Somatostatin receptor imaging in intracranial tumours

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Abstract. The somatostatin analogue [^{111}In-DTPA-D-Phe^{1}]-octreotide (^{111}In-octreotide) allows scintigraphic visualization of somatostatin receptor-expressing tissue. While it is well known that a large variety of tissues express somatostatin receptors and ^{111}In-octreotide scintigraphy has a clearly defined role in various neuroendocrine diseases, the clinical value of ^{111}In-octreotide scintigraphy in brain tumours is still under clinical investigation. In 124 patients with 141 brain lesions (63 meningiomas, 24 pituitary adenomas, 10 gliomas WHO class I and II, 12 gliomas WHO class III and IV, 11 neurinomas and 2 neurofibromas, 7 metastases and 12 other varieties: three non-Hodgkin B-cell lymphomas, two epidermoids, one abscess, one angioleiomyoma, one chordoma, one haemangiopericytoma, one osteosarcoma, one plasmacytoma and one pseudocyst), ^{111}In-octreotide scintigraphy was performed 4–6 and 24 h after i.v. injection of 110–220 MBq ^{111}In-octreotide. Planar images of the head in four views with a 128×128 matrix and single-photon emission tomographic images (64×64 matrix) were acquired, and lesions were graded according to qualitative tracer uptake. Fifty-nine of the 63 meningiomas showed moderate to intense tracer uptake. Nine of 24 pituitary adenomas were visible; the remaining 15 did not show any tracer uptake. None of the class I and II gliomas with an intact blood-brain barrier were detected whereas 11/12 class III and IV gliomas showed ^{111}In-octreotide uptake. None of the neurinomas or neurofibromas were positive. Five of seven metastases were classified as positive, as were the osteosarcoma, two of three non-Hodgkin B-cell lymphomas, one abscess, one angioleiomyoma, one chordoma and one haemangiopericytoma. The other varieties (one non-Hodgkin B-cell lymphoma, two epidermoids, one plasmacytoma and one pseudocyst) did not show ^{111}In-octreotide uptake. The results demonstrate that a large variety of intracranial lesions express somatostatin receptors and therefore can be visualized by [^{111}In-DTPA-D-Phe^{1}]-octreotide scintigraphy. This technique can be valuable in the differentiation between meningiomas and pituitary adenomas, based on qualitative tracer uptake. [^{111}In-DTPA-D-Phe^{1}]-octreotide scintigraphy allows differentiation between meningiomas and neurinomas or neurofibromas and therefore provides complementary information to computed tomography or magnetic resonance imaging. Furthermore, this technique allows differentiation between scar tissue and recurrent meningiomas postoperatively and can help in non-invasive tumour differentiation of multiple intracranial lesions, which can be of value in defining the most adequate therapeutic strategy.

Key words: Somatostatin receptor scintigraphy – Indium-111 octreotide scintigraphy – Brain tumours

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Introduction

Somatostatin is a widely distributed neuroregulatory peptide originally identified in sheep hypothalamus by Brazeau in 1973 [1]. Receptors for somatostatin are peptides located on the cell membrane of various central nervous and peripheral tissues, including tumours of neuroendocrine origin and intracranial tumours [2–6]. It is now well known that a large variety of tissues express somatostatin receptors such as leptomeninx [7], adenomas of the anterior pituitary gland [4], glial cells [8], adrenal medulla, paragangliomas, thyroid C cells, Merkel cells of the skin, pancreatic islet cells, gastrointestinal endocrine cells, bronchopulmonary tree endocrine cells, activated lymphocytes and endocrine cells in miscellaneous sites [5, 6, 9, 10]. The function of somatostatin is to inhibit the release of hormones by binding to plasma membrane receptors of hormone-secreting cells [11]. In the central nervous system somatostatin acts as a neurotransmitter and it inhibits the release of growth hormone, adrenocorticotropic hormone, prolactin and thyroid-stimulating hormone [9, 12]. Furthermore, somatostatin

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inhibits the release of many intestinal peptides such as insulin, glucagon, gastrin, motilin, gastric inhibitory peptide, vasoactive intestinal peptide, secretin, cholecystokinin, and gastric releasing peptide [9, 12, 13], and an antiproliferative effect on tumours in vitro and in vivo has been demonstrated [12]. However, endocrine functions of somatostatin are not known for all tissues [14, 15].

As somatostatin is rapidly cleared from the blood, development of long-acting somatostatin analogues like octreotide and the availability of radiolabelling with iodine-123 or indium-111 made the in vivo detection of somatostatin receptors possible [16–18]. The somatostatin analogue [^{111}In-DTPA-D-Phe^{1}]-octreotide (^{111}In-octreotide) allows scintigraphic visualization of somatostatin receptor expressing tissue [18–20]. The advantage of ^{111}In-octreotide over another radiolabelled somatostatin analogue [^{123}I-Tyr^{3}]-octreotide lies in the major renal clearance, a markedly lower accumulation of radioactivity in the hepatobiliary system and a lower background activity. The more favourable metabolic behaviour of [^{111}In-DTPA-D-Phe^{1}]-octreotide in comparison to [^{123}I-Tyr^{3}]-octreotide results in better visualization of somatostatin receptors [17, 19]. Previous clinical studies have demonstrated the usefulness of this scintigraphic technique in a number of patients with various cerebral lesions [12].

Meningiomas as well as pituitary adenomas, although generally benign and non-metastasizing tumours, may pose serious problems due to recurrences after primary therapy and local invasiveness in areas such as the clivus or the cavernous sinus. Despite advances in skull base surgery, treatment of tumours in this area often remains unsolved [21]. In an attempt to establish different modes of non-surgical treatment the concept of hormonal treatment of meningiomas was suggested [22, 23]. In cases of pituitary adenoma, unlabelled octreotide is used to reduce hormone production and to control tumour growth in acromegaly [4, 24, 25]. Reubi et al. demonstrated that the presence of somatostatin receptors in gliomas is correlated to tumour classification as in their studies low-grade malignant gliomas (WHO classes I and II) expressed somatostatin receptors while gliomas of higher grade (WHO classes III and IV) did not have measurable contents of them [5, 6, 8, 9, 14]. However, these results could not be confirmed unanimously [26]. Knowledge of the receptor status and function of cerebral lesions could provide new insights into tumour biology and reaction of different brain tumour entities, and thus might provide predictive or palliative input into therapeutic approaches. Therefore, the purpose of the present study was to define further the clinical value of somatostatin receptor scintigraphy using ^{111}In-octrotide in the diagnostic work-up of patients suffering from various intracranial tumours.

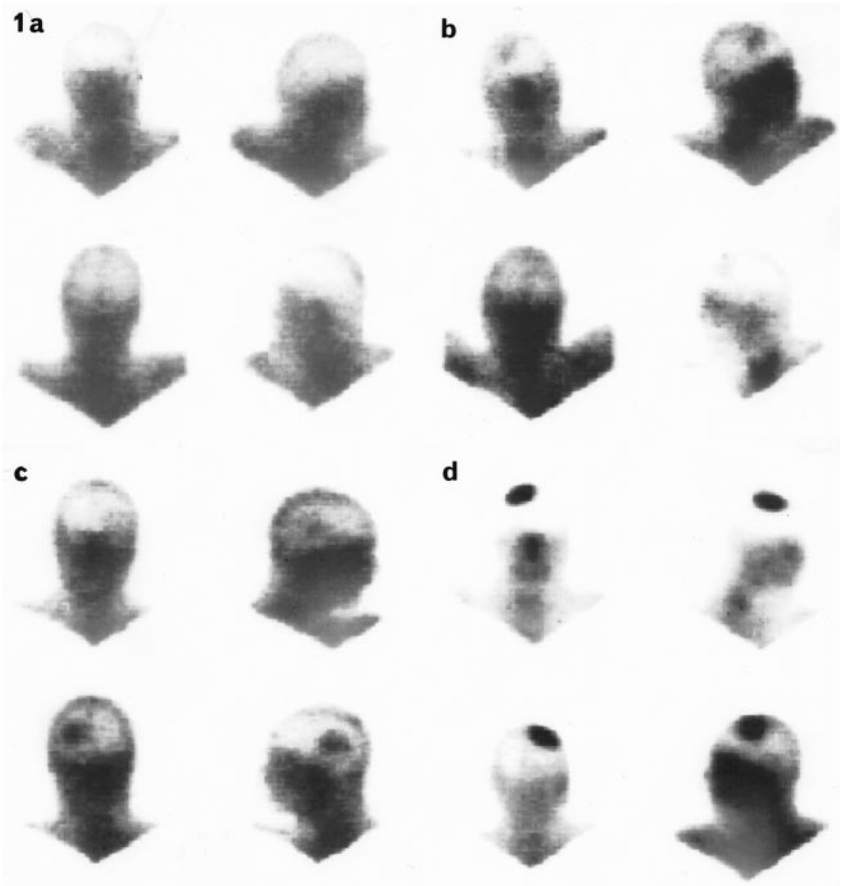

Fig. 1a–d. Planar views illustrating the grading system: No (**a**), faint (**b**), moderate (**c**) and intense (**d**) tracer uptake. Views are grouped R ant L (*upper left*), R lat (*upper right*), L post R (*lower left*), and L lat (*lower right*)

Materials and methods

From 1992 to 1996 124 patients [54 men, 70 women, mean age 49.5±15.9 years (range 5–75 years)] with a total of 141 newly diagnosed, residual or recurrent intracranial tumours were included in this study. All tumours were documented by contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI). In patients with a pituitary adenoma, growth hormone, prolactin, luteinizing hormone and follicle-stimulating hormone were measured, but subunits were not measured and no further endocrine tests were performed routinely. All patients gave their informed consent prior to scintigraphic imaging and the study was approved by the local ethics committee.

For somatostatin receptor scintigraphy ^{111}In labelled octreotide, a DTPA-bearing analogue of somatostatin ([^{111}In-DTPA-D-Phe^{1}]-octreotide; Octreo Scan 111, Mallinckrodt Diagnostica, Petten, The Netherlands), was injected intravenously at a dose of 110–220 MBq (3–6 mCi). Gamma camera images of the head were performed 4–6 and 24 h post injection. Planar (128×128 matrix, 4 views) as well as single photon emisson computed tomography (SPECT) images (64×64 matrix) were acquired with a large field of view gamma camera equipped with a medium-energy parallel-hole collimator. Energy peaks were set to 173 keV and 247 keV with a 20% window. Data from both windows were added to the acquisition frames. Acquisition parameters for planar images were 5 min per planar view, and 64 projections at 30 s for the SPET studies. SPET images were reconstructed by filtered backprojection using a Shepp-Logan filter. Reconstructed slice thickness was 6.4 mm.

A qualitative four-step grading system was employed to describe octreotide uptake, as has been used previously [27]. Qualitative evaluation of the lesions was performed by visual comparison of tumour uptake with uptake in the skull [28]. Grades were defined as follows (Fig. 1):

Grade 0: no tracer uptake, non-visualization of tumour activity
Grade I: faint tracer uptake similar to the uptake of the skull
Grade II: moderate tracer uptake with good visualization of the tumour; uptake slightly above skull uptake
Grade III: intense tracer uptake; uptake clearly above skull uptake with the lesion dominating the image

All tumours were evaluated histologically and classified according to the WHO classification. In 62 of 63 meningiomas, in all pituitary adenomas, in all gliomas/glioblastomas, in all neurinomas and neurofibromas and in all metastases, tumour volumes were calculated by using the ellipsoid equation: $\pi/6 \times a \times b \times c$. For $\pi/6$ the value 0.5 was taken and a, b and c were the diameters of the ellipsoid. This method was applied for tumours with a round to oval growth pattern, otherwise the area of the tumour in each slice was measured and the tumour volume was calculated as the sum of the areas multiplied by the slice thickness [29–31]. A Kruskal-Wallis test was performed for analysis of tumour volume versus grade of tracer uptake.

Results

In 117 of the 124 patients both planar and SPET images were obtained. Seven patients did not undergo SPET. In 90 of the 124 patients images were taken 4–6 and 24 h post injection while 34 patients had images at 4–6 h post injection only. The histological classification (according to the WHO classification) of the 141 tumours revealed 63 meningiomas, 24 pituitary adenomas (14 hormonally inactive, 8 growth hormone-secreting and 2 prolactin-secreting pituitary adenomas), 10 gliomas of WHO class I or II, 12 gliomas of WHO class III or IV, 11 neurinomas and 2 neurofibromas, 7 metastases and 12 other lesions (three non-Hodgkin B-cell lymphomas, two epidermoids, one abscess, one angioleiomyoma, one chordoma, one haemangiopericytoma, one osteosarcoma, one plas-

Table 1. Number of brain tumours classified with regard to qualitative tracer uptake

	No.	Grade 0	Grade I	Grade II	Grade III
Meningiomas	63	0	4	22	37
Pituitary adenomas	24	15	6	3	0
hormonally inactive	14	8	5	1	0
growth hormone secreting	8	6	1	1	0
prolactin secreting	2	1	0	1	0
Gliomas WHO I/II	10	10	0	0	0
Gliomas WHO III/IV	12	1	5	5	1
Neurinomas	11	11	0	0	0
Neurofibromas	2	2	0	0	0
Metastases	7	2	4	1	0
Abscess	1	0	1	0	0
Angioleiomyoma	1	0	1	0	0
B-cell NHL	3	1	0	2	0
Chordoma	1	0	1	0	0
Epidermoid	2	2	0	0	0
Haemangiopericytoma	1	0	1	0	0
Plasmacytoma	1	1	0	0	0
Pseudocyst	1	1	0	0	0
Osteosarcoma	1	0	0	0	1

NHL, non-Hodgkin's lymphoma

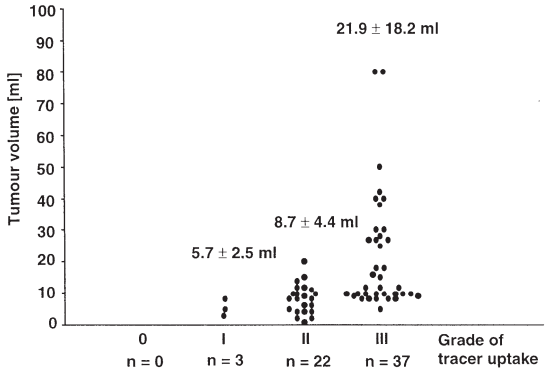

Fig. 2. Meningioma volumes in relation to qualitative grading of tumour uptake (grade 0 to grade III) in 62/63 meningioma patients. Tumour volume could not be calculated in one meningioma patient because of flat tumour growth. *n*, number of patients. Values above the dots are mean tumour volumes ± standard deviation

macytoma and one pseudocyst). Of 141 newly diagnosed, residual or recurrent intracranial tumours 94 showed grade I or higher tracer uptake. Forty-seven tumours did not demonstrate tracer uptake and were classified as grade 0. Table 1 gives the results of tracer uptake.

Meningiomas

All meningiomas showed focal tracer uptake (*n*=63/63; sensitivity: 100%). In most meningiomas tracer uptake was classified as grade II (*n*=22; 35%) or grade III (*n*=37; 59%) positive. Three meningiomas with tumour volumes between 3 and 9 ml had only grade I uptake, the fourth meningioma with grade I uptake had a very flat growth pattern so that no exact tumour volume could be calculated. One small skull base lesion with a tumour volume of 3 ml was only detected in the SPET images. Depending on location and receptor status, even small tumours with volumes of 5 ml demonstrated intense tracer uptake. Somatostatin receptor-expressing tumour tissue could be visualized in uni- as well as multifocal disease, in intraosseous and in intraorbital lesions. Fig. 2 shows the distribution of meningioma volumes versus qualitative tracer uptake. Although there is a significant relationship between tumour volume and grade of tracer uptake with higher uptake grade in larger tumours, there is considerable overlap between the groups (Kruskal-Wallis test: *P* value =0.0003).

Pituitary adenomas

Fifteen of 24 pituitary adenomas did not show any tracer uptake and 6 of 24 pituitary adenomas were faintly visible, i.e. grade I positive. Three pituitary adenomas with volumes of 10, 12 and 50 ml were moderately positive (grade II). None of the pituitary adenomas showed grade III tracer uptake. In general, tracer uptake was lower compared with meningiomas. Table 2 contains data for pituitary tumour volume, hormonal activity, tumour

Table 2. Pituitary adenomas

Patient initials, gender, age	Tumour volume (ml)	Hormonal status	Growth	Uptake grade
EN, female, 65	8	Inactive	Intra + suprasellar	0
CZ, female, 66	8	Inactive	Intra + suprasellar	0
KH, male, 57	9	Inactive	Intra + para + suprasellar	0
KK, male, 61	10	Inactive	Intra + parasellar	0
MS, male, 32	10	Inactive	Intra + para + suprasellar	0
HC, male, 69	12	Inactive	Intra + suprasellar	0
JJ, female, 63	12	Inactive	Intra + parasellar	0
CT, female, 44	12	Inactive	Intra + para + suprasellar	0
UB, male, 59	8	Inactive	Intra + parasellar	I
LH, female, 75	8	Inactive	Intra + para + suprasellar	I
CS, female, 66	9	Inactive	Intra + suprasellar	I
EK, female, 45	14	Inactive	Intra + suprasellar	I
GD, female, 43	18	Inactive	Intra + para + suprasellar	I
LL, female, 24	10	Inactive	Intra + para + suprasellar	II
FG, female, 25	2	GH	Intrasellar	0
CK, female, 28	4	GH	Intra + para + suprasellar	0
HB, male, 52	6	GH	Intra + suprasellar	0
KH, male, 29	6	GH	Intra + parasellar	0
NF, male, 33	10	GH	Intra + parasellar	0
DS, male, 31	12	GH	Intra + para + suprasellar	0
EM, female, 72	12	GH	Intra + para + suprasellar	I
HR, male, 45	12	GH	Intra + para + suprasellar	II
NQ, female, 23	2	PRL	Intrasellar	0
GS, male, 66	50	PRL	Intra + para + suprasellar	II

GH, Growth hormone secreting; PRL, prolactin secreting

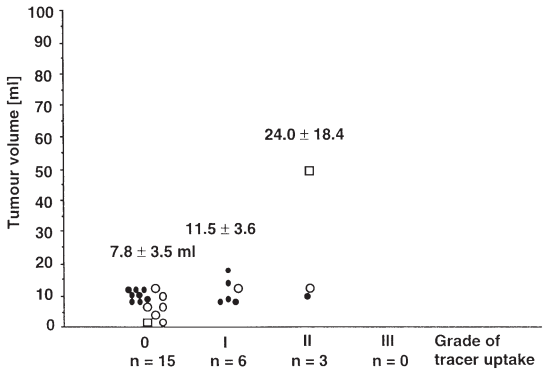

Fig. 3. Pituitary adenoma volumes in relation to qualitative grading of tumour uptake (grade 0 to grade III) in all 24 pituitary adenoma patients. *n*, number of patients. Values above the dots are mean tumour volumes ± standard deviation. Different symbols refer to endocrine status as follows: *solid circles*, hormonally inactive; *open circles*, growth hormone secreting; *open squares*, prolactin secreting

growth and tracer uptake. The pituitary adenomas with intrasellar tumour growth did not demonstrate tracer uptake. All tumours with grade I or II uptake had intra- and extrasellar (i.e. para- and/or suprasellar) tumour growth. However, there were 13 intra- and extrasellarly growing pituitary adenomas without octreotide uptake. There was overlap between pituitary adenomas and meningiomas in grade I positive tumours, so that in the case of faint tracer uptake tumour differentiation between meningiomas and pituitary adenomas may be difficult. However, all meningiomas with tumour volumes above 10 ml were at least grade II positive. Due to the spatial resolution of the gamma camera, differentiation between tumour and non-tumour tissue of the pituitary gland was not possible. Fig. 3 gives the distribution of pituitary adenoma volumes versus qualitative tracer uptake. Although there is a borderline relationship between tumour volume and grade of tracer uptake, with higher uptake grade in larger tumours there is overlap between the groups (Kruskal-Wallis test: *P* value =0.0736).

Tables 1 and 2 include the results of endocrine activities of the pituitary adenomas studied. Of 24 pituitary adenomas, 14 were hormonally inactive, eight secreted growth hormone and two secreted prolactin. Along the 14 hormonally inactive pituitary adenomas, eight did not show tracer uptake and five had grade I tracer uptake. One hormonally inactive pituitary adenoma exhibited grade II tracer uptake. Of the eight growth hormone-secreting pituitary adenomas, six did not demonstrate tracer uptake, while one had grade I and the other grade II uptake. One prolactinoma did not demonstrate tracer uptake and one large prolactinoma showed grade II tracer uptake. Thus, a relationship between tracer uptake and endocrine activity was not found.

Gliomas

Twenty-two patients with gliomas were examined. Ten gliomas were histologically classified as WHO class I or II and 12 as WHO class III or IV. None of the low-grade malignant gliomas (*n*=10, WHO class I or II) with an in-

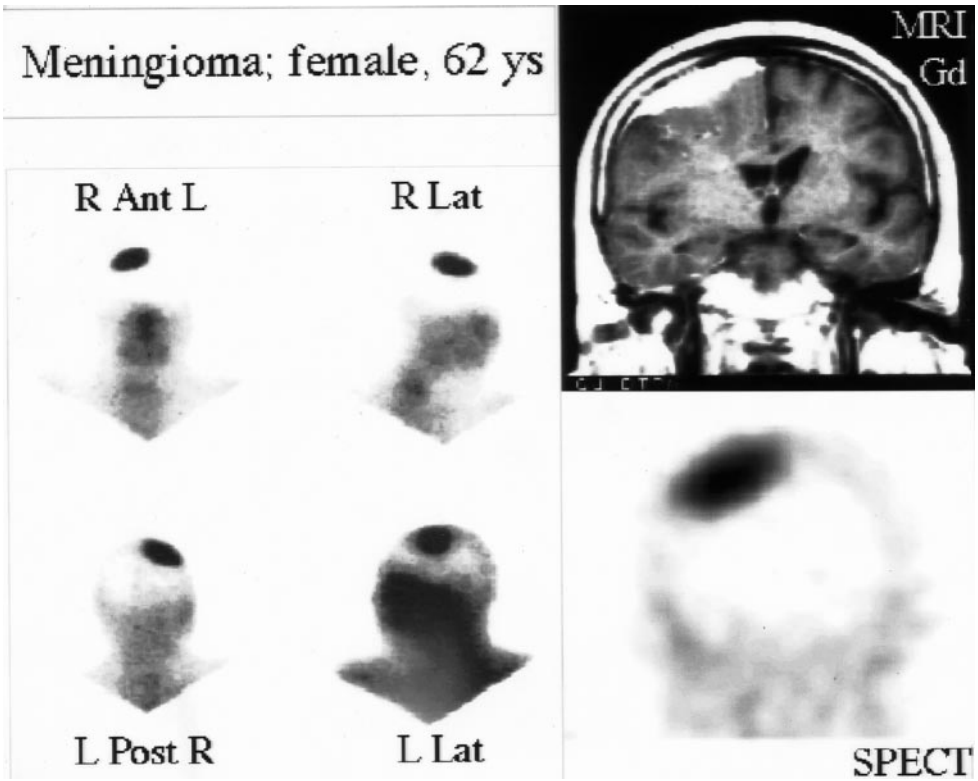

Fig. 4. Sixty-two year old woman with a meningioma in the right parietal region with intense tracer uptake

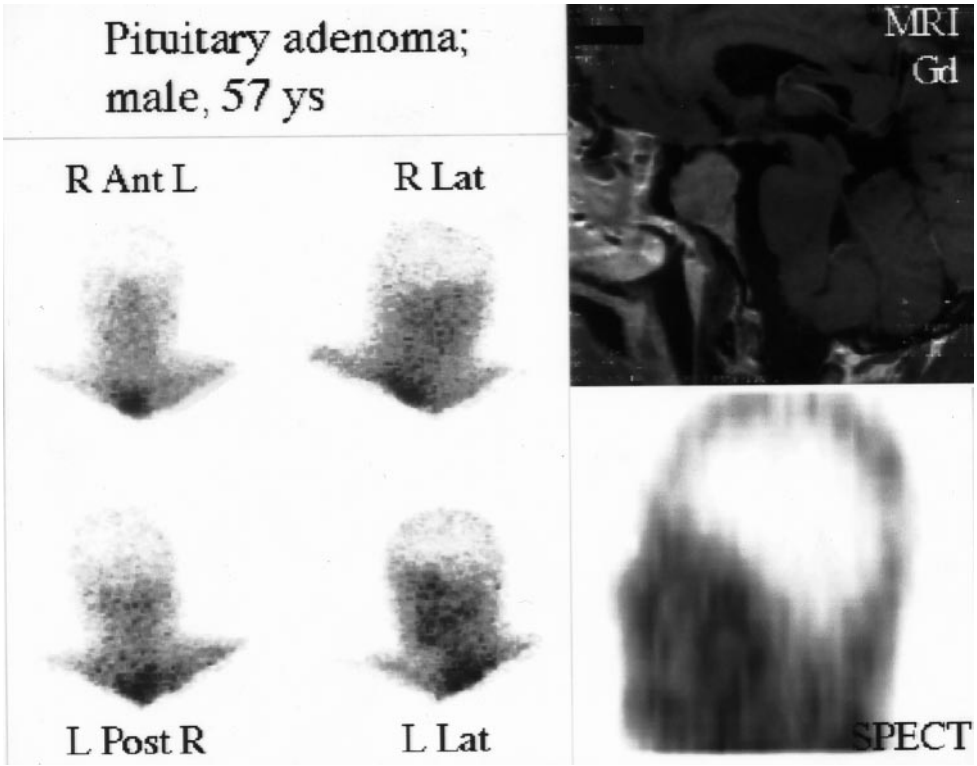

Fig. 5. Fifty-seven year old man with a hormonally inactive pituitary adenoma showing no tracer uptake

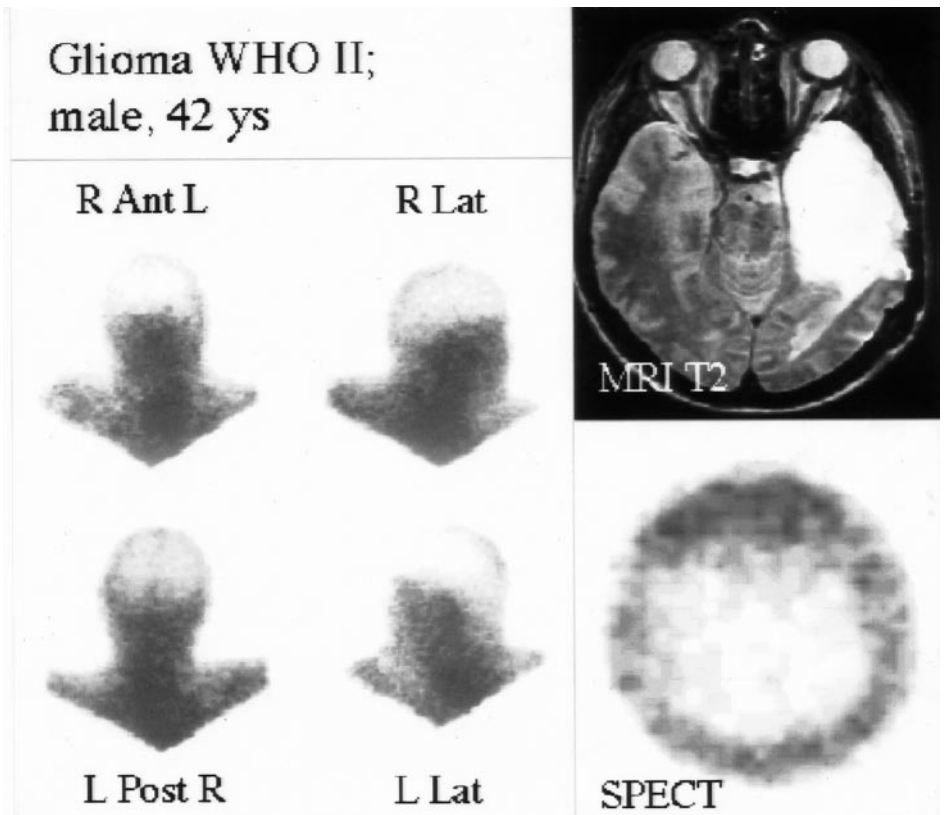

Fig. 6. Forty-two year old man with an astrocytoma of the left temporal lobe. No corresponding tracer uptake was seen

tact blood-brain barrier were detected, and the gliomas were classified with regard to tracer uptake as grade 0. The integrity of the blood-brain barrier in low-grade gliomas was defined by lack of contrast enhancement on the CT or MRI scans performed prior to somatostatin receptor scintigraphy. DTPA studies in the glioma patients were not performed routinely. Eleven of 12 high-grade malignant gliomas/glioblastomas (WHO class III or IV) showed focal uptake of the radiopharmaceutical. With regard to tracer uptake, five high-grade malignant glio-

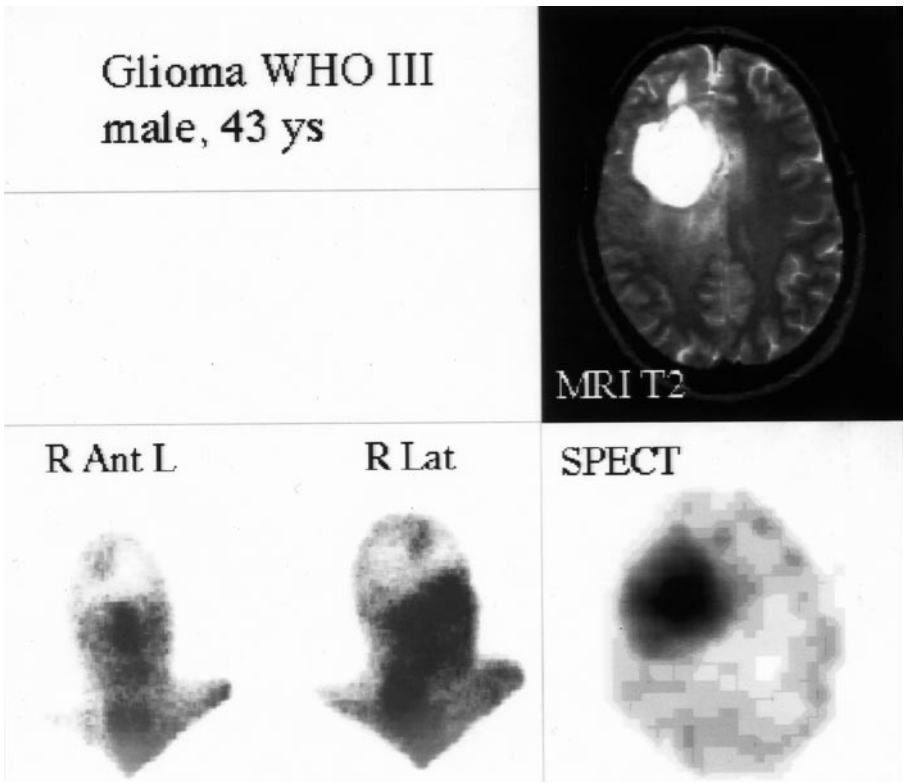

Fig. 7. Forty-three year old man with a glioma of WHO class III demonstrating faint tracer uptake on planar images. SPET delineated the tumour extent much better than did the planar views

mas were classified as grade I and five as grade II positive. One large glioblastoma demonstrated intense tracer uptake (grade III) and one glioma of WHO class III with a tumour volume of 5 ml was not detected (grade 0). Two patients with glioblastomas of WHO class IV were additionally investigated with DTPA. In these two patients DTPA imaging confirmed disruption of the blood-brain barrier.

Neurinomas and neurofibromas

Irrespective of tumour volume (2–40 ml), none of the 11 neurinomas and neither of the two neurofibromas showed any tracer uptake and were therefore classified as grade 0.

Metastases and other tumours

Of seven metastases (three bronchial adenocarcinomas, two adenocarcinomas of unknown origin and two breast carcinomas), two did not show any tracer uptake. Four patients with metastases (three bronchial carcinomas and one breast carcinoma) showed grade I tracer uptake, while one breast carcinoma metastasis of 18 ml was classified as grade II positive. The other metastases with grade 0 or grade I uptake had tumour volumes between 10 and 38 ml. Among the remaining tumours the osteosarcoma showed very intense tracer uptake (grade III), and two of the three non-Hodgkin B-cell lymphomas were grade II positive. The abscess, the angioleiomyoma, the chordoma and the haemangiopericytoma were classified as grade I positive. The two epidermoids and the pseudocyst, one of the three non-Hodgkin B-cell lymphomas and the plasmacytoma did not show ^{111}In-octreotide uptake (grade 0).

Imaging and radiopharmaceutical aspects

Visual comparison of early (4–6 h) with late (24 h) images showed a higher tumour to background uptake in the 24-h images than in the early images. Although planar images were usually diagnostic, comparison with other imaging modalities such as CT or MRI was much easier with SPET studies because tumour extent could be better delineated in relation to adjacent structures, and tumour differentiation was much easier in patients with multifocal disease. SPET was especially helpful for small tumours located at the skull base and detected additional lesions at the skull base which were not seen on planar images. No side-effects were noted during or after administration of ^{111}In-octreotide.

Discussion

In the diagnostic work-up of patients with intracranial tumours, contrast-enhanced imaging techniques such as CT and MRI have a pivotal role in defining the location and extent of tumour manifestation. Although a pre-

Table 3. Brain tumours detected by somatostatin receptor scintigraphy in relation to the total number of examined tumours in published in vivo studies in man

Author, year, reference	Patients	Meningiomas	Pituitary adenomas	Gliomas	Other brain tumours
Bohuslavizki et al., 1996 [46]	58	44 / 53	NE	NE	0 / 5
de Bruin et al., 1992 [52]	7	NE	6 / 7	NE	NE
Faglia et al., 1991 [38]	14	NE	5 / 14	NE	NE
Haldemann et al., 1995 [28]	60	7 / 7	NE	6 / 11	1 / 4
Hildebrandt et al., 1994 [21]	22	22 / 22	NE	NE	NE
Krenning et al., 1989 [16],1993 [43]	48	14 / 14	21 / 28	4 / 6	NE
Lamberts et al., 1991 [12]	31	11 / 11	12 / 14	4 / 6	NE
Lee et al., 1995 [27]	8	NE	NE	4 / 4	4 / 4
Luyken et al., 1993 [45],1994 [26]	60	36 / 36	8 / 18	12 / 19	4 / 6
Maini et al., 1993 [53	12	10 / 10	NE	NE	0 / 2
Olsen et al., 1995 [54]	30	DNA	24 / 30	DNA	DNA
Scheidhauer et al., 1993 [55]	45	20 / 20	6 / 12	7 / 12	1 / 1
Ur et al., 1992 [39]	15	NE	12 / 15	NE	NE
Verhoeff et al., 1993 [56]	1	NE	1 / 1	NE	NE
Present study	124	63/63	9/24	11/22	12/32

NE, Not examined; DNA, data not available

sumptive diagnosis can often be made on the basis of CT and MRI images, the histological diagnosis can only be made postoperatively. In the case of suspected residual or recurrent tumour it can be very difficult to distinguish viable tumour from scar tissue by CT or MRI [32]. Thus, various scintigraphic imaging techniques have been investigated in an attempt to provide complementary information to CT and MRI, to establish a histological diagnosis non-invasively prior to operation, to distinguish between residual or recurrent viable tumour and scar tissue [33, 34] and to estimate treatment response in the post-surgical and post-radiation/chemotherapy evaluation [33]. Somatostatin receptor scintigraphy is one important imaging technique in this scenario; however, somatostatin receptor scintigraphy can only demonstrate somatostatin receptor positive intracranial lesions if the blood-brain barrier is disrupted [28]. Table 3 gives a brief overview of the literature that has been published concerning somatostatin receptor imaging and brain tumours.

Somatostatin receptor scintigraphy and meningiomas

Somatostatin receptor scintigraphy does not reveal increased tracer uptake by the normal leptomeninx, although the latter contains somatostatin receptors, as proven in vitro [3, 7]. Meningiomas originate from the arachnoid layer of the leptomeninx [35] and usually have a high somatostatin receptor density [36]. The function of these somatostatin receptors, however, is not yet clear [23, 37]. Irrespective of meningioma location, in 59 of 63 patients a moderate to high uptake of ^{111}In-octreotide was found, indicating a high density of somatostatin receptors. Only four patients had faint tracer uptake. These data are consistent with in vitro data, demonstrating a high density of somatostatin receptors in meningiomas by in vitro binding assays and autoradiography [8, 36]. Our data demonstrate that tracer uptake is correlated to tumour volume. However, even small meningiomas may demonstrate uptake values from grade I to grade III, and considerable overlap exists between groups. Our findings are consistent with previous studies demonstrating that receptor density can vary greatly among meningiomas [36]. An excellent correlation has been demonstrated between the results of somatostatin receptor scintigraphy and in vitro somatostatin receptor autoradiography showing positive somatostatin receptor expression in vivo and in vitro [28]. When comparing quantitative in vitro somatostatin receptor expression and in vivo tumour to background ratios, it was possible to demonstrate a high linear correlation (r=0.97) between the intensity of the scintigraphic signal and the somatostatin receptor density in seven meningioma patients [28].

Meningiomas usually occur throughout the cranial cavity. Their location along dural planes and their lobulated, sharply demarcated contours are usually diagnostic on CT or MRI [35]. However, the enhancement pattern on MRI studies does not allow the histological distinction in the case of some skull base lesions. Thus, due to the high receptor density of meningiomas, ^{111}In-octreotide scintigraphy can be helpful in the differential diagnosis of receptor-negative tumours, e.g. optic nerve gliomas and acoustic neurinomas. It may aid in the differentiation between postoperative scar and meningioma recurrence or between acoustic neurinomas and multiple meningiomas, as well as in cases of multiple lesions in neurofibromatosis. Detection of a receptor-negative tumour in the area of the tuberculum sellae makes a meningioma highly unlikely. The high tumour uptake seen in somatostatin receptor imaging in most meningiomas

may be of clinical relevance for exact tumour delineation in cases of tumour recurrence.

It has been maintained that somatostatin receptor scintigraphy alone may not be able to distinguish between meningiomas with relatively low somatostatin receptor density and other CNS tumours with a disrupted blood-brain barrier. Thus, Haldemann et al. suggested a somatostatin receptor to brain scintigraphy index by combined somatostatin receptor and ^{99m}Tc-DTPA scintigraphy which might allow differentiation of meningiomas from gliomas [28]. However, it remains questionable whether this patient group requires imaging with both ^{111}In-octreotide and ^{99m}Tc-DTPA. Contrast-enhanced CT or MRI, usually performed prior to scintigraphy, clearly demonstrates a disrupted blood-brain barrier, and the need for differential diagnosis of meningiomas and gliomas is rare. Thus, ^{99m}Tc-DTPA scintigraphy seems to be unnecessary.

Somatostatin receptor scintigraphy and pituitary adenomas

Of the 24 pituitary adenomas investigated only nine (38%) had octreotide uptake independent of endocrine activity: 6/14 (43%) hormonally inactive, 2/8 (25%) growth hormone-secreting and 1/2 (50%) prolactin-secreting pituitary adenomas were positive. This is in accordance with in vitro studies which detected somatostatin receptors on 6 of 15 (40%) hormonally inactive pituitary tumours, but in contrast to results in the same paper which detected somatostatin receptors on 42 of 43 (98%) growth hormone-secreting pituitary adenomas using a somatostatin receptor binding assay [12]. In-vivo studies yielded very heterogeneous results, with overall sensitivities of scintigraphy for pituitary tumours between 36% [38] and 86% [12]. In one study the suprasellarly extending tumours of four acromegalic patients investigated with somatostatin receptor scintigraphy could be clearly visualized, and inactive pituitary adenomas were positive in six of eight cases (75%) [12]. Ur et al. reported 12 of 15 (80%) acromegalic patients to display having uptake of ^{123}I-labelled Tyr^3-octreotide [39]. Using [^{123}I-Tyr^3]-octreotide scintigraphy, Faglia et al. reported positive scans in three out of three acromegalic patients, in two out of eight (25%) patients with clinically nonfunctioning pituitary tumours and in none of three patients with prolactinomas. Positive scans were observed only in patients bearing tumours with high-affinity somatostatin-binding sites [38].

The relatively low sensitivity in our study may be due to: (1) different tracers, i.e. [^{111}In-DTPA-D-Phe^1]-octreotide versus [^{123}I-Tyr^3]-octreotide; (2) low overall patient numbers in all studies; (3) differential expression of somatostatin receptor subtypes [40], as synthetic somatostatin analogues display high affinity only for somatostatin receptor subtype 2 [41]; (4) inhomogeneous receptor distribution [12]; (5) lack of receptor expression: as mentioned above, somatostatin receptors have been detected on 42 of 43 growth hormone-secreting pituitary tumours, indicating that one growth hormone-secreting pituitary tumour did not express somatostatin receptors [12]; (6) partial volume effects especially in small lesions. However, in vitro receptor studies were not performed with the pituitary adenoma tissue of our patients. In our study even para- and suprasellarly extending pituitary adenomas had no or faint tracer uptake, indicating that somatostatin receptor scintigraphy can be helpful for noninvasive tumour differentiation in the pituitary area. Although there was overlap between pituitary adenomas and meningiomas in grade I positive tumours, all meningiomas with tumour volumes above 10 ml were at least grade II positive. Only three pituitary adenomas of 10, 12 and 50 ml had grade II tracer uptake and would have been incorrectly classified as meningiomas. Twenty-one pituitary adenomas were correctly identified. Tumours in the pituitary area with no or faint tracer uptake are likely to be pituitary adenomas whereas tumours in the pituitary area with intense tracer uptake are likely to be meningiomas.

Somatostatin receptor scintigraphy and gliomas

Reubi et al. demonstrated that somatostatin receptor expression in gliomas seems to be dependent on tumour differentiation [8]. In their histochemical and autoradiographic studies, 82% of low-grade malignant gliomas (WHO classes I and II) expressed somatostatin receptors while only 2% of high-grade malignant gliomas (WHO classes III and IV) did so [8, 14]. However, these results could not be confirmed unanimously as in vitro studies using a gold ligand technique to look for somatostatin-binding sites on the cell surface did not demonstrate differences in the number of binding sites in low-grade and high-grade malignant gliomas [26]. This may explain why the scintigraphic results of our study differ from results expected on the basis of in vitro tests reported elsewhere [8, 14]. In our study none of the low-grade gliomas presented tracer uptake while 11 out of the 12 high-grade gliomas were detectable. As shown in combination with ^{99m}Tc-DTPA scintigraphy in a small number of patients, glioma visualization is dependent on the disruption of the blood-brain barrier. Gliomas with an intact blood-brain barrier (WHO class I or II) did not display uptake in vivo, while gliomas with a damaged blood-brain barrier (WHO class III or IV) showed uptake of the radiopharmaceutical. Lee et al. reported similar findings [27]. Binding to activated lymphocytes which are within the oedema surrounding the tumour may be another mechanism of ^{111}In-octreotide-uptake in high-grade gliomas [42]. Furthermore, unspecific mechanisms of tracer accumulation have been discussed: ^{111}In-octreotide may accumulate in tumours by penetrating the damaged blood-brain barrier, but washout from these tumours is slow. As octreotide is a polar, water-soluble peptide, it has to be presumed that penetration into tumours is only possible with a disrupted blood-brain bar-

rier. This hypothesis is supported by the fact that none of the patients scanned with octreotide for peripheral tumours without brain pathology showed visualization of their CNS [43] despite strong somatostatin receptor expression in various human CNS regions [44]. Haldemann et al. were able to demonstrate that tumours with an intact blood-brain barrier did not show tracer uptake in vivo although somatostatin receptor autoradiography in the same cases proved the presence of somatostatin receptors by in vitro examinations of surgical biopsy specimens [28]. A further explanation for different ^{111}In-octreotide uptake in high-grade gliomas may be the expression of different subtypes of somatostatin receptors [41].

Somatostatin receptor scintigraphy and neurinomas

In accordance with the findings of other investigators, neurinomas and neurofibromas did not demonstrate tracer uptake, making ^{111}In-octreotide scintigraphy a useful technique in the differential diagnosis between meningiomas and neurinomas. In vitro binding assays demonstrated that neurinomas and neurofibromas do not express somatostatin receptors [14].

Somatostatin receptor scintigraphy in metastases and other tumours

The results in the group comprising the remaining brain pathologies confirmed that many intracranial lesions express somatostatin receptors and therefore can be visualized by ^{111}In-octreotide scintigraphy. Differential diagnosis between benign and malignant intracranial lesions and differentiation between tumour entities are not possible by means of ^{111}In -octreotide scintigraphy alone. Besides meningiomas, other tumours with intense tracer uptake do exist, as exemplified by the osteosarcoma investigated. It is remarkable that an intracranial abscess was scintigraphically positive, which may be explained by activated lymphocytes.

Imaging and radiopharmaceutical aspects

In agreement with the findings of other investigators images obtained after 24 h showed a higher tumour to background ratio than those obtained after 4–6 h [17]. Planar images were usually diagnostic, but the tomographic technique (SPET) provided better spatial resolution and anatomical orientation. SPET considerably facilitated comparison with other tomographic techniques, especially in the case of small skull base lesions and multifocal disease; indeed, it seems to be mandatory in these cases. Furthermore, SPET allows image fusion by combination of anatomical information derived from CT or MRI and physiological information derived from scintigraphy.

Diagnostic and therapeutic implications

^{111}In-octreotide scintigraphy allows non-invasive somatostatin receptor imaging in vivo and provides complementary data to CT or MRI. Somatostatin receptor scintigraphy can be especially useful in the following clinical settings if CT or MRI provides inconclusive results [45, 46]:

1. Determination of the extent of meningiomatous tumour manifestation, especially in the case of dural infiltration.
2. Differentiation between scar tissue, necrosis and meningioma recurrence; such recurrence has been estimated to occur in 19% of cases after surgery [47].
3. Differentiation between meningioma and neurinoma in the cerebellopontine angle.
4. Differentiation between optic sheet meningioma and optic nerve glioma in the orbit.
5. Differentiation between meningiomas and pituitary adenomas if CT and MRI are inconclusive: in the case of non-enhancement in the sellar region a meningioma is highly unlikely [21, 45].
6. Differentiation in multifocal disease, e.g. differentiation between neurinomas and meningiomas in neurofibromatosis type II or differentiation between meningiomas and metastatic disease: in neurofibromatosis type II there is a 20% incidence of simultaneous occurrence of acoustic neurinomas and multiple meningiomas [48].

In the case of gliomas, thallium-201 brain SPET is superior to somatostatin receptor imaging in providing complementary data to CT and MRI for the identification of viable tumour [33, 34, 49, 50] and is therefore superior to octreotide imaging. Alternatively, L-3[^{123}I]iodo-α-methyl tyrosine, with its specific uptake mechanism reflecting amino acid transport independent of disruption of the blood-brain barrier, may be suitable for the identification of viable glioma tissue [51]. In general, somatostatin receptor scintigraphy does not improve the management of patients with cerebral tumours of glial origin [26]. Thus, somatostatin receptor scintigraphy is only helpful in selected patients with brain tumours. There is no rational argument for routine somatostatin receptor scintigraphy in all patients with brain tumours.

Conclusion

Somatostatin receptor scintigraphy with ^{111}In-octreotide is a non-invasive means of obtaining additional information of relevance for therapeutic decisions in patients with intracranial tumours. However, while a good correlation between imaging results and in vitro somatostatin receptor determination has been reported in many peripheral tumours, the situation is different in the central nervous system. Only meningiomas – located outside the blood-brain barrier – usually demonstrate high tracer uptake, while intracranial tumours may be out of reach due

to the blood-brain barrier and therefore may not be detectable by somatostatin receptor scintigraphy. The results demonstrate that a large variety of intracranial lesions can be visualized by [^{111}In-DTPA-D-Phe^{1}]-octreotide scintigraphy. Somatostatin receptor scintigraphy can be valuable in the differentiation between meningiomas and pituitary adenomas as well as between meningiomas and neurinomas. Furthermore, this technique allows the differentiation between scar tissue and recurrent meningiomas postoperatively and can be helpful in differentiating tumours in patient with multifocal disease. Due to the high somatostatin receptor density, meningiomas of the skull base or the orbit may be differentiated from somatostatin receptor-negative tumours. ^{111}In-octreotide scintigraphy can demonstrate intense tracer uptake even in small meningiomatous lesions. Therefore, in vivo receptor imaging can narrow the spectrum of differential diagnoses, especially by the confirmation or exclusion of meningiomas.

Somatostatin receptor imaging may be helpful for further characterization of tumours with unclear CT or MRI findings. SPET is especially helpful in small skull base lesions and for comparison with CT or MRI. In gliomas, however, somatostatin receptor scintigraphy is usually of no clinical value as other scintigraphic techniques are superior.

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