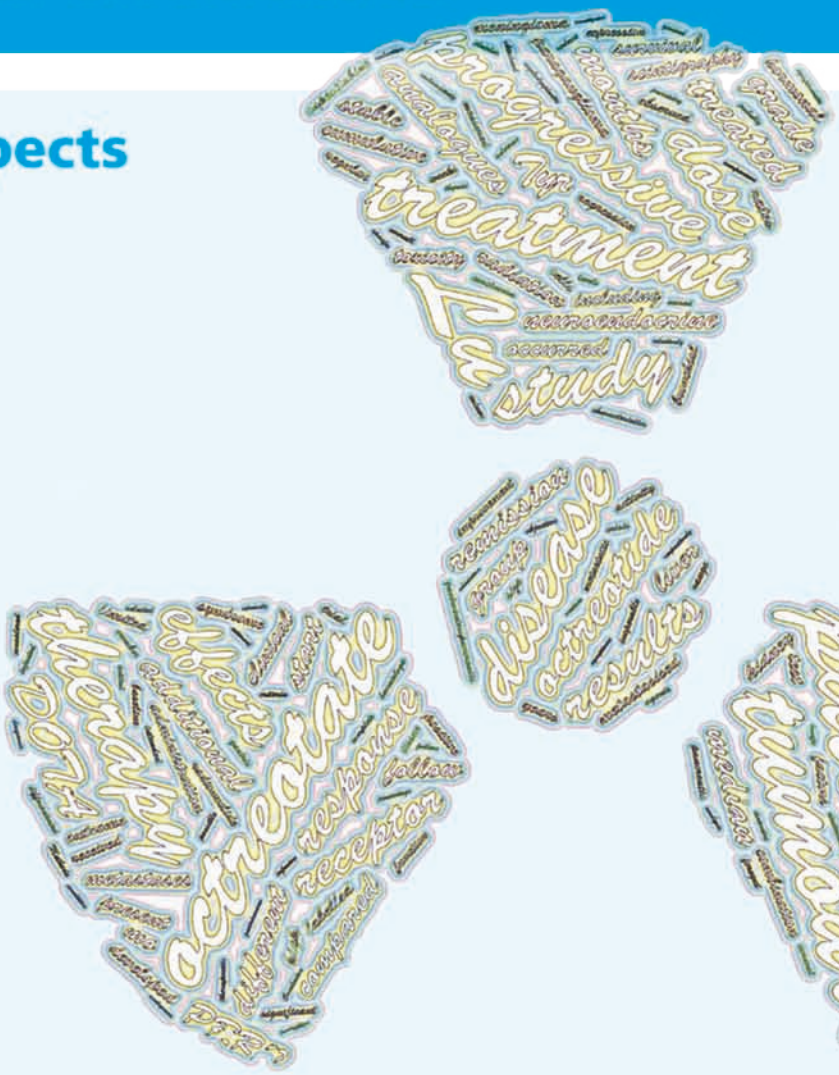
Peptide Receptor Radionuclide Therapy with ^{177}Lu-octreotate

Clinical Aspects



Martijn van Essen

Peptide Receptor Radionuclide Therapy with ^{177}Lu-octreotate: Clinical Aspects

Peptide Receptor Radionuclide Therapie met ^{177}Lu-octreotaat: Klinische Aspecten

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Colofon

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Voor mijn ouders

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Chapter 1

General Introduction

Chapter 1.1

Somatostatin Receptor Positive Tumours and Therapeutic Options

INTRODUCTION

Somatostatin is a neuropeptide with a variety of functions and is produced in several tissues. The isoform somatostatin-14 (SS-14) is more biologically active than SS-28. Its main physiological function is to inhibit secretion of hormones such as growth hormone or thyroid stimulating hormone in the pituitary, insulin or glucagon in the pancreas *(1)* and of exocrine gut secretion.

The effects of somatostatin are mediated by binding to the somatostatin receptor (sst), which are G-protein-coupled receptors. Five sst subtypes have been identified (sst_1 - sst_5) which all have different roles. The naturally occurring SS-14 and SS-28 have high affinity for all these subtypes *(1)*.

Several tumours (Table 1), amongst others gastroenteropancreatic tumours (GEPNET), have overexpression of sst on the cell surface. This makes sst a possible target for therapy with somatostatin analogues to try and inhibit the secretion of bioactive substances by these tumours and possibly to slow down tumour growth. However, the biological half-life of SS-14 and SS-28 is short, and this makes it impossible to use them for therapeutic goals. With the invention of the cyclic octapeptide octreotide, half-life increased significantly and octreotide then could be used in treatment of patients with sst-positive tumours.

Table 1. Tumours with overexpression of somatostatin receptors (not exhaustive).

Endocrine tumours:
Pituitary tumours
Gastroenteropancreatic tumours / carcinoid:
Non-functioning pancreatic
Functioning pancreatic
Insulinoma
Gastrinoma
VIP-oma
Glucagonoma
Non-pancreatic
Foregut (bronchus [including small cell lung carcinoma], thymus, stomach etc.)
Midgut (jejenum, ileum, proximal colon)
Hindgut (distal colon, sigmoid, rectum)
Paraganglioma / phaeochromocytoma
Thyroid carcinoma
Well-differentiated (papillary, follicular, Hürthle cell)
Medullary (variable extent)

Table 1. Tumours with overexpression of somatostatin receptors (not exhaustive). (continued)

Non-endocrine tumours:
Meningioma
Melanoma
Lymphoma
Breast carcinoma
Merckle cell carcinoma
Astrocytoma

Subsequently, efforts were made to take advantage of sst overexpression and perform imaging with radiolabelled somatostatin analogues. After successful clinical studies, somatostatin receptor scintigraphy with indium-111-DTPA^0-octreotide has become an important diagnostic tool in the diagnosis and work-up of patients with sst-positive tumours. A logical next step was to try to perform therapy with radiolabelled somatostatin analogues in patients with sst-positive tumours, which is the subject of this thesis.

In endocrine tumours like GEPNET, bronchial carcinoids, paraganglioma, and non-endocrine tumours like meningioma, sst_2 is the receptor with the highest overexpression *(2)* and therefore sst_2 is the most relevant target for therapy in these tumours. Somatostatin analogues with high affinity for sst_2 have therefore been developed, like octreotide, Tyr^3-octreotide and Tyr^3-octreotate.

The most studied group of sst-positive tumours originate from neuroendocrine cells situated in organs derived of the embryological gut. These tumours comprise gastroenteropancreatic neuroendocrine tumours and bronchial carcinoids. These tumours are the subject in most of the studies in this thesis and are described more in detail in the next section. In addition, paraganglioma / phaeochromocytoma, meningioma, small cell lung cancer and melanoma were studied in one chapter of this thesis and hence are also discussed briefly in this section.

GASTROENTEROPANCREATIC NEUROENDOCRINE TUMOURS, INCLUDING BRONCHIAL CARCINOIDS

In the past, gastroenteropancreatic neuroendocrine tumours were divided in carcinoid tumours and pancreatic neuroendocrine tumours, either non-functioning (no symptoms due to an excess of release of bioactive substances) or functioning (e.g. insulinoma, gastrinoma, VIPoma, etc.). The new World Health Organisation (WHO) classification does not mention carcinoid anymore (Table 2): lesions are classified as well-differentiated endo-

Table 2. WHO classification of gastroenteropancreatic endocrine tumours

Well differentiated endocrine tumour (WDET)
benign behaviour
uncertain behaviour
Well differentiated endocrine carcinoma (WDEC)
Poorly differentiated endocrine carcinoma (PDEC)

crine tumours (WDET) of benign behaviour or of uncertain behaviour, well-differentiated endocrine carcinoma (WDEC) or poorly-differentiated endocrine carcinoma (PDEC). The classification depends on the primary tumour location, the size of the tumour, the proliferation index and / or Ki-67 index, the presence of local invasion (local, vascular, perineural), the presence of metastases and tumour morphology (i.e. small cell carcinoma or not). By definition, the tumour is either WDEC or PDEC (but never WDET) if metastases are present *(3)*.

For pulmonary neuroendocrine tumours, however, a different classification is used: typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma and small cell lung cancer. In typical carcinoid, there are <2 mitoses per mm^2 and necrosis is absent. In atypical carcinoids, there are 2 to 10 mitoses per 2 mm^2 and / or necrosis is present. Although metastases are more frequent in atypical carcinoids, it can occur in typical carcinoids as well *(4)*.

It is of note that in clinical practice and many studies, the old classification is still used instead of the new WHO classification. Also in the present thesis and studies used for comparison, the classification according to the new WHO criteria often was not available.

The incidence of neuroendocrine tumours is rising according to a recent epidemiological study in the United States of America by Yao *et al. (5)*. Overall, the incidence of NET (in any stage and of any primary) was 5.25 per 100.000 persons per year in 2004, as opposed to 1.09 in 1973. However, many of these patients have localised disease only and can be cured. The increase in incidence might be caused in part by improvements in classification of these tumours. Also, endoscopy procedures for cancer screening may have contributed, especially in the detection of rectal NETs. The prevalence (number of people alive who had or have a NET) is much higher, at around 35 / 100.000, due to the long survival, especially in patients with localised, surgically cured disease.

Therapeutic options

Obtaining pathology, staging, and somatostatin receptor imaging are very important issues when making decisions about the therapeutic management of patients with neuroendo-

crine tumours. Several options are available. In this chapter, medical and radiolabelled treatments are emphasised, after a short introduction about surgical and interventional strategies.

Surgery and liver targeted interventional therapies

Surgery remains the only way to cure patients with GEPNET at this moment. Therefore this should always be considered. In patients with locally advanced disease, neo-adjuvant use of other treatment modalities could be considered to obtain tumour shrinkage, which could make surgery possible.

Also patients with distant metastases may benefit from surgery: surgical debulking can result in symptomatic relief by reducing the amounts of bioactive substances. Removal of the primary tumour should be considered in patients with localised complications like obstruction, or if complications are likely to occur later in the disease course. In addition, there are indications that patients live longer after surgical debulking or resection of the primary tumour than similar patients without surgery, but these results need to be interpreted cautiously, as there are no randomised clinical trials and preferentially (young) patients in good clinical condition with limited tumour loads undergo surgery *(6 – 10)*.

Finally, in very selected patient groups, liver transplantation has been performed and experience is still limited. It is of note that many patients eventually develop recurrent disease. Therefore liver transplantation for patients with metastatic neuroendocrine tumours remains controversial. Several groups reported results: 1-year disease-free survival ranged from 56 to 80% with 5-year disease-free survival ranging from 20 to 47%. Others reported median disease-free survival, which ranged from 23 to 33 months. Overall 5-year survival was 47% in 2 studies and median overall survival was 48 months in 1 study *(11 – 15)*.

For patients with disease primarily limited to the liver, several non-surgical, liver-targeted interventional options are available: hepatic artery (chemo-) embolisation (HA(C)E), also called transarterial (chemo-)embolisation (TA(C)E), for up to 75% liver involvement, and radiofrequency ablation (RFA), cryoablation or laser-induced thermotherapy (LITT) for limited liver involvement. The main disadvantage of these interventions is that they don't affect tumour localisations outside the liver. RFA has a high rate of local control with limited local recurrence. Disease will however almost invariably recur at other sites in the liver or elsewhere. With HAE / TAE, objective responses were achieved in around 40-75% with widely variable duration of the effect (3 to 88 months, means not described). With HACE / TACE, objective response were documented in 8 to 100%, again with variable duration (between 6 and 63 months, means between 14 and 42 months) *(16 – 17)*.

Radiotherapy

Defining the precise role of radiation therapy in GEPNET patients is hard, since most studies were performed using both clinical and radiological criteria. The most important indications for external beam radiation therapy in patients with well-differentiated NET are brain metastases, painful bone metastases or spinal metastases with (risk of) myelo-compression. Radiotherapy is used in some cases for treating the primary tumour and even more rarely in patients with abdominal / visceral lesions given the low radiation tolerability of liver parenchyma and bowel *(18)*.

Strosberg *et al.* described the use of radiotherapy in combination with 5-fluorouracil or capecitabine in patients with locally advanced pancreatic NET. Four of five patients with measurable disease had partial remissions. All patients were progression free after median duration of follow-up of 29 months *(19)*.

Medical therapy: Biotherapy with somatostatin analogues and interferon-α

Somatostatin analogues are important in the treatment of patients with GEPNET. The two commonly used analogues are octreotide (Sandostatin, Novartis) and lanreotide (Somatuline, Ipsen) and both are about equally effective *(20)*.

Somatostatin analogues are very effective in reducing symptoms that are induced by the production of bioactive substances by GEPNETs: a symptomatic response is seen in about 70% of treated patients (range from 40-100%). Somatostatin analogues frequently (37-77%) result in a biochemical response, meaning a decrease in tumour markers. However, radiological responses are rare (most studies 0-5%) *(21- 24, and references within)*.

A new and important finding about somatostatin analogues is that they seem to have an effect on progression free survival. In the PROMID study, administration of octreotide or placebo in patients with functioning and non-functioning midgut carcinoids demonstrated a median progression free survival of 14.3 months in the octreotide group and of 6 months in the placebo group *(25)*.

Most common side effects are steatorrhoea and mild abdominal pains early after start. A rare adverse event is bradycardia, which can be a reason to stop therapy. With long-term use, cholelithiasis can develop. Therefore it is recommended to perform a cholecystectomy during surgery for the primary tumour or metastases if the patients are on somatostatin analogues.

A new somatostatin analogue is SOM-230 or pasireotide. It is a cyclic hexapeptide with good affinity for sst_2 (like octreotide and lanreotide), and an improved affinity for sst_1, sst_3

and sst_5 compared to octreotide and lanreotide. It has effects in GEPNET patients with symptoms that were refractory to octreotide therapy *(26)*.

Interferon-α (IFNα) is another systemic therapy. Therapy with IFNα can reduce symptoms in functioning tumours in 40 to 50% of patients, but objective tumour responses are reported in 0-20%. Side effects are common and sometimes disabilitating. Mild side effects include flu-like symptoms. Myelosuppresion can occur, with dose-reductions necessary. Up to 50% can have chronic fatigue or depression, which can be a reason to stop therapy. Also autoimmune diseases can develop as a side effect like thyroiditis, or rarely SLE and polymyositis *(27- 29, and references within)*.

Somatostatin analogues and IFNα can be given as combination therapy. In randomised clinical studies, there was no benefit in treatment with somatostatin analogues, IFNα or their combination. In one study however, there was a reduced risk of tumour progression in patients in the combination group. Moreover, patients who do not respond well to somatostatin analogue therapy can benefit from the addition of IFNα *(30- 32)*.

Medical therapy: Chemotherapy

A short overview of chemotherapy for neuroendocrine tumour patients in general is presented in Chapter 8.2 and table 4 in Chapter 2.1.

Chemotherapy regimens using capecitabine

In Chapter 5, a toxicity study is described of the combination of lutetium-177-octreotate with capecitabine (Xeloda, an oral pro-drug of 5-fluorouracil). Therapy with capecitabine for patients with GEPNET was studied in several small studies, mostly in combination with other agents.

The combination of capecitabine and temozolomide (Temodal), which is an oral alkalyting agent, has promising anti-tumour effects in patients with pancreatic NETs. Of 30 patients treated, 20 patients had PD at start. Twenty-one patients (70%) had a partial remission (RECIST criteria) and 8 had stable disease. Progression free survival was 18 months *(33)*.

Effects of capecitabine and oxaliplatin (XELOX) were reported in 27 patients with well-differentiated NET: 30% had PR, 48% had SD and 22% had PD. Median time to progression was 20 months. Unfortunately the report used radiological, clinical and biochemical changes for response evaluation and did not clearly state if the mentioned percentages were only based on radiological criteria or not *(34)*.

A study using capecitabine (2 weeks on, 1 week off) and rofecoxib daily (a cyclo-oxygenase-2 inhibitor) was terminated after evaluating 9 patients. None of the patients had tumour remission. Seven patients had SD, but maximum duration was 6 cycles (18 weeks). Two patients continued to have PD *(35)*.

Preliminary data of a phase II study of capecitabine, oxaliplatin, and bevacizumab for metastatic or unresectable neuroendocrine tumors were recently presented. Thirty-one patients were available for response assessment, of whom 23% had PR and 71% had SD. Of note, 6 patients were not assessed because they came off-study before imaging studies were performed. Median progression free survival was 13.7 months *(36)*.

A short communication was published about therapy with capecitabine as single agent in one patient with a pancreatic NET with hepatic metastases. Therapy resulted in a complete remission, but the duration of response was not known yet *(37)*.

Another case report demonstrated partial remission in a patient with a metastasised bronchial carcinoid (high proliferation index of 42%) treated with capecitabine and liposomal doxorubicin, which lasted for 13 months *(38)*.

Chemotherapy regimens in patients with bronchial carcinoids
In Chapter 2.2, the effects of lutetium-177-octreotate are described in patients with bronchial carcinoids. Some groups have published the results of therapies specifically for patients with bronchial carcinoids. Results of the study by Granberg *et al.* are presented in Chapter 2.2 *(39)*.

Temozolomide as single agent resulted in a partial remission in 4 of 13 patients (31%) with bronchial carcinoids, and 4 patients had SD. Median time to progression was not specifically noted for these patients, but was 7 months in the entire GEPNET group of 36 patients *(40)*.

Capecitabine with oxaliplatin (XELOX) was administered to 6 patients with bronchial carcinoids: 3 had a partial remission, 2 had stable disease and 1 had progressive disease. No data on time to progression were available *(41)*.

Chemotherapy with different schedules (mostly etoposide / cis- or carboplatin, paclitaxel or docetaxel / irinotecan, and other treatments) was used in 15 patients, using 19 chemotherapy regimens. Three of 19 regimens (16%) resulted in an objective response and 9 (47%) in stable disease. No data on time to progression were reported *(42)*.

Somatostatin analogues can result in stable disease, with a reported time to progression of 10.5 months. With first-line chemotherapy (again with different schedules: etoposide / cis- or carboplatin, 5FU / cis- or carboplatin / streptozotocin, gemcitabine / carboplatin), 9 of 12 patients had 'SD or PR' of whom 2 proceeded to surgery. Median TTP (7 patients) was 12 months *(43)*.

Medical therapy: Novel molecularly targeted agents

Also multiple novel drugs and combinations are under investigation. This subject is partly discussed in Chapter 8.2 as well.

As neuroendocrine tumours are highly vascularised, several drugs that inhibit angiogenesis are studied.

Effects of bevacizumab (Avastin) with temozolomide were studied in 29 patients and resulted in a PR in 14% and SD in 79%. Remission was only achieved in patients with a pancreatic neuroendocrine tumour, not in those with carcinoid tumours. Progression free survival was not reported *(44)*.

Bevacizumab was administered in combination with 2-methoxyestradiol to 31 patients. None of the patients had an objective response, progression free survival was 11.3 months *(45)*.

Yao *et al.* presented results of a phase II, randomised study of bevacizumab versus pegylated interferon α-2b. All patients were treated with octreotide, and were randomised between bevacizumab and pegylated (PEG) interferon α-2b (stage 1 of the study). When disease became progressive or after 18 weeks, patients received all 3 drugs (stage 2 of the study). In the PEG interferon arm, 15 of 22 patients had SD (68%), and 6 had PD (27%), an additional patient at first had SD and soon after developed PD. In the bevacizumab arm, 4 of 22 patients had PR (18%), 17 had SD (77%) and one had PD. Progression free survival at 18 weeks was 95% in the bevacizumab arm and 68% in the PEG interferon arm. Overall median progression free survival (of both stages of the study) was 63 weeks *(46)*.

Yao *et al.* also reported their results of treatment with imatinib (Gleevec), a tyrosine kinase inhibitor (targeted at abl, c-kit (mast/stem cell growth factor receptor) and platelet derived growth factor receptor) in advanced carcinoid tumours: one of 27 patients had a partial remission and 17 had stable disease. Median progression free survival was 5.5 months *(47)*.

Sorafenib (Nexavar) has modest anti-tumour effects: 7 of 41 evaluable (17%) patients with a carcinoid had a MR or PR and 8/20 patients had a progression free survival of > 6 months. Thirteen of 41 evaluable patients (32%) with a pancreatic neuroendocrine tumour had a MR or PR and progression free survival was > 6 months in 14/23 patients *(48)*.

Pazopanib (GW786034, Votrient) also is a multitargeted, small molecule, tyrosine kinase inhibitor. Forty-six patients were treated in a phase II study, of whom 26 had a PNET and 20 had a carcinoid. None of the carcinoid patients had PR, 5 patients with pancreatic NET had PR. Stable disease was documented in 32 patients, and PD in 9. Progression free survival was 12.7 months in patients with carcinoid, and 11.7 in patients with pancreatic NET *(49)*.

Sunitinib (SU11248, Sutent), an oral, multitargeted tyrosine kinase inhibitor, mainly targeted at the vascular endothelium derived growth factor receptor and platelet derived growth factor receptor, and can have therapeutic effects in neuroendocrine tumours. In a phase II study, 11 of 66 patients (17%) with pancreatic neuroendocrine tumours had partial remission and 45 had stable disease. In carcinoids, sunitinib resulted in partial remission in 1 of 41 patients and in stable disease in 34. Overall median time to progression was 8 months in pancreatic NET and 10 months in carcinoids *(50)*.

Recently sunitinib was approved in Europe for the treatment of patients with unresectable or metastasised, progressive pancreatic NET based on a phase III randomised trial. Effects of sunitinib were compared with placebo. Median progression free survival was 11.4 months in the sunitinib arm versus 5.5 months in the placebo arm. It is of note that Sutent is the first treatment approved for pancreatic NET patients in the past 25 years *(51)*.

Recently, inhibitors of the mammalian target of rapamycin (mTOR) were introduced in studies for treating patients with GEP neuroendocrine tumours. Therapy with temsirolimus (Torisel) as single agent had limited anti-tumour activity *(52)*.

Everolimus (RAD-001, Afinitor) in combination with long-acting octreotide seems to have more promising anti-tumours effects. Sixty patients with low- to intermediate-grade NET, of whom 39 had PD at study entry, were treated: 17% had a PR and 75% had SD (45 patients, of whom 15 had a MR [25% of all patients]). The median progression free survival was 14 months *(53)*.

In a phase II study in patients with metastatic pancreatic NET effects of everolimus with or without somatostatin were analysed (RADIANT-1). Stratum 1 consisted of 115 patients who did not have prior treatment with somatostatin, of whom 114 patients had progres-

sive disease at start of therapy with everolimus. Stratum 2 consisted of 45 patients who already had octreotide therapy and of whom all had progressive disease at start of therapy with everolimus. In stratum 1, 10% of patients had PR, 68% had SD and 16% had PD. Median progression free survival was 9.7 months. Two-year overall survival rate was 51%. In stratum 2, 4% had PR, 80% had SD and 0% had PD. Median time to progression was 16.7 months. Two-year overall survival rate was 55% *(54)*.

In a large, phase III, randomized placebo-controlled trial in 410 patients with advanced, low- or intermediate-grade pancreatic NET patients (RADIANT-3), patients receiving everolimus 10 mg daily had a significant improvement in progression-free survival (preliminary results: 4.6 versus 11.0 months) *(55)*.

The preliminary results of a placebo-controlled phase III trial in 429 patients with progressing, well or moderately differentiated, advanced NET and a history of symptoms attributed to carcinoid syndrome (RADIANT-2) were recently presented. Median PFS with everolimus and octreotide was 16.4 months versus 11.3 months for placebo and octreotide *(56)*.

The combination of bevacizumab and everolimus also seems promising based on preliminary data. By intention-to-treat analyses, 10 patients had PR (26%), 27 SD (69%), 1 PD (3%), and in 1 response was not assessable (3%). Median progression free survival was 14.4 months *(57)*. Results of targeted therapies and recent randomised trials are summarised in tables 3 and 4.

Table 3. Non-randomised studies with molecularly targeted agents.

Therapy	Tumour	*N*	OR	SD	Median PFS or TPP (months)	Peer review
Bevacizumab + temozolomide *(44)*	Carc	12	0	92%	NA	No
	PNET	17	24%	70%	NA	
Bevacizumab + 2-methoxyestradiol *(45)*	Carc	28	0	96%	11.3	Yes
Imatinib *(47)*	Carc	27	4%	63%	5.5	Yes
Sorafenib *(48)*	Carc	41	10% + 7%MR	NA	8/20 >6 mo	No
	PNET	41	10% + 22%MR	NA	14/23 > 6 mo	
Pazopanib + Octreotide *(49)*	Carc	20	0	(70%)[a]	12.7	No
	PNET	26	19%		11.7	
Sunitinib *(50)*	Carc	41	2%	83%	10 (TTP)	Yes
	PNET	66	17%	68%	8 (TTP)	
Temsirolimus *(52)*	Carc	21	5%	57%	6 (TTP)	Yes
	PNET	15	7%	60%	10.6 (TTP)	

Table 3. Non-randomised studies with molecularly targeted agents. (continued)

Therapy	Tumour	*N*	OR	SD	Median PFS or TPP (months)	Peer review
Everolimus + Octreotide *(53)*	Carc	30	17%	80%	14.5	Yes
	PNET	30	27%	60%	11.5	
Radiant-1 *(54)*	PNET					Yes
Everolimus		115	10%	68%	9.7	
Everolimus + Octreotide		45	4%	80%	16.7	
Everolimus and bevacizumab *(57)*	LGNET	39	26%	69%	14.4	No

[a] Not further specified

Abbreviations: *Carc*, Carcinoid tumour; *LGNET*, low- to intermediate-grade neuroendocrine tumours; *N*, Number of patients with response evaluation; *OR*, Objective response; *PFS*, Progression free survival; *PNET*, Pancreatic neuroendocrine tumours; *SD*, Stable disease; *TTP*, Time to progression

Table 4. Recent randomised studies.

Study / Therapy	Tumour	N	OR	SD	Median PFS (months)	Peer review
Bevacizumab + Octreotide vs. PEG-INF + Octreotide [a] *(46)*	Carc	44			Overall: 14.5	Yes
Bevacizumab + Octreotide		22	18%	77%	PFS 95% at 18 weeks	
PEG-INF + Octreotide		22	0	68%	PFS 68% at 18 weeks	
Sunitinib vs. Placebo *(51)*	PNET	171				Yes
Sunitinib		86	9%	NA	11.4	
Placebo		85	0	NA	5.5	
Radiant-2 *(56)*	Carc	429				No
Everolimus + Octreotide		216	NA	NA	16.4	
Everolimus + Placebo		213	NA	NA	11.3	
Radiant-3 *(55)*	PNET	410				Yes
Everolimus		207	NA	NA	11.0	
Placebo		203	NA	NA	4.6	

[a] Randomised, phase II study

Abbreviations: *Carc*, Carcinoid tumour; *N*, Number of patients with response evaluation; *OR*, Objective response; *PFS*, Progression free survival; *PNET*, Pancreatic neuroendocrine tumours

Therapy with radiolabelled compounds: iodine-131-meta-iodobenzylguanidine

Iodine-131-metaiodobenzylguanidine (^{131}I-MIBG) has a structure that resembles that of noradrenalin. It is labelled with ^{131}I, which emits γ-rays (main peak at 365 keV) and β-particles (max. energy of most frequent β-particle 606 keV). ^{131}I has a half-life of 8 days. Tumour uptake depends on the presence of the vesicular monoamine transporter (VMAT), which can be visualised on ^{123}I-MIBG or ^{131}I-MIBG scintigraphy. MIBG scintigraphy is less sensitive in detecting GEPNET / carcinoid lesions than somatostatin receptor imaging, and therefore more GEPNET patients are ineligible for therapy with ^{131}I-MIBG than with radiolabelled somatostatin analogues *(58- 61)*.

There are several reports about therapy with ^{131}I-MIBG in patients with GEPNET using different treatment protocols (administered cumulative dose ranging from 2 to 59 GBq). This makes it hard to compare these studies. Reported radiological remission rates vary from 11 to 38%. Symptomatic improvement was seen in approximately 50% of patients. Survival data since start of therapy are difficult to compare: median survival from start of therapy ranged from 18 - 56 months, other studies only reported overall survival or survival since last therapy. Several reports indicate that survival seems better in symptomatic responders than in non-responders *(62- 69)*.

Therapy with radiolabelled compounds: Radionuclide therapy targeted at hepatic metastases

Hepatic metastases can be targeted by radionuclide therapy. This treatment modality involves injection of radiolabelled agents into the hepatic artery. Most commonly used products are radiolabelled microspheres (mostly resin or glass) which will strand in the small arteries. Main contra-indication is a shunt of 20% or more to the vascular bed of the lungs, and therefore a pre-therapeutic scintigraphy with ^{99m}Tc-labelled micro-particles (e.g. macro-aggregated albumin) should be done.

Several different devices are used. Remission is achieved in 40-65%, but most reports did not mention a median duration of this effect *(70- 74)*.

Apart from radiolabelled microspheres, also other radiopharmaceuticals, e.g. radiolabelled somatostatin analogues or iodine-131-metaiodobenzylguanidine (^{131}I-MIBG), can be injected into the hepatic artery. Recently, an increase of on average 3,75 in standardised uptake value of the diagnostic tracer [gallium-68-DOTA^0,Tyr^3] octreotide was demonstrated *(75)*.

17 patients had intra-arterial ^{131}I-MIBG therapy, of whom 5 had arterial infusion of extra-hepatic lesions. They stated a 69% higher mean tumour-to-background ratio after intra-arterial (IA) injection versus intra-venous (IV) injection, however this was based on an IV diagnostic dose and an IA therapeutic dose. Twelve patients (of whom 5 only

had extra-hepatic disease) received both IA and IV therapy, and then also a 69% higher mean tumour-to-background ratio was seen. When only analysing reported data of the 6 patients with hepatic metastases, who received both IV and IA therapy, a 39% higher mean tumour-to-background ratio can be calculated, which was close to being statistically significant (paired t-test: $P = 0.06$). Unfortunately, 5 of 6 patients first had IA therapy and then IV therapy, and therefore any influence of the IA therapy on the uptake of IV therapy cannot be ruled out *(76)*.

McStay *et al.* reported about the infusion of the radiolabelled somatostatin analogue ^{90}Y-DOTA-lanreotide into the hepatic artery in 23 patients, of whom 9 also underwent hepatic artery embolisation during the same session. This makes it hard to draw conclusions from this study. A total of 36 treatments were administered. The authors describe the results in 19 patients with radiological follow-up only, however 4/23 patients died before CT or MRI could be performed and had clinical signs of PD: therefore this should be regarded as PD as well. Then 8/23 had PD (35%), 12 had SD (52%) and 3 had PR (13%). When analysing the 14 patients who only had intra-arterial injection of ^{90}Y-DOTA-lanreotide, 7 still had PD (50%), 6 had SD (43%) and 1 had PR (7%). In all patients, median progression free survival was 9 months and median overall survival was 15 months *(77)*.

Limouris *et al.* published results of therapy with ^{111}In-octreotide via the hepatic artery. Only patients with hepatic metastases and with tumour uptake on pre-therapy scintigraphy that was clearly more than normal hepatic parenchyma (ratio 1.3 or more) were included. Somatostatin analogues were continued, and no renal protective agents were administered. Seventeen patients with liver metastases of GEPNET were treated and mean cumulative administered activity was 58 GBq (range 17-77 GBq). One of 17 patients had CR (6%), 8 had PR (47%), 3 had SD (18%) and 5 had PD (28%) *(78)*.

Therapy with radiolabelled compounds: Peptide Receptor Radionuclide Therapy

As indicated by the previous data summarised in table 5, there is need for more effective therapies in patients with GEPNET: therapies with high response rates, that last long and improve / spare the quality of life. Peptide Receptor Radionuclide Therapy (PRRT) with the radiolabelled somatostatin analogue lutetium-177-octreotate as single agent or in combination may be such a therapy. Effects of this treatment modality are presented in this thesis. Chapter 1.2 and 8.2 provide summaries of several PRRT studies. There is a partial overlap with the previous and next section.

Table 5. Summary of non-surgical therapies for patients with gastroenteropancreatic neuroendocrine tumours.

Therapy	OR (pooled)	SD (pooled)	Duration of response (months)	Limitations
HAE	43-74% (52%)	8-61% (36%)	4-44 [a]	-Targeted at liver only -Liver burden <75% -Often short TTP
HACE	8-100% (63%)	0-67% (26%)	8 – 44 [a]	-Targeted at liver only -Liver burden <75% -Often short TTP -Not proven to be more effective than HAE
Somatostatin analogues	0-31% (4%)	27-90% (51%)	5 - 18 [a]	-Tumour remission rare -Short TTP
Interferon-α	0-20% (11%)	64-94% (70%)	20-34 [a]	-Tumour remission rare -Side effects
Chemotherapy [b]	4–39% (19%)	8-75% (35%)	3 – 18 [a]	-Tumour remission rare -Short TTP -Side effects
Radioembolisation	39-65% (56%)	15-41% (25%)	-	-Limited availability -Targeted at liver only -No data on TTP
^{131}I-MIBG	3-38% (19%)	33-62% (55%)	13-15 [c]	-Possible in minority of GEPNET patients -When reported, short PFS

[a] range of medians
[b] see table 4 chapter 2.1 for details.
[c] median PFS
Abbreviations: *GEPNET*, Gastroenteropancreatic neuroendocrine tumour; *HAE*, Hepatic artery embolisation; *HACE*, Hepatic artery chemo-embolisation; *OR*, Objective response; *PFS*, Progression free survival; *SD*, Stable disease; *TTP*, Time to progression.
Pooled data based on studies providing data on both OR and SD.

Figure 1 represents our current view on the management of patients with inoperable / metastasised gastroenteropancreatic neuroendocrine tumours, including bronchial carcinoids. This takes into account the recent data on the effects of octreotide on progression free survival and the effects of the proliferation marker Ki-67 on the effectiveness of ^{177}Lu-octreotate *(25, 79)*. If disease is progressive and PRRT is not possible (anymore), the decision to start interventional or medical therapy is based on the dissemination of disease and clinical condition of the patient.

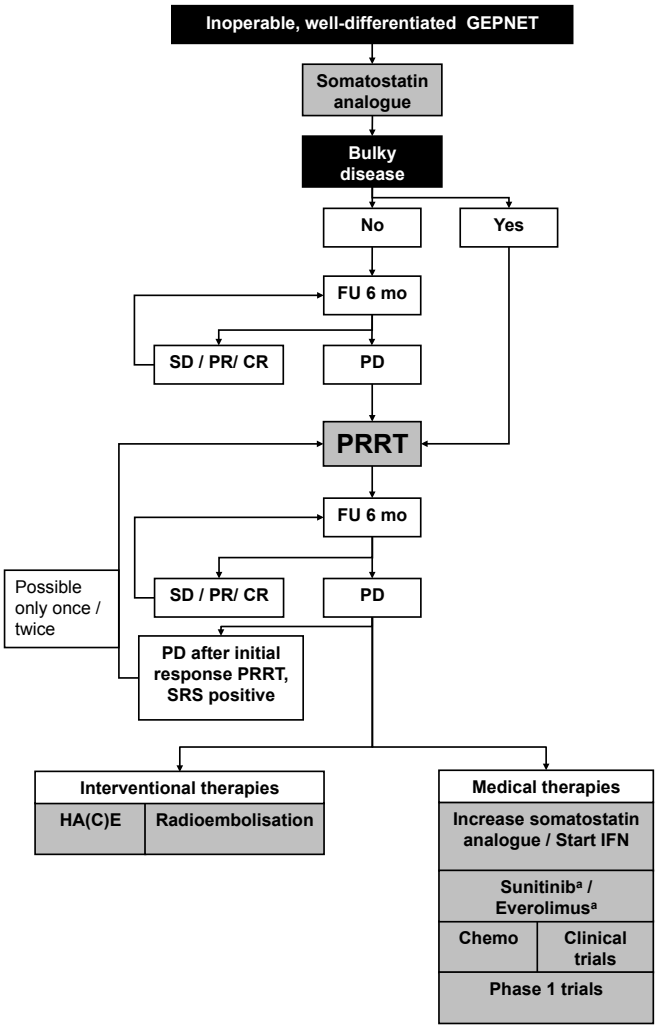

Figure 1. Proposal for the therapeutic management of patients with somatostatin receptor positive, well-differentiated gastroenteropancreatic neuroendocrine tumours (GEPNET), including bronchial carcinoids, with a Ki-67 index up to 20%.

[a] recently approved for pancreatic NET.

Abbreviations: *CR*, Complete remission; *FU*, Follow-up (CT, somatostatin receptor scintigraphy, serum Chromogranin A, other relevant neuroendocrine tumour markers); *HA(C)E*, Hepatic artery (chemo) embolisation; *IFN*, Interferon; *PD*, Progressive disease; *PR*, Partial remission; *PRRT*, Peptide receptor radionuclide therapy; *SRS*, Somatostatin receptor scintigraphy.

SOMATOSTATIN RECEPTOR POSITIVE TUMOURS OTHER THAN GEPNETS

Also various non-GEPNETs can overexpress somatostatin receptors and could possibly be treated with radiolabelled somatostatin analogues. Tumours relevant for this thesis are paraganglioma/phaeochromocytoma, meningioma, small cell lung carcinoma and melanoma. These tumours are briefly discussed here and the results of therapy with ^{177}Lu-octreotate in patients with these tumours are presented in Chapter 3.

Paraganglioma and phaeochromocytoma

Paraganglioma and phaeochromocytoma are tumours derived from chromaffin cells of neural crest origin. Chromaffin cells are named as such, because they can be visualised by staining with chromium salts. Paragangliomas are situated outside of the adrenal glands, and therefore are classified as extra-adrenal paragangliomas. Phaeochromocytomas, by definition, originate from the adrenal gland, and an alternative name therefore is intra-adrenal paraganglioma. Extra-adrenal paragangliomas can be derived from sympathetic or parasympathetic paraganglia situated from pelvis to head or from chromaffin cells in the viscera. Head and neck paragangliomas (also named glomus vagale, tympanicum, jugulare or caroticum depending on their location, or chemodectoma) are commonly derived from parasympathetic paraganglia, rather than of sympathetic origin and rarely are hormonally active. Extra-adrenal sympathetic paragangliomas usually are noradrenergic, rather than adrenergic. The most common sympathetic extra-adrenal paraganglioma is situated in the organ of Zückerkandl.

Malignancy of phaeochromocytoma and paraganglioma is only defined by the presence of metastases, not by local invasion. Metastases are defined as the presence of paraganglionic tissue in a site where this normally is absent (e.g. lymph node, liver, bone). This is to avoid confusion with multi-centricity of primary paragangliomas *(80)*.

The management of patients with phaeochromocytoma and extra-adrenal paraganglioma primarily consists of surgery when possible. For head and neck paraganglioma this may be difficult due to the vicinity of cranial nerves and large vessels. External beam radiation therapy then can be an option, especially with the newly developed stereotactic techniques or γ-knife.

In patients with localised, non-operable disease, in whom external radiotherapy is not possible either, and in patients with metastasised disease, systemic therapy must be considered, especially when disease is progressive or symptomatic. It is however advised to

resect the primary phaeochromocytoma whenever possible even in metastasised disease: this reduces the amount of bioactive substances and can prevent local symptoms.

Data on systemic therapy are scarce: a recent report indicated that chemotherapy with cyclophosphamide, vincristine and dacarbazine (CVD) can have anti-tumour effects. Of 18 patients, 2 had a CR and 8 had a PR (11% and 44% respectively) and 3 had a minor response (17%). In patients with a CR or PR (responders) a median of 23 cycles was given, whereas in non-responders a median of 5.5 cycles was administered. The median response duration was 20 months. Median survival from start of therapy was 3.3 years. There was no statistically significant difference in median survival between responders and non-responders (3.8 years and 1.8 years respectively, $P = 0.65$) *(81)*.

There is emerging evidence from case reports that sunitinib also has anti-tumour effects in paraganglioma / phaeochromocytoma. Of the 6 patients in these reports 3 had PR, 2 had tumour shrinkage in a part of the lesions, and 1 had SD with evident necrosis developing after therapy. Further clinical studies are needed to evaluate the effects of sunitinib in larger groups of patients *(82- 85)*.

Also several groups using different treatment protocols reported their result of ^{131}I-MIBG therapy in patients with paraganglioma / phaeochromocytoma. Some of these results are also presented in Chapter 3. Response, including biochemical and symptomatic responses was achieved in 30 to 63% *(86 - 89)*. With radiological criteria, objective response was achieved in 36% and 47% *(90, 91)*. Symptomatic or hormonal responders to therapy had a better survival than non-responders (4.7 years and 1.7 years respectively) *(90)*. Median progression free survival was 24 months, and median survival was 42 months *(91)*.

In Chapter 8.2 results of PRRT with radiolabelled somatostatin analogues are summarised, and in Chapter 3 results of therapy with ^{177}Lu-octreotate in paraganglioma / phaeochromocytoma are presented.

Meningioma

Meningiomas are tumours derived from the arachnoid cap cells of meninges. The vast majority is benign, but tumours can continue to grow or become malignant. Meningiomas express a variety of receptors, e.g. for progesterone, androgens and oestrogens. They also can express peptide hormone receptors like sst. According to the WHO classification, there are benign (grade I), atypical (grade II) and malignant (anaplastic, grade III) meningiomas. In most patients, management is conservative. Surgery should be attempted in

symptomatic or locally advanced meningiomas. Alternatively, external beam radiation therapy can be performed. There is no standard treatment for grade II and III meningiomas.

Data of systemic therapy for patients with tumours that cannot be operated or be irradiated are scarce. Mifepristone, a progesterone and glucocorticoid receptor antagonist seamed not effective compared to placebo *(92)*. In another study, there may be a small reduction is size (5 – 10%) or some clinical benefit *(93)*.

Hydroxyurea can rarely result in tumour shrinkage, but in most series stable disease was the best response *(94)*.

Interferon-α may have stabilising effects as well, with a median time to tumour progression of 7 months *(95, 96)*.

Interestingly, long-acting somatostatin resulted in partial radiographic remission in 44% of patients. Median time to progression was 5 months *(97)*.

In Chapter 1.2 and 8.2 results of PRRT in meningioma are summarised. In Chapter 3 results of therapy with ^{177}Lu-octreotate are discussed. Moreover, very recently Bartolomei *et al.* presented their results of therapy with [yttrium-90-DOTA^{0},Tyr^{3}] octreotide in patients with meningioma. Twenty-nine patients were enrolled: 14 had benign (grade I), 9 had atypical (grade II) and 6 had malignant (grade III) disease. Therapy resulted in disease stabilisation in 19 of 29 patients (66%) and disease was progressive despite therapy in the remaining 10 (34%). None of the patients had tumour remission. Better results were obtained in patients with grade I meningioma than in those with grade II–III. Median time to progression was 61 months in the low-grade group and 13 months in the high-grade group *(98)*.

Small cell lung carcinoma

Small cell lung carcinoma (SCLC) is a very aggressive type of lung cancer that is situated in the spectrum of neuroendocrine lung tumours. Unlike bronchial carcinoids, SCLC is rapidly growing and often diffusely metastasised at the time of diagnosis. Median survival from diagnosis ranges from 6 to 14 months. Chemotherapy (usually etoposide with cis- or carboplatin) with radiotherapy is an effective first-line therapy in patients with limited stage disease, resulting in overall responses of 80 to 90 %, including complete remissions in 50-60%. For patients with extensive disease, 60 to 80 % has a response, but CR is achieved in 15 to 20%. Unfortunately, median time to progression usually is only 8 months. Subsequent therapies then are much less effective than first-line chemotherapy and median survival then is limited to 4 months *(99- 101)*.

Chapter 3 reports results of ^{177}Lu-octreotate therapy in patients with SCLC, and Chapter 8.2 briefly describes also other PRRT studies in patients with SCLC.

Melanoma

Melanoma is an aggressive type of skin cancer. Once distant metastases have developed, effective systemic treatments are not available and median survival is limited to 9 months *(102)*.

In many trials with either immunotherapy, molecularly targeted agents or cytotoxic chemotherapy some patients do respond well, but objective responses usually are obtained in less than 25% of patients *(103, 104)*.

Several substances are under investigation for systemic radionuclide therapy that are either melanin-binding molecules or peptides related to α-melanocyte-stimulating hormone that bind to the melanocortin-1 receptor *(105)*.

Although pre-clinical reports seem promising with regard to anti-tumour effects, no data are available for therapeutic use in humans. In Chapter 3, results of therapy with ^{177}Lu-octreotate in melanoma patients are presented.

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Chapter 1.2

Peptide-Receptor Radionuclide Therapy for Endocrine Tumours

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ABSTRACT

Peptide-receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues is a promising option for the treatment of somatostatin-receptor-positive endocrine tumours. Treatment with somatostatin analogues labelled with ^{111}In, ^{90}Y or ^{177}Lu can result in symptomatic improvement, although tumour remission is seldom achieved with ^{111}In-labelled analogues. In this Review, the findings of several studies on the use of PRRT for endocrine tumours are evaluated. Large variation in the antitumour effects of ^{90}Y-octreotide was reported between studies: an objective response (≥50% tumour regression) was achieved in 9–33% of patients. After treatment with ^{177}Lu-octreotate, an objective response was achieved in 29% of patients and a minor response (25–50% tumour regression) was achieved in 16% of patients; stable disease was present in 35% of patients. Treatment with ^{177}Lu-octreotate resulted in a survival benefit of several years and markedly improved quality of life. Serious, delayed adverse effects were rare after PRRT. Although randomised, clinical trials have not yet been performed, data on the use of PRRT compare favourably with those from other treatment approaches, such as chemotherapy. If these results can be replicated in large, controlled trials, PRRT might become the preferred option in patients with metastatic or inoperable gastroenteropancreatic neuroendocrine tumours.

KEY POINTS

- Peptide-receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues is a promising treatment modality for patients with somatostatin-receptor-positive gastroenteropancreatic neuroendocrine tumours
- ^{177}Lu-octreotate resulted in tumour remission in 46% and stable disease in 35% of patients; a median time to progression of 40 months and a survival benefit of several years was indicated
- PRRT is generally well tolerated if treating physicians adhere to dose limits and renal protection is administered
- PRRT can also be effective for patients with nongastroenteropancreatic tumours, such as non-radioiodine-avid thyroid carcinoma and paraganglioma; however, further studies are needed to determine PRRT's role in this setting
- Studies are ongoing to improve the antitumour effects of PRRT, reduce its adverse effects, increase patients' long-term survival prospects, and improve their quality of life
- PRRT might become the preferred option for patients with progressive gastroenteropancreatic neuroendocrine tumours if these data can be confirmed

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumours (GEPNETs) comprise functioning or nonfunctioning tumours of endocrine cells in the pancreas and gastrointestinal neuroendocrine tumours (carcinoids). These tumours are usually slow-growing and often metastatic at diagnosis. Treatment with somatostatin analogues, such as octreotide and lanreotide, can reduce hormonal overproduction by the tumours and result in symptomatic relief for most patients with metastatic disease; however, objective, radiological responses are seldom achieved *(1-3)*. Chemotherapy in patients with GEPNETs can result in tumour shrinkage, but is associated with appreciable adverse effects, and time to progression is usually short *(4-6)*.

In the 1990s, peptide-receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues was introduced as a promising treatment modality for patients with inoperable or metastasised GEPNETs. The majority of GEPNETs express abundant levels of the somatostatin receptor, which can be visualised in patients by use of the radiolabelled somatostatin analogue, ^{111}In-diethylenetriamine pentaacetic acid (DTPA)-octreotide. Other somatostatin-receptor-positive tumours, such as paragangliomas and thyroid carcinomas, can also be visualised in this manner. Given the ability of radiolabelled somatostatin analogues to identify somatostatin-receptor-positive tumours, the next logical step was to try and use radiolabelled somatostatin analogues as a novel treatment for this group of tumours. In this Review, the data obtained from preliminary studies on PRRT for GEPNETs are evaluated, and the arguments for and against this approach are discussed.

THERAPY STUDIES

Radiolabelled somatostatin analogues generally comprise three main parts: a cyclic octapeptide (for example, Tyr^3-octreotide or Tyr^3-octreotate), a chelator (for example, DTPA or tetraazacyclododecane tetraacetic acid [DOTA]) and a radioactive element. Radioisotopes commonly used in PRRT are ^{111}In, ^{90}Y and ^{177}Lu.

^{111}In-DTPA-octreotide

Studies in the 1990s used the Auger-electron-emitting ^{111}In-DTPA-octreotide (^{111}In-octreotide) for PRRT, as somatostatin analogues labelled with β-emitting radionuclides were not available for clinical use at that time. Treatment with high doses of ^{111}In-octreotide often led to symptomatic relief in patients with metastatic neuroendocrine tumours; however, tumour shrinkage was rarely achieved *(7-9)*. For example, five of 26 patients had a decrease in tumour size of 25–50% (a minor response) on CT scans *(7)*. These patients

were treated with high doses of ^{111}In-octreotide and received a total cumulative dose of ≥20 GBq, but none had partial remission (a decrease in tumour volume of ≥50%). In another study, partial response was reported in two of 26 patients with measurable disease *(8)*. In each of these studies, the patients were in a poor clinical condition and many had progressive disease at baseline. A third study of 12 patients with carcinoids, gastrinomas or glucagonomas reported partial remission in two patients *(9)*.

The most common long-term adverse effects of ^{111}In-octreotide therapy resulted from toxic effects to the bone marrow. Serious adverse effects included leukemia and myelodysplastic syndrome in three patients who had been treated with total cumulative doses of >100 GBq and in whom bone-marrow radiation doses were estimated at >3 Gy *(7)*. One of these patients had previously been treated with chemotherapy, which might have contributed to, or caused, this complication. Anthony *et al*. *(8)*, reported renal insufficiency in one patient, which was possibly the result of pre-existing retroperitoneal fibrosis, rather than being treatment-related. Transient hepatic toxic effects were observed in three patients who had widespread liver metastases *(8)*. Another study that used a maximum cumulative dose of 33.6 GBq did not observe any cases of myelodysplastic syndrome or renal failure *(9)*.

Delpassand *et al*. *(10)*, treated 32 patients with high doses of ^{111}In-octreotide, 18 of whom received two cycles of 18.5 GBq (cumulative dose 37 GBq); 14 patients received a single cycle of 18.5 GBq. Although one patient who received a single cycle of treatment developed grade 3 thrombocytopenia, no other haematological or renal toxic effects were observed during follow-up (mean 13 months). Of the 18 patients treated with two cycles, 16 had stable disease and two had partial remission; median time to progression was not reported.

^{111}In-octreotide has also been used to treat patients with differentiated thyroid carcinoma, although tumour remission was not observed in two small studies *(7, 11)*. No objective response was demonstrated in three patients with phaeochromocytoma treated with ^{111}In-octreotide; one patient with a paraganglioma had a minor response to treatment *(7)*. Tumour regression, as assessed by CT, has been observed only in rare cases after therapy with ^{111}In-octreotide; ^{111}In-coupled peptides are not ideal for PRRT, as the short distance traveled by Auger electrons after emission means that decay of ^{111}In has to occur close to the cell nucleus to be tumouricidal.

^{90}Y-DOTA,Tyr^3-octreotide

The next generation of radionuclide therapy that targeted somatostatin receptors was the radiolabelled, modified somatostatin analogue ^{90}Y-DOTA,Tyr^3-octreotide (^{90}Y-DOTATOC). As a consequence of the replacement of phenylalanine by tyrosine as the third amino acid in the octapeptide, this analogue has an increased affinity for somatostatin-receptor

subtype 2. Furthermore, this compound has DOTA instead of DTPA as the chelator, which allows stable binding of ^{90}Y, a β-emitting radionuclide. ^{90}Y-DOTATOC has been used in several PRRT trials in various countries.

Investigators in Switzerland have performed phase I and phase II studies of ^{90}Y-DOTATOC in patients with GEPNETs (Table 1) *(12-15)*. Although a treatment protocol that administered a cumulative dose of 7.4 GBq/m^2 in two cycles *(15)* seemed most beneficial, this study was not a randomised trial that compared dosing schemes. Patients' and tumours' characteristics can be different. For example, the study that used 7.4 GBq/m^2 in two cycles *(15)* included fewer patients with carcinoid tumours than a study that administered the same dose in four cycles *(14)*; carcinoids have lower response rates to PRRT than pancreatic endocrine tumours or endocrine tumours of unknown origin.

Table 1. A comparison of preliminary studies of ^{90}Y-DOTATOC.

Parameter	Study			
	Otte *et al.* (1999) *(12)*	Waldherr *et al.* (2001) *(13)*	Waldherr *et al.* (2002) *(14)*	Waldherr *et al.* (2002) *(15)*
Tumour type	Mixed	Mainly GEPNETs	Mainly GEPNETs	Neuroendocrine
Number of patients	29	41	39	36
Phase	I and II	II	II	II
Cumulative dose of radioactivity (GBq/m^2)	6.12	6.00	7.40	7.40
Radioactivity dose per cycle (MBq/m^2)	740–3,700	925–2,035	1,850	3,700
Number of cycles	4 (6 patients received >4)	4	4	2
Progressive disease at start (%) GEPNETs	NA	81	100	100
Complete remission (%)	0	2	5	6
Partial remission (%)	7	22	18	28
Stable disease (%)	86	61	69	54
Progressive disease (%)	7	15	8	12
Number of patients with GEPNET	18	37	37	NA
Complete remission (%)	0	3	3	NA
Partial remission (%)	6	24	19	NA
Stable disease (%)	83	62	70	NA
Progressive disease (%)	11	11	8	NA
Median time to progression (months)	NA	>26	NA	NA

Table 1. A comparison of preliminary studies of ^{90}Y-DOTATOC. (continued)

Parameter	Study			
	Otte *et al.* (1999) *(12)*	Waldherr *et al.* (2001) *(13)*	Waldherr *et al.* (2002) *(14)*	Waldherr *et al.* (2002) *(15)*
Grade 3 or 4 haematological toxic effects (%)	7	5	3	3
Renal toxic effects (%)	14 (7 grade unknown, 7 grade 4 or dialysis)	None	3 (grade 2)	6 (grades 3 and 4)
Median follow-up (months)	NA	15.0	6.0	10.5
Limitations and comments	15 patients who did not receive 4 cycles were left out of the analysis 4 of 29 patients had tumour reduction of <50% Serious toxic effects mainly occurred in patients who received >4 cycles (cumulative dose >7.4 GBq/m^2) without renal protection No data on the extent of disease or amount of uptake on SRS 6 GBq/m^2 was defined as maximum tolerated dose	Limited follow-up No data on the extent of disease, amount of uptake on SRS	Limited follow-up All responses ongoing during follow-up (range 2–12 months) No data on the extent of disease or amount of uptake on SRS	Results not published in a peer-reviewed journal No details on subtypes of GEPNETs Limited follow-up All responses ongoing during follow-up (range 4–18 months) No data on the extent of disease or amount of uptake on SRS

WHO response criteria were used in all four studies.
Abbreviations: *GEPNET*, gastroenteropancreatic neuroendocrine tumour; *NA*, not available; *SRS*, somatostatin-receptor scintigraphy.

Dosimetric and dose-escalating phase I studies of ^{90}Y-DOTATOC have been performed in Milan, Italy, both with and without the administration of renal-protecting agents (Tables 2 and 3) *(16)*. No major, acute reactions were observed with doses of up to 5.6 GBq per cycle. Reversible, grade 3 haematological toxic effects occurred in 43% of patients injected with 5.2 GBq ^{90}Y-DOTATOC, which was then defined as the maximum tolerated dose per cycle. None of these patients developed acute or delayed kidney failure, although follow-up was short. Of note, however, 30 patients in the first phase of the study, who received three cycles of up to 2.59 GBq ^{90}Y-DOTATOC per cycle without renal protection, also did not develop renal failure. Another study showed that partial and complete remissions were achieved in 28% of patients (n = 87) with neuroendocrine tumours after

Table 2. Dosimetric and dose-escalating phase I studies of ^{90}Y-DOTATOC.

Parameter	Chinol *et al.* (2002) *(16)* [a]		
	Part 1a	Part 1b	Parts 1 and 2 [b]
Number of patients	30	40	111
Phase	I and II	I and II	II
Cumulative dose of radioactivity (GBq)	3.33–7.77	5.92–11.10	7.40–21.30
Dose of radioactivity per cycle (GBq)	1.11–2.59	2.96–5.55	0.90–5.50
Number of cycles	3	2	5
Progressive disease at study start (%)	NA	NA	80
Complete remission (%)	NA	NA	5
Partial remission (%)	NA	NA	22
Complete + partial remission (%)	23	21	27
Stable disease (%)	64	44	49
Progressive disease (%)	13	35	20
Median time to progression (months)	NA	NA	15
Grade 3 or 4 haematological toxic effects (%)	None	43 (at maximum tolerated dose)	NA
Renal toxic effects	None	None	NA
Limitations and comments	No renal protection No dose-limiting toxic effects No data on the extent of disease or amount of uptake on SRS	Renal protection The maximum tolerated dose per cycle was 5.18 GBq No data on the extent of disease or amount of uptake on SRS	Includes patients from parts 1a and 1b plus additional patients Results not specified for GEPNETs Outcomes of treatment could not be assessed in 4% of patients No detailed data on toxic effects No data on the extent of disease or amount of uptake on SRS

[a]Part 1a and Part 1b were studies without and with renal protection, respectively.
[b]This column presents results from this Part 1 and a subsequent Part 2 study that included patients who received ≥ 7.4 GBq. The patients enrolled in this study had a mixed tumour type; the Southwest Oncology Group criteria were used to assess response to treatment.
Abbreviations: *GEPNET*, gastroenteropancreatic neuroendocrine tumour; *NA*, not available; *SRS*, somatostatin-receptor scintigraphy.

Table 3. ^{90}Y-DOTATOC: additional analyses.

Parameter	Study [a]		
	Paganelli *et al.* (2002) *(17)*	Bodei *et al.* (2003) *(18)*	Valkema *et al.* (2006) *(19)*
Tumour type	Neuroendocrine	Mixed	Neuroendocrine
Number of patients	87	40	60 (58 with GEPNETs)
Cumulative dose of radioactivity	7.40–20.20 GBq	5.92–11.00 GBq	8.20–14.90 GBq/m^2 (4 equal doses) or 7.20–12.90 GBq/m^2 (single dose escalation)
Dose of radioactivity per cycle	1.11–5.50 GBq	2.96–5.55 GBq	0.73–3.80 GBq/m^2 (4 equal doses) or 3.60–9.30 GBq/m^2 (single dose escalation)
Number of cycles	4	2	4 (4 equal doses) or 2–3 (single dose escalation)
Response criteria	WHO	WHO	SWOG
Patients with progressive disease (GEPNET) at start	66 of 87 (76%)	NA	47 of 58 (76%)
Complete response (%)	5	3	NA
Partial response (%)	23	18	NA
Stable disease (%)	49	45	NA
Progressive disease (%)	20	33	NA
Not evaluable (%)	4	3	NA
Number of patients with GEPNET	NA	20	58
Complete response (%)	NA	0	0
Partial response (%)	NA	30	9
Stable disease (%)	NA	50	62
Progressive disease (%)	NA	20	24
Median time to progression (months)	14	10	29
Grade 3 or 4 haematological toxic effects (%)	43 at 5.18 GBq	43 at 5.18 GBq	Overall: 12 thrombocytopenia, 13 leukocytopenia, 8 anaemia; no data on relationship to dose
Renal toxic effects	None	None	>15% decline per year in 15% of patients End-stage renal failure in 3% of patients
Other toxic effects	NA	NA	MDS in 2% of patients Liver failure in 2% of patients
Follow-up duration	NA	Median 19 months	18 months after first cycle (planned)

Table 3. ^{90}Y-DOTATOC: additional analyses. (continued)

Parameter	Study [a]		
	Paganelli *et al.* (2002) *(17)*	Bodei *et al.* (2003) *(18)*	Valkema *et al.* (2006) *(19)*
Limitations and comments	Overlap with Chinol *et al.* (2002) *(16)* Therapy outcome not specified for GEPNETs No data on the extent of disease or amount of uptake on SRS	Same group of patients as in Part 1b of Chinol *et al.* (2002) *(16)* Renal protection5.18 GBq maximum tolerated dose per cycle 8 patients received <7.4 GBq	^{86}Y-DOTATOC dosimetry was performed, and renal protection was used Renal dosimetry results determined the cumulative radioactivity dose (27 Gy) 12% of patients had a minor response Median overall survival 36 months 31% of patients had end-stage neuroendocrine tumoural disease No data on the amount of uptake on SRS

[a] All were phase I and II trials.
Abbreviations: *GEPNET*, gastroenteropancreatic neuroendocrine tumour; *MDS*, myelodysplastic syndrome; *NA*, not available; *SRS*, somatostatin-receptor scintigraphy; *SWOG*, Southwest Oncology Group.

treatment with ^{90}Y-DOTATOC (Table 3) *(17)*. A subsequent, phase I study conducted by the same group reported that partial remission occurred in 29% of patients *(18)*.
A multicentre, phase I study with ^{90}Y-DOTATOC was also performed *(19)*. Sixty patients received escalating doses of radioactivity without reaching the maximum tolerated single dose. The cumulative radiation dose to the kidneys was limited to 27 Gy, as assessed by PET data on ^{86}Y-DOTATOC uptake under concomitant amino-acid infusion. Results and adverse effects are shown in Table 3. Moreover, the median overall survival (36.7 months) in this cohort was significantly longer than that in a group of 32 patients treated with ^{111}In-octreotide (12 months), who served as historical controls.

Long-term follow-up of kidney function was performed in the same group of patients *(19, 20)*. Physiological renal retention of radiolabelled somatostatin analogues occurs, so the renal radiation dose is a limiting factor in the amount of radioactivity that can be safely administered. A median annual decline in creatinine clearance of 7.3% was observed in patients treated with ^{90}Y-DOTATOC *(20)*. Several factors probably contribute to this rate of decline: the cumulative dose of radiation to the kidneys, the renal radiation dose per cycle, age, hypertension and diabetes mellitus. Radiation-induced nephropathy was histologically confirmed in two of 28 patients *(20)*. In most of the studies on ^{90}Y-DOTATOC in patients with GEPNETs, complete plus partial remission rates are 9–33%, despite differences in the various treatment protocols used; these results are better than those obtained with ^{111}In-octreotide.

^{90}Y-DOTATOC therapy has also been used in patients with nongastroenteropancreatic tumours. None of the published reports of its effects on differentiated thyroid carcinoma mentions tumour remission *(21)*. As most studies of ^{90}Y-DOTATOC did not specifically report effects of the treatment in patients with paraganglioma, phaeochromocytoma or meningioma, data about its effects on these subtypes of tumours are scarce. In the study by Otte *et al*. *(12)*, one of three patients with meningiomas achieved tumour remission and two had stable disease; one patient with phaeochromocytoma had stable disease. In the study by Bodei *et al*. *(18)*, one of two patients with meningiomas had progressive disease; the other had stable disease after treatment. However, Forrer *et al*. *(22)* have published data on the use of ^{90}Y-DOTATOC in 25 patients with paraganglioma. The patients were treated with an intended cumulative dose of 7.4 GBq/m^2 in two or four cycles; 8% had a partial response, 16% had a minor response, 44% had stable disease, and 32% had progressive disease. The median follow-up duration was 12 months.

^{177}Lu-DOTA,Tyr^3-octreotate

^{177}Lu-DOTA,Tyr^3-octreotate (^{177}Lu-octreotate) represents the third generation of somatostatin-receptor-targeted radionuclide therapies and has been used in our hospital since 2000.

The only difference between DOTA,Tyr^3-octreotate and DOTA,Tyr^3-octreotide is that the C-terminal threoninol of DOTA,Tyr^3-octreotide is replaced with the amino acid, threonine. As a result, DOTA,Tyr^3-octreotate displays improved binding to somatostatin-receptor-positive tissues when compared with DOTA,Tyr^3-octreotide. Gastroenteropancreatic tumours predominantly express subtype 2 of the somatostatin receptor *(23)*, and DOTA,Tyr^3-octreotate has a sixfold to ninefold increased affinity for this receptor subtype *in vitro* compared with DOTA,Tyr^3-octreotide *(24)*. ^{177}Lu-octreotate was very successful in terms of tumour regression and survival in an experimental model in rats *(25)*.

^{177}Lu-labelled somatostatin analogues have an important practical advantage over their ^{90}Y-labelled counterparts: ^{177}Lu is not a pure β-emitter, but also emits low-energy γ-rays, which allows direct post-therapy imaging and dosimetry. By contrast, ^{90}Y is a pure β-emitter; thus, administration of a somatostatin analogue labelled with the positron emitter ^{86}Y is required for dosimetry, despite the fact that ^{86}Y has a shorter half-life than ^{90}Y. ^{111}In-octreotate has been advocated as an alternative to ^{90}Y-octreotate for dosimetry purposes; however, Reubi *et al*. *(24)* found that use of a different metal element influences affinity for the somatostatin receptor, even when the peptide–chelator complex remains unchanged. The assumption that biodistribution of In-labelled and Y-labelled peptide analogues is comparable, therefore, has to be proven *in vivo* before the use of In-labelled substitutes can be accepted in clinical dosimetry studies.

Uptake of radioactivity, expressed as a percentage of the injected dose of ^{177}Lu-octreotate, was comparable to that of ^{111}In-octreotide in the kidneys, spleen and liver,

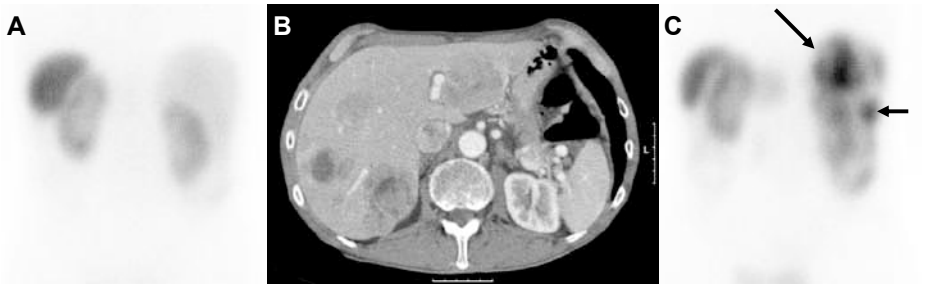

Figure 1. **(A)** Scintigraphy performed 24 h after injection of ^{111}In-octreotide did not clearly demonstrate enhanced uptake in liver metastases relative to normal liver parenchyma (posterior view). **(B)** Metastases were clearly visible on CT scan. **(C)** Scintigraphy performed 24 h after injection of ^{177}Lu-octreotate (posterior view). Liver metastases (arrows) were easily recognised.

but was increased by threefold to fourfold in four of five tumours analysed *(26)*. A clear example of this difference is shown in Figure 1. Esser *et al*. *(27)* compared the use of 3.7 GBq ^{177}Lu-octreotate and 3.7 GBq ^{177}Lu-DOTATOC for dosimetry in a therapeutic setting, in the same group of seven patients, with a 6–10 week interval. The mean delivered radioactivity dose to tumours was advantageous by a factor of 2.1 for ^{177}Lu-octreotate versus that achieved by ^{177}Lu-octreotide. High absorbed doses of ^{177}Lu-octreotate can be achieved for most tumours, with about equal doses to potentially dose-limiting organs. Therapy with ^{177}Lu-octreotate is currently administered in several institutions around the world and some groups have presented preliminary results as congress abstracts *(28, 29)*; however, only the Erasmus Medical Centre has published detailed, peer-reviewed reports. The treatment effects of ^{177}Lu-octreotate therapy were studied in a large group of patients *(6)*, (Table 4) and preliminary results were presented in two small groups of patients. Thirty patients received up to an intended cumulative radioactivity 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. This limit of 23 Gy was based on findings from external-beam radiation therapy studies, in which administration of 23 Gy led to nephrosclerosis in 1–5% of patients after 5 years *(31)*. The limit for the maximum cumulative radioactivity dose administered (29.8 GBq) was based on calculations in a limited number of patients, which indicated that this dose would result in 2 Gy to the bone marrow *(26)*. Treatment intervals were 6–10 weeks. If possible, long-acting octreotide or lanreotide injections were stopped at least 6 weeks before the initial dose, and short-acting octreotide was stopped for 24 h before therapy with ^{177}Lu-octreotate, to avoid competitive binding to the somatostatin receptor.

Table 4. A study of ^{177}Lu-octreotate.

Parameter	Kwekkeboom *et al.* (2008) *(6)*
Tumour type	Mixed
Number of patients	504
Phase	I and II
Cumulative dose of radioactivity (GBq)	22–29
Radioactivity dose per cycle (GBq)	3.7–7.4
Number of cycles	3–4
Response criteria	Southwest Oncology Group
Progressive disease at start	133 of 310 patients (43%)
Number of patients with GEPNET	310
Complete response (%)	2
Partial response (%)	28
Stable disease (%)	51
Progressive disease (%)	20
Median time to progression (months)	40
Grade 3 or 4 haematological toxic effects (%)	9.5
Renal toxic effects (%)	0.4
Other toxic effects	MDS in 0.8% of patients. Liver toxic effects in 0.6% of patients
Median follow-up (months)	19
Limitations and remarks	Remission predicted by: high radioactivity uptake on pretherapy ^{111}In-octreotide scintigraphy, limited number of liver metastases Progression predicted by: low Karnofsky performance status score, extensive disease and weight loss Published data based on single-centre experience Outcome of therapy not yet evaluated in all patients Cumulative dose of radioactivity based on kidney dosimetry (23 Gy) 16% of patients had a minor response Data available on extent of disease, amount of uptake on SRS, clinical condition Median overall survival 48 months

Abbreviations: *GEPNET*, gastroenteropancreatic neuroendocrine tumour; *MDS*, myelodysplastic syndrome; *NA*, not available; *SRS*, somatostatin receptor scintigraphy.

Between January 2000 and August 2006, 504 patients were treated (a total of 1,772 administrations of ^{177}Lu-octreotate) according to the study protocol *(6)*. Adverse effects within the first 24 h were nausea in 25% of administrations, vomiting in 10% and pain in 10%. A clinical crisis occurred in six patients with hormonally active neuroendocrine tumours after treatment; this event was the result of a massive release of bioactive substances. All six patients recovered after adequate medical treatment *(32)*. Haematological adverse effects (WHO grades 3 or 4) occurred in 3.6% of administrations (9.5% of patients) *(6)*. Mild and reversible alopecia was reported by 62% of patients. Serious, delayed adverse effects occurred in nine patients, of whom two had a decline in kidney function. One patient developed renal insufficiency 1.5 years after receiving the last treatment. Kidney failure was probably unrelated to treatment with ^{177}Lu-octreotate, as deterioration had already started before therapy; however, some contribution of the treatment to the decline in kidney function cannot be ruled out. In the second patient, levels of serum creatinine rose considerably 3 years after ^{177}Lu-octreotate therapy. This increase was thought to be unrelated to treatment with ^{177}Lu-octreotate and to result from severe and worsening tricuspid-valve insufficiency with right-sided heart failure, for which diuretics and other medication were needed.

Valkema *et al*. *(20)*, also analysed long-term effects on kidney function in patients treated with ^{177}Lu-octreotate. These researchers reported a median change in creatinine clearance of 3.8% per year, as opposed to 7.3% per year in patients treated with ^{90}Y-DOTATOC. In two of 37 patients (5%) treated with ^{177}Lu-octreotate, the decline in kidney function was >15% per year. One of these patients had several risk factors: the patient was 78 years of age and had diabetes mellitus and hypertension.

Liver toxic effects occurred in three patients who had very extensive hepatic metastases: one patient had diffuse, rapidly growing liver metastases from an aggressive endocrine pancreatic tumour *(6)*. This patient died 5 weeks after administration of the first treatment, an outcome that was probably attributable to aggressive tumour growth. Two other patients had a temporary decline in liver function that required hospitalisation. Both patients recovered and therapy was resumed with a lower dose of ^{177}Lu-octreotate per cycle without serious adverse effects. Four patients developed myelodysplastic syndrome. In one patient, myelodysplastic syndrome was most likely to have been caused by prior chemotherapy with alkylating agents. In the other three patients, myelodysplastic syndrome was most likely to be related to ^{177}Lu-octreotate therapy.

Tumour size was evaluated in 310 patients with GEPNETs (Table 4) *(6)*. Figure 2 demonstrates partial remission in a patient. In four patients with an inoperable pancreatic neuroendocrine tumour, shrinkage after therapy with ^{177}Lu-octreotate was sufficient to allow surgical removal. Resection was successful in three patients, but one patient died from postoperative complications. Median time to progression was 40 months from start of

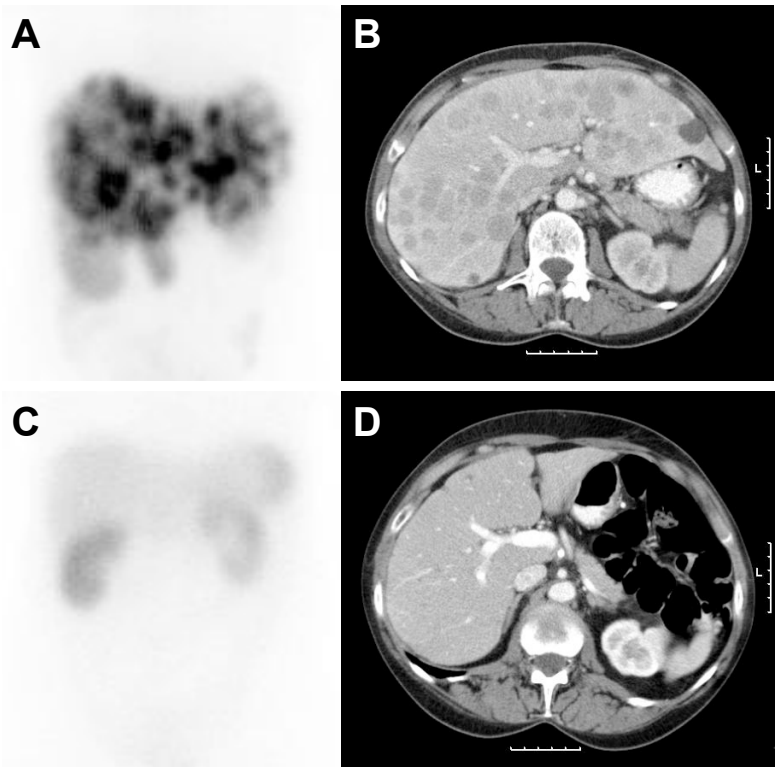

Figure 2. Extensive, diffuse, hepatic metastases were visualised on both **(A)** ^{111}In-octreotide scintigraphy and **(B)** a CT scan performed 1 month before initiation of treatment with ^{177}Lu-octreotate. The patient received a cumulative dose of 29.8 GBq. No abnormal uptake was seen on **(C)** ^{111}In-octreotide scintigraphy and **(D)** a few very small hypodense lesions were seen on contrast-enhanced CT scans performed 1 year after the end of treatment with ^{177}Lu-octreotate. The patient was classified as having partial remission.

treatment in the 249 patients who either had stable disease or tumour regression. Similar results were found in patients with foregut carcinoids *(33)*.

Median overall survival after initiation of therapy was 46 months and median disease-related survival was >48 months *(6)*. Median progression-free survival was 33 months. The most important predictive factor for survival was treatment outcome (progression versus nonprogressive disease). Other predictive factors included the extent of liver metastases, a low Karnofsky performance status score, baseline weight loss and (to a lesser degree) presence of bone metastases and gastrinoma, insulinoma or VIPoma. Compared with other treatments and epidemiological data *(34-37)*, ^{177}Lu-octreotate seems to confer a survival benefit of at least 3.5–6.0 years. The difference in survival after diagnosis between the patients treated with ^{177}Lu-octreotate and those from other studies is illustrated in Figure 3.

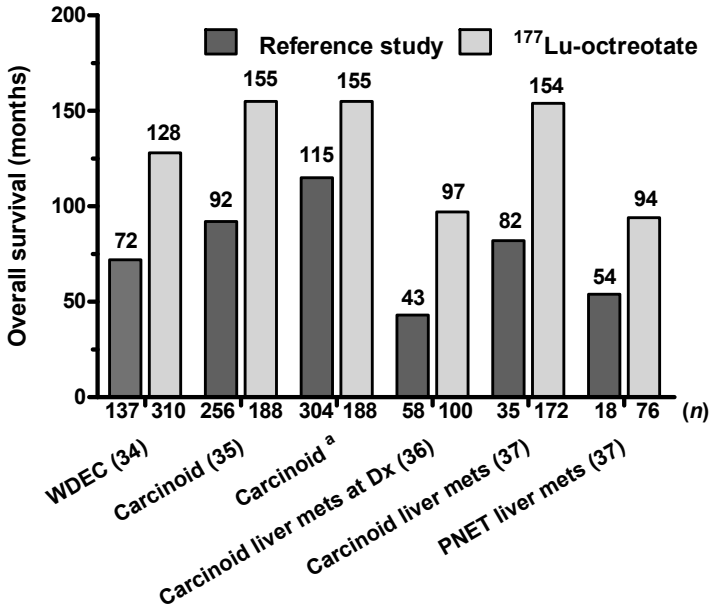

Figure 3. Overall survival in months since diagnosis in patients from epidemiological and interventional studies (dark bars) and in ^{177}Lu-octreotate-treated patients who were similar with regard to tumour type and disease stage (light bars). Patients treated with ^{177}Lu-octreotate had a survival benefit of 40–72 months. The data presented are not derived from randomised clinical trials *(34 – 37)*.
[a] update *(35)*, personal communication K. Oberg.
Abbreviations: *Dx*, diagnosis; *GEPNET*, gastroenteropancreatic neuroendocrine tumour; *mets*, metastases; *PNET*, pancreatic neuroendocrine tumour; *WDEC,* well-differentiated endocrine carcinoma.

The possibility that patients with sufficient tumoural uptake of ^{111}In-octreotide on scintigraphy have better-differentiated tumours than do those with low or absent tumoural uptake cannot be ruled out, and this difference might favourably influence tumour response and survival data. For example, patients with inadequate tumoural uptake of ^{111}In-octreotide on scintigraphy had a 5-year survival of 30%, whereas those with adequate uptake had a 5-year survival of 55% *(38)*. This study did not, however, mention the cause of death and from what time point survival was analysed (date of ^{111}In-octreotide scintigraphy or date of diagnosis). We also calculated overall survival for the subgroups of patients described by Kwekkeboom *et al. (6)*, with the addition of fictitious patients who survived only 6 months from diagnosis. They were assumed to comprise 5% of the cohort, on the basis that the incidence of poorly differentiated neuroendocrine tumours is estimated at 3% for foregut tumours *(39)*. The survival benefit for patients treated with ^{177}Lu-octreotate was 23–69 months. We clearly acknowledge that comparisons with historical controls should be interpreted very cautiously, but in our opinion the consistent survival benefit associated

with ^{177}Lu-octreotate across several other reports in similar groups of patients seems of importance.

Quality of life is another important determinant of treatment success. This parameter was evaluated in 50 patients with metastatic gastroenteropancreatic tumours treated with ^{177}Lu-octreotate *(40)*. These patients completed the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 before therapy and at follow-up (6 weeks after the last treatment cycle). Global health status and quality of life markedly improved after therapy with ^{177}Lu-octreotate. The patients reported an improvement in symptom scores for fatigue, insomnia, and pain. Improvement of quality-of-life domains was most frequently observed in patients with proven tumour regression.

^{177}Lu-octreotate therapy has also been administered to patients with nongastroenteropancreatic tumours. Teunissen *et al. (41)*, reported results in five patients with non-radioiodine-avid differentiated thyroid carcinoma. Three of these patients had Hürthle-cell thyroid carcinomas, of whom two showed tumour regression and one had stable disease after treatment. One patient with progressive, papillary thyroid carcinoma had stable disease after therapy, although a progressive, follicular thyroid carcinoma remained progressive in one patient. Treatment with ^{177}Lu-octreotate can also be effective in patients with paragangliomas and meningiomas *(42)*. After treatment, two of 12 patients with metastasised or inoperable paragangliomas showed tumour remission and another six had stable disease (including one who had proven progressive disease at entry). Three patients had progressive disease and one patient's outcome could not be determined. One of four patients who had progressive meningiomas had stable disease. The three patients who still had progressive disease after PRRT had anaplastic, exophytic, large tumours; these cancers had failed to respond to all standard treatments.

Other radiolabelled somatostatin analogues

Lanreotide can be labelled with ^{111}In for diagnostic purposes and with ^{90}Y for therapeutic use. Use of radiolabelled lanreotide has been advocated because of its increased affinity for somatostatin-receptor subtypes 3 and 4 when compared with ^{111}In-octreotide *(43)*, but this claim is questionable *(24)*. Although radiolabelled lanreotide has been used to treat patients with gastroenteropancreatic tumours, the affinity of this agent is less than that of radiolabelled DOTA,Tyr^3-octreotide or octreotate for somatostatin-receptor subtype 2, which is overexpressed in this class of tumours *(23)*.

Forrer *et al. (44)* reported the results of administering one additional cycle of 7.4 GBq ^{177}Lu-DOTATOC to patients with disease progression after an initial response to ^{90}Y-DOTA-TOC therapy. Analysis at 8–12 weeks after this treatment demonstrated progressive disease in eight of 27 treated patients (30%), stable disease in 12 (44%), minor responses in five (19%) and partial remissions in two patients (7%). Mean time to progression was 8.3

months (range 4–13 months) and eight patients were still without progressive disease. At the time of analysis, this treatment seemed safe, but follow-up was rather short. In our opinion, the low administered dose and short duration of follow-up mean that firm conclusions are hard to draw from this study.

DOTANOC is a peptide in which the third amino acid of octreotide (phenylalanine) is replaced by 1-naphthylalanine. DOTANOC has a good affinity for somatostatin-receptor subtypes 2, 3 and 5 *(45)*, which might be important for imaging and treatment of tumours with atypical expression of these subtypes. A preliminary report *(46)* demonstrated that scintigraphy with ^{111}In-DOTANOC showed higher tumour uptake than was attained with ^{111}In-octreotide in most patients. Unfortunately, background uptake was also high, which resulted in reduced tumour-to-background uptake ratios in 29 of 31 patients. PRRT with ^{177}Lu-DOTANOC resulted in tumour remission in one patient with follicular thyroid carcinoma who received 32.5 GBq and clinical improvement in one patient with Hürthle-cell thyroid carcinoma who received 14.3 GBq. Another study with ^{177}Lu-DOTANOC also seemed to indicate increased uptake in normal tissues, which resulted in an increase in the total-body dose compared with ^{177}Lu-octreotate *(47)*.

Preliminary data have been presented from a study that used ^{90}Y-octreotate *(48, 49)*. However, the treatment protocols varied and the method of response evaluation was not clearly defined. The reported results included an objective response rate of 37% and stabilisation of the disease in 39 of 75 patients (52%). In the same study, intra-arterial use of ^{90}Y-octreotate in five patients was described; however, no detailed results for this application were provided. An important issue is that, to date, reliable ^{90}Y-octreotate dosimetry is lacking.

Comparison of the therapy studies

Comparisons of the treatment effects of ^{90}Y-DOTATOC and ^{177}Lu-octreotate are very difficult, as a randomised, comparative trial has not yet been performed; however, the results obtained to date are very encouraging.

A substantial difference exists between studies that have assessed ^{90}Y-DOTATOC treatment in terms of the reported percentages of patients with tumour remission. A number of factors may account for this variation. First, the administered doses and dosing schemes can be different (dose-escalating versus fixed doses). Second, patients' and tumours' characteristics that determine treatment outcome could have a role, such as the amount of uptake on ^{111}In-octreotide scintigraphy, the total tumour burden, the extent of liver involvement, weight loss, Karnofsky performance status, and the type of neuroendocrine tumour *(5, 6, 19)*. Remission was more frequent in gastrinomas than in nonfunctioning pancreatic endocrine tumours and carcinoids in one study *(5)*, because gastrinomas often have high tumour uptake on pretherapy somatostatin-receptor scintigraphy. Conversely,

patients with functioning pancreatic neuroendocrine tumours tend to have a short time to progression and a poor prognosis *(6)*. Third, patients with a wide spectrum of somatostatin-receptor-positive tumours were treated in the various studies, and no details of the results of therapy were provided for the specific subgroups. Differences in selection of patients might, therefore, influence treatment outcome. Fourth, methodological factors could contribute to the different results of trials with the same compounds; for example, differences in tumour-response criteria and scoring of centralised versus decentralised follow-up CT. Clearly, a vital factor in the design of randomised trials is the use of detailed protocols to establish which treatment scheme and which radiolabelled somatostatin analogues or combinations of analogues are optimal.

WHEN SHOULD TREATMENT BE GIVEN?

In our study with ^{177}Lu-octreotate *(6)*, we treated patients with progressive disease at baseline and those with stable disease or in whom disease progression was not documented. Our rationale was that waiting for disease progression might have led to a serious deterioration of the clinical condition of many of these patients.

The chances of successful treatment are improved if patients are treated at an early stage of their disease, as tumour remission was positively correlated with a limited number of liver metastases, whereas disease progression was more frequent in patients with a low performance status and a high tumour load than in those without either characteristic *(5)*. In contrast to our early report in a small group of patients *(30)*, the percentage of patients who attain disease remission does not differ between those who have disease progression at baseline and those who have not *(6)*.

Two different treatment strategies can be considered. The first is to start PRRT as soon as inoperable disease has been diagnosed, regardless of progression. Alternatively, PRRT can be started only when progression is observed during close clinical and diagnostic monitoring of patients. At present, we defer PRRT until progression is observed in patients whose tumour burden is not too high. In future, a randomised trial will need to be conducted in patients who are in good clinical condition but without proven progression, to compare the effects of early initiation of PRRT with those observed when PRRT is withheld until progression is documented.

FUTURE DIRECTIONS

Further studies are needed that try to cure patients with metastasised GEPNETs. Complete remissions are infrequently achieved in clinical studies, a situation that contrasts with that

in animal studies *(25)*. One of the most important factors is that high doses of radioactivity are used in animal studies, which would result in kidney failure if the animals were kept alive long enough. Such high doses are currently not achievable in patients. Other factors may also have a role: most studies use animals with one or two subcutaneous, xenograft tumours, whereas patients generally have extensive visceral tumour loads; as a consequence, different animal models may be needed.

One way to improve the results of ^{177}Lu-octreotate or other radiolabelled somatostatin-analogue therapies is to reduce the amount of radiation to normal tissues, such as kidneys and bone marrow, or to reduce unwanted effects, which would allow the cumulative dose of radioactivity to be increased. In clinical practice, PRRT should always be administered with renal-protective agents—either lysine and arginine or a commercially available mixture of amino acids *(50)*. These amino acids reduce renal uptake of radioactivity in the proximal tubuli. Animal studies indicate that the addition of gelofusin to lysine and arginine could further decrease renal uptake *(51)*.

Another possible way to reduce the toxic effects of radiation on normal tissues is administration of amifostine. This agent is used to reduce the adverse effects of external-beam radiation therapy, and probably does not affect its therapeutic results *(52)*. Amifostine is a prodrug that must be metabolised to become active as a cytoprotective agent. Conversion to the active form is less effective in tumour cells than in normal tissue, so amifostine preferentially protects healthy tissues. Coadministration of amifostine with high-activity ^{177}Lu-octreotate clearly reduced functional renal damage in animal studies, although the effects on bone marrow are unclear *(53)*. Studies of PRRT and amifostine in patients have yet to be performed.

The use of several different radiolabelled somatostatin analogues in the same patient can be considered. Animal experiments clearly showed that ^{90}Y-labelled somatostatin analogues might be most effective for large tumours, whereas ^{177}Lu-labelled somatostatin analogues might be most effective for small tumours. In a study in animals with various tumour sizes, combined therapy with ^{90}Y-labelled octreotate and ^{177}Lu-labelled octreotate resulted in better remission rates than were achieved with either agent alone *(54)*.

Methods to increase the density of somatostatin receptors on tumours could be an interesting strategy. External irradiation upregulated expression of somatostatin and gastrin receptors in a pancreatic tumour cell line, *in vitro* and *in vivo (55)*. *In vitro* studies in human small-cell lung-cancer cells showed increased binding of ^{177}Lu-octreotate to tumour cells and increased somatostatin-receptor subtype 2 mRNA after irradiation *(56)*. Capello *et al. (57)*, demonstrated increased somatostatin-receptor density on tumours after PRRT with ^{111}In-octreotide at the time of tumour regrowth in animals. Similar results were achieved with low-dose ^{177}Lu-octreotate *(58)*. At present, no data from patients are available on this strategy.

The development of hybrid molecules is a novel way to improve treatment outcomes. For example, somatostatin analogues can be linked to another molecule, such as a chemotherapeutic agent or an arginine–glycine–aspartate (RGD) peptide. RGD peptides inhibit the growth of new vessels and induce apoptosis by activation of caspase 3 *(59)*. A hybrid of an RGD peptide and the somatostatin analogue Tyr^3-octreotate was developed and bound to the chelator DTPA, which allowed labeling with ^{111}In. This hybrid molecule had increased tumouricidal effects *in vitro* when compared with ^{111}In-octreotate, possibly as a result of induction of apoptosis; caspase 3 activity was higher in cells incubated with the hybrid molecule than in those treated with ^{111}In-octreotate *(60)*. High renal uptake of the hybrid molecule was observed *(61,62)*. As a consequence, characteristics of nonradiolabelled RGD-DTPA-octreotate and RGD-octreotate (a hybrid peptide without the chelator) were also studied *(62)*. These hybrid molecules resulted in higher caspase 3 activity than that seen with DTPA-octreotate and could, therefore, be used to increase apoptosis in neuroendocrine tumour cells. Nevertheless, extensive phase I testing has not yet been performed for these hybrid peptides.

All clinical studies of PRRT to date have been performed with somatostatin-receptor agonists, which are internalised by tumour cells. This process was assumed to increase retention times. By contrast, somatostatin-receptor antagonists are not internalised and were thought to be inappropriate for therapy if radiolabelled. Ginj *et al*. *(63)*, demonstrated that tumour retention of a ^{111}In labelled somatostatin-receptor subtype 2 antagonist was almost double that of the agonist, ^{111}In-octreotate, during the first 24 h after administration. These results were unexpected, but potentially very promising. Unfortunately, no data were shown for the amount of radioactivity retained after 24 h, which is important for estimation of the total dose of radiation to the tumour. Furthermore, no data are available on its toxic effects and biodistribution in humans.

Another interesting option is to give PRRT immediately after surgical tumour resection in patients without evident metastases. This adjuvant use of PRRT could prevent tumour spread or inhibit growth of micrometastases *(64)*. A somatostatin analogue labelled with an Auger-electron emitter or an α-emitter could be used for such applications, given the very short penetration range of these particles in tissues and the high energy of α-particles. Nevertheless, the clinical value of this method remains to be investigated.

Use of radiosensitising chemotherapeutic agents, such as 5-fluorouracil or capecitabine, could also improve PRRT. ^{90}Y-labelled antibody radioimmunotherapy in combination with 5-fluorouracil was feasible and safe *(65)*. PRRT that used ^{111}In-octreotide combined with 5-fluorouracil resulted in a symptomatic response in 71% of patients with neuroendocrine tumours *(66)*. Other trials have used capecitabine, a prodrug of 5-fluorouracil, which has the advantage of oral administration. The enzyme thymidine phosphorylase is needed to convert capecitabine to 5-fluorouracil. Many tumours express high levels of this enzyme, which result in a higher concentration of 5-fluorouracil in tumours than in normal tissues.

In addition, irradiation can upregulate expression of thymidine phosphorylase. Grade 3 haematological or other toxic effects, such as hand–foot syndrome, are rare if capecitabine is used in fairly low doses (1.6–2.0 g/m^2 daily) *(67,68)*. In a pilot study of ^{177}Lu-octreotate administered in combination with capecitabine, haematological toxic effects and capecitabine-specific adverse events were rare *(69)*. These promising preliminary results were the basis for a randomised, clinical, multicentre trial to compare ^{177}Lu-octreotate with and without capecitabine in patients with GEPNETs, which is currently underway.

CONCLUSIONS

Few effective therapies exist for patients with inoperable or metastasised GEPNETs. PRRT with radiolabelled somatostatin analogues is a promising new option for these individuals, provided that tumoural uptake of these agents is adequate on pretreatment somatostatin-receptor scintigraphy. Treatment with any of the various labelled somatostatin analogues can result in symptomatic improvement, but reduction of tumour size is seldom achieved with ^{111}In-labelled somatostatin analogues. Large variation exists in the reported antitumour effects of ^{90}Y-DOTATOC between various studies, but an objective response was achieved in 9–33% of patients. With ^{177}Lu-octreotate, objective and minor responses were achieved in 29% and 16% of patients, respectively; stable disease was present in 35% and progressive disease in 20% of patients. High tumoural uptake of radioactivity on somatostatin-receptor scintigraphy and limited numbers of liver metastases were predictive factors for tumour remission. Adverse effects of PRRT are few and mostly mild, certainly when renal-protective agents are used: serious, delayed adverse effects, such as myelodysplastic syndrome or renal failure, are rare. The median duration of responses to therapy with ^{90}Y-DOTATOC and ^{177}Lu-octreotate is 30 months and 40 months, respectively. Treatment with ^{177}Lu-octreotate seems to confer a survival benefit of several years. The data on PRRT compare favourably with those on the few alternative treatment approaches, such as chemotherapy. A potential role for PRRT in the treatment of somatostatin-receptor-positive tumours other than GEPNETs has also been described. Large, randomised clinical trials of PRRT are still needed. Nevertheless, PRRT might soon become the therapy of choice for patients with metastatic or inoperable GEPNETs.

REVIEW CRITERIA

Articles for this Review were identified using PubMed (1990–2008) and abstracts from the American Society of Clinical Oncology, Society of Nuclear Medicine and European Association of Nuclear Medicine congresses. Search terms used were “carcinoid”, “neu-

roendocrine tumour", "pancreatic neuroendocrine tumour", "gastroenteropancreatic tumours", "somatostatin", "octreotide", "lanreotide", "octreotate", "DOTATOC", "DOTATATE", "DOTANOC," and "radionuclide therapy".

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Chapter 1.3

Aims and Outline

The aims of the studies presented in this thesis are to:

1) Evaluate the effects of regular therapy with ^{177}Lu-octreotate in patients with various types of somatostatin receptor positive tumours with regard to:
    a) treatment outcome
        i) anti-proliferative effects
        ii) duration of response
    b) toxicity profile and side effects

2) Evaluate these same effects of additional therapy with ^{177}Lu-octreotate

3) Evaluate the (sub-)acute toxicity profile of the combination of ^{177}Lu-octreotate and capecitabine

In **Chapter 2.1** the results of regular therapy with ^{177}Lu-octreotate in a large number of patients with gastroenteropancreatic neuroendocrine tumours are presented with analysis of treatment outcome, survival and toxicity. Survival data are compared with data from epidemiological and interventional studies. **Chapter 2.2** describes the effects of therapy with ^{177}Lu-octreotate in patients with neuroendocrine tumours derived from the foregut. These data are presented because metastasised foregut carcinoids tend to behave more aggressively than midgut carcinoids. In **Chapter 3,** the results of PRRT with ^{177}Lu-octreotate in patients with non-GEPNETs are described: patients with somatostatin receptor positive paraganglioma, meningioma, small cell lung carcinoma and melanoma were treated using the same protocol as in GEPNET patients. In **Chapter 4**, the results of additional therapy are presented in patients who developed progressive disease after an initial good response on regular therapy with ^{177}Lu-octreotate. To try to improve the therapy outcome of ^{177}Lu-octreotate in patients with GEPNET, a new study was initiated by adding capecitabine to ^{177}Lu-octreotate. **Chapter 5** presents the results of a pilot study assessing the toxicity profile of this new combination. **Chapter 6 and 7** provide a summary of the presented data in this thesis and a general discussion. Finally, **Chapter 8** is an appendix with a detailed description of acute hormonal crises after therapy with ^{177}Lu-octreotate and with a review article about PRRT in general with some more background information than mentioned in Chapter 1.2.

Chapter 2

Anti-Tumour Effects of Regular Therapy with ^{177}Lu-octreotate in Patients with Gastroenteropancreatic Neuroendocrine Tumours

Chapter 2.1

Treatment with the Radiolabelled Somatostatin Analogue [^{177}Lu-DOTA ^{0},Tyr ^{3}] octreotate: Toxicity, Efficacy, and Survival

Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, Feelders RA, van Aken MO, Krenning EP.

J Clin Oncol. 2008;26:2124-2130.

ABSTRACT

Purpose

Despite the fact that most gastroenteropancreatic neuroendocrine tumours (GEPNETs) are slow-growing, median overall survival (OS) in patients with liver metastases is 2 to 4 years. In metastatic disease, cytoreductive therapeutic options are limited. A relatively new therapy is peptide receptor radionuclide therapy with the radiolabelled somatostatin analogue [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. Here we report on the toxicity and efficacy of this treatment, performed in over 500 patients.

Patients and methods

Patients were treated up to a cumulative dose of 750 to 800 mCi (27.8-29.6 GBq), usually in four treatment cycles, with treatment intervals of 6 to 10 weeks. Toxicity analysis was done in 504 patients, and efficacy analysis in 310 patients.

Results

Any haematologic toxicity grade 3 or 4 occurred after 3.6% of administrations. Serious adverse events that were likely attributable to the treatment were myelodysplastic syndrome in three patients, and temporary, nonfatal, liver toxicity in two patients. Complete and partial tumour remissions occurred in 2% and 28% of 310 GEPNET patients, respectively. Minor tumour response (decrease in size > 25% and < 50%) occurred in 16%. Median time to progression was 40 months. Median OS from start of treatment was 46 months, median OS from diagnosis was 128 months. Compared with historical controls, there was a survival benefit of 40 to 72 months from diagnosis.

Conclusion

Treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate has few adverse effects. Tumour response rates and progression-free survival compare favourably to the limited number of alternative treatment modalities. Compared with historical controls, there is a benefit in OS from time of diagnosis of several years.

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumours (GEPNETs) are relatively rare. The two most common types of GEPNETs, carcinoids and pancreatic neuroendocrine tumours, have incidence rates of one to 2.5 in 100,000 population per year and approximately one in 100,000 population per year, respectively *(1-8)*. However, since 5-year survival rates in patients with GEPNETs, irrespective of stage of disease, are over 60% *(5,8-11)*, their prevalence is much higher. Despite the fact that most GEPNETs are slow-growing tumours, and the popular notion that these are relatively benign tumours, median overall survival (OS) in patients with metastatic liver disease is 2 to 4 years *(9,11-14)*. In this respect, data from an analysis in over 10,000 carcinoid patients, reporting nonlocalised disease at diagnosis in 32% to 47% of cases, is of great impact *(8)*. This finding is in line with another epidemiological study that reports liver metastases at diagnosis in 22% to 33% of cases *(5)*. Also, metastases may become apparent only years after the initial presentation of a carcinoid.

In case of metastatic disease, cytoreductive therapeutic options are limited. A relatively new therapy is peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues. Here we report on the toxicity and efficacy of treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate), performed in over 500 patients with somatostatin receptor–expressing tumours. The radionuclide ^{177}Lu has a half-life of 6.7 days and emits both β-radiation and γ-radiation, allowing imaging and dosimetry after therapy. Here we present long-term follow-up and survival data in over 300 patients with GEPNETs and compare these to historical controls and published results for other treatment modalities in comparable patient groups.

PATIENTS AND METHODS

Patients

From January 2000 to August 2006, 1,772 treatments were given in 504 patients who were treated according to protocol. Tumour types were divided into carcinoids, pancreatic neuroendocrine, and neuroendocrine of unknown origin. Gastrinoma, insulinoma, and vasoactive intestinal peptide-secreting tumour (VIPoma) were only used in case of syndromes caused by hormonal hypersecretion. Inclusion criteria were tumour uptake during [^{111}In-DTPA^{0}]octreotide scintigraphy (OctreoScan, Mallinckrodt, Petten, the Netherlands) preceding the therapy that was at least as high as that in normal liver tissue, no prior treatment with other radiolabelled somatostatin analogues, serum haemoglobin ≥ 6 mmol/L, WBC count ≥ 2 x 10^{9}/L, platelet count ≥ 75 x 10^{9}/L, serum creatinine concentration ≤ 150

μmol/L or creatinine clearance ≥ 40 mL/min, and Karnofsky performance status (KPS) ≥ 50.

Preliminary results in 131 patients with GEPNETs were also reported previously *(15)*. All patients gave written informed consent to participate in the study, which was approved by the hospital's medical ethical committee.

Methods

[DOTA^0,Tyr^3]octreotate was obtained from Mallinckrodt, St Louis, MO. $^{177}LuCl_3$ was obtained from NRG, Petten, the Netherlands and Missouri University Research Reactor (MURR) and was distributed by IDB-Holland, Baarle-Nassau, the Netherlands. ^{177}Lu-octreotate was locally prepared as described before *(16)*.

Granisetron 3 mg or ondansetron 8 mg was injected intravenously and an infusion of amino acids (lysine 2.5%, arginine 2.5% in 1 L 0.9% NaCl; 250 mL/h) was started 30 minutes before the administration of the radiopharmaceutical and lasted 4 hours. The radiopharmaceutical was coadministered via a second pump system. Cycle dosages were 100 mCi (3.7 GBq) in seven patients, 150 mCi (5.6 GBq) in 16, and 200 mCi (7.4 GBq) in the remaining patients, injected in 30 minutes. The interval between treatments was 6 to 10 weeks. Patients were treated up to a cumulative dose of 750 to 800 mCi (27.8 to 29.6 GBq; corresponding with a radiation dose to the bone marrow of 2 Gy) *(16)*, unless dosimetric calculations indicated that the radiation dose to the kidneys would then exceed 23 Gy; in these cases the cumulative dose was reduced to 500 to 700 mCi.

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

In vivo measurements

The tumours on CT or MRI were measured and scored according to the Southwest Oncology Group solid tumour response criteria *(17)*, with the addition of the tumour response class minimal response (MR), pertaining to a decrease in summed squares of tumour diameters more than 25%, but less than 50%. The uptake during pretreatment [^{111}In-DTPA^0]octreotide scintigraphy was scored visually on planar images on a 3-point scale; grade 2: equal to normal liver tissue; grade 3: greater than normal liver tissue; grade 4: higher than normal spleen or kidney uptake.

Statistics

Analysis of variance (ANOVA), paired *t* tests, χ^2 tests (or, if applicable, Fisher's exact tests), Pearson's correlation tests, and logistic regression were used. For survival analysis, log-rank tests and Cox regression models were used.

RESULTS

Toxicity

In the 504 patients, acute adverse effects occurring within 24 hours after the administration of the radiopharmaceutical were nausea after 25% of administrations, vomiting after 10%, and abdominal discomfort or pain after 10%. Six patients were hospitalised within 2 days of the administration because of hormone-related crises. All recovered after adequate care (see Chapter 8.1).

Subacute, haematological toxicity, WHO grade 3 or 4, occurred 4 to 8 weeks after 3.6% of administrations, or, expressed patient-based, after at least one of several treatments in 9.5% of patients. Temporary hair loss (WHO grade 1; no baldness) occurred in 62% of patients.

Serious delayed toxicities were observed in nine patients. There were two cases of renal insufficiency, both of which were probably unrelated to ^{177}Lu-octreotate treatment. One patient had pre-existent kidney function deterioration and the other had increasing tricuspid valve insufficiency. There were three patients with serious liver toxicity. In one patient with diffuse liver metastases, liver functions deteriorated in the weeks following the first administration. The patient died of hepatic failure after 5 weeks. Because this patient experienced a similar deterioration due to rapid tumour growth after his previous course of chemotherapy, the liver failure after ^{177}Lu-octreotate treatment was considered more likely tumour growth–related than radiation induced. Two other patients, who both had multiple liver metastases, had temporary rises in serum ALT, AST, and bilirubin concentrations. In both patients, this condition resolved without causative treatment and both resumed treatment at half doses uneventfully. Lastly, myelodysplastic syndrome (MDS) occurred in four patients. In one patient, previous chemotherapy with alkylating agents was the more likely cause of MDS. In the other three patients, MDS was diagnosed 2 to 3 years after the last treatment with ^{177}Lu-octreotate, and was probably treatment related.

Efficacy

Of the 504 patients, 458 had GEPNETs. Of these, 19 were withdrawn from the study at their own request, because of treatment-unrelated morbidity, or treatment and tumour unrelated death. In two patients, treatment was stopped because of persisting thrombocytopenia. At the time of the analysis, another 79 patients were still being treated or waiting for their first or confirmatory imaging study results. Thirty-seven foreign patients were lost

Table 1. Patient, treatment, and tumour characteristics in patients with GEP tumour (*n*= 310).

Characteristic	Yes		No		Unknown	
	No. of patients	%	No. of patients	%	No. of patients	%
Male	164	53	146	47		
Somatostatin analogue use at referrral	174	56	136	44		
Age ≥ 70 *	45	15	265	85		
KPS ≤ 70 *	39	13	271	87		
Previous surgery	153	49	157	51		
Previous radiotherapy	16	5	294	95		
Previous chemotherapy	52	17	258	83		
Previous somatostatin analogue use	168	54	142	46		
Tumour type gastrinoma/insulinoma/VIPoma *	19	6	291	94		
Baseline tumour progression *	133	43	80	26	97	31
Baseline weight loss *	75	24	235	76		
Liver metastases	276	89	34	11		
Bone metastases *	68	22	242	78		
Ascites *	10	3	300	97		
Tumour uptake on baseline OctreoScan, grade *						
4	72	23				
3	232	75				
2	6	2				
Tumour mass on baseline OctreoScan [a]						
Extensive	69	22				
Moderate	204	66				
Limited	37	12				
Liver involvement on baseline CT/MRI [a]						
Extensive	85	27				
Moderate	191	62				
Absent	34	11				

Abbreviations: *GEP*, gastroenteropancreatic; *KPS*, Karnofsky performance status; *CT*, computed tomography; *VIPoma*, vasoactive intestinal peptide-secreting tumour; *MRI*, magnetic resonance imaging.
* Refers to inclusion in multivariate analyses mentioned in the text.

to follow-up after completing their therapy. Lastly, 11 patients did not have tumours that could be measured reliably.

Patient characteristics of the remaining 310 patients are listed in Table 1. There were 164 men and 146 women; mean age at treatment start was 59 years (range, 21 to 85 years).

Forty-seven patients did not receive their intended total cumulative dose of ^{177}Lu-octreotate. In 37, this was because of evident clinical disease progression or death. Treatment responses according to tumour type at 3 months after the last therapy cycle are listed in Table 2. Overall objective tumour response rate, comprising complete response (CR), partial response (PR), and MR, was 46%. Response rates in patients with gastrinomas, insulinomas, VIPomas and nonfunctioning pancreatic NETs were higher than in carcinoid tumour patients. CRs were only called if both conventional imaging (CT scanning or MRI) and the OctreoScan had normalised.

Potential prognostic factors for predicting tumour remission (CR, PR, or MR) as treatment outcome, that were analysed using (multivariate) logistic regression are marked with an asterisk in Table 1. Two significant factors resulted: uptake on the OctreoScan ($P < 0.01$), and KPS greater than 70 ($P < 0.05$).

A small percentage of patients who had either SD or MR at their first two evaluations after therapy, had a further improvement in categorised tumour response at 6 months and 12 months follow-up, occurring in 4% of patients and 5% of patients, respectively.

Three of four patients with clinically nonfunctioning neuroendocrine pancreatic tumours that were judged inoperable before treatment with ^{177}Lu-octreotate, and who had

Table 2. Tumour responses in patients with GEPNETs, 3 months after the last administration of ^{177}Lu-octreotate ($n = 310$).

Tumour type	Response										Total no. of patients
	CR		PR		MR		SD		PD		
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	
Carcinoid	1	1	41	22	31	17	78	42	37	20	188
Nonfunctioning pancreatic	4	6	26	36	13	18	19	26	10	14	72
Unknown origin			10	32	3	10	7	23	11	36	31
Gastrinoma			5	42	4	33	2	17	1	8	12
Insulinoma			3	60			1	20	1	20	5
VIPoma			1	50					1	50	2
Total	5	2	86	28	51	16	107	35	61	20	310

Abbreviations: *GEPNETs*, gastroenteropancreatic neuroendocrine tumours; *CR*, complete response; *PR*, partial response; *MR*, minimal response; *SD*, stable disease; *PD*, progressive disease; *VIPoma*, vasoactive intestinal peptide-secreting tumour.

PR, were successfully operated 6 to 12 months after their last treatment, whereas one died of postoperative complications.

Time to progression and survival

In the 249 patients who did not have progressive disease (PD) as treatment outcome, median time to progression was 40 months from start of treatment. Time to progression was analysed using Cox multivariate regression model, including the variables that are marked with an asterisk in Table 1, with an additional dichotomous variable indicating whether stable disease (SD) or remission (CR, PR, or MR) was the primary treatment outcome. Significant factors were the presence of bone metastases ($P < 0.001$), extent of liver involvement ($P = 0.001$), and gastrinoma, insulinoma, or VIPoma tumour type ($P < 0.01$).

Table 3. Significant factors predicting disease-specific survival in patients ($n = 310$).

Factor	No. of patients	Survival (months)	*p*-value
Treatment outcome			
PD	61	11	
SD	107	> 48	< 0.001
Remission	142	> 48	
Liver involvement			
Extensive	85	25	
Moderate	191	> 48	< 0.001
None	34	> 48	
KPS ≤ 70			
Yes	39	16	
No	271	> 48	0.001
Baseline weight loss			
Yes	75	30	
No	235	> 48	0.001
Presence of bone metastases			
Yes	68	37	
No	242	> 48	0.004
Tumour type gastrinoma/ insulinoma/VIPoma			
Yes	19	33	
No	291	> 48	0.04

NOTE. Significance levels pertain to Cox regression with analysis of more factors than are listed in the Table, and which are listed in Table 1and are marked with an asterisk.
Abbreviations: *PD*, progressive disease; *SD*, stable disease; *KPS*, Karnofsky performance status; *VIPoma*, vasoactive intestinal peptide-secreting tumour.

Median OS in our 310 GEPNET patients was 46 months (median follow-up 19 months; 101 deaths). Median disease related survival was more than 48 months (median follow-up 18 months; 81 deaths). Median progression-free survival was 33 months. Survival analysis using Cox regression and using the factors from Table 1 marked with an asterisk, with in addition a variable indicating whether initial tumour response was PD, SD, or remission (CR, PR, or MR), resulted in the same six significant factors both for OS and for disease-specific survival (Table 3). The most important factor predicting survival was treatment outcome (Fig 1). Median time from diagnosis to referral was 21 months, median follow-up from diagnosis 48 months. Median OS from diagnosis was 128 months, median disease-specific survival was more than 180 months.

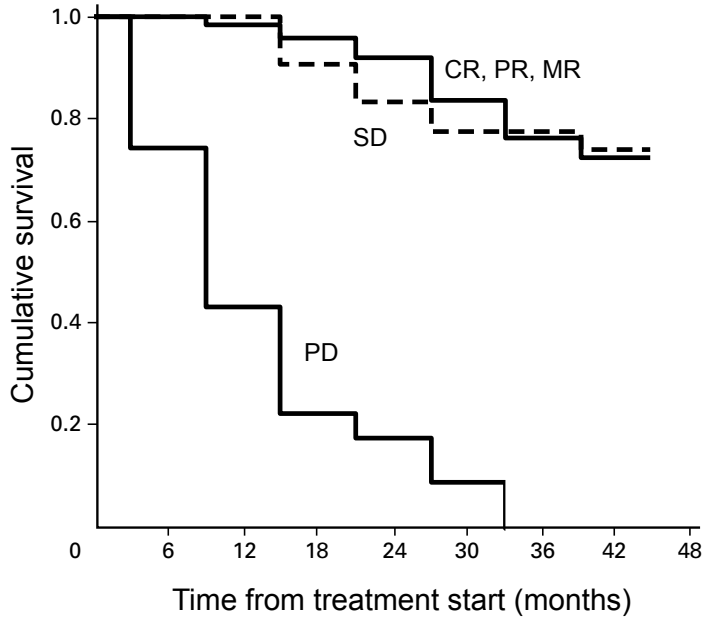

Figure 1. Disease-related survival in 310 patients according to treatment outcome. Patients with progressive disease (PD) have significantly shorter survival. Survival between other treatment outcomes did not differ significantly.
Abbreviations: *CR*, Complete response; *PR*, Partial response; *MR*, Minimal response; *SD*, Stable disease.

DISCUSSION

From our data, we conclude that the treatment with ^{177}Lu-octreotate has few adverse effects and is relatively safe. With adequate clinical scrutiny, patients who have an increased risk to develop hormone-related crises can be identified and adequate measures to contain such events can be taken. Less dramatic acute adverse effects, like nausea and vomiting, occur in a minority of patients and can usually be successfully countered by administering additional antiemetics. Also, serious haematologic toxicity is rare. Other, delayed, serious adverse events that were likely caused by the therapy with ^{177}Lu-octreotate, comprising MDS and liver toxicity, were rare and occurred in approximately 1% of patients. The MDS cases require further attention and indicate that either the radiation absorbed dose to the bone marrow or the susceptibility of the stem cells to radiation varies between patients. Models, based on the biodistribution of radioactivity in the individual patient, will therefore have to be developed for future optimisation of this therapy. Using such individualised dosimetry for kidney radiation–absorbed doses, in combination with kidney-protective amino acid infusion, resulted in the absence of serious kidney toxicity in any of our patients. Such renal toxicity has been reported in patients treated with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide, especially if no amino acids were coadministered *(18-20)*.

We found tumour size reductions, including MR, in 46% of our patients. MR was included as a separate response class because of the usual slow growth of GEPNETs, and their often partly cystic appearance, making major tumour size reductions less likely than in fast growing solid tumours after, for instance, chemotherapy or external-beam radiation. PR and CR were observed in 30% of patients. This percentage compares favourably to recent chemotherapy studies in GEPNETs, which mostly report CR and PR in less than 20% of patients. Also, the duration of the response, progression-free survival and OS are more favourable after ^{177}Lu-octreotate (Table 4).

Antiproliferative treatment options for patients with inoperable GEPNETs are limited. Somatostatin analogues, interferon-α, and their combination have their specific merit in reducing symptomatology from hormonal overproduction by GEPNETs. However, CT-assessed responses are rare, occurring in less than 5% to 10% of cases *(31-33)*. Other, nonsystemic, local ablative therapies for liver metastases are radiofrequency ablation (RFA), and liver embolisation or chemoembolisation. Studies in usually small patient series report objective response rates of 30% to 80% with response durations of 6 to 42 months (*34*). Recent single centre overviews in larger series of over 50 patients report symptomatic relief, with a mean duration of 11 months, in 70% of patients after RFA, but no data on objective responses *(11)*, whereas an objective response was found in 37% of patients after chemoembolisation, with a median duration of 14 months *(35)*. Serious procedure-related morbidity was reported in 5% of patients after RFA, and in 10% of

Table 4. Results of recent chemotherapy reports compared with treatment with ^{177}Lu-octreotate.

Regimen	Tumour type	No. of patients	PR/CR (%)	Median PFS (months)	Median OS (months)	Study (year)
STZ + doxorubicin	PNET	16	6	NA	NA	Cheng (1999) *(21)*
Dacarbazine	Carc	56	16	NA	20	Bukowski (1994) *(22)*
Dacarbazine	Carc	7	14	NA	NA	Ritzel (1995) *(23)*
FU + IFN-α	Carc/PNET	24	21	8	23	Andreyev (1995) *(24)*
Mitoxantrone	Carc/PNET	30	7	NA	16	Neijt (1995) *(25)*
Paclixatel	Carc/PNET	24	4	3	18	Ansell (2001) *(26)*
STZ + FU + doxorubicin	PNET	84	39	18	37	Kouvaraki (2004) *(27)*
Doxorubicin + FU	Carc	85	13	5	16	Sun (2005) *(28)*
STZ + FU	Carc	78	15	5	24	Sun (2005) *(28)*
Irinotecan + FU	Carc/PNET	20	5	5	15	Ducreux (2006) *(29)*
Oxaliplatin + capecitabine	Well-differentiated NET	27	30	NA	40	Bajetta et al (2007) *(30)*
^{177}Lu-octreotate	Carc/PNET	310	30	32	46	Present results

Abbreviations: *STZ*, streptozotocin; *FU*, fluorouracil; *IFN-α*, interferon-α; *PNET*, pancreatic neuroendocrine tumour; *Carc*, carcinoid; *PFS*, progression-free survival; *OS*, overall survival; *NA*, not available.

patients after chemoembolisation. Clearly, these serious adverse effects are fewer in our patients treated with ^{177}Lu-octreotate, and also the response duration is longer. Also, it is of note to realise that both methods, RFA and chemoembolisation, are performed only if major tumour load is restricted to the liver. In addition to other criteria relating to tumour size and number, intact portal bloodflow, and tumour localisation in relation to blood vessels have to be met.

Treatment with the radiolabelled somatostatin analogue [^{90}Y-DOTA^0,Tyr^3]octreotide has been and is still performed in a number of centres. PR and CR have been reported in 8% to 33% of patients, mostly in small patient groups *(19,36-39)*. Differences in treatment outcome evaluation (Response Evaluation Criteria in Solid Tumours, WHO, versus Southwest Oncology Group criteria), but especially patient inclusion bias, may account for this. In the present analysis, the two significant factors predicting favourable treatment outcome were high patient performance score and high uptake on the pretreatment OctreoScan. It is obvious that different studies can only be reliably compared if stratification for these factors is applied. From the published data, such stratified comparison cannot be performed. In our own institution, CT-assessed CR/PR occurred in only 8% of patients after treatment with [^{90}Y-DOTA^0,Tyr^3]octreotide *(39)*. Also, when we compared the residence time in tumours for [^{177}Lu-DOTA^0,Tyr^3]octreotide and [^{177}Lu-DOTA^0,Tyr^3]octreotate in the same patients in a therapeutical setting, we found a factor of 2.1 in favour of [^{177}Lu-DOTA^0,Tyr^3] octreotate *(40)*. Therefore, we think that ^{177}Lu-octreotate is the radiolabelled somatostatin analogue of choice when performing PRRT.

In a small number of patients who had inoperable pancreatic NETs that had not metastasised, tumour shrinkage subsequent to treatment with ^{177}Lu-octreotate made these patients candidates for surgery. This neoadjuvant use of PRRT, although applicable in select cases only, is of great interest, as it may cure such patients.

An important feature of the tumour response after treatment with ^{177}Lu-octreotate that we observed, is that the eventual maximal shrinkage of the tumour may take months after completing the therapy. This is most likely due to the slow growing nature of these tumours; radiation biology axioms state that radiation damage to the DNA usually results in cell death only after their reproductive integrity is tested by one or more attempts at mitotic division *(41)*. Therefore, if such attempts at cell division are few, tumour size reduction will be slow.

Time to progression in patients having CR, PR, MR, or SD was significantly shorter for patients having high tumour load in the liver or having bone metastases. These are well-known prognostic factors of poor disease evolution. More puzzling is the fact that patients with gastrinoma, VIPoma, or insulinoma had significantly shorter response durations than other patients. A faster growth pattern of tumour cells must be assumed, but direct comparisons for tumoural growth between these tumours and other NETs, like carcinoids, are lacking.

Median OS was shorter in patients having a poor performance score and those having extensive liver involvement. This implies that treatment with ^{177}Lu-octreotate should preferably be started early in the disease evolution. Because neuroendocrine tumours can be clinically stable for years, however, it is, in our opinion, good clinical practice to wait for signs of disease progression if the tumour load is moderate. Such signs should not be restricted to CT-assessed tumour growth, but also include rises in serum tumour markers, increase in symptoms, or involuntary weight loss. In patients with limited tumour load and in whom cure is potentially possible, treatment should be initiated without further delay, and the same holds true for patients with extensive tumour load, hepatomegaly, or significant weight loss, when waiting for formally assessed tumour progression would place these patients in an unfavourable starting position for treatment or would even qualify them as ineligible.

We found OS and disease-specific survival at and above 48 months. Because the treatment with ^{177}Lu-octreotate is still open for new patients, and median follow-up in relation to survival is relatively short, we also analysed our local Dutch patients separately, with subgroups that had longer follow-up. Also in these analyses, OS and disease-specific survival time were consistently at or above 48 months (data not shown). Comparing survival data in our group, either from time of diagnosis or from time of referral, with data from different epidemiologic studies or studies pertaining to a specific intervention, and limiting our data to similar subgroups of patients, we found a benefit in OS for patients treated with ^{177}Lu-octreotate, which ranged from 40 to 72 months from diagnosis (Table 5). Of course,

Table 5. Survival data in patients with neuroendocrine tumours.

Study	Study population	Period	No. of patients	Specific intervention	Median OS from referral (months)	Median OS from diagnosis (months)	Comments
Clancy *et al. (9)*	WDEC	1997-2003	137	—		72	Mean Alk Phos 155 U/L
	This study		310			128	Mean Alk Phos 214 U/L
	WDEC, Alk Phos < 127		67		51		
	This study		139		> 48		
	WDEC, Alk Phos > 127		46		19		
	This study		167		37		
Janson *et al. (10)*	Carcinoid	1978-1993	256	—		92	19% had no lesions on imaging studies (K. Oberg, personal communication, 2007)
Idem, update		1993-2005	304	—		115	
	This study		188			155	
Quaedvlieg *et al. (5)*	Dutch patients with carcinoid liver metastases at diagnosis	1992-1997	58	—		43	
	This study		100			97	
Chu *et al. (12)*	PNET with liver metastases	1970-2001	29	—	25		Concomitant chemotherapy in most
	This study		76		44		
Mazzaglia *et al. (11)*	Carcinoid liver metastases	1996-2005	35	RFA	47	82	Concomitant chemo/biotherapy in most
	This study		172		> 48	154	
	PNET liver metastases		18	RFA	35	54	
	This study		76		44	94	
Gupta *et al. (13)*	Carcinoid liver metastases	1992-2000	69	(Chemo)-Embol	34		
	This study		172		> 48		
	PNET liver metastases		54	(Chemo)-Embol	23		
	This study		76		44		
Ho *et al. (14)*	Carcinoid/PNET liver metastases	1991-2005	46	(Chemo)-Embol	33		
	This study		276		45		

Abbreviations: *OS*, overall survival; *WDEC*, well-differentiated endocrine carcinoma; *Alk Phos*, serum alkaline phosphatase concentration; *RFA*, radiofrequency ablation; *PNET*, pancreatic neuroendocrine tumour; *Embol*, embolisation.

our patients were selected on the basis of a positive somatostatin receptor status of their tumours. In theory, not including patients with poorly differentiated, somatostatin receptor–negative tumours in our series could have caused a selection bias. We therefore also calculated OS for the subgroups listed in Table 5 with the addition of fictitious patients with a survival of 6 months from diagnosis, assuming their incidence at 5% of patients. (The incidence of poorly differentiated NETs is estimated at < 3% for foregut NETs *(42)*). Even with these assumptions, the survival benefit for patients treated with ^{177}Lu-octreotate was 23 to 69 months (data not shown). We are aware that comparisons with historical controls should be interpreted with caution, but we also think that such a consistent difference with many other reports in similar patient groups cannot be ignored, and is most probably caused by a real difference in survival.

In conclusion, the therapy with ^{177}Lu-octreotate has few serious adverse effects and can be regarded safe. Tumour response rates and progression-free survival compare favourably to the limited number of alternative treatment modalities in patients with inoperable or metastasised GEPNETs. Compared to historical controls, there is a benefit in OS of several years from time of diagnosis.

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Chapter 2.2

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: ≥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.

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 radiolabelled somatostatin analogues, e.g. [^{177}Lu-DOTA^{0},Tyr^{3}]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 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 adrenocorticotropic 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 ≥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 scintgraphy (OctreoScan) 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 ≥ 2 x 10^9/L, platelets ≥ 80 x 10^9 /L, creatinine ≤150 µmol/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). $^{177}LuCl_3$ 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 ≥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 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).

Table 1. Patient characteristics at baseline.

	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)

Table 1. Patient characteristics at baseline. (continued)

	Bronchial carcinoid	Gastric carcinoid	Thymic carcinoid
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

[a] Four typical bronchial carcinoids, five atypical bronchial carcinoids
[b] Progression documented in 12 months before treatment
Abbreviations: *KPS,* Karnofsky performance score; *PD*, progressive disease; *SD*, stable 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%	
Moderate	69%	62%	0.74
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-DTPA^{0}]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.
[a] Fisher's exact test or Pearson χ^2 test
Abbreviation: *KPS*, Karnofsky performance score

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 a MR. Two patients had stable

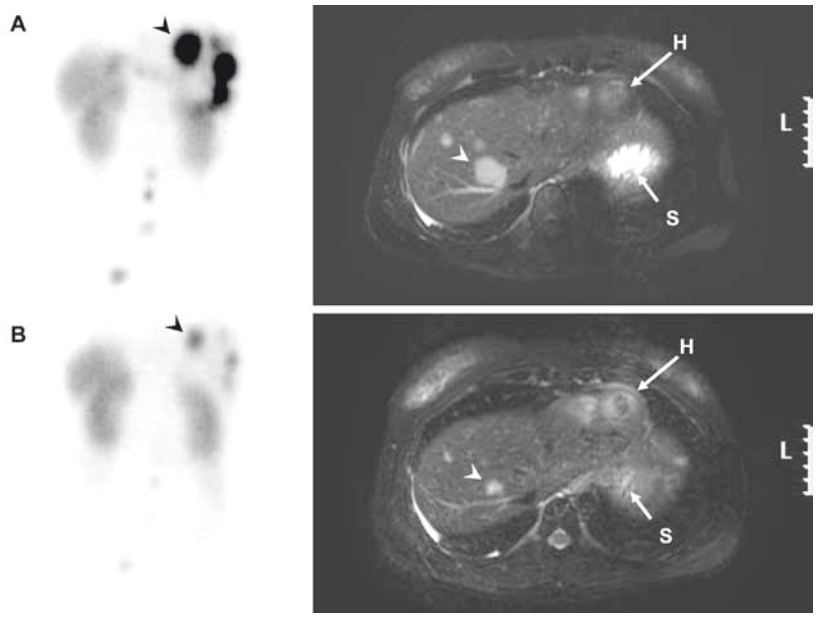

Figure 1. Treatment response with ^{177}Lu-octreotate in a patient with a metastasised bronchial carcinoid (*H* heart, *S* stomach). **(A)** Scintigraphy 24 h after the first dose of ^{177}Lu-octreotate (*left panel*) and MRI 6 weeks before starting treatment (*right panel*): the *arrowhead* indicates 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*)

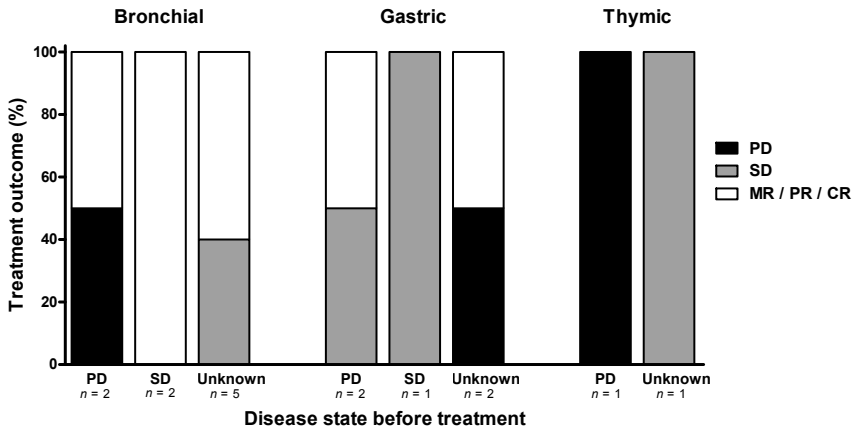

Figure 2. Effects of therapy with ^{177}Lu-octreotate in groups of carcinoid tumours in relation to disease status before treatment.
Abbreviations: *CR*, Complete remission; *MR*, Minor response; *PD*, Progressive disease; *PR*, Partial remission; *SD*, Stable disease.

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.

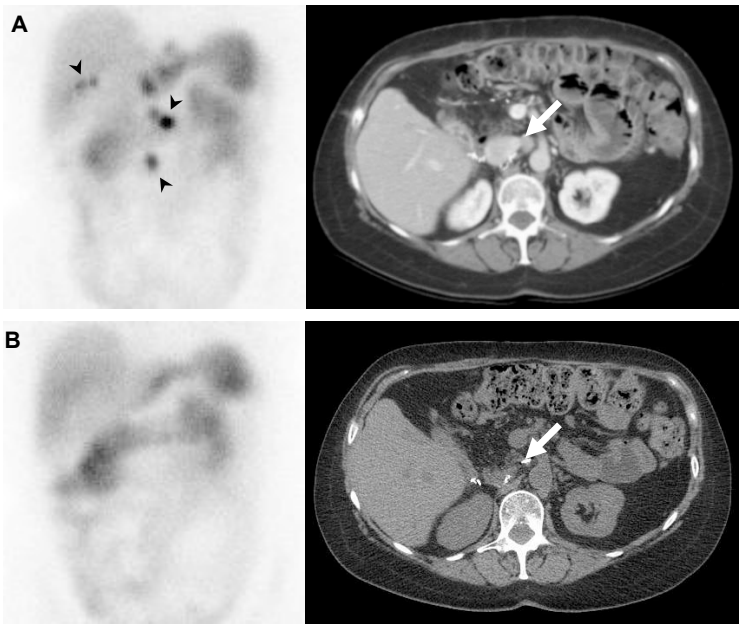

Figure 3. Treatment response with ^{177}Lu-octreotate in a patient with a metastasised gastric carcinoid. **(A)** Scintigraphy 24 h after the first dose of ^{177}Lu-octreotate (*left panel*) demonstrates multiple metastases in the abdomen (*arrowheads*). CT 6 weeks before starting treatment (*right panel*) 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*)

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 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, $p > 0.05$).

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

Outcome	Bronchial carcinoid (*n*=9)	Gastric carcinoid (*n*=5)	Thymic carcinoid (*n*=2)	All patients (*n*=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)

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

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 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 (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 (sst_2) in neuroendocrine tumours of the lung suggested that sst_2 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 symptomatic 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) fail 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

Table 4. Overview of results of peptide receptor radionuclide therapy with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide and [^{111}In-DTPA^{0}]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	NA	2 SD, 1 PD
			1 Duodenum	NA	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	NA	1 PR (3 mo), 1 SD (13 mo)
			1 Stomach	NA	1 SD (10 mo)
Valkema *et al.* (*26*) [a]	^{90}Y-DOTATOC	5.1–32.6 GBq	2 Bronchus	2	2 PD
			2 Stomach	2	2 PD
			1 Thymus	1	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	3	2 SD, 1 PD
			1 Other [c]	1	1 MR

[a] Additional data obtained from original study database
[b] Not further specified
[c] Presumably derived from mucosa of sphenoid sinus
Abbreviations: *^{90}Y-DOTATOC*, [^{90}Y-DOTA^{0},Tyr^{3}]octreotide; *CR*, complete remission; *MR*, minor response; *NA*, not available; *PD*, progressive disease; *PR*, partial remission; *SD*, stable disease; *TTP*, time to progression.

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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Chapter 3

Effects of Therapy with [^{177}Lu-DOTA^{0}, Tyr^{3}] octreotate in Patients with Paraganglioma, Meningioma, Small Cell Lung Carcinoma, and Melanoma

van Essen M, Krenning EP, Kooij PP, Bakker WH, Feelders RA, de Herder WW, Wolbers JG, Kwekkeboom DJ.

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ABSTRACT

Purpose

Therapy using the radiolabelled somatostatin analogue [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate) (DOTA is 1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid) has been used primarily in gastroenteropancreatic neuroendocrine tumours. Here we present the effects of this therapy in a small number of patients with metastasised 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 tumour size were evaluated using the Southwest Oncology Group criteria.

Results

Two of 4 patients with progressive paraganglioma had tumour 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 tumour 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 tumours. 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 antitumour effects in patients with small lung carcinoma and melanoma.

INTRODUCTION

The radiolabelled somatostatin analogue [^{177}Lu-DOTA^{0},Tyr^{3}]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 tumours. Most of the treated patients had inoperable or metastasised gastroenteropancreatic neuroendocrine tumours (GEP NETs). An analysis of the effect of ^{177}Lu-octreotate treatment on 131 patients of this group reported tumour 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 favourably with chemotherapy for these indications *(1)*. ^{177}Lu-octreotate was also used in nonradioiodine–avid differentiated thyroid carcinoma. This therapy can be effective if uptake in tumour 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 tumours—such as paragangliomas, meningiomas, small cell lung carcinomas (SCLCs), and melanomas—may have somatostatin receptor subtypes as well, these tumours were investigated.

Paragangliomas are neuroendocrine tumours derived from (extra-)adrenal autonomic (para-)sympathetic ganglia. Nuclear medicine can play a role in the management of these tumours. 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 be used as a therapy if the uptake by the tumour on ^{123}I-MIBG scintigraphy is high. Most paragangliomas also express somatostatin receptors. ^{111}In-octreotide scintigraphy is a very sensitive technique to visualise these tumours. It detects >90% of known lesions in patients with paragangliomas *(3)*. In detecting primary phaeochromocytomas, 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 phaeochromocytoma 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 metastasised non-MIBG–avid phaeochromocytomas, but this did not result in an objective response. One patient with a paraganglioma had a minor response *(5)*.

Meningiomas are tumours 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-labelled somatostatin analogues in patients with meningioma has been undertaken in selected cases, but the growth inhibition of tumours was not specifically reported *(8,9)*.

SCLC are also considered to be neuroendocrine tumours. Somatostatin receptor scintigraphy can be used to visualize the primary tumour and its metastases. All primary tumours were visualised 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 tumour regression *(12)*. However, a pilot trial in 6 patients with SCLC using [^{90}Y-DOTA^{0},Tyr^{3}] octreotide (^{90}Y-DOTATOC) 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 tumours 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 metastasised 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 tumour.

MATERIALS AND METHODS

Patients

We studied 12 patients with paragangliomas, 5 with meningiomas, 3 with SCLCs, and 2 with melanomas. All patients had tumour 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 radiolabelled somatostatin analogues. Prerequisites for treatment were haemoglobin ≥ 5.5 mmol/L (8.9 mg/dL), white blood cells ≥ 2 x 10^9/L, platelets ≥ 80 x 10^9/L, creatinine ≤ 150 µmol/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. $^{177}LuCl_3$ 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)*.

Granisetron (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 haematology, 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 tumours on CT or MRI were measured and scored according to the Southwest Oncology Group (SWOG) solid tumour 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 tumours 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 post-therapy scintigraphy on day 1, on day 3 or day 4, and on day 7. ROI 1 included the entire tumour, ROI 2 included the entire tumour 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 tumour 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 normalise the shape of the curve and make comparison possible between different patients and tumours, 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 paraganglioma 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 ± 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-metastasised disease; the other patients had distant metastases. 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 Organisation (WHO) haematologic 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 tumour deposits developed or increased temporarily after 15% of administrations. Eleven patients (50%)

Table 1. Patient characteristics.

Characteristic	No. of patients (%)			
	Paraganglioma	Meningioma	SCLC	Melanoma
Total	12 [a]	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) [b]	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 [c]	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

[a] Localisation of primary tumour: 5 head and neck, 2 renal, 2 paraspinal (1 lumbar, 1 cervical), 1 adrenal (phaeochromocytoma), 1 thoracic (glomus aorticum), 1 organ of Zuckerkandl.
[b] Liver and bone metastases of carcinoid tumour.
[c] No PD documented in 12 mo before treatment.
Abbreviations: *SCLC*, small cell lung carcinoma; *PD*, progressive disease; *SD*, stable disease.

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 tumours. Two patients had inoperable, nonmetastasised tumours. One patient had an operable tumour but refused surgery. One patient was treated on a compassionate basis despite severe anaemia 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 anaemia. 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 µg/L at baseline to 100 µg/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] tumour diameter decrease, 25%–50%) (Fig. 1); however, progression of disease was noted after 11 mo. Figure 2 demonstrates the initial tumour 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

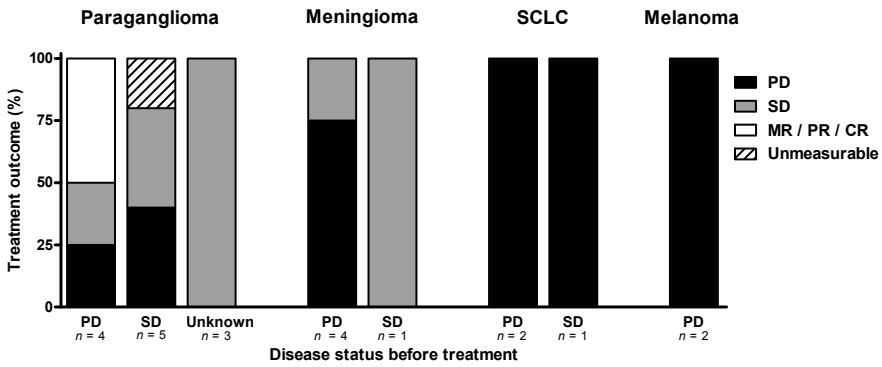

Figure 1. Effects of therapy with ^{177}Lu-octreotate in groups of tumours in relation to disease status before treatment.
Abbreviations: *PD*, Progressive disease; *SD*, Stable disease; *MR*, Minor response; *PR*, Partial remission; *CR*, Complete remission.

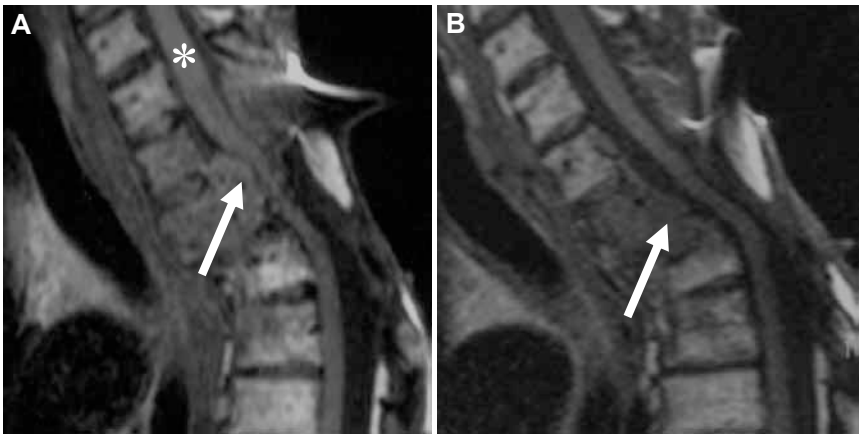

Figure 2. MR image (T1 weighted) of cervicothoracic spine of patient with phaeochromocytoma. **(A)** Baseline scan 3 mo before ^{177}Lu-octreotate therapy shows tumour extending into spinal canal (arrow, *spinal cord). **(B)** Scan 3 mo after fourth cycle of 7.4 GBq ^{177}Lu-octreotate shows reduction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

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 tumours 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 tumour (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 tumour. 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 tumours (meningioma and carcinoid), the meningioma was stable both before and after therapy. The carcinoid tumour showed a MR. This patient died 18 mo after the start of therapy because of progression of the carcinoid tumour.

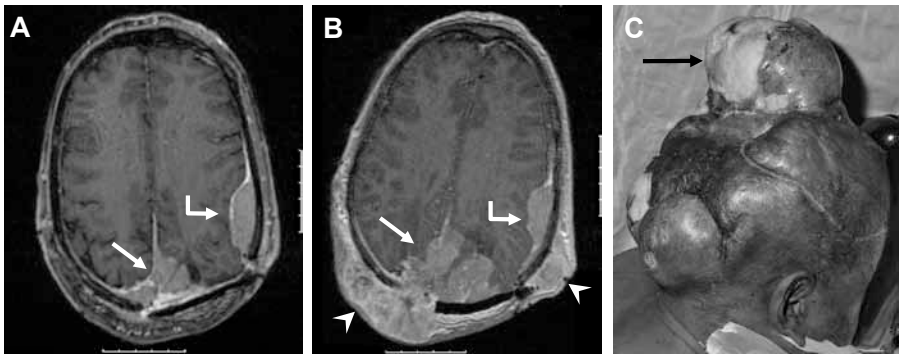

Figure 3. Example of patient with large, cranial meningioma. Patient already had undergone surgery 4 times and had had external beam radiotherapy before ^{177}Lu-octreotate. **(A)** MR image 1 wk after first cycle of ^{177}Lu-octreotate shows meningioma (arrow, curved arrow) with some extracranial involvement. **(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.

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 tumour. 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 tumour. Recurrence was noted after 10 mo and CDE was given again, resulting in tumour 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 µg/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, 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 µg/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.

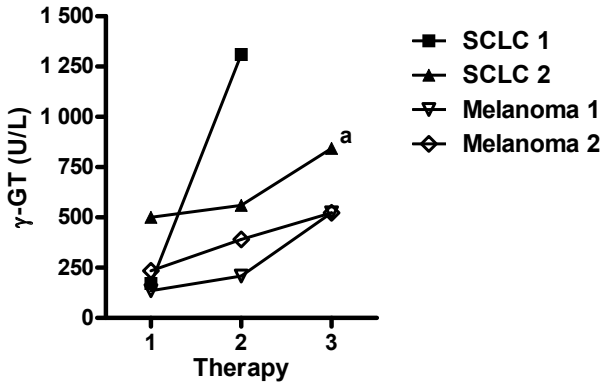

Figure 4. γGlutamylpeptidase (γGT) in patients with SCLC or melanoma with hepatic metastases. [a] Third therapy could not be given

Figure 5 shows progression in the latter patient on posttherapy scintigraphy. The patient with occlusion of the SVC seemed to have tumour 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)

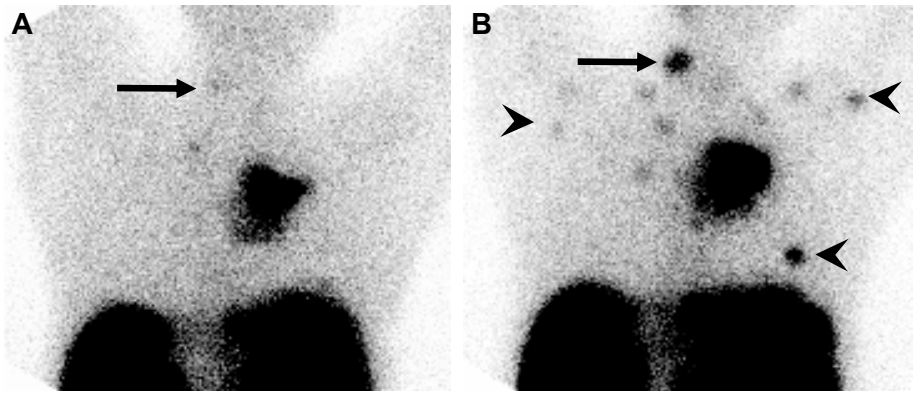

Figure 5. Scintigraphy performed 4 d after administration of 7.4 GBq ^{177}Lu-octreotate in patient with SCLC. **(A)** Scan (posterior chest) after first dose. Arrow indicates a cervical lesion. **(B)** Scan (posterior chest) after second and last dose 2 mo later. Several new lesions are visible (arrowheads).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

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 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 µg/L and increased from 75 to 216 µg/L in the other. Liver function tests also progressively deteriorated. (Fig. 4)

In the whole group, including all tumour types, we analysed whether a relation exists between treatment outcome and tumour 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 tumour 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 tumour regression were combined into 1 non-PD 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; $P = 0.31$).

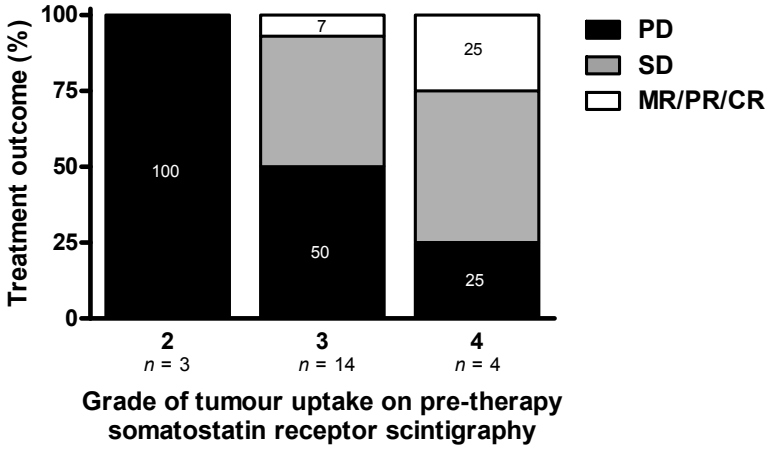

Figure 6. Relation between uptake of ^{111}In-octreotide on pretherapy somatostatin receptor scintigraphy and response to ^{177}Lu-octreotate therapy.
Abbreviations: *PD*, Progressive disease; *SD*, Stable disease; *MR*, Minor response; *PR*, Partial remission; *CR*, Complete remission.

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 tumours solely, and no matching GEP NET could be found in our database. In 2 patients, tumours were not visualised 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 tumours 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 tumour regression in 2 and disease stabilisation in 1 of 4 patients with progressive paragangliomas. Regardless of tumour stage and progression at baseline, 17% of paragangliomas displayed tumour regression. In the other types of tumours, no tumour 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 tumours 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 favourable 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 tumour play an important role. Melanoma and SCLC are very aggressive tumours once metastases are present. No really effective therapeutic options are currently available for metastasised 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 tumours might be that these tumours 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 tumours *(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 tumour cell. Because of the less-favourable response rates in non-GEP NETs, these tumours may hypothetically also expel ^{177}Lu-octreotate more rapidly than GEP NETs. This would lead to a lower amount of absorbed radiation per gram tumour tissue and, hence, a reduced chance of tumour 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 localisation, 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 visualised on ^{111}In-octreotide scintigraphy. This may be attributed to various factors. The lesions may be too small to be visualised 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 behaviour *(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 tumour 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)*. [DOTA^0,Tyr^3]octreotate has the highest affinity for sst_2 and almost none for sst_1 *(14)*. A ^{177}Lu-labelled somatostatin analogue with higher affinity for sst_1 would potentially be more effective in these tumours.

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 disease is progressive, and 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. Tumour 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 metastasised SCLC, ^{177}Lu-octreotate seems to be ineffective. Treatment with ^{90}Y-DOTA-TOC 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 radiolabelled somatostatin analogues 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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Chapter 4

Salvage Therapy with ^{177}Lu-octreotate in Patients with Bronchial and Gastroenteropancreatic Neuroendocrine Tumours

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ABSTRACT

Purpose

Regular therapy with the radiolabelled somatostatin analogue ^{177}Lu-octreotate (22.2–29.6 GBq) in patients with gastroenteropancreatic or bronchial neuroendocrine tumours results in tumour remission in 46% of patients, including minor response. We present the effects of additional therapy with ^{177}Lu-octreotate in patients in whom progressive disease developed after an initial benefit from regular therapy.

Methods

Thirty-three patients with progressive disease after an initial radiologic or clinical response were treated with additional cycles of ^{177}Lu-octreotate. The intended cumulative dose of additional therapy was 14.8 GBq in 2 cycles. Responses were evaluated using Southwest Oncology Group criteria, including minor response (tumour size reduction of ≥25% and <50%).

Results

Median time to progression (TTP) after regular therapy was 27 mo. In 4 patients, the intended cumulative dose was not achieved (2 had progressive disease, 2 had long-lasting thrombocytopenia). Haematologic toxicity grade 3 was observed in 4 patients, and grade 4, in 1. The median follow-up time was 16 mo (range, 1–40 mo). No kidney failure or myelodysplastic syndrome was observed. Renewed tumour regression was observed in 8 patients (2 partial remission, 6 minor response), and 8 patients had stable disease. Median TTP was 17 mo. Treatment outcome was less favourable in patients with a short TTP after regular cycles. Treatment effects in patients with pancreatic neuroendocrine tumours were similar to those in patients with other gastroenteropancreatic neuroendocrine tumours.

Conclusion

Most patients tolerated additional cycles with ^{177}Lu-octreotate well. None developed serious delayed adverse events. Additional cycles with ^{177}Lu-octreotate can have antitumour effects, but effects were less than for the regular cycles. This may be because of a worse clinical condition, more extensive tumour burden, or changed tumour characteristics. We conclude that this salvage therapy can be effective and is safe.

INTRODUCTION

Well-differentiated gastroenteropancreatic neuroendocrine tumours (GEP NETs) usually grow relatively slowly and can produce a variety of bioactive substances such as serotonin, insulin, and so forth, which can lead to hormone-induced symptoms. The incidence is quite low (up to 5/100,000/y for all disease stages), but the prevalence is much higher (35/100,000) *(1)*.

Few effective therapeutic options are available for patients with inoperable or metastasised GEP NETs and bronchial carcinoids. Biotherapy with somatostatin analogues or interferon can result in an improvement of symptoms caused by an excess of bioactive substances, but tumour size reduction rarely occurs *(2–4)*. Chemotherapy with various regimens can result in tumour shrinkage, but the median time to progression (TTP) is usually shorter than 18 mo *(5,6)*. Moreover, such therapies can have significant side effects and an impact on the quality of life.

Peptide receptor radionuclide therapy with the radiolabelled somatostatin analogue [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate) is a relatively new therapy. It has been used for several years now in our hospital when treating patients with somatostatin receptor–positive tumours that are inoperable or metastasised, of which GEP NETs are the largest group. Treatment with up to 29.6 GBq of ^{177}Lu-octreotate resulted in tumour size reduction of 25% or more in 46% of 310 patients, stable disease was observed in 35%, and progressive disease in 20% *(7)*. Median TTP was 40 mo, and serious side effects such as renal insufficiency or myelodysplastic syndrome occurred in 1% of patients *(7)*. These results compare favourably with those of chemotherapy regimens, although there are no randomised clinical trials at present comparing these modalities.

Several factors are predictive of either tumour regression or tumour progression after therapies with ^{177}Lu-octreotate. The less extensive liver metastases are, and the higher the tumour uptake on pretherapy somatostatin receptor scintigraphy with [^{111}In-DTPA^{0}] octreotide, the better the chances for tumour remission. On the other hand, a poorer clinical condition (i.e., Karnofsky Performance Status [KPS] $\leq$ 70) and a more extensive tumour load on pretherapy somatostatin receptor scintigraphy are associated with a higher chance that the therapy outcome will be progressive disease *(8)*.

At the moment, it is uncertain which further therapeutic steps are preferable if disease becomes progressive again after an initial response on ^{177}Lu-octreotate. Given the limited options for effective treatments in patients with progressive, well-differentiated GEP NETs, it was a logical step to study the effects of additional treatment cycles of ^{177}Lu-octreotate. Patients with an earlier benefit (i.e. radiologic response or clinical response) from regular treatment with ^{177}Lu-octreotate who later experienced progressive disease received an additional intended cumulative dose of 14.8 GBq. We present the effects of this salvage therapy and discuss both antitumour effects and side effects.

MATERIALS AND METHODS

Patients

Between October 2003 and July 2007, 42 Dutch patients were evaluated for additional therapy with ^{177}Lu-octreotate, of whom 33 patients were treated subsequently and underwent follow-up in our hospital. Before October 2003, the option for additional therapy with ^{177}Lu-ocreotate did not exist. July 2007 was chosen as the final inclusion date for this analysis to allow time for follow-up after finishing additional therapy. All patients had had benefit from prior therapy with 18.5–29.6 GBq of ^{177}Lu-octreotate and later again experienced progressive disease, documented by CT or [^{111}In-DTPA^0]octreotide scintigraphy. Benefit was defined as a radiologic tumour response (decrease in tumour size of ≥ 25%), or, in the absence of a radiologic response, as symptomatic improvement or a decrease of at least 50% in serum chromogranin A (CgA) levels or conversion of proven progressive disease in the 12 mo before the start of regular therapy into stable disease. All patients had measurable disease. All patients had tumour tissue uptake with pretherapy [^{111}In-DTPA^0] octreotide scintigraphy that was, on average, equal to or higher than the uptake in normal hepatic tissue on planar images. Patients with known somatostatin receptor–negative lesions were excluded. Prerequisites for treatment were haemoglobin ≥ 5.5 mmol/L, white blood count ≥ 2 x 10^9/L, platelets ≥ 80 x 10^9/L, creatinine ≤ 150 µmol/L, creatinine clearance ≥ 40 mL/min, and KPS ≥ 50.

Methods

[DOTA^0,Tyr^3]octreotate was obtained from Mallinckrodt. $^{177}LuCl_3$ was obtained from NRG and Missouri University Research Reactor and was distributed by IDB-Holland. ^{177}Lu-octreotate was locally prepared as described previously *(9)*.

Three milligrams of granisetron were injected intravenously as a precaution against nausea. To reduce the radiation dose to the kidneys, an infusion of amino acids (1 L of arginine 2.5% and lysine 2.5%) was started 30 min before the administration of the radiopharmaceutical and lasted for 4 h. Via a second pump system, the radiopharmaceutical was coadministered. Cycle doses of additional therapy were 7.4 GBq (or 3.7 GBq occasionally) injected in 30 min. The interval between treatments was 6–10 wk. Patients were treated up to an intended additional cumulative dose of 14.8 GBq.

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

Imaging

After therapy, planar spot images of regions with somatostatin receptor–positive pathology were obtained 24 h after the injection of the therapeutic dose of ^{177}Lu-octreotate. The acquisition time was 7.5 min.

In vivo measurements and response evaluation

The tumours on CT or MRI were measured and scored according to modified Southwest Oncology Group solid tumour response criteria *(10)*: complete response, complete disappearance of disease; partial remission, ≥50% decrease; minor response, tumour size reduction of ≥25% and <50%; progressive disease, ≥50% increase or new lesion; stable disease, neither complete remission, partial remission, minor response, nor progressive disease. Minor response was added because GEP NETs in general are slow-growing tumours and can be cystic, which makes it unlikely that they respond to treatment similarly to fast-growing solid tumours.

If patients had radiologically stable disease but were in poor clinical condition, this was regarded as treatment failure and scored as progressive disease. Biochemical markers, such as serum CgA levels, were not considered in determining treatment outcome.

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).

Statistics

The Fisher exact test was used to evaluate differences in categoric characteristics and in responses between subgroups of patients. The sign test was used to compare paired (intrapatient) characteristics of patients before starting regular therapy and before starting additional cycles. The Mann–Whitney test for nonnormally distributed variables and a *t* test were used to compare medians and means. Kaplan–Meier analysis was used to estimate median TTP and median survival. The log-rank test was used to compare these medians in subgroups of patients. For all tests, a *P* value of less than 0.05 (2-sided) was considered statistically significant.

RESULTS

Forty-two patients were evaluated for the option to receive 2 additional cycles of ^{177}Lu-octreotate at the time of progression after an initial radiologic or clinical response. Nine patients were not eligible: 2 had absent or low tumour uptake on [^{111}In-DTPA^{0}]octreotide scintigraphy. A lung carcinoma had developed in 1 patient as a secondary primary tumour, which probably determined the patient's prognosis. In 4 patients, the clinical condition was so rapidly decreasing and the estimated life expectancy so shortened that further therapy was considered not to be an option. In 1 patient, progressive disease presented as hydronephrosis due to pelvic lymphadenopathy. When the obstruction had been resolved, the clinical condition was no longer sufficient to start therapy with ^{177}Lu-octreotate. To conclude, 1 patient at first was eligible but declined further therapy until the disease progressed further. However, by that time, at the age of 87 y, the patient was no longer eligible because of a decreased clinical condition and insufficient renal function (2 x 24-h urine creatinine clearance at approximately 30 mL/min, serum creatinine of 95 µmol/L).

Thirty-three patients were eligible and received additional therapy with ^{177}Lu-octreotate. The median age at the start of additional therapy was 57 y (range, 35–75 y). Tables 1 and 2 describe baseline characteristics.

Table 1. Patient characteristics at start of additional therapy.

Characteristic	No. of patients
Response after regular treatment	
Radiologic [a]	28
CgA [b]	2
CgA, PD→SD	1
CgA, sympt, PD→SD	1
KPS [c], sympt	1
Tumour type	
Carcinoid	20
Bronchial	3
Gastric	1
Rectal	1
Midgut	15
Pancreatic NET [d]	8
NET of unknown origin	5

[a] Tumour size reduction of ≥25%.
[b] Decrease of ≥50%.
[c] Improvement of 20 points.
[d] One insulinoma, no hypoglycemic events at start additional therapy.
Abbreviations: *PD*, progressive disease; *SD*, stable disease; *PD→SD*, conversion of proven PD into SD; *sympt*, symptomatic improvement; *KPS*, Karnofsky performance score.

Table 2. Additional patient characteristics and comparisons.

Characteristic	Total group of patients at start of regular therapy	Patients with later additional therapy	
		At start of regular therapy	At start of additional therapy
	(*n* = 310)	(*n* = 33)	(*n* = 33)
KPS ≤ 70	13%	3%	9%
Gastrinoma, insulinoma, or VIPoma	6%	3%	0%
Baseline PD (≤12 mo)	43%	30%	100% [a]
Baseline weight loss [b]	24%	27%	57% (16/28) [c]
Liver metastases	89%	85%	97%
Bone metastases	22%	27%	42%
Uptake at SRS			
2	2%	6%	6%
3	75%	58%	76%
4	23%	36% [d]	18%
Tumour mass at SRS			
Limited	12%	15%	6%
Moderate	66%	67%	73%
Extensive	22%	18%	21%
Liver involvement at CT			
None	11%	15%	3%
Limited	62%	64%	73%
Extensive	27%	21%	24%
Elevated serum CgA	76%	79%	76%
Median CgA (ng/L) [e]	870	1,678	3,700
Elevated ALP	55% (169/306)	74% (23/31)	70%
Median ALP (U/L) [e]	203	165	246

[a] $P < 0.001$.
[b] ≥3-kg weight loss in 3 mo before regular therapy, ≥3-kg weight loss in 6 mo before additional therapy.
[c] $P < 0.05$, no data in 5 patients.
[d] $P < 0.05$.
[e] In patients with elevated baseline values.
Abbreviations: *KPS*, Karnofsky performance score; *VIP*, vasoactive intestinal peptide; *PD*, progressive disease; *SRS*, somatostatin receptor scintigraphy; *ALP*, alkaline phosphatase.

Cumulative doses of ^{177}Lu-octreotate therapies are presented in Figure 1. Thirty patients received 37 GBq or more. The intended dose of 14.8 GBq of ^{177}Lu-octreotate for additional therapy was not reached in 4 of the 33 patients. In 2 patients, disease progressed further after the first cycle: 1 patient started with chemotherapy because of clinical and radiologic progression, and the other patient, after an initial clinical improvement, died 6 wk after the additional treatment was started, presumably because of progressive disease. In 2 other

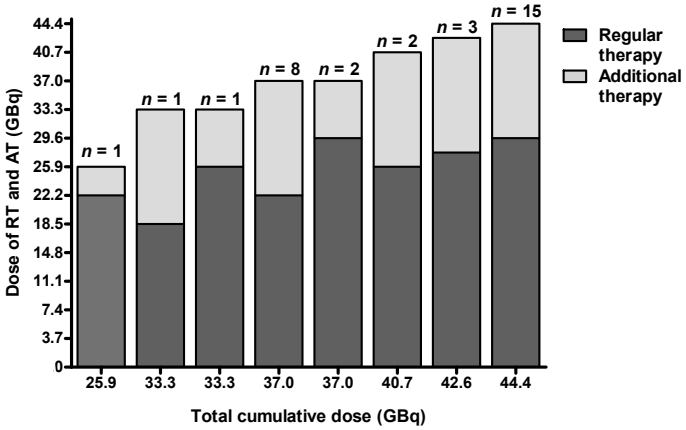

Figure 1. Dose of cumulative administered activity of ^{177}Lu-octreotate.
Abbreviations: *AT*, Additional therapy; *RT*, Regular therapy.

patients, persistent myelotoxicity after 3.7 and 7.4 GBq of ^{177}Lu-octreotate made further additional therapy impossible.

Table 2 describes baseline patient characteristics for the entire group of 310 patients who received regular therapy with ^{177}Lu-octreotate and for the 33 patients who received additional therapy later. In the latter group, baseline characteristics are presented both from the start of regular therapy and from the start of additional therapy. The patients who later received additional cycles had a different distribution of the amount of tumour uptake on pretherapy somatostatin receptor scintigraphy at the start of regular therapy compared with all 310 treated patients (Fisher exact test: $P < 0.05$). Grade 4 tumour uptake was present more often. More patients who later received additional cycles had an elevated baseline value of alkaline phosphatase of more than 120 U/L (74% vs. 55%); this difference was close to being statistically significant (Fisher exact test: $P = 0.06$).

In patients who received additional cycles, more patients had weight loss at the start of additional therapy (Fisher exact test: $P < 0.05$). More patients had bone metastases, and median CgA and median alkaline phosphatase were more elevated at the start of additional therapy, but these differences were not statistically significant. The median KPS at the start of regular therapy was 100 and at start of additional therapy was 80. This was statistically significant (sign test: $P < 0.01$).

Figure 2 demonstrates, on an intrapatient base, differences in KPS, liver involvement on CT, and extent of disease and tumour uptake on [^{111}In-DTPA^{0}]octreotide scintigraphy from the start of regular treatments to the start of additional treatments.

Subacute haematologic side effects of the additional cycles with ^{177}Lu-octreotate are presented in Table 3. In one patient with grade 3 thrombocytopenia after regular therapy, the

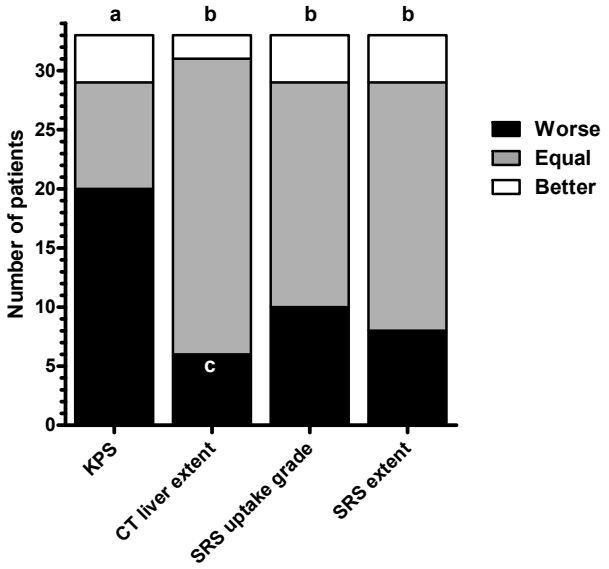

Figure 2. Intrapatient comparison of changes in baseline characteristics from start of regular therapy to start of additional therapy with ^{177}Lu-octreotate.
[a] $P < 0.01$ (sign test).
[b] Not significant (sign test).
[c] Liver metastases not present with regular therapies developed in 4 patients (1 already very diffuse); extensive liver disease developed in 2 with limited lesions.
Abbreviation: *SRS*, Somatostatin receptor scintigraphy.

platelet count decreased from 189 to 100 x 10^9/L after the first additional cycle of 7.4 GBq. Therefore, the dose of the second cycle was reduced to 3.7 GBq. No further significant decrease occurred in platelet count, and finally 3.7 GBq were given again without further toxicity.

Table 3. Haematologic toxicity.

Toxicity	Grade 2	Grade 3	Grade 4
Leukocytopenia	No therapeutic relevance	0	0
Anaemia	No therapeutic relevance	0	0
Thrombocytopenia	1 [a]	4 [b]	1 [c]

[a] Toxicity after first cycle; second cycle postponed.
[b] In 2 patients, persistent after first cycle, no further therapy possible. One patient had extensive bone metastases and grade 2 thrombocytopenia after regular therapy; other patients had long-lasting myelosuppression after regular therapy and again after additional therapy despite reduced dose of 3.7 GBq.
[c] Toxicity after second cycle.

Of the 4 patients with thrombocytopenia of ≤ 75 x 10^9/L, grade 3 or more anaemia, or leukocytopenia after regular therapy, 2 patients (50%) experienced grade 3 or more haematologic toxicity after additional therapy, and in 1 patient no follow-up was available because the patient died as a result of progressive disease after the first additional cycle. Of the 29 patients without haematologic toxicity after regular therapy as defined previously, 3 patients (10%) experienced grade 3 or more haematologic toxicity after additional therapy, and in 1 no follow-up was available because of progressive disease after the second cycle.

In no patients did myelodysplastic syndrome or kidney failure develop during the time of follow-up. One patient underwent a nephrectomy after the regular therapy because of renal cell carcinoma. He subsequently was treated with 2 additional cycles of ^{177}Lu-octreotate, with no renal failure noted after more than 2 y of follow-up. The median time of follow-up in the entire group of patients was 15.5 mo after the first additional cycles (range, 1–40 mo). This was 21 mo in the patients with at least stable disease after additional therapy. Since the start of regular therapy, the median time of follow-up for all patients was 44 mo.

Table 4 summarises the therapy outcome in the 33 studied patients. In 2 patients (6%) the additional cycles of ^{177}Lu-octreotate resulted in a partial remission, and in 6 (18%), in a minor response. Ten additional patients (30%) had radiologically stable disease after additional therapy, but 2 of those had clear clinical signs of progression (development of ascites, decrease in general condition). This was hence considered to be progressive disease as well. Therefore, 8 patients (24%) had stable disease after additional therapy, and in 17 patients (52%) disease remained progressive despite additional therapy. The median TTP after the start of additional therapy in the 16 patients with stable disease, minor response, or partial remission was 17 mo (Kaplan–Meier method, 2 patients censored at 21 mo). Figure 3 shows the disease course in 1 of the patients who responded favourably to both the regular and the additional therapy cycles.

CgA levels were measured at various moments during the disease course. Only patients with elevated CgA levels at the start of regular therapy and at the start of additional therapy

Table 4. Therapy outcome.

Outcome	Radiologic evaluation	Clinical evaluation
PD	15 (45%)	17 (52%)
SD	10 (30%) [a]	8 (24%)
MR	6 (18%)	6 (18%)
PR	2 (6%)	2 (6%)

[a] Two patients with radiologically stable disease had clear clinical signs of disease progression and were classified as having progressive disease.

Abbreviations: *PD*, progressive disease; *SD*, stable disease; *MR*, minor response; *PR*, partial remission.

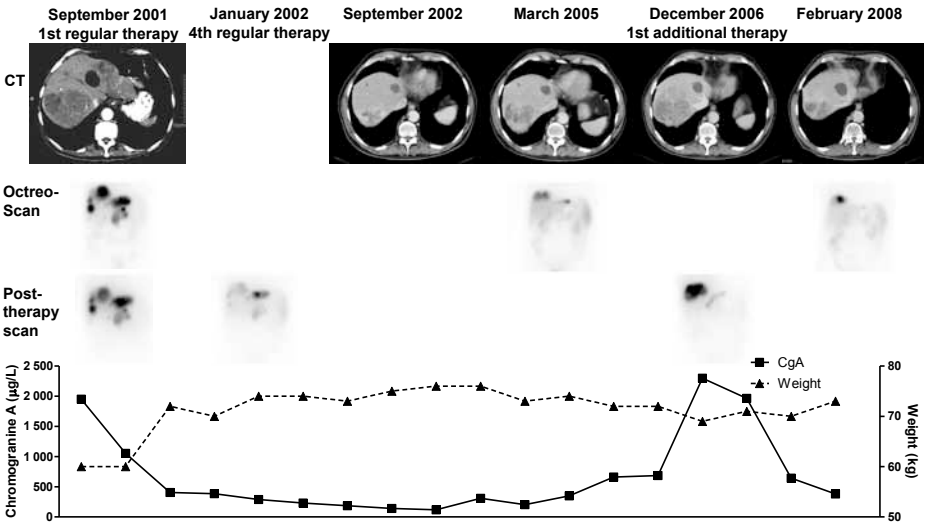

Figure 3. Disease course in patient having carcinoid with liver metastases, presenting imaging studies, serum CgA levels, and body weight over time. Patient had severe diarrhoea in 2001 with good clinical, scintigraphic, and radiologic responses after regular therapy with ^{177}Lu-octreotate in 2001. In March 2005, disease became progressive, but patient declined therapy. In December 2006, disease clearly progressed, and additional therapy with ^{177}Lu-octreotate was started. Patient again had partial remission and was still in remission 21 mo after additional therapy.

who had follow-up levels after additional therapy are included in the data shown in Figure 4. These included 23 patients, of whom 11 had progressive disease, 6 had stable disease, and 6 had minor response or partial remission after additional therapy. The figure shows that almost all patients had a clear decrease in CgA levels after regular therapy and a clear increase at the time of renewed disease progression before additional therapy. After additional therapy, CgA levels decreased mainly in the patients with a minor response or partial remission.

The median overall survival since the start of additional cycles was 15 mo. In patients with progressive disease after additional therapy, the median overall survival was 9 mo, and in the patients with stable disease or regression it was 26 mo (log-rank test: $P < 0.0001$).

The median TTP after regular therapy was 27 mo in the 33 patients who received additional cycles. In the 16 patients with a TTP of less than 27 mo, 13 (81%) still had progressive disease, 1 (6%) had stable disease, and 2 (13%) had a minor response. In the 17 patients with a TTP of 27 mo or more, 4 patients (24%) still had progressive disease, 7 (41%) had stable disease, 4 (24%) had a minor response, and 2 (12%) had a partial remission. Treatment outcome defined as progressive disease or nonprogressive disease was significantly different between the patients with a TTP of less than 27 mo after regular therapy and those having a TTP of 27 mo or more (Fisher exact test: $P < 0.01$). The median

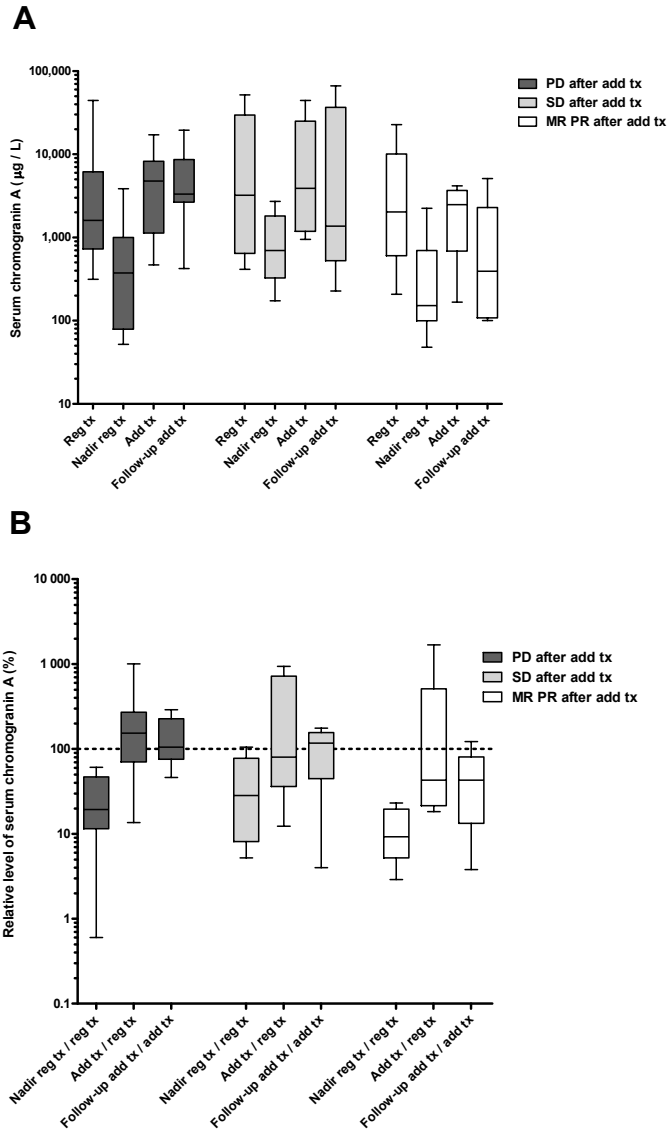

Figure 4. CgA levels in serum during course of disease. **(A)** Absolute CgA levels at various moments according to treatment outcome of additional therapy. **(B)** Relative levels of CgA, displaying change after regular therapy (ratio of nadir of CgA after regular therapy over CgA at start of regular therapy), before start of additional therapy (ratio of CgA at start of additional therapy over CgA at start of regular therapy), and after additional therapy (CgA level at follow-up after additional therapy over CgA at start of additional therapy).

No change is indicated by 100%. Boxes show medians and 25th–75th percentiles; whiskers indicate ranges. Middle lines in boxes indicate medians.

Abbreviations: *Add tx*, Additional therapy; *MR*, Minor response; *PD*, Progressive disease; *PR*, Partial remission; *Reg tx*, Regular therapy; *SD*, Stable disease.

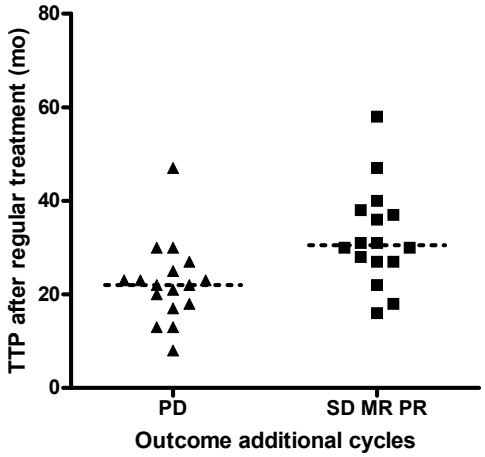

Figure 5. Outcome after additional therapy with ^{177}Lu-octreotate in relation to duration of response after regular therapy. Median TTP (indicated by line) after regular therapy in patients with progressive disease (PD) was 22 mo. This was 30 mo in patients with stable disease (SD) or remission (*t* test: $P < 0.01$). Abbreviations: *MR*, Minor response; *PD*, Progressive disease; *PR*, Partial remission; *SD*, Stable disease.

TTP after regular therapy in patients who continued to have progressive disease was 22.0 mo (mean, 22.47 mo), whereas it was 30.5 mo (mean, 32.25) in patients with stable disease or tumour shrinkage (*t* test: $P < 0.01$) (Fig. 5). Of note, 15 of 16 patients (94%) with a TTP of less than 27 mo had an elevated level of alkaline phosphatase at the start of additional therapy, as opposed to 10 of 17 patients (59%) with a TTP of 27 mo or more (Fisher exact test: $P < 0.05$).

Sixteen of the 23 patients (70%) with elevated levels of alkaline phosphatase at the start of additional cycles still had progressive disease, whereas 1 of the 10 patients (10%) with a normal alkaline phosphatase level still had progressive disease (Fisher exact test: $P < 0.01$).

The median TTP after regular therapy was 26 mo in pancreatic NET patients ($n = 8$) and 27 mo in carcinoid patients, including those having NET of an unknown primary source ($n = 25$). After additional therapy, 5 patients (63%) with pancreatic NET still had progressive disease; and in carcinoid patients, 12 (48%) had progressive disease. The proportion of progressive disease and nonprogressive disease in carcinoid patients and pancreatic NET patients was not significantly statistically different (Fisher exact test: $P = 0.69$). The median TTP in patients with pancreatic NET was 17 mo and in patients with carcinoid tumours was 20 mo (log-rank test: $P = 0.26$).

DISCUSSION

Peptide receptor radionuclide therapy with radiolabelled somatostatin analogues such as ^{177}Lu-octreotate is a promising treatment in patients with somatostatin receptor–positive NETs. Initial treatment with ^{177}Lu-octreotate can result in prolonged antitumour effects; however, disease will eventually become progressive again in most patients. We analysed the effects of additional treatment cycles with ^{177}Lu-octreotate (intended dose of 14.8 GBq) in patients with progressive disease after an initial radiologic or clinical response with 18.5–29.6 GBq of ^{177}Lu-octreotate.

The decision to administer an intended dose of 2 cycles of 7.4 GBq was made to try to avoid long-term side effects. The intended cumulative dose of the regular treatment was based on the estimation that 29.6 GBq of ^{177}Lu-octreotate would result in a bone marrow dose of 2 Gy *(9)*. If individual dosimetry had indicated that the kidney dose then would be more than 23 Gy, the intended dose was reduced. Probably these assumptions for bone marrow and kidney doses were safe because serious side effects were infrequent *(7)*. When deciding to start the additional therapies, we did not want to exceed these maximum doses for external beam radiotherapy by very much at one time.

In the 33 patients treated with additional cycles of ^{177}Lu-octreotate, renewed tumour remission was observed in 8 and disease stabilisation in 8, with a median TTP of 17 mo. In 17 patients, disease remained progressive. The treatment outcome was more favourable in patients who had a long-lasting benefit from regular therapy. Grade 3 or 4 acute haematologic toxicity occurred in 5 patients (15%), somewhat more than the 9.5% of patients in which it occurred after the regular therapy. Apparently patients with myelotoxicity after regular cycles were more susceptible to haematologic toxicity after additional therapy. In these patients, it may be advisable to start additional therapy with 3.7 GBq.

None of the patients experienced serious long-term side effects during follow-up: kidneys and bone marrow are the organs at risk, but kidney failure or myelodysplastic syndrome did not occur after additional therapy with ^{177}Lu-octreotate. However, the overall time of follow-up was relatively short, partly because some patients who had continued progressive disease were lost to follow-up or died shortly after therapy.

Although the additional therapy is safe and can result in tumour stabilisation and tumour remission, the antitumour effects are less favourable than with the initial treatments.
Several factors may play a role. First, the administered activity for the additional therapy is only half that used in regular treatment, which will result in a lower radiation dose to the tumours.

Another important factor may be that most patients had a worse clinical condition (e.g., lower KPS, weight loss) at the start of additional treatment than at the start of regular

treatments. Moreover, some patients had more extensive tumours when starting additional treatment cycles: 4 of 5 patients without hepatic metastases at the start of regular treatments had liver lesions when starting additional cycles. This is important because the extent of tumour spread was a predictive factor for disease progression after therapy (*8*). Although not statistically significant, several other factors were also higher at the start of additional therapy: the percentage of patients with bone metastases, the median serum CgA, and the median alkaline phosphatase. Elevated alkaline phosphatase levels were an important adverse prognostic factor for survival in patients with metastasised NETs *(11)*.

High tumour uptake on [^{111}In-DTPA^{0}]octreotide scintigraphy was a predictive factor for tumour remission after regular therapy *(8)*. An explanation for the less favourable results could be a decrease in the amount of tumour uptake of the radiolabelled somatostatin analogue, either by a decrease in somatostatin receptor expression or by a change in the profile of receptor subtypes. Although we could not demonstrate a statistically significantly lower tumour uptake on ^{111}In-octreotide scintigraphy at the start of additional cycles using a visual score (grades 2–4), a few patients had grade 4 uptake when starting regular treatments and only grade 3 when starting additional cycles. It would be interesting to perform a separate study of tumour dosimetry based on posttherapy scintigraphy results to more precisely determine possible differences in uptake.

Tumour dedifferentiation may also play a role. As tumours become more poorly differentiated over time, somatostatin receptor expression can become less *(12)*, and tumours can start to proliferate more rapidly. One patient had somatostatin receptor–negative vertebral lesions that became apparent shortly after finishing the additional treatment. In another patient who had a pancreatic NET, rapidly progressive liver metastases developed, and additional therapy with ^{177}Lu-octreotate was ineffective. Retrospectively, performing a biopsy to determine the proliferation index (or Ki-67 index) and considering chemotherapy in case of a high index may have been better.

Another factor can be that the patients who so far received additional treatment with ^{177}Lu-octreotate may have had more aggressive tumours at baseline than the average patient treated. In the group of patients who received additional treatments, the median TTP after regular therapy was 27 mo, whereas in the whole group it was 40 mo.

Another group also investigated additional therapy with radiolabelled somatostatin analogues in patients in whom progressive disease again developed after successful regular therapy. Forrer *et al. (13)* described the effects of 1 cycle of 7.4 GBq [^{177}Lu-DOTA^{0}-Tyr^{3}] octreotide after regular therapy with [^{90}Y-DOTA^{0}-Tyr^{3}]octreotide in 27 patients. They found no serious acute or subacute side effects. At 8–12 wk after therapy, 8 patients (30%) still had progressive disease, 12 (44%) had stable disease, 5 (19%) had a minor response, and 2 (7%) had a partial remission. There were no exact data on the duration of response: 13 patients progressed after a mean of 8.3 mo, and 8 patients still were without progressive

disease at the time of analysis. In our view, it is difficult to state exactly what these data mean given the low administered activity and relatively short time of follow-up.

The main limitations of our study are the limited time of follow-up and the small number of treated patients. However, on the basis of our study results, we are convinced the additional cycles can be worthwhile and are safe in most patients. However, it is important to consider other therapeutic options, especially if disease became progressive soon after the regular therapy cycles. Therapy with RAD001 (everolimus) and octreotide could become an alternative: the tumour-stabilising effects of this combination were promising, although tumour remissions were rare *(14)*. In patients with rapidly progressive disease, etoposide and cisplatin could be an option.

CONCLUSION

Additional treatments with ^{177}Lu-octreotate were well tolerated in most patients who responded favourably to regular treatment and eventually had renewed progressive disease. Haematologic toxicity was rare, and no serious delayed adverse events were observed, although the duration of follow-up was still limited. This salvage therapy can result in tumour stabilisation and regression, but results were less favourable than those for the initial treatments. This fact might be a result of the lower amount of administered activity, the decreased clinical condition of patients, changed tumour characteristics, and higher tumour burden.

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Chapter 5

Report on Short-Term Side Effects of Treatments with ^{177}Lu-octreotate in Combination with Capecitabine in Seven Patients with Gastroenteropancreatic Neuroendocrine Tumours

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Eur J Nucl Med Mol Imaging. 2008;35:743-748.

ABSTRACT

Purpose

Treatment with the radiolabelled somatostatin analogue ^{177}Lu-octreotate results in tumour remission in 47% of patients with gastroenteropancreatic neuroendocrine tumours. Adding capecitabine to ^{177}Lu-octreotate, as a radio-sensitiser, may enhance these anti-tumour effects. We now present the short-term toxicity profile of this novel combination.

Methods

Seven patients were treated with 7.4 GBq ^{177}Lu-octreotate and capecitabine (1650 mg/m^2 per day) for 2 weeks with an intended number of four cycles. Toxicity, and especially haematological and renal parameters, were monitored on a weekly basis for the first two cycles and 4 and 6 weeks after subsequent cycles.

Results

None of the patients had hand-foot syndrome. One patient had grade 1 stomatitis occurring after one of four cycles. Grade 3 or 4 leukopenia or neutropenia did not occur. One patient had grade 3 anaemia, but none had grade 4 anaemia. One patient had grade 2 thrombocytopenia after the fourth cycle, and one had grade 3 thrombocytopenia. Grade 4 thrombocytopenia did not occur. No significant changes in serum creatinine levels were observed. None of the patients had symptoms of cardiac ischaemia.

Conclusions

Treatment with the combination of ^{177}Lu-octreotate and capecitabine was feasible and safe considering acute and subacute side effects. We therefore started a randomised, controlled clinical trial to compare this combination with ^{177}Lu-octreotate as single agent with regard to anti-tumour effects and side effects.

INTRODUCTION

Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues can be very rewarding in patients with inoperable somatostatin receptor positive gastro-enteropancreatic neuroendocrine tumours (GEP NETs). Treatment with the radiolabelled analogue [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate (^{177}Lu-octreotate) resulted in tumour remission in 47% of 125 patients, and the median time to progression had not been reached after 36 months of follow-up *(1)*. The most frequently occurring short-term side effects of this treatment were mild reversible alopecia in 64% of patients, nausea in 31%, vomiting in 14% and an increase in pain in tumour-involved regions in 12%. WHO haematological toxicity in 131 patients treated with ^{177}Lu-octreotate was as follows: Hb grade 3 and 4 in 0.4 and 0.0%, leukopenia grade 3 and 4 in 1.3 and 0.0% and thrombocytopenia grade 3 and 4 in 1.5 and 0.2%.

Although the anti-tumour effects of therapy with ^{177}Lu-octreotate are promising and serious side effects are rare, further studies are needed to find treatments that are more effective and still have acceptable side effects. One option for improvement is to use combinations of a radiolabelled somatostatin analogue with chemotherapeutic agents as radio-sensitiser. Candidate drugs for this purpose are 5-fluorouracil (5-FU) and capecitabine, which is an oral prodrug of 5-FU. For 5-FU, the additional effect to radiation therapy has been demonstrated: The combination of external beam radiation therapy with 5-FU resulted in better anti-tumour effects than external beam radiation therapy alone in patients with cancers of stomach, pancreas, large bowel, rectum, head and neck and oesophagus (mostly with cisplatin added as well). Moreover, chemoradiotherapy with 5-FU is also successfully used in anal and bladder cancers (see *(2)* for review). External beam radiation therapy with capecitabine was as effective as external beam radiation therapy with intravenous 5-FU in patients with locally advanced rectal carcinoma, but treatment with capecitabine is more convenient for patients, as it is an oral drug *(3, 4)*. Most common specific side effects of capecitabine are hand-foot syndrome and stomatitis. These side effects occur frequently when capecitabine is used in a dose of 2,500 mg/m^2 per day in chemotherapy regimens, either as single agent or in combination with other chemotherapeutic agents. When using capecitabine as radio-sensitiser, lower doses (1,600–2,000 mg/m^2 per day) are administered, and hand-foot syndrome and stomatitis are less frequent. Another known, but rather infrequent, side effect of capecitabine and related drugs is cardiac ischaemia. This can result in myocardial infarction, also in patients without a previous history of cardiac disease *(5)*.

Most data on the combination of radiation therapy and 5-FU or capecitabine were derived from studies using external beam radiation therapy. Few data have been published about 5-FU or capecitabine in combination with radionuclide-derived radiation therapy with radiolabelled peptides or antibodies. Wong *et al. (6)* reported that treatment with

^{90}Y-labelled antibodies and 5-FU was safe in patients with metastasised colorectal cancer. PRRT with [^{111}In-DTPA^{0}]octreotide in combination with 5-FU resulted in symptomatic improvement in 71% of patients with neuroendocrine tumours *(7)*. This is much more than 13 out of 38 patients (34%) with symptomatic improvement published by Valkema *et al. (8)* who had not used 5-FU during PRRT with [^{111}In-DTPA^{0}]octreotide. We were therefore interested in combining ^{177}Lu-octreotate with capecitabine in treating patients with GEP NETs, as this might result in better treatment outcomes. A possible drawback could be an increase in side effects. We therefore started a pilot study to investigate this combination.

We here present data on the acute toxicity profile of ^{177}Lu-octreotate in combination with capecitabine in seven patients. We monitored side effects including nausea, vomiting, chest pain, hand-foot syndrome and stomatitis, haematological side effects and acute side effects on kidneys and liver: this to evaluate if this new combination is safe and feasible in patients.

MATERIALS AND METHODS

Patients

Seven patients with metastasised GEP NETs were studied. All patients had measurable disease. All patients had tumour tissue uptake with [^{111}In-DTPA^{0}] octreotide scintigraphy (OctreoScan) that was on average equal to or 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 the first treatment were haemoglobin (Hb) ≥5.5 mmol/L, WBC ≥2 × 10^{9}/L, platelets ≥100 × 10^{9}/L, serum creatinine ≤150 μmol/L and 24-h urine creatinine clearance ≥50 mL/min, and Karnofsky performance score ≥60. Haematological criteria for further treatments were: Hb ≥5.0 mmol/L, WBC ≥2 × 10^{9}/L, platelets ≥75 × 10^{9}/L. All other criteria for re-treatment were identical. All patients gave written informed consent to participate in the study, which was approved by the local medical ethical committee.

Methods

[DOTA^{0},Tyr^{3}]octreotate was obtained from Mallinckrodt (St Louis, MO, USA). $^{177}LuCl_3$ was obtained from NRG (Petten, The Netherlands) and was distributed by IDB-Holland (Baarle-Nassau, The Netherlands). ^{177}Lu-octreotate was locally prepared as described previously *(9)*.

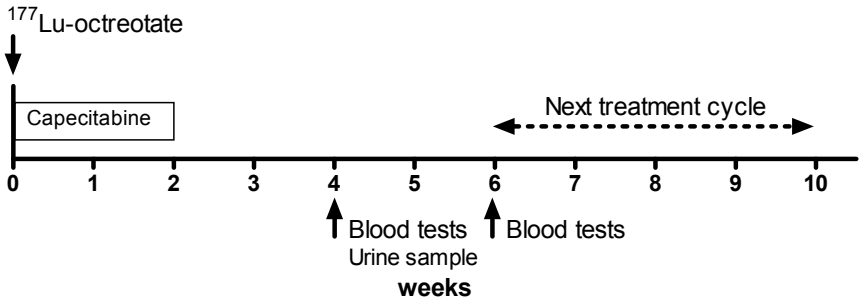

Figure 1. Time schedule of treatment with ^{177}Lu-octreotate and capecitabine and follow-up during treatment. Each regular treatment cycle consisted of an injection of ^{177}Lu-octreotate (7.4 GBq) and of capecitabine (1650 mg/m^2 per day) for 2 weeks. Blood tests were performed at 4 and 6 weeks after start of a treatment cycle. In this pilot study, blood tests were done every week only after the first and second cycles. The next treatment cycle was given 6 to 10 weeks later. The intended number of cycles was four.

Granisetron 3 mg was injected intravenously 30 min before starting the infusion of ^{177}Lu-octreotate. To reduce radiation dose to the kidneys, an infusion of amino acids (arginine 2.5% and lysine 2.5%) was also 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 29.6 GBq.

Capecitabine (Xeloda; Roche, Basel, Switzerland) 1,650 mg/m^2 per day, divided over two doses was administered orally, starting on the day of treatment with ^{177}Lu-octreotate and continuing for 14 days. Patients were instructed to report any signs of hand-foot syndrome, stomatitis or other side effects.

Routine haematology, liver and kidney function tests were performed after each therapy. This was performed every week after the first and second treatment cycle. After subsequent cycles, blood tests were performed at 4 and 6 weeks after the treatment. Figure 1 depicts the treatment schedule including blood tests.

RESULTS

Seven male patients were studied. All had metastasised GEP NETs (three non-functioning pancreatic NETs, four carcinoid tumours). Six had progressive disease, demonstrated within 12 months before start of treatment. In one patient, some growth occurred before start (interval between scans of 2 months), but this did not classify as progressive disease according to Southwest oncology group criteria. In this patient, treatment was started

because of a large hepatic tumour load. Age at start ranged from 36 to 67 years (median 62 years). None of the patients had been treated with capecitabine or other chemotherapeutic agents before.

Twenty-six treatment cycles were given: Six patients received four cycles; in one patient, treatment was stopped after two cycles because of clinically progressive disease. Side effects within 24 h after administration were: nausea with vomiting, reported by one patient after one cycle. Two patients had an increase in diarrhoea (3 of 26 cycles). Increase in pain was not reported by any of the patients. Patients also reported subacute side effects in the weeks after the treatment: Five patients had nausea at home (7 of 26 cycles), two patients vomited (5 of 26 cycles). Two patients noticed an increase in pain in tumour-involved areas (2 of 26 cycles). Six patients experienced some fatigue after a treatment cycle (7 of 26 cycles). Mild alopecia was observed in four patients.

The patients were also asked to report any side effects that are more specific for capecitabine: None of the patients had signs or symptoms of hand-foot syndrome. One patient mentioned that after the second treatment, the oral mucosa was a bit more sensitive than usual, but no mucosal abnormalities were seen (grade 1 stomatitis). None of the other patients had complaints of stomatitis (Table 1). None of the patients had chest pains. One patient with a serotonin producing metastasised midgut carcinoid developed mild oedema of the lower extremities. This was due to severely progressive tricuspid valve insufficiency proven by a cardiac ultrasound. Another patient developed oedema of the legs caused by compression of the inferior vena cava. None of the other patients had symptoms of heart failure.

Haematological toxicity is summarised in Table 2. Grade 3 or 4 leukopenia or neutropenia did not occur. One patient had grade 3 anaemia (Hb 4.9 mmol/L) after the second cycle, which resolved to grade 2 spontaneously 1 week later. In this patient, treatment was stopped after two cycles because of clear clinical progression of disease. Grade 4 anaemia did not occur. One patient had grade 2 thrombocytopenia (72×10^9/L) after the fourth treatment. In one patient, platelet count dropped to 36×10^9/L (grade 3 toxicity) after the third cycle. After recovery of platelet count to 93×10^9/L, therapy was resumed with half a dose of ^{177}Lu-octreotate (3.7 GBq) and the normal dose of capecitabine. Subsequently, platelet count again dropped to 37 x 10^9/L. Treatment with ^{177}Lu-octreotate was then

Table 1. Capecitabine-specific toxicity of treatment with ^{177}Lu-octreotate and capecitabine.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hand-foot syndrome	0	0	0	NA
Stomatitis	1 [a]	0	0	0

Numbers are patient-based (7 patients and 26 treatment cycles).

[a] After second cycle only

Abbreviation: *NA*, Not applicable.

Table 2. Toxicity of treatment with ^{177}Lu-octreotate and capecitabine

WHO Toxicity	Grade 3	Grade 4
Platelets	1[a]	0
White blood cells	0	0
Neutrophil count	0	0
Haemoglobin	1[b]	0
Serum creatinine	0	0

Numbers are patient-based (7 patients and 26 treatment cycles).
[a]This patient developed grade 3 thrombocytopenia after the third and fourth cycles.
[b]This patients had grade 3 anaemia (Hb 4.9 mmol/l) on one occasion after the second treatment, which spontaneously resolved to grade 2 1 week later.

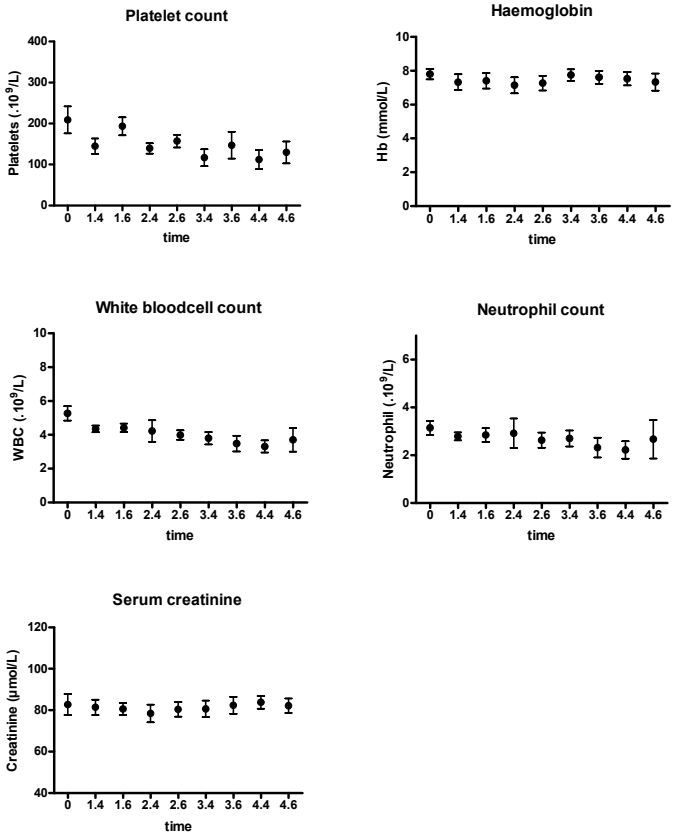

Figure 2. Course of haematological parameters and serum creatinine levels in seven patients during and after treatments with ^{177}Lu-octreotate and capecitabine (mean ± standard error of mean). Time axis: 0 represent baseline values, *x·y*: *x* represents treatment cycle, *y* represents weeks after treatment. Data after treatments 3 and 4 are based on six patients

stopped (cumulative dose 25.6 GBq) because the patient was deteriorating clinically and progression of disease was documented on CT scan. Grade 4 thrombocytopenia did not occur.

The course of haematological parameters and serum creatinine levels are shown in Fig. 2. Platelet counts at 4 weeks after treatment were consistently lower than baseline counts or counts at 6 weeks after the same treatment. No changes were noted in serum creatinine levels (no grade 2 or higher toxicity). No changes in liver function tests occurred that could be attributed to the treatment. Liver function tests deteriorated in the patient with progressive disease despite two treatment cycles.

Although not the subject of this study, it is reassuring to see that the treatment with the combination of ^{177}Lu-octreotate and capecitabine resulted in tumour size reduction in the first patient we treated (Fig. 3).

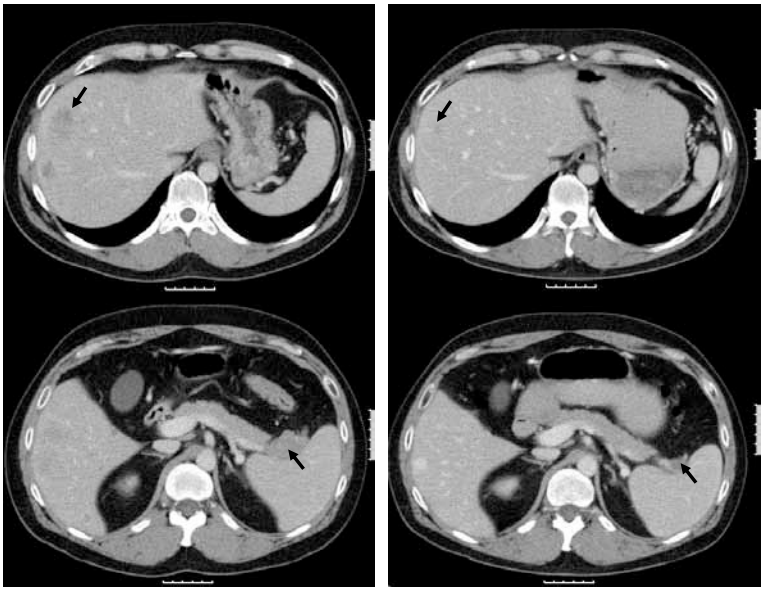

Figure 3. The first patient treated with ^{177}Lu-octreotate and capecitabine was a 36-year-old man with a metastasised pancreatic neuroendocrine tumour. Images in the *left panel* present the tumours at baseline; the *right panel* presents the situation 3 months after the fourth cycle. The patient had a partial remission

DISCUSSION

PRRT with ^{177}Lu-octreotate as single agent is effective in patients with somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours. However, strategies to increase the efficacy of such treatment should be investigated. One possible way to improve these effects is combining ^{177}Lu-octreotate with chemotherapeutic agents as radio-sensitiser. Capecitabine is often used as radio-sensitiser with external beam radiation therapy. It has attractive features for combining with radiation therapy: Capecitabine is an oral prodrug of 5-FU and has to be converted to its active form after three enzymatic converting steps. The third step is by the enzyme thymidine phosphorylase (TP). Several types of malignant cells have high expression of TP, and this can result in higher concentrations of the active form (i.e. 5-FU) in tumour cells compared to non-malignant cells *(10)*. Moreover, TP expression is induced by radiation *(11)*, which can again result in higher concentrations of 5-FU in irradiated cells. These features are also attractive for combining capecitabine with radionuclide-derived radiation therapy, like PRRT.

To our knowledge, no studies have so far been published that describe the combination of capecitabine with a somatostatin analogue labelled with a β-emitting isotope, like ^{177}Lu-octreotate, with regard to side effects. Based on the findings from a pilot study to evaluate the safeness and feasibility of this combination, we intended to make a decision to start or reject a randomised clinical trial comparing ^{177}Lu-octreotate as single agent with ^{177}Lu-octreotate in combination with capecitabine.

Haematological toxicity was infrequent. One patient had grade 2 thrombocytopenia after the fourth cycle. In one patient, WHO grade 3 thrombocytopenia occurred after the third and fourth cycles. In another patient, haemoglobin was 4.9 mmol/L on one occasion (WHO grade 3 anaemia) after the second cycle, which improved within 1 week to grade 2 anaemia.

No acute renal toxicity was observed in these patients based on measured serum creatinine levels. Of course, some subtle side effects on glomerular filtration rate or tubular function, which may only be demonstrated with more sensitive methods, like ^{99m}Tc-DTPA or ^{99m}Tc-MAG3, cannot be ruled out. However, based on serum creatinine levels alone, we may conclude that there was no clinically relevant acute renal toxicity.

None of the patients had hand-foot syndrome, and one patient had a more sensitive oral mucosa, but grade 2 or more stomatitis was not noted. The low frequency of these side effects of capecitabine in our group can be explained by the relatively low dose (approximately 825 mg/m^2 bid) used in this and other radio-sensitising studies. This is an important characteristic, as ideally, we do not want to provoke side effects that have a serious impact on quality of life in these patients who usually have a life expectancy of several years. Furthermore, nausea, vomiting and hair loss were observed, but percentages in the group treated with the combination are similar to those after treatment with ^{177}Lu-

octreotate alone. None of the patients had symptoms of cardiac ischaemia or heart failure that could be attributed to capecitabine.

Of note is that so far, only acute and subacute side effects could be registered. No data are known yet about long-term side effects. The patients treated with the combination of ^{177}Lu-octreotate and capecitabine will therefore also be closely monitored in the future to reveal potential late toxic effects, e.g. on kidney function and bone marrow. The patients will undergo blood tests every 6 months and will also collect urine for 24 h to determine creatinine clearance and proteinuria.

Based on these findings, we conclude that the combination of ^{177}Lu-octreotate with capecitabine is safe and feasible in patients with GEP NETs with regard to short-term side effects. We recently started a randomised controlled clinical trial comparing treatment with ^{177}Lu-octreotate alone to treatment with ^{177}Lu-octreotate and capecitabine. Ultimately, the results of that study will provide final data about differences in anti-tumour effects and toxicity profiles between these treatments, also on the longer term.

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Chapter 6

Summary and General Discussion

The concept of using radiolabelled somatostatin analogues in clinical practice was first introduced by Krenning *et al.* who demonstrated the presence of somatostatin receptor (sst) positive tumours *in vivo* in patients. Initially a radio-iodinated analogue was used, but soon an indium-111 labelled analogue was made ([^{111}In-DTPA^{0}] octreotide, OctreoScan) which had several advantages over the radio-iodinated form. Because options for therapy in patients with metastasised gastroenteropancreatic neuroendocrine tumours were limited, the same group started to perform peptide receptor radionuclide therapy (PRRT) with high activity of ^{111}In-octreotide. This could lead to a symptomatic improvement in patients, but tumour shrinkage was rarely achieved *(1)*.

With the development of DOTA as chelator, somatostatin analogues also could be labelled with β-emitting radionuclides like yttrium-90 (^{90}Y) or lutetium-177 (^{177}Lu). Several centres then performed studies using [^{90}Y-DOTA^{0},Tyr^{3}] octreotide (^{90}Y-DOTATOC). Since 2000, PRRT at Erasmus MC is performed with [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate (^{177}Lu-octreotate or ^{177}Lu-DOTATATE). Esser *et al*. described that the tumour residence time on average was a factor 2.1 in favour of [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate over [^{177}Lu-DOTA^{0},Tyr^{3}] octreotide, and therefore concluded ^{177}Lu-octreotate was the better analogue to use for PRRT *(2)*.

A practical advantage of ^{177}Lu over ^{90}Y is, that ^{177}Lu emits γ-rays for imaging and dosimetry, whereas ^{90}Y is a pure β-emitter and therefore is less suitable for high-quality imaging or dosimetry.

This thesis is dealing with the clinical aspects of PRRT with ^{177}Lu-octreotate. The aim of these studies was to investigate anti-tumour effects of PRRT with ^{177}Lu-octreotate in patients with several kinds of sst-positive tumours and side-effects of both regular and additional therapies, and to study the side-effects of ^{177}Lu-octreotate in combination with capecitabine. Chapter 2 and 3 presented the anti-tumour effects and side effects of this therapy in different groups of patients and different tumours. In Chapter 4 effects of additional therapy with ^{177}Lu-octreotate were discussed. In Chapter 5, the first toxicity data on the combination of ^{177}Lu-octreotate with capecitabine were reported, to determine if this combination could be used in a randomised clinical trial with ^{177}Lu-octreotate as single agent as control group.

Chapter 1.1 presented a general introduction to somatostatin, its receptors and somatostatin receptor positive tumours. The emphasis was on gastroenteropancreatic neuroendocrine tumours (GEPNETs), including bronchial carcinoids and the therapeutic management of patients with GEPNETs. This section demonstrated there are few effective therapies for such patients. Also an overview was given of other somatostatin receptor positive tumours relevant for this thesis. **Chapter 1.2** provided a review of several PRRT studies with results, drawbacks and limitations of the studies pointed out. The aims and outline of this thesis

were described in **Chapter 1.3**.

In **Chapter 2.1** the results of regular therapy with ^{177}Lu-octreotate (cumulative dose up to 29.6 GBq) were described in the largest PRRT study till then in patients with metastasised and / or inoperable GEPNETs. Previous reports were in much smaller groups of patients *(3, 4)*. Toxicity data were analysed in 504 patients: 9.5% of patients had a grade 3 or 4 haematological toxicity after any of the administrations. Serious delayed side effects that were likely to be caused by the treatment occurred in approximately 1% of patients: 3 of 504 patients developed a myelodysplastic syndrome 2-3 years after therapy, and 2 patients with extensive liver metastases temporarily had liver insufficiency. None of the patients developed renal failure due to therapy with ^{177}Lu-octreotate. Partial and complete remissions (PR and CR) were seen in 2% and 28% of 310 analysed patients. Tumour shrinkage of 25-50% (minor response, MR) was achieved in 16% of patients. In 35%, stable disease (SD) was observed. Median time to progression in patients with at least SD was 40 months. This compares favourably to data from chemotherapy. For the first time, a survival analysis after therapy with ^{177}Lu-octreotate was performed: Overall median survival was 46 months. Median disease related survival was > 48 months. Significant factors predicting shorter survival were PD as treatment outcome, extensive liver load, poor clinical condition, baseline weight loss, presence of bone metastases and having a functioning pancreatic NET. Compared to historical controls from epidemiological and intervention studies, PRRT with ^{177}Lu-octreotate resulted in a survival benefit of 40 to 72 months from diagnosis. However, these data should be interpreted with some caution, since they were not derived from randomised trials.

In **Chapter 2.2**, results of therapy with ^{177}Lu-octreotate in patients with foregut carcinoids of bronchial, gastric and thymic origin were reported. This was done because foregut carcinoids have a different embryological origin from other GEPNETs and tend to behave more aggressively if metastasised. Treatment in the patients with foregut carcinoids was as effective as in the entire group of GEPNET patients: in patients with a bronchial carcinoid, 6 of 9 patients had tumour remission (MR, PR, CR) and 2 had SD, in gastric carcinoids 2 of 5 had tumour remission and 2 had SD. In patients with thymic carcinoids, 1 had SD and 1 had PD. Effects of therapy were compared to other PRRT studies that provided data on patients with foregut carcinoids and to chemotherapy. Although not based on randomised studies, ^{177}Lu-octreotate seemed more effective in terms of objective responses and time to progression than chemotherapy and PRRT with ^{111}In-octreotide or ^{90}Y-DOTATOC.

Chapter 3 presented the effects of therapy with ^{177}Lu-octreotate in non-GEPNET patients. Patients with paraganglioma / phaeochromocytoma, meningioma, small cell lung carcinoma and melanoma were treated using the same treatment protocol as in GEPNET patients. Of 12 patients with paraganglioma, tumour remission was achieved in 2, while

treatment outcome was PD in 3 patients. In 5 patients with meningioma, 2 patients with cavernous sinus meningioma tended to have stable disease (of whom 1 had proven PD at start); the remaining 3 patients had malignant / anaplastic (WHO grade III) meningiomas and continued to have PD despite therapy. It is of note that 2 patients had very large cranial meningiomas with exophytic growth, and that 1 patient had a rapidly growing cervical meningioma with distant bone metastases. In 3 patients with metastasised SCLC and 2 patients with metastasised melanoma, the present treatment protocol with ^{177}Lu-octreotate did not result in tumour stabilisation or shrinkage. In the whole group of studied patients, those with high tumour uptake on pre-therapy ^{111}In-octreotide scintigraphy tended to have better chances for having SD or tumour shrinkage. Since therapy outcome in the studied non-GEPNETs was less favourable than in GEPNETs, we investigated whether SCLC and paraganglioma had a faster rate of eliminating ^{177}Lu-octreotate from the tumour. This could not be demonstrated. Other possible explanations for the less favourable results could be that the studied tumours are less sensitive to radiation, have more areas of hypoxia, grow more rapidly or have less somatostatin receptor subtype 2 expression. We concluded that PRRT with ^{177}Lu-octreotate can be of value in patients with paraganglioma, and in some patients with meningioma. However, in patients with SCLC or melanoma, the currently used protocol was not effective. Possibly in the future, PRRT in these patients can be considered earlier in the course of the disease or in combination with other treatment modalities.

While in Chapter 2 and 3 clinical aspects of regular therapies with ^{177}Lu-octreotate were discussed, Chapter 4 and 5 dealt with aspects of other applications of ^{177}Lu-octreotate therapy. In **Chapter 4**, we described the effects of additional therapy with ^{177}Lu-octreotate ('salvage therapy') in patients who had a favourable response after regular therapy and subsequently developed progressive disease again. In this study, not only anti-tumour effects were important to analyse, but also the side effects, since the cumulative doses regarded as being safe for kidneys and bone marrow were surpassed. Forty-eight percent of patients again had benefit from the additional therapy with ^{177}Lu-octreotate (intended cumulative dose was 14.8 GBq). Better results were seen in patients who had a long-lasting response after regular therapy and in patients without elevated serum alkaline phosphatase levels. There were no differences in treatment outcome between pancreatic NET and carcinoid tumours. Very importantly, there were no serious delayed side effects, i.e. no renal failure or myelodysplastic syndrome, although sub-acute haematological toxicity seemed somewhat more frequent than with the regular therapy. Anti-tumour effects were less favourable than seen in the regular treatments. This could be due to the lower dose of administered activity or a worse clinical condition of the patients. Moreover, disease extent was higher in some patients. Also tumour characteristics could have changed over time (dedifferentiation, faster growth, lower expression of somatostatin receptors). In

addition, the patients so far treated may have had already more aggressive tumour types than patients from the entire group: median time to progression after regular therapy was 27 months in the patients with additional therapy, whereas it was 40 months in the entire group.

The regular therapy of ^{177}Lu-octreotate results in an important number of tumour responses, which are long lasting, can improve quality of life and seems to result in a survival benefit. However, methods to try and improve these results should be investigated. One of the possible ways is to combine ^{177}Lu-octreotate with radiosensitising agents like capecitabine. Before applying such a combination in a randomised study, data about toxicity of such new combination should be obtained. These data were presented in **Chapter 5**. The intended cumulative dose of ^{177}Lu-octreotate was 4 cycles of 7.4 GBq with an interval of 6-10 weeks. With all cycles, 825 mg / m^2 capecitabine twice a day was taken for 14 days, starting on the day of the infusion of ^{177}Lu-octreotate. This pilot study comprised 7 patients to whom a total of 26 cycles of ^{177}Lu-octreotate with capecitabine was administered. None of the patients had a grade 3 or 4 neutropenia or leukocytopenia. One patient had a grade 3 thrombocytopenia, and 1 had a grade 3 anaemia. No acute adverse events on kidney function were observed. Capecitabine specific toxicity was observed in 1 patient, who had a grade 1 stomatitis after 1 of 4 cycles. None of the patients had hand-foot syndrome or complaints consistent with myocardial ischemia. Based on the findings of this small study, we decided to start an open-label, randomised, clinical trial to compare the effects of ^{177}Lu-octreotate and capecitabine to those of ^{177}Lu-octreotate as single agent in patients with GEPNETs. Results are pending, but a preliminary toxicity analysis 18 months after start of the study demonstrated no serious additional risks in the combination group. Meanwhile, two other groups reported about combining PRRT with radiosensitisers *(5, 6)*.

In the Appendix **Chapter 8.1**, a description is given of those patients who developed a hormonal crisis after therapy with ^{177}Lu-octreotate. Special care is needed for patients with bronchial carcinoids, VIPoma and phaeochromocytoma, since these patients seem especially at risk. **Chapter 8.2** provides a broader review than Chapter 1.2 of PRRT and its position in the field of other therapies for patients with somatostatin receptor positive tumours.

FINAL CONCLUSION

Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-octreotate is an important treatment modality for patients with metastasised / inoperable gastroenteropancreatic neuroendocrine tumours. It results in tumour shrinkage or stable disease in 80% of patients

with a median time to progression of 40 months. Overall median survival compared very favourably to data from other studies, indicating a survival benefit of 3-6 years. Moreover, PRRT with ^{177}Lu-octreotate is a safe therapy, with serious delayed toxicity present in approximately 1% of patients. Special care needs to be taken for patients with highly hormonally active neuroendocrine tumours, as these patients are at risk for developing a hormonal crisis. ^{177}Lu-octreotate also is an effective treatment for patients with foregut carcinoids. However, randomised clinical trials, e.g. versus octreotide, are warranted to exactly determine the role of therapy with ^{177}Lu-octreotate in the therapeutic management in GEPNET patients.

In addition, PRRT with ^{177}Lu-octreotate can be effective in patients with paraganglioma, although tumour remission was observed more rarely than in GEPNET patients and can be considered in patients with meningioma as well. Unfortunately, therapy with ^{177}Lu-octreotate, using the current protocol, was not effective in patients with small cell lung carcinoma or melanoma.

When disease becomes progressive again in GEPNET patients with an initial favourable response, additional therapy cycles with ^{177}Lu-octreotate are a valuable option. This 'salvage' therapy can still be regarded as safe, and can be effective again, especially in those patients who progressed long after starting regular therapy. None of the patients developed serious delayed side effects, indicating that the dose limits for kidney and bone marrow, that were adhered to until now and formed the basis for the cumulative dose of regular therapy, may be an underestimation.

The pilot study with the combination of ^{177}Lu-octreotate and capecitabine demonstrated that it is safe. Therefore, we started a randomised clinical trial comparing this combination with ^{177}Lu-octreotate as single agent.

Other possible new ways to improve the effects of PRRT are combinations with other chemotherapeutic or molecular-targeted agents, e.g. angiogenesis inhibitors or mTOR inhibitors. These are currently under investigation in animal studies. Also combinations of the radionuclides ^{90}Y, ^{177}Lu and ^{111}In labelled to somatostatin analogues are worthwhile to examine given the different physical properties.

Moreover, more knowledge needs to be obtained on dosimetry and radiation effects. A recent study showed a marked variation between patients with regard to bone marrow radiation dose *(7)*.

Also kidney dose is highly variable. Serious delayed side effects were very rare with the regular treatment protocol. This can imply that a certain percentage of patients could have

received a higher cumulative dose than they did if individual dosimetry could have been performed. However, this is time-consuming and therefore costly. Also more knowledge needs to be obtained about organ dose limits for PRRT, as most limits nowadays were derived from external beam radiotherapy. More research needs to be done to reduce the amount of radiation to healthy tissues or reduce the noxious effects of radiation without affecting the therapeutic effects (See 'Future directions' in Chapter 1.2 as well).

Finally, peptide receptor radionuclide using radiolabelled somatostatin analogues is effective, safe and feasible. It is of considerable value in the arsenal of physicians taking care of patients with gastroenteropancreatic neuroendocrine tumours and can become the therapy of first choice when made available widespread. Discovery of other peptide receptors and their ligands in other forms of cancer, likely will increase the use of radiolabelled peptides for imaging and treating patients with these tumours in clinical practice.

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Hoofdstuk 7

Samenvatting en Algemene Discussie

Het concept om radioactief gemerkte somatostatine analogen in de klinische praktijk toe te passen werd als eerst door Krenning *et al.* geïntroduceerd. Zij toonden *in vivo* de aanwezigheid van somatostatine receptor (sst) positieve tumoren aan bij patiënten. Aanvankelijk werd een radio-gejodeerd analoog gebruikt, maar spoedig werd een indium-111 gemerkt analoog gemaakt ([^{111}In-DTPA^{0}] octreotide, OctreoScan) wat meerdere voordelen had boven de radio-gejodeerde vorm. Omdat de therapeutische opties voor patiënten met gemetastaseerde gastro-entero-pancreatische neuro-endocriene tumoren beperkt waren, begon dezelfde groep met het uitvoeren van peptide receptor radionuclide therapie (PRRT) met hoge activiteit ^{111}In-octreotide. Dit kon tot een symptomatische verbetering leiden, maar tumorverkleining werd zelden bereikt *(1)*.

Met de ontwikkeling van DOTA als chelator konden somatostatine analogen ook gemerkt worden met β-straling uitzendende radionucliden zoals yttrium-90 (^{90}Y) of lutetium-177 (^{177}Lu). Verscheidene centra voerden toen studies uit met [^{90}Y-DOTA^{0},Tyr^{3}] octreotide (^{90}Y-DOTATOC). Sinds 2000 wordt PRRT in het Erasmus MC verricht met [^{177}Lu-DOTA^{0},Tyr^{3}] octreotaat (^{177}Lu-octreotaat of ^{177}Lu-DOTATAAT). Esser *et al*. beschreven dat de 'tumorverblijftijd' (tumour residence time) gemiddeld een factor 2.1 hoger was ten gunste van [^{177}Lu-DOTA^{0},Tyr^{3}] octreotaat in vergelijking met [^{177}Lu-DOTA^{0},Tyr^{3}] octreotide, en concludeerden daarom dat ^{177}Lu-octreotaat een beter analoog is om te gebruiken bij PRRT *(2)*.

Een praktisch voordeel van ^{177}Lu boven ^{90}Y is dat ^{177}Lu γ-stralen uitzendt voor beeldvorming en dosimetrie, terwijl ^{90}Y een pure β-straler is en daardoor minder geschikt is voor beeldvorming of dosimetrie van hoge kwaliteit.

Dit proefschrift gaat over de klinische aspecten van PRRT met ^{177}Lu-octreotaat. Het doel van de studies was om anti-tumor effecten en bijwerkingen van PRRT met ^{177}Lu-octreotaat na te gaan in patiënten met verschillende soorten sst-positieve tumoren van zowel reguliere als aanvullende behandeling, en om de bijwerkingen na te gaan van ^{177}Lu-octreotaat gecombineerd met capecitabine. Hoofdstuk 2 en 3 gaven de anti-tumor effecten weer in verschillende groepen patiënten en verschillende tumoren. In hoofdstuk 4 werden de effecten van aanvullende behandelingen met ^{177}Lu-octreotaat beschreven. In hoofdstuk 5 werden de eerste gegevens over de toxiciteit van de combinatie van ^{177}Lu-octreotaat en capecitabine gerapporteerd, om te bepalen of deze combinatie gebruikt kon worden in een gerandomiseerde, klinische studie met ^{177}Lu-octreotaat als monotherapie als controlegroep.

Hoofdstuk 1.1 was een algemene inleiding over somatostatine, de receptoren en somatostatine-receptor positieve tumoren. De nadruk lag op gastro-entero-pancreatische neuro-endocriene tumoren (GEPNETs), inclusief bronchuscarcinoïden, en op het therapeutisch beleid bij patiënten met een GEPNET. Dit hoofdstuk toonde aan dat er weinig effectieve

therapieën zijn voor zulke patiënten. Ook werd een overzicht gegeven van andere soorten somatostatine receptor positieve tumoren die relevant zijn voor dit proefschrift. **Hoofdstuk 1.2** verschafte een overzicht van meerdere PRRT studies, waarbij resultaten, minpunten en beperkingen werden getoond. De doelen en opbouw van dit proefschrift werden beschreven in **Hoofdstuk 1.3**.

In **Hoofdstuk 2.1** werden de resultaten van tot dan de grootste PRRT studie beschreven in patiënten met gemetastaseerde en/of inoperabele GEPNETs. Eerdere studies betroffen veel kleinere groepen van patiënten *(3, 4)*. Toxiciteitsgegevens werden in 504 patiënten geanalyseerd: 9.5% van de patiënten had een graad 3 of 4 hematologische toxiciteit na enige therapie. Ernstige bijwerkingen op langere termijn die waarschijnlijk veroorzaakt werden door de behandeling kwamen in ongeveer 1% van de patiënten voor: 3 van de 504 patiënten ontwikkelden 2 tot 3 jaar na therapie een myelodysplastisch syndroom, en 2 patiënten met uitgebreide levermetastasen hadden tijdelijk leverinsufficiëntie. Geen van de patiënten ontwikkelde aan de behandeling te wijten nierfalen. Partiële en complete remissies (PR en CR) werden bereikt in 2% en 28% van de 310 geanalyseerde patiënten. Tumorverkleining van 25-50% (mineure respons, MR) werd bereikt in 16% van de patiënten. In 35% werd stabiele ziekte (stable disease, SD) waargenomen. Mediane tijd tot progressie in patiënten met ten minste stabiele ziekte was 40 maanden. Dit is gunstig vergeleken met gegevens van chemotherapie. Voor het eerst werd een analyse verricht van de overleving na therapie met ^{177}Lu-octreotaat: de algemene overleving ('overall survival') was 46 maanden. Ziektegerelateerde overleving was meer dan 48 maanden. Significante factoren die een kortere overleving voorspellen waren progressieve ziekte als therapie-uitkomst, uitgebreide levermetastasen, slechte klinische conditie, gewichtsverlies bij aanvang, botmetastasen en het hebben van een functionerende NET van de pancreas. In vergelijking met historische controles uit epidemiologische studies en interventiestudies leidde PRRT met ^{177}Lu-octreotaat tot een overlevingsvoordeel van 40 tot 72 maanden vanaf de diagnose. Deze gegevens moeten echter met enige voorzichtigheid geïnterpreteerd worden, omdat ze niet voortkomen uit gerandomiseerde studies.

In **Hoofdstuk 2.2** werden de resultaten gerapporteerd van therapie met ^{177}Lu-octreotaat in patiënten met voordarmcarcinoïden. Dit werd uitgevoerd, omdat voordarmcarcinoïden een andere embryologische oorsprong hebben dan overige GEPNETs en de neiging hebben zich agressiever te gedragen als ze zijn gemetastaseerd. De behandeling was even effectief in patiënten met voordarmcarcinoïden als in de hele groep van patiënten met een GEPNET: in patiënten met een bronchuscarcinoïd hadden 6 van de 9 patiënten tumorremissie (MR, PR, CR) en 2 hadden SD, bij maagcarcinoïd hadden 2 van de 5 patiënten tumorremissie en 2 hadden SD. In patiënten met een thymuscarcinoïd, had 1 patiënt SD en een ander progressieve ziekte (progressive disease, PD). De effecten van de therapie werden vergeleken met andere PRRT studies. Hoewel niet gebaseerd op gerandomiseerde

studies, leek ^{177}Lu-octreotaat effectiever in termen van objectieve respons en tijd tot progressie dan chemotherapie of PRRT met ^{111}In-octreotide of ^{90}Y-DOTATOC.

Hoofdstuk 3 gaf de effecten van therapie met ^{177}Lu-octreotaat weer in non-GEPNET-patiënten. Patiënten met een paraganglioom / feochromocytoom, meningioom, kleincellig longcarcinoom of melanoom werden behandeld volgens het zelfde protocol als patiënten met een GEPNET. In 2 van de 12 patiënten met een paraganglioom werd tumorremissie bereikt, terwijl de therapie-uitkomst in 3 patiënten PD was. In 5 patiënten met een meningioom hadden 2 patiënten met een sinus cavernosus meningioom stabiele ziekte (van wie 1 bewezen progressieve ziekte had bij aanvang). De overige 3 patiënten hadden een maligne / anaplastisch meningioom (WHO graad III) en behielden PD ondanks therapie. Opgemerkt dient te worden dat 2 patiënten zeer grote, exofytisch groeiende craniale meningiomen hadden, en dat een patiënt een snel groeiend cervicaal meningioom had met botmetastasen op afstand. In 3 patiënten met gemetastaseerd kleincellig longcarcinoom en 2 patiënten met gemetastaseerd melanoom leidde behandeling met ^{177}Lu-octreotaat volgens het huidige therapieprotocol niet tot stabilisatie of verkleining van de ziekte. Uitgaande van alle geanalyseerde patiënten van de studie leken diegenen met hoge tumoropname op ^{111}In-octreotide scintigrafie een hogere kans op stabiele ziekte of tumorverkleining te hebben. Omdat de therapie-uitkomst in de bestudeerde non-GEPNET minder gunstig waren dan in GEPNET hebben we onderzocht of kleincellig longcarcinoom en paraganglioom een snellere eliminatiesnelheid van ^{177}Lu-octreotaat uit te tumor hadden. Dit kon niet worden aangetoond. Andere mogelijke verklaringen voor de minder gunstige resultaten kunnen zijn dat de tumoren minder gevoelig voor straling zijn, ze meer gebieden met hypoxie hebben, sneller groeien of minder expressie van somatostatine receptor subtype 2 hebben. Wij concludeerden dat PRRT met ^{177}Lu-octreotaat van waarde kan zijn voor patiënten met een paraganglioom, en in sommigen met een meningioom. Het huidig gebruikte protocol was echter niet effectief in patiënten met een kleincellig longcarcinoom of melanoom. Mogelijk kan PPRT in de toekomst vroeger in het ziektebeloop overwogen worden of in combinatie met andere behandelingsmodaliteiten.

Terwijl in Hoofdstuk 2 en 3 de klinische aspecten van de reguliere behandeling met ^{177}Lu-octreotaat werden besproken, gaan Hoofdstuk 4 en 5 over aspecten van andere toepassingen van therapie met ^{177}Lu-octreotaat. In **Hoofdstuk 4** beschreven we de effecten van aanvullende therapie met ^{177}Lu-octreotaat ('salvage therapie') in patiënten die een gunstige response hadden na reguliere therapie en vervolgens weer progressieve ziekte ontwikkelden. In deze studie was het niet alleen belangrijk om de anti-tumor effecten te analyseren maar ook de bijwerkingen, omdat de cumulatieve dosis die als veilig voor de nieren en beenmerg wordt beschouwd werd overschreden. Achtenveertig procent van de patiënten hadden baat van de aanvullende therapie met ^{177}Lu-octreotaat (beoogde

cumulatieve dosis was 14.8 GBq). Betere resultaten werden gezien in patiënten met een lang aanhoudend effect van de reguliere therapie en in patiënten zonder verhoogd alkalisch fosfatase in serum. Er waren geen verschillen in therapie-uitkomst tussen NETs van de pancreas en carcinoïd tumoren. Belangrijk is dat er geen ernstige late bijwerkingen voorkwamen, d.w.z. geen nierfalen of myelodysplastisch syndroom, hoewel sub-acute hematologische toxiciteit enigszins vaker voor leek te komen dan met de reguliere therapie. Anti-tumor effecten waren minder gunstig dan met reguliere behandelingen. Dit kan te wijten zijn aan de lagere cumulatieve dosis van toegediende activiteit of een slechtere klinische conditie van de patiënten. Bovendien was de ziekte uitgebreider in sommige patiënten. Ook kunnen de tumoreigenschappen in de loop van de tijd veranderd zijn (dedifferentiatie, snellere groei, minder expressie van somatostatine receptoren). Verder hadden de patiënten die totnogtoe behandeld werden wellicht bij aanvang al agressievere tumoren: de mediane tijd tot progressie na reguliere therapie was 27 maanden in de patiënten met aanvullende therapie, terwijl dit 40 maanden was in de gehele groep.

De reguliere therapie met ^{177}Lu-octreotaat resulteert in een belangrijk aantal patiënten tot tumor respons die lang aanhoudt, kan de kwaliteit van leven verbeteren en lijkt te leiden tot een overlevingswinst. Er moeten echter wel methodes onderzocht worden om te proberen deze resultaten te verbeteren. Een van de mogelijke manieren is om ^{177}Lu-octreotaat te combineren met radiosensitiserende middelen, zoals capecitabine. Voor zo'n combinatie in een gerandomiseerde studie kan worden toegepast moeten er gegevens verkregen worden over de toxiciteit. Deze gegevens werden gepresenteerd in **Hoofdstuk 5**. De beoogde cumulatieve dosis ^{177}Lu-octreotaat was 4 cycli van 7.4 GBq met een interval van 6-10 weken. Met elke cyclus werd tweemaal daags 825 mg/m^2 capecitabine ingenomen gedurende 14 dagen, startend op de dag van de toediening van ^{177}Lu-octreotaat. Deze verkennende studie ('pilot-studie') betrof 7 patiënten aan wie in totaal 26 cycli ^{177}Lu-octreotaat met capecitabine werden toegediend. Geen van de patiënten had een graad 3 of 4 neutropenie of leukocytopenie. Een patiënt had een graad 3 thrombopenie, en een had een graad 3 anemie. Er werden geen acute bijwerkingen op de nierfunctie waargenomen. Capecitabine specifieke toxiciteit werd gezien in 1 patiënt met een graad 1 stomatitis na 1 van de 4 cycli. Geen van de patiënten had hand-voetsyndroom of klachten passend bij myocardischemie. Op basis van de bevindingen in deze kleine studie hebben we besloten om een open-label, gerandomiseerde, klinische studie te starten om de effecten van ^{177}Lu-octreotaat en capecitabine te vergelijken met die van ^{177}Lu-octreotaat als monotherapie in patiënten met GEPNETs. De resultaten volgen, maar een voorlopige toxiciteitsanalyse 18 maanden na het starten toonde geen ernstige, bijkomende risico's in de combinatiegroep. Ondertussen hebben twee andere onderzoeksgroepen gerapporteerd over het combineren van PRRT met radiosensitiserende middelen *(5, 6)*.

In de Appendix **Hoofdstuk 8.1** wordt een beschrijving gegeven van die patiënten die een hormonale crisis ontwikkelden na therapie met ^{177}Lu-octreotaat. Speciale zorg is nodig voor patiënten met een bronchuscarcinoïd, VIPoom en feochromocytoom, omdat deze patiënten een hoger risico hierop hebben. **Hoofdstuk 8.2** geeft een breder overzicht dan Hoofdstuk 1.2 van PRRT en de positie ervan in de behandeling van patiënten met somatostatine receptor positieve tumoren.

EINDCONCLUSIE

Peptide receptor radionuclide therapie (PRRT) met ^{177}Lu-octreotaat is een belangrijke behandelingsmodaliteit voor patiënten met een gemetastaseerde / inoperabele gastro-entero-pancreatische neuro-endocriene tumor (GEPNET). Het leidt tot tumorverkleining of stabiele ziekte in 80% van de patiënten met een mediane tijd tot progressie van 40 maanden. De mediane, algemene overleving is zeer gunstig vergeleken met gegevens uit andere studies, met aanwijzingen voor een overlevingsvoordeel van 3 tot 6 jaar. Bovendien is PRRT met ^{177}Lu-octreotaat een veilige behandeling, met ernstige bijwerkingen op langere termijn in ongeveer 1% van de patiënten. Speciale zorg is nodig voor patiënten met sterk hormonaal actieve neuro-endocriene tumoren, omdat deze patiënten risico lopen op het ontwikkelen van een hormonale crisis. ^{177}Lu-octreotaat is eveneens een effectieve behandeling voor patiënten met een bronchuscarcinoïd. Er zijn echter wel gerandomiseerde, klinische studies nodig, bijvoorbeeld versus octreotide, om de rol van de therapie met ^{177}Lu-octreotaat in het therapeutisch beleid voor GEPNET patiënten precies te bepalen.

Bovendien kan PRRT met ^{177}Lu-octreotaat effectief zijn in patiënten met een paraganglioom, hoewel tumorremissie zeldzamer was dan in GEPNET patiënten. Tevens kan therapie met ^{177}Lu-octreotaat overwogen worden in patiënten met een meningioom. Helaas was therapie met ^{177}Lu-octreotaat met het huidige protocol niet effectief in patiënten met kleincellig longcarcinoom of melanoom.

Wanneer de ziekte in GEPNET patiënten progressief wordt na aanvankelijk een goede response zijn aanvullende therapiecycli met ^{177}Lu-octreotaat een waardevolle optie. Deze salvagetherapie kan nog altijd als veilig worden beschouwd en kan opnieuw effectief zijn, vooral in patiënten die lange tijd na de reguliere therapie progressie ontwikkelden. Geen van de patiënten ontwikkelde ernstige bijwerkingen op langere termijn, wat een aanwijzing kan zijn dat de dosislimieten voor nier en beenmerg, die tot nu toe gerespecteerd worden en de basis vormden voor de cumulatieve dosis van de reguliere behandeling, een onderschatting zijn.

De verkennende studie met de combinatie van ^{177}Lu-octreotaat en capecitabine toonde dat dit veilig is. Daarom zijn we een gerandomiseerde studie gestart om deze combinatie te vergelijken met ^{177}Lu-octreotaat als monotherapie.

Andere mogelijke, nieuwe manieren om de effecten van PRRT te verbeteren zijn combinaties met andere chemotherapeutische of molecuulgerichte middelen, bijvoorbeeld angiogenese remmers of mTOR remmers. Deze worden onderzocht in dierstudies. Ook combinaties van de radionucliden ^{90}Y, ^{177}Lu en ^{111}In gekoppeld aan somatostatine analogen zijn waardevol om te onderzoeken gezien de verschillen in fysische eigenschappen.

Bovendien moet er meer kennis worden verkregen over dosimetrie en stralingseffecten. Een recente studie toonde een duidelijke variatie tussen patiënten met betrekking tot de beenmergdosis *(7)*.

De nierdosis is eveneens sterk variabel. Ernstige bijwerkingen op langere termijn waren zeer zeldzaam met het protocol voor de reguliere therapie. Dit kan betekenen dat een bepaald percentage van de patiënten een hogere dosis had kunnen krijgen dan ze hebben gehad, als individuele dosimetrie verricht had kunnen worden. Dit is echter tijdrovend en daardoor duur. Verder moet er meer kennis worden opgedaan over orgaandosislimieten voor PRRT, omdat de meeste limieten afgeleid zijn van externe radiotherapie. Tevens moet er meer onderzoek verricht worden om de hoeveelheid straling naar gezonde weefsels te verminderen of de schadelijke effecten van straling af te zwakken zonder de therapeutische effecten te beïnvloeden (zie ook 'Future directions' in Hoofdstuk 1.2).

Tot slot, peptide receptor radionuclide therapie met radioactief gemerkte somatostatine analogen is effectief, veilig en toepasbaar. Het is van aanzienlijke waarde in het arsenaal van artsen die zorg dragen voor patiënten met gastro-entero-pancreatische neuro-endocriene tumoren en kan de therapie van eerste keus worden wanneer het wijder beschikbaar wordt. De ontdekking van andere receptoren en hun ligand in andere vormen van kanker zal waarschijnlijk het gebruik van radioactief gemerkte peptiden voor beeldvorming en therapie bij patiënten met deze tumoren doen toenemen in de klinische praktijk.

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Chapter 8

Appendices

Chapter 8.1

Hormonal Crises Following Receptor Radionuclide Therapy with the Radiolabelled Somatostatin Analogue [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate

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ABSTRACT

Introduction

Receptor radionuclide therapy is a promising treatment modality for patients with neuroendocrine tumours for whom alternative treatments are limited. The aim of this study was to investigate the incidence of hormonal crises after therapy with the radiolabelled somatostatin analogue [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate).

Materials and methods

All ^{177}Lu-octreotate treatments between January 2000 and January 2007 were investigated. Four hundred seventy-six patients with gastroenteropancreatic neuroendocrine tumours and three patients with metastatic phaeochromocytoma were included for analysis.

Results

Four hundred seventy-nine patients received a total of 1,693 administrations of ^{177}Lu-octreotate. Six of 479 patients (1%) developed severe symptoms because of massive release of bioactive substances after the first cycle of ^{177}Lu-octreotate. One patient had a metastatic hormone-producing small intestinal carcinoid; two patients had metastatic, hormone-producing bronchial carcinoids; two patients had vasoactive intestinal polypeptide-producing pancreatic endocrine tumours (VIPomas); and one patient had a metastatic phaeochromocytoma. With adequate treatment, all patients eventually recovered.

Conclusion

Hormonal crises after ^{177}Lu-octreotate therapy occur in 1% of patients. Generally, ^{177}Lu-octreotate therapy is well tolerated.

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumours (GEPNETs) constitute a heterogeneous group of neoplasms. Two major GEPNET subcategories are intestinal endocrine tumours or carcinoids and pancreatic neuroendocrine tumours (PNETs). These tumours are often slow growing and may be associated with typical symptoms because of excessive and uncontrolled release of various metabolically active amines and peptides, such as serotonin, gastrin, glucagon, somatostatin, insulin, vasoactive intestinal polypeptide (VIP), and substance P. Phaeochromocytomas are catecholamine-producing tumours, which generally arise in the adrenal medulla.

A so-called carcinoid crisis is a medical emergency caused by the excessive release of metabolically active amines or peptides that can occur spontaneously, after manipulation of a carcinoid tumour, during induction of anaesthesia, during surgery, endoscopy, or with chemotherapy*(1–5)*. The symptomatology involves profound flushing, hypotension, or extreme changes in blood pressure, diarrhoea, bronchoconstriction, and arrhythmias *(6)*. So far, only one case of a carcinoid crisis after therapy with a radiolabelled somatostatin analogue has been described *(7)*. Another well-recognised endocrine emergency can occur in patients with phaeochromocytomas. This is caused by the massive release of catecholamines, which can occur spontaneously, after manipulation of the tumour or during medical interventions *(8)*.

Since the year 2000, patients with somatostatin receptor-positive metastatic, inoperable GEPNETs and malignant phaeochromocytomas have been treated with the radiolabelled somatostatin analogue [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate (^{177}Lu-octreotate) in our institution. Results of ^{177}Lu-octreotate treatment in these patients are promising, with tumour size reduction in 47% of the treated patients *(9)*.

Although infrequent, hormonal release-induced crises can occur after ^{177}Lu-octreotate treatment. In this study, we describe all patients who developed a hormonal crisis in association with peptide receptor radionuclide therapy with ^{177}Lu-octreotate.

MATERIALS AND METHODS

Patients

All patients with neuroendocrine tumours treated in our institution treated with ^{177}Lu-octreotate between January 2000 and January 2007 were included in this study. All patients fulfilled the inclusion criteria for ^{177}Lu-octreotate therapy *(9)*. All patients gave written informed consent to undergo ^{177}Lu-octreotate therapy. This therapy was approved by the medical ethical committee of our hospital.

Methods

^{177}Lu-octreotate was prepared as described previously *(10)*.

Somatostatin analogue therapy was discontinued in 193 of 200 patients during ^{177}Lu-octreotate therapy. Long-acting somatostatin analogues (Sandostatin LAR, Lanreotide Autogel) were discontinued 1,5 month before therapy. Thereafter, therapy was switched to an immediate release somatostatin analogue (Octreotide) that was discontinued 1 day before ^{177}Lu-octreotate therapy. An infusion of amino acids (2.5% arginine, 2.5% lysine 1 L / 4 h) was administered to reduce the radiation dose to the kidneys, starting 30 min before administration of 7,400 MBq ^{177}Lu-octreotate. Generally, four cycles of ^{177}Lu-octreotate were given.

Routine haematology and liver and kidney function tests, as well as serum chromogranin A measurements (CgA), were performed before each therapy cycle in all patients. Additionally, 5-hydroxy-indole-acetic-acid (5HIAA) measurements in 24-h urine in the carcinoid patients, serum vasoactive intestinal peptide in the VIPoma patients, serum gastrin in gastrinoma patients, and excretion of normetanephrines and metanephrines in the 24-h urine in the patients with a metastatic phaeochromocytoma were measured (laboratory normal values: CgA < 100 μg/L, 5HIAA < 50 μmol/24 h, VIP 25–65 pg/mL, gastrin < 0.15 μg/L, metanephrines < 2 μmol/24 h, normetanephrines < 5.1 μmol/24 h).

RESULTS

Patient characteristics

Four hundred seventy-nine patients with neuroendocrine tumours were studied: 262 men (55%), and 217 women (45%). Two hundred sixty-five patients (53%) had metastatic carcinoid tumours: 52 patients (11%) had metastatic neuroendocrine tumours of unknown origin, 124 patients (26%) had non-functioning PNETs, 35 patients (7%) had functioning PNETs, and 3 patients (1%) had metastatic phaeochromocytoma. The mean age at the time of the first therapy was 56 years (range, 16–85), and the mean Karnofsky performance score was 90 (range, 50–100). The tumour burden in the majority of the patients was high with liver metastases in 88% and bone metastases in 26% of the patients. Before ^{177}Lu-octreotate therapy, 42% of patients were using somatostatin analogues to reduce hormonal symptoms. Patient characteristics are shown in Table 1.

Table 1. Patients' characteristics.

Tumour type	Number of patients	Somatostatin analogue pretreatment	Liver metastases	Bone metastases	CgA (µg/l) median (range)	Relevant laboratory findings median (range)
Carcinoids						
Digestive tract carcinoid	241	142	223	57	537 (22–787,742)	Urinary 5HIAA (µmol/24 h) 222 (7–2,048)
Bronchial carcinoid	20	7	16	13	1,252 (35–900,280)	Urinary 5HIAA (µmol/24 h) 191 (15–1,440)
Thymic carcinoid	4	0	1	1	294 (147–725)	–
Functioning PNETs						
VIPoma	3	0	3	9	153 (22–318)	VIP (pg/ml) 470 (144–710)
Insulinoma	11	3	8	4	1256 (69–21,509)	–
Gastrinoma	21	8	19	5	2,282 (111–55,715)	Gastrin (µg/l) 1.2 (0.03–22)
Non functioning PNETs	124	25	107	24	385 (26–162,710)	–
Neuroendocrine tumour of unknown origin	52	10	44	18	400 (23–29,110)	–
Metastatic phaeochromocytoma	3	1	1	2	5,666 (928–6,900)	–
Total	479	200 (42%)	422 (88%)	124 (26%)		

Abbreviations: *CgA*, serum chromogranin A; *Digestive tract carcinoid*, gastric, duodenum, short bowel, colon, and rectum carcinoids; *5HIAA*, 5-hydroxyindoleacetic acid; *PNETs*, pancreas neuroendocrine tumours; *VIP*, vasoactive intestinal peptide.
Laboratory normal values: CgA < 100 µg/l, 5HIAA < 50 µmol/24 h, VIP 25–65 pg/ml, gastrin < 0.15 µg/l.

Therapy and complications

The 479 patients received a total of 1,693 administrations of ^{177}Lu-octreotate. Mild side effects within 24 h after ^{177}Lu-octreotate therapy were nausea after 25%, vomiting after 10%, and increase of abdominal pain/discomfort after 9% of the treatment cycles.

After 10 of 1,691 (0.6%) administrations of ^{177}Lu-octreotate in six patients (1%), readmission or prolonged hospitalisation because of hormonal release-induced crisis was necessary. Two of 20 patients with bronchial carcinoids, 2 of 3 patients with a VIPoma, 1 of 241 patients with a digestive tract carcinoid, and 1 of 3 patients with a phaeochromocytoma had a crisis. All patients developing a crisis had extensive metastatic disease, all patients had liver metastases, and three also had skeletal metastases. Post-therapeutic scintigrams showing ^{177}Lu-octreotate uptake in the metastases are shown in Fig. 1. Also, all patients had clinically overt hormonal-release-related symptomatology, like flushing and severe diarrhoea. In two of these patients, hormonal symptoms were so severe that discontinuation of somatostatin analogue therapy before peptide receptor radionuclide therapy was

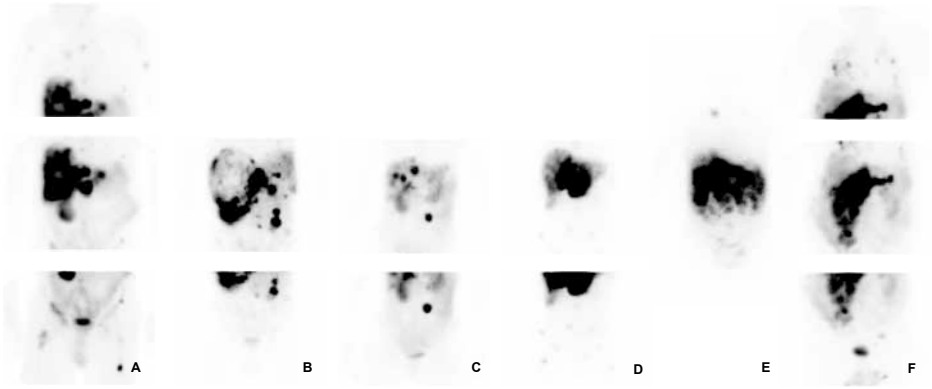

Figure 1. Post-therapy scintigrams after ^{177}Lu-octreotate of patient 1 **(A)**, patient 2 **(B)**, patient 3 **(C)**, patient 4 **(D)**, patient 5 **(E)**, and patient 6 **(F)**. *Upper row* Anterior images of the thorax, *middle row* anterior images of the abdomen, and *lower row* anterior images of the pelvic region. Note the focal increased ^{177}Lu-octreotate accumulations in liver metastases in all patients and focal uptake in bone metastases in patients 1, 2, and 4. In patient 6, there was also uptake in multiple lung metastases

impossible. Characteristics of these patients are shown in Table 2. In all six patients, the hormonal crisis occurred during the first therapy cycle; three of the six patients developed the crisis during or directly after ^{177}Lu-octreotate infusion, and the other three patients developed the crisis 48 h after^{177}Lu-octreotate infusion.

The treatment included high-dose octreotide, i.v. fluid replacement, and other supportive measures (as shown in Table 2); all patients fully recovered. In all six patients who developed a hormonal crisis after their first therapy cycle, additional precautions were taken before the administration of further therapy cycles, including continuation of somatostatin analogues, corticosteroids, prolonged observation in the hospital after therapy, and reduction of administered dosage of ^{177}Lu-octreotate. Despite these precautions, three patients developed a hormonal release-induced crisis again after a subsequent cycle of ^{177}Lu-octreotate.

Table 2. Characteristics of patients with a hormonal crisis after ^{177}Lu-octreotate treatment.

Case	Age/Sex	Tumour	Years since diagnosis	Treatment before ^{177}Lu-octreotate	Clinical symptoms before ^{177}Lu-octreotate	Relevant laboratory findings before ^{177}Lu-octreotate	Continuation of somatostatin analogues prior to ^{177}Lu-octreotate	Onset of "crisis" in relation to administration of ^{177}Lu-octreotate	Predominant symptomatology	Treatment of "crisis"	Duration of hospitalisation	Disease course
1	65/M	Bronchial carcinoid with mediastinal lymph node, liver and bone metastases	4	External radiation therapy, octreotide LAR	Flushing and diarrhoea, several carcinoid crises requiring hospitalisation	CgA 4,379 µg/l, urinary 5HIAA 399 µmol/24 h	No	Immediately	Nausea, worsening of diarrhoea, severe flushing	Fluids i.v., octreotide, corticosteroids, metoclopramide, loperamide	5 days	2 more cycles of ^{177}Lu-octreotate treatment without discontinuation of octreotide treatment. Both again leading to hormonal release requiring hospitalisation. Died after 1 year because of progressive disease
2	62/F	Bronchial carcinoid with liver and bone metastases	11	Lobectomy left upper lobe, external radiation therapy, intrabronchial laser coagulation of tumour, octreotide LAR, interferon-α	Flushing and diarrhoea, carcinoid crisis after intrabronchial laser coagulation of tumour	CgA 110,000 µg/l 978 µmol/24 h	No	After 2 days	Severe flushing, worsening of diarrhoea, dehydration	Fluids i.v., corticosteroids, octreotide	11 days	3 more cycles of ^{177}Lu-octreotate, with discontinuation of octreotide treatment without serious side effects. Died after 1 year because of progressive disease
3	53/F	VIPoma with liver metastases	1	Distal pancreatectomy, radiofrequency ablation of liver metastases, cisplatin, etoposide, octreotide LAR	Severe diarrhoea, hypokalaemia and dehydration	VIP 470 pg/ml CgA 318 µg/l	No	After 2 days	Nausea, severe diarrhoea, metabolic acidosis, hypokalaemia dehydration	Fluids i.v., potassium, metoclopramide, octreotide	4 days	3 more cycles of ^{177}Lu-octreotate, with discontinuation of octreotide treatment 1 year later improvement of general condition, less diarrhoea and less flushing

Case	Age/Sex	Tumour	Years since diagnosis	Treatment before ^{177}Lu-octreotate	Clinical symptoms before ^{177}Lu-octreotate	Relevant laboratory findings before ^{177}Lu-octreotate	Continuation of somatostatin analogues prior to ^{177}Lu-octreotate	Onset of "crisis" in relation to administration of ^{177}Lu-octreotate	Predominant symptomatology	Treatment of "crisis"	Duration of hospitalisation	Disease course
4	44/F	VIPoma with liver and bone metastases	2	Streptozine, 5-fluoracil and adriamycine, embolisation of liver metastases, lanreotide octreotide, loperamide, potassium	Flushing and diarrhoea hypokalaemia and dehydration	VIP 710 pg/ml CgA 335 µg/l	Yes	Immediately	Severe diarrhoea, metabolic acidosis, hypokalaemia, dehydration	Fluids i.v., potassium, octreotide, loperamide, metoclopramide	13 days	2 more cycles of ^{177}Lu-octreotate, with continuation of octreotide and corticosteroids. After the second cycle again hormonal crisis requiring hospitalisation. Died after 1 year because of progressive disease
5	50/M	Small intestinal carcinoid with liver metastases	15	Debulking surgery, interferon-alpha, 5-fluorouracil and leucovorin, octreotide LAR	Flushing and diarrhoea	CgA 2950 µg/l, urinary 5HIAA 902 µmol/24 h	Yes	Immediately	Nausea, vomiting, flushing, hypotension	Fluids i.v., octreotide, metoclopramide	6 days	6 more cycles of ^{177}Lu-octreotate (half dose, 3,700 MBq) without discontinuation of octreotide. After second cycle, again hormonal crisis requiring hospitalisation. Still alive after 2 years, still episodic diarrhoea
6	63/M	Malignant phaeochromocytoma with lung bone abdominal lymphnode and liver metastases	2	Adrenalectomy, α- and β-adrenergic blockade, octreotide	Nausea	Urinary normetanephrines 79 µmol/24 h, urinary metanephrines 10 µmol/24 h; CgA 6,900 µg/l	No	After 1 day	Hypotension, extensive sweating, cardiac ischaemia	Fentolamine, octreotide, bisoprolol, morfine	2 months	3 more cycles ^{177}Lu-octreotate without side effects (with continuation of octreotide and corticosteroids). Died after 1 1/2 years because of progressive disease

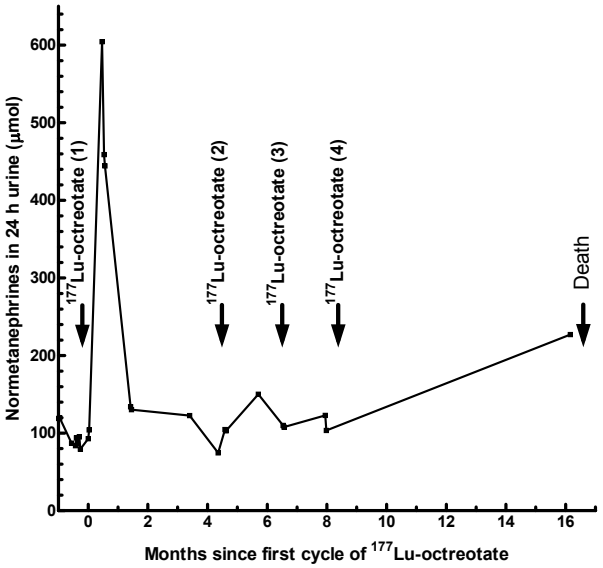

Figure 2. Normetanephrines in 24 h urine (µmol) of patient 6 after ^{177}Lu-octreotate treatment. Note the excessive release of normetanephrines after the first cycle of ^{177}Lu-octreotate. Normal value urinary normetanephrines: <5.1µmol/24 h

In two patients, hormonal release could be biochemically confirmed. We observed massive release of CgA in patient 1. CgA levels increased from 4,379 at baseline to 24,661 µg/L, 24 h after ^{177}Lu-octreotate. Multiple urinary normetanephrines measurements were performed in patient 6; severely increased excretion of normetanephrines was observed shortly after therapy with ^{177}Lu-octreotate (Fig. 2)

DISCUSSION

Hormonal crises after ^{177}Lu-octreotate therapy occur infrequently; only 6 of 479 patients with GEPNETs and malignant phaeochromocytomas had a crisis. These patients all had preexisting clinically overt symptoms like flushing and diarrhoea. All six patients had liver metastases, and three of six patients also had bone metastases. Patients who did not have a crisis after the first administration of ^{177}Lu-octreotate also did not develop a hormonal crisis after subsequent cycles.

In our series, two of three patients treated for metastatic VIPoma developed a hormonal crisis after ^{177}Lu-octreotate. VIPomas are associated with a well-defined clinical syndrome characterised by severe watery diarrhoea, hypokalemia, and metabolic acidosis (Verner–Morrison syndrome) *(11)*. Also, 2 of 20 patients treated for metastatic bronchial

carcinoid developed a carcinoid crisis. The carcinoid syndrome in patients with metastatic bronchial carcinoids is mediated by 5-hydroxytryptophan, its conversion to serotonin and/or by histamine *(12)*. The only other documented carcinoid crisis after radionuclide receptor therapy also involved a patient with a bronchial carcinoid *(7)*. Only one of the 241 patients with a carcinoid originating from the digestive tract had a hormonal crisis.

One of the three patients treated for a metastatic phaeochromocytoma developed a phaeochromocytoma crisis. Hormonal crises in phaeochromocytoma patients because of massive release of catecholamines can lead to multiple clinical features including (episodic) hypertension or hypotension, myocardial ischemia, cardiomyopathia, pulmonary edema, and shock *(13, 14)*. After ^{131}I-MIBG therapy, excessive catecholamine secretion with the above-mentioned severe symptomatology has been reported *(15, 16)*.

No serious hormonal release-induced side effects were observed in patients with other tumours; there were no episodes of severe hypoglycemia in patients with metastatic insulinoma, and none of the patients with metastatic gastrinoma, non-functioning GEPNETs, or neuroendocrine tumours of unknown origin developed a hormonal crisis after ^{177}Lu-octreotate.

The exact mechanism of increased hormonal release in the patients developing a hormonal crisis after ^{177}Lu-octreotate is not fully elucidated. Several mechanisms may have accounted for the induction of such a crisis in our patients: (1) tumour lysis because of β-irradiation from ^{177}Lu, (2) discontinuation of short-acting somatostatin analogues before ^{177}Lu-octreotate administration, (3) emotional stress response to hospitalisation and/or therapy, or (4) administration of amino acids (2.5% arginine and 2.5% lysine). These amino acids might be used as substrates for increased hormone synthesis by the tumour cells.

Arguments for tumour lysis because of β-irradiation are the relatively late onset of complaints (>24 h after therapy) in patients 2, 3, and 6. Patients 1, 4, and 5 had direct onset of complaints during ^{177}Lu-octreotate infusion; these crises cannot be explained by tumour lysis. In patients 4 and 5, the hormonal crisis might have been induced by emotional stress in combination with amino acid infusion. These patients continued their somatostatin analogue therapy. It is well known that emotional stress can provoke flushing *(17)*; therefore, it might also be possible that emotional distress, present in carcinoid patients *(18)*, might have played a role in the development of the hormonal crises in these patients. In patient 1, the hormonal crisis might also be related to discontinuation of somatostatin analogue therapy. When possible, we stop somatostatin analogues before ^{177}Lu-octreotate therapy to prevent competitive binding to the somatostatin receptors with ^{177}Lu-octreotate. The basis for this approach is the finding of a decreased ^{111}In-octreotide uptake by the tumour (although not significant) in patients continuing somatostatin analogue treatment compared to patients discontinuing somatostatin analogue treatment *(19)*.

Direct receptor-mediated hormonal release by ^{177}Lu-octreotate seems unlikely. Somatostatin receptor binding leads to decrease in hormonal secretion in the majority of patients. Therapy with somatostatin analogues in patients with metastatic carcinoid tumours results in symptomatic improvement in more than 70% of the patients and biochemical response in 50 to 60% of the patients *(20, 21)*.

All patients received further cycles of ^{177}Lu-octreotate after their first hormonal crisis. When re-treating these patients, continuation of somatostatin analogues in combination with corticosteroids is indicated *(22, 23)*. In one patient, we halved the administered activity to 3,700 MBq ^{177}Lu-octreotate to decrease potential tumour lysis because of β-irradiation. Of course, important drawback of such a treatment protocol is that the tumour-absorbed radiation dose will also be decreased.

Recommended treatment of patients with hormonal crises are high-dose somatostatin analogues i.v., i.v. fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhoea and vomiting. Patients with metastatic phaeochromocytoma should also be treated with α- and β-adrenergic blockade. From the present experience, we also recommend continuation of somatostatin analogue therapy in patients with metastatic VIPomas and bronchial carcinoids who have symptomatology of (atypical) carcinoid syndrome.

CONCLUSION

Hormonal crises after ^{177}Lu-octreotate occur infrequently. In our series, only 6 of 479 patients had such a crisis. Patients treated for VIPoma or bronchial carcinoids are most at risk. All patients with a hormonal crisis eventually recovered. Other less serious side effects shortly after ^{177}Lu-octreotate, such as nausea, vomiting, and abdominal pain, are more common and can be controlled by supportive measures. Generally, ^{177}Lu-octreotate therapy is well tolerated.

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Chapter 8.2

Peptide Receptor Radionuclide Therapy with Radiolabelled Somatostatin Analogues in Patients with Somatostatin Receptor Positive Tumours

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ABSTRACT

Peptide Receptor Radionuclide Therapy (PRRT) with radiolabelled somatostatin analogues is a promising treatment option for patients with inoperable or metastasised neuroendocrine tumours. Symptomatic improvement may occur with all of the various ^{111}In, ^{90}Y, or ^{177}Lu-labelled somatostatin analogues that have been used. Since tumour size reduction was seldom achieved with ^{111}In labelled somatostatin analogues, radiolabelled somatostatin analogues with β-emitting isotopes like ^{90}Y and ^{177}Lu were developed. Reported antitumour effects of [^{90}Y-DOTA^{0},Tyr^{3}]octreotide vary considerably between various studies: Tumour regression of 50% or more was achieved in 9 to 33% (mean 22%). With [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate treatments, tumour regression of 50% or more was achieved in 28% of patients and tumour regression of 25 to 50% in 19% of patients, stable disease was demonstrated in 35% and progressive disease in 18%. Predictive factors for tumour remission were high tumour uptake on somatostatin receptor scintigraphy and limited amount of liver metastases. The side-effects of PRRT are few and mostly mild, certainly when using renal protective agents: Serious side-effects like myelodysplastic syndrome or renal failure are rare. The median duration of the therapy response for [^{90}Y-DOTA^{0},Tyr^{3}]octreotide and [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate is 30 months and more than 36 months respectively. Lastly, quality of life improves significantly after treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. These data compare favourably with the limited number of alternative treatment approaches, like chemotherapy. If more widespread use of PRRT is possible, such therapy might become the therapy of first choice in patients with metastasised or inoperable gastroenteropancreatic neuroendocrine tumours. Also the role in somatostatin receptor expressing non-GEP tumours, like metastasised paraganglioma/phaeochromocytoma and non-radioiodine-avid differentiated thyroid carcinoma might become more important.

INTRODUCTION

Neuroendocrine gastroenteropancreatic (GEP) tumours can be divided into endocrine pancreatic tumours (either functioning or non-functioning) and carcinoids and usually are slow growing. Treatment with somatostatin analogues like octreotide and lanreotide can reduce hormonal overproduction and results in symptomatic relief in most patients with metastasised disease. However, tumour size reduction with somatostatin analogue treatment is seldom achieved *(1–3)*.

Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues is a relatively new and promising treatment modality for patients with inoperable or metastasised endocrine GEP tumours. Somatostatin receptors are present on the majority of endocrine GEP tumours and these can be visualised in patients using the radiolabelled somatostatin analogue [^{111}In-DTPA^{0}]octreotide (OctreoScan). Also other tumours, e.g. paragangliomas and thyroid carcinomas may be visualised. After the successful studies to visualise somatostatin receptor positive tumours, a logical next step was taken in trying to use radiolabelled somatostatin analogues as a treatment in these patients. Table 1 and Figure 1 provide information on the several radionuclides and peptides used for PRRT.

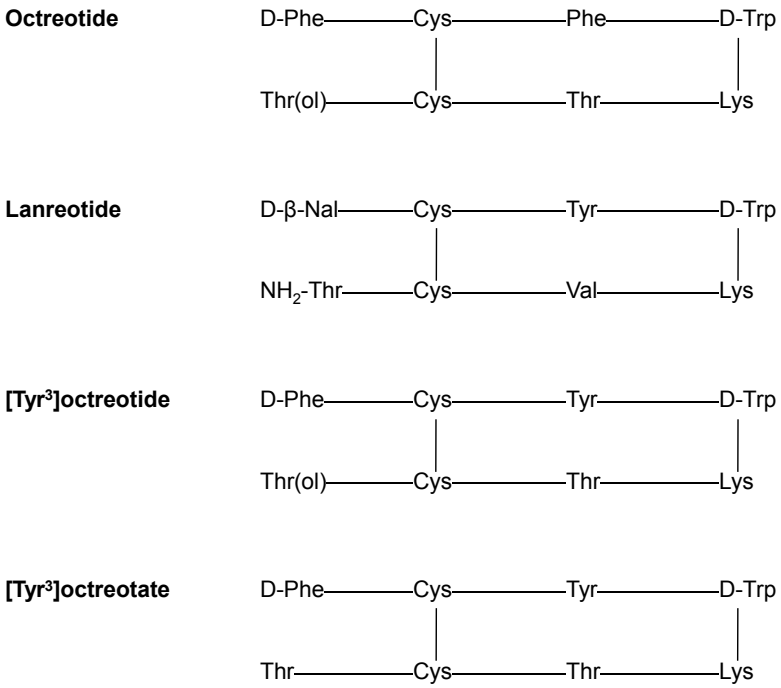

Figure 1. Amino acid sequence of several somatostatin analogues used for PRRT.

Table 1. Characteristics of radionuclides used for PRRT.

Radionuclide	Half life (days)	Emissions	Mean Energy (keV)	Maximum tissue penetration range of particle
Indium-111 (^{111}In)	2.8	γ rays	171 and 245	
		Auger electrons	3.6 and 19	10 µm
Yttrium-90 (^{90}Y)	2.7	β particles	934	12 mm
Lutetium-177 (^{177}Lu)	6.7	β particles	149	2 mm
		γ rays	208	

PRRT STUDIES WITH [^{111}IN-DTPA^{0}]OCTREOTIDE

Early studies in the mid- to late-1990s used [^{111}In-DTPA^{0}]octreotide for PRRT, because at that time no somatostatin analogues labelled with β-emitting radionuclides like ^{90}Yttrium (^{90}Y) or ^{177}Lutetium (^{177}Lu) were available. Studies with high activities of [^{111}In-DTPA^{0}] octreotide in patients with metastasised neuroendocrine tumours were encouraging with regard to symptom relief, but tumour size remission was exceptional *(4-5)*. Five of 26 patients with GEP tumours had a decrease in tumour size of between 25 and 50% (minor response, MR), as measured on CT scans *(4)*. They were treated with high activities of [^{111}In-DTPA^{0}]octreotide and received a total cumulative activity of at least 550 mCi (20GBq). None, however, had partial remission (PR). In another study with 27 patients with GEP tumours, PR was reported in 2/26 patients with measurable disease *(5)*. In both series, many patients were in a poor clinical condition and many had progressive disease at baseline. The most common long-term side effects in both series were due to bone marrow toxicity. Serious side effects consisted of leukaemia and myelodysplastic syndrome (MDS) in three patients. They had been treated with total cumulative activities of >2.7 Ci (100 GBq) and bone marrow radiation doses were estimated to be more than 3 Gy *(4)*. One of these patients had also been treated with chemotherapy previously, which may have contributed to or caused this complication. Anthony *et al. (5)* reported renal insufficiency in one patient. This was probably due to pre-existent retroperitoneal fibrosis and not treatment-related. In three patients with widespread liver metastases transient hepatic toxicity was observed.

[^{111}In-DTPA^{0}]octreotide was also used in treating patients with differentiated thyroid carcinoma. In this group, no tumour remission was observed in two studies *(4, 6)* of respectively five and nine patients. In three patients with phaeochromocytoma treated with [^{111}In-DTPA^{0}]octreotide, no objective response was demonstrated, but one patient with paraganglioma had a minor response *(4)*.

It is not surprising that CT-assessed tumour regression was observed only in rare cases. ^{111}In-coupled peptides are not ideal for PRRT because of the small particle range of Auger-electrons and therefore shorter tissue penetration compared to β-particle emitters.

PRRT STUDIES WITH [^{90}Y-DOTA^{0},TYR^{3}]OCTREOTIDE

The modified somatostatin analogue [DOTA^{0},Tyr^{3}]octreotide was used in the next generation of somatostatin receptor targeted radionuclide therapy. This analogue has a higher affinity for somatostatin receptor subtype-2, and has DOTA instead of DTPA as chelator. This allows a more stable binding of the intended β-emitting radionuclide ^{90}Y. Several phase-1 and phase-2 PRRT trials were performed using [^{90}Y-DOTA^{0}-Tyr^{3}]octreotide (^{90}Y-DOTATOC; OctreoTher) in various countries.

Different phase-1 and phase-2 studies were performed in Switzerland in patients with neuroendocrine GEP tumours *(7–10)*. A dose escalating scheme of up to a cumulative activity of 160 mCi (6GBq)/m^2 divided over four cycles was used in initial studies with amino acid infusion as renal protection in half of the patients. Four of 29 patients developed renal insufficiency. These four patients had not received renal protection. The overall response rate was 24% in patients with GEP tumours who were either treated with 160 mCi (6GBq)/m^2 *(8)*, or, in a later study, with 200 mCi (7.4GBq)/m^2 in four cycles *(9)*. In a subsequent study, with the same activity of 200 mCi (7.4GBq)/m^2 administered in two sessions, complete and partial remissions were found in one third of 36 patients *(10)*. Although the latter treatment protocol seems more beneficial, it is important to realise that this was not a randomised trial comparing two dosing schemes. The patient characteristics of the second study *(10)* were more favourable for chances of tumour remission: that study comprised far less carcinoid tumours than the first study *(9)*, whereas carcinoids clearly had a lower remission rate (10%) in their first study compared to pancreatic neuroendocrine tumours or neuroendocrine tumours of unknown origin *(9)*.

Dosimetric and dose-finding studies with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide with and without the administration of renal protecting agents were performed in Milan, Italy *(11)*. They observed no major acute reactions when administering doses up to 150mCi (5.6GBq) per cycle. In 43% of patients injected with 140mCi (5.2GBq), reversible grade 3 haematological toxicity was found and this was then defined as the maximum tolerated dose per cycle. Acute or delayed kidney failure did not develop in any of the patients, although follow-up was short. This included 30 patients in the first phase of the study who received three cycles of up to 2.59GBq per cycle without renal protection. This research group reported partial and complete remissions in 28% of 87 patients with neuroendocrine tumours (12).

The same group (13) later reported the results of a phase-1 study in 40 patients with somatostatin receptor positive tumours, including 21 with GEP tumours. The treatment

consisted of two treatment cycles with cumulative total activities ranging from 160 to 300mCi (5.9–11.1GBq). Six of 21 (29%) patients had tumour regression and median duration of the response was 9 months.

Bushnell *et al. (14)* reported a favourable clinical response in 14/21 patients treated with a total cumulative activity of 360 mCi [^{90}Y-DOTA^{0},Tyr^{3}]octreotide in three cycles. They determined this response by a scoring system that included weight, patient-assessed health score, Karnofsky performance score, and tumour-related symptoms.

[^{90}Y-DOTA^{0},Tyr^{3}]octreotide was also given as part of a multi-centre phase-1 study. Sixty patients received escalating activities up to 400 mCi (14.8GBq)/m^{2} in four cycles or up to 250 mCi (9.3GBq)/m^{2} single dose, without reaching the maximum tolerated single dose *(15)*. For renal protection, amino acids were administered concomitantly with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide. The cumulative radiation dose to kidneys was limited to 27 Gy based on positron emission tomography data using [^{86}Y-DOTA^{0},Tyr^{3}]octreotide, also under concomitant amino acid infusion. In three patients dose-limiting toxicity was observed: one transient hepatic toxicity, one thrombocytopenia grade 4 (<25 x 10^{9}/L), and one MDS. Fifty-eight patients had carcinoids or other GEP tumours. Seven patients had MR (12%) and five had PR (9%). Disease was stable in 29 patients (50%) and progressive in 14 (24%). Outcome could not be determined in three patients. In the subgroup of 41 patients with at least stable disease (SD) as treatment outcome, median time to progression was 29.3 months. Median overall survival since the start of therapy was 36.7 months, considering all patients.

In the same group of patients *(15)*, long-term follow-up of kidney function was performed. As there is physiological renal retention of radiolabelled somatostatin analogues, the renal radiation dose is a limiting factor in the amount of radioactivity that can be safely administered. Valkema *et al.* reported a median annual decline in creatinine clearance of 7.3% in patients treated with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide *(16)*. The following factors probably contribute to the rate of this decline: cumulative renal radiation dose, renal radiation dose per cycle, age, hypertension and diabetes. In two of 28 patients radiation nephropathy was histologically confirmed.

Complete plus partial remissions in most of the studies with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide in patients with GEP tumours range between 9 and 33% despite differences in various used protocols. These results are better than those obtained with [^{111}In-DTPA^{0}]octreotide.

[^{90}Y-DOTA^{0},Tyr^{3}]octreotide has been used in non-GEP tumours as well. In differentiated thyroid carcinoma however, none of the published reports mentions tumour remission (see *(17)* for review). Also small call lung carcinomas (SCLC) frequently express somatostatin receptors. A pilot study in six patients using [^{90}Y-DOTA^{0},Tyr^{3}]octreotide however showed no objective response *(18)*. Specific data about the effects of [^{90}Y-DOTA^{0},Tyr^{3}]octreotide in patients with paraganglioma/phaeochromocytoma or meningioma are scarce, because most studies did not specifically report effects of the treatment for these subtypes of

tumours. Otte *et al. (7)* reported remission in one and stable disease in two of three patients with meningiomas and stable disease in one patient with phaeochromocytoma. Of two patients with meningiomas in the study of Bodei *et al. (13)*, one had progressive disease and the other had stable disease as treatment outcome.

PRRT STUDIES WITH [^{177}LU-DOTA^{0},TYR^{3}]OCTREOTATE

[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate now is the third generation in somatostatin receptor targeted radionuclide therapy and has been used in our hospital since 2000. [DOTA^{0},Tyr^{3}] octreotate differs from [DOTA^{0},Tyr^{3}]octreotide only in that the C-terminal threoninol of the octapeptide is replaced with threonine. Compared with [DOTA^{0},Tyr^{3}]octreotide, it shows a considerable improvement in binding to somatostatin receptor positive tissues: GEP tumours mainly express somatostatin receptor subtype 2 *(19)* and Reubi *et al. (20)* reported a nine-fold increase in affinity for the this receptor subtype for [DOTA^{0},Tyr^{3}] octreotate *in vitro* compared with [DOTA^{0},Tyr^{3}]octreotide, and this was six to seven-fold for the Yttrium-labelled counterparts. This increased affinity was later demonstrated in animal experiments as well *(21)*. [DOTA^{0},Tyr^{3}]octreotate, labelled with the β- and γ-emitting radionuclide ^{177}Lu, was reported very successful in terms of tumour regression and animal survival in a rat model *(22)*.

^{177}Lu labelled analogues have a practical advantage over their ^{90}Y labelled counterparts: ^{177}Lu also emits low-energy γ-rays (10% abundance), which directly allows post-therapy imaging and dosimetry, whereas ^{90}Y is a pure β-emitter and therefore analogues labelled with the positron emitter ^{86}Y are needed for dosimetry. This then again is less reliable because of the shorter half-life (14.8h) of ^{86}Y in comparison to ^{90}Y (64h).

In a comparative study in patients, it was found that the uptake of radioactivity, expressed as percentage of the injected dose of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate, was comparable to that of [^{111}In-DTPA^{0}]octreotide for kidneys, spleen and liver, but was 3 to 4-fold higher for 4 of 5 tumours *(23)*. Figure 2 provides an example of this difference in a patient. Recently, Esser *et al. (24)* published the results of a comparison of dosimetry in a therapeutic setting using 100 mCi (3.7GBq) [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate and 100mCi (3.7GBq) [^{177}Lu-DOTA^{0},Tyr^{3}]octreotide in the same patients with an interval of 6 to 10 weeks. The mean delivered dose to tumours with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate was advantageous by a factor of 2.1 compared to [^{177}Lu-DOTA^{0},Tyr^{3}]octreotide. Therefore, [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate represents an important improvement because of the higher absorbed doses that can be achieved to most tumours with about equal doses to potentially dose-limiting organs. Also the differences in physical properties of the radionuclides are potentially in favour of ^{177}Lu because of the lower tissue penetration range of ^{177}Lu if compared with ^{90}Y. This may be especially important for small tumours.

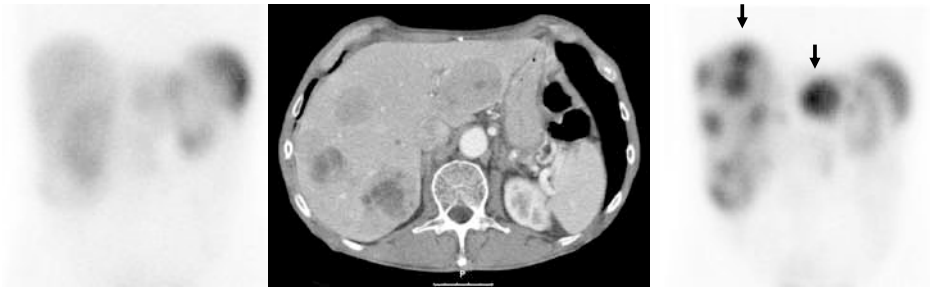

Figure 2. Difference in tumour uptake between [^{111}In-DTPA^{0}]octreotide and [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in a patient with a midgut carcinoid with liver metastases. *Left panel:* Scintigraphy 24 hours after injection of 200 MBq [^{111}In-DTPA^{0}]octreotide did not clearly demonstrate pathological uptake despite the quite large liver metastases visible on CT (*middle panel*). On SPECT images (not shown) uptake in liver metastases was equal to normal liver uptake (grade 2 uptake, see legend to Figure 4). *Right panel:* On scintigraphy 24 hours after injection of 7.4 GBq [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate liver metastases were clearly visualised (arrows).

The treatment effects of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate therapy were first described in 35 patients with neuroendocrine GEP tumours *(25)* and more recently, the effects of this treatment were reported in 131 patients with neuroendocrine GEP tumours *(26)*. Patients were treated up to an intended cumulative activity of 600–800mCi (22.2 to 29.6GBq); If dosimetric calculations indicated that the radiation dose to the kidneys would exceed 23 Gy with a dose of 29.6GBq, the cumulative activity was reduced to 22.2–27.8GBq. Fifty-five of the 131 (42%) patients had documented progressive disease (PD) within 1 year before the start of the therapy, 37 (28%) had stable disease at study entry, and in 39 (30%) information on disease progression was absent. Treatment intervals in general were 6–10 weeks. In 116 patients, the final intended cumulative activity of 22.2 to 29.6GBq was administered. In ten of the 15 remaining patients completing their treatment was not possible because of rapid progressive disease. Serious side effects occurred in two patients. In one patient, serum creatinine concentrations had risen from 60–70μmol/L to 90–100 μmol/L in the year prior to the therapy, and creatinine clearance was 41mL/min when entering the study. This patient developed renal insufficiency 1.5 years after receiving her last treatment. Tubular depositions and microangiopathy were seen on renal biopsy. The patient eventually chose not to start haemodialysis and died shortly thereafter. In another patient with diffuse, rapidly growing liver metastases from an aggressive endocrine pancreatic tumour, upper abdominal pain increased and liver functions deteriorated following the first administration. The patient developed hepatorenal syndrome and died 5 weeks thereafter.

WHO toxicity grade 3 or 4 anaemia (Hb 4.0–4.9 or <4.0mmol/L, respectively), leucocytopenia (WBC 1.0–1.9 or <1.0 x 10^{9}/L, respectively), or thrombocytopenia (platelets 25.0–49.9 or <25 x 10^{9}/L, respectively) occurred after 0.4% and 0.0%, 1.3% and 0.0%, and 1.5% and 0.2% of the administrations, respectively. Thrombocytopenia toxicity grade

2 or more occurred significantly more frequently in patients who had been treated with chemotherapy before, whereas WHO toxicity grade 2 or more leucocytopenia (especially neutropenia) occurred significantly more frequent in patients older than 70 years of age. Mean Hb, leucocytes and platelets decreased significantly during treatment, but recovered after finishing the treatment: Values of 18 – 24 months after the last therapy were not significantly different from pre-treatment values. Serum creatinine and creatinine clearance did not change significantly.

Nausea was present in 31% and vomiting in 14% of the administrations within the first 24 h after the administration. Twelve percent of patients reported mild abdominal pains, especially those with liver enlargement due to metastases. Increased hair loss was noticed by 64% of the patients, but complete alopecia did not occur; hair regrowth occurred within 3 months after the last administration.

In 125 patients tumour size could be evaluated. PD was found in 22 (18%) patients, including the ten patients who died before the intended cumulative activity was achieved, SD in 44 (35%), MR in 24 (19%), PR in 32 (26%) and complete remission (CR) was found in three (2%) patients. Figure 3 demonstrates PR in a patient. Higher remission rates were positively correlated with high uptake during pretherapy [^{111}In-DTPA^{0}]octreotide scintig-

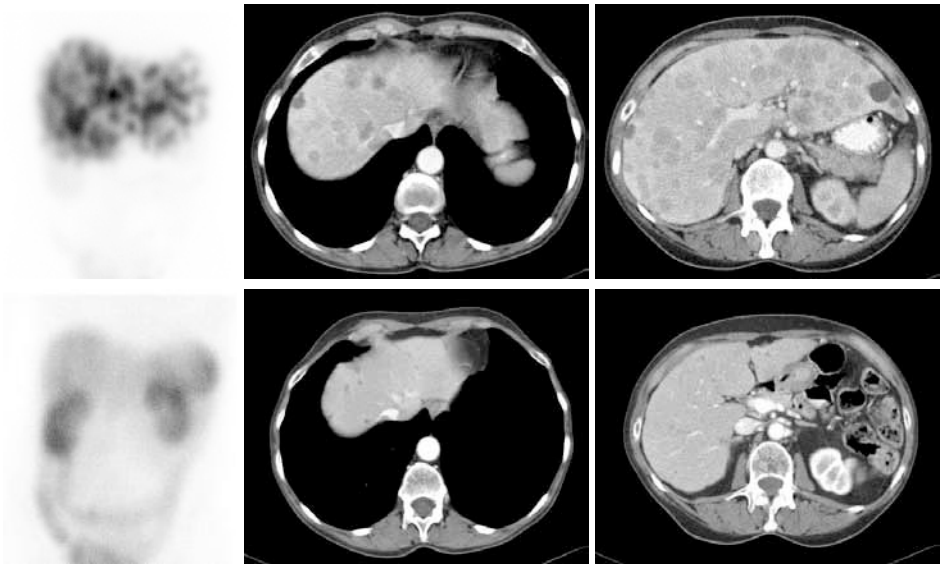

Figure 3. Example of partial remission in a patient with a metastasised carcinoid treated with 29.8 GBq [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. **Upper row:** *left panel:* scintigraphy (anterior abdomen) after first cycle with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate demonstrated extensive somatostatin receptor positive liver metastases. *Middle and right panel:* CT scan before starting treatment demonstrated these liver metastases. **Lower row:** *left panel:* scintigraphy (anterior abdomen) after fourth cycle with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate could not visualise liver metastases anymore. *Middle and right panel:* CT scan after treatment still demonstrated multiple small liver metastases, but metastases clearly regressed in size.

raphy (see Figure 4 for grading scale) and a limited number of liver metastases, whereas a low Karnofsky Performance Score, extensive disease and weight loss were predictive factors for PD. Median time to progression was more than 36 months in the 103 patients who either had SD or tumour regression (MR, PR and CR) and median follow-up was 16 months.

Also quality of life (QoL) was evaluated in 50 patients with metastatic somatostatin receptor-positive GEP tumours treated with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate *(27)*. The patients filled out the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30 before therapy and at follow-up visit 6 weeks after the last cycle. Global health status/QoL scale significantly improved after therapy with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. The symptom scores for fatigue, insomnia, and pain decreased significantly. Improvement of QoL domains was most frequently observed in patients with proven tumour regression.

An analysis in a small subgroup of patients with foregut carcinoids was performed because of their different origin from other carcinoids and GEP tumours and because they tend to behave more aggressively *(28)*. Five of nine patients with bronchial carcinoids had PR, one had MR, two had SD and one had PD. In gastric carcinoids, tumour remission was observed in two of five patients (1 CR, 1 MR), two had SD and one had PD and in thymic carcinoids one patient had SD and one had PD. Overall remission rate in these 16 patients with the studied foregut carcinoids was 50% (including MR) which was not significantly different from 47% observed in the total group of GEP tumours *(29)*.

The treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate has been studied in various non-GEP tumours as well. Teunissen *et al. (30)* reported the results in five patients with non-radioiodine-avid differentiated thyroid carcinoma (TC). Three patients had Hürthle cell TC of whom two had tumour regression on imaging studies (1 MR, 1 PR) and one had SD. One patient with progressive papillary TC had SD and in one patient with progressive follicular TC, disease remained progressive. [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate treatment can also be effective in patients with paragangliomas and meningiomas *(31)*. Two of 12 patients with metastasised or inoperable paraganglioma had tumour remission (1 PR, 1 MR, see Figure

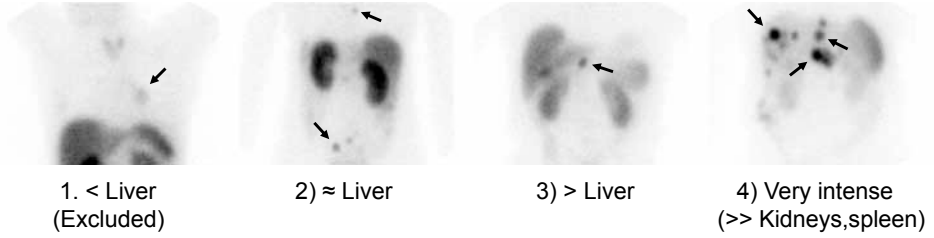

Figure 4. Grading scale (1–4) for determining tumour uptake on [^{111}In-DTPA^{0}]octreotide scintigraphy on planar imaging. Tumour uptake should be grade 2 or more for therapy with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate.

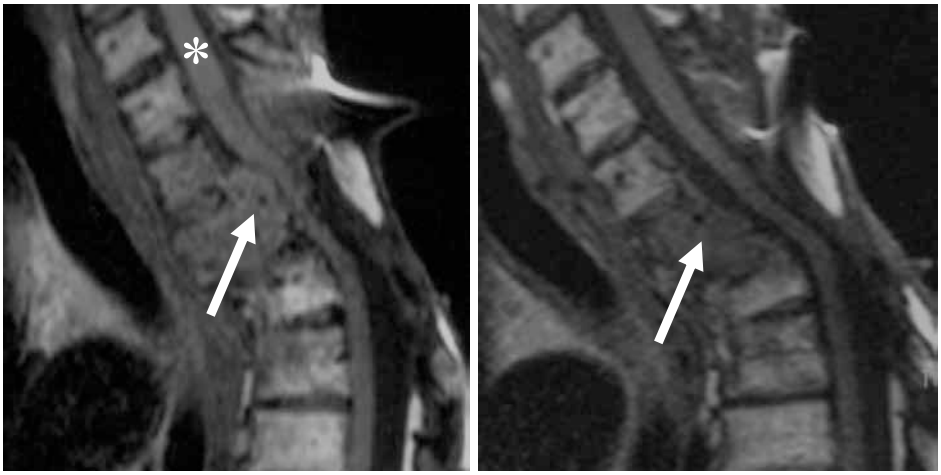

Figure 5. Minor response in a patient with hormonally active, metastasised paraganglioma after treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. *Left panel:* Vertebral metastasis (arrow) compressed the spinal cord (*) before treatment. *Right panel:* Tumour size regression (arrow). Spinal cord compression was not present anymore after the treatment. Paresthesia in the left arm decreased, but a mild paresis of that arm persisted. Moreover, the patient was able to work better and anti-hypertensive medication could be decreased.

5), six had SD (including 1 with PD at entry) and three had PD. In one patient outcome could not be determined. One of four patients with progressive meningiomas had SD. The three patients who still had PD had anaplastic, exophytic growing tumours and all standard treatments had failed. The present treatment protocol with [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate however did not have therapeutic effects in three patient with metastasised SCLC and two eye melanoma patients with rapidly progressive liver metastases: all five patients died within 5 months after starting the treatment *(31)*.

PRRT STUDIES WITH OTHER RADIOLABELLED SOMATOSTATIN ANALOGUES

Chelated lanreotide, another somatostatin analogue, can be labelled with ^{111}In for diagnostic purposes and with ^{90}Y for therapeutic use. Its has been advocated because of its increased affinity for somatostatin receptor subtypes 3 and 4 compared to [^{111}In-DTPA^{0}] octreotide *(32)*, but this claim is questionable (20). Although chelated lanreotide has been used to treat patients with GEP tumours, it shows poorer affinity than radiolabelled [DOTA^{0}, Tyr^{3}]octreotide/octreotate for the somatostatin receptor subtype-2, which is predominantly overexpressed in GEP tumours *(19)*. Thirty nine of the patients of 154 patients treated with [^{90}Y-DOTA^{0}]lanreotide had carcinoids or other GEP tumours and regressive disease (>25% reduction of tumour size) was observed in eight patients (21%), stable disease in 17 (44%) and progressive disease in 14 (36%) *(32)*. Twenty five patients with thyroid carcinoma

received [^{90}Y-DOTA^{0}]lanreotide: regressive disease was seen in three (12%), stable disease in 11 (44%) and progressive disease in 11 as well. Three patients had meningioma, of which two had SD and one had PD. Disease state at start was not reported.

Forrer *et al. (33)* reported their results of one cycle of 7.4GBq [^{177}Lu-DOTA^{0}, Tyr^{3}] octreotide in treating patients with disease progression after an initial benefit with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide treatment. Analysis at 8 – 12 weeks after the treatment in 27 treated patients, demonstrated PD in eight, SD in 12, MR in five and PR in two patients. Mean time to progression was 8.3 months (range 4 to 13 months) and eight patients were still without PD. The authors also stated that the treatment is safe, but time of follow-up was rather short. In our opinion, both the relatively low administered dose and the short time of follow-up, makes it hard to draw any firm conclusions from these data.

COMPARISON OF THE DIFFERENT STUDIES

Treatment with radiolabelled somatostatin analogues, especially if labelled with a β-emitter, is a promising new modality in the management of patients with inoperable or metastasised neuroendocrine tumours. Figure 6 provides an overview of several PRRT studies with different radiolabelled somatostatin analogues. Comparing effects of treatment with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide and [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate is very difficult, because a randomised trial between the two treatments is lacking. However, the results that were obtained with these analogues are very encouraging.

The reported percentages of tumour remission between studies with [^{90}Y-DOTA^{0},Tyr^{3}] octreotide treatment also vary quite substantially and several possible explanations can be given. The administered doses and dosing schemes differ. Some studies use dose-escalating schemes and therefore some patients had a relatively low dose, whereas others use fixed doses. Also several patient and tumour characteristics that determine treatment outcome may play a role, such as the amount of uptake on pre-therapy somatostatin receptor scintigraphy, the estimated total tumour burden, the extent of liver involvement, presence or absence of weight loss, Karnofsky Performance status and the type of neuroendocrine tumour *(15, 26)*. In addition, tumour remission was more frequent in gastrinomas compared to non-functioning pancreatic endocrine tumours and carcinoids in the study by Kwekkeboom *et al. (26)* because gastrinomas often have high tumour uptake on pre-therapy somatostatin receptor scintigraphy. Therefore, it is likely that differences in patient selection play a role in determining treatment outcome. Also more methodological factors may contribute to the different results that were found in the different centres performing trials with the same compounds, e.g. differences in tumour response criteria, and centralised vs. decentralised follow-up CT scoring. Therefore, randomised trials are

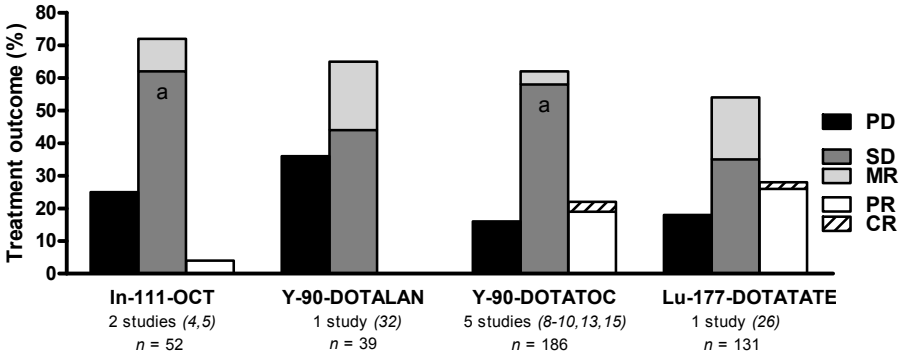

Figure 6. Overview of treatment outcome using various radiolabelled somatostatin analogues in patients with gastroenteropancreatic neuroendocrine tumours.
[a] Bar may also include an unknown percentage of patients with MR.
Abbreviations: *PD*, Progressive disease; *SD*, Stable disease: *MR*, Minor response; *PR*, Partial remission; *CR*, Complete remission. *In-111-OCT*, [^{111}In-DTPA^0]octreotide; One study (5) did not use MR. *Y-90-DOTALAN*, [^{90}Y-DOTA^0]lanreotide. *Y-90-DOTATOC*, [^{90}Y-DOTA^0,Tyr^3]octreotide; Four studies (8–10, 13) did not use MR. *Lu-177-DOTATATE*, [^{177}Lu-DOTA^0,Tyr^3]octreotate.

needed using detailed protocols in order to establish which treatment scheme and which radiolabelled somatostatin analogue or combination of analogue is optimal.

COMPARISON WITH CHEMOTHERAPY

It would have been preferable to have a randomised trial comparing PRRT to no further treatment at all to be able to evaluate the effects of PRRT more precisely. However, since patients can now be treated with PRRT in several medical centres and since the results of such treatment are so encouraging, withholding it to half of patients with symptomatic and/or progressive disease in an experimental setting cannot be ethically justified and therefore this is presently no longer possible. Tumour remissions were reported in a recent study in four of 80 (5%) patients with GEP tumours who had progressive disease at study entry and were treated with somatostatin analogues and/or interferon α [34]. This is less than the 47% in our 125 patients treated with [^{177}Lu-DOTA^0,Tyr^3]octreotate having had tumour remissions (including MR), whether they had PD at study entry or not *(26)*. It seems highly unlikely that such a clear difference is just caused by patient selection.

In well-differentiated pancreatic tumours and poorly differentiated tumours from any origin, response rates of 40–60% for single agent and combination chemotherapy were observed, whereas success rates for midgut tumours rarely exceed 20% in recent studies *(35–50)*, for a review see *(51)*. High response rates have been reported in older series with

'classical' chemotherapy *(35–37)*, but in these studies the response was not only evaluated with imaging studies, but also by biochemical responses (changes in serum tumour marker levels) and physical examination for the evaluation of hepatomegaly. Much of the discrepancy between older and more recent studies can likely be ascribed to differences in response criteria, as Cheng and Saltz *(38)* demonstrated: if they had also accepted decreases of hepatomegaly assessed with physical examination as response criterion and not only measured CT scan changes, the percentage of patients with an objective response would have increased from 6 to 25%.

Multiple novel drugs were also studied. Endostatin, an angiogenesis inhibiting agent, administered in short intravenous infusions resulted in a minor response in one patient and in stable disease in two patients with neuroendocrine pancreatic tumours in a phase 1 clinical trial *(52)*. However, in a phase 2 study, endostatin administered subcutaneous twice a day did not result in an objective response in 42 patients with advanced pancreatic neuroendocrine tumours or carcinoids *(53)*. In a study by Gross *et al.* the tyrosine kinase inhibiting drug imatinib did not result in an objective response *(54)*. Recently Yao *et al.* reported results of treatment with imatinib in advanced carcinoid tumours *(55)*: out of 27 patients, one had a partial remission and 17 had stable disease. Median progression free survival was 24 weeks. Another drug under investigation is sunitinib (SU11248). This is an oral, multitargeted tyrosine kinase inhibitor and can have therapeutic effects in neuroendocrine tumours: a phase 1 dose escalation trial resulted in an objective response in one patient with a large peritoneal metastasis from a rectal neuroendocrine tumour *(56)*. Kulke *et al.* presented preliminary results of treatment with sunitinib: seven of 52 patients (13.5%) with pancreatic neuroendocrine tumours had partial remission and 40 had stable disease. In carcinoids, sunitinib resulted in partial remission in two of 39 patients and in stable disease in 36. Data about time to progression were not reported *(57)*. Therapy with temsirolimus (an inhibitor of mTOR, mammalian target of rapamycin) as single agent did not result in an objective response *(58)*.

Not only is the proportion of patients with a tumour remission an important treatment outcome parameter, but the duration of such a response and survival as well. The median time to progression reported for chemotherapy in most of the studies is less than 18 months, regardless of the varying percentages of objective responses. In this respect, treatment with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide or [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate with a median time to progression of more than 30 and more than 36 months, respectively, compares favourably *(15, 26)*.

AT WHAT MOMENT SHOULD PRRT BE GIVEN?

We treated patients with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate who had progressive disease at baseline and also those who were stable or in whom disease progression was not documented. We did this because waiting for disease progression would probably have implied a serious deterioration of clinical condition in many of these patients.

Tumour remission was positively correlated with a limited number of liver metastases (among others), whereas disease progression was significantly more frequent in patients with a low performance status and a high tumour load *(26)*. This implies that the chances of a successful treatment are better if patients are treated in an early stage of their disease. In contrast to what we reported earlier in a much smaller group of patients *(25)*, the percentage of patients with a remission does not differ significantly between those patients who have disease progression at baseline and those who have not.

Treatment strategies could be to start PRRT as soon as inoperable disease has been diagnosed regardless of progression or, alternatively, to closely monitor patients both clinically and with imaging and laboratory studies and start PRRT as soon as progression is observed, including involuntary weight loss. It would be interesting to do a randomised trial in patients in good clinical condition without proven progression to compare the effects of early PRRT with those when PRRT is withheld until progression is documented.

OPTIONS TO IMPROVE PRRT AND FUTURE DIRECTIONS

In animal experiments, ^{90}Y-labelled somatostatin analogues may be more effective for larger tumours, whereas ^{177}Lu-labelled somatostatin analogues may be more effective for smaller tumours and their combination may be the most effective. In a study in animals with various tumour sizes, therapy with both ^{90}Y and ^{177}Lu labelled octreotate had better remission rates than either ^{90}Y or ^{177}Lu labelled octreotate alone *(59)*. Therefore, not only different radiolabelled peptides like octreotate and octreotide, and different radionuclides like ^{90}Y and ^{177}Lu, should be evaluated, but also PRRT with several combinations, preferably in a randomised clinical trial. However, reliable dosimetry with [^{90}Y-DOTA^{0}, Tyr^{3}] octreotate in humans is not available yet.

Another interesting strategy can be finding methods to increase somatostatin receptor density on tumours, either medication or irradiation induced or by transfection of the receptor gene. Irradiation can maybe be used to up-regulate receptor expression: External irradiation resulted in an up-regulation of somatostatin receptors (and gastrin receptors) in a pancreatic tumour cell line, *in vitro* and *in vivo (60)*. Capello *et al. (61)* demonstrated an increase in receptor density on tumours in animal studies after PRRT with [^{111}In-DTPA^{0}] octreotide at the time of tumour regrowth. *In vitro* studies with human small cell lung

cancer cells showed increased binding of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate and increased mRNA for somatostatin receptor subtype 2 after irradiation *(62)*. However, human data are lacking.

A completely different way to possibly improve treatment outcome in neuroendocrine tumours is the development of hybrid molecules, i.e. somatostatin analogues linked to another molecule like a chemotherapeutic agent or so-called RGD peptides. Arginine-Glycine-Aspartate (RGD) peptides can induce apoptosis by activation of caspase-3 and inhibit growth of new vessels (see *(63)* and references within). A hybrid of an RGD-peptide and the somatostatin analogue [Tyr^{3}]octreotate was developed with DTPA as chelator allowing labelling with ^{111}In. This results in the radiolabelled hybrid peptide RGD[^{111}In-DTPA]octreotate. This entire molecule was internalised, mainly via somatostatin receptor subtype 2 in neuroendocrine tumour cells *(64)*. Capello *et al.* demonstrated an enhanced tumouricidal effect *in vitro* of RGD[^{111}In-DTPA]octreotate compared to [^{111}In-DTPA] octreotate. This was most likely caused by induction of apoptosis since caspase-3 activity was significantly higher in cells incubated with RGD[^{111}In-DTPA]octreotate compared to [^{111}In-DTPA]octreotate *(65)*. Unfortunately, biodistribution studies showed a high renal uptake of RGD[^{111}In-DTPA]octreotate *(64, 66)* which limits the dose that can be safely administered. Therefore, characteristics of non-radiolabelled RGD-DTPA-octreotate and the hybrid RGD-octreotate (a hybrid peptide without chelator) were studied as well (66). RGD-DTPA-octreotate and RGD-octreotate resulted in a higher caspase-3 activity than DTPA-octreotate and might therefore be used to increase apoptosis in neuroendocrine tumour cells. It would be interesting to study the combination of a radiolabelled somatostatin analogue like [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate and non-radiolabelled hybrids like RGD-DTPA-octreotate or RGD-octreotate, as the combination might result in better response rates.

The use of radiosensitising chemotherapeutical agents may also be one of the future directions to improve PRRT. ^{90}Y-labelled antibody radioimmunotherapy in combination with 5-fluorouracil (5-FU) as radiosensitiser is feasible and safe *(67)*. Also, sensitisation with 5-FU, combined with PRRT using [^{111}In-DTPA^{0}]octreotide resulted in a symptomatic response in 71% of patients with neuroendocrine tumours *(68)*, which is more frequent than in other studies using only [^{111}In-DTPA^{0}]octreotide as treatment *(4, 5)*. Numerous trials to investigate the effects of (fractionated) external beam radiotherapy with chemotherapy have been performed and 5-FU was used in many of these. More recent trials used the prodrug of 5-FU, capecitabine, which has the advantage of oral administration. Moreover, many tumours have a higher amount of thymidine phosphorylase (TP) resulting in a higher rate of converting the inactive form into the active form than normal tissues and, in addition, irradiation can induce an upregulation of TP *(69)*. If capecitabine is used in relatively low doses (1600–2000mg/m^{2}/day), grade 3 haematologic or other toxicity such as hand-foot syndrome is rare *(69, 70)*. For these reasons, we recently started a pilot

trial using capecitabine and [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate and plan to do a randomised multi-centre trial comparing treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate with and without capecitabine in patients with GEP tumours.

CONCLUSIONS

Peptide Receptor Radionuclide Therapy (PRRT) with radiolabelled somatostatin analogues is a promising treatment option for patients with inoperable or metastasised neuroendocrine tumours. Tumour regression can be obtained with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide and [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate and symptomatic improvement may occur with all of the various ^{111}In, ^{90}Y, or ^{177}Lu-labelled somatostatin analogues that have been used. The side-effects of PRRT are few and mostly mild, certainly when using kidney protective agents and the median duration of the therapy response for both [^{90}Y-DOTA^{0},Tyr^{3}]octreotide and [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate is more than 30 months. Median overall survival in patients treated with [^{90}Y-DOTA^{0},Tyr^{3}]octreotide was 36.7 months. Lastly, quality of life improves significantly after treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. These data compare favourably with the limited number of alternative treatment approaches, like chemotherapy. If more widespread use of PRRT is possible, such therapy might become the therapy of first choice in patients with metastasised or inoperable gastroenteropancreatic neuroendocrine tumours. Also the role in non-GEP tumours, like metastasised paraganglioma/phaeochromocytoma and non-radioiodine-avid differentiated thyroid carcinoma might become more important.

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Abbreviations

5-FU	5-fluorouracil
5HIAA	5-hydroxyindoleacetic acid
ACTH	adrenocorticotropic hormone
Carc	carcinoid
CgA	chromogranin A
Ci	curie
CR	complete remission
CT	computer tomography
DOTA	1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid
DOTALAN	$DOTA^0$-lanreotide
DOTATOC	$DOTA^0$-Tyr^3-octreotide
DOTATATE	$DOTA^0$-Tyr^3-octreotate
DTPA	diethylenetriaminepentaacetic acid
ER	elimination rate
GBq	gigabecquerel
GEPNET	gastroentoeropancreatic neuroendocrine tumor
Gy	gray
Hb	haemoglobin
^{111}In	indium-111
IFNα	interferon-alpha
keV	kiloelectronvolt
KPS	Karnofsky performance score
^{177}Lu	lutetium-177
MEN	multiple endocrine neoplasia
MIBG	metaiodobenzylguanidine
MBq	megabecquerel
mCi	millicurie
MDS	myelodysplastic syndrome
MR	minor response
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid

mTOR	mammalian target of rapamycin
NET	neuroendocrine tumour
OS	overall survival
PET	positron emission tomography
PNET	pancreatic neuroendocrine tumour
PD	progressive disease
PR	partial remission
PRRT	peptide receptor radionuclide therapy
RFA	radiofrequency ablation
RECIST	response evaluation criteria in solid tumours
RGD	arginine – glycine – aspartate
ROI	region of interest
SCLC	small cell lung carcinoma
SD	stable disease / standard deviation
SRS	somatostatin receptor scintigraphy
sst	somatostatin receptor
SWOG	southwest oncology group
TC	thyroid carcinoma
TP	thymidine phosphorylase
TTP	time to progression
Tyr	tyrosine
VIP	vasoactive intestinal (poly)peptide
WBC	white blood cell count
WHO	world health organisation
^{90}Y	yttrium-90

Dankwoord


progressive
dose
treatment
study
disease
results
therapy
effects
patients
tumours

Promoveren doe je niet alleen! De afgelopen jaren ben ik bijgestaan door familie, vrienden en veel fijne collega's op de afdeling. Een woord van dank is dus zeker op zijn plaats.

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Biography


progressive
dose
treatment
study
disease
octreotide
results
therapy
octreotate
effects
response
reception
patients
tumours
somatostatin

Martijn van Essen was born on October 22, 1976 in Rotterdam. In 1995 he graduated from the Marnix Gymnasium in Rotterdam. He started medical school in Antwerp, Belgium that year and obtained his medical degree in 2002. He then worked as a resident at the department of Neurology in the Groene Hart Hospital, Gouda and Sint-Lucas Andreas Hospital, Amsterdam. While looking for a career in Nuclear Medicine, he also worked at the department of Internal Medicine, again in the Groene Hart Hospital, Gouda.

In 2005 he started his clinical research project at the department of Nuclear Medicine at the Erasmus MC, Rotterdam, under the supervision of Prof. dr. E.P. Krenning and Dr. D.J. Kwekkeboom. The results of this research project are presented in this thesis. Since June 2009 he has been working as a nuclear medicine resident in training. As part of this, he worked at the department of Internal Medicine in the Reinier de Graaf Hospital, Delft and at the department of Radiology at the Erasmus MC. He hopes to obtain the registration as nuclear medicine physician in June 2013.

In 2007 he met Inger Verhey. They live together in The Hague and got married in 2010. They are the happy parents of Sven since April 2011.

List of Publications

ACCEPTED AND PUBLISHED MANUSCRIPTS

1.
Neoadjuvant downsizing by internal radiation: a case for preoperative peptide receptor radionuclide therapy in patients with pancreatic neuroendocrine tumors.
Ezziddin S, Lauschke H, Schaefers M, Meyer C, **van Essen M**, Biersack HJ, Kwekkeboom DJ, Ahmadzadehfar H.
Clin Nucl Med. 2012;37:102-104.

2.
Mifepristone Effects on Tumor Somatostatin Receptor Expression in Two Patients with Cushing's Syndrome due to Ectopic Adrenocorticotropin Secretion.
de Bruin C, Hofland LJ, Nieman LK, van Koetsveld PM, Waaijers AM, Sprij-Mooij DM, **van Essen M**, Lamberts SW, de Herder WW, Feelders RA.
J Clin Endocrinol Metab. 2012;97:455-62

3.
Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate.
Khan S, Krenning EP, **van Essen M**, Kam BL, Teunissen JJ, Kwekkeboom DJ.
J Nucl Med. 2011;52:1361-1368.

4.
Salvage therapy with ^{177}Lu-octreotate in patients with bronchial and gastroenteropancreatic neuroendocrine tumors.
van Essen M, Krenning EP, Kam BL, de Herder WW, Feelders RA, Kwekkeboom DJ.
J Nucl Med. 2010;51:383-390.

5.
Peptide receptor radionuclide therapy in patients with gastroenteropancreatic neuroendocrine tumors.
Kwekkeboom DJ, de Herder WW, van Eijck CH, Kam BL, **van Essen M**, Teunissen JJ, Krenning EP.
Semin Nucl Med. 2010;40:78-788.

6.
Somatostatin-receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors.

Kwekkeboom DJ, Kam BL, **van Essen M**, Teunissen JJ, van Eijck CH, Valkema R, de Jong M, de Herder WW, Krenning EP.
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7.
Peptide-receptor radionuclide therapy for endocrine tumors.
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Peptide Receptor Radionuclide Therapy with radiolabelled somatostatin analogues in patients with somatostatin receptor positive tumours.
Van Essen M, Krenning EP, De Jong M, Valkema R, Kwekkeboom DJ.
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Peptide receptor radionuclide therapy with ^{177}Lu-octreotate in patients with foregut carcinoid tumours of bronchial, gastric and thymic origin.
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13.
Effects of therapy with [^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate in patients with paraganglioma, meningioma, small cell lung carcinoma, and melanoma.
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Unnecessary surgery for acute abdomen secondary to ACE inhibitor use.
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BOOK

Monoclonal Antibody and Peptide-Targeted Radiotherapy of Cancer.
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Chapter 4: Peptide Receptor Radionuclide Therapy in Patients with Somatostatin Receptor-Positive Neuroendocrine Tumors.
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Publisher: Wiley; 1 edition (August 9, 2010), ISBN-13: 978-0470243725

Portfolio


progressive
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PHD PORTFOLIO SUMMARY

Summary of PhD training and teaching activities

1. PhD training	
	Year
In-depth courses	
- Radiation safety, level 3, TU Delft, Delft	2009
- Neuroendocrine tumour course, Uppsala, Sweden	2005
Presentations / posters at conferences	
- Annual Congress European Association of Nuclear Medicine (EANM) 2006, Athens, Greece (oral)	2006
- EANM 2006, Athens, Greece (oral)	2006
- Symposium 'Nederlandse Vereniging voor Nucleaire Geneeskunde', Rotterdam	2006
- Refereeravond UZ GENT 2007, Ghent, Belgium (oral)	2007
- EANM 2007, Copenhagen, Denmark (oral)	2007
- EANM 2008, Munich, Germany (oral)	2008
- Annual congress of the Society of Nuclear Medicine (SNM) 2009, Toronto, Canada (oral)	2009
- Perspectives on Lung Cancer 2009 Brussels, Belgium (oral)	2009
- INKEP meeting, Erasmus MC, Rotterdam (oral)	2009
- International Postgraduate Symposium on Lung Cancer, Samos, Greece (oral)	2010
- Southern Symposium on Foregut Cancers 2011, Cork, Ireland (oral)	2011
- European NeuroEndocrine Tumour Society (ENETS) congress 2007, Barcelona, Spain (poster)	2007
- ENETS congress 2008, Paris, France (poster)	2008
- Regional Nuclear Medicine evening symposia, several occasions	2005 - 2012
International conference without presentation or poster	
- ENETS 2010, Berlin, Germany	2010

2. Teaching activities	
	Year
Supervising practicals and excursions	
- Medical students 2nd year	2009, 2011 - 2012
- Education Nuclear Medicine at start internships	2011 - 2012
Other	
- In-hospital, for nuclear medicine technologist	2006
- For guests from other hospitals at several occasions: Principles and effects of peptide receptor radionuclide therapy	2005 - 2009