Peptide receptor radionuclide therapy with ^{177}Lu -octreotate in patients with foregut carcinoid tumours of bronchial, gastric and thymic origin

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Abstract

Purpose Foregut carcinoid tumours have a different embryological origin than other gastroenteropancreatic neuroendocrine tumours (GEP NETs). In the total group of GEP NETs ($n=131$), treatment with ^{177}Lu -octreotate resulted in tumour remission in 47% of patients, with a median time to progression (TTP) of >36 months. As patients with foregut carcinoids may respond differently, we here present the effects of this treatment in a subgroup of patients with foregut carcinoids of bronchial, gastric or thymic origin.

Methods Nine patients with bronchial, five with gastric and two with thymic carcinoids were treated. All patients had metastasised disease. The intended cumulative dose of ^{177}Lu -octreotate was 22.2–29.6 GBq. Southwest Oncology Group criteria were used for response evaluation.

Results *Bronchial carcinoids*: Five patients had partial remission, one had minor response (MR, tumour size reduction: $\geq 25\%$, $<50\%$), two had stable disease (SD) and one had progressive disease (PD). Median TTP was 31 months. *Gastric carcinoids*: One patient had complete remission, one had MR and two had SD, including one with PD at baseline. One patient developed PD. *Thymic carcinoids*: One patient had SD. In the other patient, disease remained progressive. *All patients*: Overall remission rate was 50%, including MR.

Conclusion ^{177}Lu -octreotate treatment can be effective in patients with bronchial and gastric carcinoids. Its role in thymic carcinoids cannot be determined yet because of the limited number of patients. The overall remission rate of 50% in patients with the studied foregut carcinoids is comparable to that in the total group of GEP NETs.

Keywords ^{177}Lu -octreotate · Foregut carcinoid · Bronchial carcinoid · Gastric carcinoid · Thymic carcinoid

Introduction

Carcinoid tumours belong to the group of gastroenteropancreatic neuroendocrine tumours (GEP NETs). These tumours often express somatostatin receptor subtype 2, which can be visualised with ^{111}In -octreotide scintigraphy (somatostatin receptor scintigraphy, SRS) [1]. If SRS is positive, peptide receptor radionuclide therapy with radio-labelled somatostatin analogues, e.g. [^{177}Lu -DOTA⁰,Tyr³] octreotate (^{177}Lu -octreotate) may be used in treating patients with GEP NETs. According to their origin, carcinoid tumours can be subdivided into three groups [2]: foregut, midgut and hindgut carcinoids. Foregut carcinoid tumours are derived from neuroendocrine cells of the embryologically most proximal part of the gut (from sinuses to duodenum), including lungs, thymus, pancreas and gall bladder. The most common forms of foregut carcinoids are of bronchial and gastric origin: approximately 24% of all carcinoids arise from lung and 6% from stomach. Carcinoids of thymic origin are very rare (less than 1% of all carcinoids) [3].

In 2000, the World Health Organisation (WHO) introduced a revised clinicopathological classification of GEP

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NETs [4]. In this classification, carcinoid is no longer mentioned. A distinction is made between well-differentiated neuroendocrine tumours, well-differentiated neuroendocrine carcinomas and poorly differentiated neuroendocrine carcinomas, with the origin of the tumour and the clinical syndrome added. However, the term “carcinoid” is still used frequently in clinical practice. Yet in the WHO classification of lung tumours of 1999, bronchial carcinoid tumours are still mentioned as a subgroup of epithelial lung tumours [5].

Carcinoid tumours account for at least 0.4% of lung tumours in epidemiological studies [6] and up to 5% in surgical series [7]. Based on histology, bronchial carcinoids can be classified in two groups: typical (around 85%) and atypical (around 15%) [8]. This classification has prognostic consequences: 5-year survival in patients with typical bronchial carcinoids was found to be 90%, compared with 69% in those with atypical bronchial carcinoids [8]. Diarrhoea and cutaneous flushing (carcinoid syndrome) occur in around 8% of patients with bronchial carcinoids. About 6% of bronchial carcinoids produce adrenocorticotrophic hormone (ACTH) and as a result cause Cushing’s syndrome [8].

Gastric carcinoids are classified into three groups [9]. Type 1 gastric carcinoid is the most common (70–80% of all gastric carcinoids) and is associated with chronic atrophic gastritis. Gastric acid production is absent and serum gastrin levels are elevated. Its metastatic potential is less than 5%. Type 2 gastric carcinoid is less common (5–10%) and is associated with high serum gastrin levels due to gastrinomas as part of multiple endocrine neoplasia-1 (MEN-1) syndrome with consequent high gastric acid production. Metastases develop in 7–12%. Type 3 gastric carcinoids are not associated with any other medical condition and therefore are called sporadic gastric carcinoids. Sporadic gastric carcinoids have a risk of metastasising of 50–100%. [see 10 and 11 for a review and references within].

Thymic carcinoids can occur sporadically or as part of MEN-1 syndrome and occur more frequently in male than in female patients [12]. Thymic carcinoids metastasise frequently or are often inoperable because of locoregional infiltrative growth. A study by Fukai et al. reported that in 10 out of 13 patients distant metastases developed after total resection of the primary tumour and local lymph node metastases, some as late as 8 years postoperatively [13]. Carcinoid syndrome in patients with thymic carcinoid occurs very rarely (less than 1%), whereas ectopic Cushing’s syndrome occurs in up to 17% [12].

Currently the radiolabelled somatostatin analogue ^{177}Lu -octreotate is administered in our hospital when treating patients with somatostatin receptor subtype 2-positive tumours. This treatment results in tumour size reduction in 47% in patients from the total group of GEP NETs,

including 19% minor response (MR, tumour size reduction $\geq 25\%$, $< 50\%$) [14]. Because of their different embryological origin, the present study was performed to evaluate whether foregut carcinoid tumours of bronchial, gastric and thymic origin respond differently to treatment with ^{177}Lu -octreotate in comparison with the total group of GEP NETs.

Materials and methods

Patients

The study population comprised nine patients with metastasised bronchial carcinoids, five with metastasised gastric carcinoids and two with metastasised thymic carcinoids. No patients with carcinoid tumours of certain duodenal or pancreatic origin were referred for treatment. Patients were consecutively referred to our hospital. All patients had measurable disease. All patients had tumour tissue uptake with [^{111}In -DTPA 0]octreotide scintigraphy (OctreoScan $^{\text{®}}$) that was on average higher than uptake in normal hepatic tissue on planar images. Patients with known somatostatin receptor-negative lesions were excluded. Patients had not been treated with other radiolabelled somatostatin analogues before. Prerequisites for treatment were haemoglobin (Hb) ≥ 5.5 mmol/l, WBC $\geq 2 \cdot 10^9$ /l, platelets $\geq 80 \cdot 10^9$ /l, creatinine ≤ 150 $\mu\text{mol/l}$ and creatinine clearance ≥ 40 ml/min, and Karnofsky performance score (KPS) ≥ 50 . All patients gave written informed consent to participation in the study, which was approved by the medical ethical committee of the hospital.

Methods

[DOTA 0 ,Tyr 3]octreotate was obtained from Mallinckrodt (St Louis, MO, USA). $^{177}\text{LuCl}_3$ was obtained from NRG (Petten, the Netherlands) and Missouri University Research Reactor (Columbia, MO, USA) and was distributed by IDB-Holland (Baarle-Nassau, the Netherlands). ^{177}Lu -octreotate was locally prepared as described previously [15].

Granisetron 3 mg was injected intravenously, as a precaution against nausea. In order to reduce radiation dose to the kidneys, an infusion of amino acids (arginine 2.5% and lysine 2.5%) was started 30 min before the administration of the radiopharmaceutical and lasted 4 h. Via a second pump system, the radiopharmaceutical was co-administered. Cycle doses were 7.4 GBq, injected in 30 min. The interval between treatments was 6–10 weeks. Patients were treated up to an intended cumulative dose of 22.2–29.6 GBq; if dosimetric calculations done on post-therapy scans 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. The dose of the last cycle was then adjusted to 3.7 or 5.55 GBq, administered in 30 min as well.

Routine haematology, liver and kidney function tests, and hormone measurements were performed before each therapy, as well as with follow-up visits. Computed tomography (CT) or magnetic resonance imaging (MRI) was performed within 3 months before the first therapy, and 6–8 weeks, 3 months and 6 months after the last treatment, and thereafter every 6 months.

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 4 and day 7 or 8 for kidney dosimetry. Counts (20% window) from the 208-keV γ peak were collected. The acquisition time was 7.5 min.

In vivo measurements

The tumours on CT or MRI were measured and scored according to modified Southwest Oncology Group (SWOG) solid tumour response criteria [16]. MR was defined as a tumour size reduction of $\geq 25\%$ and $< 50\%$. MR was added since GEP NETs in general are slow-growing tumours and can be cystic, which makes it unlikely that

they respond similarly to treatment as fast-growing solid tumours.

The uptake during pre-treatment [^{111}In -DTPA 0]octreotide scintigraphy was scored visually on planar images using the following four-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).

Statistics

Kaplan-Meier survival analysis was used to estimate median time to progression (TTP) in the group of patients with bronchial carcinoids. Fisher's exact test or Pearson χ^2 test was used to evaluate differences in frequencies of characteristics or responses between groups. *P* values of < 0.05 were considered statistically significant.

Results

Baseline patient characteristics per disease are presented in Table 1. Sixteen patients were included. Age ranged from 37 to 76 years (median 57 years) and Karnofsky performance status (KPS) at entry ranged from 70 to 100 (median 90). All patients had metastasised disease. In five patients (31%), progression of disease was documented on CT or MRI in the 12 months before starting ^{177}Lu -octreotate. ^{177}Lu -octreotate was the first therapy to be given in three

Table 1 Patient characteristics at baseline

Disease	Bronchial carcinoid	Gastric carcinoid	Thymic carcinoid
Total no. of patients	9 ^a	5	2
Sex			
M/F	6/3	2/3	2/–
Age, years			
Median (range)	62 (37–75)	50 (47–76)	53 (40–65)
KPS			
Median (range)	90 (80–100)	90 (70–100)	90 (90)
Hormonal syndrome			
Carcinoid syndrome	2	–	–
Cushing's syndrome	–	–	1
Uptake of OctreoScan			
Grade 3	8	5	2
Grade 4	1	–	–
Tumour status at baseline			
PD ^b	2	2	1
SD	2	1	–
Unknown	5	2	1
Prior therapies			
None	–	2	1
Surgery	8	3	–
Chemotherapy	1	2	1
Radiotherapy	2	–	1

PD progressive disease, SD stable disease

^a Four typical bronchial carcinoids, five atypical bronchial carcinoids

^b Progression documented in 12 months before treatment

patients. Fifteen patients (94%) had grade 3 uptake on pre-therapy SRS and one patient (6%) had grade 4 uptake. In the total group of GEP NETs, 3% had grade 2 uptake, 78% had grade 3 uptake and 19% had grade 4 uptake [14]. This difference was not statistically significant (Fisher's exact test, $p>0.05$).

Frequencies of several predictive factors for progressive disease as treatment outcome that were significant for the whole group of GEP NETs are presented in Table 2 for patients with foregut carcinoids and for patients from the total group of GEP NETs [14]. None of the differences was statistically significant (Fisher's exact test or Pearson χ^2 test).

WHO grade 3 haematological toxicity occurred in three patients. Grade 4 haematological toxicity did not occur. Patients reported nausea after 25% of administrations. Although nausea was mostly mild, vomiting occurred in 12% of all administrations. Four patients reported pain in tumour-involved regions (i.e. in 10% of all administrations). Seventy-five percent of patients had mild hair loss after the treatment. No alopecia was reported.

Nine patients with bronchial carcinoids were treated. In two patients, metastases were present in the chest only. All other patients had distant metastases. None of the patients had other neuroendocrine tumours consistent with a MEN syndrome. Two patients had proven progressive disease (PD) in the 12 months before starting treatment with ^{177}Lu -

octreotate. Four patients had typical bronchial carcinoids and five had atypical bronchial carcinoids. Two patients had symptoms consistent with carcinoid syndrome. None of the patients had symptoms, signs or biochemical abnormalities indicating ectopic ACTH production. Two patients did not achieve the intended cumulative dose: one because of disease progression and the other because of persistent myelosuppression. Five of nine patients (56%) had partial remission (PR) (Fig. 1). One of nine patients had an MR. Two patients had stable disease (SD) as treatment outcome. In one patient with PD at baseline, disease remained progressive and the intended cumulative dose was not achieved. Treatment outcome is summarised in Fig. 2. Two patients died, one 13 months and the other 15 months after start of treatment with ^{177}Lu -octreotate. Seven patients were still alive after a median follow-up of 36 months (range 23–74 months). To evaluate differences in treatment outcome according to histological subtype, patients with proven atypical carcinoids were compared with patients with typical carcinoid. Four of five patients with atypical carcinoids had remission (3 PR, 1 MR), compared with two of the four patients with typical bronchial carcinoid (2 PR), (Fisher's exact test, $p>0.05$). In the group of patients with bronchial carcinoids, an estimation of median TTP was made using a Kaplan-Meier curve. In four patients, TTP was reached after 9, 13, 20 and 31 months. In four patients, disease remained unchanged after 11, 21, 24 and 34 months' follow-up. The estimated median TTP was 31 months.

^{177}Lu -octreotate was administered to five patients with gastric carcinoids. All patients had type 3 (sporadic) gastric carcinoids and all had distant metastases. None of the patients had symptoms due to the release of hormones. Two patients had proven PD in the 12 months before starting treatment. All patients achieved the intended cumulative dose. One patient had complete remission (CR) of disease (Fig. 3). Disease remained unchanged during the follow-up of 11 months. One patient had MR, which remained unchanged for 8 months' follow-up. Two patients, including one with PD at baseline, had SD. In the patient with PD at baseline, TTP was 11 months. In the other patient, disease was radiologically stable for 12 months' follow-up, but became clinically progressive after 16 months' follow-up. Finally, one patient developed PD despite the treatment (Fig. 2). Estimated median TTP in this group was 16 months (Kaplan-Meier curve, $n=4$, two censored patients). Three patients died, respectively 6, 17 and 21 months after start of treatment with ^{177}Lu -octreotate. Two patients were still alive after a follow-up of 18 and 21 months.

Two patients with thymic carcinoids were included in the trial. Both were men. One patient had PD at baseline and was also treated with 5-fluorouracil between the administrations of ^{177}Lu -octreotate. Despite treatments, disease

Table 2 Baseline characteristics in respect of factors that predict chances of tumour progression during treatment with ^{177}Lu -octreotate in patients from the total group of GEP NETs ($n=125$) and in patients from the group with foregut carcinoids ($n=16$)

	Foregut carcinoid	Total group of GEP NETs [14]	p value ^a
Tumour mass			
Limited	19%	17%	0.74
Moderate	69%	62%	
Extensive	13%	21%	
Liver metastases			
None/moderate	81%	73%	0.56
Extensive	19%	27%	
Weight loss			
Absent	69%	82%	0.19
Present	31%	18%	
KPS			
>70	94%	83%	0.47
≤70	6%	17%	

Tumour mass was judged on [^{111}In -DTPA⁰]octreotide scintigrams, and liver involvement was judged on CT/MRI. Weight loss was scored positive if it at least amounted to 1 kg per month, existing for at least 3 months

KPS Karnofsky performance score

^a Fisher's exact test or Pearson χ^2 test

Fig. 1 Treatment response with ^{177}Lu -octreotate in a patient with a metastasised bronchial carcinoid (*H* heart, *S* stomach). **a** Scintigraphy 24 h after the first dose of ^{177}Lu -octreotate (*left panel*) and MRI 6 weeks before starting treatment (*right panel*): the *arrowhead* indicates one of multiple liver metastases. **b** Scintigraphy 24 h after the last dose of ^{177}Lu -octreotate (*left panel*): the *arrowhead* indicates decrease in uptake in one of the liver metastases. MRI 5 months after finishing the treatment (*right panel*) visualises tumour regression (*arrowhead*)

remained progressive. Because of this, the intended cumulative dose was not achieved. The other patient had MEN-1 syndrome and had Cushing's syndrome due to ectopic ACTH production for which he underwent bilateral adrenalectomy. Disease status at baseline was not known. He had SD after treatment. TTP was 17 months.

Therapeutic effects are summarised in Table 3. Considering all 16 patients, response rate was 50%. This includes 6% CR, 31% PR and 13% MR. SD was present in 31% and PD in 19%. In the total group of GEP NETs, overall response rate was 47% (2% CR, 26% PR, 19% MR), SD was present in 35% and PD in 18% [14]. This difference was not statistically significant (Fisher's exact test, $p > 0.05$).

Discussion

The purpose of the present study was to evaluate whether results of peptide receptor radionuclide therapy (PRRT) with ^{177}Lu -octreotate in patients with foregut carcinoid tumours are different from those in patients from the total group of gastroenteropancreatic neuroendocrine tumours (GEP NETs). This is because foregut carcinoids are of a different embryological origin than other GEP NETs and survival of patients with metastasised foregut carcinoids is shorter compared to patients with metastasised midgut carcinoids [17]. The results of the present study indicate that the overall tumour response rates with ^{177}Lu -octreotate treatment in the studied foregut carcinoids are comparable

Fig. 2 Effects of therapy with ^{177}Lu -octreotate in groups of carcinoid tumours in relation to disease status before treatment. *CR* complete remission, *MR* minor response, *PD* progressive disease, *PR* partial remission, *SD* stable disease

Fig. 3 Treatment response with ^{177}Lu -octreotate in a patient with a metastasised gastric carcinoid. **a** Scintigraphy 24 h after the first dose of ^{177}Lu -octreotate (*left panel*) demonstrates multiple metastases in the abdomen (*arrowheads*). CT 6 weeks before starting treatment (*right panel*) visualises a lymph node metastasis between the aorta and inferior vena cava (*arrow*). **b** Scintigraphy 24 h after the last dose of ^{177}Lu -octreotate (*left panel*) demonstrates that pathological uptake in the abdomen has disappeared. CT 5 months after finishing the treatment (*right panel*) can no longer visualise the lymph node (*arrow*)

to those in the whole group of GEP NETs. In foregut carcinoids of bronchial, gastric or thymic origin, overall response rate was 50%. In the total group of GEP NETs, the overall response rate was 47% [14]. This difference was not statistically significant. Especially patients with bronchial carcinoids can respond well to treatment with ^{177}Lu -octreotate: tumour regression was achieved in six of nine patients. There was no significant difference in treatment outcome between atypical and typical bronchial carcinoids. In gastric carcinoids, two out of five patients had tumour regression, including one with a CR. All patients had type 3 gastric carcinoids, which tend to behave more aggressively than other types. The role of treatment with ^{177}Lu -octreotate in thymic carcinoid is not yet clear, since only two patients were treated: one had progression and one had stable disease for 17 months. Certainly more patients with bronchial, gastric and thymic carcinoids have to be

included in our study to determine the effect of ^{177}Lu -octreotate in this group more precisely.

A previous study in GEP NET patients demonstrated a positive correlation between high tumour uptake on pre-therapy SRS and high remission rates [14]. In that study, also patients with rather low tumour uptake on pre-therapy SRS were studied, i.e. tumour uptake equal to normal liver uptake (grade 2). In the present study, however, all patients had tumour uptake that was higher than liver uptake on pre-therapy SRS (grade 3 or 4), and this could explain why results in foregut carcinoids are comparable to those in the whole group of carcinoids, despite their more aggressive behaviour. However, since in the study of Kwekkeboom et al. [14] only 4 of 125 patients (3%) had grade 2 uptake, the lack of patients with grade 2 uptake in the present study probably affected the present results only mildly or not at all. On the other hand, in the present study only one patient

Table 3 Tumour responses in 16 patients with foregut carcinoids treated with ^{177}Lu -octreotate

Values are *n*, with % in parentheses
CR complete remission,
PR partial remission, *MR* minor response, *SD* stable disease, *PD* progressive disease

Outcome	Bronchial carcinoid (<i>n</i> =9)	Gastric carcinoid (<i>n</i> =5)	Thymic carcinoid (<i>n</i> =2)	All patients (<i>n</i> =16)
CR	—	1 (20)	—	1 (6)
PR	5 (56)	—	—	5 (31)
MR	1 (11)	1 (20)	—	2 (13)
SD	2 (22)	2 (40)	1 (50)	5 (31)
PD	1 (11)	1 (20)	1 (50)	3 (19)
CR + PR + MR	6 (67)	2 (40)	—	8 (50)

(6%) had grade 4 uptake (tumour uptake much more than normal liver uptake), whereas 19% of patients in the total group of GEP NETs had grade 4 uptake. These differences in tumour uptake on pre-therapy SRS were not statistically significant.

The study in the total group of GEP NETs demonstrated some factors that predict a higher chance of progressive disease despite the treatment with ^{177}Lu -octreotate [14]. These factors were: high tumour mass, extensive liver metastases, weight loss and low KPS. Since the difference in the frequencies of these factors is not statistically significant, the role of these factors is limited when comparing the results of therapy in patients with the studied foregut carcinoid tumours and those in patients from the total group of GEP NETs. The observed remission rates are therefore reliably comparable.

Although remission rates in patients with the studied foregut carcinoids are comparable to those in patients with other GEP NETs, our study suggests that median TTP is shorter. We found a median TTP of 31 months in bronchial carcinoids (range of duration of follow-up 9–34 months, median 20.5 months), which is less than the median TTP of more than 36 months in the group of all GEP NETs (range of duration of follow-up 7–44 months, median 16 months) [14]. In gastric carcinoids the estimated TTP was 16 months; however, the group was very small ($n=4$) and in two patients TTP was not yet known. This possibly shorter median TTP is not unexpected, since epidemiological research indicates a shorter survival for metastasised bronchopulmonary carcinoids compared with the total group of metastasised carcinoids. The Surveillance Epidemiology and End Results (SEER) database reports a 5-year

survival of 38.5% in patients with distant metastases from any primary carcinoid site, whereas it is limited to 25.6% in patients with metastasised bronchial carcinoid [17]. It is of note that 5-year survival in patients with metastasised gastric carcinoids is 21.2% [17].

It is important to realise that all patients in the present study had tumours with strong expression of somatostatin receptors (sst): tumour uptake on SRS was higher than normal liver tissue in all patients. A study on expression of sst subtype 2 (sst₂) in neuroendocrine tumours of the lung suggested that sst₂ mRNA content is related to the degree of tumour differentiation [18]. This may imply that the treated patients in the study all had relatively well differentiated tumours, whereas epidemiological databases about survival include poorly differentiated tumours as well. Hence, the treatment results obtained in this study are not valid for the total group of patients with foregut carcinoids. To our knowledge, no data are available about what proportion of all patients with bronchial, gastric or thymic carcinoids has low or absent somatostatin receptor expression and what proportion would therefore not be eligible for the treatment with ^{177}Lu -octreotate.

Comparison of ^{177}Lu -octreotate treatment in patients with metastasised foregut carcinoid tumours with other treatment modalities is difficult, as specific data are scarce. Kwekkeboom et al. provided an overview of results of several chemotherapy regimens in the total group of GEP NETs, including carcinoids. Treatment with ^{177}Lu -octreotate performed better than these regimens, especially when considering TTP [see 14 for in-depth comparison]. Granberg et al. [19] reported their experience in treating patients with bronchial carcinoids. Biotherapy resulted in symptom-

Table 4 Overview of results of peptide receptor radionuclide therapy with [^{90}Y -DOTA⁰,Tyr³]octreotide and [^{111}In -DTPA⁰]octreotide in patients with foregut carcinoid tumours

Study	Radiolabelled peptide	Cum. dose	Carcinoid origin	PD at start	Outcome (TTP)
Otte et al. [22]	^{90}Y -DOTATOC	4.8–8.9 GBq/m ²	3 Thymus 1 Duodenum	NA NA	2 SD, 1 PD 1 SD
Waldherr et al. [23]	^{90}Y -DOTATOC	6.0 GBq/m ²	7 Bronchus	7	1 CR, 1 PR, 5 SD
Waldherr et al. [24]	^{90}Y -DOTATOC	7.4 GBq/m ²	3 Bronchus	3	3 SD
Bodei et al. [25]	^{90}Y -DOTATOC	5.92–11.1 GBq	2 Bronchus 1 Stomach	NA NA	1 PR (3 mo), 1 SD (13 mo) 1 SD (10 mo)
Valkema et al. [26] ^a	^{90}Y -DOTATOC	5.1–32.6 GBq	2 Bronchus 2 Stomach 1 Thymus	2 2 1	2 PD 2 PD 1 SD
Anthony et al. [27]	[^{111}In -DTPA ⁰]octreotide	13.3–26.6 GBq	4 Foregut ^b	NA	1 PR, 3 SD
Valkema et al. [28] ^a	[^{111}In -DTPA ⁰]octreotide	40.5–58.0 GBq	3 Bronchus 1 Other ^c	3 1	2 SD, 1 PD 1 MR

^{90}Y -DOTATOC [^{90}Y -DOTA⁰,Tyr³]octreotide, CR complete remission, MR minor response, NA not available, PD progressive disease, PR partial remission, SD stable disease, TTP time to progression

^a Additional data obtained from original study database

^b Not further specified

^c Presumably derived from mucosa of sphenoid sinus

atic improvement of carcinoid syndrome in 7 of 16 patients. Anti-proliferative effects, however, were limited as disease progressed in 21 of 25 patients. Best results with chemotherapy were achieved with cisplatin/etoposide: two of eight patients had an objective response and one had stable disease. TTP was limited (7 months). With other chemotherapy regimens, no objective response was reported and maximum response duration was 12 months in a patient treated with streptozotocin/5-fluorouracil. Those results are less favourable than the results with ^{177}Lu -octreotate. We therefore think that ^{177}Lu -octreotate could be considered if somatostatin analogues (or interferon) fails and tumour uptake on SRS is grade 2 or more.

Peptide receptor radionuclide therapy is also possible with radiolabelled somatostatin analogues other than ^{177}Lu -octreotate, e.g. ^{111}In -octreotide and [^{90}Y -DOTA 0 ,Tyr 3]octreotide (^{90}Y -DOTATOC). The mentioned radionuclides have distinct physical properties. ^{111}In emits Auger electrons and γ -rays. The Auger electrons have a maximum penetration range in tissue of 10 μm . ^{90}Y is a β -emitter with a maximum penetration range in tissue of 12 mm and ^{177}Lu is a β -emitter with a maximum particle range in tissue of 2 mm. It also emits γ -rays, which allows imaging and dosimetry [20]. These differences in particle range might have therapeutic consequences in the future as most patients have tumours of various sizes. In a study in animals with various tumour sizes, therapy with both ^{90}Y - and ^{177}Lu -labelled octreotate yielded better remission rates than therapy with either ^{90}Y - or ^{177}Lu -labelled octreotate alone [21]. However, a benefit of the combination of ^{90}Y -octreotate and ^{177}Lu -octreotate in patients has not been confirmed, because a randomised clinical trial is lacking. Table 4 provides an overview of results of treatment with ^{111}In -octreotide and ^{90}Y -DOTATOC [22–28] in patients with foregut carcinoid tumours. In this overview, the study with the largest number of patients reported tumour remission in two (1 CR, 1 PR) and stable disease in five out of seven patients with progressive, bronchial carcinoids. Specific data on TTP for patients with foregut carcinoids are lacking in most of these studies (Table 4). In general, results of treatment with ^{177}Lu -octreotate in foregut carcinoid tumours in terms of tumour regression seem favourable compared to treatment with ^{111}In -octreotide and ^{90}Y -DOTATOC. This may be partly because of the higher affinity of [DOTA 0 ,Tyr 3]octreotate compared with [DOTA 0 ,Tyr 3]octreotide for sst $_2$ [29], which is the most frequently expressed subtype on GEP NETs [30] and certainly because the physical properties of ^{177}Lu are better suited for therapy than those of ^{111}In when labelled to a somatostatin analogue. However, comparison of these other treatments with treatment using ^{177}Lu -octreotate is difficult. The number of studied patients was small in all reports. Different inclusion criteria were used and the patient

conditions at baseline may have varied. Response criteria may have differed, and some reports had dose escalation as their purpose and therefore some patients had a relatively low cumulative dose [see 31 for in-depth comparison].

In conclusion, ^{177}Lu -octreotate treatment can be effective in patients with sst $_2$ -positive bronchial and gastric carcinoids. Its role in thymic carcinoids cannot be determined yet because of the limited number of patients. The overall remission rate of 50% in patients with foregut carcinoids of bronchial, gastric and thymic origin is comparable with that in the total group of gastroenteropancreatic neuroendocrine tumours.

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