

Somatostatin receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors

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Abstract

Somatostatin receptor imaging (SRI) with [¹¹¹In-DTPA⁰]octreotide has proven its role in the diagnosis and staging of gastroenteropancreatic neuroendocrine tumors (GEPNETs). Newer radiolabeled somatostatin analogs which can be used in positron emission tomography (PET) imaging, and which have a higher affinity for the somatostatin receptor, especially receptor subtype-2, have been developed. It would be desirable, however, if one radiolabeled analog became the new standard for PET imaging, because the current application of a multitude of analogs implies a fragmented knowledge on the interpretation of the images that are obtained in clinical practice. In our view, the most likely candidates for such a universal PET tracer for SRI are [⁶⁸Ga-DOTA⁰,Tyr³]octreotate or [⁶⁸Ga-DOTA⁰,Tyr³]octreotide. Treatment with radiolabeled somatostatin analogs is a promising new tool in the management of patients with inoperable or metastasized neuroendocrine tumors. Symptomatic improvement may occur with all ¹¹¹In-, ⁹⁰Y-, or ¹⁷⁷Lu-labeled somatostatin analogs that have been used for peptide receptor radionuclide therapy (PRRT). The results that were obtained with [⁹⁰Y-DOTA⁰,Tyr³]octreotide and [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate are very encouraging in terms of tumor regression. Also, if kidney protective agents are used, the side effects of this therapy are few and mild, and the median duration of the therapy response for these radiopharmaceuticals is 30 and 40 months respectively. The patients' self-assessed quality of life increases significantly after treatment with [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate. Lastly, compared to historical controls, there is a benefit in overall survival of several years from the time of diagnosis in patients treated with [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate. These data compare favorably with the limited number of alternative treatment approaches. If more widespread use of PRRT can be guaranteed, such therapy may well become the therapy of first choice in patients with metastasized or inoperable GEPNETs.

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Introduction

Peptide receptor scintigraphy in man started with the *in vivo* demonstration of somatostatin receptor-positive tumors in patients using a radioiodinated somatostatin analog (Krenning *et al.* 1989). Later, other radiolabeled somatostatin analogs were developed, and two of these subsequently became commercially available. Also, over the past decade, positron emission tomography (PET) tracers for somatostatin receptor imaging (SRI) were developed, and the superiority of the image

quality as well as the increased sensitivity in tumor site detection using these newer tracers and PET cameras has been reported by various research groups.

Starting in the 1990s, attempts at treatment with radiolabeled somatostatin analogs were undertaken in patients with inoperable and/or metastasized neuroendocrine tumors. Improvements in particularly the peptides used (with higher receptor affinity) and the radionuclides that were applied (with β instead of γ emission), together with precautions to limit the

radiation dose to the kidneys and the bone marrow, led to better results with a virtually negligible percentage of serious adverse events.

The first part of this review will deal with somatostatin receptor-based imaging, the second part with somatostatin receptor-based radionuclide therapy. In both sections, we attempt to summarize the results obtained with each method available to date, compared to other methods in current use and, where relevant, historical controls. The final section of this review gives a summing up and suggestions for the future.

Somatostatin receptor-based radionuclide imaging

Because the radioiodinated somatostatin analog that was first used for imaging in patients, [$^{123}\text{I},\text{Tyr}^3$]-octreotide, had several drawbacks, soon a chelated and ^{111}In -labeled somatostatin analog, [$^{111}\text{In-DTPA}^0$]-octreotide, was developed. [$^{111}\text{In-DTPA}^0$]octreotide (OctreoScan, Covidien, Petten, The Netherlands) is commercially available and is the most commonly used agent for SRI. The recommended scanning protocol for [$^{111}\text{In-DTPA}^0$]octreotide scintigraphy as well as the scanning results is summarized below.

The preferred dose of [$^{111}\text{In-DTPA}^0$]octreotide (with at least $10\ \mu\text{g}$ of the peptide) is about 200 MBq. With such a dose, it is possible to perform single-photon emission computed tomography (SPECT), which may increase the sensitivity to detect somatostatin receptor-positive tissues and gives a better anatomical delineation than planar views. The acquisition of sufficient counts per view and also obtaining spot images with a sufficient counting time instead of performing whole-body scanning with a too low count density are other important points that may make the difference between a successful localizing study and a disappointing one. For a scanning protocol, view the procedure guideline for somatostatin receptor scintigraphy with [$^{111}\text{In-DTPA}^0$]octreotide, published by the Society of Nuclear Medicine (Balon et al. 2001).

[$^{111}\text{In-DTPA}^0$]octreotide scintigraphy: normal scintigraphic findings and artifacts

Normal scintigraphic features include visualization of the thyroid, spleen, liver, and kidneys, and in a proportion of patients the pituitary gland (Fig. 1). Also, the urinary bladder and the bowel are usually visualized to a variable degree. The visualization of the pituitary, thyroid, and spleen is due to receptor binding. Uptake in the kidneys is for the most part due to reabsorption of the radiolabeled peptide in the renal

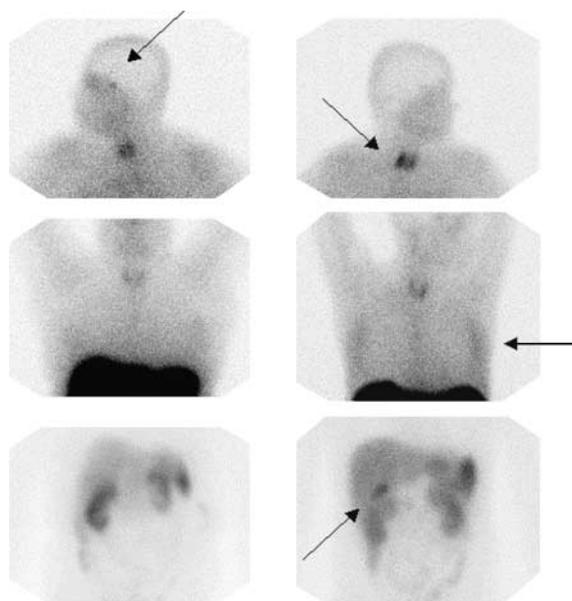


Figure 1 Normal distribution in SRI. Variable visualization of the pituitary and thyroid (arrows, upper panel). Faint breast uptake can sometimes be seen in women (right middle panel, arrow). Normal uptake in the liver, spleen, and the kidneys, and also some bowel activity in the lower panel. Gallbladder visualization in the lower right panel (arrow). Anterior views.

tubular cells after glomerular filtration. There is a predominant renal clearance of the somatostatin analog, although hepatobiliary clearance into the bowel also occurs, necessitating the use of laxatives in order to facilitate the interpretation of abdominal images.

False-positive results of SRI with [$^{111}\text{In-DTPA}^0$]octreotide have been reported. In virtually all cases, the term ‘false-positive’ is a misnomer because somatostatin receptor-positive lesions that are not related to the pathology, for which the investigation is performed, are present. Many of these have been reviewed by Gibril et al. (1999). The most common of these are radiation pneumonitis, accessory spleen, focal collection of stools, surgical scar tissue, gallbladder uptake, nodular goiter, ventral hernia, bacterial pneumonia, respiratory infections, common cold (nasal uptake), cerebrovascular accident, concomitant granulomatous disease, diffuse breast uptake, adrenal uptake, urine contamination, and concomitant second primary tumor.

Diminished uptake in the spleen due to ongoing treatment with (unlabeled) octreotide may occur, which may be accompanied by a lower liver uptake. In case of hepatic metastases, this phenomenon may be misinterpreted as a better uptake in the liver metastases. During octreotide treatment, the uptake of [$^{111}\text{In-DTPA}^0$]octreotide in somatostatin receptor-positive tumors is also diminished. This may lead to

a lower detection rate of somatostatin receptor-positive lesions, although there are also reports of improved tumor-to-background ratio after pretreatment with nonradioactive octreotide. Other causes for a potential false-negative study are: the presence of unlabeled somatostatin, either because of octreotide therapy or resulting from production of somatostatin by the tumor itself; the presence of different somatostatin receptor subtypes that have different affinities for the radioligand, which may be important especially in patients with insulinomas and medullary thyroid carcinomas; the presence of liver metastases of neuroendocrine tumors that have a similar degree of tracer accumulation as the normal liver and so appear isointense (Tables 1 and 2).

Imaging results of [¹¹¹In-DTPA⁰]octreotide scintigraphy in neuroendocrine and other tumors

Somatostatin receptors have been identified *in vitro* in a large number of human neoplasias. A high incidence and density of somatostatin receptors are found, in particular, in neuroendocrine tumors, such as pituitary adenoma, pancreatic islet cell tumor, carcinoid, pheochromocytoma, paraganglioma, medullary thyroid cancer, and small cell lung carcinoma (Reubi 1997). Tumors of the nervous system including meningioma, neuroblastoma, and medulloblastoma also express very often a high density of somatostatin receptors. But also tumors not known to be classically originating from endocrine or neural cells, such as lymphoma, breast cancer, renal cell cancer, hepatocellular cancer, prostate cancer, sarcoma, and gastric cancer, can express somatostatin receptors. In the majority of these tumors, the somatostatin receptor subtype-2 is predominantly expressed, although low amounts of

Table 1 Pitfalls and causes of potential misinterpretation of positive results with [¹¹¹In-DTPA⁰]octreotide scintigraphy

Radiation pneumonitis
Accessory spleen
Focal collection of stools
Surgical scar tissue
Gallbladder uptake
Nodular goiter
Ventral hernia
Bacterial pneumonia
Respiratory infections
Common cold (nasal uptake)
Cerebrovascular accident
Concomitant granulomatous disease
Diffuse breast uptake
Adrenal uptake
Urine contamination
Concomitant second primary tumor

Table 2 Causes of potential misinterpretation of negative results with [¹¹¹In-DTPA⁰]octreotide scintigraphy

Presence of unlabeled somatostatin, either because of octreotide therapy or resulting from production of somatostatin by the tumor itself, may lower tumor detectability
Different somatostatin receptor subtypes have different affinities for the radioligand; variable tumor differentiation and receptor expression also influence tumor detectability. This may be important especially in patients with insulinomas and medullary thyroid carcinomas
Liver metastases of neuroendocrine tumors may appear isointense because of a similar degree of tracer accumulation by the normal liver. Correlation with anatomic imaging and/or SPECT imaging may be helpful

other somatostatin receptor subtypes may be concomitantly present (Reubi *et al.* 2001). It should also be emphasized that selected nontumoral lesions may express somatostatin receptors. For instance, active granulomas in sarcoidosis express somatostatin receptors on the epithelioid cells, and inflamed joints in active rheumatoid arthritis express somatostatin receptors, preferentially located in the proliferating synovial vessels (Reubi *et al.* 1994). The expression of somatostatin receptors is therefore not specific for tumoral pathologies.

Imaging results in tumors and other diseases are listed and subdivided according to the reported sensitivity of SRI with [¹¹¹In-DTPA⁰]octreotide in Table 3.

Common indications for [¹¹¹In-DTPA⁰]octreotide scintigraphy include the detection and localization of a variety of neuroendocrine and other tumors and their metastases, the staging of patients with neuroendocrine tumors, the follow-up of patients with known disease, and lastly the selection of patients with inoperable and/or metastatic tumors for peptide receptor radionuclide therapy (PRRT).

Newer ligands for SRI

^{99m}Tc-Depreotide (Neotect, Diatide, Londonderry, NH, USA) is another commercially available somatostatin analog that has been approved specifically for the detection of lung cancer in patients with pulmonary nodules (Menda & Kahn 2002). Because of the relatively high abdominal background and the impossibility to perform delayed imaging due to the short half-life of the tracer, it is less suited for the detection of abdominal neuroendocrine tumors (Lebtahi *et al.* 2002).

[¹¹¹In-DOTA]lanreotide is a SRI agent with a slightly different affinity profile than [¹¹¹In-DTPA⁰]octreotide (Reubi *et al.* 2000). In comparison with [¹¹¹In-DTPA⁰]octreotide, it has a lower sensitivity to

Table 3 Sensitivity of somatostatin receptor imaging using [$^{111}\text{In-DTPA}^0$]octreotide*High sensitivity*

Pituitary tumors (Kwekkeboom *et al.* 1999)
 GEPNETs
 Gastrinomas (De Kerviler *et al.* 1994, Gibril *et al.* 1996)
 Nonfunctioning endocrine pancreatic tumors (Krenning *et al.* 1993, Lebtahi *et al.* 1997)
 Functioning endocrine pancreatic tumors except insulinomas (Krenning *et al.* 1993, Lebtahi *et al.* 1997)
 Carcinoids (Kwekkeboom *et al.* 1993a, Westlin *et al.* 1993, Ahlman *et al.* 1994, Kalkner *et al.* 1995)
 Paragangliomas (Kwekkeboom *et al.* 1993b, Telischi *et al.* 2000, Duet *et al.* 2003)
 Small cell lung cancer (Kirsch *et al.* 1994, Kwekkeboom *et al.* 1994, Bombardieri *et al.* 1995, Reisinger *et al.* 1998)
 Meningiomas (Haldemann *et al.* 1995, Schmidt *et al.* 1998)
 Sarcoidosis and other granulomatous diseases (Vanhagen *et al.* 1994, Kwekkeboom *et al.* 1998)
 Graves' disease and Graves' ophthalmopathy (Postema *et al.* 1994, Krassas *et al.* 1995)

Intermediate sensitivity

Insulinoma (Krenning *et al.* 1993, Zimmer *et al.* 1996)
 Medullary thyroid carcinoma (Kwekkeboom *et al.* 1993c, Tisell *et al.* 1997, Adams *et al.* 1998)
 Differentiated thyroid carcinoma (including Hurthle cell carcinoma) (Postema *et al.* 1996, Gulec *et al.* 1998, Haslinghuis *et al.* 2001)
 Breast cancer (Van Eijck *et al.* 1994)
 Lymphoma (NHL, HL) (Lugtenburg *et al.* 2001a,b)
 Pheochromocytoma (Van der Harst *et al.* 2001)
 Astrocytoma (Schmidt *et al.* 1998)

High sensitivity, detection rate >75%; intermediate sensitivity, detection rate 40–75%. Sensitivity is either patient or lesion based. GEPNET, gastroenteropancreatic neuroendocrine tumor; NHL, non-Hodgkin lymphoma; HL, Hodgkin's lymphoma.

demonstrate neuroendocrine tumors, but it may have advantages in other tumors, for instance in differentiated thyroid cancer (Virgolini *et al.* 2002).

Also, other somatostatin analogs labeled with γ -emitting radionuclides have been proposed, and more recently analogs labeled with positron-emitting radionuclides have been tested in patients. Especially, the latter analogs that are used for imaging with PET cameras or hybrid PET-CT cameras have great potential because of two advantages that they have over γ -emitting analogs. First, many of them have a better affinity for the somatostatin receptor subtype-2, which is most commonly expressed by neuroendocrine tumors, and also there are some analogs that target other somatostatin receptor subtypes better, and are therewith potentially also useful for visualizing tumors that express these other receptor subtypes, but not the subtype-2. Secondly, the better spatial resolution of PET imaging and the combined anatomical and functional information that is obtained with the hybrid

PET-CT technique result in a higher sensitivity of this type of scanning. An overview of clinical results in patients with gastroenteropancreatic neuroendocrine tumors (GEPNETs) obtained with somatostatin analogs other than [$^{111}\text{In-DTPA}^0$]octreotide (OctreoScan) is given in Table 4.

Reviewing the results with these newer analogs, there are also causes for concern. First, many studies that compare these newer analogs, either compare to [$^{111}\text{In-DTPA}^0$]octreotide scintigraphy using inadequate scanning protocols, or they describe comparisons between two or more new analogs and therefore lack a validated reference method. Secondly, the multitude of new PET analogs that are applied leads to a situation in which each center has to build up its own knowledge on normal findings and artifacts of their scanning methods. This hampers the exchange of data and their shared interpretation. It is, however, likely that one of the new PET analogs, [$^{68}\text{Ga-DOTA}^0$, Tyr 3]octreotide or [$^{68}\text{Ga-DOTA}^0$, Tyr 3]octreotate, becomes the new standard for SRI using PET. This is because these somatostatin analogs have a high affinity for the somatostatin receptor subtype-2, and because ^{68}Ga is a generator product instead of a cyclotron-produced product, a relatively simple labeling can be performed on an everyday basis. An additional reason why [$^{68}\text{Ga-DOTA}^0$, Tyr 3]octreotide or [$^{68}\text{Ga-DOTA}^0$, Tyr 3]octreotate is the likely new standard analog for PET imaging is that their ^{90}Y - or ^{177}Lu -labeled counterparts are used for PRRT, and that it seems desirable that the peptide that is used in diagnostic imaging mimicks as closely as possible the peptide that is used for therapy.

Other radionuclide-coupled ligands that are independent of the presence of somatostatin receptors for visualization of the tumors have also been tested in patients with GEPNETs. The oldest of these, ^{123}I -MIBG, performs poorer than [$^{111}\text{In-DTPA}^0$]octreotide scintigraphy (Quigley *et al.* 2005).

^{18}F -FDG PET scanning has gained importance for tumor staging and treatment response evaluation for a number of tumor types. The method is based on glucose consumption by the tumors, and therefore, fast growing tumors usually show high tracer uptake. However, ^{18}F -FDG PET is less suited for GEPNETs, because of their slow growing nature. Therefore, it is recommended only in cases with negative SRI findings (Belhocine *et al.* 2002), a situation which usually correlates with more aggressive behavior and faster growth.

Newer PET radioligands that have been clinically tested in patients with GEPNETs comprise ^{18}F -DOPA and ^{11}C -5-hydroxy-tryptophan (Koopmans *et al.* 2006, 2008).

Table 4 Results of the clinical application of somatostatin receptor imaging using various ligands in patients with gastroenteropancreatic neuroendocrine tumors

Radioligand	Reported results	Comments	References
[^{99m} Tc-EDDA/HYNIC ⁰]octreotate	Better than [¹¹¹ In-DTPA ⁰]octreotide	[¹¹¹ In-DTPA ⁰]octreotide scan protocol inadequate	Hubalewska-Dydejczyk <i>et al.</i> (2006)
[⁶⁸ Ga-DOTA ⁰ ,Tyr ³]octreotide	[⁶⁸ Ga-DOTA ⁰ ,Tyr ³]octreotide	No comparison to [¹¹¹ In-DTPA ⁰]octreotide	Gabriel <i>et al.</i> (2007)
[^{99m} Tc-HYNIC ⁰]octreotide	PET better than other two methods		
[¹¹¹ In-DOTA ⁰]octreotide			
[⁶⁸ Ga-DOTA ⁰ ,Tyr ³]octreotide	Better than [¹¹¹ In-DTPA ⁰]octreotide SPECT	[¹¹¹ In-DTPA ⁰]octreotide scan protocol inadequate	Buchmann <i>et al.</i> (2007)
[Gluc-Lys ⁰ ,[¹⁸ F]FP]octreotate	Better than [¹¹¹ In-DTPA ⁰]octreotide		Meisetschläger <i>et al.</i> (2006)
[⁶⁸ Ga-DOTA ⁰ ,Tyr ³]octreotide	Better than [¹¹¹ In-DTPA ⁰]octreotide	[¹¹¹ In-DTPA ⁰]octreotide scan protocol inadequate	Hofmann <i>et al.</i> (2001)
[⁶⁸ Ga-DOTA,1-naphthylalanin ³]octreotide	Useful information additional to CT	No comparison to [¹¹¹ In-DTPA ⁰]octreotide	Fanti <i>et al.</i> (2008)
[⁶⁸ Ga-DOTA,1-naphthylalanin ³]octreotide	Better than ¹⁸ F-DOPA	No comparison to [¹¹¹ In-DTPA ⁰]octreotide	Ambrosini <i>et al.</i> (2008)
^{99m} Tc-Depreotide	Inferior to [¹¹¹ In-DTPA ⁰]octreotide		Lebtahi <i>et al.</i> (2002)
[¹¹¹ In-DOTA]lanreotide	Inferior to [¹¹¹ In-DOTA ⁰ ,Tyr ³]octreotide	No comparison to [¹¹¹ In-DTPA ⁰]octreotide	Virgolini <i>et al.</i> (2002)

PET with these ligands was reported to be more sensitive than SRI with [¹¹¹In-DTPA⁰]octreotide. These PET ligands, however, have to be synthesized in the close vicinity of or in the hospital where the administration to the patient is to take place. Also, both ¹⁸F-DOPA and ¹¹C-5-hydroxy-tryptophan, unlike the radiolabeled somatostatin analogs used in PET, lack a sequel in PRRT.

Somatostatin receptor-based radionuclide therapy

GEPNETs, which comprise functioning and nonfunctioning endocrine pancreatic tumors and carcinoids, are usually slow growing. When metastasized, treatment with somatostatin analogs results in reduced hormonal overproduction and symptomatic relief in most cases. Treatment with somatostatin analogs is however seldom successful in terms of tumor size reduction (Arnold *et al.* 1993, Janson & Oberg 1993, Ducreux *et al.* 2000). However, it was recently shown that the long-acting somatostatin analog Octreotide LAR significantly lengthens time to tumor progression compared with placebo in patients with functionally active and inactive metastatic midgut NETs (Rinke *et al.* 2009).

A new treatment modality for patients with inoperable or metastasized endocrine GEP tumors is the use of radiolabeled somatostatin analogs. The majority of endocrine GEP tumors possess somatostatin receptors and can therefore be visualized with

SRI. A logical sequence to this tumor visualization *in vivo* was therefore to also try to treat these patients with radiolabeled somatostatin analogs. Virtually without exception, the patients who were treated with PRRT had well-differentiated GEPNETs (grade 1 or 2 according to the World Health Organization (WHO) classification). In the sections that follow on different forms of PRRT, reported tumor responses are based on WHO or South-Western Oncology Group criteria, unless stated differently.

Studies with [¹¹¹In-DTPA⁰]octreotide

Because at that time no other chelated somatostatin analogs labeled with β -emitting radionuclides were available, early studies in the mid- to late 1990s used [¹¹¹In-DTPA⁰]octreotide for PRRT. Initial studies with high dosages of [¹¹¹In-DTPA⁰]octreotide in patients with metastasized neuroendocrine tumors were encouraging with regard to symptom relief, but partial remissions (PRs) were exceptional. Two out of 26 patients with GEPNETs who were treated with high dosages of [¹¹¹In-DTPA⁰]octreotide, and received a total cumulative dose of more than 550 mCi (20 GBq), had a decrease in tumor size between 25 and 50% as measured on CT scans (Valkema *et al.* 2002). None, however, had PR (Table 5). In another study in 27 patients with GEPNETs, PR was reported in 2/26 patients with measurable disease (Anthony *et al.* 2002; Table 5). Both series had relatively high numbers of patients who were in a poor clinical condition upon study entry. Also, many had progressive disease when

Table 5 Tumor responses in patients with gastroenteropancreatic neuroendocrine tumors, treated with different radiolabeled somatostatin analogs (adapted with permission from Kwekkeboom et al. (2005a) copyright 2005 Society of Nuclear Medicine, Inc.)

	Ligand	Patient number	Tumor response					CR + PR (%)
			CR	PR	MR	SD	PD	
Center (reference)								
Rotterdam (Valkema et al. 2002)	[¹¹¹ In-DTPA ⁰] octreotide	26	0	0	5 (19%)	11 (42%)	10 (38%)	0
New Orleans (Anthony et al. 2002)	[¹¹¹ In-DTPA ⁰] octreotide	26	0	2 (8%)	NA	21 (81%)	3 (12%)	8
Milan (Bodei et al. 2003)	[⁹⁰ Y-DOTA ⁰ ,Tyr ³] octreotide	21	0	6 (29%)	NA	11 (52%)	4 (19%)	29
Basel (Waldherr et al. 2001, 2002a)	[⁹⁰ Y-DOTA ⁰ ,Tyr ³] octreotide	74	3 (4%)	15 (20%)	NA	48 (65%)	8 (11%)	24
Basel (Waldherr et al. 2002b)	[⁹⁰ Y-DOTA ⁰ ,Tyr ³] octreotide	33	2 (6%)	9 (27%)	NA	19 (57%)	3 (9%)	33
Rotterdam (Valkema et al. 2006)	[⁹⁰ Y-DOTA ⁰ ,Tyr ³] octreotide	58	0	5 (9%)	7 (12%)	33 (61%)	10 (19%)	9
Rotterdam (Kwekkeboom et al. 2008)	[¹⁷⁷ Lu-DOTA ⁰ , Tyr ³]octreotate	310	5 (2%)	86 (28%)	51 (16%)	107 (35%)	61 (20%)	29

entering the study. The most common toxicity in both series was due to bone marrow suppression. Serious side effects consisted of leukemia and myelodysplastic syndrome (MDS) in three patients who had been treated with total cumulative doses of >2.7 Ci (100 GBq) (and estimated bone marrow radiation doses of more than 3 Gy; Valkema et al. 2002). One of these patients had also been treated with chemotherapy, which may have contributed to or caused this complication. Anthony et al. (2002) reported renal insufficiency in one patient, which was probably not treatment related, but due to preexistent retroperitoneal fibrosis. Transient liver toxicity was observed in three patients with widespread liver metastases. Although in both series favorable effects on symptomatology were reported, CT-assessed tumor regression was observed only in rare cases. This is not surprising, since ¹¹¹In-coupled peptides are not ideal for PRRT because of the small particle range and therefore short tissue penetration.

Studies with [⁹⁰Y-DOTA⁰,Tyr³]octreotide

The next generation of somatostatin receptor-mediated radionuclide therapy used a modified somatostatin analog, [Tyr³]octreotide, with a higher affinity for the somatostatin receptor subtype-2, and a different chelator, DOTA instead of DTPA, in order to ensure a more stable binding of the intended β -emitting radionuclide ⁹⁰Yttrium (⁹⁰Y). Using this compound (⁹⁰Y-DOTATOC; OctreoTher), different phase-1 and -2 PRRT trials have been performed.

Otte et al. (1999) and Waldherr et al. (2001, 2002a; Basel, Switzerland) reported different phase-1 and -2 studies in patients with GEPNETs. In their first reports, using a dose-escalating scheme of four treatment sessions up to a cumulative dose of 160 mCi (6 GBq)/m², and at which time renal protection with amino acid infusion was not performed in half of the patients, renal insufficiency developed in 4/29 patients. The overall response rate in patients with GEPNETs who were either treated with 160 mCi (6 GBq)/m² (Waldherr et al. 2001), or, in a later study, with 200 mCi (7.4 GBq)/m² in four doses (Waldherr et al. 2002a), was 24% (Table 5). In a subsequent study, with the same dose of 200 mCi (7.4 GBq)/m² administered in two sessions, complete and PRs were found in one-third of 36 patients (Waldherr et al. 2002b; Table 5). It should be emphasized, however, that this was not a randomized trial comparing two dosing schemes.

Chinol et al. (2002) (Milan, Italy) described dosimetric and dose-finding studies with [⁹⁰Y-DOTA⁰, Tyr³]octreotide with and without the administration of kidney-protecting agents. No major acute reactions were observed up to an administered dose of 150 mCi (5.6 GBq) per cycle. Reversible grade 3 hematological toxicity was found in 43% of patients injected with 140 mCi (5.2 GBq), which was defined as the maximum tolerated dose per cycle. None of the patients developed acute or delayed kidney failure, although follow-up was short. Partial and complete remissions were reported by the same group in 28% of 87 patients with neuroendocrine tumors (Paganelli et al. 2002).

In a more detailed publication from the same group, Bodei *et al.* (2003) reported the results of a phase-1 study in 40 patients with somatostatin receptor-positive tumors, of whom 21 had GEPNETs. Cumulative total treatment doses ranged from 160 to 300 mCi (5.9–11.1 GBq), given in two treatment cycles. Six of 21 (29%) patients had tumor regression (Table 5). Median duration of the response was 9 months.

Another study with [$^{90}\text{Y-DOTA}^0, \text{Tyr}^3$]octreotide is a multicenter phase-1 study which was performed in Rotterdam (The Netherlands), Brussels (Belgium), and Tampa (USA), in which 58 patients received escalating doses up to 400 mCi (14.8 GBq)/m² in four cycles or up to 250 mCi (9.3 GBq)/m² single dose, without reaching the maximum tolerated single dose (Valkema *et al.* 2006). The cumulative radiation dose to kidneys was limited to 27 Gy. All received amino acids concomitant with [$^{90}\text{Y-DOTA}^0, \text{Tyr}^3$]octreotide for kidney protection. Three patients had dose-limiting toxicity: one had liver toxicity, one had thrombocytopenia grade 4 (<25 × 10⁹/l), and one had MDS. Out of 58 patients, five (9%) had PR and seven (12%) had a minor response (MR; 25–50% tumor volume reduction; Table 5). The median time to progression in the 44 patients who had either stable disease (SD), MR, or PR was 30 months (Valkema *et al.* 2003).

Bushnell *et al.* (2003) (Iowa City, USA) reported a favorable clinical response as determined by a scoring system that included weight, patient-assessed health score, Karnofsky score, and tumor-related symptoms, in 14/21 patients who were treated with a total cumulative dose of 360 mCi [$^{90}\text{Y-DOTA}^0, \text{Tyr}^3$]octreotide in three treatment cycles.

Despite differences in protocols used, complete plus PRs in most of the different studies with [$^{90}\text{Y-DOTA}^0,$

Tyr^3]octreotide are in the same range, in between 10 and 30%, and therefore better than those obtained with [$^{111}\text{In-DTPA}^0$]octreotide.

Studies with [$^{177}\text{Lu-DOTA}^0, \text{Tyr}^3$]octreotate

The somatostatin analog [DTPA⁰, Tyr³]octreotate differs from [DTPA⁰, Tyr³]octreotide only in that the C-terminal threoninol is replaced with threonine. Compared with [DTPA⁰, Tyr³]octreotide, it shows an improved binding to somatostatin receptor-positive tissues in animal experiments (De Jong *et al.* 1998). Also, its DOTA-coupled counterpart, [DOTA⁰, Tyr³]octreotate, labeled with the β- and γ-emitting radionuclide ¹⁷⁷Lutetium (¹⁷⁷Lu) was reported to be very successful in terms of tumor regression and animal survival in a rat model (Erion *et al.* 1999). Reubi *et al.* (2000) reported a ninefold increase in affinity for the somatostatin receptor subtype 2 for [DOTA⁰, Tyr³]octreotate if compared with [DOTA⁰, Tyr³]octreotide, and a six- to sevenfold increase in affinity for their Yttrium-loaded counterparts (Table 6).

In a comparison in patients, it was found that the uptake of radioactivity, expressed as percentage of the injected dose of [$^{177}\text{Lu-DOTA}^0, \text{Tyr}^3$]octreotate, was comparable to that after [$^{111}\text{In-DTPA}^0$]octreotide for kidneys, spleen, and liver, but was three- to fourfold higher for four of five tumors (Kwekkeboom *et al.* 2001). Therefore, [$^{177}\text{Lu-DOTA}^0, \text{Tyr}^3$]octreotate potentially represents an important improvement because of the higher absorbed doses that can be achieved to most tumors with about equal doses to potentially dose-limiting organs and because of the lower tissue penetration range of ¹⁷⁷Lu if compared with ⁹⁰Y, which may be especially important for small tumors. Also, when we compared the residence time in tumors for [$^{177}\text{Lu-DOTA}^0, \text{Tyr}^3$]octreotide and

Table 6 Affinity profiles (IC₅₀) for human sst₁–sst₅ receptors of a series of somatostatin analogs

Peptide	sst ₁	sst ₂	sst ₃	sst ₄	sst ₅
Somatostatin-28	5.2 (0.3)	2.7 (0.3)	7.7 (0.9)	5.6 (0.4)	4.0 (0.3)
Octreotide	> 10 000	2.0 (0.7)	187 (55)	> 1000	22 (6)
DTPA-octreotide	> 10 000	12 (2)	376 (84)	> 1000	299 (50)
In-DTPA-octreotide	> 10 000	22 (3.6)	182 (13)	> 1000	237 (52)
DOTA-[Tyr ³]octreotide	> 10 000	14 (2.6)	880 (324)	> 1000	393 (84)
DOTA-[Tyr ³]octreotate	> 10 000	1.5 (0.4)	> 1000	453 (176)	547 (160)
DOTA- <i>lan</i> reotide	> 10 000	26 (3.4)	771 (229)	> 10 000	73 (12)
Y-DOTA-[Tyr ³]octreotide	> 10 000	11 (1.7)	389 (135)	> 10 000	114 (29)
Y-DOTA-[Tyr ³]octreotate	> 10 000	1.6 (0.4)	> 1000	523 (239)	187 (50)
Y-DOTA- <i>lan</i> reotide	> 10 000	23 (5)	290 (105)	> 10 000	16 (3.4)

All values are half maximal inhibitory concentration (IC₅₀) (S.E.M.) in nM (adapted from Reubi *et al.* (2000) with kind permission from Springer Science + Business Media: copyright 2000 European Journal of Nuclear Medicine). No data are available for Lu-loaded somatostatin analogs.

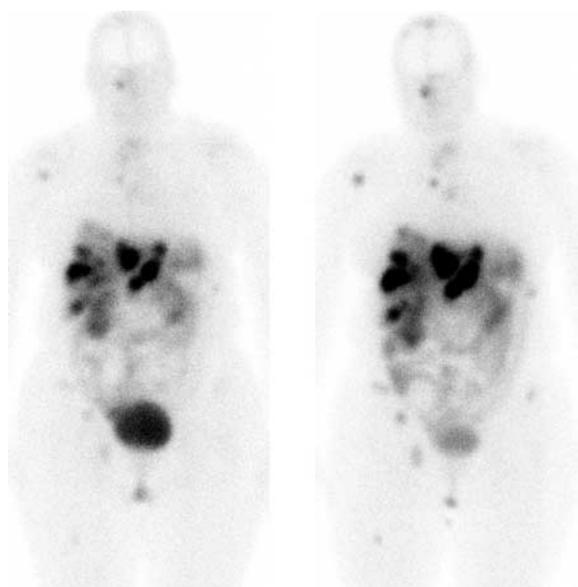


Figure 2 Planar anterior scintigrams 1 day after the administration of 3700 MBq (100 mCi) of [$^{177}\text{Lu-DOTA}^0,\text{Tyr}^3$]octreotide (left) or [$^{177}\text{Lu-DOTA}^0,\text{Tyr}^3$]octreotate (right) in the same patient with liver and bone metastases from a GEPNET. Note the higher uptake in the tumor sites after [$^{177}\text{Lu-DOTA}^0,\text{Tyr}^3$]octreotate, with similar uptake in liver and spleen (adapted from Esser *et al.* (2006) with kind permission from Springer Science + Business Media: copyright 2006 European Journal of Nuclear Medicine and Molecular Imaging).

[$^{177}\text{Lu-DOTA}^0,\text{Tyr}^3$]octreotate in the same patients in a therapeutic setting, we found a factor 2.1 in favor of [$^{177}\text{Lu-DOTA}^0,\text{Tyr}^3$]octreotate (Esser *et al.* 2006; Fig. 2). We therefore think that [$^{177}\text{Lu-DOTA}^0,\text{Tyr}^3$]octreotate is the radiolabeled somatostatin analog of choice when performing PRRT.

Consistent with two earlier reports (Kwekkeboom *et al.* 2003, 2005b), a recent analysis of the side effects and treatment outcome of [$^{177}\text{Lu-DOTA}^0,\text{Tyr}^3$]octreotate therapy was described in 504 and 310 patients with neuroendocrine GEP tumors respectively (Kwekkeboom *et al.* 2008).

In the 504 patients, acute side effects occurring within 24 h after the administration of the radiopharmaceutical were nausea after 25% of administrations, vomiting after 10% of administrations, and abdominal discomfort or pain after 10% of administrations. Six patients were hospitalized within 2 days of the administration of the radiopharmaceutical because of hormone-related crises (De Keizer *et al.* 2008). All patients recovered after adequate care.

Subacute, hematological toxicity, WHO toxicity grade 3 or 4, occurred 4–8 weeks after 3.6% of administrations, or, expressed patient-based, after at least one of several treatments in 9.5% of patients.

Factors that were associated with a higher frequency of hematological toxicity grade 3 or 4 were age over 70 years at treatment start, a history with previous chemotherapy treatment, creatinine clearance (estimated with Cockcroft's formula) ≤ 60 ml/min, and the presence of bone metastases. When these factors were tested together in multivariate logistic regression, low creatinine clearance was a significant factor both for grade 3/4 thrombocytopenia ($P < 0.001$), as for any hematological grade 3/4 toxicity ($P < 0.001$), whereas a history with previous chemotherapy was less significant in predicting thrombocytopenia ($P < 0.05$; Fig. 3). Creatinine clearance ≤ 60 ml/min was significantly more frequent in patients aged 70 or more ($P < 0.001$, χ^2 test; Fig. 3). Temporary hairloss (WHO grade 1; no baldness) occurred in 62% of patients.

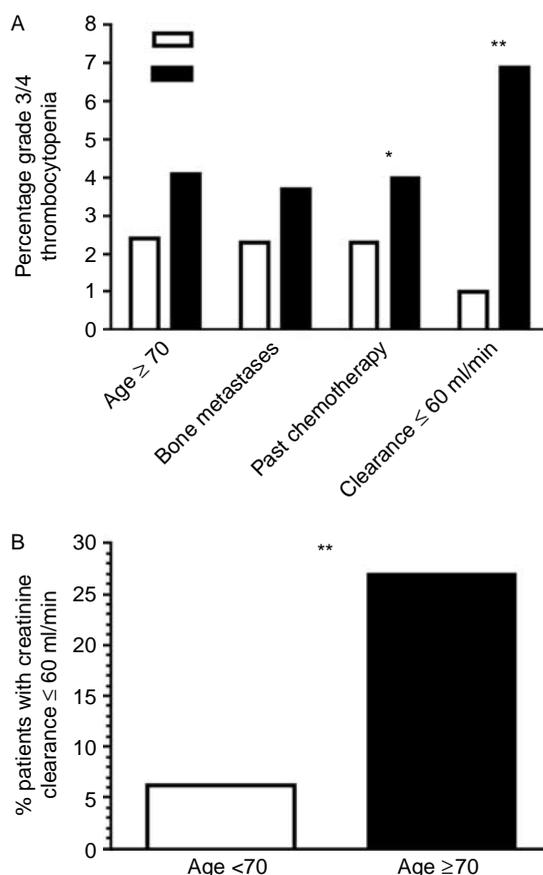


Figure 3 Factors that are associated with a higher frequency of thrombocytopenia (WHO grade 3 or 4 toxicity) after treatment with [$^{177}\text{Lu-DOTA}^0,\text{Tyr}^3$]octreotate. * $P < 0.05$; ** $P < 0.001$, logistic regression (upper panel). Low creatinine clearance at start of treatment was more frequent in older age (lower panel, $P < 0.001$, χ^2 test). Open bars, factor not present; closed bars, factor present (Data adapted with permission from Kwekkeboom *et al.* (2008) copyright 2008 American Society of Clinical Oncology. All rights reserved).

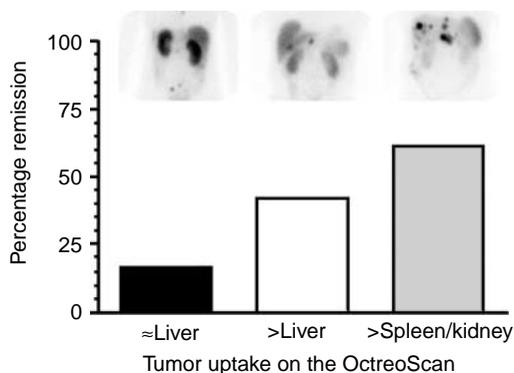


Figure 4 Relationship between the chances of achieving a tumor remission (MR, PR, or CR) after treatment with [^{177}Lu -DOTA 0 ,Tyr 3]octreotate and visually scored tumor uptake on the pretherapeutic OctreoScan. Examples of uptake scores are indicated (Data adapted with permission from Kwekkeboom *et al.* (2008) copyright 2008 American Society of Clinical Oncology. All rights reserved).

Serious delayed toxicities were observed in 9 out of 504 patients. There were two cases of renal insufficiency, both of which were probably unrelated to ^{177}Lu -octreotate treatment. Serious liver toxicity occurred in three patients, and was probably treatment related in two of them. Lastly, MDS occurred in four patients, and was potentially treatment related in three patients.

Treatment responses according to tumor type at 3 months after the last therapy cycle were analyzed in 310 patients. Overall, objective tumor response rate, comprising CR, PR, and MR, was 46%. Prognostic factors for predicting tumor remission (CR, PR, or MR) as treatment outcome were uptake on the OctreoScan ($P < 0.01$; Fig. 4), and Karnofsky Performance Score (KPS) > 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 categorized tumor response at 6 months and 12 months of follow-up, occurring in 4% of patients and 5% of patients respectively (Figs 5 and 6).

Three of four patients with clinically nonfunctioning neuroendocrine pancreatic tumors that were judged inoperable before treatment with ^{177}Lu -octreotate, and who had PR, were successfully operated 6–12 months after their last treatment, whereas one died of post-operative complications.

Median time to progression was 40 months from start of treatment. Median overall survival (OS) in our 310 GEP tumor patients was 46 months (median follow-up 19 months; 101 deaths). Median disease-related survival was > 48 months (median follow-up 18 months; 81 deaths). Median progression-free survival was 33 months. The most important factor predicting survival was treatment outcome. Low KPS and liver involvement were also very significant predicting factors.

Quality of life

Another study evaluated the quality of life (QoL) in our first 50 Dutch patients with metastatic somatostatin receptor-positive GEP tumors treated with [^{177}Lu -DOTA 0 ,Tyr 3]octreotate (Teunissen *et al.* 2004). The patients completed the European Organization for the Research and Treatment of Cancer QoL Questionnaire C30 (Aaronson *et al.* 1993) before therapy and at follow-up visit 6 weeks after the last cycle. A significant improvement in the global health status/

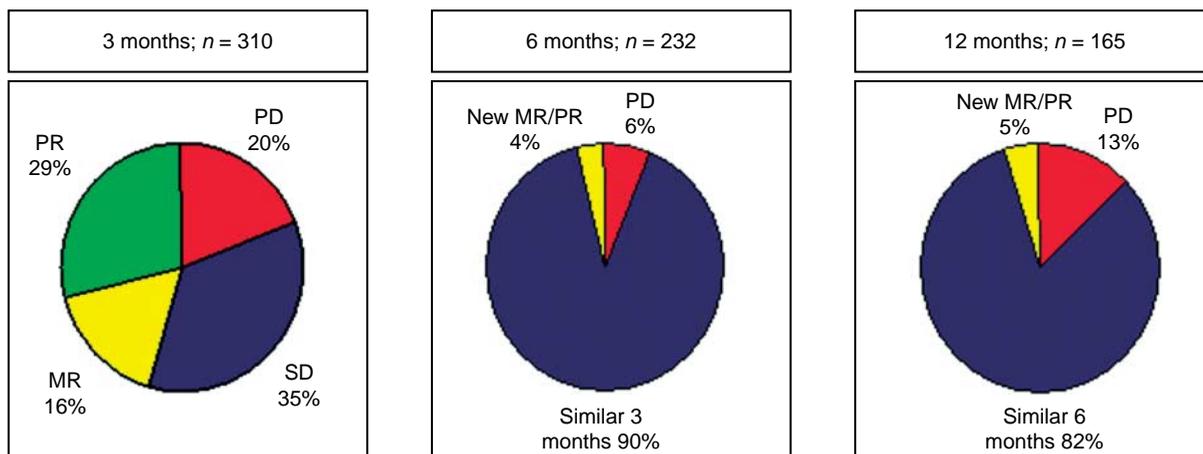


Figure 5 Treatment outcome changes during follow-up. Patient numbers are indicated and decrease due to loss of patients who have PD and because of variable follow-up. There is a small but important percentage of patients who continue to have CT-assessed tumor shrinkage during prolonged follow-up (yellow pie parts).

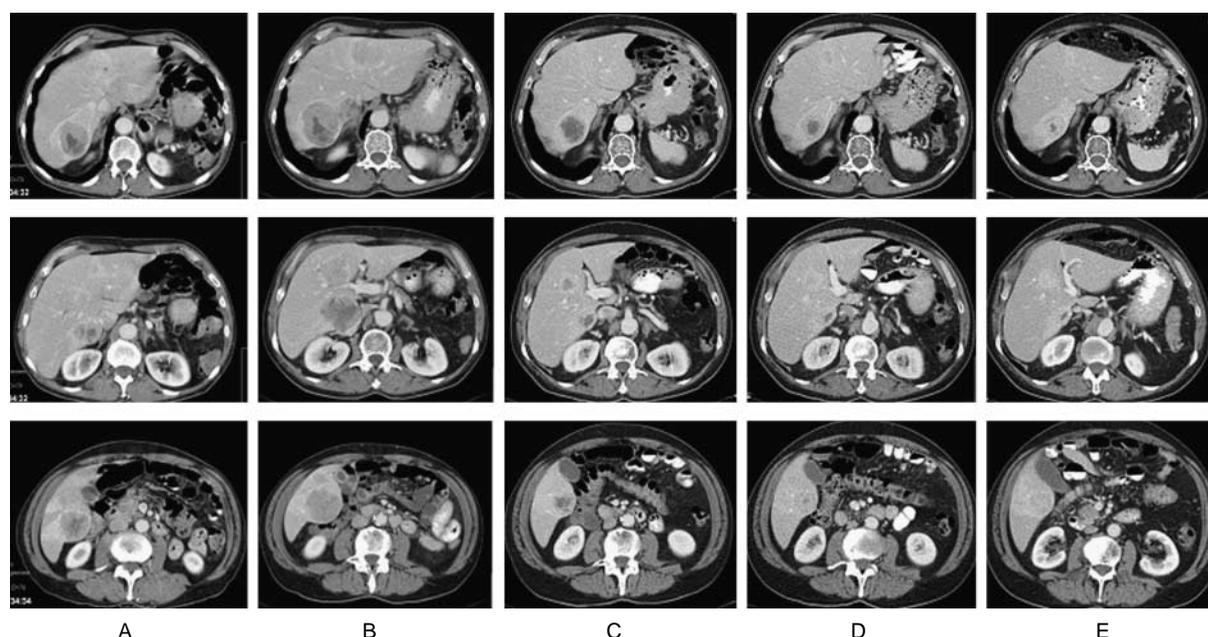


Figure 6 Serial CT scans with identical tumor sites in the liver in a patient with metastatic pancreatic neuroendocrine tumor. (A) Three months before start of therapy. (B) Before start of therapy. PD compared to A. (C) Six weeks after the last therapy cycle: tumor regression (PR). (D) Three months after the last therapy cycle: further regression. (E) Six months after the last therapy cycle: ongoing tumor regression.

QoL scale was observed after therapy with [^{177}Lu -DOTA 0 ,Tyr 3]octreotate. Furthermore, significant improvement was observed in the role, emotional, and social function scales. The symptom scores for fatigue, insomnia, and pain decreased significantly. Patients with proven tumor regression most frequently had an improvement of QoL domains. However, because of the lack of a control group in this study, some placebo effect cannot be ruled out completely.

Comparison of treatment with [^{177}Lu -DOTA 0 , Tyr 3]octreotate with other PRRT

Treatment with radiolabeled somatostatin analogs is a promising new tool in the management of patients with inoperable or metastasized neuroendocrine tumors. The results that were obtained with [^{90}Y -DOTA 0 ,Tyr 3]octreotide and [^{177}Lu -DOTA 0 ,Tyr 3]octreotate are very encouraging, although a direct, randomized comparison between the various treatments is lacking. Also, the reported percentages of tumor remission after [^{90}Y -DOTA 0 ,Tyr 3]octreotide treatment vary. This may have several causes: the administered doses and dosing schemes differ: some studies use dose-escalating schemes, whereas others use fixed doses; also, there are several patient and tumor characteristics that determine treatment outcome, such as amount of uptake on the OctreoScan, the estimated total tumor burden,

and the extent of liver involvement. Therefore, differences in patient selection may play an important role in determining treatment outcome. Other factors that can have contributed to the different results that were found in the different centers performing trials with the same compounds may be differences in tumor response criteria, and centralized versus decentralized follow-up CT scoring.

From our analysis in patients treated with [^{177}Lu -DOTA 0 ,Tyr 3]octreotate, we learned that the two significant factors predicting favorable 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. Also, in order to establish which treatment scheme and which radiolabeled somatostatin analogs or combination of analogs is optimal, randomized trials are needed.

Chelated lanreotide, another somatostatin analog, labeled with ^{111}In for diagnostic purposes and with ^{90}Y for therapeutic use has been advocated because of its better binding than [^{111}In -DTPA 0]octreotide to the somatostatin receptor subtypes 3 and 4 (Virgolini *et al.* 2002). This claim can be questioned (Reubi *et al.* 2000). Although this compound has been used to treat patients with GEP tumors, it shows poorer affinity than

radiolabeled [DOTA⁰, Tyr³]octreotide/octreotate for the somatostatin receptor subtype-2, which is predominantly overexpressed in GEP tumors (Reubi *et al.* 2000; Table 6).

Wehrmann *et al.* (2007) compared the biodistribution of [¹⁷⁷Lu-DOTA⁰]octreotate and [¹⁷⁷Lu-DOTA⁰,1-naphthylalanin³]octreotide [¹⁷⁷Lu-DOTA⁰]NOC in patients, and concluded that tumor uptake and absorbed dose were comparable for both radioligands, whereas whole-body retention was lower for [¹⁷⁷Lu-DOTA⁰]octreotate, and therefore the authors advocate the use of [¹⁷⁷Lu-DOTA⁰]octreotate.

Preliminary data have been presented of a study using ⁹⁰Y-labeled [DOTA⁰,Tyr³]octreotate (Baum *et al.* 2004a,b). However, the treatment protocols vary and the way of response evaluation was not clearly defined. The reported results were an objective response rate (PR) of 37% (28/75) and a stabilization of the disease in 39/75 patients (52%). In the same study, the intra-arterial use of [⁹⁰Y-DOTA⁰,Tyr³]octreotate in five patients was described. However, no detailed results for this application were provided. An important issue is that to date reliable dosimetry for [⁹⁰Y-DOTA⁰,Tyr³]octreotate is lacking.

Comparison of survival data

Because the treatment with [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate is still open for new patients, and median follow-up in relation to survival is relatively short, we also analyzed our local, Dutch patients separately with subgroups that had longer follow-up. The results from these analyses point out that both overall and disease-specific survival time are consistently at or above 48 months. These numbers compare favorably to those reported in the literature. Clancy *et al.* (2006) reported a significantly shorter survival in patients with elevated serum alkaline phosphatase concentrations at referral compared to those who had normal values. We found the same, but in our patients treated with ¹⁷⁷Lu-octreotate, survival from referral was longer. Even more striking was the difference in median OS from diagnosis: 128 vs 72 months, despite the fact that in our group mean serum alkaline phosphatase concentration was higher, indicating more advanced liver involvement and worse prognosis (Fig. 7). 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 ¹⁷⁷Lu-octreotate, which ranged

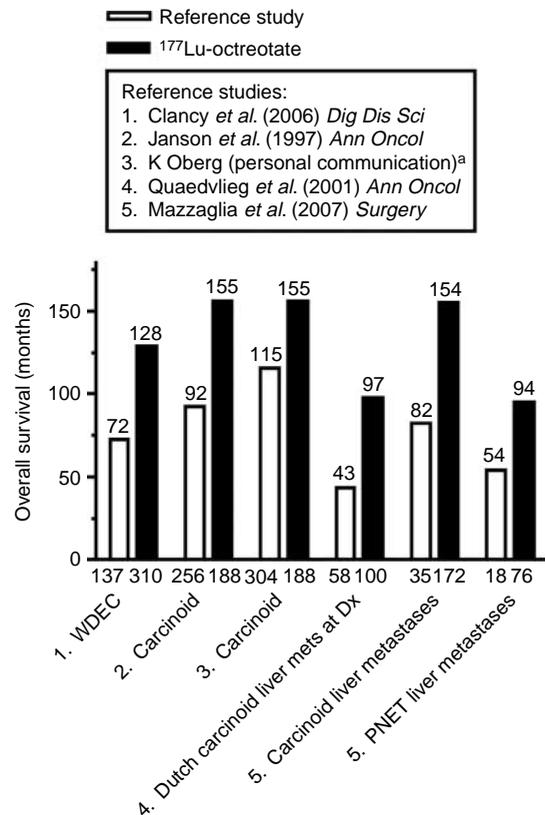


Figure 7 Overall, survival in months since diagnosis in patients from observational and interventional studies (blue bars) and in similar patients with regard to tumor type and disease stage treated with [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate (red bars). There is a survival benefit of 40–72 months in patients treated with [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate (Data adapted with permission from Kwekkeboom *et al.* (2008) copyright 2008 American Society of Clinical Oncology. All rights reserved). Dx, diagnosis; WDEC, well-differentiated endocrine carcinoma; PNET, pancreatic neuroendocrine tumor. ^aK Oberg and D J Kwekkeboom, personal communication.

from 40 to 72 months from diagnosis (Fig. 7). 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 it is most probably caused by a real difference in survival.

Comparison with chemotherapy

In order to better evaluate the response to PRRT, it would have been preferable that a randomized trial was performed comparing PRRT to no further treatment at all. This however, is presently no longer possible, since patients can be treated with PRRT in several medical centers and since the results of such treatment are so impressive that withholding it to half

of the patients in an experimental setting cannot be ethically justified. However, Faiss *et al.* (2003) reported tumor remissions in 4 out of 80 (5%) GEP tumor patients who had progressive disease at study entry and were treated with somatostatin analogs and/or interferon- α . By contrast, we found tumor remissions in 46% of our patients who were treated with ^{177}Lu -octreotate, whether or not they had PD at study entry (Kwekkeboom *et al.* 2008). It seems highly unlikely that such a difference could have been caused by patient selection.

Apart from the proportion of patients with a tumor remission, the duration of such a response is another important treatment outcome parameter. Reported response rates for single agent and combination chemotherapy in patients with GEPNETs are for instance as high as 40–60% for well-differentiated pancreatic tumors and poorly differentiated tumors from any origin, whereas success rates for midgut tumors rarely exceed 20% in recent studies (Bukowski *et al.* 1994, Andreyev *et al.* 1995, Neijt *et al.* 1995, Ritzel *et al.* 1995, Cheng & Saltz 1999, Ansell *et al.* 2001; Table 7), for a review see O'Toole *et al.* (2004). High response rates have been reported in older series (Moertel *et al.* 1980, 1992, Moertel 1983), but in these studies the response evaluation also included biochemical responses (changes in serum tumor marker levels) as well as physical examination for the evaluation of hepatomegaly. Indeed, much of the discrepancy between older and more recent studies can be ascribed to differences in response criteria, as is illustrated in a more recent study by Cheng & Saltz (1999) who described that their percentage of patients

with an objective response would have increased from 6 to 25% if they had accepted not only measured CT scan changes as response criteria, but also decreases of hepatomegaly assessed with physical examination. Despite the varying percentages of objective responses that have been reported for chemotherapy, the median time to progression in most of the studies is <18 months. In this respect, treatment with ^{90}Y -octreotide or ^{177}Lu -octreotate performs considerably better with a median time to progression of 30 and 40 months respectively (Valkema *et al.* 2003, Kwekkeboom *et al.* 2008).

Not only response rate, but also the duration of the response, progression-free survival, and OS are more favorable after ^{177}Lu -octreotate treatment than in recent reports on chemotherapy (Table 7).

Novel drugs

Multiple new drugs are under investigation in patients with GEPNETs. The combination of capecitabine (Xeloda, an oral pro-drug of 5-fluorouracil (5-FU)) and temozolomide (Temodal, Temodar, an oral alkylating agent) resulted in PR in 12 of 17 patients, and SD in 5. After a median time of follow-up of 12 months, none of the patients had developed progression (Strosberg *et al.* 2008).

As neuroendocrine tumors are highly vascularized, several drugs that inhibit angiogenesis are studied. Effects of bevacizumab (Avastin, Hoffmann la Roche AG, Grenzach-Wyhlen, Germany) with temozolomide were studied in 29 patients and resulted in a PR in 14% and SD in 79% (Kulke *et al.* 2006). Seven of 41 (17%) evaluable patients with metastasized carcinoid who

Table 7 Results of recent chemotherapy reports compared to treatment with [^{177}Lu -DOTA⁰,Tyr³]octreotate

Regimen	Tumor types	Patient number	PR/CR (%)	Median PFS (mo)	Median OS (mo)	Study (year)
STZ + doxorubicin	PNET	16	6	NA	NA	Cheng & Saltz (1999)
Dacarbazine	Carc	56	16	NA	20	Bukowski <i>et al.</i> (1994)
Dacarbazine	Carc	7	14	NA	NA	Ritzel <i>et al.</i> (1995)
FU + IF- α	Carc/PNET	24	21	8	23	Andreyev <i>et al.</i> (1995)
Mitoxantrone	Carc/PNET	30	7	NA	16	Neijt <i>et al.</i> (1995)
Paclitaxel	Carc/PNET	24	4	3	18	Ansell <i>et al.</i> (2001)
STZ + FU + doxorubicin	PNET	84	39	18	37	Kouvaraki <i>et al.</i> (2004)
Doxorubicin + FU	Carc	85	13	5	16	Sun <i>et al.</i> (2005)
STZ + FU	Carc	78	15	5	24	Sun <i>et al.</i> (2005)
Irinotecan + FU	Carc/PNET	20	5	5	15	Ducreux <i>et al.</i> (2006)
Oxaliplatin + capecitabine	Well-differentiated NET	27	30	NA	40	Bajetta <i>et al.</i> (2007)
^{177}Lu -octreotate	Carc/PNET	310	30	32	46	Kwekkeboom <i>et al.</i> (2008)

STZ, streptozotocin; FU, 5-fluorouracil; IF- α , interferon- α ; PNET, pancreatic neuroendocrine tumor; Carc, carcinoid; PFS, progression-free survival; OS, overall survival; NA, not available (adapted with permission from Kwekkeboom *et al.* (2008) copyright 2008 American Society of Clinical Oncology. All rights reserved).

were treated with sorafenib (Nexavar) had MR or PR, and 8/20 patients had a progression-free survival of >6 months. Thirteen of 41 evaluable patients (32%) with a pancreatic NET had MR or PR and progression-free survival was >6 months in 14/23 patients (Hobday *et al.* 2007). Yao *et al.* (2007) reported their results of treatment with imatinib in advanced carcinoid tumors: one out of 27 patients had PR and 17 had SD. Median progression-free survival was 5.5 months.

Sunitinib (SU11248, Sutent), an oral, multitargeted tyrosine kinase inhibitor, has also been tested in patients with GEPNETs. In a phase II study, 11 of 66 patients (17%) with pancreatic NET had PR and 45 had SD. In patients with carcinoids, sunitinib treatment resulted in PR in 1 of 41 patients and SD in 34. Overall, median time to progression was 8 months in pancreatic NET and 10 months in carcinoids. (Kulke *et al.* 2008).

Recently, inhibitors of the mammalian target of rapamycin were introduced in studies for treating patients with GEPNETs. Therapy with temsirolimus (Torisel, Pfizer, NY, USA) as single agent had limited anti-tumor activity (Duran *et al.* 2006). Everolimus

(RAD001, Certican) in combination with long-acting octreotide seems to have more promising anti-tumor effects. Sixty patients of whom 39 had PD at study entry were treated: 17% had PR and 75% had SD. The median progression free survival was 14 months (Yao *et al.* 2008). However, some of these studies present preliminary data, reported as congress abstracts, and full reports or confirmatory studies have to be awaited.

Timing of treatment

In patients treated with [$^{177}\text{Lu-DOTA}^0\text{Tyr}^3$] octreotate, median OS was shorter in patients having a poor performance score and those having extensive liver involvement. This implies that treatment with [$^{177}\text{Lu-DOTA}^0\text{Tyr}^3$]octreotate should preferably be started early in the disease evolution. Because GEPNETs can be clinically stable for years; however, it is, in our opinion, good clinical practice to wait for signs of disease progression if the tumor load is moderate. Such signs should not be restricted to CT-assessed tumor growth, but also include rises in serum tumor markers, increase in symptoms, or

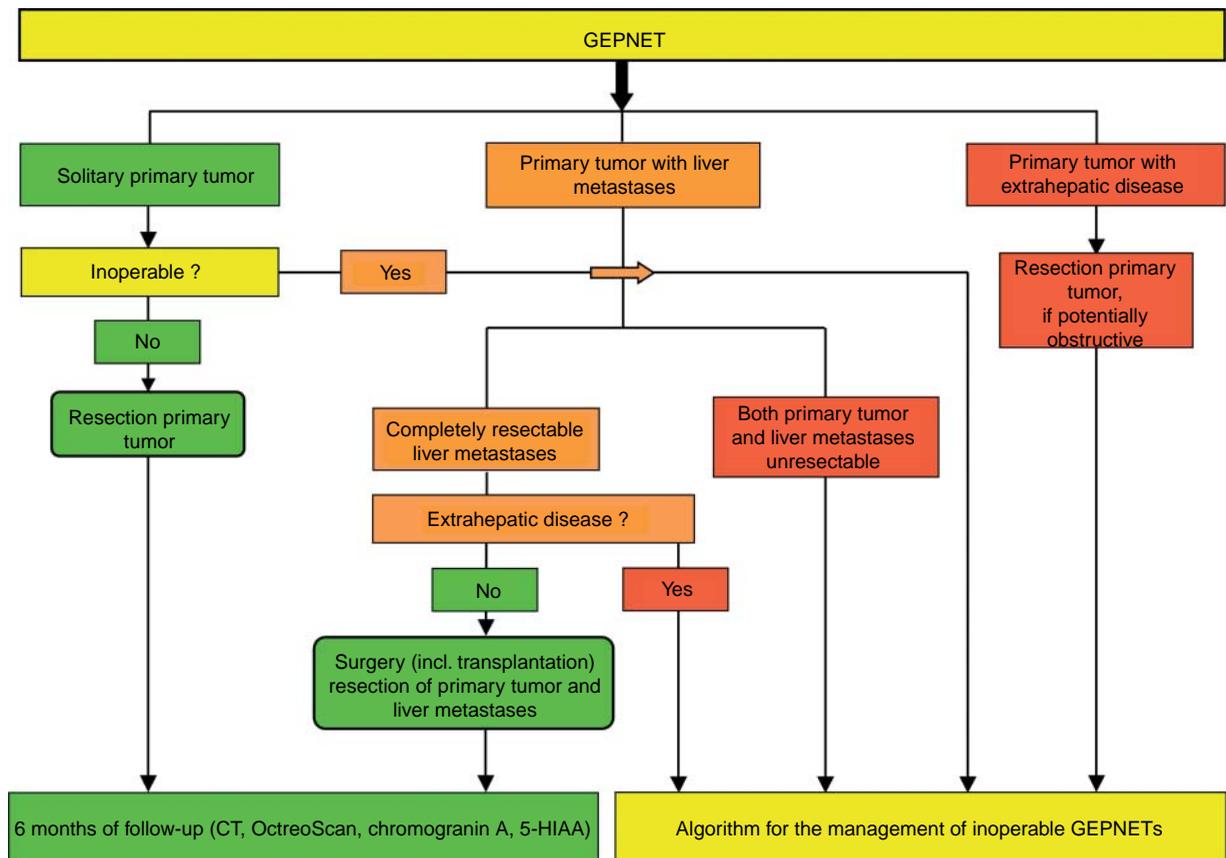


Figure 8 Algorithm for the treatment of patients with GEPNETs.

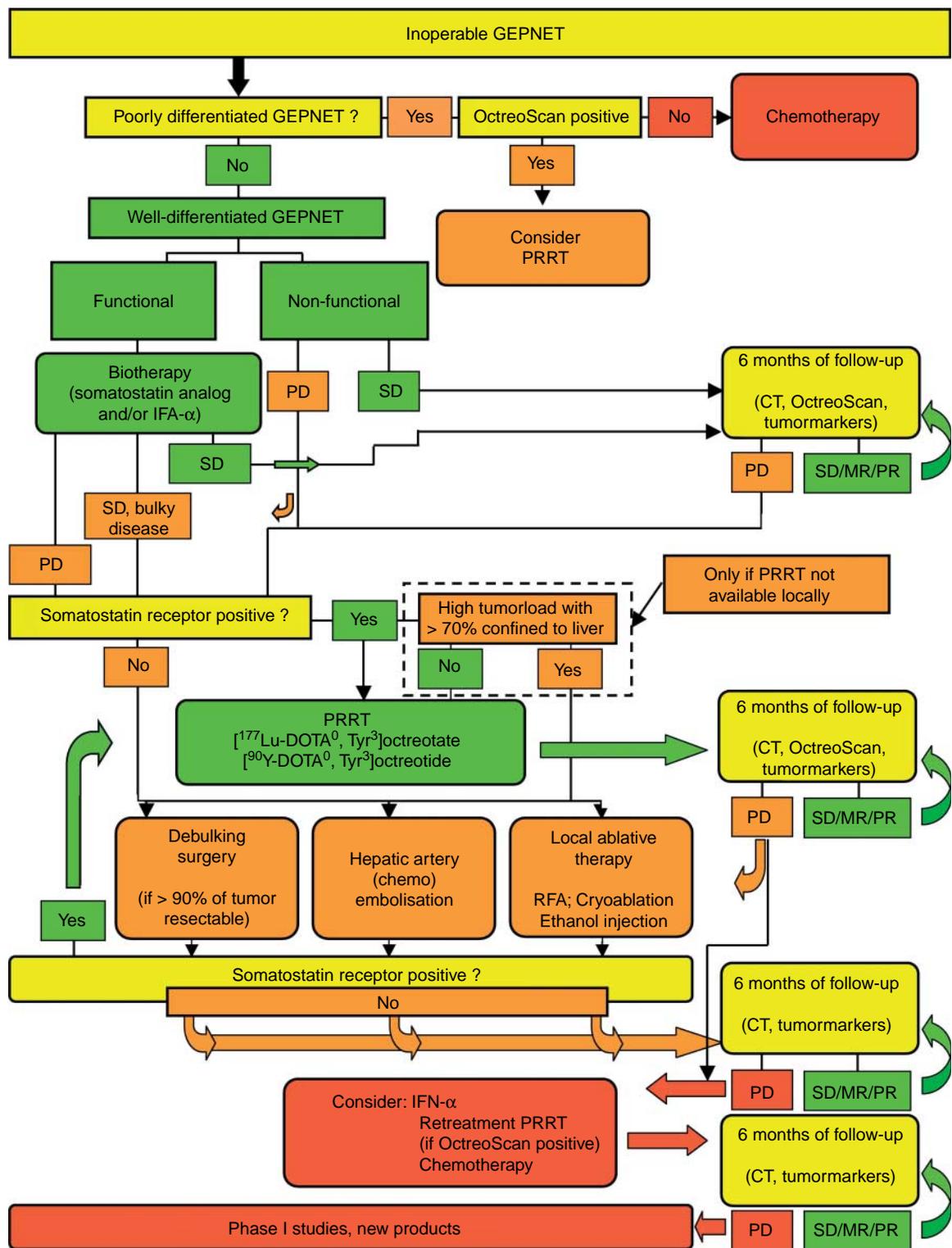


Figure 9 Algorithm for the treatment of patients with inoperable and/or metastasized GEPNETs. IFN- α , interferon- α ; RFA, radio frequency ablation.

involuntary weight loss. In patients with very limited tumor load and in whom cure is potentially possible, treatment should be initiated without further delay, and the same holds true for patients with extensive tumor load, hepatomegaly, or those with significant weight loss, when waiting for formally assessed tumor progression would place these patients in an unfavorable starting position for treatment or would even qualify them as ineligible.

Options to improve PRRT

From animal experiments, it can be inferred that ^{90}Y -labeled somatostatin analogs may be more effective for larger tumors, whereas ^{177}Lu -labeled somatostatin analogs may be more effective for smaller tumors, but their combination may be the most effective (De Jong *et al.* 2002). Therefore, apart from comparisons between radiolabeled octreotate and octreotide, and between somatostatin analogs labeled with ^{90}Y or ^{177}Lu , PRRT with combinations of ^{90}Y - and ^{177}Lu -labeled analogs should also be evaluated.

Future directions to improve this therapy may also include the use of radiosensitizing chemotherapeutic agents. Chemosensitization with 5-FU in combination with ^{90}Y -labeled antibody radioimmunotherapy is feasible and safe (Wong *et al.* 2003). Also, chemosensitization with 5-FU, combined with [^{111}In -DTPA]octreotide treatment resulted in symptomatic response in 71% of patients with neuroendocrine tumors (Kong *et al.* 2005), whereas other studies using only [^{111}In -DTPA]octreotide treatment reported such responses in lower percentages (Anthony *et al.* 2002, Valkema *et al.* 2002). Numerous trials to the effects of combined chemotherapy and (fractionated) external beam radiotherapy have been performed. In many of these, 5-FU was used. More recent trials used the prodrug of 5-FU, capecitabine, which has the advantage of oral administration. Also with the combination of radiotherapy and capecitabine, an increased efficacy in terms of tumor growth control was reported if compared to radiotherapy as single treatment modality (Rich *et al.* 2004). If capecitabine is used in relatively low doses (1600–2000 mg/m² per day), grade 3 hematologic or other toxicity is rare (Dunst *et al.* 2002, Rich *et al.* 2004). For these reasons, after proving the safety of the combined therapy (Van Essen *et al.* 2008), we started a randomized multicenter trial comparing treatment with ^{177}Lu -octreotate with and without capecitabine in patients with GEPNETs.

Also, attempts to improve the results of this type of therapy may focus on further reducing the radiation absorbed dose to normal tissues and organs, like

kidneys and bone marrow, or at increasing the receptor density on the tumors, for instance via receptor upregulation. Both strategies may increase the therapeutic window.

Lastly, individualized dosimetry for each patient is desirable. Both kidney absorbed dose and bone marrow absorbed radiation dose vary widely between patients (Kwekkeboom *et al.* 2001, Förrer *et al.* 2009). This means that with fixed-dose regimens that show relatively few side effects, a proportion of patients is undertreated. Tailored dosimetry, currently based on urine collection, repeated imaging and blood sampling after therapy, is time consuming. However, such an individualized calculation of the maximum cumulative doses that can be given to a certain patient may in a considerable part of the patients result in higher cumulative doses that can safely be administered. Improvements in methods as well as consensus on standards for dosimetry would greatly stimulate the clinical acceptance of individualized dosimetry.

Place of PRRT in the treatment of patients with GEPNETs

The place and role that treatment with [^{177}Lu -DOTA⁰,Tyr³]octreotate or [^{90}Y -DOTA⁰,Tyr³]octreotide has in the management of patients with inoperable or metastasized GEPNETs, according to our clinical practice, is outlined in Figs 8 and 9. These are flow schemes that summarize the treatment options and the clinical decision making in such patients.

Conclusions

SRI with [^{111}In -DTPA⁰]octreotide has proven its role in the diagnosis and staging of GEPNETs. Newer radiolabeled somatostatin analogs which can be used in PET imaging, and which have a higher affinity for the somatostatin receptor, especially receptor subtype-2, have been developed. It would be desirable, however, if one radiolabeled analog became the new standard for PET imaging, because the current application of a multitude of analogs implies a fragmented knowledge on the interpretation of the images that are obtained in clinical practice. In our view, the most likely candidates for such a universal PET tracer for SRI are [^{68}Ga -DOTA⁰,Tyr³]octreotate or [^{68}Ga -DOTA⁰,Tyr³]octreotide.

Treatment with radiolabeled somatostatin analogs is a promising new tool in the management of patients with inoperable or metastasized neuroendocrine tumors. Symptomatic improvement may occur with all ^{111}In -, ^{90}Y -, or ^{177}Lu -labeled somatostatin analogs

that have been used for PRRT. The results that were obtained with [⁹⁰Y-DOTA⁰,Tyr³]octreotide and [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate are very encouraging in terms of tumor regression. Also, if kidney protective agents are used, the side effects of this therapy are few and mild, and the duration of the therapy response for both radiopharmaceuticals is more than 30 months. The patients' self-assessed QoL increases significantly after treatment with [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate. Lastly, compared to historical controls, there is a benefit in OS of several years from the time of diagnosis in patients treated with [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate. These data compare favorably with the limited number of alternative treatment approaches. If more widespread use of PRRT can be guaranteed, such therapy may well become the therapy of first choice in patients with metastasized or inoperable GEPNETs.

Declaration of interest

Eric Krenning is a member of the advisory board of Biosynthesa and Novartis, and a consultant of Biosynthesa and Covidien. He receives research or material support from Covidien, Novartis, and Biosynthesa, and is a shareholder in Biosynthesa. Dik Kwekkeboom is a shareholder in Biosynthesa.

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