

Reassessment of quantitative thallium-201 brain SPECT for miscellaneous brain tumors

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In order to reassess the value of quantitative thallium-201 brain SPECT in the differentiation of miscellaneous brain tumors, we studied a total of 89 patients—35 pre-operative patients suspected of having a brain tumor and 54 post-operative patients with a brain tumor. We came to the conclusion that quantitative Tl-201 brain SPECT was very useful in discriminating cerebral radiation necrosis from recurrent tumor, estimating residual tumor burden, and detecting tumor regrowth earlier in postoperative patients. In preoperative patients, however, Tl-201 SPECT cannot be used effectively to differentiate glioma from other intracranial tumors, although intense uptake of Tl-201 may provide evidence of glioblastoma or a hypervascular lesion.

Key words: ^{201}Tl -chloride, brain tumor, cerebral necrosis, radiotherapy, brain SPECT

INTRODUCTION

THE DIFFERENTIATION of cerebral necrosis after radiotherapy from recurrent glioma is a clinically challenging problem. Although magnetic resonance imaging (MRI) and computed tomography (CT) are excellent anatomic imaging methods for detecting mass lesions, both have limitations in discriminating between cerebral radiation necrosis and recurrent glioma,¹⁻⁵ as well as in the grading of glioma.⁶ Positron emission tomography (PET) studies with fluorine-18-fluorodeoxyglucose (^{18}F -FDG) and carbon-11-methionine have been shown to assist in discriminating between cerebral radiation necrosis and tumor recurrence, but the limited availability and high cost of performing PET studies restrict clinical application.⁷⁻⁹

It has been reported that thallium-201 (^{201}Tl) is preferentially taken up by high-grade astrocytoma, but little or none is taken up by low-grade astro-

cytoma or cerebral necrosis.¹⁰⁻¹⁵ Quantitative ^{201}Tl single photon emission tomography (SPECT) may play a role in differentiating cerebral necrosis from tumor recurrence. However, the value of ^{201}Tl SPECT remains uncertain and several questions are unanswered in the clinical setting. Firstly, a preliminary comparative study with ^{201}Tl and ^{18}F -FDG has suggested a disparity in the detection of recurrent glioma and the differentiation between cerebral necrosis and recurrence.¹⁶ Secondly, few series of ^{201}Tl SPECT studies have been published containing sufficient numbers of cases to prove the value of ^{201}Tl SPECT. Thirdly, it remains to be seen whether ^{201}Tl SPECT will be of value in the preoperative differentiation of glioma from other miscellaneous brain tumors.

The purpose of this study is to reassess the value of ^{201}Tl SPECT in differentiating between glioma and other malignant or benign lesions before operation and between cerebral radiation necrosis and recurrence of brain tumor in follow-up.

MATERIALS AND METHODS

A total of 89 patients—35 preoperative patients with suspected brain tumor and 54 postoperative

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patients with confirmed brain tumor—underwent ^{201}Tl SPECT in order to assess preoperative findings, postoperative findings, and the implication of delayed imaging. These 89 patients were 48 males and 41 females, with an age range of 14 to 80 years (mean age, 56 years). The disease classification is shown in Table 1. Histological confirmation was available in all brain tumors. Recurrent brain tumors in 26 patients and cerebral radiation necrosis in 6 patients were all confirmed by re-operation. The 20 patients with recurrent glioma were histologically classified as having glioblastoma (10), astrocytoma Grade III (9) and gemistocytic astrocytoma (1). Sixteen patients treated with trimodal therapy, consisting of surgery, radiotherapy and chemotherapy, had no evidence of residual tumors on concomitantly available CT and/or MRI with contrast medium. Among these 16, nine had histological glioblastomas, three anaplastic astrocytomas, two gemistocytic astrocytomas, one oligodendroglioma, and one Grade II astrocytoma. Seven patients died, 6 of recurrent tumor at an average of 19 months after the ^{201}Tl study, and one of pneumonia at 2 months after the ^{201}Tl study. Four patients are alive as of this writing, but one of these 4 developed recurrence at 39 months after the ^{201}Tl study. Three patients were lost to follow-up and 2 patients were transferred to other hospitals.

Non-neoplastic diseases, including cerebrovascular disease, abscess, encephalitis, and arteriovenous malformation (AVM), were diagnosed from the clinical course and by imaging procedures, such as CT, MRI, and angiography. All but one of the 54 patients in the postoperative group had a follow-up of at least one year after the initial ^{201}Tl SPECT study in order to assess prognosis.

All of the 89 patients had early SPECT images taken 10 minutes after iv injection of 111 MBq

(3 mCi) of ^{201}Tl . Of these, 16 patients also had delayed SPECT images taken 4 hours after the injection. All images were acquired over 32 minutes with continuous rotation over 360° , by means of a dual head rotation camera (Toshiba 90A E1) with 20 mm spatial resolution in FWHM. We used a 10% symmetrical window at 71 KeV. Each reconstructed slice was two pixels thick (10.6 mm). A 64×64 matrix with a Butterworth filter and filtered back projection by means of Chesler's algorithm were used to reconstruct images in the transverse plane. A uniformity correction matrix and a center of rotation correction were applied to each image. Neither tissue attenuation correction nor scatter subtraction was processed.

An operator-defined, rectangular region of interest (ROI) was drawn over a lesion on the slice showing the greatest activity. In creating a rectangular ROI, we tried to make a larger ROI in order to cover an entire lesion. Similarly, a ROI over the contralateral, presumably healthy, brain was created by performing a horizontal flip of the initially defined ROI. But a ROI was created in the normal area adjacent to a lesion when the lesion was located on the midline. Count ratios of a lesion to the normal brain (L/N) were calculated from the rectangular ROI for the quantitative analysis. Furthermore, count ratios of the lesion seen on the delayed image to that seen on the early image (D/E) were calculated. Ten postoperative patients with brain tumor underwent follow-up ^{201}Tl imaging to monitor tumor recurrence.

RESULTS

1. Preoperative assessment

Grading of gliomas: Three patients with glioblas-

Table 1 Patient population

Pre-operation group		Post-operation group	
Glioma	11	Recurrent tumor	26
Metastasis	8	{ Glioma 20 { Metastasis 6	
Meningioma	2		
Hemangioblastoma	1	Radiation necrosis	6
Cavernous angioma	1	Residual tumor after operation	6
Malig. lymphoma	1	Status during or after treatment	16
Liposarcoma	1	(No evidence of recurrence at the time of ^{201}Tl study)	
Epidermoid cyst	1		
C V D	6		54
Abscess	1		
Encephalitis	1		
A V M	1		
	35		

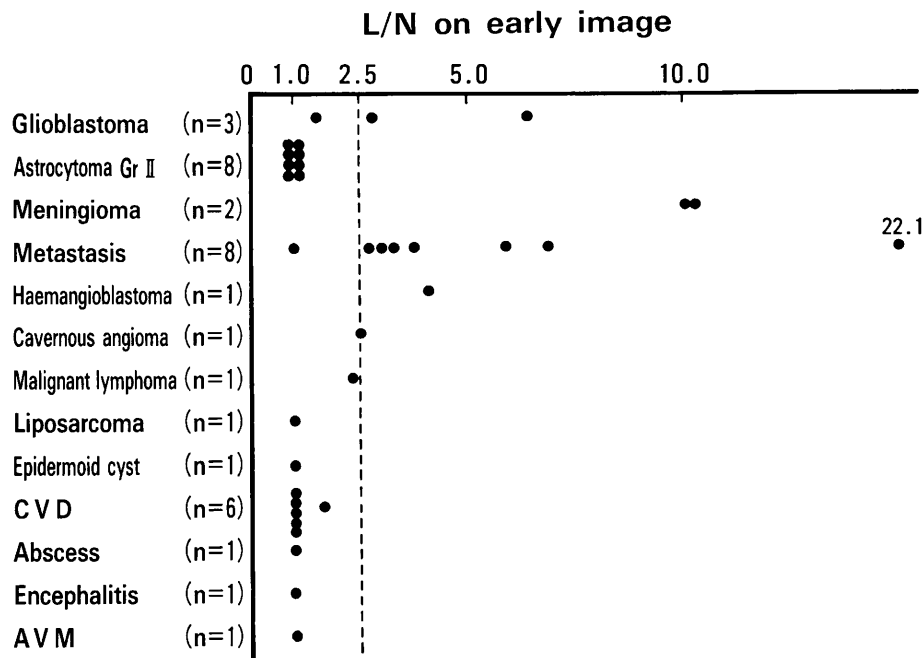


Fig. 1 The values of thallium-201 index (L/N) on early images in patients with intracranial disease.

toma had L/N ratios of 1.6, 2.8, and 6.4, respectively. In 8 patients with Grade II astrocytoma, on the other hand, there was a subtle uptake to no uptake of ^{201}Tl , making it impossible to create a ROI over the lesions. The ratio in these individuals was rated at 1.0 (Fig. 1).

Differentiation between glioma and other miscellaneous tumors: In 2/2 patients with meningioma and 7/8 (87.5%) with cerebral metastasis, L/N ratios were greater than 2.5. This was in contrast to the 2.5 or less in all patients with non-neoplastic diseases. The L/N ratio was 22.1 for hypervascular metastasis from thyroid cancer, 3.96 for hemangioblastoma, 2.51 for cavernous angioma, and 2.29 for malignant lymphoma.

2. Postoperative assessment

Differentiation between radiation necrosis and tumor recurrence: In 32 patients with recurrent or residual tumor, L/N ratios ranged from 1.7 to 12.6, with a mean of 4.15 ± 2.18 on early images. All but one of the patients had L/N ratios greater than 2.5. Pathological diagnoses were glioblastoma (n=14), anaplastic astrocytoma (n=10), malignant meningioma (n=2), and cerebral metastases including adenocarcinoma (n=3), squamous cell carcinoma (n=1), renal cell carcinoma (n=1), and seminoma (n=1).

In 6 patients with cerebral radiation necrosis, however, L/N ratios were always 2.5 or less on early

images, with a mean of 2.06 ± 0.25 ($p < 0.001$) (Fig. 2). These results confirmed the validity of ^{201}Tl brain SPECT in differentiating cerebral radiation necrosis from tumor recurrence.

Differentiation between residual tumor and post-therapy cerebral changes: All of the 6 patients with residual tumor after operation had L/N ratios of greater than 2.5, with a mean of 5.04 ± 1.46 . All but one the 16 patients who had no evidence of residual tumor after having undergone combined treatment with surgical debulking, radiotherapy and chemotherapy had an L/N ratio of 2.5 or less, with a mean of 1.51 ± 0.58 ($p < 0.001$) (Fig. 3). Among these 16 patients, eight had visibly increased uptake on early images.

Follow-up studies in post-operative patients with brain tumor: In follow-up ^{201}Tl SPECT studies of 10 post-operative patients, an L/N ratio greater than 2.5, as calculated on early images, correlated with either a residual or a recurrent tumor, but an L/N ratio of 2.5 or less is associated with an absence of residual tumor (Fig. 4). In two patients with recurrent tumor, the L/N ratio decreased to 2.5 or less after treatment; one of these 2 had pathologically proven cerebral radiation necrosis before developing tumor recurrence. A 28-year-old male patient with gemistocytic astrocytoma in whom the L/N ratio increased from 1.0 to 2.4 after treatment, as shown in Fig. 4, is still alive at 4 years after the ^{201}Tl study.

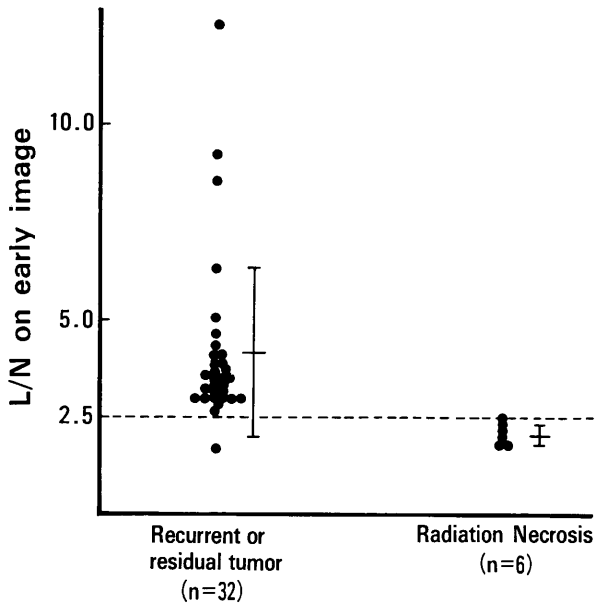


Fig. 2 The values of thallium-201 index (L/N) on early images in patients with recurrent or residual tumor and patients with cerebral radiation necrosis.

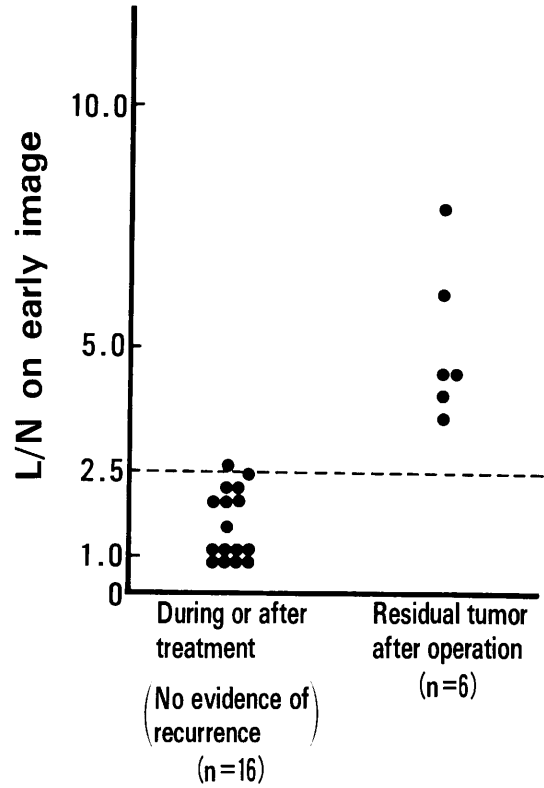


Fig. 3 The values of thallium-201 index (L/N) on early images in patients without evidence of tumor recurrence during or after treatment and patients with residual tumor after operation.

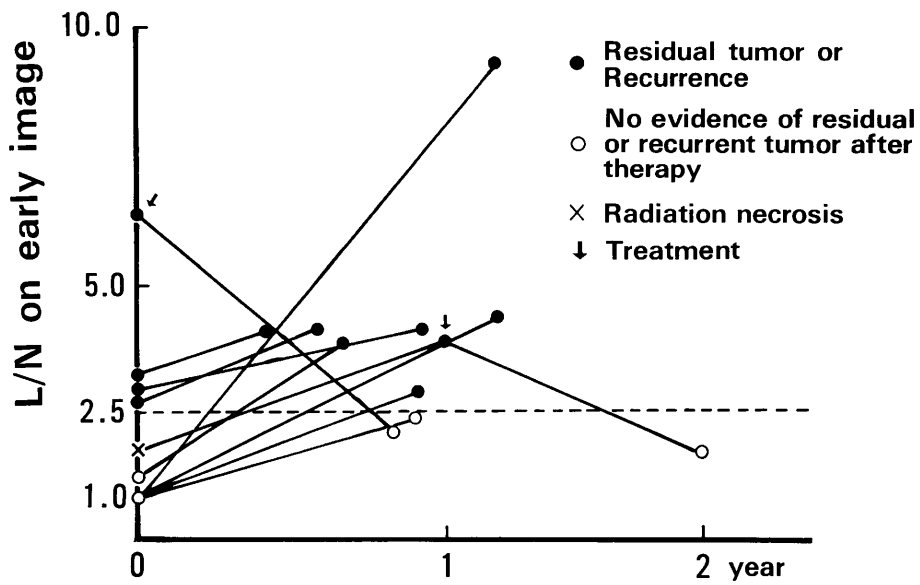


Fig. 4 Relationship of changes in thallium-201 index (L/N) on early images as a function of therapy and outcome.

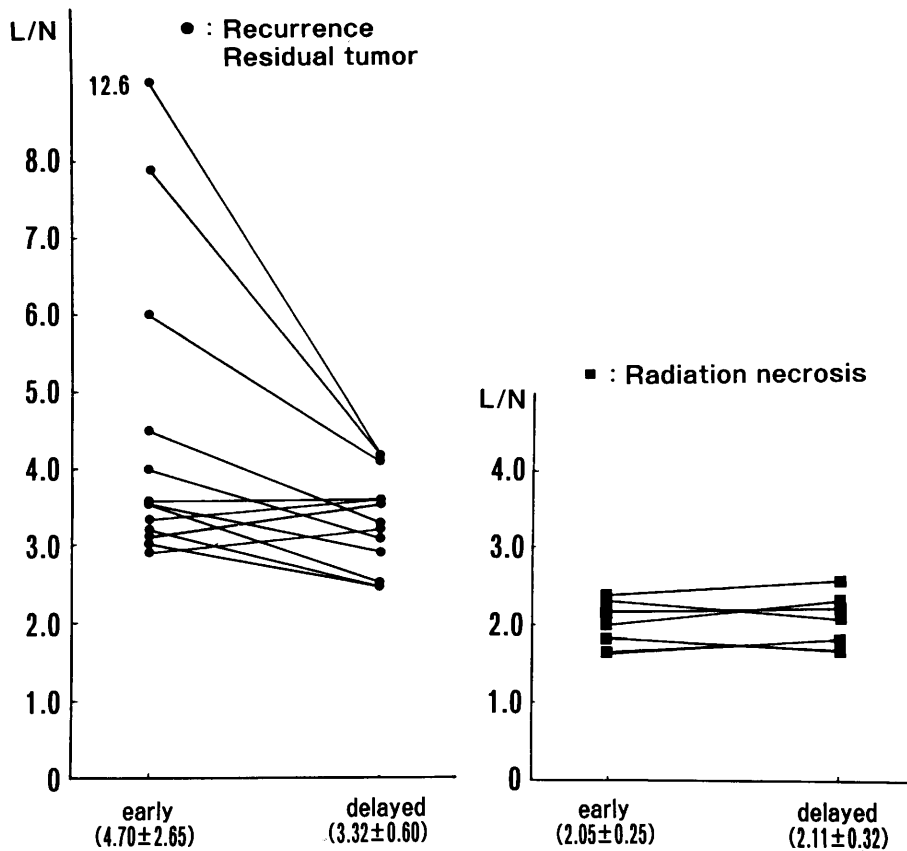


Fig. 5 Changes of the values of thallium-201 index (L/N) on early and delayed images.

3. Implication of delayed images

Of 13 patients with residual or recurrent tumor, L/N ratios on the delayed images were less in 9 patients (69%) and slightly greater in the remaining 4 patients (13%). The three patients with marked washout of ^{201}Tl had recurrent glioblastoma (Fig. 5). In a group of patients with cerebral radiation necrosis, there were little differences between the L/N ratios for early and delayed images (Fig. 5). Mean D/E ratios were 1.17 ± 0.20 for both tumor recurrence and residual tumor, and 1.17 ± 0.08 for cerebral radiation necrosis. For healthy brain parenchyma ($n=89$), it was 1.32 ± 0.25 .

DISCUSSION

The prognosis of high-grade glioma remains poor, in spite of recent advances in combined method treatment. High dose radiotherapy is an integral part of the treatment because of the limited ability to achieve total surgical resection of the lesion. However, there is evidence to show that cerebral radiation necrosis is a frequent event in patients with high dose radiotherapy. The majority of radiation necrosis cases were depicted on initial CT scans as central low density areas with irregular peripheral enhancement

and as an increase in size with peripheral hypodense areas on follow-up scans. It is well known that cerebral necrosis and recurrent brain tumor are essentially indistinguishable by CT, MRI, and clinical findings.¹⁻⁵

^{201}Tl SPECT is known to be useful in differentiating radiation necrosis from recurrent primary brain tumor. It has also been shown that ^{201}Tl is preferentially taken up by viable tumor cells but not by necrotic tissues,¹¹ and that it may be subtly taken up by cerebrovascular disease.^{10,13} Black et al.¹² reported that ^{18}F -FDG PET and ^{201}Tl scans closely correlated with each other in a group of patients with brain tumor, although the number of patients in their series was too small for definitive conclusions to be drawn. On the other hand, McKusick et al.¹⁶ reported in a preliminary series that ^{201}Tl imaging was inferior to ^{18}F -FDG PET imaging for the detection of recurrent primary brain tumor.

Our quantitative ^{201}Tl brain SPECT study in a large number of patients revealed that the ^{201}Tl uptake index (L/N ratio) is useful in discriminating cerebral radiation necrosis from recurrent tumor. In addition, ^{201}Tl was found to be taken up by residual tumor, a finding in agreement with those of

earlier studies, confirming the validity of quantitative ^{201}Tl brain SPECT in the postoperative patient population with cerebral tumor. There were differences between L/N ratios in residual tumor and post-therapy changes, making it possible to differentiate between them. The results of follow-up studies in postoperative patients indicated that ^{201}Tl brain SPECT could be a useful means of detecting tumor regrowth soon after operation, because CT, MRI and angiography have limited ability to differentiate recurrence from necrosis though they can detect mass lesions.

Whether or not ^{201}Tl SPECT is capable of detecting smaller lesions is unclear. However, our experience indicated that it can detect greater than 2 cm in diameter, even if deep seated. L/N ratios and baseline L/N ratio of 2.5 would change to some degree according to the SPECT equipment, filtered back projection algorithm, and precorrection method. Routine use of attenuation correction, although not used in our series, may improve the quantitative assessment of brain tumors.

In our series, one patient whose ^{201}Tl SPECT changed from negative to positive had tumor recurrence in an area pathologically proven to be necrotic. In such a case we suspect that the recurrence may have originated in a few remaining viable tumor cells that studded the necrotic tissue.

Quantitative ^{201}Tl brain SPECT was not always capable of differentiating glioma from other intracranial tumors, although low grade astrocytoma and non-malignant lesions including cerebrovascular disease showed little or no tracer uptake. This was in contrast to high ^{201}Tl uptake in glioblastoma. ^{201}Tl brain SPECT cannot therefore be used effectively to distinguish glioma from other brain tumors in preoperative patients. Lesions with high ^{201}Tl uptake may reflect glioblastoma or hypervascular tumors, such as meningioma, hemangioblastoma and metastasis from thyroid cancer. But lesion with no ^{201}Tl uptake may reflect low-grade glioma, or non-malignant lesions including cerebrovascular disease, AVM and encephalitis. ^{201}Tl SPECT may be helpful in the histological differentiation of gliomas because glioblastoma is highly suspected when there is visible ^{201}Tl uptake, although there were no preoperative patients with anaplastic astrocytoma or oligodendroglioma in our series.

Mountz et al.¹³ showed from their microautoradiographic experiment that the mechanism of ^{201}Tl sequestration by high-grade glioma is due to its preferential uptake into tumor cells. Preferential tracer uptake involved in the mechanism may reflect an increase in the sodium potassium adenosine triphosphatase (Na^+/K^+ -ATPase) action on viable tumor cell membrane.¹⁷ This could in part explain

the absence of abnormal ^{201}Tl accumulation in high-grade glioma treated with radiation and/or chemotherapy due to decreased or destroyed cell membrane active transport. On the other hand, both the extent of normal or neovascular blood flow and the integrity of the blood brain barrier appear to be important factors in ^{201}Tl uptake since the majority of tumors with avid tracer uptake on the early images were hypervascular as assessed by CT/MRI or angiography. Minimal uptake of ^{201}Tl by cerebral necrosis is probably related to destruction of the blood brain barrier; necrotic tissue has neither vascularity nor an intact mechanism of the Na^+/K^+ -ATPase pump. Conversion from a high to a low ^{201}Tl index between early and delayed images may be dependent in part on the ^{201}Tl washout rate which is also a function of regional blood flow in the lesion; this is the basis for redistribution in ^{201}Tl myocardial scintigraphy.

The present reassessment of quantitative ^{201}Tl brain SPECT provides support for its use in differentiating cerebral necrosis from recurrent tumor estimating residual tumor burden soon after tumor-ectomy, and detecting tumor regrowth earlier in the postoperative patient, since findings in both CT and MRI are usually nonspecific. In preoperative patients, however, quantitative ^{201}Tl brain SPECT cannot be used to distinguish glioma from other brain tumors.

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