery.

DISCUSSION

^{201}Tl can localize in primary and metastatic tumors. The mechanism of uptake is unknown, but the reported potential clinical usefulness of ^{201}Tl is probably related to its mechanism of localization. Actual uptake appears to be related to a combination of factors, including regional brain blood flow, BBB permeability, and cellular uptake that may involve transmembrane transport into viable tumor cells (*2,3,7*). Increased BBB permeability alone will not necessarily increase ^{201}Tl uptake because non-neoplastic lesions with BBB breakdown, such as areas of radiation necrosis or resolving hematoma, will have little or no ^{201}Tl uptake (*8*). ^{201}Tl acts biologically very much like potassium. The distribution of ^{201}Tl, like that of potassium, probably depends on regional blood flow and cellular membrane adenosine triphosphatase activity. Experimental evidence suggests that the ionic movements of thallium and potassium are related to active transport through an adenosine triphosphate cell membrane pump (*7*) and that ^{201}Tl uptake is related to cellular growth rates (*4*). The localization of ^{201}Tl is, therefore, unique compared with that of other standard radionuclide tracers or iodinated contrast material because its uptake reflects viable tumor and not simply BBB breakdown (*2,7*).

TABLE 2
Radioactive Change on Delayed Imaging Compared with Early Imaging by Visual Assessment

Group	Increase		No change	Decrease	Sum
	Clear	Slight			
Brain tumor					
High-grade	8	6	0	1	15
Low-grade	1	5	6	14	26
Sum	9	11	6	15	41

In the ^{201}Tl imaging of patients with brain tumors in this study, visual assessment showed that on early Tl imaging, abnormal ^{201}Tl accumulation was seen in the brain tumor site revealed on CT. There was no evident discrepancy between patients with various tumors in the rates of early ^{201}Tl uptake. However, delayed ^{201}Tl images obtained 3 h later showed that in 15 patients with high-grade or metastatic lesions, radioactivity increased clearly in 8 patients, increased slightly in 6 patients, and decreased in 1 patient. In 26 patients with low-grade or benign tumors, radioactivity increased clearly in 1 patient and increased slightly in 5 patients; no change was seen in 6 patients, and decreased radioactivity was noted in 14 patients on delayed ^{201}Tl imaging. If we distinguish the high-grade or metastatic lesions from the low-grade or benign tumors according to the change in uptake of radioactivity on delayed ^{201}Tl images, there was overlapping in 13 cases.

The results of semiquantitative analysis of 41 patients with brain tumors indicated that in 14 of 15 patients with high-grade or metastatic lesions, the retained indices were equal to or greater than 1.13, and the average retained index was 1.26 ± 0.28. In 24 of 26 patients with low-grade or benign tumors, the retained indices were not greater than 1.11, and the average retained index was 0.96 ± 0.24. These results indicate that ^{201}Tl uptake and retention in brain tumors are relative to the histologic grade of the tumor. This finding agrees with published data (*7,9–12*). Semiquantitative analysis can not only increase the sensitivity and specificity to localize and predict brain tumor type but also help to identify the areas for biopsy to reduce unrecognized sampling errors during needle biopsies of brain tumors (*4,8*).

The methods of treatment for brain tumors consist of surgery, chemotherapy, and irradiation. The aim of therapy is to destroy the tumor, but some tumors are near vital centers in the brain or grow into important nerve tissue;

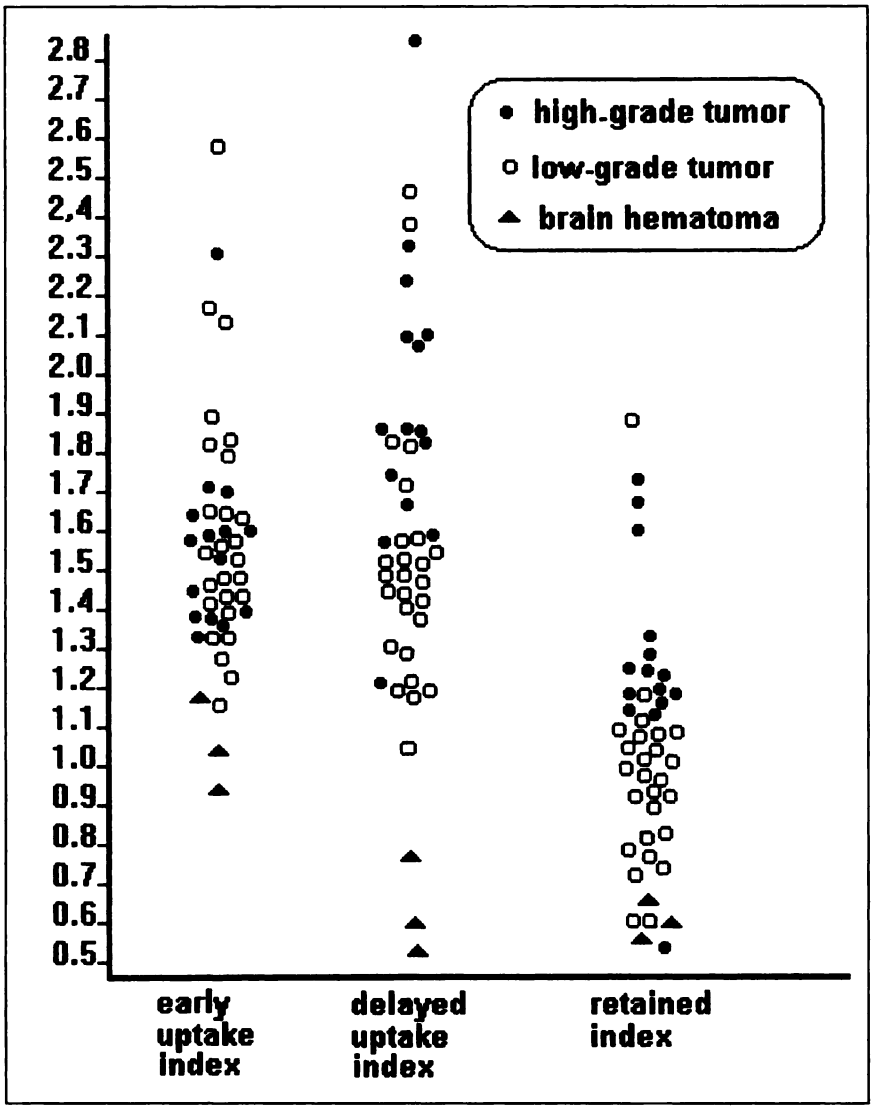

FIGURE 5. Distribution diagram of early and delayed uptake indices and retained index.

TABLE 3
Results of Semiquantitative Analysis of Patients with Various Tumors

Pathologic group	No. of patients	Uptake index		Retained index
		Early	Delayed	
Low-grade brain tumor				
Meningioma	4	1.75 ± 0.36	1.35 ± 0.17	0.80 ± 0.21
Neurinoma	1	2.58	2.34	0.91
Gliosis	1	1.79	1.82	1.02
Teratoma	1	1.51	1.16	0.77
Astrocytoma, grades I–II	13	1.55 ± 0.26	1.50 ± 0.33	1.00 ± 0.30
Oligodendroglioma, grades I–II	6	1.43 ± 0.15	1.46 ± 0.23	1.02 ± 0.10
Sum	26	1.59 ± 0.32	1.50 ± 0.33	0.96 ± 0.24
High-grade brain tumor				
Astrocytoma, grades III–IV	6	1.52 ± 0.35	1.79 ± 0.43	1.25 ± 0.40
Glioblastoma multiforme	1	1.70	2.10	1.20
Medulloblastoma	2	1.59/1.70	1.88/2.10	1.18/1.24
Metastatic lesion	6	1.56 ± 0.09	2.00 ± 0.43	1.28 ± 0.23
Sum	15	1.56 ± 0.23	1.92 ± 0.38	1.26 ± 0.28

Data are expressed as mean ± SD.

TABLE 4
Results of Brain CT or MRI in 41 Patients with Various Tumors

Pathologic group	No. of patients	Type of lesion							
		Tumor	Occ.	Gli.	Ast.	Oli.	Met.	Abs.	Men.
Low-grade brain tumor									
Meningioma	4			2					2
Neurinoma	1	1							
Gliosis	1	1							
Teratoma	1			1					
Astrocytoma, grades I–II	13	5	2	4	1	1			
Oligodendroglioma, grades I–II	6			4		2			
Sum	26	7	2	11	1	3			2
High-grade brain tumor									
Astrocytoma, grades III–IV	6	2		4					
Glioblastoma multiforme	1			1					
Medulloblastoma	2	1		1					
Metastatic lesion	6	1		1			3	1	
Sum	15	4		7			3	1	

Tumor = neoplasm in brain, but pathology is unclear; Occ. = occupying lesion in brain, but pathogeny is unclear; Gli. = glioma; Ast. = astrocytoma; Oli. = oligodendroglioma; Met. = metastatic tumor; Abs. = abscess; Men. = meningioma.

these tumors cannot be differentiated or separated from normal brain tissue and cannot be removed completely by surgery or irradiation. Necrosis and edema occur concurrently after surgery or irradiation. It is very important, but difficult, to distinguish residual or recurrent tumor from surgical changes, necrosis, inflammation, and edema. ^{201}Tl brain imaging was shown in a large series by Kaplan et al. (*7*) to be better correlated with residual high-grade glioma tissue than was CT scanning or imaging with other radionuclide agents such as ^{99m}Tc-glucoheptonate or ^{67}Ga. In this study, 9 of the12 patients who had further ^{201}Tl imaging after surgery showed residual tumor, and this imaging technique can detect residual or recurrent tumor earlier than can CT. Holman and Devous (*13*) and Carvalho et al. (*14*) suggested that ^{201}Tl brain imaging, when applied with brain blood-flow perfusion SPECT imaging, can increase the sensitivity and specificity to detect and distinguish tumor recurrence.

CONCLUSION

This study indicates that ^{201}Tl is an excellent tracer for brain tumor imaging. Early and delayed ^{201}Tl brain imaging can be used not only for detection and localization of brain tumors but also for preoperative prediction of the grades of gliomas, distinguishing benign from malignant tumors, and differentiating high-grade from low-grade malignant brain tumors. This imaging technique can also be used to determine whether there is residual or recurrent tumor in treated patients and may accurately assess response to therapy.

On the basis of the results of this study, we recommend that early and delayed ^{201}Tl SPECT brain imaging be combined for diagnosis and staging of brain tumors. Determination of the ^{201}Tl retained index is an ideal method for distinguishing the histologic grade of brain tumors. Using this method of semiquantitative analysis, a high-grade or metastatic tumor could be considered if the ^{201}Tl retained index > 1.14, and a low-grade or benign tumor could be considered if the ^{201}Tl retained index < 1.10.

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REFERENCES

1. Tonami N, Hisada K. Clinical experience of tumor imaging with 201-Tl-chloride. *Clin Nucl Med.* 1977;2:75–81.
2. Ancri D, Basset JY, Lonchampt MF, et al. Diagnosis of cerebral lesions by thallium 201. *Radiology.* 1978;128:417–422.
3. Sun D. *Radionuclide Brain Imaging* [in Chinese]. Hangzhou, China: Hangzhou University Publishing House; 1998:262–287.
4. Kim KT, Black KL, Marciano D, et al. Thallium-201 SPECT imaging of brain tumors: methods and results. *J Nucl Med.* 1990;31:965–969.
5. Kernohan JW, Mabon RF, Svien HJ, et al. A simplified classification of the gliomas. *Mayo Clin Proc.* 1949;24:71–75.
6. Ancri D, Basset JY. Diagnosis of cerebral metastases by thallium 201. *Br J Radiol.* 1980;53:443–453.
7. Kaplan WD, Takvorian T, Morris JH, et al. Thallium-201 brain tumor imaging: a comparative study with pathologic correlation. *J Nucl Med.* 1987;28:47–52.
8. Black KL, Hawkins RA, Kim KT, et al. Use of thallium-201 SPECT to quantitate malignancy grade of gliomas. *J Neurosurg.* 1989;71:342–346.
9. Sjoholm H, Elmqvist D, Rehncrona S, et al. SPECT imaging of gliomas with thallium-201 and technetium-99m HMPAO. *Acta Neurol Scand.* 1995;91:66–70.
10. Oriuchi N, Tanura M, Shibazaki T, et al. Clinical evaluation of thallium-201 SPECT in supratentorial gliomas: relationship to histologic grade, prognosis and proliferative activities. *J Nucl Med.* 1993;34:2085–2089.
11. Jinnouchi S, Hoshi H, Ohnishi T, et al. Thallium-201 SPECT for predicting histological types of meningiomas. *J Nucl Med.* 1993;34:2091–2094.
12. Yoshi Y, Saton M, Tetsuya Y, et al. The role of thallium-201 single photon tomography in the investigation and characterization of brain tumor in man: their response to treatment. *Eur J Nucl Med.* 1993;20:39–45.
13. Holman BL, Devous MD. Functional brain SPECT: the emergence of a powerful clinical method. *J Nucl Med.* 1992;33:1888–1904.
14. Carvalho PA, Schwartz RB, Alexander E III, et al. Extracranial metastatic glioblastoma: appearance on thallium-201-chloride/technetium-99m-HMPAO SPECT imaging. *J Nucl Med.* 1991;32:322–324.