
The Diagnostic Value of ^{123}I -IMP SPECT in Non-Hodgkin's Lymphoma of the Central Nervous System

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N-isopropyl-*p*-[^{123}I]iodoamphetamine (IMP) SPECT is of low diagnostic value in patients with brain tumors, because brain tumors are visualized as uptake defects. Some reports have described non-Hodgkin's lymphoma of the central nervous system (CNS) as showing high uptake on delayed ^{123}I -IMP SPECT images, suggesting its usefulness in diagnosing CNS lymphoma. In this study, we investigated the clinical value of ^{123}I -IMP SPECT as a diagnostic tool for CNS lymphoma. **Methods:** Ninety-six patients with brain tumors, including 12 patients with CNS lymphoma, underwent ^{123}I -IMP SPECT. Eleven patients had primary CNS lymphoma, and 1 had a parenchymal brain metastasis from a breast lymphoma. The total number of lesions was 18, 14 of which were in the cerebral parenchyma, 3 in the brain stem, and 1 in the ventricle. Early SPECT images were initiated 15–30 min after intravenous injection of 111 MBq ^{123}I -IMP, and delayed images were collected 4 h later. SPECT images were visually analyzed with a color-grading scale. Tumor-to-normal activity ratio (T/N) and tumor-to-cerebellum activity ratio (T/C) were calculated for both early and delayed images for semiquantitative analysis. **Results:** By visual estimation, more than a 3-cm³ volume of CNS lymphoma was detected as an obvious focus of increased accumulation on delayed images. All other brain tumors tested appeared as decreased accumulation on delayed images. T/Ns and T/Cs on delayed images of CNS lymphomas, including tumors less than 3 cm³ in volume, were 1.48 ± 0.42 and 1.08 ± 0.16 , respectively. These ratios in patients with glioma (0.30 ± 0.05 and 0.31 ± 0.07 respectively) or meningioma (0.34 ± 0.10 and 0.41 ± 0.17 , respectively) showed a significant difference from those in patients with CNS lymphoma ($P < 0.0005$). **Conclusion:** ^{123}I -IMP SPECT is a helpful tool for diagnosing CNS lymphoma.

Key Words: brain neoplasm; non-Hodgkin's lymphoma; SPECT; *N*-isopropyl-*p*-[^{123}I]iodoamphetamine

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Since the introduction of CT and MRI, the reported incidence of non-Hodgkin's lymphoma of the central nervous system (CNS) has increased (1). The incidence of primary CNS lymphoma, in particular, has increased, tre-

bling in the last decade, partly because of an increase in the number of immunocompromised patients, including those with AIDS, those undergoing chemotherapy, and those with transplanted organs (1,2). Because of the characteristic appearance and localization of CNS lymphoma on CT scans and MR images, its diagnosis may have become more straightforward in recent years. In some cases, CNS lymphoma may be difficult to distinguish from other CNS disorders, such as glioblastoma, meningioma, degenerative diseases, multiple sclerosis, infectious disease, or cerebral infarction (3).

N-isopropyl-*p*-[^{123}I]iodoamphetamine (IMP) SPECT (4,5) is a noninvasive diagnostic tool for measuring regional cerebral blood flow (6) and has been used to evaluate cerebral infarction, dementia, and other brain disorders (7,8). ^{123}I -IMP SPECT may not be greatly useful in patients with brain tumors, because SPECT images of brain tumors appear as defects even though tumors are hypervascular on cerebral angiography (9–11). Exceptional cases have been reported that show an accumulation of IMP in brain tumors (12–14). Most of these cases have exhibited high uptake on early images only, and few cases have been reported as showing a high accumulation on delayed images (15–20). Most of these cases were of CNS lymphoma, suggesting that lymphoma cells can take up IMP and that delayed accumulation on ^{123}I -IMP SPECT images may be characteristic of CNS lymphoma (15,16,18,20). As far as we can determine, however, only 4 cases of CNS lymphoma examined with ^{123}I -IMP SPECT have been reported in the literature. The aim of this study was to investigate the value of ^{123}I -IMP SPECT as a diagnostic tool for CNS lymphoma.

MATERIALS AND METHODS

Patient Population

Ninety-six patients with histologically verified brain neoplasms underwent ^{123}I -IMP SPECT between February 1991 and June 1999. Twelve patients (7 men, 5 women; age range, 43–81 y; mean age, 65.7 y) had CNS lymphoma, and 84 had other types of brain tumors (13 glioblastomas, 17 anaplastic astrocytomas, 7 low-grade astrocytomas, 15 meningiomas, 4 pituitary adenomas, 4 teratomas, 3 craniopharyngiomas, 3 neurinomas, 5 metastatic lung cancers, 3 metastatic breast cancers, 2 metastatic colon cancers, 1 metastatic

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renal cell carcinoma, 2 metastatic nasopharyngeal adenoid cystic carcinomas, 1 lacrimal gland pleomorphic adenocarcinoma, and 4 metastases of unknown origin). The 12 patients with CNS lymphoma included 11 with primary CNS tumors and 1 with a parenchymal metastatic cerebral lesion from a breast lymphoma. Associated lesions outside the CNS were evaluated by systemic investigations, which included bone, ^{67}Ga -labeled, or $^{99\text{m}}\text{Tc}$ -labeled scintigrams and whole-body CT scans. In this study, no patient was known to be infected with HIV. The incidence of HIV positivity in Japan is low (21). Eight patients had solitary lesions, and 4 had multiple (each had 2) lesions. One patient in the latter group was assessed as having a recurrent lesion of the brain stem. The total number of lesions was 18; 14 were in the cerebral parenchyma, 3 in the brain stem, and 1 in the ventricle. This study was approved by the institutional research ethics board, and informed consent was obtained from all patients or their guardians.

^{123}I -IMP SPECT

^{123}I -IMP SPECT was performed with a rotating gamma camera (Starcam, 400AC/T; General Electric Medical Systems, Milwaukee, WI), and data were obtained from 64 projections in a 64×64 matrix using a general-purpose collimator with a sampling time of 20 s. One hundred eleven megabecquerels ^{123}I -IMP (Nihon Medi-Physics, Inc., Takarazuka, Japan) were administered intravenously. The patients' eyes were covered by a blindfold for 15 min before and after injection. Data collection for early SPECT images was initiated 15–30 min after tracer injection (early image), and data for delayed SPECT images were collected after 4 h (delayed image). All data were collected at an attenuation of 0.1/cm, and the tomographic data were reconstructed using a filtered backprojection algorithm. The orbitomeatal line was determined from the right lateral planar image before scanning using marks on the right eye and right external auditory meatus with $^{99\text{m}}\text{Tc}$ hot spots [0.3 mCi (11.1 MBq)] and was used for the transaxial sections as well. Each slice was 8 mm thick.

Data Analysis

SPECT images were assessed visually and semiquantitatively. For the visual analysis, the axial, coronal, and sagittal SPECT images of all tumors in our series were displayed using a color-grading scale. The slice with the maximal ^{123}I -IMP activity in the known tumor area was chosen for analysis. The color-graded SPECT images of brain tumors were visually estimated in comparison with normal brain and classified as 1 of 4 patterns: high, normal, low, or defect. These assessments were classified by 3 experienced neurosurgeons who were aware of the CT location of the tumor. No further details about the histology of the tumor were disclosed during image analysis. The 3 observers independently assessed 97 SPECT scans and showed good agreement with one another ($\kappa > 0.9$ for interobserver agreement).

For semiquantitative analysis, 10 gliomas (4 glioblastomas, 4 anaplastic astrocytomas, and 2 low-grade gliomas) and 10 meningiomas (3 meningotheliomatous type, 3 fibroblastic type, and 4 transitional type) were chosen as controls. It is important to distinguish CNS lymphoma from other, more common CNS neoplasms, such as gliomas and meningiomas, because unlike CNS lymphoma, they benefit from surgical intervention. The regions of interest (ROIs) were first drawn on the images in the slice showing the highest count density in the tumor. Preoperative CT scans or MR images were used as anatomic guides, and the homologous (contralateral) ROI was determined by creating a mirror image of the initially defined region on the contralateral hemisphere. A

tumor-to-normal activity ratio (T/N) was obtained from the ratio of the average counts per pixel in the tumor over the average counts per pixel in the homologous contralateral region. For midline lesions, a mirror-image ROI using a horizontal rather than vertical symmetry axis was used (22). If the region had 2 separate lesions contralateral to each other, a horizontal axis was also used in their evaluation. The tumor-to-cerebellum activity ratio (T/C) was determined from the average counts per pixel in the tumor over the average counts per pixel in the ROI, with a fixed 30-mm width drawn over the cerebellar cortex (23). Tumor volume (in cubic centimeters) was calculated as the tumor height \times vertical length \times transverse length \times 0.5, with the vertical length measured from the axial MRI slice and the transverse length measured from the coronal MRI slice.

Statistical Analysis

Data are expressed as mean \pm SD. Statistical significance was determined using the Student *t* test. $P < 0.05$ was considered statistically significant.

RESULTS

Detailed data describing each CNS lymphoma patient are presented in Table 1. All the patients with CNS lymphoma showed ^{123}I -IMP uptake on the delayed-phase image because they did not show low accumulation or defect on the delayed SPECT image. Some cases of lymphoma showed low accumulation on the early image. Illustrative cases are shown in Figures 1 and 2. All CNS lymphomas greater than 3.0 cm³ in volume were seen to have high accumulation on the delayed image. These characteristic accumulations on the delayed image were observed in all cases, including the brain stem lesion and the intraventricular lesions. In our series, all other histologic tumor types were visualized as low accumulation or defects on both early and delayed images (Figs. 3 and 4), except for some meningiomas that showed normal accumulation on early images only. These meningiomas showed intratumoral retention of contrast medium on the late venous phase of angiography.

The T/Ns and T/Cs of CNS lymphomas, gliomas, and meningiomas are shown in Table 2. On early images, the T/Ns and T/Cs of CNS lymphomas were significantly different from those of gliomas ($P < 0.05$) but not from those of meningiomas ($P = 0.10$ and 0.59, respectively). On delayed images, the T/Ns and T/Cs of CNS lymphomas were significantly different from both gliomas and meningiomas ($P < 0.0005$).

DISCUSSION

^{123}I -IMP SPECT and Brain Tumors

^{123}I -IMP is a lipid-soluble radiopharmaceutical agent whose early distribution pattern reflects regional cerebral blood flow (5), because IMP shows high first-pass uptake by brain tissues with nonspecific amine binding sites and reveals slow washout. The possibility has been suggested that brain tumors are visualized as defects on ^{123}I -IMP SPECT because of a lack of binding sites for IMP or because of the absence of the intracellular metabolic pathway for

TABLE 1
Clinical Features and ¹²³I-IMP SPECT Results for Patients with Non-Hodgkin's Lymphoma of Central Nervous System

Patient no.	Age (y)	Sex	Tumor type	Tumor location	Tumor volume (cm ³)	Visual image		T/N		T/C	
						Early	Delayed	Early	Delayed	Early	Delayed
1	77	F	Metastasis	L thalamus to temporoparietal region	6.2	Low	High	0.77	1.30	0.51	1.36
2	69	M	Primary	Midbrain	5.4	Normal	High	1.16	1.25	0.80	0.92
3	62	M	Primary	Splenium of corpus callosum	12.0	High	High	1.92*	2.25*	1.06	1.23
				R paraventricle	4.0	Low	High	0.62*	1.31*	0.53	0.95
4	72	F	Primary	L paraventricle	3.6	Low	High	0.60*	1.42*	0.50	1.00
				Intraventricular region	7.4	High	High	2.01	2.72	0.75	0.95
5	81	F	Primary	L parietal region	2.5	Low	Normal	0.41	1.00	0.41	1.05
6	73	M	Primary	L temporal region	3.2	Normal	High	1.14	1.53	0.95	1.11
7	74	M	Primary	Corona radiata to centrum semiovale	2.5	Normal	Normal	1.00	1.14	0.70	0.84
8	48	M	Primary	R basal ganglia	6.0	Low	High	0.50	1.42	0.45	0.96
				Midbrain	3.0	Normal	High	0.85	1.20	0.74	1.04
9	58	F	Primary	R parietal region	4.5	Normal	High	ND	ND	ND	ND
				L basal ganglia	2.4	Normal	Normal	ND	ND	ND	ND
10	43	M	Primary	R parietal region	5.0	Normal	High	1.07*	1.41*	0.68	1.20
				L parietal region	4.0	Normal	High	1.03*	1.35*	0.67	1.10
11	52	M	Primary	Pons	3.4	High	High	1.76	1.54	1.35	1.05
				R parietooccipital region	4.6	Normal	High	1.00	1.40	0.96	1.00
12	79	F	Primary	L frontal region	9.4	Low	High	0.59	1.52	0.43	1.42

*Mirror image ROI using horizontal symmetry axis was used.

Metastasis = metastatic intracranial lymphoma from extracranial origin; primary = primary intracranial lymphoma; ND = no data.

Patient 1 had metastatic lymphoma from breast origin. Patients 2, 3, 8, 9, and 10 had 2 separated lesions. Patient 10 had recurrent lesion in pons.

IMP (9,11). Although some brain tumors with high IMP uptake in the early phase have been reported (12–14,16), dynamic SPECT scan studies have revealed that these accumulations resulted from intravascular retention of ¹²³I-IMP (16).

Delayed SPECT images may reflect the distribution of hydrophilic metabolites of IMP resulting from further oxidation of the aliphatic side chain (24). The clinical significance of delayed images remains uncertain (7,10). To our knowledge, only 8 patients with brain tumors showing high uptake in the delayed phase have been described in the literature. We summarize these patients in Table 3. Although 1 patient with malignant astrocytoma was reported (16), this case was exceptional in the light of previous studies (10,11). Moretti et al. (25) showed that normal astrocytes, unlike astrocytoma cells, take up IMP. Nakano et al. (16) reported 1 case of metastatic brain tumor but did not describe its histology or tissue of origin.

Diagnosing CNS Lymphoma and ¹²³I-IMP SPECT

Although MRI and CT are useful in detecting mass lesions, including CNS lymphoma, CNS lymphoma is difficult to distinguish from other CNS disorders (3). Ruiz et al. (26) reported the value of ²⁰¹Tl brain SPECT for differentiating CNS lymphoma from *Toxoplasma* encephalitis. Hoffman et al. (27) suggested that FDG PET may have a potential role in differentiating lymphoma from infectious CNS disorders. Both ²⁰¹Tl SPECT and FDG PET may be useful diagnostic tools for CNS lymphoma. FDG PET can

evaluate lesions less than 1 cm in diameter with high spatial resolution. The role of ²⁰¹Tl SPECT and FDG PET has been limited to distinguishing between neoplastic and non-neoplastic abnormalities in AIDS patients. PET is not widely available because of its high cost. Biopsy, especially stereotactic biopsy as a less invasive technique, is essential in cases that are confusing. In some cases, biopsy may fail to confirm the diagnosis because of reactive glial tissue, infiltrating T cell lymphocytes, and necrotic tissue in CNS lymphomas. For these reasons, another modality is necessary to confirm the diagnosis. With early diagnosis of CNS lymphoma using noninvasive techniques, whole-brain radiation therapy can be initiated in hopes of improving survival and decreasing hospitalization time.

Nakano et al. (16), Ohkawa et al. (18), and Yoshizawa et al. (20) each reported a case of primary CNS lymphoma that revealed high uptake on delayed images. Kitanaka et al. (15) reported a case of metastatic CNS lymphoma showing high accumulation on delayed SPECT images. Those authors suggested that the unusual increased accumulation of IMP on delayed images might be specific for CNS lymphomas. In that study of 19 brain tumors, CNS lymphoma was the only histologic type showing high uptake on delayed images using ¹²³I-IMP SPECT. An increase in the concentration of nonspecific amine receptors on CNS lymphoma cells has been suggested as a mechanism for the increased uptake of ¹²³I-IMP (15,18). This hypothesis has yet to be confirmed because few patients with CNS lymphoma have been

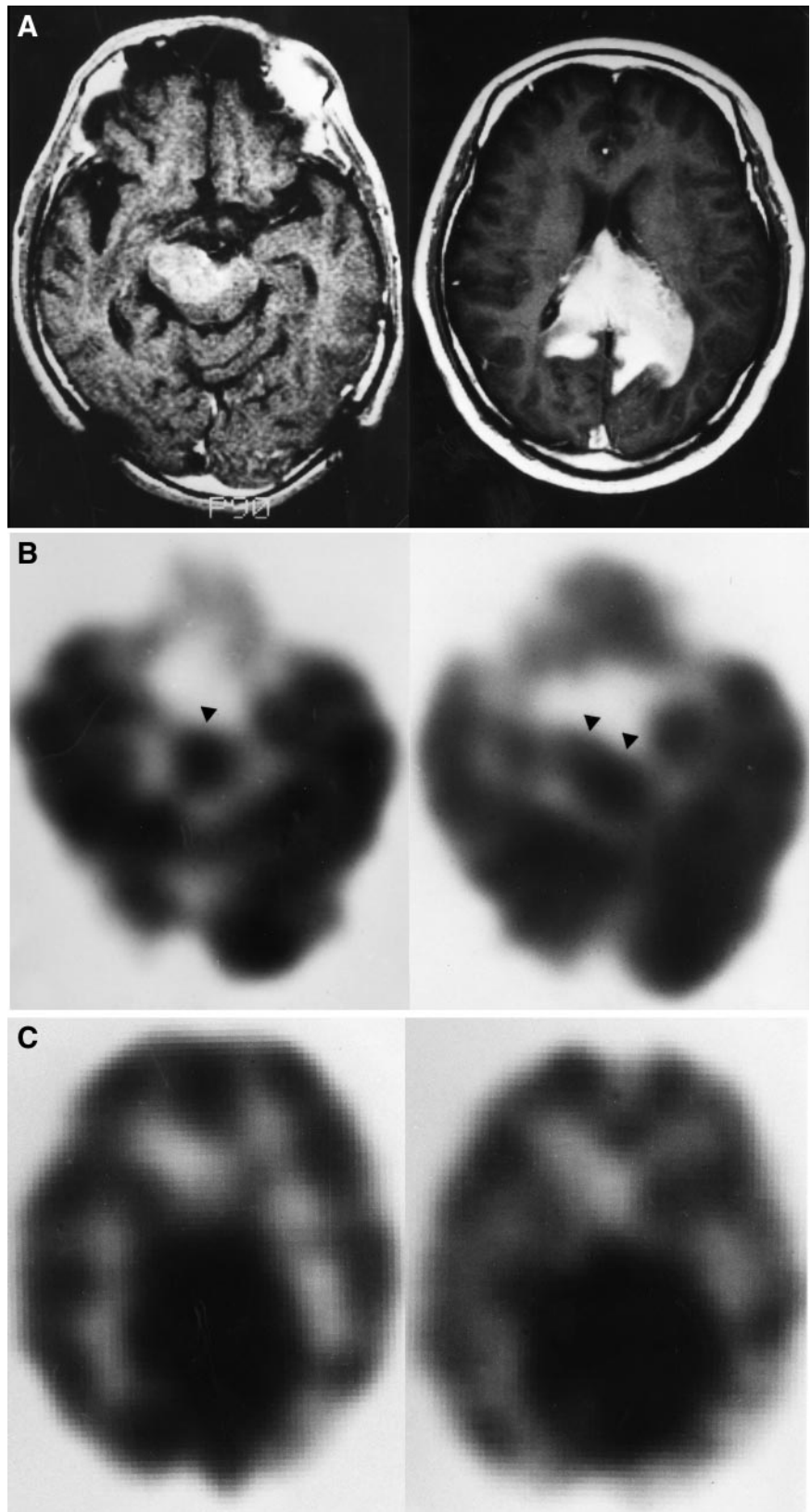


FIGURE 1. A 69-y-old man with CNS lymphoma (patient 2). (A) T₁-weighted MR image with gadolinium-diethylenetriamine-pentaacetic acid shows homogenous enhancing lesions in midbrain and corpus callosum. (B) Midbrain tumor shows normal and high accumulation (arrowheads) on early (left) and delayed (right) SPECT images, respectively. (C) Early (left) and delayed (right) ¹²³I-IMP SPECT images reveal increased uptake at corpus callosum.

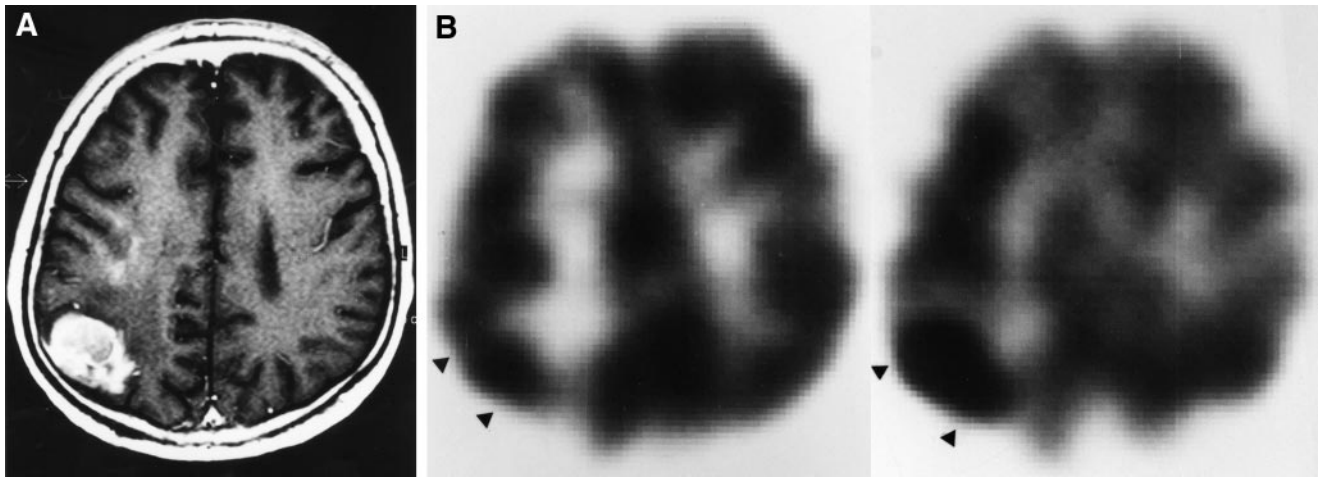


FIGURE 2. A 52-y-old man with CNS lymphoma (patient 11). (A) T₁-weighted MR image with gadolinium-diethylenetriaminepentaacetic acid shows heterogeneously enhancing mass in right parieto-occipital area. Mass is difficult to distinguish from high-grade glioma on MR image only. (B) ¹²³I-IMP SPECT images show normal and increased accumulation (arrowheads) corresponding to tumor on early (left) and delayed (right) images, respectively.

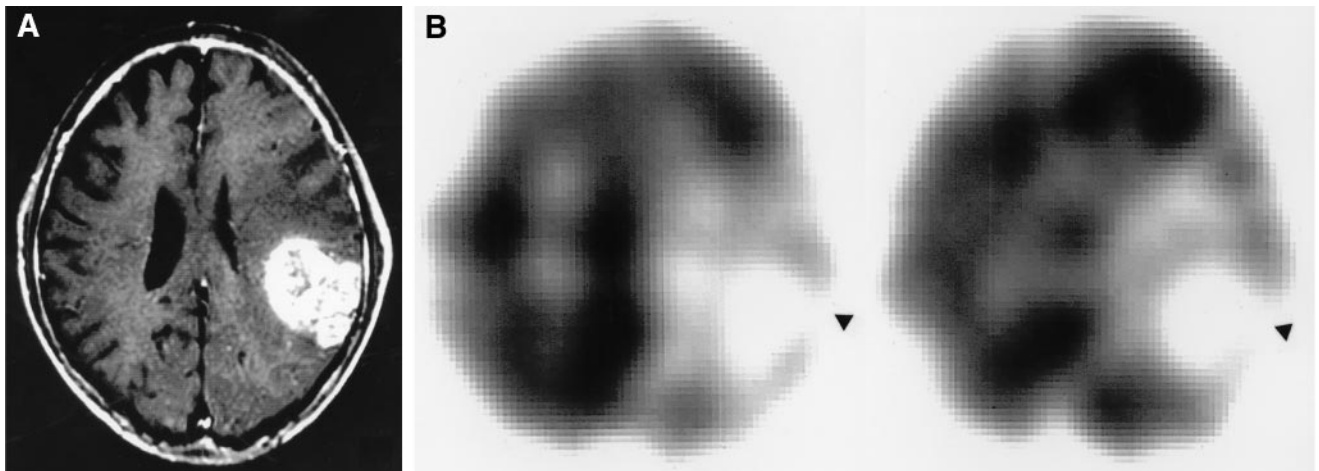


FIGURE 3. A 72-y-old man with glioblastoma. (A) T₁-weighted MR image with gadolinium-diethylenetriaminepentaacetic acid shows heterogeneously enhancing mass in left parietal region. (B) ¹²³I-IMP SPECT images show defect (arrowheads) corresponding to tumor on both early (left) and delayed (right) images. T/Ns on early and delayed images are 0.23 and 0.21, respectively. T/Cs on early and delayed images are 0.18 and 0.20, respectively.

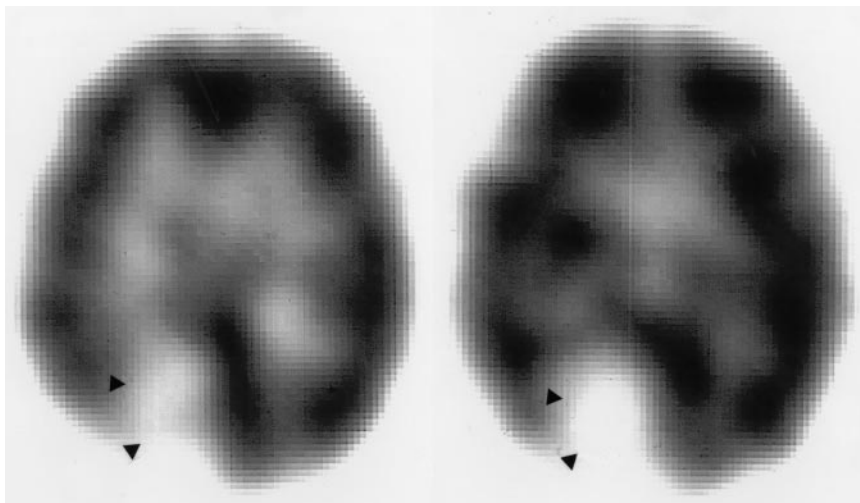


FIGURE 4. A 71-y-old woman with right parasagittal meningioma. ¹²³I-IMP SPECT images show low accumulation and defect (arrowheads) corresponding to tumor on early (left) and delayed (right) images, respectively. T/Ns on early and delayed images are 0.53 and 0.48, respectively. T/Cs on early and delayed images are 0.18 and 0.14, respectively.

TABLE 2
Results of Semiquantitative Analysis of CNS Lymphoma, Gliomas, and Meningioma

Diagnosis	T/N		T/C	
	Early	Delayed	Early	Delayed
CNS lymphoma	1.03 ± 0.47	1.48 ± 0.42	0.67 ± 0.21	1.08 ± 0.16
Glioma*	0.30 ± 0.10†	0.30 ± 0.05†	0.31 ± 0.09†	0.31 ± 0.07†
Meningioma‡	0.56 ± 0.46§	0.34 ± 0.10†	0.59 ± 0.49	0.41 ± 0.17‡

*Data were obtained from 4 glioblastomas, 4 anaplastic astrocytomas, and 2 low-grade gliomas. Uptake did not significantly differ among these 3 groups.

† $P < 0.05$.

‡Data were obtained from 10 meningiomas of 3 different histologic subtypes (3 meningotheliomatous, 3 fibroblastic, 4 transitional). Uptake did not significantly differ among histologic subtypes.

§ $P = 0.10$.

|| $P = 0.59$ vs. CNS lymphoma.

studied by ^{123}I -IMP SPECT and because ^{123}I -IMP can no longer be obtained in some countries. $^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamine oxime (HMPAO) and $^{99\text{m}}\text{Tc}$ -ethyl cysteinate dimer (ECD) are other radiopharmaceuticals used for measuring regional cerebral blood flow, but their uptake in CNS lymphoma has not been examined. The mechanism of HMPAO and ECD uptake into brain differs from that of IMP. The former is related to the intracellular content of glutathione (28), whereas the latter is associated with intracellular and membranous esterase activity (29).

Clinical Significance of ^{123}I -IMP SPECT for Diagnosing CNS Lymphoma

We assessed the findings of ^{123}I -IMP SPECT in 18 CNS lymphomas through visual and semiquantitative analyses. Our results indicate that both visual analysis and semiquantitative evaluation with T/N and T/C are potentially useful in distinguishing CNS lymphoma from other types of brain tumors. CNS lymphomas more than 3.0 cm³ in volume were detected as obvious foci of high accumulation, including brain stem tumors and intraventricular tumors. In tumors less than 3 cm³ in volume, the contrast was not sufficient to detect the tumor as a definite area of high accumulation. This finding might have been caused in part by uptake of IMP into

normal brain as well as into CNS lymphoma and by the low spatial resolution of our imaging system. In evaluating tumors less than 3 cm³ in volume, semiquantitative analysis is recommended to enhance efficacy.

Distinguishing between CNS lymphoma and CNS toxoplasmosis in AIDS patients is a clinical challenge. Our study had no HIV-positive patients. Future studies should evaluate the role of ^{123}I -IMP SPECT in patients with AIDS.

CONCLUSION

Delayed ^{123}I -IMP SPECT images of patients with CNS lymphoma showed specific accumulations corresponding to the actual tumor mass. This finding confirmed the clinical usefulness of ^{123}I -IMP SPECT in diagnosing CNS lymphoma and in differentiating CNS lymphoma from other types of brain tumors. Future studies will be valuable for evaluating the role of ^{123}I -IMP SPECT in detecting CNS lymphoma in AIDS patients.

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TABLE 3
Patients Previously Reported with Increased ^{123}I -IMP Uptake on Delayed SPECT

Patient no.	Study	Age (y)	Sex	Diagnosis	^{123}I -IMP SPECT results	
					Early	Delayed
1	Nakano et al. (16)	65	M	Primary CNS lymphoma	Low	High
2	Nakano et al. (16)	58	F	Malignant astrocytoma	Low	High
3	Nakano et al. (16)	58	F	Metastatic brain tumor (histology was not described)	Low	High
4	Ohkawa et al. (18)	73	M	Primary CNS lymphoma	High	High
5	Nishizawa et al. (17)	44	M	Metastatic brain tumor (metastasis from bronchial carcinoid tumor)	High	High
6	Kitanaka et al. (15)	42	F	Secondary CNS lymphoma (metastasis from breast lymphoma)	High	High
7	Takano et al. (19)	34	M	Primary CNS melanoma	High	High
8	Yoshizawa et al. (20)	37	F	Primary CNS lymphoma	High	High

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