Clinical Evaluation of Thallium-201 SPECT in Supratentorial Gliomas: Relationship to Histologic Grade, Prognosis and Proliferative Activities

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We performed ^{201}Tl SPECT and cell kinetic studies on 28 presurgical patients with supratentorial gliomas by administering bromodeoxyuridine (BUdR). All patients had surgery and had follow-up for more than 25 mo. In patients with grade IV glioma (198.1% ± 32.8%, n = 10), the ^{201}Tl index, expressed as the count rate of the tumor site to the count rate over the contralateral normal region, was significantly higher than that in patients with grade III glioma (140.5% ± 15.1%, n = 4, $p < 0.01$) or low-grade glioma (104.1% ± 22.6%, n = 14, $p < 0.001$). A significant correlation was observed between the ^{201}Tl index and BUdR-positive cells in excised tumor specimens ($r = 0.67$, $p < 0.001$). The ^{201}Tl index of the 12 patients who died was higher than those who survived (173.2% versus 122.4%, $p < 0.01$). These results show the clinical utility of ^{201}Tl brain SPECT in imaging supratentorial glioma and that the ^{201}Tl index is representative of proliferative activity of the tumor.

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Several imaging modalities have been used to predict histopathological diagnosis, grading and prognosis of glioma and other brain tumors. Contrast enhancement studies in CT and MRI are widely employed for these purposes, but they, as well as radionuclide scintigraphy with ^{99m}Tc-pertechnetate, depend mainly on the disruption of the blood-brain barrier in the tumor (*1–5*). Although PET studies have also been reported to evaluate malignant lesions by measuring increased regional glucose metabolism or amino acid uptake (*6–10*), they are expensive and available in only a few centers.

Radiothallium (^{201}Tl) is one of the most widely employed radiopharmaceuticals, not only for myocardial imaging but also for imaging tumors of the thyroid, lung and soft tissues (*11–14*). Some authors have reported the usefulness of ^{201}Tl for localizing brain tumors, distinguishing high-grade malignancy from benign or low-grade malignancy (*15–19*) and estimating the extent of residual tumor or recurrence (*17*).

In order to elucidate the clinical usefulness of ^{201}Tl brain SPECT in patients with supratentorial gliomas, we performed ^{201}Tl brain SPECT on 28 presurgical patients and measured the proliferative activities of neoplastic tissues using bromodeoxyuridine (BUdR), a thymidine analogue, which is specifically incorporated into the DNA synthetic phase (S-phase) of the cell cycle (*20–23*). Patients were followed up for more than 25 mo after surgery.

MATERIALS AND METHODS

Patients

Thallium-201 SPECT studies were performed on 28 patients (mean age 45.6 yr) with supratentorial gliomas prior to surgical resection (Table 1). Tumor sizes ranged from 3 to 9 cm. Histological diagnosis was confirmed by examining neoplastic tissues according to the Kernohan (*24*) classification. Histological diagnosis was as follows: 1 patient with oligodendroglioma, 13 patients with grade II astrocytoma, 4 patients with grade III astrocytoma and 10 patients with grade IV astrocytoma. Oligodendroglioma and grade II astrocytoma were grouped together as low-grade gliomas.

Technique

Thallium-201 SPECT. SPECT imaging was initiated 15 min after intravenous injection of 111 MBq (3 mCi) of ^{201}Tl (Nihon Medi-Physics Co., Ltd., Nishinomiya, Japan). A SPECT instrument (Shimadzu Corp., Kyoto, Japan) equipped with three arrays of ring-type detectors was used and 0.7 to 1×10^6 counts per slice on 64 × 64 matrix were acquired with a 20% symmetric window at 74 keV. Butterworth and Ramachandran filters were used to reconstruct images in the transverse plane. Each image was corrected for tissue attenuation with the standard method using ^{201}Tl in a phantom. In-plane spatial resolution was 11 mm (FWHM).

Regions of interest (ROIs) were drawn around the site of the greatest activity of ^{201}Tl in the tumor. If the lesion showed no ^{201}Tl uptake, CT or MRI was used to determine the appropriate ROI. A homologous ROI was drawn over the contralateral analogous normal brain region. The ^{201}Tl index was defined as the ratio of

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TABLE 1

Summary of 28 cases with supratentorial gliomas

Patient No.	Age (yrs)	Sex	Histologic grade	Tumor location	Size of tumor (mm)	Duration * (months)	CE on CT †	^{201}Tl uptake ‡	^{201}Tl index (%)	BUdR-LI (%)	Extent of resection	Prognosis § (months)
1	67	F	IV	r.temporal	35	1	+	++	258	9	subtotal	11
2	50	F		l.parietal	40	2	+	++	202	3	partial	11
3	53	F		l.frontal	45	1	+	++	172	8	subtotal	26
4	63	F		r.temporal	45	1	+	++	202	14	subtotal	15
5	20	M		r.lat.ventricle	60	4	+	++	203	6	partial	12
6	58	M		l.frontal	60	3	+	++	176	9	subtotal	10
7	24	M		r.temporal	40	5	+	++	141	11	subtotal	27
8	35	M		l.parietal	50	1	+	++	228	2	subtotal	>40
9	45	M		l.frontal	50	1	+	++	215	8	subtotal	17
10	56	M		l.parietal	60	4	+	++	220	6	partial	19
11	45	F	III	l.frontal	55	9	+	++	162	4	subtotal	38
12	53	M		r.temporal	30	4	+	++	146	5	subtotal	17
13	26	M		l.temp-occip.	40	2	+	+	122	2	subtotal	>34
14	49	M		l.frontal	50	1	+	+	132	3	subtotal	>33
15	37	M	I or II	r.frontal	30	3	±	-	91	<1	subtotal	>57
16	38	M		r.cerebellum	50	3	-	-	90	0	total	>56
17	22	F		l.frontal	40	5	±	-	77	<1	subtotal	>50
18	45	M		l.parietal	35	192	+	-	113	0	partial	>50
19	54	F		l.parietal	35	4	+	-	100	3	subtotal	30 ¶
20	40	F		l.frontal	40	1	+	-	101	0	subtotal	31 **
21	58	M		l.basal ggl.	40	120	±	-	89	<1	partial	>41
22	29	M		r.parieto-occip.	60	1	+	++	177	<1	subtotal	>35
23	24	F		l.frontal	60	5	-	-	95	0	subtotal	>34
24	12	M		l.temporal	24	22	+	+	120	<1	subtotal	>34
25	50	M		l.temporal	35	2	-	-	100	<1	partial	>32
26	33	M		r.frontal	30	2	+	-	96	<1	partial	>31
27	62	F		l.thalamus	35	4	+	-	106	2	partial	>29
28	54	M		l.frontal	25	140	-	-	102	0	extensive	>25

* Duration of symptoms from the onset

† Contrast enhancement on CT: + definite ± faint - none

‡ ^{201}Tl uptake: ++ intense + moderate - none

§ Prognosis : died after months from the SPECT

>: survived months from the SPECT

¶ recurrent glioblastoma 20 months after resection

** recurrent glioblastoma 18 months after resection

r; right l; left

average counts per pixel in the tumor ROI to the average counts per pixel in the contralateral normal ROI region. The interval from the SPECT study to tumor resection ranged from 1 to 37 days (average 8.4 ± 7.6 days).

CT examinations were performed on all patients using a General Electric CT/T OM B8800JD with intravenous contrast enhancement. Each slice was 10 mm thick.

Measurement of BUdR Labeling Index (BUdR-LI). Each patient received 200 mg/m^2 of BUdR (Sigma Chemical Co., London, UK) intravenously 1 hr before surgery (*22,23*). Tumor specimens obtained at surgery were fixed in chilled 70% ethanol, embedded in paraffin and cut into 6-μm thick slices. The section was deparaffinized with xylene and rinsed with ethanol and distilled water. Tissue sections were incubated for 30 min in methanol with 0.3% H_2O_2 to avoid nonspecific reaction of peroxydase in tissue. An immunohistochemical staining technique was used to detect BUdR-labeled cells (*21–23*). Tissue sections were denatured with 2N HCl, immersed in purified anti-BUdR monoclonal antibodies (Becton Dickinson, Mountain View, CA), and reacted with peroxydase-conjugated anti-mouse rabbit antibodies (Zymed, South San Francisco, CA). Finally, the slides were rinsed with phosphate-buffered saline and reacted with di-aminobenzidine tetrahydrochloride and H_2O_2 in Tris buffer for 10–15 min. These slides were lightly counterstained with eosin solution.

The labeling index of BUdR of each slide was defined as the percentage of BUdR-positive cells among 500 tumor cells in viable tissue that showed a homogeneous distribution of tumor cells on microscopic examination.

An unpaired Student's t-test was used for statistical analysis.

RESULTS

Thallium-201 accumulation in the lesion was evaluated by visual inspection and the ^{201}Tl index. The degree of ^{201}Tl uptake in the tumor correlated with the histological grade of gliomas. Twelve of the 14 patients (except Patients 22 and 24) with low-grade glioma showed no accumulation of ^{201}Tl at the tumor site, and ^{201}Tl indices were lower than 113%.

Patient 22, a 29-yr-old man with a contrast-enhancing mass in the right parieto-occipital subcortex on the CT scan, had a histological diagnosis of resected tissue that was pilocytic astrocytoma. Patient 24, a 12-yr-old boy with von Recklinghausen disease, had a ring-like enhancing mass lesion in the left temporal lobe. Their ^{201}Tl indices were 177% and 120%, respectively. BUdR-LI was also less than 3% in all 14 patients with low-grade glioma. Two patients (nos. 19 and 20), who were diagnosed with low-grade glioma during surgery, died at 30 and 31 mo follow-up, respectively.

Patient 19 is a 54-yr-old female with an enhancing mass in the left parietal lobe on CT. Thallium-201 SPECT showed no uptake of ^{201}Tl in the lesion and her BUdR-LI was 3%. Tumor recurrence, however, was confirmed by CT scan 20 mo after subtotal resection. A second ^{201}Tl SPECT scan demonstrated marked uptake of ^{201}Tl at the site of the recurrent tumor (^{201}Tl index = 201%).

Patient 20 is a 40-yr-old female with a low-grade glioma (Fig. 1). The initial ^{201}Tl SPECT scan (Fig. 1B) revealed a ^{201}Tl index of 101% and a BUdR-LI of 0%. A second ^{201}Tl SPECT scan (Fig. 1D) was obtained 19 mo after the operation and showed a ^{201}Tl index of 157%; glioblastoma was confirmed during the second operative procedure.

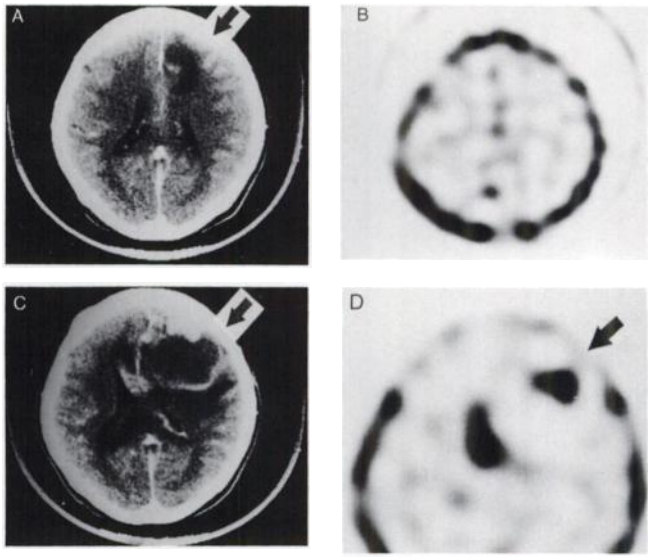

FIGURE 1. Patient 20, a 40-yr-old female with low-grade glioma. Contrast-enhanced CT scan demonstrates a low-density mass in the left frontal lobe (arrow) with enhancement in the medial portion (A). The SPECT image obtained 15 min after i.v. administration shows no accumulation in the lesion (B). Thallium-201 index, 101%; BUdR-LI, 0%. A contrast-enhanced CT scan (C) performed 19 mo after the first CT scan demonstrates a ring-like enhanced mass in the left frontal lobe with a central low-density area (arrow). Marked edema and mass effect are shown. Thallium-201 brain SPECT performed the next day (D) demonstrates markedly increased accumulation in the medial and anterolateral margin of the lesion (arrow). Thallium-201 index, 157%; BUdR-LI, 19%. Histological diagnosis was glioblastoma. The patient died 31 mo after the initial study.

In the four patients with grade III glioma, all showed a definite accumulation of ^{201}Tl at the lesion site and ^{201}Tl indices ranging from 122% to 162%. BUdR-LIs were 2%–5%. Two patients died 17 and 38 mo after surgery.

All ten patients with grade IV glioma showed intense accumulation in the tumor sites, with ^{201}Tl indices higher than 141% (mean 198.1% ± 32.8%, n = 10). BUdR-LIs ranged from 2% to 14%. Only one patient survived for 40 mo, dying 11–27 mo after surgery. Contrast-enhanced CT of the tumor was observed in all 14 patients with grades III and IV gliomas; these patients also had intense accumulation of ^{201}Tl at the tumor site. On the other hand, 7 of 14 patients with low-grade glioma showed contrast enhancement and only two showed significant ^{201}Tl uptake without a clearcut correlation between contrast-enhanced CT and the ^{201}Tl index.

A clear correlation was seen between the ^{201}Tl index and BUdR-LI (Fig. 2). Both ^{201}Tl index and BUdR-LI correlated with the histological grade of the glioma. The ^{201}Tl index (198.1% ± 32.8%, n = 10) and the BUdR-LI (7.6% ± 3.4%, n = 10) in patients with grade IV glioma were significantly higher than those of low-grade glioma patients

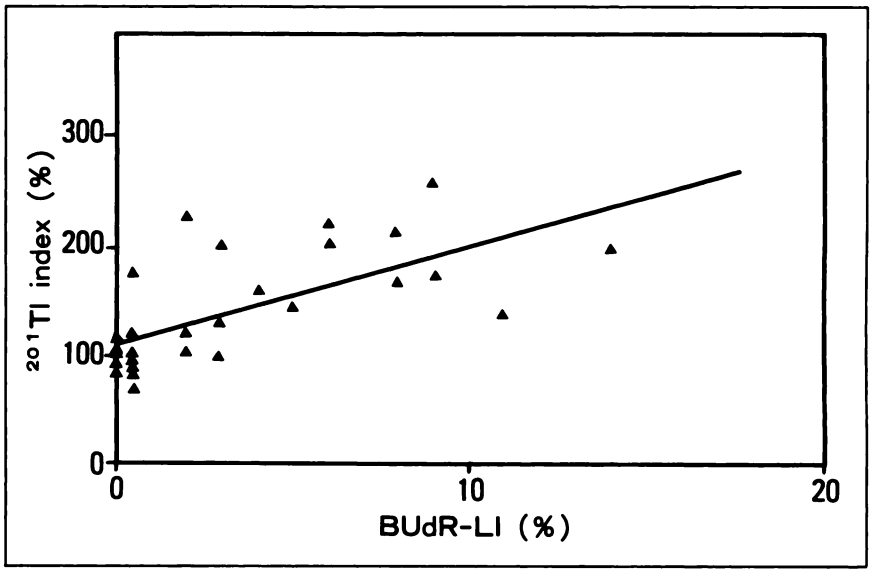

FIGURE 2. Correlation between the ^{201}Tl index and the BUdR-LI in patients with glioma. Significant correlation was observed ($n = 28$, $r = 0.67$, $p < 0.001$).

(104.1% ± 22.6%, 0.61% ± 0.83% respectively, n = 14, $p < 0.001$).

The mean ^{201}Tl index and BUdR-LI in patients who died after surgery were significantly higher than those who survived 25 mo after surgery (Table 2).

The ^{201}Tl index was useful for predicting histological grade of the excised tumor and for estimating the prognosis of patients with supratentorial gliomas. There was a significant statistical difference between grade IV glioma and low-grade glioma in both the ^{201}Tl index and BUdR-LI, and a significant correlation was noted between ^{201}Tl index and BUdR-LI. BUdR-LI was able to predict the S-phase fraction of tumors after choosing a representative region of distribution of BUdR-positive cells even though the specimens contained necrotic cells or increased vascular components.

DISCUSSION

The extent of ^{201}Tl uptake in gliomas seems to reflect not only histological grade but also proliferative potential (*25,26*). Previous studies have reported the utility of ^{201}Tl SPECT in distinguishing low-grade from high-grade gliomas (*17*). Our study clearly demonstrates ^{201}Tl SPECT's ability to predict the prognosis of patients with gliomas. The ^{201}Tl indices in patients who died within 38 mo of surgery were significantly higher than those in patients who survived 25 mo after surgery. Two (14%) of 14 patients with low-grade glioma died 30 and 31 mo after surgery. In patients with recurring tumors, a second ^{201}Tl SPECT study demonstrated markedly increased uptake of ^{201}Tl in the area of the lesion. In four patients with grade III glioma, two had relatively high ^{201}Tl indices and poor outcomes.

Viable appearing tumor cells are not always distributed homogeneously in neoplastic tissue. SPECT's spatial resolution is so limited that the ^{201}Tl index may be affected by the histological heterogeneity of neoplastic tissue, resulting in an underestimation of tumor grade. It should be noted, however, that ^{201}Tl uptake by brain tumors does not always correlate with the tumor's histological grade nor with clinical outcome. Ancri et al. reported that ^{201}Tl uptake was visualized in patients with meningiomas and cerebral infarctions (*15*). For example, in the present study, we presented Patient 22 who had a low-grade glioma. His ^{201}Tl index was 177% and his BUdR-LI was less than 1%, but his prognosis was good. No clear-cut correlation was observed between ^{201}Tl uptake and the degree of contrast enhancement of the tumor on CT. Indeed the exact mechanism of ^{201}Tl uptake in brain tumors remains to be elucidated.

In conclusion, ^{201}Tl brain SPECT reveals apparently viable, malignant neoplastic tissues and noninvasively predicts the degree of the tumor fairly well. Thallium-201 SPECT also predicts patient prognosis by quantifying the ^{201}Tl uptake ratio. Evaluation of residual neoplastic tissues and early detection of recurrence or malignant transformation with ^{201}Tl SPECT are useful in the management of patients with supratentorial gliomas.

TABLE 2
Comparison of ^{201}Tl index and BUdR-LI in Patients with Glioma Who Died or Were Living During the 25-Month Follow-up

Patients	^{201}Tl index	BUdR-LI
Dead (n = 12)	173.2 ± 44.7	6.7 ± 3.7
Living (n = 16)	122.4 ± 44.5*	1.2 ± 1.5†

*$p < 0.01$.
†$p < 0.001$.

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EDITORIAL

Thallium-201 SPECT in the Evaluation of Gliomas

There is a growing body of literature which suggests that ^{201}Tl is useful in evaluating cerebral tumors (*1–5*).

Kaplan et al. reported that ^{201}Tl planar brain scans correlated better with residual glioma tissue than CT, ^{99m}Tc-gluconate or ^{67}Ga scans in 29 patients with grade 3 and 4 gliomas, thus proving that ^{201}Tl scanning is an indicator for viable tumor burden (*3*). Mountz et al. developed a method to quantify ^{201}Tl uptake in high-grade astrocytomas by assessing the tumor-to-cardiac uptake ratio and concluded that this uptake ratio, when tested serially, could provide an accurate estimate of residual viable tumor burden or recurrence during or after therapy.

Black and Kim et al. utilized ^{201}Tl SPECT to obtain a semiquantitative ^{201}Tl uptake index of brain tumor counts normalized to homologous contralateral hemisphere activity. They showed that this ^{201}Tl index was useful in separating high-grade from low-grade gliomas. This technique can reduce unrecognized sampling errors during needle biopsies of high-grade tumors misdiagnosed as low-grade tumors due to inadequate biopsy materials (*4,5*). It is essential to accurately define glioma grade since the survival of patients with grades 3 and 4 is considerably shorter than that of patients with low-grade glioma.

PET with ^{18}F-fluorodeoxyglucose or [^{11}C]methyl-L-methionine has been shown to correlate with glioma grade and therefore predict patient survival (*6–8*). However, PET is expensive and not widely available. With the exception of PET studies, other imaging modalities such as CT and MRI are not very reliable in distinguishing high-grade from low-grade gliomas.

In this issue of the *Journal*, Oriuchi et al. report on ^{201}Tl brain SPECT imaging in patients with supratentorial gliomas. The authors correlate the imaging findings with proliferative activity of the tumors and prognosis (*9*). This group obtained a semiquantitative ^{201}Tl index of the tumor to normal brain tissue and in 28 presurgical patients observed a significant correlation between the ^{201}Tl index and bromodeoxyuridine (BUdR)-positive cells in excised tumor specimens ($r = 0.67$, $p < 0.001$) after administering BUdR. This method seems to be effective in evaluating tumor cell proliferation and therefore can aid in select-

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