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Combined ^{201}Tl and ^{67}Ga brain SPECT in patients with suspected central nervous system lymphoma or germinoma: Clinical and economic value

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Background: Surgical resection is costly and an unfavorable prognostic factor for primary central nervous system (CNS) lymphoma and germinoma patients. ***Objective:*** To assess the diagnostic and economic impact of combined ^{201}Tl and ^{67}Ga brain SPECT on the management of patients suspected of having CNS lymphoma or germinoma. ***Methods:*** Sequential ^{201}Tl and ^{67}Ga brain SPECT was performed in 40 patients with cranial tumors to assess the diagnostic and economic impact of combined ^{201}Tl and ^{67}Ga SPECT on the management of patients suspected of having CNS lymphoma or germinoma. All intracranial masses were pathologically confirmed. The final diagnoses of a total of 47 foci were: 11 non-Hodgkin's lymphomas in 10 patients, 3 germinomas in 2 patients, 10 glioblastomas in 9 patients, 10 cerebral metastases in 8 patients, 13 meningiomas in 11 patients. Decision-tree sensitivity analysis for pretest probability regarding expected cost saving was performed for introduction of the combined study. ***Results:*** All but one focus of CNS lymphomas or germinomas (92.9%, 13/14) exhibited more intense uptake of ^{67}Ga than of ^{201}Tl ($p < 0.001$). All foci of glioblastomas (10/10) and meningiomas (13/13), and 60% of metastatic foci (6/10) exhibited higher uptake of ^{201}Tl than of ^{67}Ga ($p < 0.035$). Expected cost saving in the 1% to 50% range of pretest probability of CNS lymphoma or germinoma would be from minus $842US to plus $2,047US per patient for introduction of the combined study, because of substitution of stereotactic biopsy for craniotomy. The pretest probability was the key factor for cost saving of the combined study. ***Conclusions:*** A ^{67}Ga-positive and ^{201}Tl-positive pattern with more intense uptake of ^{67}Ga than ^{201}Tl probably suggests CNS lymphoma or germinoma. This combination study appears to be cost-effective only in patients highly suspected of having CNS lymphoma or germinoma.

Key words: brain neoplasms, cost-benefit, brain SPECT, ^{67}Ga citrate, ^{201}Tl chloride

MORPHOLOGICAL EVALUATION by computed tomography (CT) and magnetic resonance imaging (MRI) has been widely used to detect intracranial masses. In combination with clinical information, the predictive accuracy of tumor characterization by CT and/or MRI has been reported to be in the range of 85% to 90% in prospective studies by experienced investigators.[1] Despite the recent development of anatomical imaging modalities, it is still difficult to accurately evaluate and differentiate intracranial masses. Some investigators have reported that functional nuclear medicine imaging, such as single-photon emission tomography (SPECT)[2–8] and positron emission tomography (PET),[9–16] have a potential for more accurate evaluation of cerebral glioma than CT and MRI. Even after a single SPECT or PET study, however, it might be difficult to speculate on or diagnose the histopathology of

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intracranial masses, even though they allow pathological grading of glioma and meningioma.[2–11,13–17]

We have published other papers on the usefulness of combined study of ^{201}Tl and ^{67}Ga brain SPECT in patients with primary central nervous system (CNS) lymphoma.[18,19] It allows differentiation of CNS lymphoma from other brain tumors and inflammatory lesions better than a single ^{201}Tl or ^{67}Ga brain SPECT study.

There have been several controversies concerning the optimal treatment of CNS lymphoma and intracranial germinoma.[20–24] Partial surgical resection is costly and an unfavorable prognostic factor for CNS lymphoma patients,[20] and an initial combined ^{201}Tl and ^{67}Ga brain SPECT study might prevent unnecessary craniotomies on CNS lymphoma patients if it could diagnose the disease in patients suspected of having CNS lymphoma. Germinoma is also a malignant primary neoplasm that can be cured by conventional radiation therapy alone or chemoradiation therapy. Thus, accurate and preoperative diagnoses of CNS lymphoma and germinoma are critical to eliminating unnecessary craniotomy in terms of cost-effectiveness.

The aim of our study was to assess the diagnostic and economic impact of combined ^{201}Tl and ^{67}Ga brain SPECT on the management of patients suspected of having CNS lymphoma or intracranial germinoma.

MATERIALS AND METHODS

Subjects: We examined 40 patients (a total of 47 foci, 15 males, 25 females) ranging in age from 13 to 81 years old (mean 55.3 years) who were found to have single or multiple intracranial, deeply situated masses suspected of being CNS lymphoma or intracranial germinoma, otherwise not eliminated on contrast-enhanced CT and/or MRI. All subjects gave their informed consent prior to their inclusion in the study. All patients underwent craniotomy or stereotactic biopsy after CT and/or MRI and combined ^{201}Tl and ^{67}Ga brain SPECT. All intracranial masses were pathologically confirmed. The final diagnoses of a total of 47 foci were: 10 B-cell and 1 T-cell non-Hodgkin's lymphoma in 10 patients, 3 germinomas in 2 patients, 10 glioblastomas in 9 patients, 6 adenocarcinomas, 3 squamous cell carcinomas, and 1 oat cell carcinoma in 8 patients with cerebral metastasis, and 6 transitional, 3 psammomatous, 3 atypical, and 1 meningothelial meningioma in 11 patients. Thus, gliobastoma, metastatic brain tumor, and meningioma were included as the diseases to be differentiated from primary CNS lymphoma or germinoma.

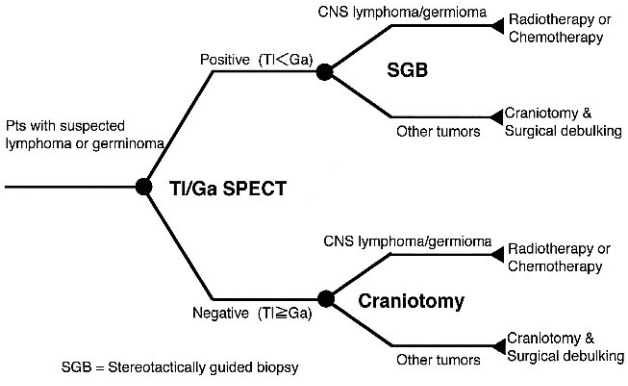


Fig. 1 Decision-tree for the combined ^{201}Tl and ^{67}Ga SPECT in patients suspected of having CNS lymphoma or germinoma.

Table 1 Patient characteristics and visual and semi-quantitative results of ^{201}Tl and ^{67}Ga SPECT in patients with CNS lymphoma and germinoma

Pt no.	Age/Sex	Histological diagnosis	Size (mm)	^{201}Tl		^{67}Ga		Comparison of visual tracer uptake
				Visual	T/N	Visual	T/N	
Lymphoma								
1	71/M	T-cell	15 × 15	+	2.8	++	3.2	^{201}Tl < ^{67}Ga
2	70/M	B-cell	28 × 20	++	3.2	+++	6.4	^{201}Tl < ^{67}Ga
3	53/F	B-cell	35 × 30	++	3.2	+++	6.4	^{201}Tl < ^{67}Ga
			20 × 20	–	1.0	++	3.1	^{201}Tl < ^{67}Ga
4	81/F	B-cell	30 × 20	++	3.1	+++	5.5	^{201}Tl < ^{67}Ga
5	33/M	B-cell	30 × 35	++	3.2	+++	6.0	^{201}Tl < ^{67}Ga
6	60/F	B-cell	35 × 25	++	3.0	++	2.2	^{201}Tl = ^{67}Ga
7	71/F	B-cell	35 × 30	++	3.3	+++	5.5	^{201}Tl < ^{67}Ga
8	70/M	B-cell	40 × 30	++	3.3	+++	6.5	^{201}Tl < ^{67}Ga
9	66/M	B-cell	40 × 35	++	3.2	+++	6.0	^{201}Tl < ^{67}Ga
10	60/M	B-cell	30 × 25	++	3.1	+++	5.5	^{201}Tl < ^{67}Ga
Germinoma								
1	19/M	pure germinoma	25 × 20	++	3.0	+++	4.9	^{201}Tl < ^{67}Ga
			11 × 10	++	3.0	+++	3.9	^{201}Tl < ^{67}Ga
2	44/F	pure germinoma	30 × 25	++	3.1	+++	3.5	^{201}Tl < ^{67}Ga

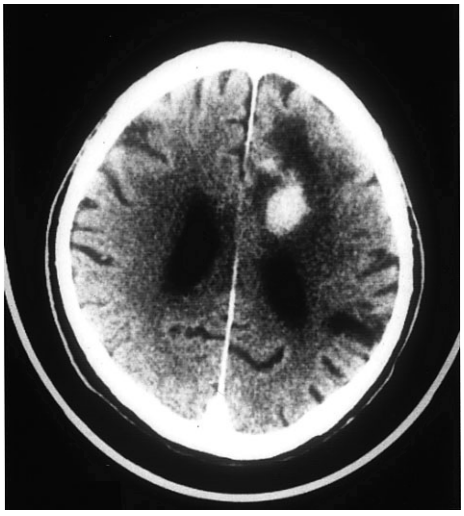
The ^{201}Tl and ^{67}Ga SPECT studies in each patient were performed sequentially and separately. The ^{201}Tl SPECT study was performed first, and the ^{67}Ga SPECT study 2 to 7 days later. Patients received intravenous injections of 111 MBq (3 mCi) each of ^{201}Tl chloride and ^{67}Ga citrate. Ten to fifteen minutes after the ^{201}Tl injection, the patients were imaged with a three-headed camera (GCA-9300A/HG, Toshiba, Tokyo) equipped with fan-beam collimators and set at a 71 keV peak with a 20% window. Sixty views (3 × 20; 6°/step), each registered over 45 s, were recorded using a 64 × 64 matrix corresponding to a pixel dimension of 6.8 × 6.8 mm. Transaxial tomograms were reconstructed by filtered back projection (Butterworth filter; order 8, cutoff 0.17 cycles/pixel). Slice thickness was 6.8 mm.

Forty-eight hours after the ^{67}Ga injection, the patients were imaged with a two-headed camera (GCA-72000A/DI, Toshiba, Tokyo) equipped with middle-energy collimators. Three energy analyzers were used for acquisition, with settings of 93 keV, 185 keV, and 300 keV, respectively, and a 20% window. Sixty views (2 × 30; 6°/step), each registered over 30 s, were recorded using a 64 × 64 matrix corresponding to a pixel dimension of 6.8 × 6.8 mm. Transaxial tomograms were reconstructed by filtered back projection (Butterworth filter; order 8, cutoff 0.12 cycles/pixel). Slice thickness was 6.8 mm.

Data analysis: Visual and semi-quantitative analyses were performed. Tracer uptake was evaluated and classified into four grades by two independent experienced nuclear medicine physicians blinded to the results of morphological imaging. The grading was as follows: grade 0, normal findings with no increased tracer uptake; grade 1, less intense uptake than skull/scalp uptake; grade 2, intense uptake similar to skull/scalp uptake; grade 3, more intense uptake than skull/scalp uptake.

An operator-defined, rectangular region of interest (ROI), with various sizes from 1.25 × 1.50 cm^2 to 3.75 × 4.25 cm^2, was drawn over the lesion on the slice showing the greatest activity. The purpose of using rectangular ROIs was to make them large enough to cover the entire lesion, but when the lesion exhibited a ring-like tracer uptake the ROI was drawn around the site on the ring with the most intense uptake. Similarly, an ROI over the contralateral, presumably healthy brain was created by horizontally flipping the initial ROI. An ROI was created in the normal area adjacent to the lesion when the lesion was located in the midline. Count ratios of the tumors to normal brain (T/N) were calculated from the rectangular ROI for semi-quantitative analysis.

Meta-analysis: *N*-isopropyl-*p*-[^{123}I]iodoamphetamine (^{123}I-IMP) focal uptake on delayed SPECT images has been documented to be a useful observation for diagnosing CNS lymphoma.[25,26] To compare the results of our combined study and those of ^{123}I-IMP delayed SPECT



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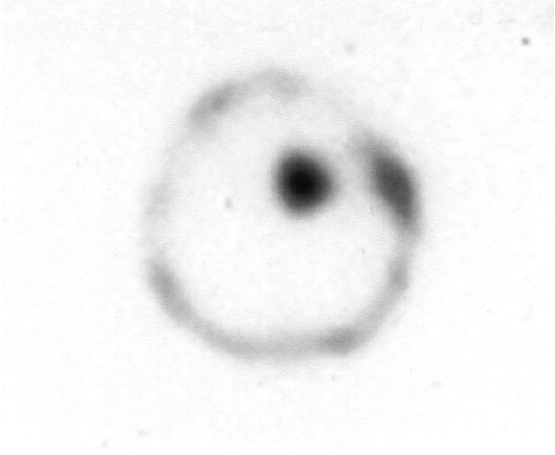

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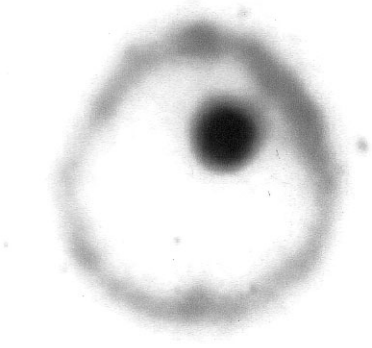

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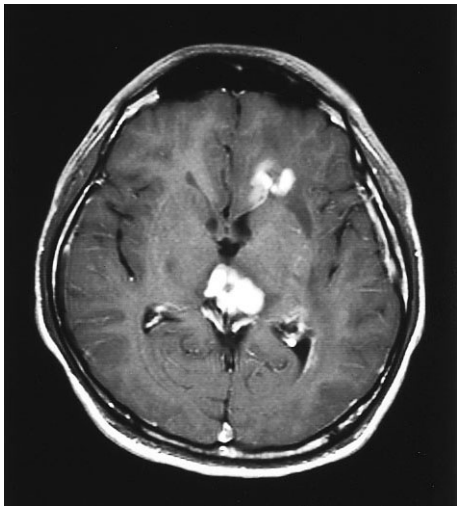
Fig. 2 A 70-year-old male with CNS lymphoma in the left frontal lobe (a: Contrast CT, b: ^{201}Tl SPECT, c: ^{67}Ga SPECT). The combined ^{201}Tl and ^{67}Ga SPECT study shows a ^{67}Ga-positive and ^{201}Tl-positive pattern with ^{67}Ga uptake (T/N ratio: 6.4) greater than ^{201}Tl uptake (T/N ratio: 3.2).



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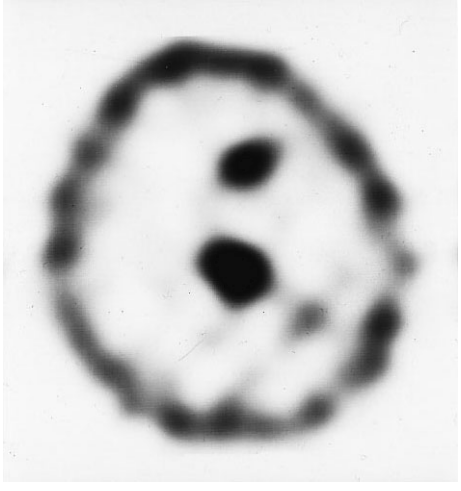

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Fig. 3 A 19-year-old male with intracranial pure germinomas (a: Contrast MRI, b: ^{201}Tl SPECT, c: ^{67}Ga SPECT). The two foci exhibit a ^{67}Ga-positive and ^{201}Tl-positive pattern with ^{67}Ga uptake (T/N ratio: 4.9, 3.9) greater than ^{201}Tl uptake (T/N ratio: 3.0, 3.0).

images, meta-analysis for the diagnosis of CNS lymphoma was performed to obtain mean sensitivity, specificity, and accuracy data for each study.

Economic assessment: If adopted in clinical settings, the combined study may be cost-beneficial in the management of patients suspected of having CNS lymphoma or germinoma because it may prevent unnecessary craniotomies. Cost-saving was calculated by using decision-tree and the Bayesian analysis on the assumption that SPECT findings positive for CNS lymphoma or germinoma lead to stereotactic biopsy instead of craniotomy in patients suspected of having primary CNS lymphoma or germinoma (Fig. 1). The cost of combined ^{201}Tl and ^{67}Ga SPECT, stereotactic biopsy, and craniotomy was 110,760 yen ($886US), 18,400 yen ($147US), and 833,000 yen ($6,664US), respectively, based on reimbursement by the national insurance system in Japan. It was assumed that both stereotactically guided biopsy and craniotomy were a 100% accurate method with a 0% mortality. Sensitivity analysis for pretest probability (prevalence, that is an estimated proportion of patients with CNS lymphoma or germinoma to all brain tumor patients who are supposed to undergo the combined study) on expected cost saving was performed. Since the accuracy of the medical examination is a key factor in cost-effectiveness, cost saving was calculated when the sensitivity and specificity of the combined study for diagnosing CNS lymphoma or germinoma were assumed to have a reasonable value. The costs in US dollars were calculated at a yen-dollar conversion rate of 125 yen to $1.00US.

RESULTS

All eleven foci of CNS lymphomas and three foci of germinomas yielded a ^{67}Ga-positive and ^{201}Tl-positive pattern, and ten (90.9%) of the lymphomas and three (100%) of the germinomas exhibited more intense uptake of ^{67}Ga than of ^{201}Tl (Table 1) (Figs. 2, 3). By contrast, all 10 foci of glioblastoma (100%) exhibited higher uptake of ^{201}Tl than of ^{67}Ga (Table 2). Of the 10 foci with cerebral metastasis, six (60.0%) exhibited higher uptake of ^{201}Tl than of ^{67}Ga (Table 3). All 13 foci of meningioma (100%) exhibited higher uptake of ^{201}Tl than ^{67}Ga (Table 4). The differences in the T/N ratios between ^{201}Tl and ^{67}Ga were statistically significant in each disease group (Table 5) (two-tailed Student's t-test for paired data or Wilcoxon's matched pair signed rank test). The mean T/N ratio of ^{67}Ga SPECT was highest in the patients with primary CNS lymphoma. In visual assessment, all but one focus of CNS lymphomas or germinomas (92.9%, 13/14) exhibited more intense uptake of ^{67}Ga than of ^{201}Tl. All foci of glioblastomas (10/10), meningiomas (13/13), and 60% of metastatic foci (6/10) exhibited higher uptake of ^{201}Tl than of ^{67}Ga.

Meta-analysis for diagnoses of CNS lymphoma and

Table 2 Patient characteristics and visual and semi-quantitative results of ^{201}Tl and ^{67}Ga SPECT in patients with glioblastoma

Pt no.	Age/ Sex	Histological diagnosis	Size (mm)	^{201}Tl		^{67}Ga		Comparison of visual tracer uptake
				Visual	T/N	Visual	T/N	
1	23/F	glioblastoma	35 × 35	++	4.9	+	2.3	^{201}Tl > ^{67}Ga
2	51/M	glioblastoma	48 × 30	+++	9.1	–	1.0	^{201}Tl > ^{67}Ga
			41 × 26	++	3.1	+	2.0	^{201}Tl > ^{67}Ga
3	66/M	glioblastoma	35 × 30	+++	7.2	++	3.0	^{201}Tl > ^{67}Ga
4	49/F	glioblastoma	28 × 26	++	4.2	+	2.1	^{201}Tl > ^{67}Ga
5	71/M	glioblastoma	35 × 35	+++	10.1	+++	7.2	^{201}Tl > ^{67}Ga
6	58/F	glioblastoma	30 × 20	+++	11.5	+++	4.9	^{201}Tl > ^{67}Ga
7	66/M	glioblastoma	40 × 40	+++	11.4	+++	2.5	^{201}Tl > ^{67}Ga
8	13/F	glioblastoma	30 × 25	+++	6.0	+++	4.5	^{201}Tl > ^{67}Ga
9	53/M	glioblastoma	50 × 45	+++	5.3	+	1.7	^{201}Tl > ^{67}Ga

Table 3 Patient characteristics and visual and semi-quantitative results of ^{201}Tl and ^{67}Ga SPECT in patients with cerebral metastasis

Pt no.	Age/ Sex	Histological diagnosis	Size (mm)	^{201}Tl		^{67}Ga		Comparison of visual tracer uptake
				Visual	T/N	Visual	T/N	
1	66/M	adenocarcinoma	23 × 18	++	3.6	++	3.4	^{201}Tl = ^{67}Ga
2	67/F	adenocarcinoma	25 × 22	+++	11.5	+	1.6	^{201}Tl > ^{67}Ga
3	63/F	adenocarcinoma	18 × 12	++	2.2	+	1.5	^{201}Tl > ^{67}Ga
			18 × 15	++	2.7	–	1.0	^{201}Tl > ^{67}Ga
4	64/M	adenocarcinoma	20 × 15	++	2.7	++	2.2	^{201}Tl = ^{67}Ga
5	52/F	adenocarcinoma	20 × 15	–	1.0	–	1.0	^{201}Tl = ^{67}Ga
6	76/F	squamous cell carcinoma	98 × 40	+++	13.9	+++	13.0	^{201}Tl = ^{67}Ga
			10 × 10	+++	4.2	++	2.8	^{201}Tl > ^{67}Ga
7	71/M	squamous cell carcinoma	55 × 45	+++	10.2	++	2.2	^{201}Tl > ^{67}Ga
8	67/F	oat cell carcinoma	30 × 25	+++	13.6	++	2.3	^{201}Tl > ^{67}Ga

Table 4 Patient characteristics and visual and semi-quantitative results of ^{201}Tl and ^{67}Ga SPECT in patients with meningioma

Pt no.	Age/ Sex	Histological diagnosis	Size (mm)	^{201}Tl		^{67}Ga		Comparison of visual tracer uptake
				Visual	T/N	Visual	T/N	
1	60/F	meningothelial meningioma	53 × 40	+++	12.3	++	2.2	^{201}Tl > ^{67}Ga
2	51/F	atypical meningioma	45 × 40	+++	8.5	+	1.7	^{201}Tl > ^{67}Ga
3	60/F	atypical meningioma	36 × 8	++	3.0	+	1.5	^{201}Tl > ^{67}Ga
4	75/F	atypical meningioma	60 × 50	+++	10.8	+++	3.4	^{201}Tl > ^{67}Ga
5	64/F	psammomatous meningioma	52 × 50	+++	11.5	+	1.2	^{201}Tl > ^{67}Ga
			10 × 10	++	4.8	–	1.0	^{201}Tl > ^{67}Ga
			12 × 8	++	5.1	–	1.0	^{201}Tl > ^{67}Ga
6	65/F	transitional meningioma	50 × 40	+++	12.5	+	2.4	^{201}Tl > ^{67}Ga
7	61/F	transitional meningioma	45 × 35	+++	10.2	++	2.2	^{201}Tl > ^{67}Ga
8	57/F	transitional meningioma	25 × 25	+++	5.0	–	1.0	^{201}Tl > ^{67}Ga
9	54/F	transitional meningioma	40 × 35	+++	9.6	++	1.5	^{201}Tl > ^{67}Ga
10	54/F	transitional meningioma	25 × 25	+++	10.9	++	2.5	^{201}Tl > ^{67}Ga
11	42/F	transitional meningioma	25 × 22	+++	5.3	–	1.0	^{201}Tl > ^{67}Ga

germinoma by combined ^{201}Tl and ^{67}Ga SPECT showed a sensitivity of 94.1%, specificity of 91.7%, and accuracy of 92.4%. Meta-analysis for diagnosis of CNS lymphoma by ^{123}I-IMP delayed SPECT showed a sensitivity of 87.5%, specificity of 97.3%, and accuracy of 95.9% (Table 6).

Assuming that the sensitivity and specificity of the combined study for diagnosing CNS lymphoma or germinoma are 90% and 90%, respectively, the sensitivity analysis shows that the cost-saving provided by the introduction of combined ^{201}Tl and ^{67}Ga SPECT would increase as the pretest probability of CNS lymphoma or germinoma increases (Fig. 4). Pretest probability of CNS lymphoma or germinoma was the key factor for cost saving of the

Table 5 T/N ratios (mean ± S.D.) of ^{201}Tl and ^{67}Ga in patients with CNS lymphoma, germinoma, meningioma, glioblastoma, or cerebral metastasis

		T/N ratio (mean ± S.D.)	
		^{201}Tl	^{67}Ga
CNS lymphoma	(n = 11)	2.95 ± 0.63	5.12 ± 1.46 ($p < 0.016$)
Germinoma	(n = 3)	3.03 ± 0.05	4.10 ± 0.59
	(Lymphoma plus germinoma: $p < 0.001$)		
Meningioma	(n = 13)	8.38 ± 3.17	1.74 ± 0.72 ($p < 2.2 \times 10^{-6}$)
Glioblastoma	(n = 10)	7.28 ± 2.90	3.12 ± 1.78 ($p < 0.001$)
Cerebral Metastasis	(n = 10)	6.56 ± 4.85	3.10 ± 3.38 ($p < 0.035$)

Table 6 Meta-analysis for diagnosing CNS lymphoma and germinoma by combined ^{201}Tl and ^{67}Ga SPECT and ^{123}I-IMP delayed SPECT

^{201}Tl and ^{67}Ga SPECT	Sensitivity	Specificity	Accuracy
Current study*	13/14	33/36	46/50
Fujii et al.[19]**	3/3		
	94.1% (16/17)	91.7% (33/36)	92.4% (49/53)
^{123}I-IMP delayed SPECT			
Akiyama et al.[26]	9/12	84/84	
Yamamoto et al.[25]	1/1		
Yoshikai et al.[32]	10/11	41/41	
Nakano et al.[33]	1/1	7/9	
Nishizawa et al.[34]		0/1	
Ohkawa et al.[35]	1/1		
Fukahori et al.[36]	5/5	49/49	
Yoshizawa et al.[39]	1/1		
Takano et al.[38]		1/1	
Nishimura et al.[37]		0/2	
	87.5% (28/32)	97.3% (182/187)	95.9% (210/219)

*: CNS lymphoma and germinoma
**: CNS lymphoma only

combined ^{201}Tl and ^{67}Ga brain SPECT study. The reason for this is that less expensive stereotactic biopsy would replace costly craniotomy. The cost saving enabled by the introduction of combined ^{201}Tl and ^{67}Ga SPECT for a 1% to 50% pretest probability of CNS lymphoma or germinoma would range from minus $842US to plus $2,047US per patient. The threshold value requires greater than approximately 15% pretest probability in order for the combined study to reduce costs.

DISCUSSION

While anatomical imaging plays a key and ever more important role in patients with cerebral tumors, it suffers from several specific limitations. There are no specific CT and/or MRI findings that allow differentiation of CNS lymphomas and germinoma from other neoplasms of the brain. All types of CNS lymphoma are frequently found in the basal ganglia, corpus callosum, and periventricular white matter, and while the pattern of enhancement varies, it is usually homogeneous, except in AIDS patients. On CT scans some CNS lymphomas closely mimic meningioma.[27,28]

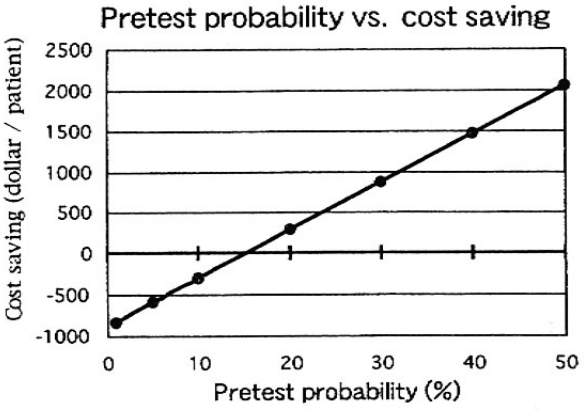

Fig. 4 Results of the sensitivity analysis for CNS lymphoma pretest probability ranging from 1% to 50% in regard to expected cost saving (US dollar) per patient enabled by the introduction of combined ^{201}Tl and ^{67}Ga SPECT in place of craniotomy. The combined study was assumed to have the sensitivity of 90% and specificity of 90% for diagnosing CNS lymphoma or germinoma.

On the other hand, numerous studies have demonstrated that functional and metabolic brain SPECT studies allow accurate delineation of infiltrating tumors, detection of tumor recurrence, and differentiation of brain tumors from non-neoplastic lesions.[2–17] Recently, there have been documents reporting that radiolabeled amino acids, such as L-[methyl-^{11}C]methionine (MET), *O*-(2-[^{18}F]fluoroethyl-L-tyrosine (FET), and iodine-123 α-methyl-tyrosine (^{123}I-IMT), show promise as tracers for metabolic characterization of intracerebral lesions,[29,30] but they are available in only a few institutions, whereas both ^{201}Tl and ^{67}Ga are easily and widely available in clinical settings.

In our series, combined ^{201}Tl and ^{67}Ga brain SPECT was useful for differentiating CNS lymphoma and germinoma from other cerebral tumors, with results showing a ^{67}Ga-positive and ^{201}Tl-positive pattern with more intense uptake of ^{67}Ga than of ^{201}Tl in patients with CNS lymphoma or germinoma. Meta-analysis showed that the sensitivity, specificity, and accuracy of the combined study for diagnosing CNS lymphoma and germinoma were 94.1% (16/17), 91.7% (33/36), and 92.4% (49/53), respectively.

Tumor resection is not necessarily the treatment of

choice in patients with primary CNS lymphoma or germinoma. Radiation therapy alone after stereotactic biopsy is regarded as a rational treatment for patients with CNS lymphoma or germinoma.[20,24] Stereotactic biopsy instead of craniotomy would result in shorter hospital stays. Especially in patients with germinoma, histology is the most important prognostic factor; therefore all patients should have surgical conformation of their diagnosis so that adequate treatment can be given.[31] Our results show that this combined study has a potential of determining whether patients suspected of having CNS lymphoma or germinoma undergo stereotactic biopsy or craniotomy. Furthermore, this combined study may be useful for evaluation of therapy, or to determine progression for patients with CNS lymphoma or germ cell tumors, especially to avoid "second-look operations."

This approach may find the greatest clinical application in HIV/AIDS patients, organ transplant patients or others subjected to prolonged immunosuppression, in whom the incidence of primary CNS lymphoma is high, especially in the presence of enhanced lesions on CT scan or MR imaging. In addition, candidates would be patients with cerebral tumors, which are contiguous with the ependyma or leptomeninges or are deeply situated in the basal ganglia, corpus callosum, and periventricular white matter on CT scan.[27,28] The pattern of enhancement varies but is generally marked and usually homogeneous except in patients with AIDS. In the case of germinoma, candidates should be patients with a mass adjacent to the pineal region.

Meta-analysis: ^{123}I-IMP delayed SPECT is probably capable of helping differentiate CNS lymphoma from benign lesions and other malignant brain tumors. A few investigators, however, have reported that cerebral tumors other than CNS lymphoma also exhibited increased uptake on ^{123}I-IMP delayed SPECT images. Meta-analysis in the literature[25,26,32–39] has shown a sensitivity, specificity, and accuracy of ^{123}I-IMP SPECT for diagnosing CNS lymphoma of 87.5% (28/32), 97.3% (182/187), and 95.9% (210/219), respectively.

^{123}I-IMP SPECT probably has another drawback in that it is incapable of detecting small foci of CNS lymphoma because the uptake of ^{123}I-IMP by CNS lymphomas is less intense than that of ^{67}Ga. T/N ratios of ^{67}Ga SPECT in CNS lymphoma patients were much higher than those of ^{123}I-IMP delayed SPECT (5.12 ± 1.46 vs. 1.48 ± 0.42 or 1.27 ± 0.23).[26,32] It is important that stereotactic biopsy be used to sample areas with the most viable tumor cells, especially in CNS lymphomas of HIV/AIDS patients, since they usually have cavitary lesions.[19,40–42] Thus, ^{67}Ga SPECT seems more useful in pinpointing sites for stereotactic biopsy than ^{123}I-IMP SPECT, since ^{67}Ga is incorporated into viable tissue or active cells, but not into necrotic tissue.

Cost-effectiveness: Assuming that the sensitivity and specificity of the combined study for diagnosing CNS lymphoma or germinoma are 90% and 90%, respectively, the cost saving enabled by introducing the combined study for suspected CNS lymphoma or germinoma would be from minus $842US to plus $2,047US per patient. The break-even point requires greater than approximately 15% pretest probability of CNS lymphoma or germinoma. The pretest probability is the key factor for cost saving. This means that the higher the pretest probability is, the greater the cost saving becomes. To obtain higher pretest probability for CNS lymphoma or germinoma, it is very important to perform the combined study only in patients highly suspected of having CNS lymphoma or germinoma. In other words, the combined study should be limited to patients whose diseases are difficult to diagnose by morphological imaging such as CT or MRI.

Study limitations: Our study may be criticized for the small number of patients and the absence of patients with inflammatory diseases or infectious processes, or cerebral tumors other than meningioma, glioblastoma, and cerebral metastasis. Inflammatory diseases frequently have characteristic symptoms and laboratory data, and CNS lymphoma and germinoma incorporate both ^{201}Tl and ^{67}Ga, with higher uptake of ^{67}Ga than of ^{201}Tl, whereas brain abscesses and inflammatory diseases exhibit a ^{201}Tl-negative, ^{67}Ga-positive or ^{201}Tl-negative, ^{67}Ga-negative pattern.[40–42]

It is important for the differential diagnosis to perform both visual assessment and semi-quantitative analysis using T/N value. The T/N values may be unreliable when a focus has less intense uptake and is small, especially with an ROI less than 15 mm in diameter, though the subjects had no such lesions.

The patient population included subjects with multiple foci, who were not candidates for craniotomy. We did not evaluate cytological examination of the cerebrospinal fluid or germ cell markers. The patients may not undergo neurosurgical intervention if these examinations are positive.

One can argue that it would be more cost-effective to biopsy patients before the decision making for a craniotomy because the cost of the combined study was $886US and the cost of a biopsy was $147US. However, stereotactic biopsy needs hospitalization, general anesthesia, and some examinations for the biopsy. The net cost for a biopsy exceeds $886US.

Conclusion: The results of combined ^{201}Tl and ^{67}Ga SPECT showing a ^{67}Ga-positive and ^{201}Tl-positive pattern with ^{67}Ga uptake greater than ^{201}Tl uptake suggests CNS lymphoma or germinoma. This combination study appears to be cost-effective only in patients highly suspected of having CNS lymphoma or germinoma.

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