PET Imaging of Somatostatin Receptors Using [^{68}GA]DOTA-D-Phe^{1}-Tyr^{3}-Octreotide: First Results in Patients with Meningiomas

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Imaging of somatostatin receptors (SSTRs) using [^{111}In]diethylenetriaminepentaacetic-acid-octreotide (DTPAOC) has proven to be helpful in the differentiation of meningiomas, neurinomas or neurofibromas, and metastases as well as in the follow-up of meningiomas. A drawback of the SPECT method is its limited sensitivity in detecting small meningiomas. Because of PET's increased spatial resolution and its ability to absolutely quantify biodistribution, a PET tracer for SSTR imaging would be desirable. **Methods:** 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic-acid-D-Phe^{1}-Tyr^{3}-octreotide (DOTATOC) was labeled using the positron-emitting generator nuclide ^{68}Ga. We acquired dynamic PET images over 120 min after intravenous injection of 175 MBq [^{68}Ga]DOTATOC in 3 patients suffering from 8 meningiomas (WHO I°; 7- to 25-mm diameter). Patients' heads had been fixed using individually shaped fiber masks equipped with an external stereotactic localizer system to match PET, CT, and MRI datasets. **Results:** [^{68}Ga]DOTATOC was rapidly cleared from the blood (half-life α, 3.5 min; half-life β, 63 min). Standardized uptake values (SUVs) of meningiomas increased immediately after injection and reached a plateau 60–120 min after injection (mean SUV, 10.6). No tracer could be found in the surrounding healthy brain tissue. All meningiomas (even the 3 smallest [7- to 8-mm diameter]) showed high tracer uptake and could be visualized clearly. Tracer boundaries showed a good correspondence with the matched CT and MRI images. PET provided valuable additional information regarding the extent of meningiomas located beneath osseous structures, especially at the base of the skull. **Conclusion:** According to our initial experiences, [^{68}Ga]DOTATOC seems to be a very promising new PET tracer for imaging SSTRs even in small meningiomas, offering excellent imaging properties and a very high tumor-to-background ratio.

Key Words: somatostatin receptors; DOTATOC; ^{68}Ga; PET; meningioma

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Using morphologic imaging methods such as CT or MRI on tumors near the base of the skull, it can be difficult to differentiate between meningioma, neurinoma or neurofibroma, and metastasis.

As shown by reverse transcriptase polymerase chain reaction (*1*), meningiomas express the somatostatin receptor (SSTR) subtype 2. Therefore, [^{111}In]diethylenetriaminepentaacetic-acid-octreotide (DTPAOC) SPECT is a valuable technique for differentiating meningiomas, neurinomas, and neurofibromas, as well as for the postsurgical follow-up of patients with meningiomas. Furthermore, SSTR imaging could be valuable in distinguishing between meningiomas and pituitary adenomas based on qualitative tracer uptake (*2*). However, a major drawback of [^{111}In]DTPAOC SPECT is its difficulty in detecting meningiomas with a diameter $<$ 2.7 cm or a volume $<$ 10 mL (*3*).

A new somatostatin analog, 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic-acid-D-Phe^{1}-Tyr^{3}-octreotide (DOTATOC), was recently developed. DOTA is a chelator that ensures high in vivo stability of the corresponding Y^{3+} and In^{3+} chelates. Replacing Phe^{3} with Tyr in the octapeptide increases the hydrophilicity for a potentially more efficient kidney clearance and leads to a higher $SSTR_2$ affinity (*4*). The new analog shows a high affinity (half-maximal-inhibitory concentration [IC_{50}] = 14 nmol/L) for human $SSTR_2$ (*5*), which suggests that [^{90}Y]DOTATOC is a promising radiopharmaceutical for receptor-based radionuclide therapy. [^{111}In]DOTATOC is of potential value for scintigraphic evaluation of patients with SSTR-positive lesions, such as most neuroendocrine tumors. In nude mice bearing the AR4–2J tumor, tumor uptake of both [^{90}Y]- and [^{111}In]DOTATOC 4 h after injection was 5 times higher than with [^{111}In]DTPAOC, whereas kidney retention could be reduced by nearly 50% (*4*).

Because of PET's increased spatial resolution and its ability to quantify biodistribution, SSTR imaging with PET would be desirable. For that reason, DOTATOC was la-

beled with the positron emitter ^{68}Ga. This pilot study shows our initial experience using this new PET tracer in patients suffering from meningiomas.

MATERIALS AND METHODS

DOTA^0-D-Phe^1-Tyr^3-octreotide was synthesized as described in the literature (*4*). ^{68}Ga (half-life, 68.3 min; β^+ 88%; Eβ^+ maximum, 1,900 keV) was obtained in 0.5 mL 0.5N HCl from a ^{68}Ge/^{68}Ga radionuclide generator developed by our radiochemistry section. To this eluate 3 μL 1 mmol/L Ga^{3+} were added, followed by evaporation to dryness and redissolution in 200 μL 0.05 mol/L acetate buffer pH 4.8. [^{68}Ga]DOTATOC was prepared by adding 14 μL 1 mmol/L aqueous DOTATOC solution and heating the mixture for 15 min at 95°C. Subsequently, the pH was adjusted to 7.0 and uncomplexed ^{68}Ga was retained on a reversed phase cartridge (SepPAK; Waters Corp., Milford, MA), whereas [^{68}Ga]-DOTATOC could be eluted with ethanol. After evaporation of the organic solvent, the compound was redissolved in 5.0 mL 0.01 mol/L phosphate-buffered saline pH 7.4. Specific activities obtained were 15–18 MBq ^{68}Ga/nmol of ligand. The preparations were checked by paper chromatography (Whatman No. 1 [Whatman, Maidstone, U.K.], methanol-to-water ratio, 55/45). Typically, >96% of the radioactivity migrated with an R_f ~0.6 corresponding to [^{68}Ga]DOTATOC.

Before stereotactic radiotherapy, dynamic PET scans were acquired (ECAT EXACT HR$^+$ [Siemens/CTI, Knoxville, TN]; 3D-Mode; 256 × 256 matrix; iterative ordered-subset expectation maximization reconstruction) over 120 min after intravenous bolus injection of 175 MBq [^{68}Ga]DOTATOC in 3 patients with 8 meningiomas (WHO I°; 7- to 25-mm diameters). After the nature of the procedure had been fully explained to them, written informed consent was obtained from all patients. The study was approved by the ethical committee of the University of Heidelberg (Heidelberg, Germany).

Venous blood samples were drawn at 5, 10, 30, 60, 90, and 120 min after injection for calculation of clearance data. Half-life α (0–10 min after injection) and half-life β (60–120 min after injection) of each patient were obtained from the time–activity curves by calculating least squares fits.

Stereotactic correlation allows a precise matching of CT, MRI, PET, and SPECT datasets even in the absence of anatomic structures, using an external reference system. The reference system must be compatible for all imaging modalities and positioning of the patient must be exactly reproducible. Each patient's head was fixed in place using an individually shaped and tightly fitted fiber mask. For image fusion with the corresponding CT and MR images, we used an external acrylic localizer system consisting of 4 V-shaped tubes (0.8-mm inner diameter) filled with 30 MBq ^{140}Nd. ^{140}Nd decays with a half-life of 3.4 d to the positron emitter ^{140}Pr (half-life, 3.4 min).

Gadolinium-DTPA- (Magnevist, Schering AG, Berlin, Germany) enhanced MRI was performed on a 1.5-T whole-body MRI system (Magnetom SP; Siemens, Erlangen, Germany), acquiring T1- and T2-weighted spinecho sequences using the stereotactic localizer described previously in this article. Furthermore, CT scans were acquired before and after contrasting, with heads fixed in the localizer system. After fitting the external localizers, PET, CT, and MRI datasets were realigned. The tracer uptake was expressed as standardized uptake value:

$$\left(\text{SUV} = \frac{\text{tissue activity concentration [kBq/g]}}{\text{injected dose [kBq]/bodyweight [g]}}\right).$$

Mean SUVs in regions of interest placed over meningiomas and pituitary glands (70% isocontour) as well as over both temporal lobes were calculated and corrected for partial volume effect.

RESULTS

At 10 min after injection, about 80% of the [^{68}Ga]-DOTATOC was rapidly cleared from blood because of extravasation with a half-life α of 3.5 min (renal clearance not included). Renal clearance of the compound showed a half-life β of 63 min.

The uptake in meningiomas as well as in pituitary glands increased rapidly after injection (Fig. 1A). At 20 min after injection the mean SUV reached 8.9 for meningiomas and 6.9 for pituitary glands. In meningiomas the SUVs reached a plateau between 60 and 120 min (range, 4.5–33.0; mean, 10.6 ± 9.6 [n = 8]). In contrast to this plateau, SUV of the pituitary glands further increased between 60 and 120 min after injection, from 9.1 to 11.4 (Fig. 1A).

Because of the intact blood–brain barrier, we found no accumulation of [^{68}Ga]DOTATOC in the surrounding brain tissue (mean SUV, 0.05 ± 0.04) later than 10 min after injection. The ratio of uptake in the meningiomas to uptake in the brain tissue showed an exponential rise to a maximum of 730 at 120 min after injection (Fig. 1B).

All meningiomas, including small lesions (3 meningiomas; diameter range, 7–8 mm) showed high tracer uptake and could clearly be separated from surrounding brain and bone tissues (Fig. 2). Tracer boundaries showed a good correspondence with the matched CT and MR images. Meningiomas may pose serious problems because of local osseous invasiveness. Compared with the morphological techniques, PET provides valuable additional information regarding the extent of meningiomas located beneath osseous structures, especially at the skull base (Fig. 2).

DISCUSSION

Using [^{68}Ga]DOTATOC PET, all meningiomas could be identified as lesions with very high tumor-to-background ratios. Even small meningiomas (7-mm diameter) showed high tracer uptake and could clearly be delineated from bone, healthy brain, and soft tissues. Therefore, [^{68}Ga]-DOTATOC PET seems to be a promising method to overcome the previously reported (*3*) difficulties of [^{111}In]-DTPAOC SPECT in detecting meningiomas with diameters < 2.7 cm. Besides the higher resolution of the PET method compared with SPECT, a further improvement is caused by the receptor binding characteristics of the DOTATOC compounds, as was recently shown in vitro (*5*). A marked increase of $SSTR_2$ affinity was found for [Ga]-DOTATOC (IC_{50} 2.5 nmol/L) compared with the Y-labeled

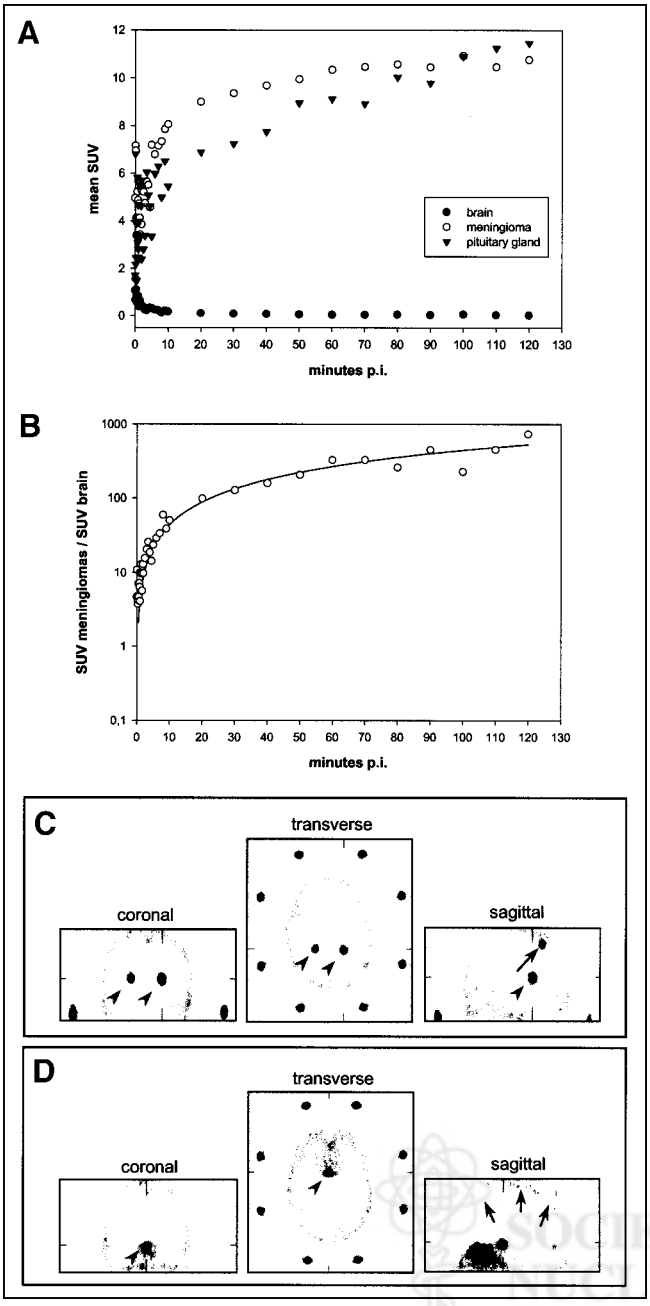

FIGURE 1. (A) Mean SUV for meningiomas, pituitary glands, and healthy brain tissue, 0–120 min after injection of 175 MBq [^{68}Ga]DOTATOC. (B) Contrast ratio of meningiomas to healthy brain tissue, 0–120 min after injection. (C) Coronal, transaxial, and sagittal PET scans of two intraventricular (arrowheads) and one parietal meningioma (arrow). Stereotactic localizer system surrounding skull. (D) Physiologic SSTR expression of pituitary gland (arrowheads) and meninges (arrows). Stereotactic localizer-system surrounding skull.

compound (IC_{50} 11 nmol/L) as well as with [In]DTPAOC (IC_{50} 22 nmol/L).

Using PET, the possibility of calculating absolute as well as relative quantitative parameters might facilitate the differentiation between meningiomas and pituitary adenomas as suggested for [^{111}In]DTPAOC SPECT (*2*). Clinical applications of this SSTR-imaging technique may lead to improved characterization of tumors near the base of the skull in cases of unclear MRI findings in tumors to be treated by radiosurgery alone or in patients at high risk for stereotactic biopsy. In this setting, a differentiation between meningiomas and neurinomas or optic nerve gliomas, as well as a differentiation between multifocal diseases (cerebral metastases, neurofibromatosis type II) would be desirable (*2*). Furthermore, the assessment of SSTR density may be used for a noninvasive grading of meningiomas and for the planning of surgery or stereotactic radiotherapy to de-

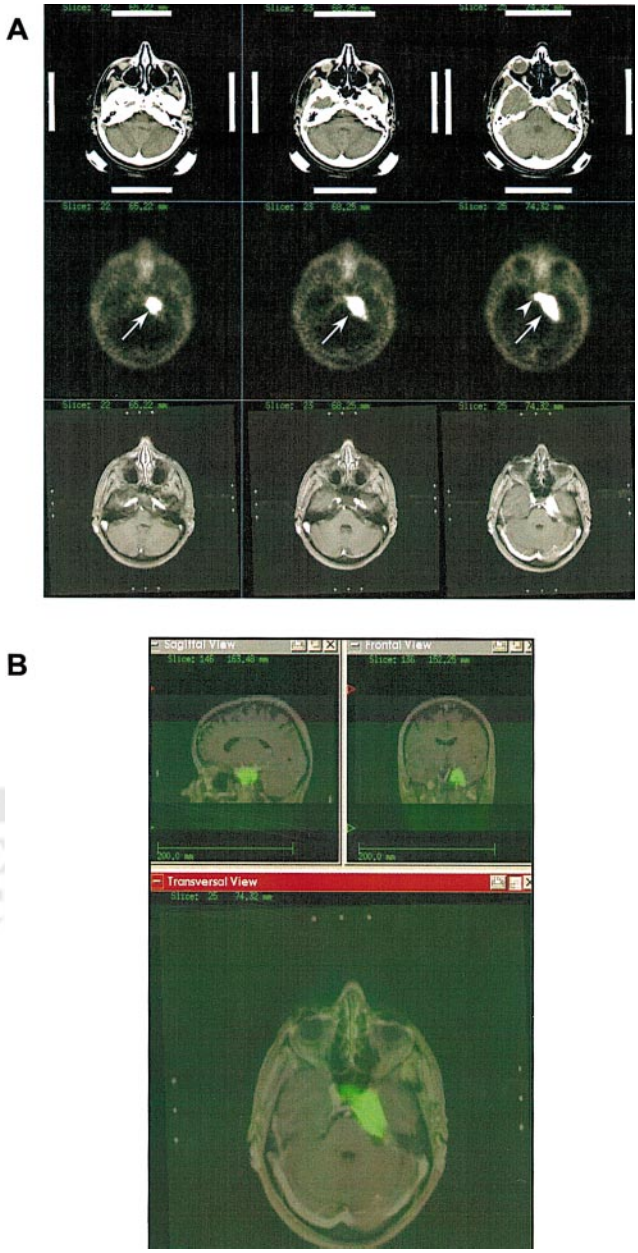

FIGURE 2. (A) Realigned CT, PET, and MRI scans of medial temporal/sphenoidal meningioma (arrow) beneath pituitary gland (arrowhead). (B) Image fusion of same patient (color coded, PET; black and white, MRI).

lineate the extent of meningiomatous manifestation and to differentiate meningeal infiltration from meningeal reaction. In the follow-up of patients after surgery or stereotactic radiotherapy, distinguishing scar tissue from necrosis and meningioma recurrence could have a significant impact on determining treatment for patients (*2*). All those applications for [^{111}In]DTPAOC SPECT could benefit from the better spatial resolution, the higher sensitivity, and the possibility of quantification provided by [^{68}Ga]DOTATOC PET. Diagnosis of neuroendocrine tumors, including search for primaries and metastases as well as the dosimetry performed before [^{90}Y]DOTATOC radionuclide therapy might be a further important application of [^{68}Ga]DOTATOC PET. The clinical impact of this new PET tracer compared with [^{111}In]DTPAOC has to be evaluated in further studies.

CONCLUSION

According to our initial experiences in a limited number of patients, [^{68}Ga]DOTATOC seems to be a very promising new PET tracer for imaging SSTRs even in small meningiomas. It offers excellent imaging properties and very high tumor-to-background ratios. Additionally, labeling of the ligand with ^{68}Ga is easy to perform and generator production of the tracer may ensure its continuous availability. Further evaluation of [^{68}Ga]DOTATOC in a larger number of patients seems to be justified.

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