# Somatostatin Receptor Scintigraphy in Central Nervous System Tumors: Role of Blood-Brain Barrier Permeability

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Somatostatin receptors are expressed in meningiomas and low-grade gliomas, raising the hope that scintigraphy with $^{111}$In-DTPA-D-Phe1-octreotide might be helpful in the in vivo localization, differential diagnosis and postoperative/postradiotherapy brain tumor follow-up. **Methods:** Indium-111-DTPA-D-Phe1-octreotide scintigraphy and brain scintigraphy using $^{99m}$Tc-DTPA as a nonspecific tracer for blood-brain barrier integrity were simultaneously performed in 60 patients with CNS tumors using dual-isotope acquisition mode SPECT. For 23 patients, the scintigraphic findings were also compared with in vitro somatostatin receptor autoradiography of surgical biopsy specimens. **Results:** In meningiomas (located outside the blood-brain barrier), the somatostatin receptor scan showed all tumors and scintigraphic signal intensity correlating with in vitro SSR density positive in all meningiomas. Less contrast was seen on $^{99m}$Tc-DTPA scans. In all tumors inside the blood-brain barrier, the $^{111}$In-DTPA-D-Phe1-octreotide scan visualized the tumors with a disrupted blood-brain barrier, as seen by $^{99m}$Tc-DTPA scintigraphy. Discrepancies, however, were observed between somatostatin receptor scintigraphy and in vitro receptor autoradiography. **Conclusion:** Combined somatostatin receptor and $^{99m}$Tc-DTPA scintigraphy may be helpful for noninvasive differentiation between meningiomas and other CNS tumors. False-negative scans were observed as a result of shielding by the intact blood-brain barrier. Interpretation of negative and positive somatostatin receptor scans in CNS tumors must therefore be done with caution.

**Key Words:** indium-111-DTPA-D-Phe1-octreotide; somatostatin receptors; blood-brain barrier

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Many tumors are known to express somatostatin receptors (SSR), and SSR imaging with $^{111}$In-DTPA-D-Phe1-octreotide has been shown to be of clinical relevance in neuroendocrine tumors, particularly islet cell carcinomas, carcinoids and medullary thyroid carcinomas (*1–4*). Furthermore, the imaging-based determination of SSR positive tumors seems relevant for subsequent somatostatin analog treatment (*2*).

Central nervous system (CNS) tumors are among those that express SSR to varying degrees. Of the meningiomas, virtually all (*5*) express SSR as shown by SSR autoradiography, while SSR expression in gliomas seems dependent on tumor differentiation. Low-grade gliomas, such as astrocytomas, express SSR at a high percentage (82%), while glioblastomas are rarely (2%) SSR-positive (*6*). Therefore, SSR imaging of brain tumors could provide clinically relevant information in the presurgical and follow-up management of such patients (*7,8*). Moreover, it has been suggested that in patients with neuroblastoma (*9*) or breast cancer (*10*) tumors with SSR may have a different prognosis compared to SSR-negative tumors.

Because octreotide is a polar, water soluble peptide (eight amino acids), it must be presumed from earlier experience with brain scintigraphy (*11–13*) that it may only penetrate into those tumors with a disrupted blood-brain barrier (BBB). Indeed, all patients scanned with labeled octreotide for peripheral tumors without brain pathology were shown to have no visualization of their CNS (*3*), despite strong SSR expression in various human CNS regions (*14*). In order to elucidate the role of the BBB in SSR scintigraphy of patients with CNS tumors, we studied the integrity of the BBB in a dual-isotope technique, using $^{99m}$Tc-DTPA as a nonspecific tracer. Scans were performed the day prior to surgery. The results of in vivo SSR imaging were compared with in vitro SSR autoradiography of surgical biopsy specimens and in some strongly SSR-positive tumors. Ex vivo autoradiography with $^{111}$In-DTPA-D-Phe1-octreotide injected the day prior to surgery was also performed.

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## MATERIALS AND METHODS

### Patients

Between November 1992 and June 1994, 60 patients were scanned for somatostatin receptors of radiologically documented CNS mass lesions. In 23 of these patients (10 female, 13 male; mean age 52 yr, range 17–71 yr; 22 brain tumors, 1 spinal tumor) simultaneous SSR/$^{99m}$Tc DTPA imaging was performed and biopsy specimens for histology and SSR autoradiography were obtained.

### SSR/$^{99m}$Tc-DTPA Scintigraphy

A mean dose of 100 MBq $^{111}$In-DTPA-D-Phe1-octreotide (*15*) was intravenously injected. Two hours later 740 MBq $^{99m}$Tc-DTPA was injected. SPECT was performed 4 hr after $^{111}$In-DTPA-D-Phe1-octreotide injection (2 hr after $^{99m}$Tc-DTPA) on a triple-head gamma camera (Picker) with multiple peak acquisition (high-energy collimator, 64 × 64 matrix, 15% windows for the $^{99m}$Tc and both $^{111}$In peaks; reconstruction using Butterworth filter; distance between transversal slices 5.5 mm). Total counts in the transversal slices were typically five times higher for $^{99m}$Tc than $^{111}$In.

### Scan Quantification

Qualitative evaluation of the lesions was performed by visually comparing tumor uptake with uptake in the controlateral occipital skull (+: tumor uptake less than occipital skull; ++: tumor uptake comparable to occipital skull; +++: tumor uptake greater than occipital skull). For semiquantitative evaluation of SSR scans, the transverse tomographic slice with highest tumor contrast was selected in each patient and a tumor ROI was manually drawn. A tumor-to-background ratio was then calculated as the ratio of average count rates per pixel of the tumor ROI to a background ROI over the controlateral skull. To determine the SSR-to-brain scintigraphy index, the tumor ROIs drawn in the $^{111}$In reconstructions were used in the same transverse tomographic slices for the $^{111}$In and $^{99m}$Tc reconstructions. The SSR-to-brain scintigraphy index was then determined as the ratio of the $^{111}$In to $^{99m}$Tc tumor ROI count rates after normalization with the total counts in the slice. In negative scans the SSR-to-brain scintigraphy index was set to be 1.0. Statistical analysis of SSR-to-brain scintigraphy index was performed using Wilcoxon rank sum test (normal approximation; with continuity correction of 0.5).

### Ex Vivo Autoradiography

Ex vivo autoradiography was performed in selected tumors (*16*). These tumors were resected surgically 24 hr after the patients were injected with $^{111}$In-DTPA-D-Phe1-octreotide. The gamma spectra of two specimens highly positive in SSR/$^{99m}$Tc-DTPA scintigraphy (meningiomas) showed activity only in the two $^{111}$In peaks with no detectable peak in the $^{99m}$Tc energy region 24 hr after injection. The specimens were frozen immediately and cut 20 $\mu$m thick on cryostat. For ex vivo autoradiography the sections were apposed to Betamax (Amersham) films for 1 to 3 wk. Once the $^{111}$In related radioactivity had disappeared, adjacent sections of these tissues were also processed for in vitro receptor autoradiography using $^{125}$I-Tyr-3-octreotide (*17*).

### SSR In Vitro Autoradiography

The presence of somatostatin receptors in the various specimens was investigated by in vitro receptor autoradiography on 20-$\mu$m thick frozen sections of tissue. This technique has previously been described in detail for various types of tumoral and nontumoral tissues (*5,6,14*). Iodine-125-Tyr3-octreotide, which has previously been shown to specifically label somatostatin receptors, was used as the radioligand (*17*). The autoradiograms were quantitatively analyzed by means of a computer-assisted image processing system (*6,18*). Radioactive polymer standards for iodinated compounds were used for this purpose (*18*). The content of somatostatin receptors in tumors is represented by four categories (*19*):

- +++ represents tumors with very strongly positive somatostatin receptors (>3000 dpm/mg tissue).
- ++ represents tumors with strongly positive somatostatin receptor density (1000–3000 dpm/mg tissue).
- + represents tumors with positive somatostatin receptor density (<1000 dpm/mg tissue).
- Negative absence of somatostatin receptors defined as an optical density on the films from total binding lower than twice the nonspecific binding.

## RESULTS

### SSR/$^{99m}$Tc-DTPA Scintigraphy

A total of 15 lesions were detected in 23 SSR/$^{99m}$Tc-DTPA scans. The results are summarized in Table 1. All positive SSR lesions had positive $^{99m}$Tc-DTPA scans and all negative SSR scans had negative $^{99m}$Tc-DTPA scans. In meningiomas (Table 1; Patients 1–7) all SSR scans were positive, most of them strongly positive. A higher contrast was noted in the SSR scan compared to the $^{99m}$Tc-DTPA scan. In all tumors within the BBB results of SSR scintigraphy and $^{99m}$Tc-DTPA were concordant. Negative scintigrams were found in five gliomas grade I–III, two neurinomas and one ependymoma (Table 1; Patients 8–15). Positive scintigrams were found in four gliomas grade IV, one oligodendroglioma III, one low-grade astrocytoma, one neurinoma and a non-Hodgkin lymphoma (Table 1; Patients 16–23). In two patients with negative SSR/$^{99m}$Tc-DTPA scans and in one patient with positive SSR/$^{99m}$Tc-DTPA scan 24 hr images ($^{111}$In peaks only) we saw results identical with the 4 hr images (Table 1; Patients 8, 9, 20).

### Comparison of SSR/$^{99m}$Tc DTPA Scans with In Vitro SSR Autoradiography

In meningiomas (Table 1; Patients 1–7) there was an excellent correlation between the results of SSR scintigraphy and in vitro SSR autoradiography showing positive SSR expression in vivo and in vitro in all patients. Figure 1 shows an example of the concordant positive results of the SSR/$^{99m}$Tc-DTPA scans, in vitro detection of a high density of SSR and the corresponding ex vivo autoradiography in a meningioma.

Comparing quantitative in vitro SSR expression and in vivo tumor-to-background ratios (SSR scans), we discovered a good linear correlation ($r = 0.97$) between the intensity of the scintigraphic signal with the SSR density. The two meningiomas with the relatively lowest SSR density also showed the lowest tumor-to-background ratios, while the two meningiomas with the highest tumor-to-background signals were found to express the highest SSR density.

Discordance was noted, however, in most tumors lo-

**TABLE 1**

| Patient no. | Age (yr) | Sex | Histological diagnosis | SSR scan* qual. (tumor-to-background ratio) | $^{99m}$Tc-DTPA scan* | SSR-to-brain scintigraphy index† | In vitro SSR autoradiography‡ | Ex vivo autoradiography | Corticosteroid medication§ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 46 | F | Meningioma | +++ (16.6) | ++ | 5.4 | +++ (8510) | Positive | — |
| 2 | 41 | F | Meningioma | +++ (20.5) | +++ | 4.1 | +++ (9150) | Positive | 150 (3) |
| 3 | 47 | F | Meningioma | +++ (23.5) | +++ | 3.2 | +++ (9750) | Positive | 150 (14) |
| 4 | 66 | M | Meningioma | +++ (30.5) | +++ | 2.4 | +++ (10080) | Positive | 45 (18) |
| 5 | 70 | F | Meningioma | +++ (4.1) | +++ | 2.2 | +++ (4930) | Positive | 50 (13) |
| 6 | 50 | F | Meningioma | ++ (1.3) | + | 2.2 | +++ (3100) | Positive | 150 (1) |
| 7 | 63 | F | Meningioma | + (1.0) | + | 1.5 | ++ (2700) | Not tested | 150 (1) |
| 8 | 59 | M | Glioma II | Negative (4 and 24 h) | Negative | 1.0 | ++ (1790) | Not tested | 75 (11) |
| 9 | 34 | M | Astrocytoma II | Negative (4 and 24 h) | Negative | 1.0 | ++ (2000) | Not tested | — |
| 10 | 40 | M | Astrocytoma II | Negative | Negative | 1.0 | Negative | Not tested | 150 (8) |
| 11 | 50 | M | Astrocytoma II–III | Negative | Negative | 1.0 | +++ (5410) | Negative | — |
| 12 | 45 | M | Astrocytoma III | Negative | Negative | 1.0 | +++ (3020) | Not tested | 75 (7) |
| 13 | 60 | M | Ependymoma | Negative | Negative | 1.0 | + (90) | Not tested | 150 (1) |
| 14 | 56 | M | Neurinoma | Negative | Negative | 1.0 | Negative | Not tested | — |
| 15 | 53 | F | Neurinoma | Negative | Negative | 1.0 | Negative | Not tested | — |
| 16 | 17 | M | Low-grade astrocytoma | ++ (1.6) | ++ | 1.4 | + (370) | Not tested | — |
| 17 | 57 | F | Oligodendroglioma III | +++ (3.9) | +++ | 1.1 | ++ (1250) | Not tested | 150 (5) |
| 18 | 51 | M | Glioma IV | +++ (3.2) | +++ | 1.3 | Negative | Not tested | 150 (11) |
| 19 | 71 | M | Glioma IV | ++ (1.6) | ++ | 1.1 | Negative | Not tested | 75 (11) |
| 20 | 58 | M | Glioma IV | 4 h: +++ (3.3) 24 h:+++ (4.0) | +++ | 0.9 | Negative | Not tested | 150 (5) |
| 21 | 51 | F | Glioma IV | +++ (2.0) | ++ | 1.0 | Negative | Not tested | 150 (8) |
| 22 | 38 | F | Neurinoma | ++ (1.5) | ++ | 0.9 | Negative | Not tested | 150 (4) |
| 23 | 69 | M | Non-Hodgkin's lymphoma | +++ (3.8) | +++ | 1.4 | Negative | Not tested | 150 (4) |

*Qualitative tumor signal (visually): +++ greater, ++ same, + less than controlateral occipital skull; for SSR scans the measured values of tumor-to-background ratios as average count rates per pixel of the tumor ROI to a background ROI over the controlateral skull are given in parenthesis.

†Ratio of $^{111}$In to $^{99m}$Tc count rates in identical tumor ROI after normalization with the total counts in the $^{111}$In and $^{99m}$Tc reconstructions.

‡Quantitative SSR densities: +++ represents tumors with very strongly positive somatostatin receptors (>3000 dpm/mg tissue), ++ represents tumors with strongly positive somatostatin receptor density (1000–3000 dpm/mg tissue), + represents tumors with positive somatostatin receptor density (<1000 dpm/mg tissue). Negative means absence of somatostatin receptors, defined as an optical density on the films from total binding lower than twice the nonspecific binding. Measured values in parenthesis.

§Equivalent to daily intake of prednisone in mg (duration in days) at time of SSR scan.

cated within the BBB. In the eight tumors with negative scans (Table 1; Patients 8–15) the SSR autoradiography in the same patients proved the presence of SSR by in vitro examination of surgical biopsy specimens in five out of eight tumors. In all the patients with false-negative SSR scans, the $^{99m}$Tc-DTPA scan showed no evidence of disruption of the BBB. Figure 2 shows such a discordance between the negative SSR/$^{99m}$Tc-DTPA scans and the detection of SSR in in vitro receptor autoradiography in a low-grade astrocytoma. Figure 3 shows the concordant negative SSR/$^{99m}$Tc-DTPA scans and the absence of tumoral SSR in in vitro autoradiography in an astrocytoma grade II. A high density of SSR is demonstrated in vitro in the surrounding normal brain tissue, but not seen scintigraphically because it lies within an intact BBB. In the eight patients with positive SSR/$^{99m}$Tc-DTPA scans (Table 1; Patients 16–23), in vitro SSR autoradiography detected SSR expression in only two instances (in a low-grade astrocytoma and in an oligodendroglioma III). Figure 4 shows such discordance between positive SSR/$^{99m}$Tc-DTPA scans and negative in vitro receptor autoradiography in a neurinoma. Despite the high in vitro SSR level of some of the astrocytomas having an intact BBB, these SSR could not be identified in vivo. Conversely, even a very low number of SSR in vitro with disrupted BBB may allow its in vivo visualization (Table 1). In the 16 tumors located inside the BBB comparison of in vitro SSR densities with tumor-to-background ratios in the SSR scan showed no correlation ($r = -0.36$).

### Ex Vivo Autoradiography

Selected tumors with positive SSR scans (Table 1) were shown to be labeled in situ with $^{111}$In-DTPA-D-Phe1-octreotide as measured by ex vivo autoradiography. Essentially identical results to in vivo $^{111}$In-DTPA-D-Phe1-octreotide scintigraphy were found. Interestingly, one astrocytoma, which was shown to contain SSR in the in vitro receptor autoradiography, was negative in the in vivo

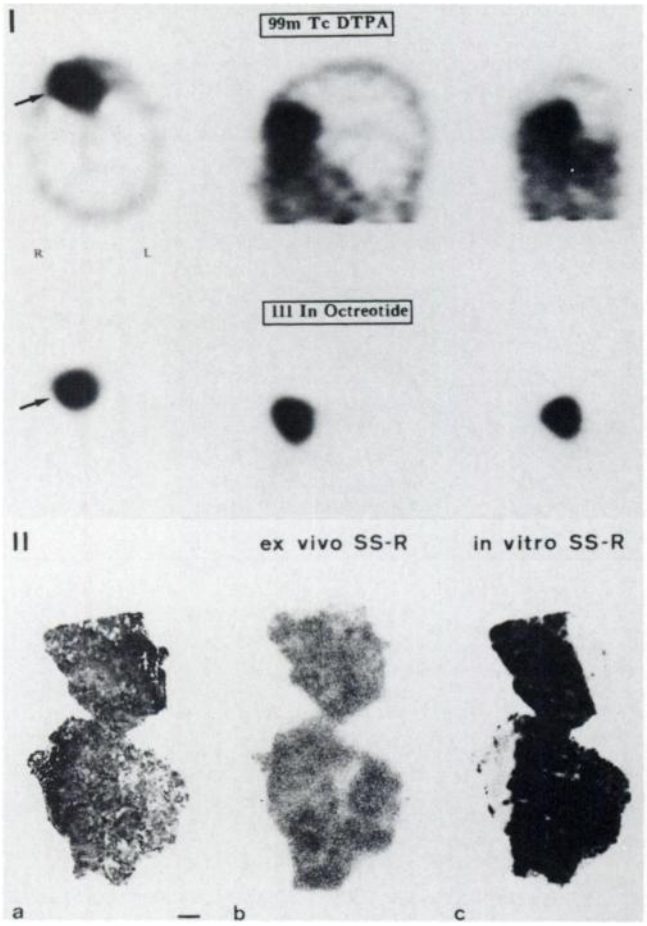


**FIGURE 1.** Concordance between positive SSR/$^{99m}$Tc-DTPA scans and very strongly positive SSR expression in vitro in a meningioma. I: Technetium-99m-DTPA and SSR scans in Patient 4 with right frontal meningioma. II: Corresponding histology (HE staining; IIa), ex vivo autoradiography with $^{111}$In-DTPA-D-Phe1-octreotide (IIb) and strong positive in vitro SSR autoradiography with [125I-Tyr3]-octreotide (total binding; IIc). Arrow: Tumor. Note the higher contrast in SSR compared to $^{99m}$Tc-DTPA scintigraphy (SSR-to-brain scintigraphy index 2.4).

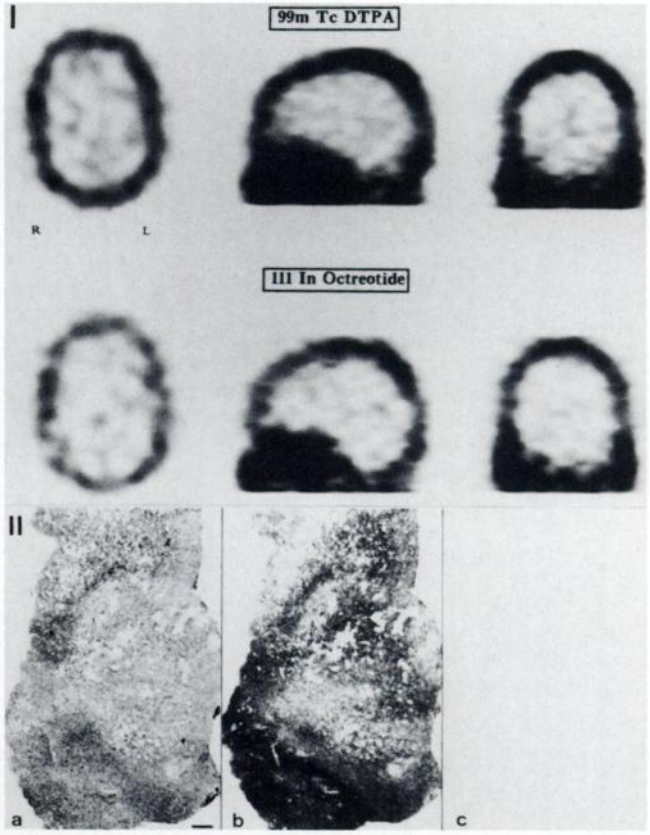


**FIGURE 2.** Discordance between negative SSR/$^{99m}$Tc-DTPA scans but very strongly positive SSR expression in vitro in an astrocytoma. I: Negative $^{99m}$Tc-DTPA and SSR scans in Patient 12 with right frontal low-grade astrocytoma. II: Corresponding histology (HE staining; IIa), strong positive in vitro SSR autoradiography with [125I-Tyr3]-octreotide (total binding; IIb) and autoradiogram showing nonspecific binding (in presence of an excess of unlabeled octreotide; IIc).

$^{111}$In-DTPA-D-Phe1-octreotide/$^{99m}$Tc-DTPA scans and in the ex vivo autoradiography.

### SSR-to-Brain Scintigraphy Index

In order to differentiate between various CNS lesions, we have introduced a SSR-to-brain scintigraphy index, which was calculated for all SSR/$^{99m}$Tc-DTPA scans (scan time 4 hr after $^{111}$In-DTPA-D-Phe1-octreotide and 2 hr after $^{99m}$Tc-DTPA injection, respectively). The results are listed in Table 1. For meningiomas, the SSR-to-brain scintigraphy index was 2.99 ± 1.35 (mean ± s.d.), in the other CNS tumors 1.07 ± 0.15. When comparing these two groups, a highly significant difference ($p = 0.0002$) was noted, as shown in Figure 5. As an example, the SSR and $^{99m}$Tc-DTPA scans of Patient 22 with radiologically suspected meningioma but low (0.9) SSR-to-brain scintigraphy index is shown in Figure 4. The histology revealed a neurinoma.

## DISCUSSION

Many radiopharmaceuticals have been used in an attempt to improve the difficult identification and grading of brain tumors, to estimate response to treatment and to elucidate the often difficult differential diagnosis between tumor recurrence, necrosis and edema in the postsurgical and post radiation/chemotherapy evaluation of patients with CNS tumors. Among these are $^{99m}$Tc pertechnetate, $^{99m}$Tc glucoheptonate, $^{67}$Ga citrate and in particular $^{201}$Tl, but their uptake into brain tumors is related to BBB function to a varying degree (*20–25*). Surface epitopes such as somatostatin or epidermal growth factor receptors offer the potential of specific in vivo characterization of tumors depending on receptor expression in histologically different tumors (*7*). However, interpretation of imaging results in CNS tumors may be complicated by the pivotal role played by an intact or disrupted BBB for correctly assessing the role of radioligands which act throughout a receptor-mediated mechanism. The present study is the first report aimed at evaluating SSR imaging in CNS tumors preoperatively by comparison of three different parameters in all patients

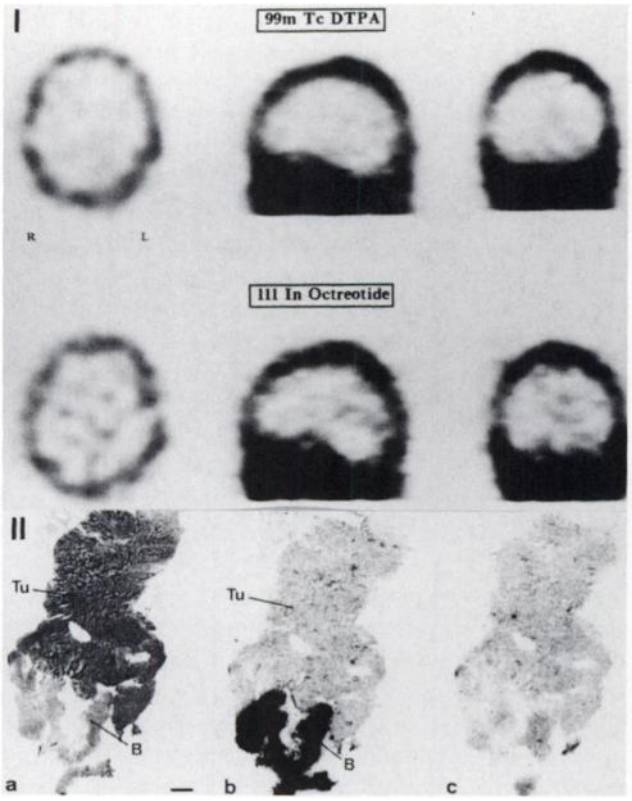


**FIGURE 3.** Concordance between negative SSR/$^{99m}$Tc-DTPA scans and absence of SSR expression in vitro in an astrocytoma. I: Negative $^{99m}$Tc-DTPA and SSR scans in Patient 10 with right frontotemporal grade II astrocytoma. II: Histology (HE staining, IIa) showing the tumor (Tu) and adjacent normal brain tissue (B). In vitro SSR autoradiography (total binding; IIb) shows SSR only in the normal brain tissue. (IIc) represents nonspecific binding.

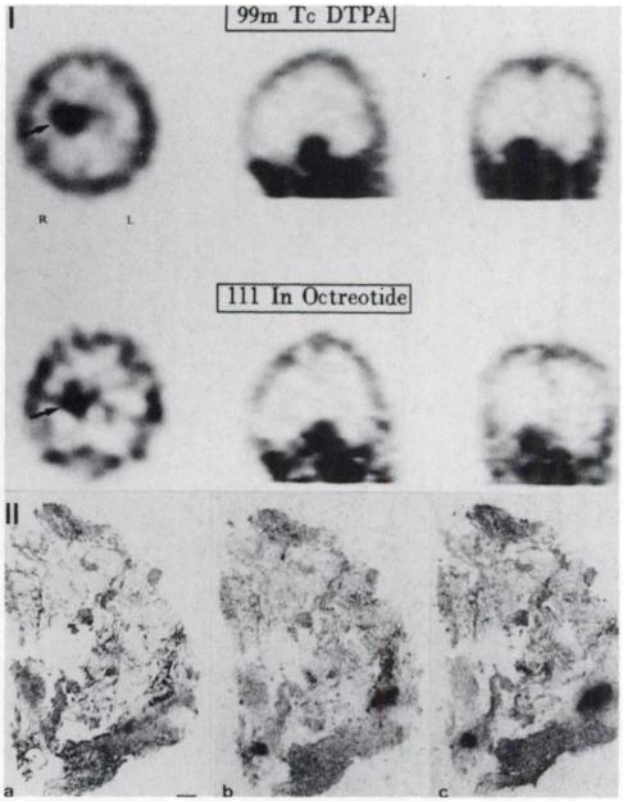


**FIGURE 4.** Discordance between positive SSR/$^{99m}$Tc-DTPA scans and absence of SSR expression in vitro in a neurinoma. I: Positive SSR and $^{99m}$Tc-DTPA scans in Patient 22 with neurinoma of right cavum trigeminale. II: Histology (HE staining) showing the tumor sample (IIa). Autoradiography (total binding; IIb); nonspecific binding (IIc); showing the absence of SSR on the tumor. Note that in this patient a meningioma was suspected radiologically. However, the low SSR-to-brain scintigraphy index (0.9), reflecting comparable contrast in the SSR and $^{99m}$Tc-DTPA scans, made this diagnosis unlikely in the preoperative scintigraphy. Arrow: Tumor.

examined: (1) in vivo SSR scintigraphy using $^{111}$In-DTPA-D-Phe1-octreotide, (2) testing BBB integrity using $^{99m}$Tc-DTPA brain scintigraphy (simultaneously acquired with SSR scintigraphy), and (3) in vitro SSR autoradiography. Furthermore, this study compares quantitatively the intensity of the scintigraphic signal in the SSR scans with in vitro SSR densities.

Tumor visualization was seen in all patients with meningiomas. Meningiomas are known to express a high density of SSR and are located outside the BBB. This is in accordance with the results reported in previous studies (*1,8,26,27*), showing positive SSR scans in all meningiomas. Most tumors showed intense $^{111}$In-DTPA-D-Phe1-octreotide uptake but in a few patients (e.g., in Patients 6 and 7) lower uptake was seen, likely due to a lower density of SSR. There was a less intense uptake noted in the $^{99m}$Tc-DTPA scintigraphy, suggesting that nonspecific $^{99m}$Tc-DTPA extravasation results in less contrast compared to the specific receptor binding in SSR scintigraphy in all tumors. We note an excellent correlation between in vivo SSR imaging (tumor-to-background ratio) and in vitro SSR autoradiography (SSR density) in meningiomas. This indicates that the positive SSR scans in these tumors reflect specific receptor binding, and that the degree of intensity in the SSR scans reflects the density of SSR in the tumors.

The high tumor-to-background contrast seen in SSR imaging of most meningiomas may be of clinical relevance for exact tumor delineation in cases of tumor recurrence, in which the exact tumor extent may be difficult to judge by CT alone. While SSR scintigraphy alone (judged by tumor-to-background ratio) will not be able to distinguish between meningiomas with relatively low SSR density (e.g. in Patients 6 or 7) and other CNS tumors with disrupted BBB, we introduced combined SSR/$^{99m}$Tc-DTPA scintigraphy, allowing the calculation of the SSR-to-brain scintigraphy index, which appears to be more sensitive for distinction between these two groups of tumors. This highly significant difference in the SSR-to-brain scintigraphy index between meningiomas and the other CNS tumors may be explained pathophysiologically by the high density of SSR in meningiomas and their localization outside the BBB. The difference in SSR-to-brain scintigraphy index might be of clinical relevance in certain localizations (e.g. skull base, orbita, spinal tumors or tumors of the cerebello-pontine

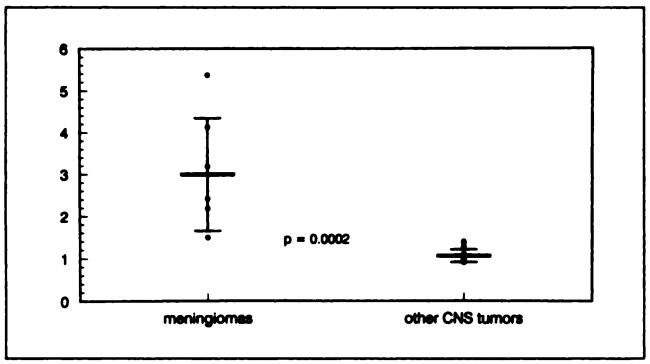


**FIGURE 5.** SSR-to-brain scintigraphy index in meningiomas versus SSR-to-brain scintigraphy index in other CNS tumors. Ratio of $^{111}$In to $^{99m}$Tc in identical tumor ROIs after normalizing a corresponding transversal SPECT slice for identical total counts. Seven meningiomas (2.99 ± 1.35) are compared with 16 nonmeningioma CNS tumors (7 gliomas I–III, 4 gliomas IV, 3 neurinomas, 1 ependymoma and 1 NHL; 1.07 ± 0.15). Mean and s.d. (error bar) are indicated.

angle), where conventional radiological methods sometimes fail to discriminate between meningioma, neurinoma or metastasis. The accuracy of the discrimination between meningiomas and other CNS tumors is presently being studied in a larger number of patients and preliminary results (*28*) confirm the high sensitivity of the SSR-to-brain scintigraphy index for discrimination between these two groups of CNS tumors; combined SSR and $^{99m}$Tc-DTPA scintigraphy may be helpful for better preoperative characterization and surgical management of such tumors, and may even become an alternative to biopsy in meningiomas that are to be treated with percutaneous radiotherapy alone.

In contrast to meningiomas, discordance between $^{111}$In-DTPA-D-Phe1-octreotide scintigraphy and in vitro SSR autoradiography was found in most tumors located inside the BBB. In particular, 63% of the tumors expressing somatostatin receptors by in vitro SSR autoradiography, including four gliomas grade II–III, could not be visualized in vivo by scintigraphy. These results do not conform with the first reports on SSR imaging in low-grade gliomas (*8*), but are in accordance with more recent reports on larger number of patients (*26,29,30*) where negative SSR imaging was found in most low-grade gliomas. The lack of in vivo SSR visualization may not be explained by low SSR expression in these tumors since highly SSR positive tumors (e.g., in Patients 11 and 12) were not visualized while a tumor with a lower SSR density (Patient 16) had a positive SSR scan. It has been presumed that the false-negative SSR scans in these tumors result from an intact BBB preventing octreotide from reaching the receptors on the tumor cells. Based on simultaneous scintigraphic examination of SSR and BBB integrity and in vitro SSR autoradiography in the same patients, our study proves that somatostatin receptors in gliomas are indeed shielded in vivo by an intact BBB.

Conversely, in the eight scintigraphically positive tumors located inside the BBB, false-positive SSR scans, i.e., scintigraphic visualization of SSR negative tumors, were detected in six out of eight tumors. In only two, scintigraphically positive gliomas, the presence of SSR was confirmed in vitro while no SSR expression was observed in the other six neoplasms. All patients with such false-positive SSR scans showed a disruption of the BBB in the $^{99m}$Tc-DTPA scan. As shown in Patient 20 with a glioblastoma, the false-positive scintigraphic signal 4 hr after injection of $^{111}$In-DTPA-D-Phe1-octreotide may not be explained by blood-pool activity since no reduction of tumor-to-background ratio was observed 24 hr after injection. The results of other authors (*26,29,30*) who examined SSR scintigraphy in brain tumors systematically 4 and 24 hr after injection of $^{111}$In-DTPA-D-Phe1-octreotide also support this: neither reduction of the scintigraphic signal nor qualitative difference at 24 hr compared to the 4 hr images was reported in primary brain tumors, where—in contrast to the periphery—no physiological background activity is observed in the surrounding normal brain. We assume that the mechanism of false-positive SSR scintigraphy in patients with CNS tumors is due mainly to nonspecific accumulation/trapping of the $^{111}$In-DTPA-D-Phe1-octreotide molecule in these tumors, with the disrupted BBB acting as a semi-permeable membrane, comparable to the findings from earlier brain scintigraphy using polar radiopharmaceuticals (*11–13*). No evidence was found that nontumoral SSR positive cells (such as activated lymphocytes) or phagocytosis of the $^{111}$In-DTPA-D-Phe1-octreotide molecule might explain these results since in vitro SSR autoradiography showed no SSR positive cells.

There is experimental evidence that SSR can be downregulated by corticosteroids (*31*). This may be a matter of concern, since many brain tumor patients are under corticosteroid therapy. The fact that several patients with corticosteroid therapy had SSR positive tumors in vitro, however, suggests strongly that the SSR are still present under these conditions, even if a partial downregulation cannot be excluded. It is interesting that the three patients with short preoperative corticosteroid therapy were those with a comparably lower density of SSR (Table 1; Patients 6, 7 and 13).

SSR scintigraphy seems to be of limited clinical value for CNS tumors inside the BBB, especially in respect to the differential diagnosis and follow-up examinations of gliomas where false-negative or false-positive scans were found in 9 out of 11 patients. Furthermore, there is presently no strong rationale for selecting brain tumor (in particular glioma) patients with positive SSR scans for eventual octreotide treatment; in vitro data in meningioma (*2*) do not suggest any antiproliferative effect of octreotide.

Proteins (e.g., monoclonal antibodies and their fragments) are promising tools, especially in the field of tumor imaging, and much interest has been given to these specific molecules in the past decade. Smaller peptides, such as the somatostatin analog octreotide, offer the advantage of higher tumor-to-background ratios. The rapid development

of SSR imaging over the last few years (*3*), as well as the increasing interest in peptide scintigraphy (*32*), emphasize the clinical interest in modern, tumor-avid molecules recognizing specific epitopes or receptors. While good correlation between imaging results and in vitro SSR determination has been reported in many peripheral tumors, our results show a different situation in the central nervous system. Good correlation between scintigraphic findings and receptor expression is found only in tumors located outside the BBB, such as meningiomas. In other tumors, an additional hurdle—the BBB—impedes access to normal or neoplastic brain tissue by the octreotide peptide from the intravascular compartment and disruption of the BBB may result in nonspecific tracer accumulation.

## CONCLUSIONS

SSR imaging in CNS tumors shows different results depending on whether the tumor is within or outside the blood brain barrier. In meningiomas (outside the BBB) tumor visualization is achieved in all patients and the intensity of the scintigraphic signal correlates with the tumor cell SSR density. Distinction between meningiomas and other CNS tumors is possible when combined with $^{99m}$Tc-DTPA brain scintigraphy, allowing the calculation of the SSR-to-brain scintigraphy index. Therefore, SSR imaging of CNS tumors may be helpful for further characterization of those tumors with unclear CT or MRI findings. In tumors located inside the BBB, however, SSR scintigraphy provides only limited clinical information since SSR imaging here is dependent on the integrity or disruption of the BBB and does not necessarily reflect the SSR status of the tumor. Octreotide is the first peptide extensively used in clinical nuclear medicine and, therefore, often considered as a model for peptide scintigraphy (*32*). Our results call for great caution when it comes to interpretation of negative and positive scintigrams in the CNS when intravenously administered radiolabeled peptides as well as other polar receptor ligands are used.

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