Annals of Nuclear Medicine Vol. 17, No. 5, 387–392, 2003

Extraosseous accumulation of bone scanning agents in malignant brain tumors: Comparison to semi-quantitative evaluation with ^{99m}Tc SPECT/^{201}Tl SPECT and histological findings

Aya SUZUKI,* Takashi TOGAWA,** Junpei KUYAMA,** Tadaki NAKAHARA,** Toshihiko IUCHI,*** Masaru OGA,*** Katsunobu OSATO*** and Toshinao TAKENOUCHI****

*Oral Surgery, Department of Oral Restitution, Division of Oral Health Sciences, Graduate School, Tokyo Medical and Dental University
**Division of Nuclear Medicine, Chiba Cancer Center
***Division of Neurological Surgery, Chiba Cancer Center
****Division of Surgical Pathology, Chiba Cancer Center

Although ^{201}Tl chloride (Tl) SPECT has been used in the differential diagnosis between recurrence of malignant brain tumor and necrosis after treatment, it is not generally recognized as a definite modality to distinguish them. We conducted a preliminary study using Tl SPECT and ^{99m}Tc-MDP or ^{99m}Tc-HMDP (Tc) SPECT because it has been said that extraosseous accumulation was caused by calcium deposits in necrotic tissues. In our study, for the purposes of clarifying the mechanism of extraosseous uptake and the correlation between extraosseous accumulation of bone-scanning agent and tumor viability in malignant brain tumors, we compared whether Tc uptake was correlated with the histopathological findings and further performed semi-quantitative evaluation between Tc SPECT and Tl SPECT. The correlation coefficients between the ratio of tumor to normal skull count obtained from Tc SPECT (Tc-T/N) and those of tumor to normal brain count (T/N) and to normal scalp count (T/S) both obtained from Tl SPECT were calculated. Using contrast enhanced CT (CE-CT) or contrast enhanced MRI (CE-MRI), 8 of 10 cases showed intensely ring-enhanced tumor with necrotic lesion. Histopathologically, 7 of 8 cases whose tumor had been resected before treatment had necrosis with increased vascularity or bleeding. Of the remaining 2 cases one case, malignant lymphoma had only hypervascularity by biopsy, while the other one was excluded for resection after treatment. Three of these 8 cases whose CE-CT or CE-MRI showed necrotic lesions exhibited Tc and Tl accumulations in the area corresponding to necrosis. In contrast, 2 showed no Tc nor Tl uptake. Tc-T/N had no significant correlation with any of early-, delayed-T/N or T/S. In conclusion, there was no significant correlation between Tc and Tl uptakes by malignant brain tumors in semi-quantitative evaluation.

Key words: extraosseous accumulation, malignant brain tumor, semi-quantitative evaluation, ^{201}Tl, ^{99m}Tc-(H)MDP

INTRODUCTION

WHEN ^{99m}Tc bone scintigraphy is performed, we can often detect extraosseous uptake by various organs or tumors. Despite so many cases and so many studies conducted to solve the mechanism of ^{99m}Tc extraosseous accumulation, this phenomenon remains unexplained, and there have been numerous explanations for extraosseous uptake. Some authors have reported extraosseous accumulation in brain tumors using ^{99m}Tc bone scintigraphy[1–5] but no one evaluated extraosseous accumulation with ^{99m}Tc SPECT (single photon emission CT) . We exhibited two cases of primary malignant brain tumor which showed

Received December 9, 2002, revision accepted April 29, 2003.

For reprint contact: Aya Suzuki, D.D.S., Division of Nuclear Medicine, Chiba Cancer Center, 666–2, Nitona-cho, Chuo-ku, Chiba 260–8717, JAPAN.
E-mail: asuzuki@chiba-cc.jp

extraosseous accumulation evaluated with ^{99m}Tc-methylene diphosphonate (MDP) or ^{99m}Tc-hydroxy methylene diphosphonate (HMDP) (Tc) SPECT and ^{201}Tl chloride (Tl) SPECT in the previous case report.[6] Although Tl SPECT has been used in the differential diagnosis between recurrence of malignant brain tumor and necrosis, it is not generally recognized as a definite modality to distinguish them. We conducted a preliminary study using Tl SPECT and Tc SPECT because extraosseous accumulation is caused by calcium deposits in necrotic tissues. In this study we compared Tc uptake with the histopathological findings, and further performed semiquantitative evaluation using Tc SPECT and Tl SPECT to investigate the mechanism of extraosseous uptake and the correlation between extraosseous accumulation of bone-scanning agent and tumor viability in malignant brain tumor.

Table 1 Sex, age and histopathological diagnoses of 10 patients

	sex	age	Histopathological findings
Case 1	male	54	Glioblastoma
Case 2	female	58	Malignant lymphoma (by biopsy)
Case 3	male	74	Metastatic SCC (esophageal Ca origin)
Case 4	female	51	Metastatic carcinoma (lung Ca origin, postradiotherapy)
Case 5	male	68	Glioblastoma
Case 6	male	61	Metastatic SCLC (lung Ca origin)
Case 7	female	49	Metastatic mucoepidermoidcarcinoma (uterine Ca origin)
Case 8	male	62	Metastatic adenocarcinoma (lung Ca origin)
Case 9	male	70	Metastatic adenocarcinoma (lung Ca origin)
Case 10	male	70	Metastatic tumor (lung Ca origin)

SCC = squamous cell carcinoma
Ca = carcinoma

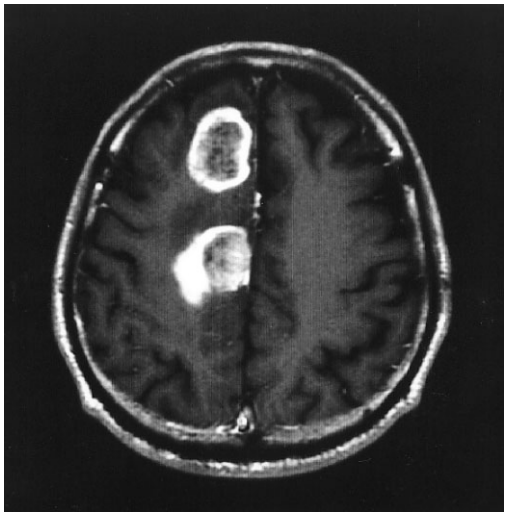
MATERIALS AND METHODS

Ten patients diagnosed as having intracranial extraosseous uptake with Tc SPECT who had been investigated using Tc bone scintigraphy between April, 2001 and September, 2002 were enrolled in this study. Those 10 patients consisted of 7 males and 3 females, aged 49 to 74 years, and 3 of the 10 patients had primary malignant brain tumors and the other seven metastatic malignant brain tumors (Table 1). All 10 patients were investigated using Tl scintigraphy and contrast enhanced CT (CE-CT) or contrast enhanced MRI (CE-MRI). As to 8 of 10 who underwent tumor resection before treatment, Tc bone scintigraphy, Tl scintigraphy and CE-CT or CE-MRI were performed 1–16 days (mean 8 days), 3–22 days (mean 9 days), and 1–14 days (mean 10 days) before operation, respectively. Tc bone scintigraphy was performed 2–3 hours after the intravenous injection of 740 MBq Tc. On the other hand, at 15 minutes and 120 minutes postinjection of 111 MBq Tl , early and delayed Tl SPECTs were taken. SPECTs were obtained using a triple head rotating gamma camera (GCA9300DI TOSHIBA) equipped with a low-energy fan-beam collimator, acquiring images every 4 degrees for 30 seconds each in an acquisition matrix of 256 × 256 for Tc SPECT and that of 128 × 128 for Tl SPECT. Acquisition time were 30 min for 360 degrees. Fan-beam data were converted to parallel-beam projection data in a 128 × 128 and a 64 × 64 matrix for Tc and Tl SPECT, respectively. The slices were reconstructed using the filtered back projection algorithm with the Ramp and Butterworth filter. The photopeak was set for 140 keV and 71 keV for Tc and Tl SPECT, respectively. A 20% symmetric window was used for Tc SPECT and Tl SPECT. In each slice where the highest uptake of Tc or Tl was noted, regions of interest (ROI) were drawn around the lesions with high activity of those radiopharmaceuticals corresponding to tumors in CE-CT or CE-MRI. When there was discordance between the

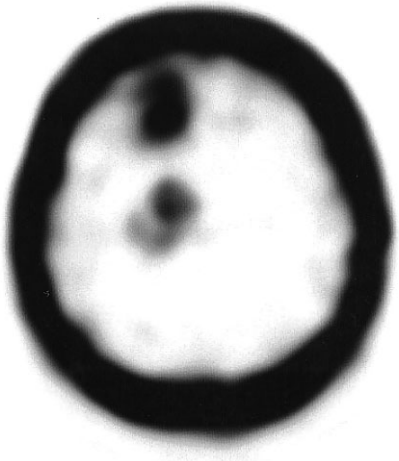
Table 2 Morphological method, histopathological examination and Tc SPECT and Tl SPECT

	Morphological method	Necrosis	Increased vascularity	Bleeding	Tc uptake in LIL***	Tl uptake in LIL***
Case 1	CE-MRI	+	+	−	−	−
Case 2	CE-CT	−*	+*	−*	+	+
Case 3	CE-MRI	+	−	+	+	−
Case 4	CE-MRI	**	**	**	+	+
Case 5	CE-MRI	+	−	+	+	+
Case 6	CE-MRI	+	−	+	−	+
Case 7	CE-MRI	+	−	−	+	+
Case 8	CE-MRI	+	+	−	+	−
Case 9	CE-MRI	+	+	−	−	−
Case 10	CE-MRI	+	−	+	+	+

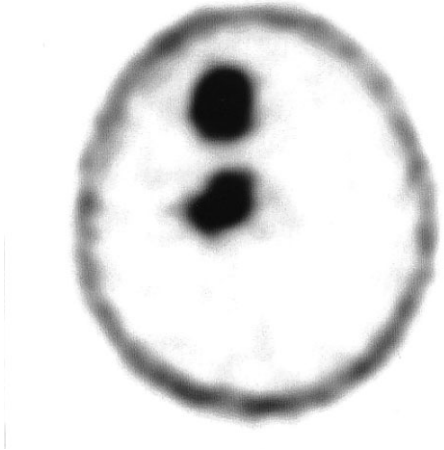
* Histopathological finding of Case 2 was obtained by biopsy.
** Histopathological finding of Case 4 was not referred as tumor resection had been performed after radiotherapy.
*** LIL: low intensity lesion on morphological method.



a



b



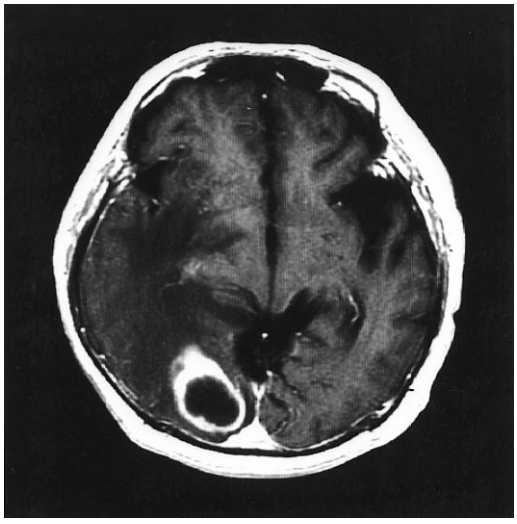
c

Fig. 1 a: Two ring-enhanced lesions were obtained in the right frontal lobe in CE-MRI (TR: 500, TE: 11). b: Tc SPECT of anterior tumor showed two sites with Tc uptake corresponding to necrosis in CE-MRI. c: Tl SPECT of anterior tumor exhibited two areas showing Tl activity corresponding to necrotic lesions in CE-MRI.

lesion with Tc uptake and that with Tl uptake, ROIs were set up in different areas. All 10 cases had ring-like lesions in CE-CT or CE-MRI, which showed as intense enhancement as bone cortex of skull in CE-CT or bone medulla of skull in CE-MRI. ROIs were automatically drawn by setting a threshold value of 50% to the maximum count of tumor in Tc SPECT and 80% in Tl SPECT. Regarding normal region, on the contralateral side, oval area in normal brain and a part of the scalp were selected in Tl SPECT. In Tc SPECT normal region was set up in a part of the skull on the contralateral side. Tc-T/N means the ratio of counts of ROI corresponding to extraosseous accumulation of Tc bone scanning agent to that of normal skull. As to Tl SPECT, T/N and T/S stand for the ratios of counts of ROI of tumor to those of normal region in brain and scalp, respectively. We evaluated whether Tc and Tl accumulated in the region shown as necrotic area in CE-CT or CE-MRI. Low density areas in ring-enhanced lesion were necrosis verified by histopathological study. If a patient had multiple lesions with extraosseous uptake, we regarded the one which had the most intense uptake as the focus. Furthermore Tc SPECT and Tl SPECT were compared with histopathological findings consisting of 8 results by resected tumors. One case which had histopathological finding by biopsy and one case which had tumor extraction after radiotherapy were excluded. All patients provided informed consent.

RESULTS

Table 2 shows the morphological methods, and the results of histopathological examination, Tc SPECT and Tl SPECT. All 10 cases showed intensely ring-enhanced tumors in contrast enhanced CT (CE-CT) or contrast enhanced MRI (CE-MRI). With respect to the histopathological findings, necrosis with hypervascularity (Cases 1, 8, 9) or bleeding (Cases 3, 5, 6, 10) was present in 7 of 10 cases with intensely ring-enhanced lesion in CE-CT or CE-MRI. Of the remaining 2 cases, one case, malignant lymphoma showed only increased vascularity by biopsy and the other one (Case 4) was excluded because of resection at postradiotherapy. So, in cases 2 and 4, their low intensity area in CE-CT or CE-MRI could not be investigated pathologically. Comparing CE-CT/CE-MRI with Tc/Tl SPECT by visual evaluation, among 8 cases showing ring-like enhanced lesion in CE-CT or CE-MRI, 3 cases showed Tc and Tl accumulation in the site appearing like necrosis, 2 cases showed no Tc nor Tl uptake. Two tumors exhibited only Tc uptake, and one tumor did only Tl uptake in necrotic area (Table 2). Figure 1a showed two ring-enhanced lesions in the right frontal lobe in CE-MRI (TR: 500, TE: 11) of the patient diagnosed with glioblastoma (Case 5). The necrotic lesion of anterior tumor took up Tc and Tl in Tc SPECT and Tl SPECT (Fig. 1b, Fig. 1c). In Figure 2a, a ring-enhanced area of right occipital lobe was obtained in CE-MRI (TR: 500, TE: 11) of the



a

c

b

Fig. 2 a: There was an intensely contrasted area in the right occipital lobe using CE-MRI (TR: 500, TE: 11). b: In Tc SPECT of occipital tumor, there was no accumulation of Tc in the lesion corresponding to necrosis in CE-MRI. c: In Tl SPECT of parietal tumor, doughnut-shaped Tl uptake, which had no accumulation in the site appearing to necrosis in CE-MRI, was disclosed.

patient diagnosed to have metastatic adenocarcinoma (Case 9). Tc SPECT and Tl SPECT of the occipital lobe exhibited increased uptake to the region shown as enhanced lesion on CE-MRI and no uptake in the necrotic site (Fig. 2b, Fig. 2c). Correlation coefficients of early T/N, delayed T/N, early T/S and delayed T/S to Tc-T/N were 0.0359, 0.0321, 0.1997 and 0.1293, respectively. Figure 3 shows the correlation between Tc-T/N and early T/S.

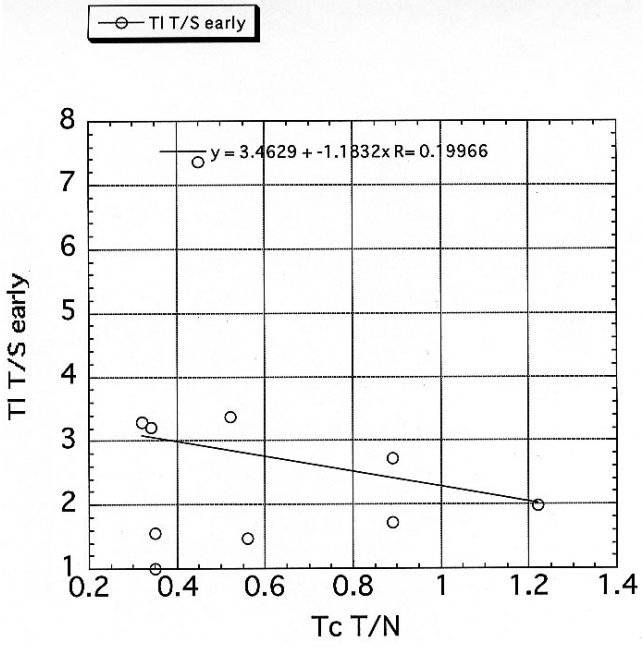


Fig. 3 Correlation between Tc-T/N and early T/S.

DISCUSSION

Extraosseous uptakes in ^{99m}Tc phosphate complexes scintigraphy have been reported to be found in malignant tumors,[7] benign tumors,[8] cerebral infarction,[4] myocardial infarction[9] and ectopic calcinosis[10,11] and so on. Numerous hypotheses are available to explain the mechanism of extraosseous accumulation. Increased vascularity, capillary permeability, abnormal cellular calcium metabolism, abnormality in binding of ^{99m}Tc phosphate complexes to phosphate enzymes, and binding of ^{99m}Tc phosphate to immature collagen have all been proposed as the mechanism.[12]

In this study, histopathological findings showed necrosis with hypervascularity or bleeding in 7 of 8 cases whose tumors were resected without therapy. But the result could not lead to the conclusion that extraosseous uptake

was caused by the presence of calcium in necrotic lesion. Our study showed 3 cases (Cases 1, 6, 9) of 8 cases with no Tc uptake in necrotic lesion of CE-MRI. If accumulation of Tc was caused only by calcium deposition in necrosis, this result would not be obtained. ^{99m}Tc phosphate complexes are useful in the diagnosis in acute myocardial infarction.[13–17] In previous studies about ^{99m}Tc-labeled pyrophosphate in infarcted myocardium, the authors concluded that the uptake of technetium chelates in myocardial infarcts may be due to the formation of polynuclear complexes with denatured macromolecules rather than to the deposition of calcium in mitochondria.[18] On the other hand, Buja et al. noted concentration of ^{99m}Tc phosphorus (^{99m}Tc-P) radiopharmaceutical in acute myocardial infarct results from selective adsorption of ^{99m}Tc-P with various forms of tissue calcium stores but is reflected by physicochemical properties of tissue calcium stores and local blood flow.[9]

As to brain tumor, Tl SPECT has been used in evaluating the malignancy of tumors,[19–22] differential diagnosis between recurrence of tumor and necrosis,[23,24] investigation of response to treatment[25–27] and differential diagnosis[28] because Tl is a radiopharmaceutical which accurately reflects tumor viability.[29] It is said that Na^+-K^+ ATPase pump, local blood flow and destruction of blood brain barrier (BBB) affect the uptake of Tl.[20,30] Ohnishi et al. suggest that thallium index (early index and delayed index) has a good correlation with intensity of enhancement in CE-CT images caused by destruction of BBB.[31] But our study revealed that concentration of Tc and Tl had no correlation with intensity of tumor in CE-CT or CE-MRI. Furthermore 4 (Cases 5, 6, 7, 10) of 8 cases which had histopathological report of resected tumor before therapy revealed Tl uptake in necrotic lesion of CE-MRI and one (Case 6) of 4 cases showed no Tc uptake in the area. In a previous study by Front,[32] tumors with permeable vessel or increased vascularity were demonstrated to invoke high uptake of Tc. Brain tumors have blood vessels anatomically different from normal ones. High grade malignant tumor has edema resulting from hyperpermeability.[33]

Tc-T/N had no significant correlation with early T/N, delayed T/N, early T/S or delayed T/S, but it is interesting that there were inverse correlations in all comparison. Sehweil et al. concluded that the mechanism of Tl uptake of tumors is similar to that in myocardium, and sodium potassium pump activity appears to be more important than tumor blood flow.[34] It is likely that uptakes of both Tc and Tl preferentially depend on their peculiar biochemical mechanisms from our semi-quantitative study. So the fact that semi-quantitative evaluation showed inverse correlation suggests that the much more non-viable cells a tumor had, the higher Tc-T/N was. In conclusion, extraosseous accumulation was caused by not only a single factor but multiple factors, such as necrosis, increased vascularity, permeability of vessels, and Tc uptake did not correlate with Tl uptake in semi-quantitative study of malignant brain tumors. More studies in this area, involving many cases or consisting of brain tumors with the same pathological findings are needed.

REFERENCES

1. Yasuda E, Yoshida H, Ichikawa H, Matsuo S, Kimura T, Kanamori I, et al. Extraosseous accumulation of ^{99m}Tc-MDP—with special reference to intratumor accumulation. *Rinsho Hoshasen* 1983; 28: 851–857. (in Japanese)
2. Sty JR, Starshak RJ, Casper JT. Extraosseous accumulation of ^{99m}Tc-MDP. Metastatic intracranial neuroblastoma. *Clin Nucl Med* 1983; 8: 26–27.
3. Ozarda AT, Legaspi JR, Haynie TP. Detection of a brain metastasis from osteosarcoma with ^{99m}Tc-methylene diphosphonate bone scanning. *Eur J Nucl Med* 1983; 8: 552–554.
4. Grames GM, Jansen C, Carlsen EN, Davidson TR. The abnormal bone scan in intracranial lesions. *Radiology* 1975; 115: 129–134.
5. Chaudhuri TK, Chaudhuri TK, Gulesserian HP, Christie JH, Tonami N. Extraosseous noncalcified soft-tissue uptake of ^{99m}Tc-polyphosphate. *J Nucl Med* 1974; 15: 1054–1056.
6. Suzuki A, Togawa T, Kuyama J, Nakahara T, Yui N, Iuchi T, et al. Extraosseous accumulation of ^{99m}Tc phosphonate complexes in primary brain tumor evaluated with SPECT. *Ann Nucl Med* 2002; 16: 495–498.
7. Shiomi S, Kuroki T, Hasegawa I, Nishio H, Azuma K, Ochi H. Accumulation of ^{99m}Tc-HMDP in hepatic metastasis from colon carcinoma without detectable calcification. *Ann Nucl Med* 1996; 10: 347–349.
8. Rengachary SS, Batnitzky S, Arjunan K. Diagnosis of intracranial meningioma with radionuclide bone scan. *Surg Neurol* 1980; 14: 337–341.
9. Buja LM, Tofe AJ, Kulkarni PV, Mukherjee A, Parke RW, Franci MD, et al. Sites and mechanisms of localization of technetium-99m phosphorus radiopharmaceuticals in acute myocardial infarcts and other tissues. *J Clin Invest* 1977; 60: 724–740.
10. Yoshida S, Fukumoto M, Yoshimura N, Oobayashi K, Takada Y. Ectopic accumulation of ^{99m}Tc-HMDP in primary lung cancer in comparison with CT findings. *Ann Nucl Med* 1996; 10: 329–333.
11. Togawa T, Hoshi K, Kimura K, Sato T, Matsuda S, Uchida T, et al. A case of adult T-cell leukemia with metastatic calcification. *Eur J Nucl Med* 1985; 10: 90–92.
12. Rosenthall L. ^{99m}Tc-methylene diphosphonate concentration in soft tissue malignant fibrous histiocytoma. *Clin Nucl Med* 1978; 3: 58–61.
13. Parkey RW, Bonte FJ, Meyer SL, Atkins JM, Curry GL, Stokely EM, et al. A new method for radionuclide imaging of acute myocardial infarction in humans. *Circulation* 1974; 50: 540–546.
14. Corbett JR, Lewis M, Willerson JT, Nicod PH, Huxley RL, Simon T, et al. ^{99m}Tc-pyrophosphate imaging in patients with acute myocardial infarction: comparison of planar imaging with single-photon tomography with and without blood pool overlay. *Circulation* 1984; 69: 1120–1128.
15. Fujiwara Y, Itoh T, Douiuchi J, Ochi T, Kokubu T, Murase

K, et al. Quantitative analysis of acute myocardial infarction using single photon emission computed tomography using technetium-99m pyrophosphate. *J Cardiogr* 1986; 16: 555–562.
16. Krause T, Hohnloser SH, Kasper W, Schumichen C, Reinhardt M, Moser E. Assessment of acute myocardial necrosis after cardiopulmonary resuscitation and cardioversion by means of combined thallium-201/technetium-99m pyrophosphate tomography. *Eur J Nucl Med* 1995; 22: 1286–1291.
17. Kawano M, Taki J, Kinuya S, Higuchi T, Nakajima K, Miyazaki Y, et al. Improvement of ^{99m}Tc-pyrophosphate scintigraphy in detection of acute myocardial infarction: combined with ^{99m}Tc-tetrofosmin. *KAKU IGAKU (Jpn J Nucl Med)* 2001; 38: 707–713. (in Japanese)
18. Dewanjee MK, Kahn PC. Mechanism of localization of ^{99m}Tc-labeled pyrophosphate and tetracycline in infarcted myocardium. *J Nucl Med* 1976; 17: 639–646.
19. Slizofski WJ, Krishna L, Kasetos CD, Black P, Miyamoto C, Brown SJ, et al. Thallium imaging for brain tumors with results measured by semiquantitative index and correlated with histopathology. *Cancer* 1994; 74: 3190–3197.
20. Igase K, Oka Y, Ohta S, Murakami Y, Kumo Y, Sasaki S. Usefulness of thallium-201 single photon emission computed tomography to quantify the malignancy grade of brain tumors. *Neurol Med Clir (Tokyo)* 1996; 36: 434–439.
21. Kallen K, Heiling M, Andersson AM, Brun A, Holtas S, Ryding E, et al. Evaluation of malignancy in ring enhancing brain lesions on CT by thallium-201 SPECT. *J Neurol Neurosurg Psychiatry* 1997; 63: 569–574.
22. Higa T, Maetani S, Kobayashi Y, Nabeshima S. ^{201}Tl SPECT compared with histopathologic grade in the prognostic assessment of cerebral gliomas. *Clin Nucl Med* 2001; 26: 119–124.
23. Kosuda S, Shinoyama Y, Kamata N, Suzuki K, Tanaka Y, Nakamura O, et al. Differential diagnosis between recurrence of brain tumor and radiation necrosis by ^{201}Tl SPECT. *Nippon Igaku Hoshasen Gakkai Zasshi* 1991; 51 (4): 415–421. (in Japanese)
24. Serizawa T, Ono J, Odaki M, Hirai S, Sato M, Matsuda S, et al. Differentiation between tumor recurrence and radiation injury after gamma knife radiosurgery for metastatic brain tumors: value of serial thallium-201 chloride SPECT. *Jpn J Neurosurg (Tokyo)* 2001; 10: 726–732. (in Japanese)
25. Yoshii Y, Satou M, Yamamoto T, Yamada Y, Hyodo A, Nose T, et al. The role of thallium-201 single photon emission tomography in the investigation and characterization of brain tumors in man and their response to treatment. *Eur J Nucl Med* 1993; 20: 39–45.
26. Seo H, Sato K, Fujita T, Yamada K, Nakai O, Komatani A. Sequential changes in SPECT using ^{201}Tl chloride during the treatment of intracranial gliomas. *No To Shinkei* 1993; 45: 537–543. (in Japanese)
27. Tomura N, Kobayashi M, Seino Y, Ishikawa H, Watarai J, Kato T, et al. Usefulness of ^{201}TlCl-SPECT in the evaluation of radiation and chemotherapy for brain tumors. *Nippon Igaku Hoshasen Gakkai Zasshi* 1993; 53: 484–486. (in Japanese)
28. Kojima Y, Kuwana N, Noji M, Tosa J. Differentiation of malignant glioma and metastatic brain tumor by thallium-201 single photon emission computed tomography. *Neurol Med Chir (Tokyo)* 1994; 34 (9): 588–592.
29. Kaplan WD, Takvorian T, Morris JH, Rumbaugh CL, Connolly BT, Atkins HL. Thallium-201 brain tumor imaging: comparative study with pathologic correlation. *J Nucl Med* 1987; 28: 47–52.
30. Lorberboym M, Baram J, Feibel M, Hercberg A, Lieberman L. A prospective evaluation of thallium-201 single photon emission computerized tomography for brain tumor burden. *Int Radiat Oncol Biol Phys* 1995; 32: 249–254.
31. Ohnishi H, Koizumi K, Uchiyama G, Yamaguchi M, Okada J, Ogata H, et al. Evaluation of malignancy and viability of brain tumors by ^{201}Tl SPECT: the correlation between ^{201}Tl SPECT and pathology, clinical progress and the intensity of enhancement on CT images. *Nippon Igakun Hoshasen Gakkai Zasshi* 1994; 54: 1388–1398. (in Japanese)
32. Front D. Scintigraphic assessment of vascularity and blood-tissue barrier of human brain tumors. *J Neural Neurosurg Psychiatry* 1978; 41: 18–23.
33. Nakagawara J, Fukuoka S, Takahashi S, Takahashi M, Satoh K, Suematsu K, et al. Assessment of vascularity and permeability in brain tumor using SPECT and ^{99m}Tc-DTPA-human albumin in relation to ^{201}Tl SPECT. *KAKU IGAKU (Jpn J Nucl Med)* 1993; 31: 117–124. (in Japanese)
34. Sehweil AM, Mckillop JH, Milroy R, Wilson R, Abdel-Dayem HM, Omar YT. Mechanism of ^{201}Tl uptake in tumors. *Eur J Nucl Med* 1989; 15: 376–379