Indium-111-Pentetreotide Imaging in Intra-axial Brain Tumors: Comparison with Thallium-201 SPECT and MRI

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Highly undifferentiated glial tumors do not express somatostatin receptors (SSR) in contrast to low-grade astrocytomas which contain SSR. To differentiate a malignant glioma from a low-grade astrocytoma and to distinguish an SSR-positive intra-axial brain tumor from an SSR negative one, ^{111}In-pentetreotide brain SPECT was prospectively undertaken. **Methods:** Eight patients with intra-axial brain tumors (three glioblastoma multiforme, one low-grade astrocytoma, one lymphoma, one medulloblastoma, one neurocytoma and one metastatic tumor) were studied. Thallium-201 and ^{111}In-pentetreotide brain SPECT were performed with a 3- to 4-day interval before surgery. The SPECT findings were compared with those of Gd-enhanced MRI. **Results:** Increased uptake of ^{111}In-pentetreotide was observed in all of the patients with glioblastoma multiforme (Grade +++ in two and Grade + in one) despite lack of SSR. Low-grade astrocytoma exhibited minimal uptake of ^{111}In-pentetreotide (Grade +). Remaining tumors had intense uptake of ^{111}In-pentetreotide. Thallium-201 SPECT showed similar findings to those of ^{111}In-pentetreotide scintigraphy except in two patients with glioblastoma multiforme: One with ^{201}Tl negative scan showed increased uptake of ^{111}In-pentetreotide and the other showed increased thallium uptake but minimal uptake of ^{111}In-pentetreotide. The uptake pattern of both ^{201}Tl and ^{111}In-pentetreotide appeared to correlate with Gd-enhanced MRI. **Conclusion:** Indium-111-pentetreotide scintigraphy is sensitive in the detection of intra-axial brain tumors; however, it has no role in assessing the tumor grading and in the definition of the receptor profile.

Key Words: brain tumors; indium-111-pentetreotide; thallium-201; SPECT; somatostatin; magnetic resonance imaging

J Nucl Med 1995; 36:537–541

Somatostatin is a neuroregulatory peptide synthesized in a wide variety of human tissues. It has been reported that high-affinity cell membrane somatostatin receptors (SSR) are present in most tumors, including those with amine precursor uptake and decarboxylation characteristics: pituitary tumors, endocrine pancreatic tumors, carcinoids, paragangliomas, small-cell lung cancers, medullary thyroid carcinomas and pheochromocytomas. In addition, lymphomas and a certain proportion of breast cancers contain SSR (*1,2*).

Receptors are present in meningiomas, oligodendrogliomas, neuroblastomas, and medulloblastomas. Highly undifferentiated glial tumors do not express SSR as compared to the differentiated glial tumors (*3–6*).

Radiolabeling of the somatostatin analog pentetreotide with ^{123}I or ^{111}In is now available. Several published reports demonstrated successful localization of SSR-positive tumors (*7–11*). However, few attempts were intended to differentiate a low-grade astrocytoma from a highly undifferentiated glioma with radiolabeled somatostatin analogs. The patients with intra-axial brain tumors underwent both ^{201}Tl and ^{111}In-pentetreotide imaging because ^{201}Tl SPECT is known to be effective in the grading of glial tumors (*12,13*). The scan findings were compared to MRI findings to evaluate whether ^{111}In-pentetreotide scintigraphy is useful in differentiating benign and malignant tumors or SSR-positive and SSR-negative tumors.

MATERIALS AND METHODS

Eight patients (five men, two women and one child, aged 4–65 yr) with pathologically proven intra-axial brain tumors were included in this study: three cases of glioblastoma multiforme (GM), one case each of low-grade astrocytoma, medulloblastoma, lymphoma, neurocytoma and metastasis from renal cell cancer. All patients underwent MRI before brain SPECT. T1 and T2-weighted images and gadolinium-DTPA (Gd)-enhanced images were obtained. Thallium-201 and ^{111}In-pentetreotide scans were obtained within 1 wk before surgery.

Thallium SPECT was performed 30 min after intravenous injection of 111 MBq (3 mCi) of ^{201}Tl on a dual-headed gamma camera equipped with low-energy, high-resolution, parallel-hole collimators (ADAC, Milpitas, CA). Four hours later, a delayed scan was obtained. Three to four days after the thallium SPECT scan, an ^{111}In-pentetreotide scan was obtained. Indium-111-chloride (111 MBq) was dispensed into the vial containing ^{111}In-pentetreotide (Mallinckrodt Medical, St. Louis, MO) and incubated for 30 min. Radiochemical purity was assessed by silica gel-impregnated, thin-layer chromatography (Gelman Science, Ann Arbor, MI). Over 98% of the ^{111}In was labeled to the ^{111}In-pentetreotide. Four and 24 hours after the injection, brain SPECT

Received May 4, 1994; revision accepted Sept. 20, 1994.

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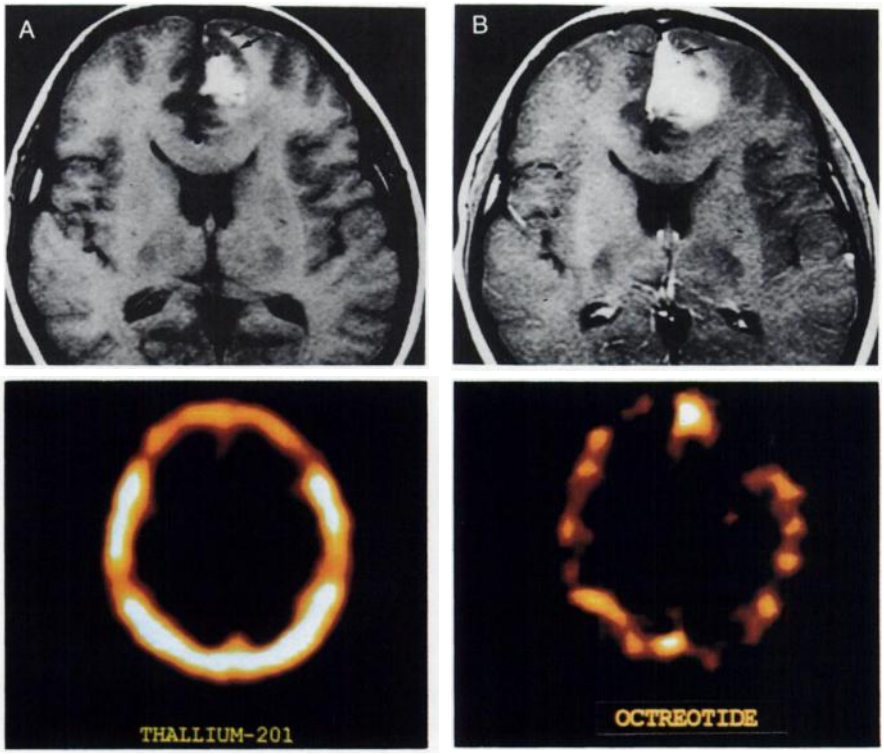

FIGURE 1. A 21-yr-old female with glioblastoma multiforme at the left frontal lobe. (A) Precontrast T1-weighted MRI shows increased signal intensity representing hemorrhagic necrosis at left frontal lobe in the vicinity of the anterior interhemispheric fissure. Surrounding low signal intensity of tumor tissue can be observed (arrows). (B) Gd-enhanced MRI depicts strong contrast enhancement along the periphery of the tumor (arrows). (C) Thallium-201 SPECT shows no radiotracer uptake within the tumor. (D) Indium-111-pentetreotide image demonstrates increased uptake along the periphery of the tumor margin, which is well matched with Gd-enhancement pattern on MRI.

images were obtained with a gamma camera equipped with medium-energy general purpose collimators. Sixty-four projections with an acquisition time of 40 sec/view were acquired in 64 × 64 matrices with 5.6 degrees of angular increments. The images were reconstructed with a filtered backprojection method using a Butterworth filter (cut-off frequency of 0.35 cycle/cm, order no. 5). Attenuation correction was not performed.

The thallium or indium activity within the tumor was assessed visually and scored.

Grade +++	intensity is higher than that of the scalp.
Grade ++	intensity is similar to that of the scalp.
Grade +	intensity is lower than that of the scalp.
Grade 0	nonvisualization of tumor activity.

The ^{111}In-pentetreotide images were compared with those of ^{201}Tl SPECT as to whether ^{111}In-pentetreotide uptake is inversely correlated with thallium uptake in gliomas or if the former is able to discriminate the presence or absence of SSR in tumors. The relationship between the Gd-enhancement pattern on MRI and that of radiotracer uptake was also evaluated.

RESULTS

In the patients with glioblastoma multiforme (n = 3), MRI showed intense ring-type or heterogeneous enhancement. Thallium images showed Grade +++ intensity in one, Grade ++ in another and Grade 0 in another patient.

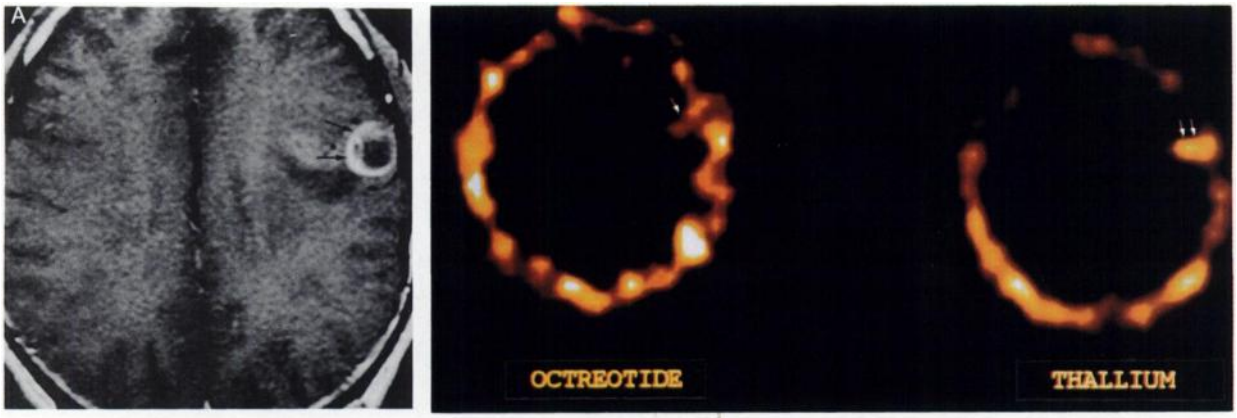

FIGURE 2. A 36-yr-old male with glioblastoma multiforme at left fronto-parietal region. (A) Gd-enhanced MRI shows ring enhancement of tumor mass (arrows) and low signal intensity, non-enhancing lesion at the infero-medial aspect of the tumor. (B) Both thallium and octreoscan show partial uptake of the radiotracers (arrows). The intensity of ^{111}In-pentetreotide is less than that of thallium.

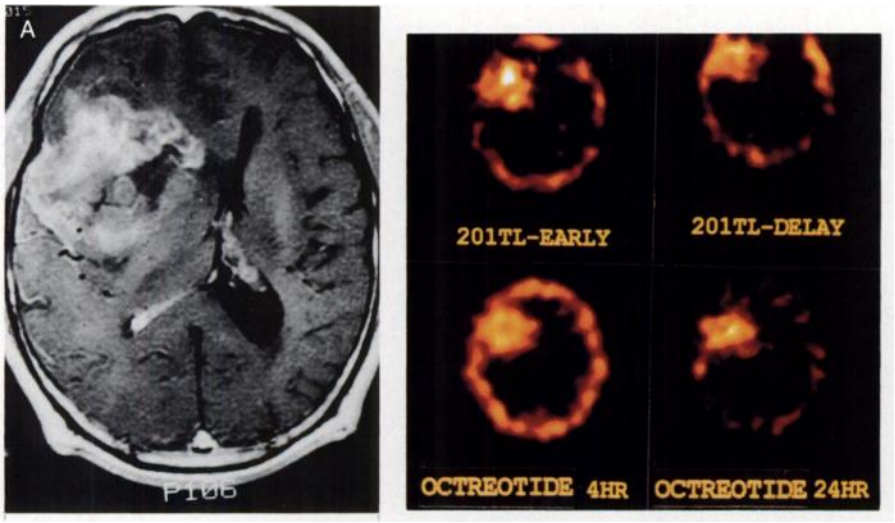

FIGURE 3. A 65-yr-old male with glioblastoma multiforme at the right frontotemporal area. (A) Gd-enhanced MRI shows a large tumor mass with irregular inhomogenous contrast enhancement and compression of ipsilateral lateral ventricle. (B) Thallium and an ^{111}In-pentetreotide image reveal intense radiotracer uptake on both early and delayed studies.

Grade +++ intensity was observed in two, and grade + in one on ^{111}In-pentetreotide image. When the ^{111}In-pentetreotide scintigraphic findings were compared with those of thallium images, a disparity of the uptake pattern could be observed. A patient with Grade 0 intensity on thallium scan had intense, Grade +++ activity on ^{111}In-pentetreotide scintigraphy along the margin of the tumor in which strong gadolinium enhancement was observed on MRI (Fig. 1). In another patient, Grade ++ of thallium activity was shown, however, uptake of ^{111}In-pentetreotide was less than thallium activity (Grade +). In this case, the area of radiotracer uptake is smaller than that of gadolinium enhancement on MRI (Fig. 2). The other patient had strong Grade +++ activity on both thallium and ^{111}In-pentetreotide scan and showed intense gadolinium enhancement (Fig. 3).

In the patient with low-grade astrocytoma, MRI showed a low signal intensity mass lesion without contrast-enhancement on T1-weighted images. Both thallium and ^{111}In-pentetreotide imaging showed partial uptake at the lateral margin of tumor (Grade + on ^{111}In-pentetreotide scan and Grade ++ on thallium scan) (Fig. 4).

All remaining tumors—metastatic tumor from renal cell cancer (Fig. 5), lymphoma, medulloblastoma and neurocytoma—revealed intense Grade +++ activity on both thallium and ^{111}In-pentetreotide images as well as intense gadolinium enhancement within the tumors on MRI. Delayed thallium and ^{111}In-pentetreotide image did not appear to be helpful in the detection or characterization of these tumors. All data are summarized in Table 1.

DISCUSSION

Grading of glial-derived tumors has been a clinical and pathological problem. Thallium-201 SPECT is widely utilized in clinical trials for the differentiation of these tumors, since it is believed to be preferentially taken up by active

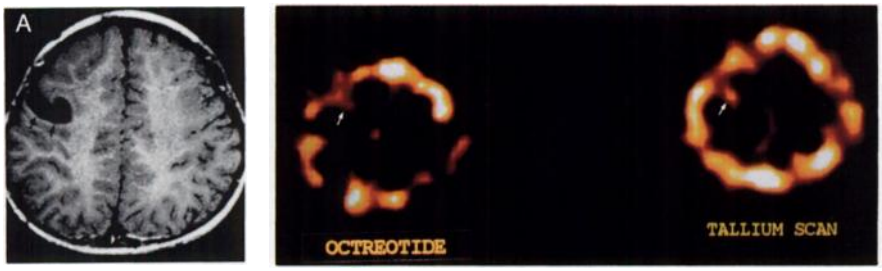

FIGURE 4. A 4-yr-old child with a low-grade astrocytoma at right frontal lobe. (A) Gd-enhanced MRI shows a nonenhancing low signal intensity mass (arrows). (B) SPECT images show minimal uptake of radiotracers at the lateral aspect of the tumor (arrows).

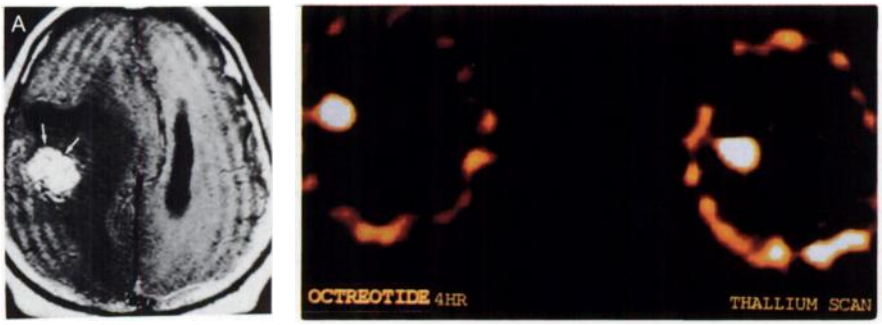

FIGURE 5. A 57-yr-old male with metastatic tumor from renal cell carcinoma at right parietal lobe. (A) Gd-enhanced MRI shows strong enhanced nodular lesion (arrows) with surrounding low intensity brain edema. (B) SPECT images show marked increased uptake within the tumor mass.

TABLE 1
Summary of SPECT and MRI Findings

Patient no.	Pathology	Gd-Enhancement	^{201}Tl	^{111}In-pentetreotide	SSR
1	GM	Nodular and heterogeneous	+++	+++	neg
2	GM	Ring-type	++	+	neg
3	GM	Marginal	0	+++	neg
4	Astrocytoma	None	++	+	pos
5	Lymphoma	Ring and nodular	+++	+++	pos
6	Medulloblastoma	Ring and heterogeneous	+++	+++	pos
7	Neurocytoma	Heterogenous	+++	+++	?
8	Metastasis	Nodular	+++	+++	pos

GM = glioblastoma multiforme; SSR = somatostatin receptor (obtained from in vitro data published in the literature); neg = negative; pos = positive.

tumor cells, especially in malignant cells (*12*). The ^{201}Tl scan, however, is limited due to thallium uptake within benign lesions such as tuberculosis, active sarcoidosis and fungal diseases (*14,15*). Therefore, more specific agents to distinguish malignant from benign tumors are required.

Recently, ^{111}In-pentetreotide scintigraphy was evaluated for the in vivo detection and localization of SSR-positive tumors. In vitro studies have demonstrated that low-grade astrocytomas contain SSR but high-grade astrocytomas do not express SSR. Therefore, we assumed that ^{111}In-pentetreotide imaging might be effective in the differentiation of benign and malignant astrocytomas. Contrary to the in vitro study, our results demonstrated strong uptake of ^{111}In-pentetreotide in two of three malignant gliomas, mild increased uptake in one patient, but minimal uptake in low-grade astrocytoma.

In an effort to distinguish an SSR-positive from a SSR-negative tumor, the ^{111}In-pentetreotide scan did not seem to be effective since SSR-negative tumors as well as SSR-positive tumors (*16,17*) showed intense uptake of ^{111}In-pentetreotide in our study. Similar results have been reported by Scheidhauer (*18*) and Luyken (*19*). In neurocytoma, which resembles oligodendroglioma light microscopically but has features of neuroendocrine differentiation ultrastructurally (*20*), intense uptake of ^{111}In-pentetreotide was seen. Until now, it was uncertain, however, whether or not neurocytoma has SSR.

The mechanism of intense uptake of ^{111}In-pentetreotide within SSR-negative tumors is uncertain. A damaged blood-brain barrier (BBB) might play a key role in radiotracer retention. Another possible explanation is binding of ^{111}In-pentetreotide to the activated lymphocytes within the tumors (*21*); however, pathologic specimens obtained from SSR-negative tumors in our study did not demonstrate neoplastic lymphocytic infiltration. Therefore, we assumed that ^{111}In-pentetreotide accumulated in these tumors by penetrating the damaged BBB and a poor washout from the tumors. In low-grade astrocytoma, new capillaries in the tumor tissue resemble normal cerebral capillaries with maintenance of BBB (*22,23*) to prevent binding of ^{111}In-pentetreotide to the receptors despite an abundance of SSR. In this case, ^{201}Tl may not be effective in demonstrating tumors.

The neurocytoma, categorized as a benign tumor, showed intense uptake of both ^{111}In-pentetreotide and ^{201}Tl and revealed strong gadolinium enhancement. The intense thallium uptake in neurocytoma is contrary to the reported theory that thallium is preferentially taken up by malignant tumors. Therefore, an altered BBB might play a major role in the accumulation of radiotracer within tumor tissues.

In conclusion, a ^{111}In-pentetreotide scan is sensitive in the detection of intra-axial brain tumors with a damaged BBB, however, it does not seem to be SSR-specific nor can it differentiate a malignant glioma from a low-grade astrocytoma on the basis of SSR expression.

ACKNOWLEDGMENTS

The authors thank Anthony MinYen Chai, regional director of Mallinckrodt Medical for the kind donation of ^{111}In-pentetreotide and Mr. C. H. Lee, Mr. C. H. Kim, Mr. S. J. Pyo and Mr. J. W. Chang for their excellent technical assistance.

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