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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}Indium labelled somatostatin analogues, radiolabelled somatostatin analogues with beta-emitting isotopes like ^{90}Y and ^{177}Lu were developed. Reported anti-tumour 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/pheochromocytoma and non-radioiodine-avid differentiated thyroid carcinoma might become more important.

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}Indium-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 I and Figure 1 provide information on the several radionuclides and peptides used for PRRT.

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Table I. Characteristics of radionuclides used for PRRT.

Radionuclide	Half life (days)	Emissions	Mean Energy (keV)	Maximum tissue penetration range of particle
^{111}Indium (^{111}In)	2.8	γ rays	171 and 245	
		Auger electrons	3.6 and 19	10 μm
^{90}Yttrium (^{90}Y)	2.7	β particles	934	12 mm
^{177}Lutetium (^{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 beta-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 (20 GBq). 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.

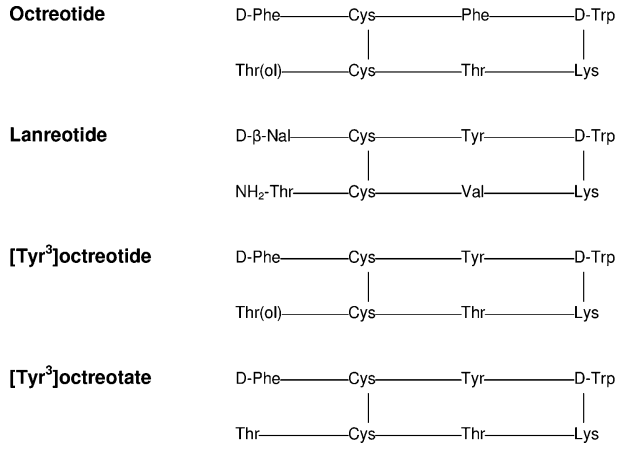

Figure 1. Amino acid sequence of several somatostatin analogues used for PRRT.

[^{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 pheochromocytoma 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 beta-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 beta-emitting radionuclide ^{90}Y. Several phase-1 and phase-2 PRRT trials were performed using [^{90}Y-DOTA^{0}-Tyr^{3}]octreotide (^{90}Y-DOTA-TOC; 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 (6 GBq)/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 (6 GBq)/m^2 [8], or, in a later study, with 200 mCi (7.4 GBq)/m^2 in four cycles [9]. In a subsequent study, with the same activity of 200 mCi (7.4 GBq)/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 150 mCi (5.6 GBq) per cycle. In 43% of patients injected with 140 mCi (5.2 GBq), 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 2.59 GBq 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 300 mCi (5.9–11.1 GBq). 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 (14.8 GBq)/m^2 in four cycles or up to 250 mCi (9.3 GBq)/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 ($<25\star10^9$/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/pheochromocytoma 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 pheochromocytoma. 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 an 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 ninefold 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 sevenfold 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 beta and gamma 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 gamma-rays (10% abundance), which directly allows post-therapy imaging and dosimetry, whereas ^{90}Y is a pure beta-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 (14.8 h) of ^{86}Y in comparison to ^{90}Y (64 h).

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 (3.7 GBq) [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate and 100 mCi (3.7 GBq) [^{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.

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 600–800 mCi (22.2 to 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 activity was reduced to 22.2–27.8 GBq. 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 29.6 GBq was administered. In ten of the 15 remaining patients completing their treatment was not possible because of rapid progressive

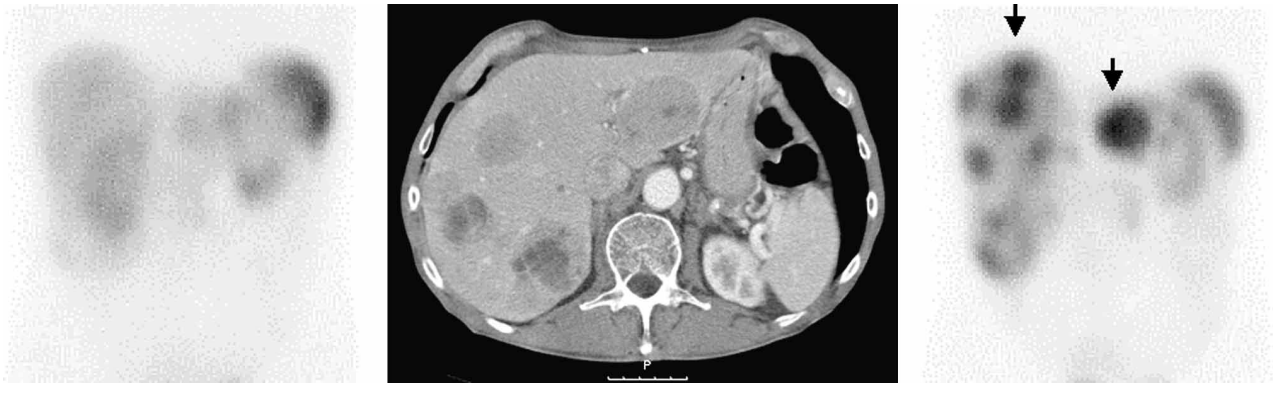

Figure 2. Difference in tumour uptake between [^{111}In-DTPA^{0}]octreotide and [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in a patient with a midgut carcinoid with liver metastases. *Left panel:* Scintigraphy 24 hours after injection of 200 MBq [^{111}In-DTPA^{0}]octreotide did not clearly demonstrate pathological 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).

disease. Serious side effects occurred in two patients. In one patient, serum creatinine concentrations had risen from 60–70 umol/l to 90–100 umol/l in the year prior to the therapy, and creatinine clearance was 41 ml/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 anemia (Hb 4.0–4.9 or <4.0 mmol/L, respectively), leucocytopenia (WBC 1.0–1.9 or $<1.0*10^9$/L, respectively), or thrombocytopenia (platelets 25.0–49.9 or $<25*10^9$/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 scintigraphy (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 Organization 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 [Figure 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].

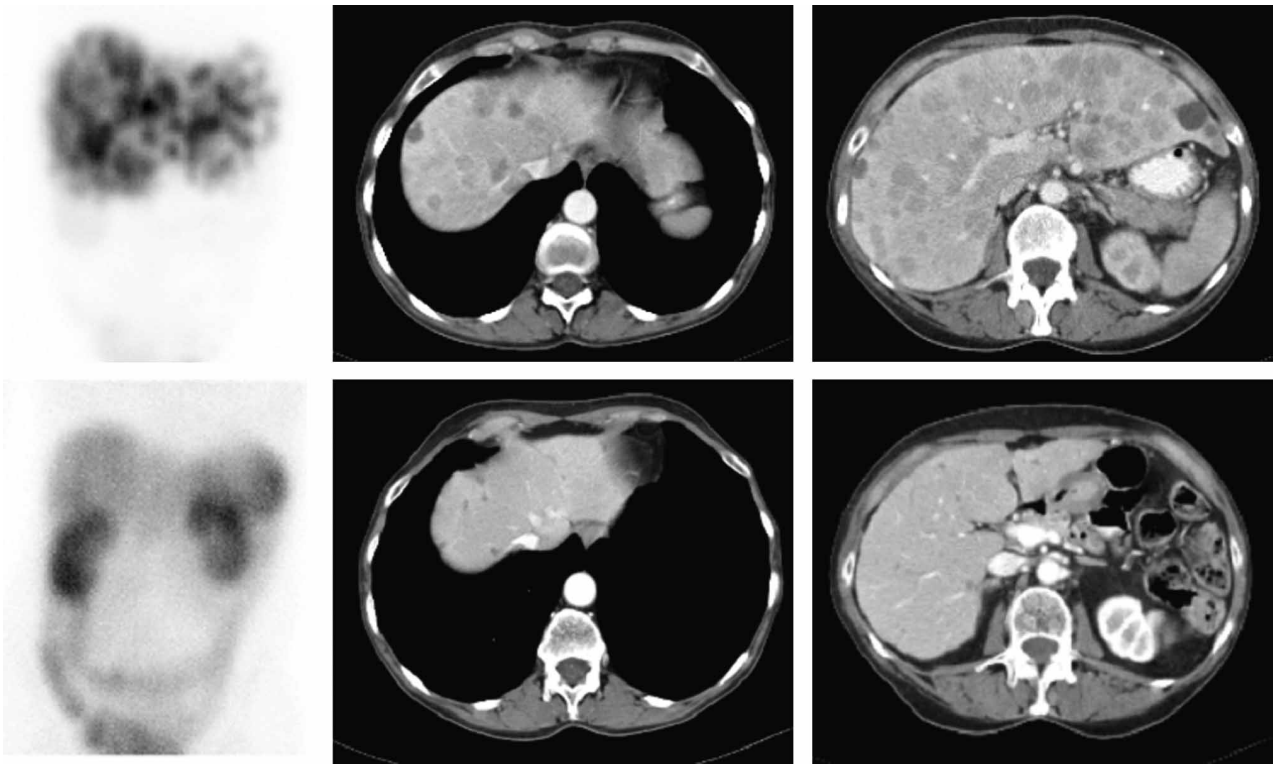

Figure 3. Example of partial remission in a patient with a metastasised carcinoid treated with 29.8 GBq [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. **Upper row:** *left panel:* scintigraphy (anterior abdomen) after first cycle with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate demonstrated extensive somatostatin 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.

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

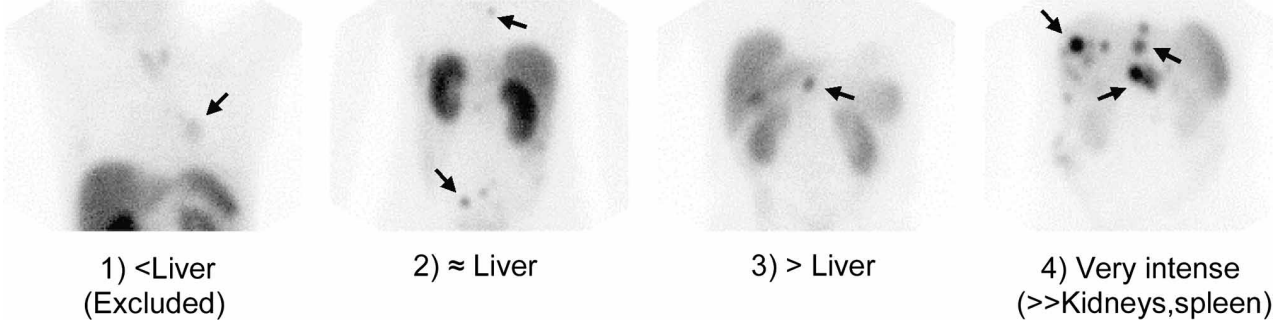

Figure 4. Grading scale (1–4) for determining tumour uptake on [^{111}In-DTPA^{0}]octreotide scintigraphy on planar imaging. Tumour uptake should be grade 2 or more for therapy with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate.

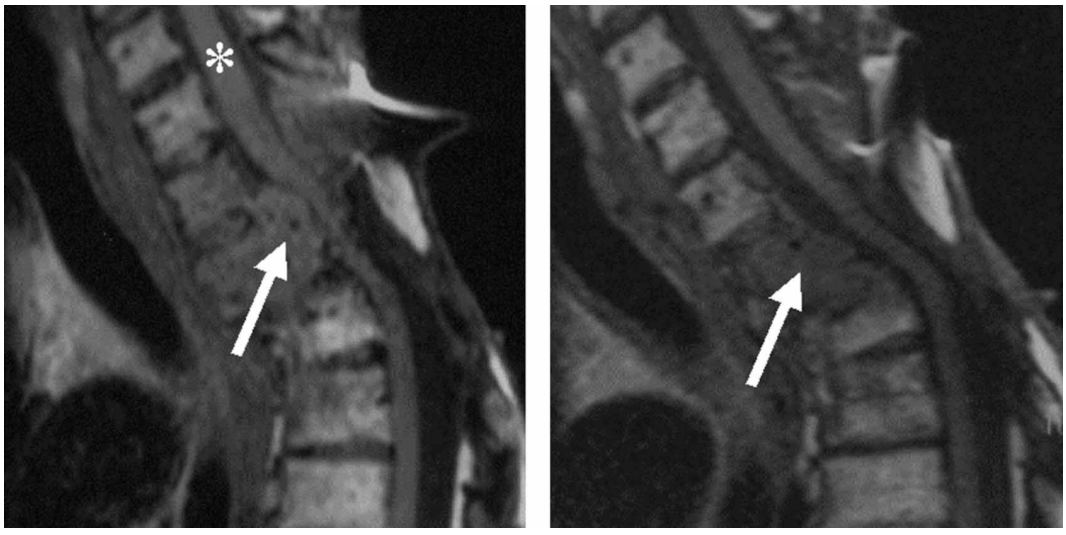

Figure 5. Minor response in a patient with hormonally active, metastasised paraganglioma after treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. *Left panel:* Vertebral metastasis (arrow) compressed the spinal cord (*) before treatment. *Right panel:* Tumour size regresssion (arrow). Spinal cord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

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 7.4 GBq [^{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 beta-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

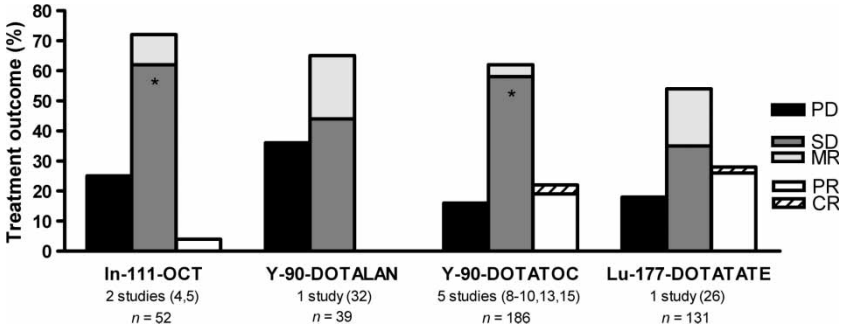

Figure 6. Overview of treatment outcome using various radiolabelled somatostatin analogues in patients with gastroenteropancreatic neuroendocrine tumours.

* Bar may also include an unknown percentage of patients with MR.

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.

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 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 alpha [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 (1 600–2 000 mg/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 inproves 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/pheochromocytoma and non-radioiodine-avid differentiated thyroid carcinoma might become more important.

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