

Effects of Therapy with [^{177}Lu -DOTA⁰, Tyr³]Octreotate in Patients with Paraganglioma, Meningioma, Small Cell Lung Carcinoma, and Melanoma

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Therapy using the radiolabeled somatostatin analog [^{177}Lu -DOTA⁰, Tyr³]octreotate (^{177}Lu -octreotate) (DOTA is 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid) has been used primarily in gastroenteropancreatic neuroendocrine tumors. Here we present the effects of this therapy in a small number of patients with metastasized or inoperable paragangliomas, meningiomas, small cell lung carcinomas (SCLCs), and melanomas. **Methods:** Twelve patients with paraganglioma, 5 with meningioma, 3 with SCLC, and 2 with eye melanoma were treated. Three meningiomas were very large and exophytic and all standard treatments had failed. Patients with melanoma had rapidly progressive disease (PD). The intended cumulative dose of ^{177}Lu -octreotate was 22.2–29.6 GBq. Effects of the treatment on tumor size were evaluated using the Southwest Oncology Group criteria. **Results:** Two of 4 patients with progressive paraganglioma had tumor regression and 1 had stable disease (SD). Of 5 patients with stable paraganglioma, 2 had SD, 2 had PD, and in 1 patient treatment outcome could not be determined. Paraganglioma was stable in 3 patients in whom the disease status at the beginning of therapy was unknown. One of 4 patients with progressive meningioma had SD and 3 patients had PD. One patient with stable meningioma at the beginning of therapy had SD. All patients with SCLC or melanoma died within 5 mo after starting therapy because of tumor progression. Although not statistically significant, a positive trend was found between high uptake on pretherapy somatostatin receptor scintigraphy and treatment outcome. **Conclusion:** ^{177}Lu -Octreotate can be effective in patients with paraganglioma and meningioma. Response rates are lower than those in patients with gastroenteropancreatic neuroendocrine tumors. Most meningiomas were very large. Further studies are needed to confirm the treatment outcome because of the limited number of patients. ^{177}Lu -Octreotate did not have antitumor effects in patients with small lung carcinoma and melanoma.

Key Words: ^{177}Lu -octreotate; paraganglioma; meningioma; small cell lung carcinoma; melanoma

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The radiolabeled somatostatin analog [^{177}Lu -DOTA⁰, Tyr³]octreotate (^{177}Lu -octreotate) (DOTA is 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid) has been used for 6 y in our hospital for treating patients with somatostatin receptor–positive tumors. Most of the treated patients had inoperable or metastasized gastroenteropancreatic neuroendocrine tumors (GEP NETs). An analysis of the effect of ^{177}Lu -octreotate treatment on 131 patients of this group reported tumor regression in 47%, stable disease (SD) in 35%, and progressive disease (PD) in 19%. The median time to progression (TTP) was >36 mo. These results compare very favorably with chemotherapy for these indications (1). ^{177}Lu -Octreotate was also used in non-radioiodine–avid differentiated thyroid carcinoma. This therapy can be effective if uptake in tumor deposits on somatostatin receptor scintigraphy with ^{111}In -octreotide (OctreoScan; Mallinckrodt) is equal to or higher than liver uptake. Of 3 patients with Hürthle cell thyroid carcinoma treated with ^{177}Lu -octreotate, 2 patients had regression and one had SD (2). As other tumors—such as paragangliomas, meningiomas, small cell lung carcinomas (SCLCs), and melanomas—may have somatostatin receptor subtypes as well, these tumors were investigated.

Paragangliomas are neuroendocrine tumors derived from extraadrenal autonomic parasympathetic ganglia. Nuclear medicine can play a role in the management of these tumors. Metaiodobenzylguanidine (MIBG) is structurally similar to noradrenaline and is transported into the chromaffin cells and subsequently stored in the secretory vesicles. This allows imaging with ^{123}I -MIBG. ^{131}I -MIBG can

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be used as a therapy if the uptake by the tumor on ^{123}I -MIBG scintigraphy is high. Most paragangliomas also express somatostatin receptors. ^{111}In -Octreotide scintigraphy is a very sensitive technique to visualize these tumors. It detects >90% of known lesions in patients with paragangliomas (3). In detecting primary pheochromocytomas, somatostatin receptor scintigraphy is less sensitive than ^{123}I -MIBG, partially because of interference from the high physiologic uptake of ^{111}In -octreotide by the kidneys nearby. However, ^{111}In -octreotide scintigraphy can be useful in staging patients with metastatic pheochromocytoma because imaging with ^{123}I -MIBG is less sensitive in this group (4). ^{111}In -Octreotide has been used in high doses as a therapy in 3 patients with metastasized non-MIBG-avid pheochromocytomas, but this did not result in an objective response. One patient with a paraganglioma had a minor response (5).

Meningiomas are tumors derived from cap cells adherent to the dura mater, mostly close to the arachnoid villi or skull base foramina. They express different kinds of receptors. Meningiomas are frequently somatostatin receptor positive (6), and somatostatin receptor scintigraphy may be used to differentiate remnant or recurrent meningioma from nonspecific hyperperfusion during postsurgical follow-up (7). Treatment with ^{90}Y -labeled somatostatin analogs in patients with meningioma has been undertaken in selected cases, but the growth inhibition of tumors was not specifically reported (8,9).

SCLC are also considered to be neuroendocrine tumors. Somatostatin receptor scintigraphy can be used to visualize the primary tumor and its metastases. All primary tumors were visualized in a study of 26 SCLC patients, but its use is limited in staging (10). In another study, only 45% of distant metastases were detected (11). In an animal study with human SCLC cell line xenografts, treatment with ^{177}Lu -octreotate resulted in marked tumor regression (12). However, a pilot trial in 6 patients with SCLC using [^{90}Y -DOTA 0 ,Tyr 3]octreotide (^{90}Y -DOTATOC) (DOTA is 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid) showed no objective response. In that study only 26% of the known extrathoracic metastases were detected on pretherapy ^{111}In -octreotide scanning (13).

Melanomas arise from cells of the neural crest and may express somatostatin receptors as well. ^{111}In -Octreotide has the highest affinity for somatostatin receptor subtype 2 (sst $_2$) (14). Messenger RNA (mRNA) for this receptor subtype was demonstrated in 83% of cutaneous melanomas and in 96% for sst $_1$. Octreotide scintigraphy imaged 63% of tumors in patients with regional or distant metastases (15). Immunohistochemical staining for sst $_2$ in uveal melanoma was positive in all specimens; however, staining for sst $_1$ was not performed in that study (16). At present, no effective treatment is available for metastasized melanoma.

In this study, we report the effects of ^{177}Lu -octreotate treatment in a limited number of patients with somatostatin receptor-positive paragangliomas, meningiomas, SCLCs, and

melanomas and attempt to relate the outcome of this treatment to factors that pertain specifically to each type of tumor.

MATERIALS AND METHODS

Patients

We studied 12 patients with paragangliomas, 5 with meningiomas, 3 with SCLCs, and 2 with melanomas. All patients had tumor tissue uptake with [^{111}In -DTPA 0]octreotide (DTPA is diethylenetriaminepentaacetic acid) (OctreoScan) scintigraphy that was equal to or higher than uptake in normal hepatic tissue on planar images. Patients had not been treated before with other radiolabeled somatostatin analogs. Prerequisites for treatment were hemoglobin ≥ 5.5 mmol/L (≥ 8.9 mg/dL), white blood cells $\geq 2 \times 10^9/\text{L}$, platelets $\geq 80 \times 10^9/\text{L}$, creatinine ≤ 150 $\mu\text{mol/L}$ (≤ 1.70 mg/dL), creatinine clearance ≥ 40 mL/min, and Karnofsky performance status (KPS) ≥ 50 . All patients gave written informed consent to participate in the study, which was approved by the medical ethical committee of the hospital.

Methods

[DOTA 0 ,Tyr 3]Octreotate was obtained from Mallinckrodt. $^{177}\text{LuCl}_3$ was obtained from the Nuclear Research and Consultancy Group and the Missouri University Research Reactor and was distributed by IDB-Holland. ^{177}Lu -Octreotate was prepared locally as described previously (17).

Gransetron (3 mg) was injected intravenously. To reduce the radiation dose to the kidneys, an infusion of amino acids (2.5% arginine and 2.5% lysine) was started 30 min before the administration of the radiopharmaceutical and lasted 4 h. The radiopharmaceutical was coadministered via a second pump system. The dose administered in each cycle was 7.4 GBq, injected in 30 min. The interval between treatments was 6–10 wk. Patients were treated up to an intended cumulative dose of 22.2–29.6 GBq. If dosimetric calculations indicated that the radiation dose to the kidneys would exceed 23 Gy with a dose of 29.6 GBq, the cumulative dose was reduced to 22.2–27.8 GBq. To obtain this cumulative dose, the dose of the fourth cycle was 3.7 or 5.55 GBq, injected in 30 min as well.

Routine hematology, liver and kidney function tests, and hormone measurements were performed before each therapy as well as on follow-up visits. CT or MRI was performed within 3 mo before the first therapy, within 6–8 wk, 3 mo, and 6 mo after the last treatment, within every 6 mo thereafter.

Imaging

Planar spot images of the upper abdomen and other regions with somatostatin receptor-positive pathology were obtained 24 h after injection of the therapeutic dose of ^{177}Lu -octreotate. Upper abdominal images were also obtained on day 3 or day 4 and on day 7 or day 8 for kidney dosimetry. Counts from the 208-keV (20% window) γ -peak were collected. The acquisition time was 7.5 min per view. For dosimetry, counts from a standard with a known aliquot of the injected dose were collected over 3 min.

In Vivo Measurements

The tumors on CT or MRI were measured and scored according to the Southwest Oncology Group (SWOG) solid tumor response criteria (18).

The uptake during pretreatment [^{111}In -DTPA 0]octreotide scintigraphy was scored visually on planar images using the following 4-point scale: lower than (grade 1), equal to (grade 2), or higher

than (grade 3) normal liver tissue; or higher than normal spleen or kidney uptake (grade 4).

Estimation of the elimination rate (ER) of ^{177}Lu -octreotate from tumors was done as follows to evaluate the differences between SCLC and paraganglioma on one hand and GEP NETs on the other. Counts in 3 regions of interest (ROI) were measured on posttherapy scintigraphy on day 1, on day 3 or day 4, and on day 7. ROI 1 included the entire tumor, ROI 2 included the entire tumor and surrounding area for calculating counts in background, and ROI 3 included a standard with a known aliquot of the injected dose. The counts in these ROIs were used to calculate the percentage uptake in the tumor of the injected dose, using the same method as for kidney dosimetry. Because we were only interested in a difference in shape of the curve displaying the amount of radioactivity in time, no attenuation correction was done. To normalize the shape of the curve and make comparison possible between different patients and tumors, radioactivity at 24 h after injection was then set at 100 and expressed as a fraction of this on day 3 or day 4 and on day 7 according to the measured radioactivity. Radioactivity at 400 h after injection was assumed to be zero. These 4 values were plotted and the area under the curve was calculated to give an estimate of the ER. The ER in para-

ganglioma and SCLC (ER_{NG}) was compared with the ER in GEP NET (ER_{G}) with a resemblance in size, location, and grade of uptake on posttherapy scintigraphy.

Statistics

The Fisher exact test was used in testing for significant differences in treatment outcome between groups of different grade of uptake on ^{111}In -octreotide scintigraphy. To compare ER_{G} and ER_{NG} , we used the unpaired *t* test, as the Kolmogorov–Smirnov test indicated that both ER_{G} and ER_{NG} are normally distributed. $P < 0.05$ was considered to be statistically significant. Values of ER are given as mean \pm SD.

RESULTS

Patient Characteristics, Side Effects, and Responses

Baseline characteristics of the patients are shown in Table 1. Twenty-two patients were included. Age ranged from 22 to 74 y (median, 46 y). The median KPS at entry was 85 (range, 60–100). Seven patients (32%) had non-metastasized disease; the other patients had distant metastases.

TABLE 1
Patient Characteristics

Characteristic	No. of patients (%)			
	Paraganglioma	Meningioma	SCLC	Melanoma
Total	12*	5	3	2
Sex				
M	6 (50)	2 (40)	2 (67)	1 (50)
F	6 (50)	3 (60)	1 (33)	1 (50)
Age (y)				
Mean	39.7	54.6	65.7	68.5
Range	22–55	41–67	63–67	63–74
Metastases				
None	3 (25)	3 (60)	1 (33)	—
Liver only	2 (17)	—	1 (33)	2 (100)
Bone only	5 (42)	1 (20)	—	—
Liver and bone	2 (17)	1 (20) [†]	1 (33)	—
^{111}In -Octreotide uptake				
Grade 2	1 (8)	—	1 (33)	1 (50)
Grade 3	7 (58)	5 (100)	2 (67)	1 (50)
Grade 4	4 (33)	—	—	—
Disease state at baseline				
PD	4 (33)	4 (80)	2 (67)	2 (100)
SD [‡]	5 (42)	1 (20)	1 (33)	—
Unknown	3 (25)	—	—	—
Prior therapies				
None	2 (17)	—	—	1 (50)
Surgery	9 (75)	3 (60)	—	1 (50)
Chemotherapy	4 (33)	2 (40)	3 (100)	—
Radiotherapy	7 (58)	5 (100)	2 (67)	—
^{177}Lu -Octreotate cumulative dose (GBq)	14.8–29.6	14.8–29.6	7.4–14.8	22.2

*Localization of primary tumor: 5 head and neck, 2 renal, 2 paraspinal (1 lumbar, 1 cervical), 1 adrenal (pheochromocytoma), 1 thoracic (glomus aorticum), 1 organ of Zuckerkandl.

[†]Liver and bone metastases of carcinoid tumor.

[‡]No PD documented in 12 mo before treatment.

SCLC = small cell lung carcinoma; PD = progressive disease; SD = stable disease.

Three patients (14%) had grade 2 uptake on ^{111}In -octreotide scintigraphy, 15 patients (68%) had grade 3 uptake, and 4 patients (18%) had grade 4 uptake. Twelve patients (55%) had PD within 1 y before starting treatment with ^{177}Lu -octreotate. The other patients had SD or the baseline disease status was unknown. Three patients (14%) had not had therapies before ^{177}Lu -octreotate. Other patients had undergone surgery, chemotherapy, or radiotherapy or a combination of these.

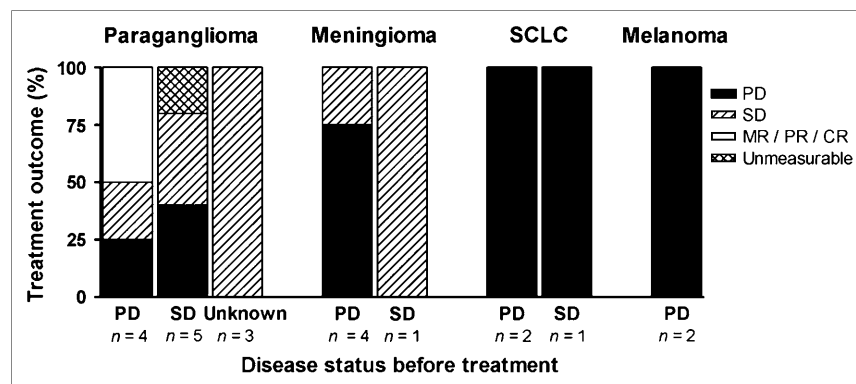
World Health Organization (WHO) hematologic toxicity grade 4 occurred in 1 patient. WHO grade 3 toxicity was not noted in any patient. The onset or aggravation of nausea was present after 49% of administrations of ^{177}Lu -octreotate. This was mild, in general; however, vomiting occurred in 18% of administrations. Pain in the sites of tumor deposits developed or increased temporarily after 15% of administrations. Eleven patients (50%) reported hair loss, primarily during the first weeks after a cycle. This was mild and never resulted in complete alopecia.

Twelve patients had paraganglioma. Table 1 indicates the distribution of the primary tumors. Two patients had inoperable, nonmetastasized tumors. One patient had an operable tumor but refused surgery. One patient was treated on a compassionate basis despite severe anemia and thrombocytopenia requiring several blood transfusions. Because the thrombocytopenia was probably paraneoplastic, this was considered not to be an exclusion criterion. Nine patients received the intended dose of 22.2–29.6 GBq ^{177}Lu -octreotate. Treatment had to be stopped in 2 patients because of persistent thrombocytopenia and anemia. One patient died because of disease progression after a cumulative dose of 14.8 GBq ^{177}Lu -octreotate. One patient had a partial remission (PR). (Fig. 1) In this patient, plasma chromogranin A (CgA) decreased from 326 $\mu\text{g/L}$ at baseline to 100 $\mu\text{g/L}$ before the last cycle of ^{177}Lu -octreotate. Unfortunately, a myelodysplastic syndrome (MDS) developed in this patient. MDS was most probably a complication of prior chemotherapy (dacarbazine, adriamycin, ifosfamide), given the very short interval of 4 mo between the last dose of ^{177}Lu -octreotate and the development of MDS. The interval between the last cycle of chemotherapy

and the development of MDS was 22 mo. One patient had a minor response ([MR] tumor diameter decrease, 25%–50%) (Fig. 1); however, progression of disease was noted after 11 mo. Figure 2 demonstrates the initial tumor reduction. Six patients, including 1 with initial PD, had SD, 3 patients had PD, and no data are available for 1 patient because of the absence of measurable disease on CT. Two years after the first cycle, liver function tests and CgA still have not changed. The median TTP in patients with paragangliomas cannot be determined yet. Follow-up ranged from 4 to 30 mo (median, 13 mo). The TTP was 11 and 15 mo in 2 patients. In 6 others, disease remained unchanged for the time of follow-up. Two patients died during follow-up: 1 patient 9 mo after starting ^{177}Lu -octreotate and the other patient after 24 mo. PD developed in both patients during treatment.

Five patients with meningioma were treated with ^{177}Lu -octreotate. Two patients had extremely large, exophytic, cranial tumors and 1 patient also had cervical metastases. One patient had a large, exophytic, cervical meningioma with rapid progression. These 3 patients had WHO grade III (malignant/anaplastic) meningiomas and all standard treatments had failed. Two patients had a cavernous sinus meningioma. The WHO grade was unknown, as no biopsy had been performed. One of these patients also had a neuroendocrine tumor (carcinoid) with somatostatin receptor-positive metastases in the bone and liver. Three patients received the intended dose of 29.6 GBq ^{177}Lu -octreotate. One patient decided to stop treatment after cumulative administration of 22.2 GBq. The patient with cervical meningioma received a cumulative dose of 14.8 GBq ^{177}Lu -octreotate and died shortly after the second cycle because of progression of the tumor. Two patients with exophytic, cranial meningioma still had PD (Fig. 3 depicts progression in one of these patients). Two patients, including one with PD at baseline, with cavernous sinus meningioma, had SD (Fig. 1) after therapy. In the patient with the double tumors (meningioma and carcinoid), the meningioma was stable both before and after therapy. The carcinoid tumor showed a MR. This patient died 18 mo after the start of therapy because of progression of the carcinoid tumor.

FIGURE 1. Effects of therapy with ^{177}Lu -octreotate in groups of tumors in relation to disease status before treatment. PD = progressive disease; SD = stable disease; MR = minor response; PR = partial remission; CR = complete remission.



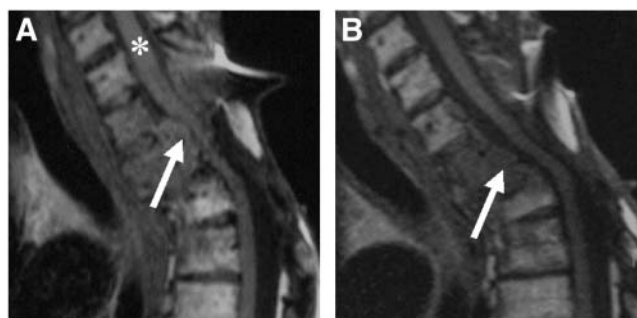


FIGURE 2. MR image (T1 weighted) of cervicothoracic spine of patient with pheochromocytoma. (A) Baseline scan 3 mo before ^{177}Lu -octreotate therapy shows tumor extending into spinal canal (arrow, *spinal cord). (B) Scan 3 mo after fourth cycle of 7.4 GBq ^{177}Lu -octreotate shows reduction in tumor extension into spinal canal (arrow).

Three patients with a SCLC were studied. The KPS at baseline ranged from 60 to 90. One patient had an initial complete response (CR) after chemotherapy with carboplatin and etoposide, followed by external beam radiotherapy of the primary tumor. The CR lasted 16 mo. Then recurrence was noted and topotecan was started without response. ^{177}Lu -Octreotate was started 4 mo after the recurrence. The second patient had a CR after 5 cycles of cyclophosphamide, doxorubicin, and etoposide (CDE), followed by external beam radiotherapy of the primary tumor. Recurrence was noted after 10 mo and CDE was given again, resulting in tumor regression. One month later, treatment with ^{177}Lu -octreotate was started. During this therapy, plasma neuron-specific enolase (NSE) rose from 165 to 321 mg/L and plasma CgA increased from 45 to 116 $\mu\text{g/L}$. The patient had liver metastases and had progressive liver enzyme disturbances (Fig. 4; SCLC 2, third treatment could not be given.). The third patient had 8 cycles of carboplatin and etoposide, resulting in a PR followed by imatinib and gefitinib. Then 1 cycle of ^{177}Lu -octreotate was given. Because of occlusion of the superior vena cava (SVC), external beam radiotherapy and a cycle of adriamycin,

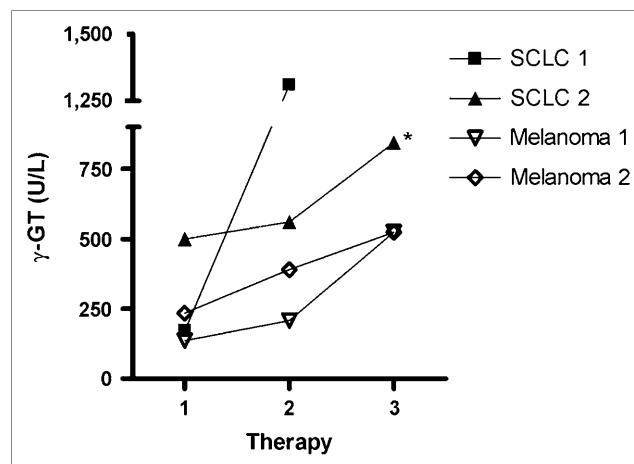


FIGURE 4. γ -Glutamylpeptidase (γ -GT) in patients with SCLC or melanoma with hepatic metastases. *Third therapy could not be given.

vincristin, and cyclophosphamide were given. Then the second cycle of ^{177}Lu -octreotate was administered. Plasma NSE rose from 236 mg/L just before the first cycle to 905 mg/L before the second cycle and plasma CgA increased from 362 to 1,077 $\mu\text{g/L}$. This patient had liver metastases as well, and liver enzymes progressively deteriorated (Fig. 4; SCLC 1). The 2 patients discussed first had progression, despite the administration of ^{177}Lu -octreotate, and died before finishing all planned cycles of the treatment: 1 patient after administering 7.4 GBq and the other after administering 14.8 GBq. Figure 5 shows progression in the latter patient on posttherapy scintigraphy. The patient with occlusion of the SVC seemed to have tumor regression on the CT scan but died because of a pulmonary embolus after a cumulative dose of 14.8 GBq ^{177}Lu -octreotate. We have classified this as PD. (Fig. 1)

Finally, 2 patients had melanoma of the eye with liver metastases. Both had rapidly PD at baseline. The KPS at baseline was 80 and 100. Both patients received a cumulative dose of 22.2 GBq ^{177}Lu -octreotate. In 1 patient, this was

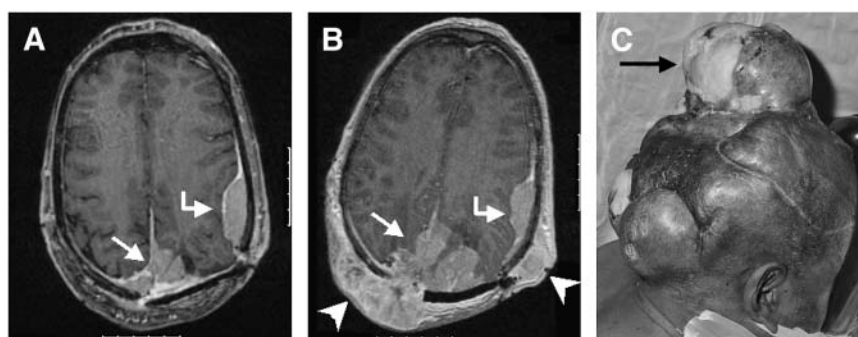


FIGURE 3. Example of patient with large, cranial meningioma. Patient already had undergone surgery 4 times and had had external beam radiotherapy before ^{177}Lu -octreotate. (A) MR image 1 wk after first cycle of ^{177}Lu -octreotate shows meningioma (arrow, curved arrow) with some extracranial involvement. (B) MR image 1 mo after final dose of ^{177}Lu -octreotate. Intracranial part of meningioma has increased (arrows). Extracranial, exophytic parts have increased as well (arrowheads). (C) Photograph of patient 18 mo after last dose of ^{177}Lu -octreotate (view from right, posterooblique). Patient had undergone surgery and had had external beam radiotherapy again and had just finished 6 cycles of cisplatin without therapeutic effect. Arrow indicates very large, extracranial part of meningioma with ulcerated skin.

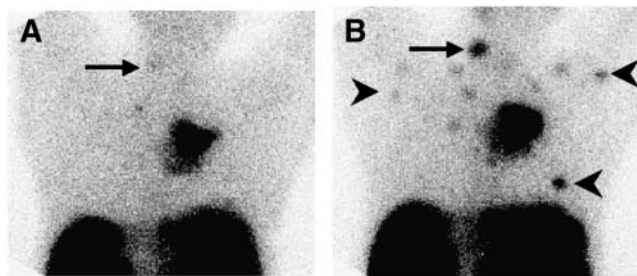


FIGURE 5. Scintigraphy performed 4 d after administration of 7.4 GBq ^{177}Lu -octreotate in patient with SCLC. (A) Scan (posterior chest) after first dose. Arrow indicates a cervical lesion. (B) Scan (posterior chest) after second and last dose 2 mo later. Several new lesions are visible (arrowheads). Uptake in lesions already present on first scan has increased (arrow).

the intended dose. Both still had PD (Fig. 1) and both died: 1 patient 4 mo and the other 5 mo after the first dose. Plasma CgA increased in 1 patient from 93 to 191 $\mu\text{g/L}$ and increased from 75 to 216 $\mu\text{g/L}$ in the other. Liver function tests also progressively deteriorated. (Fig. 4)

In the whole group, including all tumor types, we analyzed whether a relation exists between treatment outcome and tumor uptake on ^{111}In -octreotide scintigraphy. All 3 patients (1 paraganglioma, 1 melanoma, 1 SCLC) with grade 2 uptake had PD. In 14 patients (6 paraganglioma, 5 meningioma, 2 SCLC, 1 melanoma) with grade 3 uptake, 50% had PD, 43% had SD, and 7% had tumor regression. In 4 patients (4 paraganglioma) with grade 4 uptake, these values were 25%, 50%, and 25%, respectively (Fig. 6). We tested for a significant difference in treatment outcome between groups of different uptake on ^{111}In -octreotide scintigraphy. Because of the small number of patients, grade 2 uptake and grade 3 uptake were both considered to belong to the low-uptake group, and grade 4 uptake was considered to belong to the high-uptake group. For treatment outcome, SD and tumor regression were combined into 1 non-PD

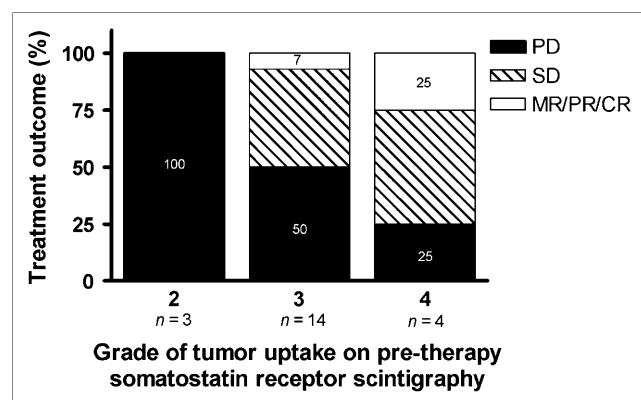


FIGURE 6. Relation between uptake of ^{111}In -octreotide on pretherapy somatostatin receptor scintigraphy and response to ^{177}Lu -octreotate therapy. PD = progressive disease; SD = stable disease; MR = minor response; PR = partial remission; CR = complete remission.

group. No statistically significant difference was found in treatment outcome (non-PD vs. PD) between the patients with high uptake and those with low uptake (2-tailed Fisher exact test; $P = 0.31$).

In 2 of 3 patients with SCLC, an estimation of the ER of ^{177}Lu -octreotate was determined. In 1 patient this was impossible because of a technical problem. In 3 of 12 patients with paraganglioma determining the ER was not possible. One patient had cranial tumors solely, and no matching GEP NET could be found in our database. In 2 patients, tumors were not visualized at all 3 time points. In 11 patients with SCLC ($n = 2$) or paraganglioma ($n = 9$), (non-GEP NETs), ER was measured (ER_{NG}) and compared with ER in 11 patients with GEP NETs (ER_{G}). The mean ER_{NG} was 129.7 ± 16.7 and mean ER_{G} was 127.6 ± 24.8 . This difference was not significant (unpaired t test; $P = 0.82$).

DISCUSSION

Paraganglioma, meningioma, SCLC, and melanoma are all tumors that may express somatostatin receptor subtypes. In GEP NETs, response rates up to 47% were achieved using ^{177}Lu -octreotate (1). The best results in the present study are tumor regression in 2 and disease stabilization in 1 of 4 patients with progressive paragangliomas. Regardless of tumor stage and progression at baseline, 17% of paragangliomas displayed tumor regression. In the other types of tumors, no tumor reduction was observed. One of 4 patients with progressive meningioma had SD after therapy. In all other patients, disease remained stable or progressed. Patients with SCLC or melanoma, especially, had the worst treatment outcome. All of these tumors remained progressive and all patients died within 5 mo after starting therapy.

In general, results of treatment with ^{177}Lu -octreotate in the studied group are less favorable than in carcinoids and GEP NETs. At entry, the KPS ranged from 60 to 100 (median, 85), so a poor performance status does not seem to be the cause of this difference in treatment outcome. Probably the following characteristics of the type of tumor play an important role. Melanoma and SCLC are very aggressive tumors once metastases are present. No really effective therapeutic options are currently available for metastasized melanoma. In SCLC, initial response rates of chemotherapy are good. In a study with etoposide, cisplatin, and fractionated external beam radiotherapy, an overall response rate of 87% was seen in patients with limited disease, but the rate of disease-free survival at 2 y was only 24%–29% (19).

One of the reasons for our relatively disappointing results in the studied tumors might be that these tumors are less sensitive to radiation than carcinoids and GEP NETs. Meningioma can be large and hypoxia can be present in a part of meningioma. Radiotherapy is less effective then because of decreased formation of oxygen radicals (20). Melanomas, including uveal melanomas, are relatively resistant to radiation, requiring higher radiation doses and

shorter intervals between irradiation than most other tumors (21). Fifty-nine percent of patients with paraganglioma, all patients with meningioma, and 67% of patients with SCLC had had prior external beam radiation therapy. This may have led to the development of radioresistance.

With chemotherapy, several proteins of the adenosine triphosphate binding cassette (ABC) transporter family become activated, which excrete drugs from the tumor cell. Because of the less-favorable response rates in non-GEP NETs, these tumors may hypothetically also expel ^{177}Lu -octreotate more rapidly than GEP NETs. This would lead to a lower amount of absorbed radiation per gram tumor tissue and, hence, a reduced chance of tumor remission. To investigate this factor, we made an estimation of the ER of ^{177}Lu -octreotate from SCLC and paraganglioma and compared this with the ER from GEP NETs with a resemblance in localization, size, and uptake on posttherapy scintigraphy. We found no significant difference in the ER between these groups and, therefore, can assume there is no difference in the ER of ^{177}Lu -octreotate; thus, this cannot explain the rather disappointing results in non-GEP NETs.

Also, the number, affinity, and subtype of somatostatin receptors may play a role. In SCLC, not all metastases may be visualized on ^{111}In -octreotide scintigraphy. This may be attributed to various factors. The lesions may be too small to be visualized or may be situated close to tissues with high physiologic uptake. It was also reported that prior or concomitant therapies might affect uptake of somatostatin (11). However, no uptake or very low uptake may indicate a low number, expression, or affinity of somatostatin receptors as well. This means that these lesions will have absent or very low uptake of ^{177}Lu -octreotate. Less expression of somatostatin receptors was reported in high-grade bronchial carcinoids and SCLC compared with low-grade bronchial carcinoids as an expression of their more aggressive behavior (22). Disease progression during therapy with ^{177}Lu -octreotate in patients, however, is possibly caused by an absence of somatostatin receptors on some lesions and also by new receptor-positive lesions that develop during therapy, as seen in 1 patient of the present study. Although not statistically significant, the trend we found between the uptake and the effect of therapy underscores the importance of tumor uptake on ^{111}In -octreotide scintigraphy in evaluating the feasibility of therapy with ^{177}Lu -octreotate. In a previous study in a larger group of patients with GEP NETs, high uptake on ^{111}In -octreotide scintigraphy significantly correlated with higher remission rates with ^{177}Lu -octreotate therapy (1). Melanoma cells express mRNA for sst_1 more often than for sst_2 (15). $[\text{DOTA}^0, \text{Tyr}^3]\text{Octreotate}$ has the highest affinity for sst_2 and almost none for sst_1 (14). A ^{177}Lu -labeled somatostatin analog with higher affinity for sst_1 would potentially be more effective in these tumors.

In paraganglioma, therapy with ^{177}Lu -octreotate was effective in some patients. We believe it could have a role in the management of this disease. Certainly when the dis-

ease is progressive, lesions are non- ^{131}I - or ^{123}I -MIBG-avid, whereas ^{111}In -octreotide scintigraphy is positive. Comparison of ^{177}Lu -octreotate with ^{131}I -MIBG is rather difficult, because a head-to-head trial has never been done. Tumor response rates in patients with paraganglioma with ^{131}I -MIBG therapy with single doses ranging from 3.6 to 11.1 GBq and with cumulative doses between 3.6 and 85.9 GBq (mean, 18.1 GBq) are 30%, with only very rarely complete remission (23). In a study with a median single dose of 29.6 GBq ^{131}I -MIBG (range, 14.3–32.0 GBq) and a median cumulative dose of 37.6 GBq (range, 14.3–62.5 GBq), 3 of 12 patients had a complete remission (24). However, in both studies, the results of the treatment were evaluated not only by using CT criteria but also by using hormonal responses.

In meningiomas, our present opinion is that this therapy could be used if the disease is slowly progressive and other options are absent or are not considered effective. Three of the treated patients had very large, exophytic meningiomas, which might respond differently from regular meningiomas. If ^{177}Lu -octreotate is given earlier in the course of the disease or in combination with other therapies, results could possibly be better.

In metastasized SCLC, ^{177}Lu -octreotate seems to be ineffective. Treatment with ^{90}Y -DOTATOC was ineffective in all 6 patients with SCLC as well (13). Therefore, we have decided not to treat patients with SCLC with ^{177}Lu -octreotate anymore.

In the 2 patients with eye melanoma that we treated, ^{177}Lu -octreotate did not have a therapeutic effect either. In a phase 1 study with ^{90}Y -DOTATOC, 1 patient with melanoma was included, but that treatment was also ineffective (8). We have also stopped including patients with eye melanoma for ^{177}Lu -octreotate therapy on the basis of the results of the present study.

Our study has limitations. The number of patients studied was small. Given the dismal treatment outcome in this and other studies with radiolabeled somatostatin analogs in patients with SCLC (13) or melanoma (8), however, we recommend not to treat these patients with ^{177}Lu -octreotate anymore using the present treatment protocol. In patients with paraganglioma or meningioma, it is important to treat more patients to further evaluate the effect of ^{177}Lu -octreotate.

CONCLUSION

^{177}Lu -Octreotate can have therapeutic effects in paraganglioma and meningioma. However, response rates are lower compared with carcinoids and GEP NETs. Further studies are needed to confirm these preliminary results. Although not statistically significant, a positive trend was found between the high uptake on pretherapy somatostatin receptor scintigraphy and the treatment outcome. The present treatment protocol with ^{177}Lu -octreotate does not seem to have clinical effects in SCLC and melanoma.

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