Endocrine Tumours

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Molecular Radiation on Target

Peptide Receptor Radionuclide Therapy
with
Lutetium-octreotate

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Endocriene tumoren
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Doelgerichte moleculaire straling

Peptide receptor radionuclide therapie met Lutetium-octreotaat

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Voor Papa

CONTENTS

1

General introduction

1.1

Management of patients with neuroendocrine tumours

The discovery of the neuropeptide somatostatin (SS) in 1973 by Guillemin and co-workers at the Salk Institute [1] and the extensive work on the function of peptides, including SS, by the group of Schally *et al.*[2], for which both received the Nobel prize in 1977, was an important step towards the current knowledge of neuroendocrine tumours. Almost two decades later, its counterpart, the somatostatin receptor (SSTR) was characterized by Yamada *et al.*[3,4]. Furthermore, the widespread presence and functions within the body of both the hormone and its ligand has been intensively studied. The polypeptide somatostatin comprises several peptides formed after different posttranslational processing of the pre-prosomatostatin protein encoded by a single gene. Only two of these small peptides, somatostatin-14 and somatostatin-28, are biologically active and are the most common somatostatin peptides present in the peripheral and central nervous system (CNS). The somatostatin-14 and somatostatin-28 isoforms consist of 14 and 28 amino acids, respectively. The entire somatostatin-14 sequence is present in the C-terminus of somatostatin-28. The predominant biologically active isoform is somatostatin-14. The relative proportions of somatostatin-14 and somatostatin-28 differ among various somatostatin-producing tissues. However, somatostatin-14 and somatostatin-28 display overlapping physiological functions. Both somatostatin-14 and somatostatin-18 are produced by neuroendocrine, inflammatory, and immune cells in response to ions, nutrients, neuropeptides, neurotransmitters, thyroid and steroid hormones, growth factors, and cytokines [5].

The somatostatin peptides exert their regulatory biological role after binding to an SSTR. At present, five different human SSTRs, named SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5 have been identified and cloned [3,4]. All five SSTRs belong to the superfamily of G-protein-coupled receptors with seven transmembrane domains and have been identified throughout the CNS, endocrine and exocrine glands. All five subtypes bind somatostatin-14 and somatostatin-28 with high affinity. Although the different SSTR subtypes are 40% to 60% structurally homologous, each subtype has its specific role in signalling between cells and the different tissues. The most prominent role, however, is the inhibitory effect of somatostatin on the secretion of hormones in various organs such as the inhibition of growth hormone, prolactin and thyroid stimulating hormone within the pituitary or inhibition of glucagon and insulin release within the pancreas.

Somatostatin receptors are expressed in various tissues such as the CNS, anterior pituitary, the endocrine and exocrine pancreas, the gastrointestinal tract and the adrenals, but neuroendocrine tumours also frequently express somatostatin receptors. Table 1 summarizes the characteristics of somatostatin receptor expression in neuroendocrine tumours.

Table 1. Somatostatin receptor expression in neuroendocrine tumours

Receptor incidence	Pancreatic and gut endocrine tumours: 80-100% Insulinomas: 50-70%
Receptor density	Commonly high
Receptor distribution	Commonly homogeneous
Receptor expression	Well-differentiated tumour > undifferentiated tumour
Receptor subtype expression frequency	SSTR2 >> SSTR1=SSTR5> SSTR3 >>SSTR4
Receptor localisation	Usually cell membrane bound, especially SSTR2

Adapted from Reubi [7]

The receptor density is high in the majority of cases but may vary between the tumours. Undifferentiated endocrine tumours express less often SSTRs and if so, the density is reported to be low [6,7]. The SSTR most commonly expressed in endocrine tumours is the SSTR2.

Incidence

The age-standardised incidence of carcinoids, the most common gastroenteropancreatic neuroendocrine tumour (GEP-NET), described as the age-standardised incidence per 100,000 inhabitants per year, is approximately 1-2/100,000 [8]. The lowest percentage of patients is reported in Italy, whereas the highest number has been reported in the USA [9,10]. A slight preponderance in women was reported in Europe, whereas in the USA a higher incidence was found among black people [8]. Interestingly, the incidental finding of carcinoid tumours during autopsies is much higher and is reported to be about 1% [11]. In a recent Dutch study, the primary site of NETs was reported to be within the gastrointestinal tract (62%), especially the appendix (27%), followed by the small bowel (13%). Thereafter, the lungs and mediastinum are the second most common localisation of neuroendocrine tumours.

Modlin *et al.* [12], who used the Surveillance, Epidemiology, and End Results database (SEER, 1973–1991) registry, reported the overall incidence of nonlocalised carcinoids at the time of diagnosis as 45.3% in a total of 5468 carcinoid patients. The frequently during surgery incidentally encountered appendiceal carcinoid was demonstrated to be nonlocalised in 35.4%. Carcinoids originating from different anatomical sites, like the pancreas, small intestine or colon, were encountered more frequently with metastasis at diagnosis (76.1%, 70.7% and 71.2%, respectively). Pancreatic NETs

of which up to 40% are non-functioning, have about 50% hepatic metastases at diagnosis [13]. In twelve percent of patients who present with metastatic disease, the primary site remains unknown [8].

Histology and classification

In the last century several classifications of GEP-NETs have been applied. Obern-dorfer, who was the first to characterize these tumours, reported the existence of rare epithelial tumours in the gut that have a relatively monotonous structure and exhibit a less aggressive or indolent nature than gut derived carcinomas [14]. The latter characteristic feature of the tumour made him choose the name 'carcinoid'. Until 1963, all GEP-NETs tumours were referred to as carcinoids. At that time, Williams and Sandler divided the carcinoids into fore-, mid- and hindgut carcinoids, according to their embryologic origin [15]. This classification was never fully accepted by clinicians mainly because of the wide range of differences of morphology, function and biology that could be found within one single class of tumours. In 1980, the first World Health Organization (WHO) classification of endocrine gastrointestinal tumours was introduced. Endocrine tumours were subdivided based on cell type into enterochromaffin cell, gastrin cell and unspecified carcinoids [16]. This classification caused misunderstanding between pathologists and clinicians because for the latter group the term carcinoid was mainly reserved for patients who had symptoms due to the secretion of hormones by the tumour. Obviously, the WHO definition did not cover the whole morphological, biological and clinical spectrum of GEP-NETs. A more structured WHO classification was introduced in 2000 [17,18]. The new classification is based on a combination of pathological and clinical features with parameters specific for each organ from which the endocrine tumours originate. All GEP-NETs are grossly divided into three main categories: (1) well-differentiated endocrine tumours, further subdivided into tumours with benign and with uncertain biological behaviour; (2) well-differentiated endocrine carcinomas or low grade; and (3) poorly differentiated endocrine carcinomas or high grade (Table 2).

Because poorly differentiated tumours have a highly aggressive course, these neoplasms are profoundly different from the other subgroups and, therefore, require a more aggressive therapeutic approach (see further in this chapter). A further distinction was made according to the specific organ localisations. The stomach, duodenum (and proximal jejunum), ileum (including the distal jejunum), appendix, colon-rectum, and pancreas were distinguished. Besides the histopathological characteristics and primary site of origin, the endocrine tumours are classified into whether biologically active substances/hormones are produced and secreted and thereby distinguished into functioning or non-functioning endocrine tumours.

Table 2. WHO classification of gastroenteropancreatic endocrine tumours

Tumour Site	Well differentiated endocrine tumour (Benign behaviour)	Well differentiated endocrine tumour (Uncertain behaviour)	Well differentiated endocrine carcinoma (Low grade malignant)	Poorly differentiated endocrine carcinoma (High grade malignant)
Pancreas	Confined to pancreas < 2cm	Confined to pancreas ≥ 2cm	Well to moderately differentiated Gross local invasion and/or metastases	Small cell carcinoma Necrosis common
	< 2 mitoses per 10 HPF	> 2 mitoses per 10 HPF	Mitotic rate often higher (2-10 per 10 HPF)	> 10 mitosis per 10 HPF
	< 2% Ki-67 positive cells No vascular invasion	> 2% Ki-67 positive cells or vascular invasion	Ki-67 index > 5%	> 15% Ki-67 positive cells Prominent vascular and/ or perineural invasion
Stomach	Confined to mucosa-submucosa ≤ 1 cm. No vascular invasion	Confined to mucosa-submucosa >1 cm or vascular invasion	Well to moderately differentiated Invasion to muscularis propria or beyond or metastases	Small cell carcinoma
Duodenum, upper jejunum	Confined to mucosa-submucosa ≤ 1 cm. No vascular invasion	Confined to mucosa-submucosa > 1 cm or vascular invasion	Well to moderately differentiated Invasion to muscularis propria or beyond or metastases	Small cell carcinoma
Ileum, colon, rectum	Confined to mucosa-submucosa ≤ 1 cm (small intestine)	Confined to mucosa-submucosa > 1 cm (small intestine)	Well to moderately differentiated Invasion to muscularis propria or beyond or metastases	Small cell carcinoma
	≤ 2 cm (large intestine). No vascular invasion	> 2 cm (large intestine) or vascular invasion		
Appendix	Non-functioning Confined to the appendiceal wall	Enteroglucagon-producing Confined to subserosa	Well to moderately differentiated Invasion to mesoappendix or beyond or metastases	Small cell carcinoma
	≤ 2 cm. No vascular invasion	> 2 cm or vascular invasion		

HPF, high power field. Adapted from Ramage et al. 2005 [19]

Functioning endocrine tumours or carcinomas are still traditionally named according to the hormone(s) that are produced such as gastrinomas, insulinomas and vasoactive intestinal peptide-omas ('VIPomas') [20]. The term carcinoid is reserved for the functioning well-differentiated endocrine tumours, which produce and secrete serotonin and thereby cause the so-called carcinoid syndrome. The term malignant carcinoid is reserved for the functioning well-differentiated endocrine carcinomas. Poorly differentiated (usually small cell) endocrine carcinoma, which is characterised by high grade malignancy, is no longer associated with the term carcinoid.

With the use of the new WHO classification the individual tumour within the heterogeneous group of endocrine tumours can be better classified according to their histology, biological behaviour and clinical presentation. Most of the endocrine tumours, including those described within this thesis are well-differentiated, slow growing and have a relative good prognosis. With respect to the tumours described in this thesis, the terms 'endocrine' and 'neuroendocrine' can be considered synonymous. Since the results described within the present thesis are compared with studies from the past, the tumour nomenclature may differ from the most recent WHO definitions. Where possible the new WHO classification is used.

TREATMENT

Evaluation of therapy outcome

The treatment of GEP-NETs is extremely variable and different treatment modalities are currently used and developed. To have insight in and for comparison with the reported outcomes of the different treatment options, it is necessary to be familiar with the methods, which are used to measure and compare the outcomes of treatment.

The most obvious treatment outcome or endpoint of a study, especially in early phase II clinical trials, is tumour reduction. However, it is often not clear which tumour response criteria have been used or what is meant with partial response or remission (PR), stable disease (SD) or progressive disease (PD) mentioned in the those studies. Most studies discussed in this general introduction use established criteria, such as the criteria of the WHO, Response Evaluation Criteria in Solid Tumours (RECIST) or criteria defined by the Southwest Oncology Group (SWOG). Definitions of these different criteria are shown in Table 3.

The use of this type of criteria allows better comparison of results among patients treated differently. However, to fully understand and compare clinical trials it is important to realize these differences. The most important difference between these criteria lies within the method of measuring the tumours (bidimensional

versus unidimensional). This may lead to different response outcome in the same patient when other criteria are used. As the definition of progressive disease is also different in all criteria, differences can be expected especially when establishing the number of patients with PD [21]. Also, although outcome of therapy based on tumour size measurement seems to be straightforward, it has the disadvantage that it does not take into account that inhibition of tumour growth, resulting in SD, can be also of significant clinical benefit and vice versa; that response does not per se imply clinical benefit when information about side-effects, quality of life and time to progression (TTP) is lacking. Furthermore, only morphological information on radiological imaging is currently used in assessing tumour responses following the mentioned criteria, whereas information of metabolic response assessed by molecular imaging (e.g. Fluorodeoxyglucose-Positron Emission Tomography, FDG-PET) is not taken into account, but may be possibly at least as important. In several studies, it is reported that metabolic response had additional value to morphological response data [22, 23]. In the management of GEP-NETs, for example, controversy exists in the clinical importance of the occurrence of abdominal fibrosis commonly seen in carcinoid patients. This evidence of disease will remain stable in follow-up but has no meaning in terms of disease activity. Nonetheless, it will be included in the assessment of morphological response. It is therefore not unlikely that in the future the current criteria for response evaluation in GEP-NETs will include response criteria based on both morphological response and assessment of metabolic response by molecular imaging or even that results of molecular imaging can serve as a surrogate measure of therapeutic efficacy.

In most phase III trials and some phase II trials more stringent endpoints like survival, progression free survival (PFS), and TTP are used. These endpoints are more logical when considering tumour response in terms of metabolic activity, especially since more and more cancer therapeutics are based on the inhibition of tumour cell growth rather than the induction of tumour cell death or apoptosis in conventional cytotoxic strategies. Furthermore these endpoints have the advantage of assessing the therapeutic efficacy within a specific patient population rather than for the individual patient. Obviously however, these trials require the inclusion of more patients and longer, carefully monitored follow-up. Therefore, data on PFS and TTP are often lacking in reports on anti-tumour activity of recently developed anti-cancer agents. The different and most commonly used definitions of survival and corresponding endpoints, are given in Table 4.

Table 3. Definition of response according to WHO, RECIST and SWOG criteria.

Criteria	Tumour size measurement	CR	PR	SD	PD
WHO [a]	Sum of products (bidimensional)	Disappearance of all known disease	≥ 50% decrease of all lesions; no new lesion, no progression of any lesions	Neither PR nor PD criteria are met	≥ 25% increase of a single lesion; new lesion(s); no CR, PR, or SD documented before increased disease
		Confirmation ≤ 4 weeks	Confirmation ≤ 4 weeks	Confirmation ≤ 4 weeks	
RECIST [b, c]	Sum of maximum diameters of target lesions (unidimensional)	Complete disappearance of all target and non-target lesions	≥ 30% decrease of all target lesions; no new lesion(s); no progression of disease	Neither PR nor PD criteria are met	≥ 20% increase, new lesion(s); no CR, PR, or SD documented before increased disease
		Confirmation ≤ 4 weeks	Confirmation ≤ 4 weeks	Confirmation ≤ 4 weeks	
SWOG [d]	Sum of products of the perpendicular diameters of all measurable lesions (bidimensional)	Complete disappearance all measurable and evaluable disease	≥ 50% decrease of at least one measurable lesion; no progression of evaluable disease; no new lesions	Neither CR, PR nor PD criteria are met	≥ 50% or increase of 10 cm^2 increase, or clear worsening of any evaluable disease, or reappearance of any lesion which had disappeared, or appearance of any new lesion/ site, or failure to return for evaluation due to death or deteriorating condition
		Confirmation at 6 weeks	Confirmation at 6 weeks	Confirmation at 6 weeks	

WHO, World Health Organization; SWOG, Southwest Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumours; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

(a) Cancer 1981; 47:207-214
(b) J Natl Cancer Inst 2000; 92:205-216
(c) target lesions, all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs
(d) Investigational New Drugs 1992; 10: 239-253

The most important treatment outcome is whether the studied therapy can alter the natural history of progression of the patients' disease or increase of survival. Methods to study the latter endpoint can be found in survival analysis studies. However, the slowly progressive or indolent nature of the disease present in most patients makes that survival analysis of GEP-NETs requires a study with a long follow-up period. Furthermore, this can be a disadvantage in terms of determining the effectiveness of therapy within a limited period of time. Also, careful monitoring during follow-up, preferably in the hospital where the patient was treated, is not always practically feasible. In an ideal situation, survival analysis contains a matched control group, which in some studies is, for practical and ethical reasons, not available. An alternative option is to look at historical controls. However, this method does not take into account the problem of a different patient mix and historical time-frame dependent factors such as differences in available therapeutic options for the disease or development of more sensitive diagnostic modalities.

Table 4. Definition of survival and endpoints for clinical trials

Survival Term	Definition†	Endpoint
Overall survival (OS)	The percentage of subjects in a study who have survived for a defined period of time. Usually reported as time since diagnosis or treatment.	Death from any cause
Disease-specific survival	The percentage of subjects in a study who have survived a particular disease for a defined period of time. Only deaths from the disease being studied are counted. Subjects who died from some other cause are not included in the calculation. Usually reported as time since diagnosis or treatment.	Death from the disease studied
Time to progression (TTP)	A measure of time after a disease is diagnosed (or treated) until the progressive disease occurs.	Progressive disease according to trial response criteria
Progression-free survival (PFS)	One type of measurement that can be used in a clinical study or trial to help determine whether a new treatment is effective. It refers to the probability that a patient will remain alive, without the disease getting worse.	Progressive disease or cancer-related death
Disease-free survival	Length of time after treatment during which no cancer is found. Can be reported for an individual patient or for a study population.	Relapse
Survival rate	The percentage of people in a study or treatment group who are alive for a given period of time after diagnosis. This is commonly expressed as 5-year survival.	NA

† *these definitions were quoted from the National Cancer Institue (NCI) website: www.cancer.gov; NA, not applicable*

Other factors, which are important to report, include changes in disease-related symptoms, adverse reactions/complications and side-effects. In most cases, except for life-threatening complications, these factors are not influencing the primary endpoints of the study, such as response to treatment, TTP or survival, but are important in judging the influence of the therapy on normal daily life and non-intended effects of therapy. Together, these effects have their impact on the so-called quality of life.

Quality of life is an entity that is difficult to define, and hence, difficult to assess. Probably one of the main reasons for this is that it differs for any given individual. Nonetheless, standardised methods to assess quality of life have been developed during the last decades. These assessments of quality of life have become a commonly and increasingly used endpoint in many oncology trials.

One of the currently used methods to assess quality of life is the QLQ-C30 questionnaire developed by the European Organization of Research and Treatment of Cancer (EORTC) and can be used for evaluation in all types of cancers. For specific cancers add-on modules have been developed including a separate module for GEP-NETs [24]. Besides the EORTC QLQ-C30 questionnaire many other instruments have been developed. However, despite the many different methods available to measure quality of life, reports on GEP-NETs often lack the assessment of quality of life. Comparison of changes in quality of life between treatments is, therefore, not possible.

Surgery

Resection of the primary tumour is the only curative treatment option and remains the cornerstone in the treatment of patients with GEP-NETs. Surgery with curative intent can be successful, especially in appendiceal carcinoids. The appendix is one of the most common single site for carcinoid tumour [9]. Although rare, it is considered the most common type of appendiceal primary malignant lesion, and is found in 0.3-0.9% of patients undergoing appendectomy [25]. Small appendiceal endocrine tumours (< 1 cm) have an excellent prognosis with a 5-year survival rate of 94% after appendectomy. Larger tumours (> 2 cm) require right hemicolectomy. Hemicolectomy should also be considered in tumours 1–2 cm in size if (a) the mesoappendix is involved; (b) angioinvasion is demonstrable; and (c) a high proliferative index / Ki-67 level is apparent, and (d) when tumours are located at the base of the appendix with positive margins [26, 27]. The 5-year survival rate for patients with more than local disease is 85% [27]. In contrast, surgery with curative intent is often not possible in patients with endocrine tumours in adjacent areas such as the ileum and distal jejunum. At the time of diagnosis the tumours are commonly larger than 2 cm and have already invaded the muscularis propria. Typical findings at laparotomy are a

small primary tumour with large mesenteric metastases with marked surrounding mesenteric fibrosis or desmoplastic reaction due to local effects of serotonin and growth factors produced by the tumour [28]. The primary tumour and mesenteric metastases should be removed by wedge resection of the mesentery and limited intestinal resection, and lymph node metastases ought to be cleared as efficiently as possible by dissection in the area of the mesenteric artery and its branches. This approach has been recommended since without this management patients are at risk to develop abdominal complications, such as intestinal obstruction due to extensive mesenteric desmoplastic reaction or encasement of mesenteric vessels. The latter may cause periodic intestinal ischemia or segmental gangrene with subsequent risk of perforation. If the primary tumour and mesenteric metastases appear radically removed, the patients may remain symptom-free for a long period of time. However, after 5-10 years of follow-up, tumour recurrences occur frequently with liver metastases in more than 80% of patients with long follow-up [29]. Besides frequent recurrence after initial resection with curative intent, cumulative analysis of all types of endocrine tumours showed that in 45% of cases metastases were already evident at the time of diagnosis [12].

In the case of metastases, of which liver metastases are most frequent, surgery with the intention to cure is unlikely to succeed. In these cases surgery of the primary tumour in a palliative setting can be beneficial to the patient in terms of improvement of quality of life. High tumour load of the primary may cause significant morbidity, including secretion of high amounts of hormones and risk of mechanical bowel obstruction, and decreased survival.

The spectrum of clinical presentation in patients with liver metastases may range from patients with progressive liver disease, accompanied by extreme clinical syndromes secondary to increased hormone production, to cases in which patients have been known to live for decades with remarkably large liver metastases without symptomatology. Yao *et al.* [30] indicated that surgery in patients in whom the tumour was still in situ and who had also liver involvement with a limited number of metastases, might be rewarding in terms of extended survival. Sixteen patients had complete surgical resection of their metastases of whom ten had synchronous resection of their primary tumour. The total group had a 5-year survival of 70%. Patients with a limited number of liver metastases (< 5) had a favourable disease-free survival of 46 months compared to 20 months in patients with more than 4 liver metastases. It was concluded that even in patients with hepatic metastases surgery has to be considered.

Furthermore, if the tumour bulk in the liver is too extensive for complete resection, surgery might also have a place in palliation. Several studies have pointed out that

for patients in whom cytoreductive surgery or tumour debulking of more than 90% of the tumour can be achieved, surgery should be offered as it may prolong survival and alter the natural history of the disease process [31, 32]. Recently, a new plea for this aggressive surgical approach of advanced-stage carcinoid tumours was published by Boudreaux *et al.* [33]. This approach included surgical resection of the primary tumour when possible to prevent life threatening abdominal complications (such as intestinal obstruction, ischaemia or perforation), prophylactic cholecystectomy to negate the possibility of future gall stone development associated with long-term octreotide therapy and staged debulking as comorbidities would allow. In patients in whom such an approach was performed major complications was encountered in 17%, minor complications in 39%. Nonetheless, according to the authors, these surgical interventions in patients with advanced-stage disease provided significant improvements in quality of life and patient survival. However, despite these studies that advocate an aggressive approach, such an approach has not been implemented in all specialised centres. In the Netherlands, for example, major surgery in GEP-NETs such as described by Boudreaux is not widely accepted. Reason for a less aggressive approach is probably a combination of factors including the reported high complication rate, the lack of randomised controlled studies and lack of quality of life data. Therefore, although the results of abovementioned aggressive surgical approach could benefit patients with GEP-NETs in terms of outcome, survival and quality of life, randomised controlled studies with long follow-up, including properly designed quality of life assessment are necessary.

Liver transplantation

Orthotopic liver transplantation (OLT) has been progressively abandoned for the management of hepatic metastatic disease of most carcinomas because of the unacceptable high recurrence rate which does not justify the cost of the procedure and the utilization of scarce donor organs. However, in patients with GEP-NETs, the tumours are usually slow-growing (with the exception of patients with poorly differentiated endocrine tumours). Moreover, metastases are often only confined to the liver and, therefore, OLT can be a valuable treatment option. Especially since the quality of life of these patients is often poor due to pain and debility related to hepatomegaly and/or hormone production, endocrine GEP tumours are one of the few malignancies where hepatic metastases are not a contraindication to liver transplantation. Obviously, partial hepatectomy, followed by debulking or cytoreductive surgery are the first options that have to be reviewed in any patient. In most cases, however, partial hepatectomy is not possible because of multifocal and bilateral localisation of disease which is present in approximately 90% of patients who present with liver metastases [34]. When medical therapy or interventions (local ablation/hepatic arterial embolisation) also fail to control the disease in terms of progression and/or symptoms, the option of an OLT comes in view.

Most reports on OLT are single centre studies that describe a limited number (maximum of 19) of patients with a median follow-up ranging from 11 to 54 months [35]. Therefore, the outcome of OLT in terms of survival rates can only be based on the three large multi-centre studies with 30 or more patients included [36-38]. Although the primary goal of OLT in most cases is cure, documented recurrence-free 5-year survival rates in these studies were relatively low, ranging from 17 to 24% [37, 38]. Reported 1- and 5-year true survival rates after transplantation range from 58-68% and 35-47% [39], respectively and are higher than historical controls, which have documented 5-year survival rates of approximately 30% [40]. However, randomised studies are lacking and since the publication of these studies several new therapeutic strategies on OLT have evolved, which increase the overall survival, especially within the group of patients with distant metastases [9].

Interesting findings were reported in the largest retrospective multi-centre analysis to date [38]. Four factors related to outcome were identified. Subsequently, a proportional hazards model indicated that age at or above 50 and synchronous upper abdominal exenteration or Whipple's procedure were independent factors of poor outcome, whereas location of the primary tumour (lung or bowel) and pre-OLT somatostatin analogue treatment were favourable prognostic factors. Patients with favourable prognostic indicators had an overall 5-years survival of 65% and median survival of more than 8 years. In contrast, patients who had extended operation with abdominal exenteration or Whipple's operation had 1- and 5-year survival of 50% and 31%, respectively. The role of tumour biology as determined by three different immunohistochemical markers, Ki-67, E-cadherin and p53, was reported in the largest single centre study [41]. Using the combination of Ki-67 and E-cadherin the authors were able to show significant differences between long-term survivors and patients who died early after OLT.

In contrast to the relatively good results of OLT, the postoperative mortality is high, reported to be 10% at 30 days and 14% at 60 days [38]. This high mortality rate is probably one of the reasons why OLT has not been implemented in the management of patients with GEP-NETs in most transplantation centres, including those in the Netherlands. Furthermore, surgeons often hesitate to perform OLT at the time metastatic spread is evident, because of the risk of early tumour spread secondary to the effects of immunosuppression after OLT.

In conclusion, liver transplantation for metastatic GEP-NETs is controversial. When considered, the overall consensus is that OLT should be considered only in carefully selected individuals, based on the patients' age (<50 years), extension of intended surgery and Ki-67/ E-cadherin expression. However, the exact role, including finding optimal histopathological clinical criteria to predict clinical outcome and the exact

timing of OLT, need to be defined in large multi-centre based prospective studies.

Furthermore, treating physicians should, at the point of defining the best treatment for the individual patient, always realize that although not impossible, cure after OLT is improbable. This means that OLT in a patient with extended hepatic disease will usually be considered as the last possible option for effective palliation and improvement of survival. Furthermore, it may be questioned whether at that time of disease evolution, the patient is still a candidate for major surgery.

LOCAL THERAPY

External Beam Radiation

External beam radiation therapy (EBRT) never had an important role in the management of patients with the relatively radioresistant GEP-NETs. Furthermore, the location of liver and abdominal metastases limits the use of traditional EBRT. Therefore, reports on the effectiveness of EBRT in patients with neuroendocrine tumours are limited. However, occasionally, EBRT has been applied for locally inoperable carcinoid and pancreatic islet cell carcinomas [42, 43]. Small series of patients treated with EBRT of which the largest included a total of sixty patients indicated that only in selected patients substantial symptomatic improvement can be achieved [44, 45]. These reports should be regarded separately from those that describe EBRT in patients with brain and bone metastases who have spinal cord compression or bone pain due to local tumour expansion. In those cases, EBRT remains the standard palliative therapy [45].

Hepatic Artery (Chemo) Embolisation

Hepatic artery embolisation (HAE) in GEP-NETs is based on the fact that metastases receive most of their blood supply from the hepatic artery. In contrast, the normal hepatic parenchyma receives 20-25% of its blood supply from the hepatic artery and 75-80% from the portal vein. HAE will induce tumour necrosis by selective induction of temporary but complete ischaemia in hypervascular liver metastases by blocking branches of the hepatic artery and thus the oxygen supply.

The combination of localised delivery of a cytotoxic compound followed by embolisation is called hepatic artery chemoembolisation (HACE). This intravascular technique makes it possible to deliver a cytotoxic drug in very close proximity to the tumour cells. For HACE, the cytotoxic agent most often used is doxorubicin (Adriamycin). However, other cytotoxins and/or combinations have also been used [46, 47-49].

Candidates for embolisation are patients who have advanced stage disease with multiple liver metastases that are not amenable to surgical cure. However, in HA(C)E, despite advances in interventional techniques, careful patient selection is required, as disease- and also treatment-related adverse effects may be significant. Absolute contraindications include portal vein thrombosis, liver failure and biliary reconstruction (i.e. after a Whipple procedure). Relative contraindications can be tumour load exceeding 50% of the liver, contrast allergy, more extrahepatic than hepatic disease, and poor performance status of the patient [50, 51].

The embolisation procedure is in most patients followed by a complex of symptoms and reactions such as mild and transient nausea and vomiting (50–70%), abdominal pain (50–60%), fever up to 38.5 °C (30–60%) and raised liver transaminases (100%) often referred to as the post-embolisation syndrome [52]. Such symptoms are easily controlled, but patients should be made aware that such symptoms might persist for several days. Major complications are rarely seen, but renal and liver failure and bleeding peptic ulcers have been observed.

Furthermore, embolisation may lead to serious complications in individual patients (gallbladder ischaemia, pancreatitis, liver abscess, vascular damage and aneurysm formation, hepatorenal syndrome and hormonal crisis). The mortality rate in the major series is less than 5% [53]. Considering the risk of complications and relatively high mortality rate, chemoembolisation has to be performed in experienced hands and specialised centres, which are not widely available.

Although HACE has not been compared in a randomised manner with HAE to date, encouraging results suggest that embolisation combined with intra-arterial chemotherapy is at least as effective as without chemotherapy. Tumour response rates after chemoembolisation are given in Table 5.

Objective tumour response rates are widely variable and range from 33 to 79%[46-49, 55-58]. Median duration of response varied from 6–21 months. Differences in number of patients and tumour type studied, protocol and tumour response evaluation criteria used and choice of cytotoxic compound employed varied widely which makes interpretation and comparison between the different studies very difficult. Furthermore, in most patients chemoembolisation was not performed as first-line therapy. These patients had additional medical therapy (e.g. octreotide s.c.) before or during treatment which can be a confounding factor in the observed results. Interestingly, in the largest study to date, predictors of efficacy were identified[57]. Arterial enhancement on abdominal computed tomography and body mass index (BMI) were factors that were positively correlated with TTP in multivariate analysis, thus suggesting that the cytoreductive effect on the tumour by HACE requires

hypervascularity of the tumour. The question why the BMI has an effect on tumour response after HACE is more complicated. Several hypotheses are mentioned including (a) an inverse correlation of BMI with tumour aggressiveness and (b) higher dosages given to patients with elevated BMI as the injected dose of chemotherapy was based on the body surface area. Still, no clear evidence for these explanations is present and, therefore, the results are still under debate. Furthermore, although it was not a randomised study, results with streptozotocin suggested an at least equal therapeutic efficacy compared to doxorubicin. Streptozotocin was therefore recommended to be used with HACE, thereby saving the cardiotoxic doxorubicin for possible necessary subsequent intravenous chemotherapy.

Radioembolisation

The technique of radioembolisation involves the administration of microspheres labelled with radioactive isotopes to induce hepatic artery occlusion and simultaneously deliver local irradiation. This technique, developed by the group of Grady [59] in the sixties, was initially introduced as a safe procedure in the management of liver metastasis of carcinoid tumours in 1971 [60]. The method, reintroduced in 1994 by the group of Shapiro [61], was performed in twenty-four patients with liver metastasis, including six patients with metastatic GEP-NETs. In this preliminary phase I study in 1994, glass microspheres loaded with ^{90}Y were used. Although encouraging data were presented, it was until recently that more reports on radioembolisation in patients with metastasized GEP-NETs treated with ^{90}Y-microspheres were published [62, 63]. In eight patients with unresectable neuroendocrine hepatic metastases Murthy *et al.*[63] reported one PR, four cases of SD, and three cases of PD. Median survival times were 14 months (range, 3-15 months) from the time of treatment and 36.5 months (range, 16-105 months) from the time of diagnosis of hepatic metastases.

In another report, hundred thirty-seven patients, including 19 patients with GEP-NETs underwent 225 administrations of ^{90}Y microspheres by arterial infusion [62]. Based on WHO criteria, 43% of all lesions demonstrated PR, 47% had SD and 10% had PD. Limitations of this study included the heterogeneous group studied, without specified tumour responses per subgroup. Furthermore, the reported response per lesion was studied rather than the clinically more relevant response per patient. Unfortunately, the median survival rate of 25.9 months for neuroendocrine tumours in a subgroup analysis was the only specific data given on GEP-NETs. Future research on the use of radiolabelled microspheres in the cohort of patients with GEP-NETs, as was mentioned, will be important to delineate its role in the management of GEP-NET patients.

Table 5. Chemoembolisation in gastroenteropancreatic neuroendocrine tumours

References	No. Patients/ Tumour Type *	Chemotherapy†	Sustained relief (%) in symptomatic patients	5-HIAA decrease (>50%, CARC only)	Percentage Objective Response (criteria)	Median response duration (months)
Therasse, 1993 [47]	23/ CARC	DOX	100	91	35 (WHO)	–
Ruszniewski, 1993 [46]	18/CARC, 5/ ICC	DOX	73	57	33 (WHO)	21
Perry, 1994 [48]	15/CARC, 15/ ICC	DOX	90	–	79‡ (WHO in 19/24 pts)	–
Clouse, 1994 [55]	14/CARC§	DOX	90	69	78 (WHO)	8.5
Diaco, 1995 [56]	10/CARC	CDDP, MMC, DOX‖	100	–	60 (unknown)	42.5 (mean, 6 pts)
Ruszniewski, 2000 [58]	8/CARC, 7/ ICC	STZ (1.5 g/m^2)	67	50	53 (WHO)	10.5
Roche, 2003 [49]	10/CARC, 4 other	DOX	70	75	71 (WHO, including MR)	–
Marrache, 2007 [57]	31/CARC, 36 other**	DOX (23), STZ (44)	91	65	37 (RECIST)	14.5

*NA, not applicable; * CARC, carcinoid tumours; ICC, islet cell tumour; †, DOX, doxorubicin (adriamycin); STZ, streptozocin; MMC, mitomycin C; CCDP, cisplatin; 5-HIAA, 5-hydroxyindoleacetic acid; ‡, > 50% decrease of hormonal secretion and/or > 50% decrease in tumour size; §, mostly carcinoid; all 14 tumours were functionally active; ||, including sequential intra-arterial 5-fluorouracil and daily octreotide acetate administration; **, 36 patients including ICC; partly adapted from O'Toole 2003* [54]

Also recently, ^{90}Y-lanreotide has been used intra-arteriously within the liver of 23 patients with GEP-NETs, with encouraging results. It was reported that 3 out of 19 (16%) evaluable patients had PR, 12 (63%) had SD and 4 (21%) had continued disease progression. Four patients died before therapy evaluation could be performed. However, since these patients most probably died because of the treated disease, they should have been included in the reported results. The corrected outcome would be 3 out of 23 (13%) patients having PR, 12 out of 23 (52%) SD, and 4 out of 23 (17%) PD despite treatment. Symptomatic control was observed in 14 out of 23 (61%) [64]. Intrahepatic-arterial injection of radiolabelled substances may achieve higher intratumoural concentrations and may be of value in treating isolated hepatic lesions. However, in the management of disseminated GEP-NETs, which is the case in most patients, radioembolisation is probably less helpful, especially in the long-term control of the disease.

Local ablative therapy

Local, imaging-guided ablation techniques, such as radiofrequency ablation (RFA), laser induced thermotherapy (LITT) or cryotherapy are widely used to induce tumour reduction in inoperable hepatocellular carcinomas and liver metastases from colorectal carcinomas [65, 66]. RFA uses radiofrequency waves that are converted to heat. It is applied with an electrode directly in the centre of a tumour and subsequently results in cellular destruction at temperatures above 60 °C. LITT is based on almost the same principle except that with this technique the heat is induced by a laser beam. Hepatic cryotherapy or ablation involves freezing and thawing of liver tumours by means of a cryoprobe inserted into the tumours. All these techniques have the advantage that normal liver tissue is preserved.

A few small series and case reports of these different techniques have shown excellent results with tumour responses in up to 97% of patients with neuroendocrine hepatic metastases [67-70]. Furthermore, the largest study of 34 patients treated with RFA, including 18 with carcinoid, 9 with islet cell tumours and 7 with medullary thyroid carcinoma, showed symptom relief in 95% of patients with significant or complete symptom control in 80%, with a mean duration of 10 months (range 6–24 months) [67]. Disadvantages of these therapies, however, include (a) high rate of reported complications, such as abscess formation, haemorrhage and biloma, (b) liver metastases are treated only, and (c) only intrahepatic tumours with relatively small volume are treated. In large clinical trials with RFA, it was demonstrated that eradication of tumours with diameter of less than 4 cm is more likely than that of larger tumours [71]. However, recently Veenendaal *et al.* [70] reported that with the use of simultaneous multiple fibre LITT or bipolar RFA, ablation of tumours as large as 7 cm in diameter and up to 7 lesions in one session is feasible. Still, numerous lesions and close proximity to the main vessels of the liver remain the most important

reasons not to perform LITT or RFA, and to start other therapies. Cryotherapy was also reported successful in terms of symptom control and objective tumour responses [65, 72, 73]. This type of therapy can therefore be regarded as an important supplement to surgical resection and allows regional destruction of lesions not amenable to resection.

Unfortunately, carefully conducted (large) prospective studies for these different local therapies are lacking. Nonetheless, with an overall complication rate of 5-10% and a mortality rate of 0.5% for RFA and LITT in large studies with non-neuroendocrine tumours [74-76], local therapeutic modalities such as these can be considered in selected patients with a limited number of local hepatic recurrences or new metastases developing during follow-up if other inclusion criteria are met as well.

MEDICAL THERAPY

Somatostatin analogues

When surgery is no longer an option in patients with metastatic disease and symptoms occur, most patients are treated with somatostatin analogues. The octapeptide analogues of somatostatin, of which octreotide and lanreotide are the most commonly used, are cyclic peptides that are resistant to peptidase degradation. Consequently, a prolonged half life of 1.5-2 hours is achieved, which is considerably longer than that of the native forms of somatostatin (1-2 minutes). Furthermore, these somatostatin analogues differ from native forms of somatostatin in their affinity to the different receptor subtypes as these analogues exhibit high affinity to the SSTR2 and 5, moderate affinity to the SSTR3 and very low affinity to the SSTR1 and SSTR4, whereas the native somatostatin forms have high affinity to all somatostatin receptor subtypes. However, since SSTR2 is expressed in more than 80% of the classical midgut carcinoid tumours and in 50-80% of the endocrine pancreatic tumours, these stable somatostatin analogues are suitable for therapy. Besides providing symptomatic relief by suppression of hypersecretion of hormones and thereby improvement or maintenance of the patients' quality of life, therapy with somatostatin analogues can inhibit tumour growth. The efficacy of somatostatin analogue therapy can be divided into subjective, biochemical and objective tumour responses. In the first trial in 25 symptomatic carcinoid patients who were treated with octreotide subcutaneously (150 μg three-times daily), symptomatic improvement (reduction of flushing and/or diarrhoea) was observed in 22/25 (88%) patients. Biochemical response, which was defined as a 50% or more decrease of 5-hydroxyindoleacetic acid (5-HIAA) levels, was observed in 17/25 (72%) of patients. The median duration of the biochemical response was 12 months (range 1 to more than 18 months) [77]. The cause of diminished effectiveness of octreotide analogues in the long-term, a well-recognised phenomenon, has not been not fully elucidated yet [78]. However, as

somatostatin receptor scintigraphy with the simultaneous use of octreotide analogs in patients is relatively unaffected and therefore withdrawal probably not mandatory [79, 80], it is likely that this phenomenon of tachyphylaxis or therapy resistance is based on a post-membrane receptor defect rather than involving the somatostatin receptor itself.

In a meta-analysis, which compiled the studies that followed the first trial, Gorden *et al.* [81] reported symptomatic improvement in 92% and biochemical responses in 66%. Reduction of tumour size was noted in only 8% and stable disease in 85%.

Beside administration of somatostatin analogues by daily injection, slow-release formulations became available, which can be considered an important improvement in the daily management of patients. Long-acting release Sandostatin (Sandostatin-LAR®; once every 2-4 weeks) and lanreotide prolonged release (Lanreotide-PR®; once every two weeks) in which octreotide or lanreotide have been incorporated into microspheres of a biodegradable polymer, are able to control the symptoms as well as the short-acting formulations, however without the burden of daily subcutaneous injections [82].

Common early side-effects, especially with the daily formulation, include nausea, abdominal cramps, loose stools, mild steatorrhoea and flatulence. Most side-effects start quickly after administration and are dose-dependent, but subside spontaneously after the first weeks of treatment [83]. Persistent side-effects of somatostatin analogues are few. However, paradoxical diarrhoea can occur. Furthermore, induction of gall-stones has been reported in up to 13-60% in patients with acromegaly on long-term octreotide treatment [84]. However , in many of these patients bile sludge is present instead of full blown stones. Furthermore, only in a small minority of patients with real stones, these become symptomatic.

Patients with functioning tumours often use the long acting release formulation (LAR) of octreotide, like Sandostatin-LAR, with doses up to 30 mg/month. However, up to 40% of the patients need rescue medication several times a week for the acute control of symptoms [83]. Woltering *et al.* [85] demonstrated that doses of 30 mg/month lead to plasma levels of 5x the K_d of octreotide for the SSTR2 ($K_d \approx 1x10^{-9}$ mol/L), but fail to achieve the plasma concentrations that will completely saturate the SSTR2. It was concluded that this could explain the need for higher doses in some patients and that frequent measurement of octreotide blood levels could guide octreotide therapy. Furthermore, the use of LAR, at doses of 60 mg/month was advocated in those patients with poor symptom control or tumour growth despite normally dosed LAR therapy.

In summary, somatostatin analogues are highly effective in the symptomatic management of patients with overt symptoms of GEP-NETs. However, it is still controversial whether treatment with somatostatin analogues must be started in order to induce inhibition of proliferation of the tumour, if progression occurs in patients without symptoms or with non-functional tumours. The dose should then preferably be within the high range of the normal dosage scheme. However, it must be stressed that because of the small chances of success in relation to the high costs, the use of somatostatin analogues as an anti-neoplastic therapy is questioned by many [86].

Interferon

Interferon (IFN)-alpha was introduced in the early 1980s as a treatment option in patients with GEP-NETs by the group of Öberg [87]. In a recent meta-analysis they reported the results of treatment with recombinant IFN-alpha [88]. The median dose used was 5 million units of IFN-alpha every other day subcutaneously. The median biochemical response rate from pooled studies was 44% and the median tumour response rate 11%. However, no survival analysis was available, as most published studies were not randomised controlled. Furthermore, frequent adverse reactions to IFN-alpha included temporary 'flu-like' symptoms, chronic fatigue syndrome and mental depression. The latter two can develop in varying severity at various grades in up to 50% of patients. Auto-immune reactions were also reported and occurred in 15-20% of patients. Most frequent of these was thyroid dysfunction. The significantly higher incidence and severity of adverse effects, and lower biochemical response rate compared with somatostatin analogues makes IFN-alpha not the first choice of medical therapy in patients with GEP-NETs.

Combined therapy with IFN-alpha and somatostatin analogues was proposed to increase the antiproliferative therapeutic effect. Several studies indeed reported encouraging results of the addition of IFN-alpha to octreotide [89, 90]. However, in contrast to these studies, the first prospective, randomized, multi-centre trial that studied the effect of somatostatin analogue (lanreotide), IFN-alpha and their combination for therapy of metastatic GEP-NETs indicated that no significantly higher antiproliferative effect could be achieved with the addition of IFN-alpha to lanreotide [91]. When both therapies were compared as single therapy, no differences were evident. However, treatment with lanreotide was generally well tolerated and only a few minor side-effects occurred. IFN-alpha related side-effects were more common than those attributable to lanreotide [91].

Systemic Chemotherapy

The use of chemotherapy in patients with GEP-NETs is limited because of disappointing results and high incidence of major side-effects. Most objective

responses were reported in well-differentiated pancreatic or duodenal tumours. Single-agent chemotherapy demonstrated lack of objective responses and high toxicity and was therefore replaced by combinational chemotherapy in studies that followed. The best results were obtained with the combination of streptozotocin with either doxorubicin or fluorouracil (5-FU). Objective responses for the combination of streptozotocin with 5-FU in GEP-NETs as published by Moertel *et al*. ranged from 45 to 63% [92, 93], whereas the combination of streptozotocin and doxorubicin had similar objective responses in up to 69% [92, 94]. However, these impressive results were never reproduced in later studies. Interestingly, Cheng *et al*. [95] who reported on the effect of combination therapy with streptozotocin and doxorubicin had only 1 out of 16 (6%) patients with major objective response by standard CT criteria.

The difference between their results and those from Moertel *et al*. [92] was explained by the differences in the response criteria used, which included clinical measurement of hepatomegaly on physical examination, or measurement on radionuclide liver-spleen scanning, as an indicator of a major objective response in the early studies by Moertel *et al*. [93, 96]. Nonetheless, others have reported relatively higher objective response rates of 36%-55% [94, 97, 98]. Mean duration of responses in the studies that used streptozotocin and doxorubicin ranged from 14-22 months. At this moment, the combination of doxorubicin and streptozotocin is regarded as the standard chemotherapy in patients with progressive well-differentiated endocrine pancreatic or duodenal carcinoma [98, 99]. In patients with well-differentiated carcinoid of midgut origin the best results, in terms of the highest objective response, was also reported with doxorubicin and streptozotocin [100]. Forty percent of patients had an objective response. These results, however, were only established in a small number of patients and were never reproduced since then.

With the use of streptozotocin and doxorubicin major side-effects have to be taken into account. Streptozotocin can induce renal impairment. Renal insufficiency in up to 30% of patients treated with streptozotocin was reported. Therefore, the kidneys are dose limiting [93]. Obviously, careful monitoring of renal function is necessary to prevent renal damage. Cardiac function is the dose limiting factor for chemotherapy with doxorubicin. Development of doxorubicin-associated cardiomyopathy is dose-dependent and congestive heart failure was reported in more than 4 percent of patients who had received a cumulative dose of 500-550 mg of doxorubicin per square meter. Incidence rose to more than 18 percent at doses over 550 mg m^{-2} [101].

Other chemotherapeutic agents, like dimethyltriazenoimidazole carboxamide (DTIC) or dacarbazine proved to have minimal activity in patients with metastatic carcinoid tumours or neuroendocrine pancreatic tumours [102-104]. An overview of the most studied chemotherapy modalities is given in Table 6.

Table 6. Results and side-effects of chemotherapy in patients with neuroendocrine tumours

Regimen	Tumour Types	No. of Patients	PR and CR (%)	Median Response Duration (months)	Haematologic Toxicity Grade 3 and 4 (%)	Nausea and Vomiting (%)	Other Major Side-effects	Study
Doxorubicin	CARC	33	21*	4	NA	NA	—	Moertel [96]
5-FU	CARC	19	26*	3	NA	NA	—	Moertel [96]
STZ /5-FU	CARC	43	33*	7	NA	NA	—	Moertel [96]
STZ	NEP	42	36*	17	0	83	Renal toxicity, 29%; liver failure, 2%	Moertel *et al.* [93]
STZ /5-FU	NEP	42	63*	17	29	85	Renal toxicity, 31%	Moertel *et al.* [93]
STZ / 5-FU	NEP	33	45*	7	25	81	Diarrhoea, 33%; renal insufficiency, 7%	Moertel *et al.* [92]
STZ / doxorubicin	NEP	36	69*	20	5	80	Diarrhoea, 5%; renal insufficiency, 4%; heart failure, 9%	Moertel *et al.* [92]
STZ / doxorubicin	NEP	16	6	>18	19	NA	Diarrhoea, 19%; cardiac toxicity, 19%	Cheng and Saltz [95]
DTIC	CARC	15	13	4	NA	NA	—	Van Hazel *et al.* [104]
DTIC	CARC	56	16	3	29	88	Diarrhoea, 23%	Bukowski *et al.* [102]
DTIC	CARC/NEP	7	14	NA	NA	0	—	Ritzel *et al.* [103]
5-FU / IFN-α	CARC/NEP	24	21	13	42	NA	Diarrhoea, 8%	Andreyev *et al.* [105]
Mitoxantrone	CARC	35	9	14	32	26	—	Neijt *et al.* [106]
Paclitaxel	CARC/NEP	24	4	3	61	63	Diarrhoea, 54%; neurologic toxicity, 61%	Ansell *et al.* [107]

Abbreviations: PR, partial remission; CR, complete remission; DTIC, dimethyltriazenoimidazole carboxamide; 5-FU, fluorouracil; STZ, streptozotocin; CARC, carcinoid; NEP, neuroendocrine pancreatic tumour; NA, not available; IFN-α, interferon-alpha.
** Response evaluation including biochemical responses and physical examination for evaluation of hepatomegaly.*
Adapted from Kwekkeboom et al. [108]

In recent years, new chemotherapeutic agents and regimens have been evaluated, including high dose paclitaxel administered with granulocyte-colony stimulating factor, docetaxel, gemcitabin and irinotecan in combination with 5-FU and Leucovorin [107, 109-111]. However, most therapy strategies proved to be disappointing in GEP-NET patients and some of them had considerably toxicity profiles. Promising is the use of temozolomide, a cytotoxic alkylating agent that was specifically developed as an oral and less toxic alternative to DTIC, in combination with thalidomide. This combinational regimen was used in 29 patients with metastatic carcinoid (n=15), pheochromocytoma (n=3), or pancreatic neuroendocrine tumours (n=11) [112]. Radiologic response according to RECIST criteria was documented in 5 (45%) patients with pancreatic NETs, 1 (33%) patient with pheochromocytoma and 1 (7%) patient with a carcinoid tumour. Therefore, this study suggests more efficacy with this regimen in patient with pancreatic NETs than in carcinoid tumours.

Poorly differentiated endocrine carcinomas (PDEC) are preferentially treated with the combination of etoposide and cisplatin. High response rates with objective tumour response in up to 65% of patients were reported [113, 114]. However, the duration of response was often very limited and rarely exceeded 10 months. In addition, reported percentages of nephrotoxicity and neutropenia were high. In the most recent phase II clinical study in 78 patients with PDEC, patients were treated with a three-drug regimen of paclitaxel, carboplatin, and etoposide [115]. Forty-one (56%) patients had major responses (of whom 15% complete response). Survival data showed median, 2-year, and 3-year survival rates of 14.5 months, 33%, and 24%, respectively.

Clearly, the combination of cisplatin/carboplatin and etoposide with or without an additional chemotherapeutic agent is currently the most effective therapeutic regimen of systemic chemotherapy for PDEC provided the patient has adequate organ function and performance status.

In conclusion, within the currently published European guidelines for the Management of patients with GEP-NETs as proposed by the European Neuroendocrine Tumour Society (ENETS) chemotherapy using combinations of streptozotocin, doxorubicin and 5-FU is indicated in patients with progressive advanced metastatic or symptomatic diffuse metastatic foregut NETs with liver metastases, not in NETs from midgut origin [116]. Also, in colorectal NETs with moderately to well-differentiated histopathology chemotherapy has no role within the therapeutic armamentarium [117]. Cisplatin/carboplatin plus etoposide is recommended in patients with NETs with poorly differentiated (i.e. above 20% Ki-67 positive cells) tumours regardless of the origin of the primary [118, 119].

Meta- [^{131}I] Iodobenzylguanidine (MIBG) Therapy

Meta-iodobenzylguanidine (MIBG) is an arkyl-guanidine derivative, structurally similar to noradrenaline, which utilizes the vesicular monoamine transporters and is incorporated into vesicles or neurosecretory granules in the cytoplasm [120]. However, it is not significantly metabolized. MIBG shows little binding to post-synaptic receptors and causes little or no pharmacological response [121]. It may be labelled by ^{123}I for imaging or ^{131}I for both imaging and therapy.

MIBG scintigraphy has been used for many years to visualize carcinoid tumours as it is concentrated in endocrine cells [122]. This method was initially developed to detect tumours arising from chromaffin cells such as phaeochromocytomas, paragangliomas and neuroblastomas with overall reported high sensitivity of approximately 90% and specificity as high as 99% [122, 123]. Although with lower sensitivity, MIBG scintigraphy was thereafter utilized to detect neuroendocrine tumours. However, MIBG scintigraphy in carcinoid tumours, including the initially used diagnostic ^{131}I-MIBG scintigraphy, has shown lower sensitivity than ^{111}In-octreotide scintigraphy. In a recent review, the cumulutive results of twenty years of experience with MIBG, including MIBG scintigraphy, median detection rate and sensitivity of 50% and 76%, respectively, was shown [124]. In contrast, the largest review, that included pooled imaging data from 35 centers with in total more than 1200 patients with carcinoid tumours, described that ^{111}In-octreotide scintigraphy has a median detection rate of 89% (range 67% to 100%) and a median sensitivity of 84% (57% to 93%) [125]. Furthermore, imaging with ^{123}I-MIBG has a poor sensitivity in identifying islet cell tumours [126]. Interestingly, within the few studies that compared ^{123}I-MIBG and somatostatin receptor scintigraphy in carcinoid tumours, a complementary role of ^{123}I-MIBG scintigraphy has been noted either as a different intensity or as a different pattern of uptake in non-octreotide avid regions [126, 127]. In one report in which a direct comparison between these two imaging modalities was performed, comparable results with sensitivities of about 84% were demonstrated, whereas the combination of these scans increased the sensitivity to 95% [127]. It was concluded that ^{111}In-octreotide scintigraphy is more sensitive in detecting metastatic lesions from GEP-NETs than ^{123}I-MIBG scintigraphy, with the latter imaging modality useful in the occasional patient who has MIBG-avid lesions, but did not show any uptake with the initially performed ^{111}In-octreotide scintigraphy [128].

Besides diagnostic and staging purposes of MIBG scintigraphy in GEP-NETs, it can also be used to identify patients for ^{131}I-MIBG therapy. ^{131}I-MIBG therapy has the advantage that the treatment targets all sites of disease, including distant metastases, as was shown on ^{123}I-MIBG scintigraphy performed before therapy. Treatment

protocols vary between different centres. The usually prescribed doses of ^{131}I-MIBG range between 7.4 and 11.2 GBq (200–300 mCi), administered at 3-6 months interval. Occasionally, doses up to 14.8 GBq (400 mCi) per treatment are used. To minimize thyroidal ^{131}I uptake, potassium iodide (120-150 mg/d) is given before, during, and several days after the therapy.

Reported tumour responses after ^{131}I-MIBG therapy in patients with metastatic carcinoid disease range from 13-35% [129-132], with objective tumour shrinkage in 15% and 13% of patients in the two largest studies comprising 52 and 75 patients, respectively, who could be evaluated with CT/MRI [129, 132].

In general, biochemical response, which was defined as significant reduction in the tumour marker levels such as chromogranin A or 5-HIAA, did not follow the tumour response and was demonstrated in 37-46% [130, 132].

Symptomatic control was demonstrated in even a higher proportion of patients. In 49 to 87% ^{131}I-MIBG therapy patients had a decrease of symptoms [130, 132-134]. Furthermore, besides this obvious palliative effect, ^{131}I-MIBG therapy also proved to be cost-effective. Pathirana *et al.* [133] evaluated 12 patients with carcinoid syndrome and found a significant reduction in octreotide dosages in 8 patients after ^{131}I-MIBG therapy, which resulted in decreased use of octreotide and thereby minimized costs, even including the costs of the ^{131}I-MIBG therapies.

Although symptom alleviation has been well described in the majority of patients, and partial tumour responses do occur, complete radiographic responses have not been reported with ^{131}I-MIBG treatment.

Reports on survival in patients with neuroendocrine tumours (including carcinoids) treated with ^{131}I-MIBG are few. Recently, two studies reported survival benefit when patients with carcinoid tumour were treated with at least 15 GBq ^{131}I-MIBG given over 6 months [132, 135]. Furthermore, symptomatic response to treatment in patients who had progressive disease was associated with an improvement of median survival of 44 months (5.76 versus 2.09 years) compared with patients who had no symptomatic response [132]. Interestingly, objective tumour response and reduction of hormone levels did not correlate with improved survival in the studied patients. Within the same study, a direct, linear dose dependent relation was found between initial dose and survival. An initial dose of 400 mCi ^{131}I-MIBG was recommended for further studies.

In general, ^{131}I-MIBG treatment is well tolerated with side-effects limited to nausea or vomiting in 24-72 hr after administration, mild hepatic dysfunction with spontaneous

recovery and temporary myelosuppression 4-6 weeks post-therapy. Only incidentally patients may develop significant side-effects such as severe myelosuppression, especially when extensive metastatic spread within the bone marrow is present, or hepatic failure in patients with widespread liver metastases [136]. Furthermore, the frequency and severity of most haematological side-effects are clearly (cumulative) dose dependent [130, 132].

Methods to enhance ^{131}I-MIBG uptake with the intent to increase the effectiveness of therapy were explored and included the use of premedication, such as nifedipine and unlabelled MIBG, or the intra-arterial delivery of the dose. Blake *et al*. [137] found a 2-fold increase in tumour uptake after premedication with nifedipine in patients with malignant phaeochromocytoma. Hoefnagel *et al*. [138] achieved an improved tumour to non-tumour (T/NT) ratio increase of 7.8–111.4% at 24 hr on ^{131}I labelled ('hot') MIBG scintigraphy in 17 of 24 patients with carcinoid tumours by pre-treating them with cold MIBG. The authors claim that this could be an advantage considering ^{131}I-MIBG therapy in carcinoid patients with initial low uptake on MIBG scintigraphy, facilitating higher ^{131}I-MIBG uptake in metastatic lesions after pre-treating with cold MIBG. However, the demonstrated increase was based on an increase of T/NT ratios instead of absolute uptake values. Therefore, a decrease of background uptake, which is likely after cold MIBG, could have accounted for the observed increase of T/NT ratio as well.

In another study, intra-arterial treatment compared to intravenous administration of ^{131}I-MIBG in patients with mostly carcinoids resulted in up to 4-fold higher tumour uptake (mean 1.7-fold) of ^{131}I-MIBG in liver metastases [139]. Again, the reported higher tumour uptake was in fact a higher tumour to whole-body activity ratio instead of absolute tumour uptake. Intra-arterial treatment with ^{131}I-MIBG was claimed to be a safe alternative to standard intravenous application.

In none of the abovementioned studies the potential benefit of the enhanced ^{131}I-MIBG uptake in terms of effectiveness was studied. Randomised studies between unenhanced versus enhanced ^{131}I-MIBG delivery, which also include measurement of absolute uptake values are warranted to asses the true potential benefit of these therapeutic strategies.

In conclusion, internal irradiation therapy with ^{131}I-MIBG is generally safe and well tolerated with only a few acute and long-term adverse effects. ^{131}I-MIBG therapy appears to offer effective palliation with symptomatic control. Despite the fact that objective tumour responses can be found only in a minority of patients, studies suggest that there may be a survival benefit.

Peptide Receptor Radionuclide Therapy

As mentioned earlier somatostatin receptors are present on the majority of GEP-NETs. Besides targeted therapy with somatostatin analogues like octreotide or lanreotide, the tumours can be visualised in patients using the radiolabelled somatostatin analogue [^{111}Indium-DTPA°]octreotide (OctreoScan®). The next logical step after the successful imaging was to try to use radiolabelled somatostatin analogues as a treatment in these patients. Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues is a relatively new and promising treatment modality for patients with inoperable or metastasised GEP-NETs. Chapter 1.2 of this thesis gives a review of the role and therapeutic place of PRRT in the whole armamentarium of treatment modalities in the management of patients with endocrine tumours.

MOLECULAR THERAPY

Recently, there has been increasing interest in the use of molecularly targeted therapy for patients with metastasised endocrine tumours. Especially molecular targets within the tumour cell such as the Bcl-2 and Bax gene, which are both involved in the cascade of apoptosis and vascular endothelial growth factor (VEGF) which is involved in angiogenesis, but also platelet derived growth factor (PDGF), epithelial growth factor receptor (EGFR) and mammalian target of rapamycin (mTOR) which are factors known to be involved in control of growth, have become molecular targets for therapy. Targeted therapies with inhibitors and antibodies against these molecular targets are currently clinically tested. A summary of the different therapies and stage of clinical trials is given in Table 7.

Therapy with imatinib (Glivec®), a receptor tyrosine kinase (TK) inhibitor, which targets the activated portion of the BCR-ABL oncoprotein and the tyrosine kinases of the c-kit receptor and PDGF receptor, has been successfully applied in patients with chronic myeloid leukaemia [140] and in gastrointestinal stromal tumours [141]. Both PDGF and PDGF receptors are expressed in endocrine tumours. Therefore, the effect of imatinib was evaluated in a phase II trial in patients with advanced carcinoid tumours. One out of 27 patients had an objective response, 17 had stable disease, and 9 had progressive disease as evaluated by the RECIST criteria [142].

Therapy which targets angiogenesis is currently clinically evaluated and can be grouped by mechanism of targeting: (1) by counteracting VEGF with monoclonal antibodies, such as the VEGF blocking humanized monoclonal antibody bevacizumab (Avastin®); (2) small molecules that inhibit the receptor TK domains of the VEGF and PDGF receptor, such as sunitinib (Sutent®), sorafenib (Nexavar®) and (3) other compounds with different antiangiogenic mechanisms, such as thalidomide (Thalomid®) or endostatin [143].

Although not yet published in peer-reviewed journals, several trials are planned or already ongoing. The preliminary results of these trials are in general promising and have been presented on scientific meetings.

The first preliminary reported clinical trial on bevacizumab therapy in GEP-NETs was performed in 44 patients with advanced carcinoid tumours who were on stable doses of octreotide. Patients were randomized to additionally receive either bevacizumab 15 mg/kg on an every 3 weeks basis or pegylated interferon alpha-2b weekly (0.5 μg/kg) during 18 weeks [145]. Bevacizumab was superior to pegylated interferon alpha-2b both in terms of progression free survival and suppression of tumour blood flow measured by functional computed tomography scan. This result led to the planned phase III trial in which patients with advanced poor-prognosis carcinoid tumour under control with depot octreotide will be randomized to receive either additionally interferon alpha-2b subcutaneously or bevacizumab.

Small multi-TK inhibitors, such as sunitinib, sorafenib and valatanib, are currently investigated for their effect in patients with GEP-NET. Clinical results have been only published for sunitinib which has been approved in patients with metastatic renal cell carcinoma [146]. Preliminary data of a large phase II trial with 106 patients reported a 15% objective response in patients with metastatic islet cell carcinomas and 2% objective response in patients with carcinoid tumours, along with high rates of disease stabilization (75% for islet cell carcinomas and 93% for carcinoids)[147]. These studies suggest that tyrosine kinase inhibition may be a useful therapeutic strategy in this disease. However, whether these patients had progressive disease at study entry, which is important to judge the outcome of stable disease in relative slow-growing tumours was not indicated. Furthermore, unfortunately, no definitive peer-reviewed publication followed this preliminary report yet.

Gefitinib, a small-molecule inhibitor of the EGFR tyrosine kinase domain, is currently studied in patients with GEP-NET, and preliminary data showed that one of 40 patients with carcinoids had PR [148]. Within the group of islet cell carcinomas (n=31), 2 had PR and 1 MR. In patients with carcinoid disease, 23 of 38 (61%) and in patients with islet cell carcinomas, 9 of 29 (31%) were progression-free at 6 months, which was considered promising. In addition, 32% (12/38) of carcinoid and 14% (4/29) of islet cell carcinoma patients had a longer (at least 4 months) TTP than the TTP documented prior to study entry. Side-effects with high-grade toxicity were infrequent. Clearly, gefitinib can be promising in the treatment of GEP-NETs in the future.

Table 7. Molecular targeted agents in gastroenteropancreatic neuroendocrine tumours

Agent	Generic name (Trade Mark)	Stage of development
VEGF monoclonal antibody		
	Bevacizumab (Avastin®).	In phase-III development
Small multi-tyrosine kinase inhibitor		
	Sunitinib (Sutent®)	Phase-II completed
	Vatalanib	Phase-II in progress
	Sorafenib (Nexavar®)	Phase-II in progress
	Pazonpanib	Phase-II in progress
PDGFR/ c-kit/ bcr-abl inhibitor		
	Imatinib (Glivec®)	Phase-II completed
EGFR inhibitor		
	Gefitinib (Iressa®)	Phase-II completed
mTOR inhibitor		
	Everolimus (RAD001; Certican®)	In phase-III development
	Temsirolimus (CCI-779)	Phase-II completed
Other		
	Bortezomib (Velcade®)	Phase-II completed

VEGF, vascular endothelial growth factor; PDGFR, platelet-derived growth factor receptor; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin

Adapted from Yao et al. [144]

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that is essential in the control of cell growth, protein synthesis, and autophagy. Inhibition of mTOR may inhibit abnormal cell proliferation, tumour angiogenesis, and abnormal cell metabolism and thereby potentially be effective as a cancer therapy [149].

Although not published to date, the first phase II human clinical trials with mTOR inhibitors in low-grade GEP-NETs are currently underway. Preliminary data on the use of 10 mg of oral everolimus daily combined with 30 mg intramuscular depot of octreotide every 4 weeks showed that 10 out of 60 (17%) patients had PR, 45 (75%) had SD and 5 (8%) had PD [150]. This outcome is more than could be expected from the use of a long-acting octreotide formula alone. However, an effect of octreotide

treatment, whether direct or synergistical with everolimus cannot be excluded. Everolimus was well tolerated in combination with octreotide. To evaluate the effect in larger patient groups further research in clinical trials is planned.

In the first published study with temsirolimus, two out of 36 (6%) patients (21 with carcinoid, 15 with islet cell carcinoma) who received intravenous temsirolimus on a weakly basis, achieved PR by RECIST criteria. Twenty-three out of 36 (64%) of patients had PR or SD [151]. Surprisingly, the authors concluded that temsirolimus appears to have little activity and does not warrant further single-agent evaluation in advanced neuroendocrine carcinomas. However, as was clearly explained by O'Donnell and Ratain [152], 64% patients with tumour control after therapy and a 1-year progression free rate of 40% in a group of treated patients that had progressive disease at entry of the study is suggestive of drug activity beyond the natural course of disease and thus an effective therapy. Furthermore, the outcome compares favourably with agents like somatostatin analogues and interferon-alpha that were previously studied in GEP-NETs. Therefore, it was concluded that further research on the effectiveness of temsirolimus as a single-agent therapy in GEP-NETs should not be abandoned. The authors made clear that single-arm studies have to be carefully analysed or even abandoned and that randomised trials are superior for studying new therapeutic agents.

In conclusion, the recent developments in molecularly targeted therapy in general oncology have renewed the interest of treatment of patients with GEP-NETs with systemic therapy. Preliminary results from mostly phase II clinical studies are promising, but large confirmatory studies are warranted.

CONCLUDING REMARKS

This review indicates the variety of therapeutic approaches and the multitude of techniques that can be employed in the treatment of patients with GEP-NETs, especially when metastatic disease is evident. At that moment the management of GEP-NETs patients is a difficult, but challenging task. An example of an algorithm for clinical decision making is given in Figures 1a and 1b. Figure 1a displays the management of patients with limited (resectable) disease, whereas in Figure 1b the therapeutical strategies are pointed out with the intent to decrease the tumour burden as much as possible to establish an increase of patients' well-being and survival. Nonetheless, not always the best therapeutical option is chosen as therapeutic decisions are often based upon the technique locally available and/ or on the evidence level of expert opinion. Therefore, therapeutic management decisions for this group of patients has to be placed in a multidisciplinary team-based setting, so that the best therapeutical option for each individual patient can be chosen. Specialists within such a team should ideally include an endocrinologist, oncologist, (endocrine specialised)

surgeon, (intervention) radiologist, nuclear medicine physician and pathologist. Furthermore, in patients with severe pain, a radiotherapist or anaesthesiologist should be consulted for optimal palliation. Also, since the patients are suffering from a rare disease, treatment and follow-up should, if practically feasible, be performed in a tertiary (university) referral hospital with facilities for expert treatment. In this way, the full spectrum of treatment modalities can be offered and applied so that optimal management of patients with these tumours is guaranteed.

Figure 1a. Initial management of gastroenteropancreatic neuroendocrine tumours (GEP-NETs)

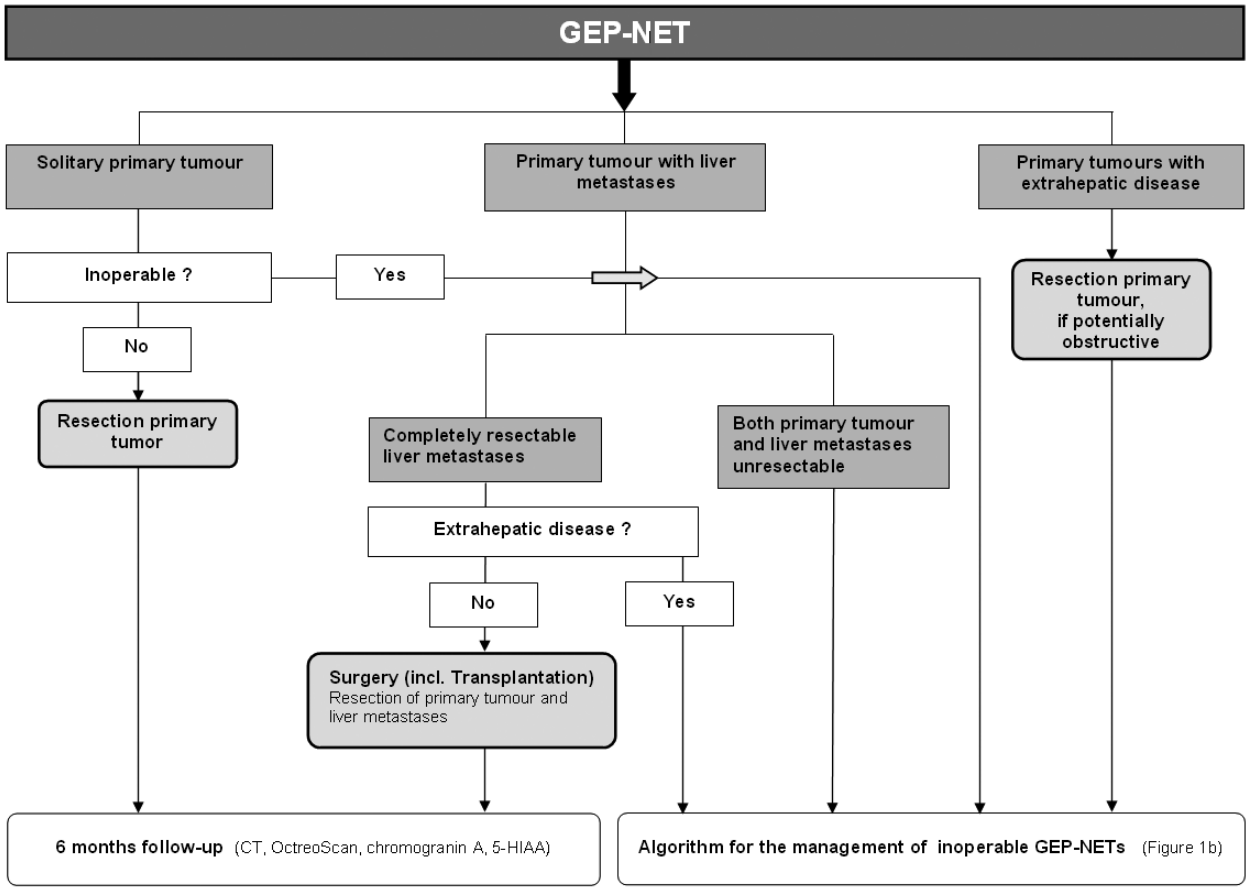
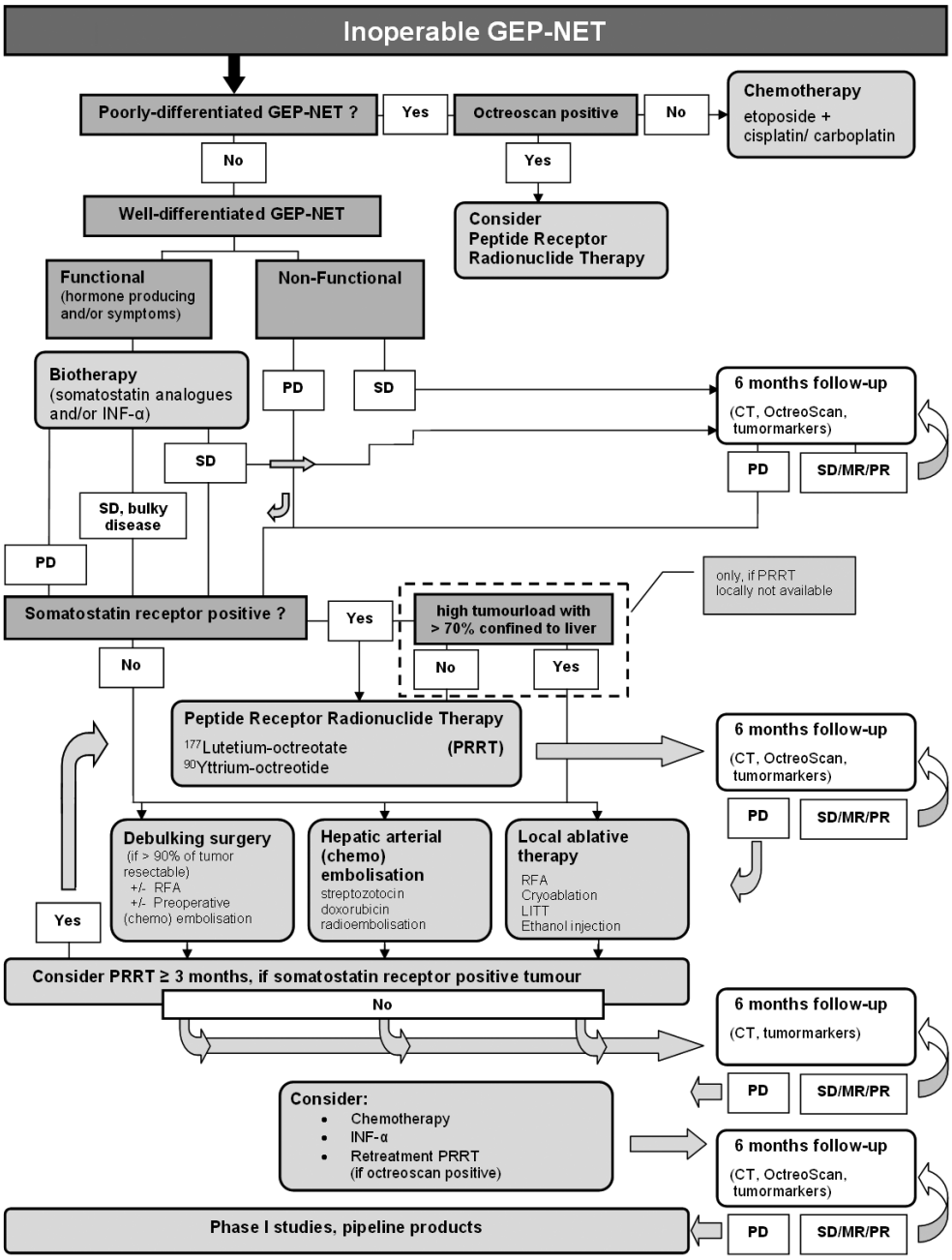


Figure 1b. Management of metastatic gastroenteropancreatic neuroendrocrine tumours (GEP-NETs)



Abbreviations: IFN-α, interferon-α; RFA, radiofrequency ablation; LITT, laser-induced Interstitial thermotherapy; PD, progressive disease; SD, stable disease; MR, minor response; PR, partial response

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Peptide receptor radionuclide therapy

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Abstract

Peptide receptor radionuclide therapy is a new treatment modality for patients with inoperable or metastasised neuroendocrine gastroenteropancreatic tumours. After the successful implementation of somatostatin receptor scintigraphy in daily clinical practice, the next logical step was to increase the radiation dose of the administered radiolabelled somatostatin analogue in an attempt to induce tumour shrinkage. Since then, an increasing number of patients has been successfully treated with this approach, resulting in a substantial numbers of patient with objective tumour shrinkage. Serious side-effects have been rare. This article reviews the effectiveness of the different radiolabelled somatostatin analogues used, the currently known side-effects and the survival data available. Furthermore, clinical issues, including indication and timing of therapy, are discussed. Finally, important directions for future research are briefly mentioned to illustrate that, although the currently available results already suggest a favourable outcome compared with other systemic therapies, new strategies are being developed to increase efficacy.

INTRODUCTION

Somatostatin receptor (SSTR) scintigraphy, which was developed in the late 1980s, has become an important image modality in patients with SSTR-positive tumours [1,2]. This is not only because of its high sensitivity for visualising somatostatin-positive tumours and thereby its ability to localise otherwise undetectable disease, but also because of the selection of known metastatic disease for peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues. This new modality of targeted therapy is very promising, especially in patients with inoperable or metastatic gastroenteropancreatic (GEP) tumours (i.e. gastrointestinal carcinoids and functioning and non-functioning pancreatic endocrine tumours).

RADIONUCLIDES AND SOMATOSTATIN ANALOGUES IN PEPTIDE RECEPTOR RADIONUCLIDE THERAPY

Several radiolabelled somatostatin analogues are currently used to treat patients with SSTR-positive metastasised GEP tumours. These conjugates all consist of a somatostatin analogue, such as octreotide or octreotate, a complexing moiety (or chelator) and a radionuclide. The chelator, which is attached to the somatostatin analogue, allows a stable connection between the analogue and the radionuclide. The basic principle of tumour-targeting after systemic administration of the conjugate involves binding to SSTRs, which are expressed on the cell surface of the tumour cell, followed by effective internalisation of the radionuclide-peptide complex [3–5]. The emitted radiation can damage the DNA, which may subsequently lead to the induction of cell death. In clinical practice, different combinations of radionuclides and somatostatin analogues are used to target the SSTR-positive tumour. These analogues differ from each other in their affinity for the various SSTR subtypes. This variable affinity is important because it can have great influence on the clinical effectiveness of the radiolabelled somatostatin analogue. The available radionuclides and somatostatin analogues used will be discussed.

Radionuclides in peptide receptor radionuclide therapy

Indium (^{111}In), yttrium (^{90}Y) and lutetium (^{177}Lu) have been the most frequently used radionuclides for targeted radiotherapy in the various clinical trials over the past decade. Differences in the physical properties of these radionuclides, which are important for the effectiveness of the therapy, relate to, for example, emitted particles, particle energy and tissue penetration range (Table 1).

^{111}In, coupled via the chelator DTPA to *D*-Phe^{1}-octreotide ([^{111}In-DTPA^{0}]octreotide; ^{111}In-octreotide), was used in the first clinical trials in which patients with metastasised GEP tumours were treated with radiolabelled somatostatin analogues [6–8].

Table 1. Physical characteristics of the radionuclides used in peptide receptor radionuclide therapy

Radionuclides	Emitted Particle	Particle energy (mean keV)	Maximum Tissue Penetration Range (~ number of cells *)	Half-life (days)
Indium (^{111}In)	Auger electrons γ- radiation	3 and 19 keV 171 and 245 keV	10 μm (< 1)	2.8
Yttrium (^{90}Y)	β-radiation	935 keV	12 mm (~ 600)	2.7
Lutetium (^{177}Lu)	β-radiation γ- radiation	130 keV 113 and 208 keV	2 mm (~ 100)	6.7

** Number of cells based on an average tumour cell size of 20 μm; ~, approximately*

Besides γ-radiation, which makes ^{111}In a suitable radionuclide for imaging, it emits both Auger and conversion electrons with a medium-to-short tissue penetration range (0.02–10 and 200–500 μm, respectively). In vitro PRRT studies with [^{111}In-DTPA^{0}]octreotide showed that the therapeutic effect was dependent on internalisation, which enables the Auger electrons to reach the nucleus [9]. These results suggest that the Auger electrons and not the conversion electrons can be held responsible for the reported tumour responses with ^{111}In-labelled somatostatin analogues. In an attempt to increase the efficacy of PRRT, clinical trials that followed used β-emitting radionuclides, such as ^{90}Y or ^{177}Lu. Radionuclides emitting β-radiation have greater therapeutic potential since the emitted particle range exceeds the cell diameter [10–12].

Furthermore, the ability to irradiate neighbouring cells is an advantage with tumours, such as breast carcinomas, that are characterised by a heterogeneous SSTR tissue distribution, with regions of high density next to regions that lack receptor expression[13]. As expected, the clinical and preclinical studies in which ^{90}Y- or ^{177}Lu-coupled somatostatin analogues were used demonstrated more effectiveness in terms of tumour shrinkage than was reported with somatostatin analogues coupled to ^{111}In [14–17]. O'Donoghue *et al.* [12], who used a mathematical model to examine tumour curability and its relationship to tumour size for 22 β-emitting radionuclides, calculated an optimal tumour diameter for cure of 34 and 2 mm for ^{90}Y and ^{177}Lu, respectively. With respect to these calculations, the preclinical studies by de Jong *et al.* [14,18], in which Lewis rats bearing SSTR-positive pancreatic CA20948 tumours of different sizes (0.1–15 cm^2) were treated with [^{177}Lu-DOTA^{0},Tyr^3]octreotate

(^{177}Lu-DOTATATE) and [^{90}Y-DOTA^{0},Tyr^{3}]octreotide (^{90}Y-DOTATOC) are of special interest. After treatment with ^{177}Lu-DOTATATE (total cumulative dose 555 MBq, maximum estimated tumour dose 60 Gy), a higher cure rate was observed in the group of rats bearing small tumours (< 1 cm^2) than in the rats bearing larger tumours (> 1 cm^2, mean approximately 5 cm^2). In contrast, treatment with a single dose of 370 MBq ^{90}Y-DOTATOC, leading up to a maximum of 60 Gy in the medium-sized (3–9 cm^2) tumours, showed less cure within the group of rats bearing small (< 1 cm^2) tumours compared with the rats bearing medium-sized tumours (Figure 1) [19]. These results suggested that treatment with a combination of ^{90}Y- and ^{177}Lu-labelled somatostatin analogues can be more effective in the treatment of multiple tumours that differ in size than can one of the analogues separately. Recently, de Jong *et al.* [20] reported the results of such a combination versus single analogue therapy. In rats bearing both a small (< 0.5 cm^2) and a large tumour (7–9 cm^2), significantly better survival was observed after PRRT with the combination of 185 MBq (half-dose) ^{90}Y-DOTATOC and 278 MBq (half-dose) ^{177}Lu-DOTATATE than after a single full dose of 370 MBq ^{90}Y-DOTATOC or 555 MBq ^{177}Lu-DOTATATE. To translate these results to the clinical setting with patients with GEP tumours, ^{90}Y-labelled somatostatin analogues may be more effective in larger tumours, whereas ^{177}Lu-labelled somatostatin analogues may be more effective in smaller tumours, with the combination of both radionuclides as the most suitable therapy for the clinical situation in which most patients have tumour metastases varying in size.

Unfortunately, randomised controlled clinical studies comparing the therapeutic efficacy of ^{90}Y and ^{177}Lu somatostatin analogues or combination-based regimens are still lacking.

Somatostatin analogues in peptide receptor radionuclide therapy

The various ^{111}In-, ^{90}Y- or ^{177}Lu-labelled somatostatin analogues differ in their affinity for the expressed SSTRs. Five human SSTR subtypes (SSTR1–SSTR5) that bind native human somatostatin (SS14) and its high-affinity 28 amino acid precursor (SS28) have been cloned [21–23]. However, their affinities for synthetic somatostatin analogues differ considerably. The 'cold' analogue octreotide, which is frequently used to control symptoms related to hormone overproduction by GEP tumours, binds with high affinity to SSTR2 and with low affinity to SSTR3 and SSTR5, whereas it does not bind to SSTR1 and SSTR4 [24,25]. Furthermore, autoradiography studies by Reubi *et al.* [26] demonstrated that, after labelling octreotide, via DTPA, with ^{111}In, the affinities to SSTR2 and SSTR5 were diminished (Table 2).

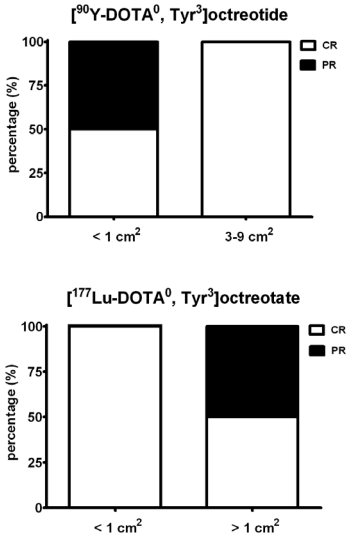

Figure 1. Cure rate (expressed as percentage of cured rats) found in groups of rats bearing CA20948 tumours of different indicated sizes after treatment with 370 MBq [^{90}Y-DOTA°,Tyr^3]octreotide or 555 MBq [^{177}Lu-DOTA°,Tyr^3]octreotate (maximum estimated tumour dose of 60 Gy for both treatments). CR, complete response; PR, partial response. (Modified from de Jong *et al.* [14]).

However, despite the change in affinities, SSTR2 remains the receptor subtype for which [^{111}In-DTPA°]octreotide has the highest affinity. Hofland *et al.* [27] demonstrated that the uptake of [^{111}In-DTPA°]octreotide in the SSTR-positive organs of mice was predominantly determined by SSTR2. Moreover, John *et al.* [28] demonstrated that a positive [^{111}In-DTPA°]octreotide scintigram in patients with neuroendocrine tumours is mainly the result of SSTR2 expression, whereas SSTR1, SSTR3, SSTR4 and probably SSTR5 are less important. Radiolabelled somatostatin analogues that had a higher affinity for SSTR2 than did ^{111}In-octreotide, and were therefore potentially more effective for therapy, thus became available. Small structural changes in the radioligand molecule, for example a different radionuclide, chelator or peptide, revealed distinct differences in the binding properties of the analogue for the various SSTR subtypes (Table 2) [26].

In animal experiments, several ^{111}In-labelled somatostatin analogues showed a higher specific uptake than ^{111}In-labelled [DTPA°]octreotide in SSTR-positive organs [5]. Furthermore, the analogue [DOTA°, Tyr^3]octreotate has a ninefold higher affinity for SSTR2 compared with [DOTA°, Tyr^3]octreotide, whereas the affinities for SSTR3 and SSTR5 were found to be lower [26]. In line with the higher affinity for SSTR2, biodistribution studies on ^{111}In-octreotide and ^{177}Lu-DOTATATE scintigraphy showed a three- to fourfold higher tumour uptake in four out of five patients with

somatostatin-positive tumours, of whom three had GEP tumours [29]. As most GEP tumours are known to predominantly express SSTR2, all clinical studies selected a radiolabelled somatostatin analogue for PRRT with at least a high affinity for SSTR2.

CLINICAL STUDIES

The outcome of several phase I and phase II PRRT studies, in which different radiolabelled somatostatin analogues were used, has been published. In addition, it has become apparent that the bone marrow and kidneys are the most important dose-limiting organs in this type of therapy.

Table 2. Affinity profiles (IC50) a for human SSTR1-SSTR5 (hSSTR1-5) of a series of somatostatin analogues

Peptides	hSSTR1	hSSTR2	hSSTR3	hSSTR4	hSSTR5
SS-28	5.2 ± 0.3 (19)	2.7 ± 0.3 (19)	7.7 ± 0.9 (19)	5.6 ± 0.4 (19)	4.0 ± 0.3 (19)
Octreotide	>10,000 (5)	2.0 ± 0.7 (5)	187 ± 55 (3)	>1,000 (5)	22 ± 6 (5)
DTPA-octreotide	>10,000 (6)	12 ± 2 (5)	376 ± 84 (5)	>1,000 (5)	299 ± 50 (6)
^{111}In-octreotide	>10,000 (5)	22 ± 3.6 (5)	182 ± 13 (5)	>1,000 (5)	237 ± 52 (5)
DOTATOC	>10,000 (7)	14 ± 2.6 (6)	880 ± 324 (4)	>1,000 (6)	393 ± 84 (6)
^{90}Y-DOTATOC	>10,000 (4)	11 ± 1.7 (6)	389 ± 135 (5)	>10,000 (5)	114 ± 29 (5)
DOTALAN	>10,000 (7)	26 ± 3.4 (6)	771 ± 229 (6)	>10,000 (4)	73 ± 12 (6)
^{90}Y-DOTALAN	>10,000 (3)	23 ± 5 (4)	290 ± 105 (4)	>10,000 (4)	16 ± 3.4 (4)
DOTA-OC	>10,000 (3)	14 ± 3 (4)	27 ± 9 (4)	>1,000 (4)	103 ± 39 (3)
^{90}Y-DOTA-OC	>10,000 (5)	20 ± 2 (5)	27 ± 8 (4)	>10,000 (4)	57 ± 22 (4)
DTPA-Tyr^3-octreotate	>10,000 (4)	3.9 ± 1 (4)	>10,000 (4)	>1,000 (4)	>1,000 (4)
^{111}In-DTPA-Tyr^3-octreotate	>10,000 (3)	1.3 ± 0.2 (3)	>10,000 (3)	433 ± 16 (3)	>1,000 (3)
DOTA-Tyr^3-octreotate	>10,000 (3)	1.5 ± 0.4 (3)	>1,000 (3)	453 ± 176 (3)	547 ± 160 (3)
^{90}Y-DOTA-Tyr^3-octreotate	>10,000 (3)	1.6 ± 0.4 (3)	>1,000 (3)	523 ± 239 (3)	187 ± 50 (3)

Modified from Reubi et al. [26]

[a] *All values are IC_{50} ± SEM in nM. The number of experiments is in parenthesis.*

[^{111}In-DTPA^{0}]octreotide

The first radiolabelled somatostatin analogue therapy in GEP patients with advanced-stage disease was based on the administration of high dosages of ^{111}In-octreotide, which at that time was available for diagnostic purposes (Table 3) [6,7,30,31].

The total cumulative dose varied from 3.1 GBq up to 160.0 GBq. In a report by Valkema *et al.* [6], in which the outcome of ^{111}In-octreotide treatment in 50 patients with SSTR-positive tumours was reviewed, 15 out of the 26 (58%) GEP patients had a stabilisation of their metastatic disease, and two out of 26 (8%) showed minor remission, defined as a reduction in tumour size of between 25% and 50%. Patients with stable disease and minor remission (17 out of 26; 65%) were considered to have shown a beneficial therapeutic effect as all patients had documented progressive disease at study entry. In another report by Anthony *et al.* [30], 2 out of 26 (8%) patients had a partial remission, whereas 21 out of 26 (81%) had stable disease. Buscombe *et al.* [31] reported the outcome of ^{111}In-octreotide therapy in 12 GEP patients treated with cumulative activities as high as 36.6 GBq. Seven out of the 12 (58%) patients had stable disease 6 months after the last therapy, 2 (17%) demonstrated partial remission and 3 (25%) had progressive disease despite treatment.

Table 3. Peptide receptor radionuclide therapy with ^{111}In-octreotide in patients with GEP tumours

				Response [a]			
Authors [Ref.]	**No. of patients**	**PD before therapy**	**Cum dose (GBq)**	**PR**	**MR [b]**	**SD**	**PD**
Valkema *et al.* [6]	26	24/26 (92%) (clinical and/or imaging based)	4.7-160.0	0	2 (8%)	15 (58%)	9 (35%)
Anthony *et al.* [30]	26	100% (clinical and/or imaging based)	6.7-46.6	2 (8%)	N/I	20 (77%)	4 (15%)
Buscombe *et al.* [31]	12	100% (biochemical or imaging based)	3.1-36.6	2 (17%)	N/I	7 (58%)	3 (25%)

Cum dose, cumulatieve dose of ^{111}In-octreotide; N/I, not indicated
[a] Criteria of Tumour Response: PR (partial remission), > 50%reduction of tumour size; SD (stable disease), < 25% reduction or increase of tumour size; PD (progressive disease), > 25% increase of tumour size.
[b] Modification of SWOG criteria including MR (minor remission), between 25 and 50% reduction in tumour size.

All the clinical PRRT studies reported encouraging and promising results, especially in terms of clinical benefit and biochemical responses. Reported cases of objective tumour shrinkage were, however, few. These outcomes suggested that the anti-tumour effect of ^{111}In-octreotide is not ideal for PRRT, at least for visible GEP tumours. However, experimental data in rats have shown that high doses of ^{111}In-octreotide can inhibit the growth of liver metastases after injecting SSTR2 receptor-positive tumour cells into the portal vein [32]. These results suggest that PRRT with ^{111}In-labelled analogues might be effective in the treatment of micro-metastases or metastatic spread during initial surgery. Clinical studies that could confirm these observations are, however, lacking.

[^{90}Y-DOTA^{0},Tyr^{3}]octreotide, [^{90}Y-DOTA]lanreotide and [^{90}Y-DOTA^{0},Tyr^{3}]-octreotate

In the clinical trials that followed the PRRT with ^{111}In-labelled analogues, ^{90}Y-labelled analogues were used. A summary of these studies is shown in Table 4.

In 1998, Otte *et al.* [33] reported the first results of 10 patients with SSTR-positive tumours treated with ^{90}Y-DOTATOC. Two out of 10 patients had partial remission and six stable disease; in two patients, ^{18}F-deoxyglucose positron emission tomography, after a single dose of ^{90}Y-DOTATOC, showed a substantial reduction of ^{18}F-deoxyglucose uptake in the tumour. In the studies that followed, the response rates (complete and partial remission) in patients with GEP tumours, who were treated with either 6.0 GBq/m^2 or 7.4 GBq/m^2, were 10 out 37 (27%) and 8 out of 37 (22%), respectively [16,34]. To determine whether a decrease in the number of treatments, but at the same time maintaining the maximum cumulative dose of 7.4 GBq/m^2 due to an increase of dosage per treatment, could increase the objective response another study was performed [35]. Twelve out of 35 patients (34%) had complete or partial remission, which indicated a higher percentage of tumour regression. No increase in the number of side-effects was reported. Although these results suggested that an increase of dose, and as a consequence a decrease in the number of therapeutic injections, could be more beneficial, it must be stressed that this was not a randomised controlled trial and the number of treated patients was low. Nonetheless, the variation of protocol characteristics, such as the number of treatments, the doses per treatment or the length of treatment interval, are of great interest and may play an important role in the reported outcome of PRRT studies. Randomised controlled studies on the effects of these variables are therefore needed.

Clinical studies performed in Milan also used ^{90}Y-DOTATOC to treat various SSTR positive tumours [36–40]. Recently, Bodei *et al.* [40] reported their experience with ^{90}Y-DOTATOC, in which a total of 141 patients with various, SSTR positive tumours were treated. An objective response (complete or partial remission) of 26%

was observed. More precisely, 23% of patients who had progressive disease before therapy (113 out of 141; 80%) had complete or partial remission, whereas in the group with stable disease (28 out of 141; 20%), 32% had complete or partial remission. Unfortunately, the specified treatment outcome according to tumour type was not given. It was, however, reported that most of the patients who had a favourable outcome had neuroendocrine GEP tumours. In a more detailed study from Milan, the outcome of therapy in 40 patients with SSTR-positive tumours was reported [39]. The cumulative dose of ^{90}Y-DOTATOC, which was given in two cycles, ranged from 5.9 to 11.1 GBq. In the group with GEP tumours, this therapy regimen resulted in partial remission in 6 out of 21 patients (29%), whereas 11 out of 21 (52%) had stable disease and 4/21 (19%) had progressive disease. Valkema *et al.* [41] reported the preliminary results of a multicentre phase I study performed in Rotterdam, Brussels and Tampa. The objective was to define the maximum tolerated single and four-cycle doses of ^{90}Y-DOTATOC [6,11,14]. Escalating doses up to 14.8 GBq/m^2 in four doses or up to 9.3 GBq/m^2 in a single dose were administered to a total of 60 patients. Four of the 54 (7%) patients who were treated with their maximum allowed dose had partial remission, 7 out of 54 (13%) had minor remission, and 33 out of 54 (61%) showed stabilisation of their disease. Anti-tumour effect in terms of improvement of response, according to the SWOG (Southwest Oncology Group) tumour response criteria, including stable disease and minor remission in patients with progressive disease at the start of therapy, was reported as 65% [41]. The median time to progression of that same group had not been reached at 26 months [42].

In a European multicentre study (MAURITIUS), another ^{90}Y-labelled somatostatin analogue, ^{90}Y-DOTA-lanreotide, was used to treat 39 GEP patients. The total cumulative dose ranged from 1.9 GBq to 8.6 GBq (50–232 mCi) of ^{90}Y-DOTA-lanreotide [15]. Eight out of 39 (20%) patients showed minor remission, and 17 out of 39 (44%) had stable disease. The first results of the therapeutic efficacy in patients with SSTR-positive tumours with the somatostatin analogue [^{90}Y-DOTA^0,Tyr^3]octreotate (^{90}Y-DOTATATE) were recently reported by Baum *et al.* [43,44]. Twenty-eight out of 75 (37%) patients had partial remission, and 39 out of 75 (52%) demonstrated stable disease after therapy. Therefore, ^{90}Y-DOTATATE might also be a promising ^{90}Y-labelled somatostatin analogue. Despite the differences in somatostatin analogues and protocols used in the various ^{90}Y-based PRRT studies, the reported results of therapy in terms of complete and partial remission percentages, ranging up to 37% (Table 4), indicated an improvement in therapeutic effectiveness compared with the studies with ^{111}In-labelled octreotide.

Table 4. Peptide receptor radionuclide therapy with ^{90}Y- and ^{177}Lu-labeled somatostatin analogues in patients with GEP tumours

Authors [Ref.]	No. of Patients	PD at baseline	Response *					
			CR	PR	MR ‡	SD	PD	CR + PR
[^{90}Y-DOTA^{o}, Tyr^{3}]octreotide								
Otte *et al.* 1999 [48] }	16	N/I	0	1 (6%)	N/I	14 (88%)	1 (6%)	1/16 (6%)
Waldherr *et al.* 2001 [34]	37	34/37 (84%)	1 (3%)	9 (24%)	N/I	23 (62%)	4 (11%)	10/37 (27%)
Waldherr *et al.* 2002 [16]	37	37/37 (100%)	1 (3%)	7 (19%)	N/I	26 (70%)	3 (8%)	8/37 (22%)
Waldherr *et al.* 2002 [35]	35	35/35 (100%)	2 (6%)	10 (29%)	N/I	19 (54%)	4 (11%)	12/35 (34%)
Bodei *et al.* 2003 [39]	21	N/I	0	6 (29%)	N/I	11 (52%)	4 (19%)	6/21 (29%)
Valkema *et al.* 2003 [41]	54	41/54 § (76%)	0	4 (7%)	7 (13%)	33 (61%)	10 (19%)	4/54 (7%)
[^{90}Y-DOTA]lanreotide								
Virgolini *et al.* 2002 [15]	39	39/39 (100%)	0	0	8 (20%)	17 (44%)	14 (36%)	0/39 (0%)
[^{90}Y-DOTAo,Tyr^{3}]octreotate								
Baum *et al.* 2004 [43,44]	75	67/75 (89%)	0	28 (37%)	N/I	39 (52%)	8 (11%)	28/75 (37%)
[^{177}Lu-DOTA^{o},Tyr^{3}]octreotate								
Kwekkeboom *et al.* 2003 [45]	76	29/76 (38%)	1 (1%)	22 (29%)	9 (12%)	30 (39%)	14 (18%)	23/76 (30%)

* *Criteria of Tumour Response (SWOG); CR (complete remission), no evidence of disease; PR (partial remission), > 50% reduction of tumour size; SD (stable disease), < 25% reduction or increase of tumour size; PD (progressive disease), > 25% increase of tumour size;* ‡*, modification of SWOG criteria including MR (minor remission), between 25 and 50% reduction of tumour size; N/I, not indicated;* §*, Valkema, personal communication*

[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate

The first results of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-DOTATATE) therapy were described in a study of 35 patients with neuroendocrine GEP tumours, who had a follow-up of 3–6 months after receiving their final dose [17]. Patients were treated with escalating dosages from 100 to 150, and a maximum of 200 mCi (3.7, 5.6 and 7.4 GBq, respectively) ^{177}Lu-DOTATATE, up to a final cumulative dose of 600–800 mCi (22.2–29.6 GBq), with treatment intervals of 6–9 weeks. The effects of the therapy on tumour size were evaluable in 34 patients. Three months after the final administration, a complete remission was found in one patient (3%), a partial remission in 12 (35%), stable disease in 14 (41%) and progressive disease in seven (21%), including three patients who died during the treatment period.

In an update on this treatment in 76 patients with GEP tumours [45], complete remission was found in one patient (1%), partial remission in 22 (29%), minor remission in 9 (12%), stable disease in 30 (40%), and progressive disease in 14 patients (18%). The effect of ^{177}Lu-DOTATATE therapy on tumour size, uptake on post-therapy scintigraphy, liver enzymes and the tumour marker chromogranin A in a patient who showed partial remission is shown in Figure 2. Six out of 32 patients who had induced stable disease or tumour regression after the therapy and were also evaluated after 12 months (mean 18 months from therapy start) developed progressive disease; in the other 26, the tumour response was unchanged. Median time to progression was not reached at 25 months from the beginning of therapy. In a more recent evaluation of response in a total of 131 GEP tumour patients, these outcomes were confirmed, with a median time to progression of more than 36 months [46].

Comparison of the different treatments

Treatment with ^{90}Y- and ^{177}Lu-labelled somatostatin analogues is very encouraging in terms of tumour shrinkage. However, direct comparison to evaluate the optimal treatment remains difficult. Differences in treatment protocol, such as administered doses, dosing schemes and the tumour response criteria used, can be responsible for the observed differences in treatment outcome. Therefore, randomised controlled trials are necessary to define the optimal PRRT and treatment scheme.

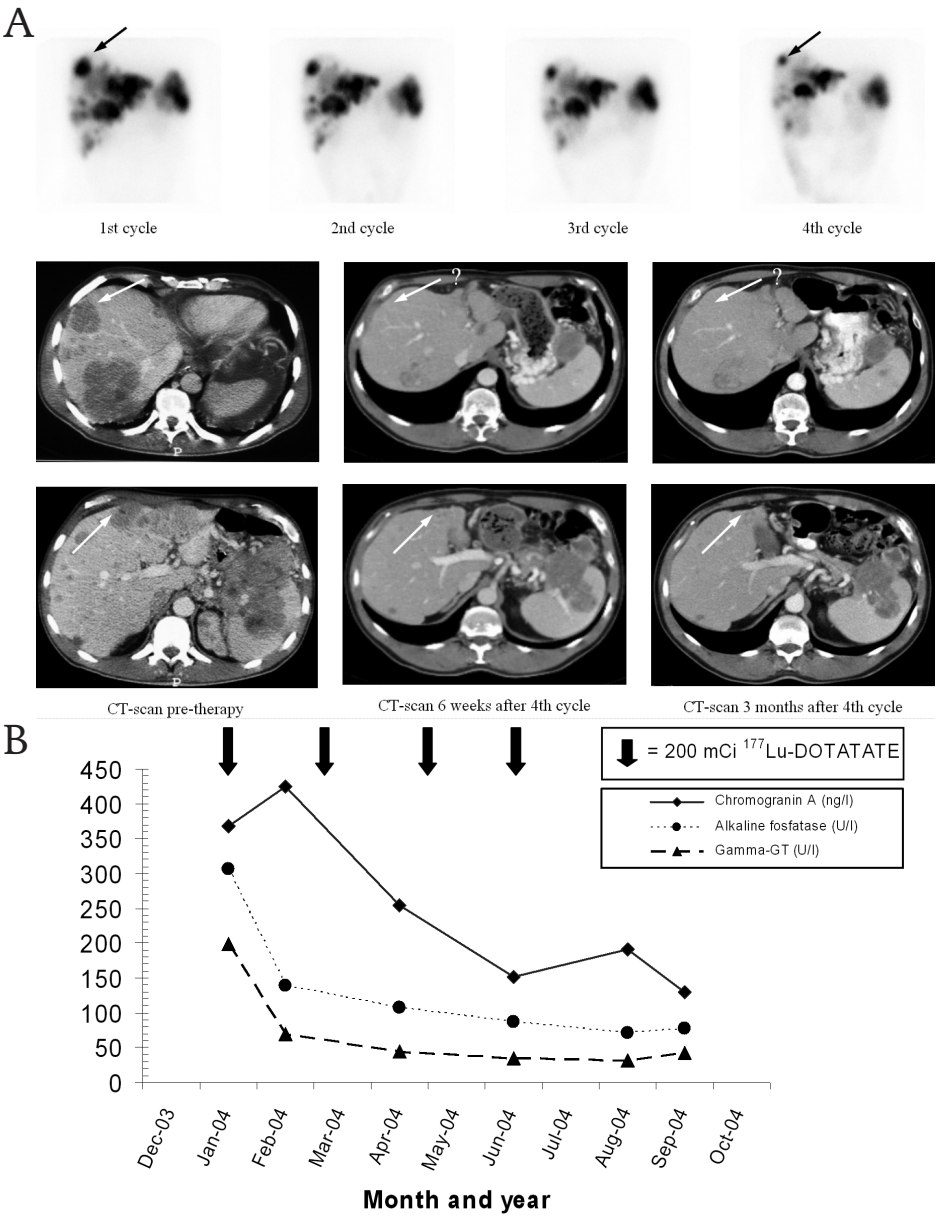

Figure 2. Baseline and follow-up data of a patient with carcinoid with liver metastases. (**A**) Post-therapy scintigraphy after each cycle is shown (top row). Note the decrease of uptake of [^{177}Lu-DOTA°,Tyr^{3}]octreotate on the last scintigraphy scan in comparison with the first (black arrows indicating the index lesion). At 3 and 6 months after four cycles of therapy, the patient had a partial remission (> 50% decrease in tumour volume on computed tomography; white arrows indicate the index lesion) (bottom row). (**B**) Regression of the tumour mass was accompanied by a decrease in serum concentration of alkaline phosphatase (reference range 0–119 U/l), gamma-glutamyl transpeptidase (gamma-GT; reference range 0–49 U/l) and the tumour marker chromogranin A (reference range 10–100 ng/ml).

SIDE-EFFECTS AND RADIATION TOXICITY

Adverse reactions observed after PRRT can be divided into direct side-effects and the more delayed effects of radiotoxicity. Direct effects commonly mentioned during and after therapy are nausea, vomiting and abdominal pain [17,30,34]. In general, these side-effects occur in a minority of patients and are easily treated with anti-emetics or pain medication. Mild hair loss was observed in patients treated with ^{177}Lu-DOTATATE, but hair growth had normalised at follow-up 3–6 months after the last administration [17]. Beside these mild side-effects, more serious toxicity may occur, especially to the bone marrow, kidneys and liver. The reported percentages of these side-effects or toxicities are shown in Table 5.

Table 5. Side-effects in patients with somatostatin receptor-positive (GEP and non GEP) tumours treated with different radiolabelled somatostatin analogues

Author [Ref.]	Radioligand	Number of Patients	Grade 3-4 Haematologic Toxicity §			Other Toxicities
			Platelets	Haemo-globulin	White blood cells	
Valkema *et al.* [6]	[^{111}In-DTPA^{0}]octreotide	50	10%	15%	2%	3 AML/MDS
Anthony *et al.* [30]	[^{111}In-DTPA^{0}]octreotide	27	7%	11%	7%	3 Liver, 1 Renal
Bodei *et al.* [39]	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	40	7%	3%	7%	
Otte *et al.* [48]	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	29	3%	7%	0%	4 Renal *
Waldherr *et al.* [16]	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	39	0	3%	0%	1 Renal
Valkema *et al.* [41]	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	60	12%	1%	2%	1 MDS, 1 Liver, 1 Renal
Kwekkeboom *et al.* [45]	[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	200	3%	8%	13%	1 MDS, 2 Liver ‡, 1 Renal

Percentages are based on patient numbers. AML: acute myeloid leukaemia; MDS: myelodysplastic syndrome
§, Most of the mentioned haematologic toxicities were transient. See reference for more detailed information;
**, No amino-acid infusion in half of the patients;*
‡ personal communication, Kwekkeboom et al.

Haematological toxicity

Haematological toxicities of grade 3–4 for haemoglobin, white blood cells and platelets were reported up to a maximum of 15% [16,30,39,45,47,48]. In general, the decrease in blood cell count was transient, and transfusion was only occasionally needed. More serious side-effecs were reported from a clinical trial in which 50 patients were treated with ^{111}In-octreotide [6]. Leukaemia and myelodysplastic syndrome were reported in three patients who had been treated with total cumulative doses of over 2.7 Ci (100 GBq), with an estimated cumulative bone marrow radiation dose of about 3 Gy. One patient, who developed acute myeloid leukaemia 17 months after the first dose of ^{111}In-octreotide, had had chemotherapy and treatment with interferon before PRRT. The other two patients, who had had no previous cytotoxic therapy, developed myelodysplastic syndrome after more than 3 years. None of the 44 patients who were treated with a cumulative dose lower than 100 GBq developed myelodysplastic syndrome or leukaemia. In a phase I trial with ^{90}Y-DOTATOC in which the objective was to define the maximal tolerated single and four-cycle doses, one patient had myelodysplastic syndrome 2 years after the start of PRRT; this patient had also had previous chemotherapy [41]. In the report by Kwekkeboom *et al.* [45], who studied the patients treated with ^{177}Lu-DOTATATE as PRRT, one patient in the whole group of patients who had been treated or were being treated up to that time (201 patients, 637 administrations) developed myelodysplastic syndrome. This patient had also previously received chemotherapy. In summary, haematological toxicity in PRRT is in general mild and reversible, and the risk of developing myelodysplastic syndrome or leukaemia is low if certain dosing limits are respected.

Renal toxicity

Chelated somatostatin analogues are cleared predominantly by the kidneys. An accumulation and retention of these analogues within the kidney occurs but is not SSTR mediated [49]. Because of the rapid clearance, [^{111}In-DTPA^{0}]octreotide can be safely applied for diagnostic use without any damage to the kidneys [1,50]. For therapeutic use, however, the renal accumulation and the relatively long renal effective half-life of the radiopharmaceutical can be dose-limiting. In external beam radiation therapy, renal absorbed doses of 23 Gy (fractions of 2 Gy) may cause nephropathy in 5% of patients in 5 years, whereas 28 Gy leads to a 50% risk over the same period [51]. However, since PRRT is applied as continuous low-dose radiation with intracellular accumulation, a maximum cumulative dose limit of 23 Gy may not be applicable. The first reports on acute (6–12 months after radiation exposure) and late (1–5 years after exposure) renal side-effects appeared after the use of ^{90}Y-DOTATOC in various clinical trials [33,52–54]. The results suggested that a cumulative dose of ^{90}Y-DOTATOC of more than 7.4 GBq/m^2 might be a risk factor for renal insufficiency [33]. However, some years later, a case report of a patient who developed late-onset renal insufficiency with a total cumulative dose of less than 7.4 GBq/m^2

indicated that even less radiation can cause renal damage at a later time point [53]. In contrast, no renal toxicity was found in patients treated with [^{111}In-DTPA^{0}]octreotide[6]. The difference between ^{111}In and ^{90}Y with regard to the induction of radiation nephropathy may be explained by the difference in the particle range emitted (10 μm versus approximately 12 mm, respectively). The Auger electrons emitted by ^{111}In within the tubular cells do not reach the radiosensitive glomeruli. This particle range advantage might also be the reason why only one patient of a group of 201 patients treated with ^{177}Lu-DOTATATE developed renal failure [45]. Although the number of patients reported with radiation nephropathy was relatively low, and the potential benefit for the patients outweighed the risk of occurrence of this severe complication, it became clear that PRRT-induced radiation nephropathy was difficult to predict with the currently applied maximum cumulative dose limits. Two recent studies in which patients were treated with ^{90}Y-DOTATOC provided more insight into individual kidney dosimetry and its importance in PRRT [55,56]. These studies indicated that, apart from the total renal radiation dose, the dose volume, fractionation rate and clinical parameters of hypertension, diabetes and age are relevant risk factors for the development of a loss of renal function. Kidney protection methods to prevent damage to the kidney from high absorbed doses with each administration are obviously of importance. The most important method currently used to reduce the renal uptake of radioactivity in PRRT is the use of amino acid solutions, which can be easily co-administered during therapy. Preclinical studies have shown that the infusion of positively charged amino acids, mainly L-lysine and L-arginine, are able to reduce the tubular reabsorption of radiolabelled somatostatin analogues in rats [57]. Clinical studies have proved that co-infusion with a combination of the L-lysine and L-arginine or a mixed amino acid solution on the day of therapy led to a reduction in renal uptake of between 20 and 47% [29,39,58,59]. Higher doses of amino acids are more effective but have the disadvantage of inducing a higher incidence of side-effects, such as nausea, vomiting and, especially with higher doses of L-lysine, hyperkalaemia [59,60].

Liver toxicity

Most patients treated with PRRT in the clinical trials studied had liver metastases. The extent of liver involvement ranged from a single lesion to diffuse liver involvement with pronounced hepatomegaly. It is therefore not unlikely that PRRT can induce hepatocellular radiation injury. In clinical practice, however, it may be difficult to distinguish an increase of liver function parameters induced by radiation from a subtle progression of liver metastases. Anthony *et al.* [30] reported three patients (from a total of 27), treated with ^{111}In-octreotide, in whom a temporary increase in liver function parameters (grade 3 liver toxicity on World Health Organization toxicity grading) was observed. All three patients had a tumour replacement of more than 75% of their hepatic parenchyma and treatment-associated necrosis

on the computed tomography scans. In patients with less extensive liver disease, changes in liver function parameters did not occur. A significant increase in liver function parameters after the administration of ^{90}Y-DOTATOC was reported in two studies [41,61]. Valkema *et al.* [41] reported one transient grade 3 toxicity in a group of 60 patients treated with ^{90}Y-DOTATOC (phase I study). In another study, 15 patients with proven liver metastases (of whom 12 had extensive liver involvement, defined as 25% or more) from neuroendocrine tumours were treated with three cycles of 120 mCi (4.4 GBq) each [61]. In only four of these 15 patients, one or more of the three liver enzymes that were measured - serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase - increased at least one grade, according to the World Health Organization common toxicity criteria, from baseline to final follow-up measurement (4–6 weeks post cycle 3). It was concluded that patients with diffuse SSTR-positive hepatic metastases could be treated with a cumulative administered activity of 360 mCi (13.2 GBq) of ^{90}Y-DOTATOC with only a small chance of developing mild acute or subacute hepatic injury. In the group of patients treated with ^{177}Lu-DOTATATE, significantly increased liver function parameters (grade 4 liver toxicity) was evident in two patients after the first cycle of treatment (D.J. Kwekkeboom, personal communication, 2004). One patient, who suffered from a rapidly growing neuroendocrine tumour with extensive liver involvement, clinically progressed to liver failure within 3 weeks and died shortly thereafter. Whether the aggressive nature of the tumour or the PRRT-induced toxicity led to this fatal condition remains unclear. The other patient, who after the first therapy developed dyspnoea, acute abdominal pain and increased liver function parameters, was hospitalised for several weeks. Gradually, the liver function parameters and hyperbilirubinaemia returned to pre-therapy levels. Treatment with ^{177}Lu-DOTATATE was continued for 6 months after the first therapy with a reduced dose of 1.9 GBq followed by a third administration of 4.1 GBq without any acute side-effects.

CLINICAL PRACTICE

In patients with metastasised GEP tumours, for whom surgery is no longer an option, PRRT can be an effective alternative therapeutic modality with limited side-effects. The results in terms of tumour volume reduction, as shown in the different clinical trials, are very encouraging and seem to compare favourably with chemotherapy. No randomised controlled study has, however, been performed to confirm this. Although proven effective in a substantial percentage of patients, PRRT has not been widely recognised as alternative systemic therapy. Instead, the 'wait-and-see' approach often remains the mainstay of initial management in patients with unresectable disease. The rationale for this approach is found in the natural history of well-differentiated GEP tumours not receiving treatment, in which tumours can be indolent for many years and the well-being of patients, even with metastasised

tumours, can be unchanged for many years. However, the reported studies on PRRT clearly indicate that patients with documented progressive disease or a substantial increase in symptoms can benefit from this therapy. The recognition of the possible benefit of PRRT for patients with GEP tumours is increasing, but its implementation within the whole therapeutic array is rather poor. Factors that contribute to this include the fact that PRRT is a relatively new therapeutic modality, the lack of approved radiopharmaceuticals, which is in part related to increased governmental demands, and therapy-related costs.

Indications for peptide receptor radionuclide therapy

Candidates for PRRT are those patients with inoperable GEP tumours who have progressive disease or symptomatology that is difficult to manage with medication. If it is agreed that the malignancy is inoperable, the tumour has to be SSTR-positive, based on tumour uptake on ^{111}In-octreotide scintigraphy. Furthermore, the amount of tumour uptake has to be equal to or higher than that of normal liver tissue (according to criteria previously described by Krenning *et al.* [10]).

High uptake during ^{111}In-octreotide scintigraphy has been shown to be correlated with tumour regression after PRRT [17]. Additionally, because of the radiation to the bone marrow and the risk of temporary bone marrow suppression, patients need to fulfil certain minimal haematological criteria. Kidney function has to be determined before therapy to exclude patients with signs of impending renal failure (glomerular filtration rate < 40 ml/minute). The presence of bone metastases, which occur in a minority of patients, is no exclusion criterion. As a rule, if a tumour response occurs, all tumour sites decrease in size. However, cystic and bone lesions seem to respond in a more protracted way than the more common, solid liver metastases. Up until now, no systematic study has been performed to address the issue of a possible differential response of metastases based on their location. The full patient selection criteria are summarised in Table 6.

Timing of therapy

There is currently no consensus about when to start PRRT in patients with GEP tumours. The stage of disease at which the diagnosis is made is highly variable and ranges from a localised, non-metastatic primary tumour to more advanced or end-stage disease with hepatomegaly and ascites. In a recent report in which the relationship between delay of diagnosis, extent of disease and survival in 115 patients with carcinoid was studied, a mean delay in the diagnosis of 66 months was found[62]. It was concluded that the diagnosis of carcinoid is difficult, and therefore a delay of diagnosis by physicians is common. Strikingly, the delay of the diagnosis did not correlate with the extent of the disease. However, the extent of the disease did correlate with survival.

Table 6. Criteria for peptide receptor radionuclide therapy in patients with GEP tumours

Inclusion
Sufficient tumour uptake on ^{111}In-octreotide scintigrams
Haematology
Platelet count ≥ 75-100 x 10^9/L
White blood cell count ≥ 2-3.5 x 10^9/L
Haemoglobin ≥ 5.0 mmol/L
Kidney function
Creatinin (serum) ≤ 150 µmol/L or creatinine clearance ≥ 40 ml/min
Karnofsky Performance Status ≥ 50
Life expectancy > 6 months
Exclusion
Chemotherapy within 6 weeks prior to treatment start
Pregnancy/ lactation

Patients with primary tumours and lymph node metastases were less likely to die of carcinoid disease than patients with hepatic metastases, carcinomatosis or extra-abdominal metastases. Unfortunately, reports on PRRT with explicit survival data are few. In the multicentre trial with ^{111}In-octreotide [6], it was reported that PRRT for end-stage patients with a higher tumour burden was less likely to have a favourable outcome than for patients with lower tumour burden or in a better general condition. Survival data in a group of 27 patients treated with ^{111}In-octreotide presented by Anthony *et al*. [30] suggested a survival benefit in patients treated with ^{111}In-octreotide. The number of patients studied was, however, low, and the survival data of the treated group were compared with data from a historical control group. In the studies with ^{177}Lu-DOTATATE, it was suggested that, because of the high success rate of the therapy, the low incidence of side-effecs and the high median time to progression (> 36 months), its use can be advocated in patients with metastasised, unresectable GEP tumours without waiting for tumour progression [17,63].

Another argument in favour of early treatment is that neuroendocrine tumours can dedifferentiate in the course of the disease and thereby lose the expression of SSTRs. Treatment with radiolabelled somatostatin analogues will then be impossible[17]. However, whether early treatment would benefit patients with metastasised, unresectable GEP tumours in terms of longer survival remains to be studied and should imply randomisation into groups with and without PRRT. At this moment,

when there seems to be proof that PRRT is an effective therapy, such a survival study seems unethical.

Another issue, regarding the question whether we should treat patients with PRRT or not at an early stage of the disease, is the benefit in terms of clinical response and quality of life. Not all studies address this issue. There is, however, a growing awareness of its importance in clinical oncology trials, especially in therapies for which cure is not the primary goal and survival gains are low or unknown [64]. As a consequence, the more recent PRRT reports have included data on the clinical effectiveness of therapy. Two studies with ^{90}Y-DOTATOC provided evidence for a favourable clinical response in 60–70% of the patients [47,65]. In patients treated with ^{177}Lu-DOTATATE, quality of life assessment showed a significant improvement in the global health/quality of life score (Δ score +9.2, scale range 0–100, $P<0.01$), especially in those patients with proven tumour regression (Δ score +10.5, $P<0.05$) (Figure 3) [66]. Although the assessment methods for identifying clinical changes differ in these studies, the combined results suggest that patients may experience a clinical benefit from PRRT.

FUTURE DEVELOPMENTS

A direction of future research to improve current PRRT for GEP tumours includes the development of new stable somatostatin analogues with a high affinity for the different SSTR subtypes. The new analogue [DOTA^0-1-naphthyl^3]octreotide (DOTANOC), for example, is an analogue that has a high affinity for SSTR2, SSTR3 and SSTR5 [67]. It might therefore be a promising analogue to be used for treatment of patients with tumours that not bear only SSTR2, but also express SSTR3 and/or SSTR5. Furthermore, combined treatment with different radiolabelled somatostatin analogues, analogous to the favourable response with combinational chemotherapy in solid tumours compared with single-agent therapy, is of great interest. This approach will of course be limited by the combined toxicity of the radiolabelled peptides. Preclinical PRRT studies with ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE indicate that there is an optimal tumour size in terms of the efficacy of tumour reduction for each radionuclide. As most patients have metastatic disease with tumours of different sizes, combination PRRT could achieve higher cure rates compared with single-agent therapy. Higher cure rates are possible when the density of expressed SSTRs is enhanced. In vitro and in vivo studies show that the irradiation of neuroendocrine AR42J (rat pancreatic tumour) cells can upregulate the expression of SSTR2 and gastrin receptors [68]. PRRT after the upregulated expression of SSTR2 may lead to a higher uptake of the radiolabelled peptide and consequently a higher therapeutic efficacy. Most research in PRRT is focused on the different SSTR subtypes. Neuroendocrine tumours may, however, coexpress other tumour-specific peptides, such as vasoactive intestinal peptide, cholecystokin, bombesin and GLP-1 receptors [69].

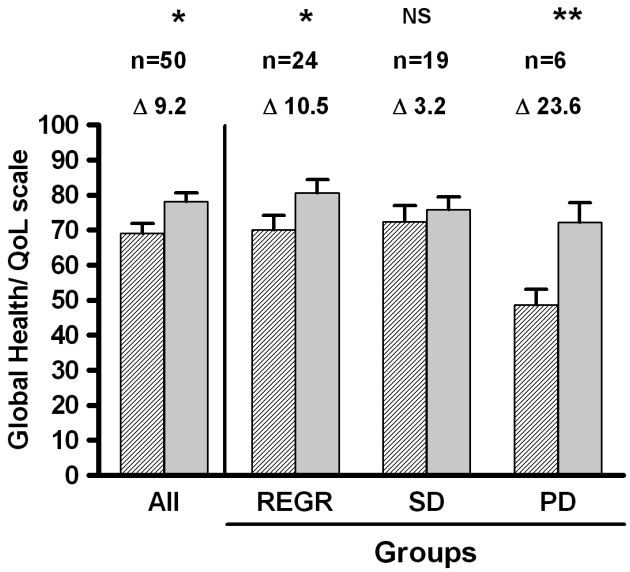

Figure 3. Global health/quality of life scale scores of all the patients (n=50) and the different outcome groups according to tumour evaluation before (hatched bars) and 3 months after (grey bars) ^{177}Lu-octreotate therapy. REGR, regression (complete, partial and minor remission); SD, stable disease; PD, progressive disease. Standard errors of the mean are shown; *P<0.05; **P<0.01; NS, not significant (two-sided analysis of variance; P<0.05 was considered significant). (Modified from Teunissen *et al.*[66]).

The concomitant expression of these receptors could be used in the future in a multireceptor PRRT to target more efficiently GEP tumours in each patient individually. This approach could, especially in tumours with a heterogeneous or even a reciprocal receptor distribution, be very favourable in terms of achieving a more homogenous distribution of the absorbed radiation dose within the tumour mass. The combination of PRRT with surgery and/or chemotherapy as a multimodality treatment strategy is of interest and requires the start of randomised trials to prove whether current results can be improved. Studies that can also be considered are the use of PRRT combined with surgery in an adjuvant setting to irradiate occult metastases, or PRRT as debulking therapy followed by surgery in patients with inoperable but limited local disease. External beam radiotherapy in combination with chemotherapy such as gemcitabine, which is a known potent radiation sensitiser, has been shown to have favourable effects in patients with non-small-cell lung cancer [70]. Although the patients were treated with external radiotherapy, gemcitabine and other radiosensitising agents with concurrent PRRT might prove effective in the future.

SUMMARY

PRRT holds great promise for the future regarding the treatment of various cancers. Using radiolabelled peptides, which bind with high affinity to specific receptors on cancer cells, it is possible to target the cancer efficiently. In GEP tumours, radiolabelled somatostatin analogue therapy has been proven to be effective. Dose-limiting organs are the bone marrow and the kidneys. With the currently used maximum allowed dose, PRRT is relatively safe, and serious side-effects are rare. It is impossible to conclude from the available literature which radiolabelled somatostatin analogue can be regarded as the most effective therapy. Also, the development of therapy strategies with combinations of different radionuclides, which is underway, is of interest as these strategies may in future provide an increase in therapeutic efficacy.

Practice points

- PRRT with β-emitting agents such as ^{90}Y and ^{177}Lu can induce tumour shrinkage in patients with somatostatin-positive GEP tumours
- octreotide scintigraphy is used to select candidates for PRRT
- a high uptake during octreotide scintigraphy is correlated with a favourable outcome of therapy
- the co-administration of amino acids during PRRT is essential to minimise the risk of renal toxicity
- blood examination before each cycle of PRRT is necessary as bone marrow suppression is a known risk of PRRT

Research Agenda

The following areas are of interest in optimising PRRT:

- the development of new somatostatin analogues with a high affinity for different SSTR subtypes
- randomised controlled (multicentre) trials to compare the therapeutic efficacy of ^{90}Y- and ^{177}Lu-labelled somatostatin analogues, and their use in combination
- the development of different peptide analogues with a high affinity
- the implementation of multimodality treatment strategies:
  - surgery with adjuvant PRRT
  - PRRT for debulking before surgery
  - chemotherapy as a radiosensitiser for PRRT
- methods to upregulate the expression of SSTRs in vivo
- the reduction of kidney and bone marrow uptake

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1.3

Aims and outline of the thesis

The overall aims of the work presented in this thesis are:

- to evaluate the effect of treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in the treatment of patients with inoperable, metastasised somatostatin receptor positive endocrine gastroenteropancreatic tumours in terms of:

  i. Toxicity
  ii. Effects on tumour size
  iii. Side-effects
  iv. Quality of life

- to investigate the feasibility of peptide receptor radionuclide therapy in patients with non-radioiodine avid differentiated thyroid carcinoma.

In **chapter 2.1** the first results of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate therapy as a novel peptide receptor radionuclide therapy (PRRT) in a small series of patients with inoperable endocrine gastroenteropancreatic (GEP) tumours are presented with emphasis on the feasibility of therapy regarding toxicity and side-effects. Additionally, the first results of therapy outcome in terms of objective tumour responses were reported. Besides the results of therapy outcome in a larger group of patients (n=131), **chapter 2.2** is focused on predictive factors for a favourable tumour response or tumour progression. Furthermore, the first results on the long-term outcome of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate therapy are presented and a comparison with chemotherapy is made. **Chapter 3** is focused on the quality of life in patients with endocrine GEP tumours treated with [^{177}Lu- DOTA^{0},Tyr^{3}]octreotate, whereas **chapter 4** describes long-term changes in hormonal status after therapy. The differential uptake of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate versus [^{177}Lu- DOTA^{0},Tyr^{3}]octreotide is evaluated in **chapter 5.** In **chapter 6.1** the feasibility of therapy with [^{177}Lu- DOTA^{0},Tyr^{3}]octreotate in patients with non-radioiodine-avid differentiated thyroid carcinoma is evaluated. **Chapter 6.2** reviews both the diagnostic and therapeutic use of radiolabelled somatostatin analogues in the management of patients with non-radioiodine-avid differentiated thyroid carcinoma. A summary and general discussion, including recommendations for future research completes this thesis (**chapter 7**).

2

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

2.1

Treatment of patients with gastroenteropancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate

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Abstract

Medical treatment and chemotherapy are seldom successful in achieving objective tumour reduction in patients with metastatic neuroendocrine tumours. Treatment with the radiolabelled somatostatin analogue [^{90}Y-DOTA^{0},Tyr^{3}]octreotide may result in partial remissions in 10–25% of patients. The newer analogue [DOTA^{0},Tyr^{3}]octreotate (octreotate) has a ninefold higher affinity for the somatostatin receptor subtype 2 as compared with [DOTA^{0},Tyr^{3}]octreotide. Also, labelled with the beta- and gamma-emitting radionuclide ^{177}Lu, it has proved very successful in achieving tumour regression in animal models. The effects of ^{177}Lu-octreotate therapy were studied in 35 patients with neuroendocrine gastro-entero-pancreatic (GEP) tumours who underwent follow-up for 3–6 months after receiving their final dose. Patients were treated with doses of 100, 150 or 200 mCi ^{177}Lu-octreotate, to a final cumulative dose of 600– 800 mCi, with treatment intervals of 6–9 weeks. Nausea and vomiting within the first 24 h after administration were present in 30% and 14% of the administrations, respectively. WHO toxicity grade 3 anaemia, leucocytopenia and thrombocytopenia occurred after 0%, 1% and 1% of the administrations, respectively. Serum creatinine and creatinine clearance did not change significantly. The effects of the therapy on tumour size were evaluable in 34 patients. Three months after the final administration, complete remission was found in one patient (3%), partial remission in 12 (35%), stable disease in 14 (41%) and progressive disease in seven (21%), including three patients who died during the treatment period. Tumour response was positively correlated with a high uptake on the OctreoScan, limited hepatic tumour mass and a high Karnofsky Performance Score. Because of the limited efficacy of alternative therapies, many physicians currently adopt an expectant attitude when dealing with patients with metastatic GEP tumours. However, in view of the high success rate of therapy with ^{177}Lu-octreotate and the absence of serious side-effects, we advocate its use in patients with GEP tumours without waiting for tumour progression.

INTRODUCTION

Neuroendocrine gastro-entero-pancreatic (GEP) tumours, which comprise pancreatic islet cell tumours, non-functioning neuroendocrine pancreatic tumours and carcinoids, are usually slow growing. If the tumour is localized, the therapy of choice is surgery. When a metastatic tumour causes a syndrome by hormonal overproduction (i.e. carcinoid syndrome, hypergastrinaemia), treatment with somatostatin analogues results in symptomatic relief in most cases. In terms of objective tumour reduction (complete and partial remission), however, treatment with somatostatin analogues is seldom successful, whether or not it is given in combination with interferon-α [1-3].

A new development in cyto-reductive therapy for GEP tumours is the use of radiolabelled somatostatin analogues. Initial studies with high doses of [^{111}In-DTPA°]octreotide (^{111}In-octreotide; OctreoScan) in patients with metastatic neuroendocrine tumours were encouraging, although partial remissions were exceptional [4, 5]. However, ^{111}In-coupled peptides are not ideal for peptide receptor radionuclide radiotherapy (PRRT) because of the small particle range and therefore short tissue penetration. Therefore, another radiolabelled somatostatin analogue, [^{90}Y-DOTA°,Tyr^3]octreotide, was developed. Using this compound, partial remissions have been reported in 10–25% of patients with neuroendocrine tumours [6-8].

Recently, it was reported that the somatostatin analogue [DOTA°,Tyr^3]octreotate has a ninefold higher affinity for the somatostatin receptor subtype 2 as compared with [DOTA°,Tyr^3]octreotide [9]. Also, labelled with the beta- and gamma-emitting radionuclide ^{177}Lu, this compound was shown to be very successful in achieving tumour regression and animal survival in a rat model [10]. In a comparison in patients, we found that the uptake of radioactivity, expressed as a percentage of the injected dose of [^{177}Lu-DOTA°,Tyr^3]octreotate (^{177}Lu-octreotate), was comparable to that after ^{111}In-octreotide for kidneys, spleen and liver, but was three- to fourfold higher for four of five tumours [11]. We concluded that ^{177}Lu-octreotate potentially represents an important improvement because of (a) the higher absorbed doses that can be delivered to most tumours with about equal doses to potentially dose-limiting organs and (b) the lower tissue penetration range of ^{177}Lu as compared with ^{90}Y, which may be especially important for small tumours.

In this study we present the first data on the side effects as well as the antitumoral effects of ^{177}Lu-octreotate therapy in 35 patients with GEP tumours, who had a follow-up of 3–6 months after receiving their final dose.

MATERIALS AND METHODS

Patients

Thirty-five patients with GEP tumours were studied. All patients had tumour uptake on the OctreoScan preceding the therapy that was at least as high as the uptake in the normal liver tissue. None of the patients had received prior treatment with other radiolabelled somatostatin analogues. Eight patients used Sandostatin s.c.; this medication was discontinued from 1 day before to 1 day after the treatment. Prerequisites for treatment were: Hb ≥6 mmol/l, WBC ≥2×10^{9}/l, platelets ≥80×10^{9}/l, creatinine ≤150 μmol/l and Karnofsky Performance Score ≥50.
All patients gave written informed consent to participate in the study, which was approved by the medical ethical committee of the hospital.

Methods

[DOTA^{0},Tyr^{3}]octreotate was obtained from Mallinckrodt, St Louis, Mo., USA. $^{177}LuCl_3$ was obtained from NRG, Petten, the Netherlands and Missouri University Research Reactor (MURR), Missouri, Mo., USA, and was distributed by IDB, Baarle-Nassau, the Netherlands. ^{177}Lu-octreotate was prepared as described previously [11].

Granisetron 3 mg was injected i.v. and an infusion of amino acids (lysine 2.5%, arginine 2.5% in 1 l 0.9% NaCl; 250 ml/h) was started 30 min before the administration of the radiopharmaceutical and lasted up to 3.5 h afterwards. The radiopharmaceutical was co-administered via a second pump system. The treatment doses of 100 mCi were injected in 20 min and those of 150 and 200 mCi were injected in 30 min. The interval between treatments was 6–9 weeks. Patients were treated up to a cumulative dose of 750–800 mCi (27.8–29.6 GBq) (corresponding to a radiation dose to the bone marrow of 2 Gy) [11], unless dosimetric calculations indicated that the radiation dose to the kidneys would then exceed 23 Gy; in these cases the cumulative dose was reduced to 600–700 mCi.

Routine haematology, liver and kidney function tests, hormone measurements and serum tumour markers were measured 1 week prior to each therapy, as well as at follow-up visits. EORTC quality of life forms (QLQ-C30) [12] were filled out by the patients at each visit.

CT or MRI scanning was done within 3 months before the first therapy, and 6–8 weeks, 3 months and 6 months after the last treatment.

In vivo measurements

The tumours on the CT or MRI scans were measured and scored according to the WHO solid tumour response criteria. The uptake on the pretreatment OctreoScans was scored visually on planar images on a 4-point scale: grade 1, lower than normal liver tissue uptake; grade 2, equal to normal liver tissue uptake; grade 3, greater than normal liver tissue uptake; grade 4, higher than normal spleen/kidney uptake.

Statistics

Analysis of variance (ANOVA), paired *t* tests and chi-square tests were used. *P* values <0.05 were considered significant.

RESULTS

The study population comprised 14 men and 21 women with a mean age of 54 years (range 19–78 years). Twelve had carcinoid tumour, 12 neuroendocrine pancreatic tumour, 8 neuroendocrine tumour of unknown origin and 3 gastrinoma.

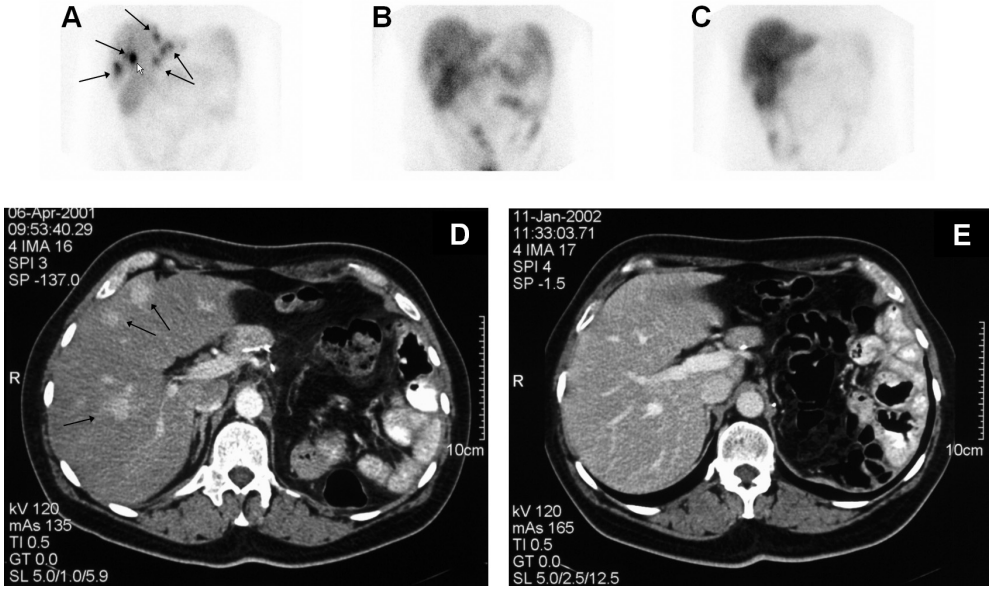

Figure 1A–C. Planar scans of the abdomen, 3 days after the injection of 200 mCi ^{177}Lu-octreotate in a patient with liver metastases of an operated neuroendocrine pancreatic tumour. **A** After the first treatment; **B** after the second treatment; **C** after the fourth treatment. Note the loss of intensity of uptake in the liver lesions (*arrows* in **A**). This sign virtually always indicates a tumour volume response. **D, E** CT scans of the same patient: before treatment (**D**) and 3 months after the last treatment (**E**). Tumour (*arrows* in **D**) is not demonstrated on **E**. Neither MRI nor OctreoScan could demonstrate definite tumour deposits at that time.

Twelve patients had been operated in the past, 1 had had radiotherapy, 3 had had chemotherapy and 14 had been treated with octreotide (Sandostatin).

Sixteen of the 35 (46%) patients had documented progressive disease within 1 year before the start of the therapy. Cycle doses were 100 mCi in seven patients,150 mCi in 14 and 200 mCi in the remaining 14. Higher dosages were not administered, since 200 mCi $^{177}LuCl_3$ is typically bound to 180–300 µg [DOTA^0,Tyr^3]octreotate, and higher doses would result in a lower percentage tumour uptake owing to receptor saturation. In 30 patients, the final intended cumulative dose of 600-800 mCi was administered. Three of the five remaining patients had progressive disease and died before completing their treatment; the other two patients, who were both elderly, stopped their treatment after reaching a cumulative dose of 600 mCi because of the burden they felt the treatment to be.

Table 1. Tumour responses in 34 patients, 3 months after the final administration of ^{177}Lu-octreotate. Three patients with PD died before reaching their final dose.

	RESPONSE				Total
Tumour type	CR	PR	SD	PD	
Carcinoid		4 (33%)	6 (50%)	2 (17%)	12
NE Pancreas	1 (8%)	1 (8%)	7 (58%)	3 (25%)	12
NE unknown origin		4 (57%)	1 (14%)	2 (29%)	7
Gastrinoma		3 (100%)			3
Total	1 (3%)	12 (35%)	14 (41%)	7 (21%)	34

WHO toxicity grade 2 or 3 anaemia (Hb 4.95–6.2 or 4.0–4.9 mmol/l, respectively), leucocytopenia (WBC 2.0–2.9 or 1.0–1.9×10^9/l, respectively) and thrombocytopenia (platelets 50–74.9 or 25.0–49.9×10^9/l, respectively) occurred after 8% and 0%, 5% and 1%, and 3% and 1% of the administrations, respectively. Toxicity grade 2 or 3 leucocytopenia or thrombocytopenia occurred in two out of three (67%) patients who had had previous chemotherapy, as against seven out of 32 (22%) patients who had not. Mean haematological parameters rose again during the follow-up after the final administration. Serum creatinine, creatinine clearance and serum HbA1c did not change significantly (data not shown). In patients without thyroid hormone medication, serum TSH and fT4 levels did not change. In women, serum LH and FSH concentrations did not change significantly; in men, serum testosterone decreased and serum LH concentrations increased significantly. Also inhibin-B concentrations decreased and serum FSH levels increased significantly.

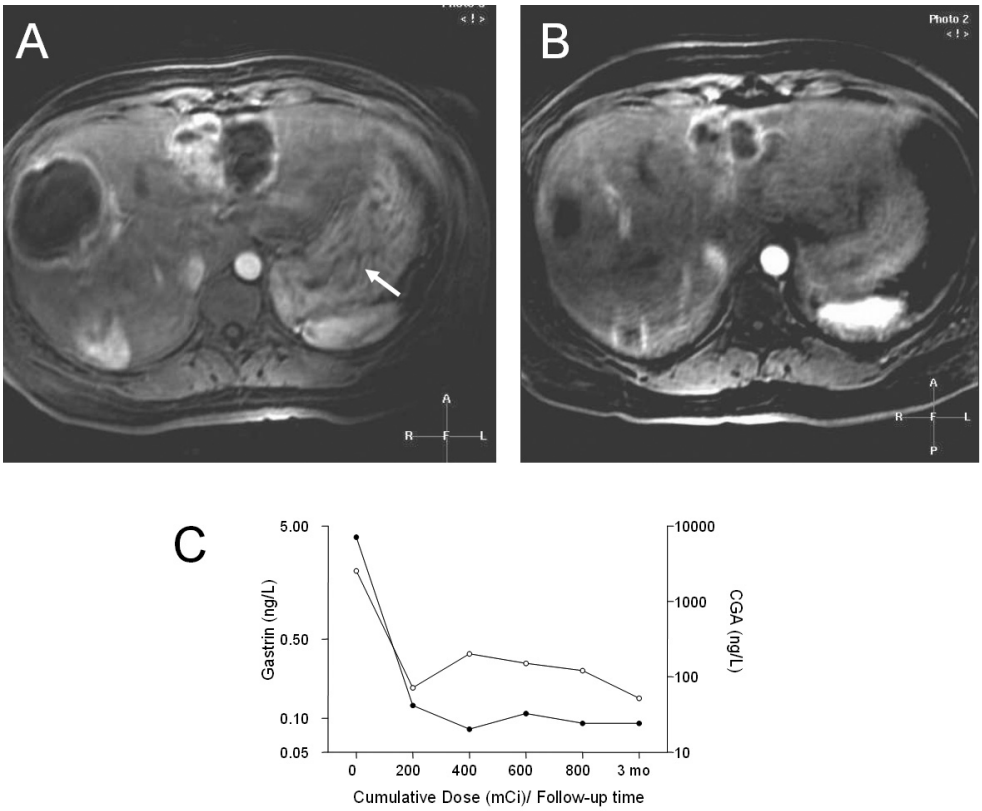

Figure 2. A, B MRI scans in a woman with hepatic metastases of a gastrinoma. Before treatment (**A**) she was inoperable because of the size and localization of the metastases. Three months after completion of her treatment with 800 mCi ^{177}Lu-octreotate she had a PR (**B**). Note also that the hypertrophy of the gastric wall (*arrow* in A) had diminished. Concomitantly, serum concentrations of gastrin (*closed dots*) and chromogranin-A (*open dots*) had decreased markedly (**C**). At 6 months the MRI showed no further regression. The patient underwent left partial hepatectomy and the two right-sided lesions were drained and injected with alcohol. MRI 3 months after surgery showed further regression of the right-sided lesions.

The effects of the therapy on tumour size were evaluable in 34 patients. Three months after the final administration (on average 9 months from the start of the treatment), a complete remission (CR), evaluated with CT scanning, MRI and somatostatin receptor imaging, was found in one patient (3%), partial remission (PR) in 12 (35%), stable disease (SD) in 14 (41%) and progressive disease (PD) in 7 (21%), including the three patients who died during the treatment period (Table 1) (Figs. 1, 2). Follow-up evaluation 6 months after the final therapy was available for 19 of the 34 patients. All seven patients who had PR after 3 months still had PR after 6 months; in 10 of the 12 patients with SD, the evaluation was unchanged, whereas one had a minimal response (MR) and one had PD.

Tumour response (CR or PR) was significantly more frequent in patients whose tumours had a high uptake on the OctreoScan [6/7 (86%) with grade 4 uptake vs. 7/27 (26%) with grade 2 or 3 uptake; chi-square test: $P<0.05$]. Five out of the seven patients (71%) with PD had hepatomegaly and diffuse liver metastases vs 6 out of 27 (22%) with CR, PR or SD (chi-square test: $P<0.05$). Tumour response was more frequent in patients with documented PD within 1 year before the start of the treatment (8/15; 53%) than in those without (5/19; 26%), although this difference was not statistically significant ($P=0.11$; chi-square test). Of the 15 patients with documented PD before the start of the treatment, 3 (20%) had SD at follow-up. Patients who had a Karnofsky Performance Score of less than 80 before the treatment more frequently had PD (5/8; 63%) than those who had higher scores (2/26; 8%) ($P<0.01$; chi-square test).

The serum tumour marker chromogranin-A was elevated in 29 patients. During the treatment and follow-up, there was a clear decrease in serum chromogranin-A concentrations in patients with PR or CR, whereas these concentrations were virtually unchanged in patients with SD, and initially showed an increase in patients with PD (Fig. 3).

The patient-assessed quality of life, according to the EORTC-QLQ30 questionnaire, was evaluated in 25 patients. Ten patients were excluded because of progressive disease/death ($n=5$) or missing forms during the follow-up period ($n=5$, foreign patients). Scores before the start of the treatment, after receiving 400–600 mCi ^{177}Lu-octreotate and at follow-up 3 months after the final treatment were evaluated. There were no significant differences for functional scales or single symptom scales. The global health scale, on which patients were asked to assign marks regarding both their general health and their quality of life, and which ranged from 0 to 100, was judged as higher than 70 by nine patients (36%) before the start of the treatment, by 17 (68%) patients during the treatment and by 16 (64%) patients after the treatment ($P<0.05$; chi-square test).

DISCUSSION

There are few treatment options for metastatic GEP tumours. The use of radiolabelled somatostatin analogues for tumour regression is a promising new development. With [^{90}Y-DOTA°,Tyr^3]octreotide, PR (or CR) has been reported in 10–25% of patients with neuroendocrine tumours [6-8]. In the present study we found objective tumour shrinkage in 38% of the patients, but PD before the start of the treatment was documented in only 46% of the patients. This last fact is important, because documented PD was present in more than 80% of patients in two of the reported series treated with [^{90}Y-DOTA°, Tyr^3]octreotide [6, 8]. As with chemotherapy, an objective tumour response after PRRT is more likely in patients with (fast) growing

tumours. Indeed, in our series we also found a trend towards a more favourable treatment outcome in patients with documented PD before the start of the treatment. It may therefore be concluded that the percentage of patients with significant tumour shrinkage in our study might have been even higher had the percentage of patients with PD prior to treatment been comparable to that in studies with [^{90}Y-DOTA^{0}, Tyr^{3}]octreotide. The side-effects of treatment with ^{177}Lu-octreotate are few and mostly transient, with mild bone marrow depression as the most common finding. Neither renal nor pituitary function deteriorated in any of our patients. Other side-effects can be ascribed to the radiation dose to the testes in men. This dose leads to significantly lower serum testosterone and inhibin-B levels which in turn give rise to higher serum LH and FSH concentrations, thereby substantiating that the pituitary function is unimpaired.

The patient-assessed global health score improved in 30% of patients during the treatment and the follow-up period. This is an important finding which reflects the improvement in patient well-being and stresses the scarcity of side-effects as perceived by patients. The fact that other scores mainly addressing symptoms did not change significantly is likely due to the diversity of symptoms between patients, the use of Sandostatin by symptomatic patients and the small size of the patient group.

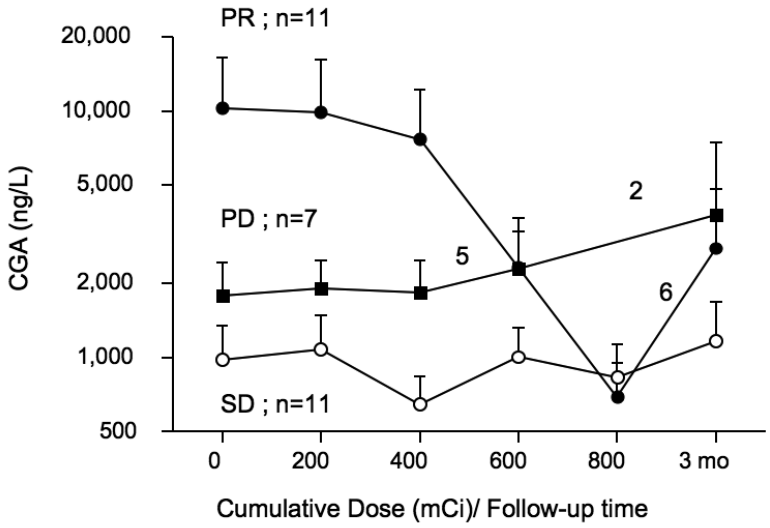

Figure 3. Serum chromogranin-A concentrations during and after therapy in patients with PR, SD or PD. The reduction in the number of patients during the course of the follow-up was due to death or missing values. Note the logarithmic y-axis.

Many physicians adopt an expectant attitude when dealing with patients with metastatic GEP tumours owing to the low success rates of chemotherapy protocols. However, given that treatment with ^{177}Lu-octreotate resulted in PR (or CR) in 38% of our patients, this attitude may be questioned. Although there was a (statistically non-significant) tendency towards more frequent tumour regression in patients who had documented PD before the start of the treatment, those of our patients who had an objective tumour response more frequently had a limited tumour load. This implies that waiting for tumour progression might place patients in a worse position, as PD during or after treatment was more frequent in patients with an extensive tumour load, especially in the liver. We therefore advocate treatment with ^{177}Lu-octreotate at an earlier stage of metastatic disease, when even CR may be possible. Another argument in favour of early treatment is that neuroendocrine tumours can dedifferentiate in the course of the disease, and lose their somatostatin receptors, making treatment with radiolabelled somatostatin analogues impossible. If serious side-effects of treatment with ^{177}Lu-octreotate remain absent during longer patient follow-up, such treatment could also be considered in an adjuvant setting in patients with neuroendocrine tumours who are operated on with curative intent.

Lastly, as it has been shown in animal experiments that ^{90}Y-labelled somatostatin analogues are more effective for larger tumours and ^{177}Lu-labelled somatostatin analogues are more effective for smaller tumours [13, 14], combination therapy with ^{90}Y-labelled and ^{177}Lu-labelled octreotate may be tried in the near future. Such therapy might yield even better results than treatment with either of the radionuclides alone [15].

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2.2

Radiolabeled somatostatin analog [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in patients with endocrine gastroenteropancreatic tumors

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Abstract

Purpose

There are few treatment options for patients with metastasized or inoperable endocrine gastroenteropancreatic (GEP) tumors. Chemotherapy can be effective, but the response is usually less than 1 year. Here, we present the results of treatment with a radiolabeled somatostatin analog, [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate).

Patients and methods

One hundred thirty-one patients with somatostatin receptor-positive tumors were treated with up to a cumulative dose of 600 to 800 mCi (22.2 to 29.6 GBq) of ^{177}Lu-octreotate.

Results

One patient developed renal insufficiency, and another patient developed hepatorenal syndrome. Creatinine clearance did not change significantly in the other patients. WHO hematologic toxicity grade 3 or 4 occurred after less than 2% of the administrations. We observed complete remission in three patients (2%), partial remission in 32 patients (26%), minor response (tumor diameter decrease of 25% to 50%) in 24 patients (19%), stable disease (SD) in 44 patients (35%), and progressive disease (PD) in 22 patients (18%). Higher remission rates were positively correlated with high uptake on pretherapy somatostatin receptor imaging and a limited number of liver metastases, whereas PD was significantly more frequent in patients with a low performance score and extensive disease. Median time to progression in 103 patients who either had SD or tumor regression was more than 36 months.

Conclusion

Treatment with ^{177}Lu-octreotate results in tumor remission in a high percentage of patients with GEP tumors. Serious side effects are rare. The median time to progression compares favorably with chemotherapy. Results are better in patients with a limited tumor load. Therefore, early treatment, even in patients who have no PD, may be better.

INTRODUCTION

Endocrine gastroenteropancreatic (GEP) tumors, which comprise pancreatic islet-cell tumors, 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. However, treatment with somatostatin analogs is seldom successful in terms of tumor size reduction [1-3].

A new treatment modality for 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 using the radiolabeled somatostatin analog [^{111}In-DTPA^{0}]octreotide (OctreoScan; Mallinckrodt, St Louis, MO). Therefore, a logical sequence to this tumor visualization in patients was to also try to treat these patients with radiolabeled somatostatin analogs. Initial studies with high dosages of [^{111}In-DTPA^{0}]octreotide in patients with metastasized neuroendocrine tumors were encouraging, although partial remissions (PRs) were exceptional [4,5]. This is not surprising because ^{111}In-coupled peptides are not ideal for peptide receptor radionuclide radiotherapy (PRRT) because of the small particle range and, therefore, short tissue penetration of the Auger electrons.

Another radiolabeled somatostatin analog that is used for PRRT is [^{90}Y-DOTA^{0},Tyr^{3}]octreotide. Several phase I and II PRRT trials have been performed using this compound. Complete remissions (CRs) and PRs have been reported in 7% to 33% of patients with neuroendocrine tumors [6-11].

The somatostatin analog [DOTA^{0},Tyr^{3}]octreotate has a nine-fold higher affinity for the somatostatin receptor subtype 2 compared with [DOTA^{0},Tyr^{3}]octreotide in vitro[12]. Also, labeled with the beta- and gamma-emitting radionuclide ^{177}Lu, this compound was shown to be successful in terms of tumor regression and animal survival in a rat model [13]. In a comparison in patients, we found that the uptake of radioactivity, expressed as percentage of the injected dose of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate), was comparable to that after [^{111}In-DTPA^{0}]octreotide for kidneys, spleen, and liver but was three- to four-fold higher for four of five tumors [14]. In a preliminary report on the results of this treatment in the first 35 patients with endocrine GEP tumors [15], we found CRs and PRs in 38% of the patients. No serious side effects were observed. Here, we present the results of treatment with ^{177}Lu-octreotate in a large series of patients with endocrine GEP tumors. Also, we analyzed whether certain patient or tumor-related factors predict a favorable treatment response or predict the duration of such a response.

PATIENTS AND METHODS

Patients

One hundred thirty-one patients with endocrine GEP tumors were studied. All patients had tumor tissue uptake during [^{111}In-DTPA^{0}]octreotide scintigraphy preceding the therapy that was at least as high as the uptake in the normal liver tissue. None of the patients had received prior treatment with other radiolabeled somatostatin analogs. Four patients had previously been treated with embolization, and one patient was treated with chemoembolization for liver metastases. Prerequisites for treatment were hemoglobin (Hb) ≥ 6 mmol/L, WBC ≥ 2 x 10^9/L, platelets ≥ 80 x 10^9/L, creatinine ≤ 150 μmol/L or creatinine clearance ≥ 40 mL/min, and Karnofsky performance score (KPS) ≥ 50. The preliminary results in 35 patients were also reported previously elsewhere [15]. All patients gave written informed consent to participate in the study, which was approved by the medical ethical committee of the hospital.

Methods

[DOTA^{0},Tyr^{3}]octreotate was obtained from Mallinckrodt (St Louis, MO). $^{177}LuCl_3$ was obtained from NRG (Petten, the Netherlands) and Missouri University Research Reactor (Columbia, MO) and was distributed by IDB (Baarle-Nassau, the Netherlands). ^{177}Lu-octreotate was locally prepared as described previously [14].

Granisetron 3 mg was injected intravenously, and an infusion of amino acids (lysine 2.5% and arginine 2.5% in 1 L 0.9% NaCl; 250 mL/h) was started 30 minutes before the administration of the radiopharmaceutical and lasted 4 hours. Via a second pump system, the radiopharmaceutical was coadministered. Cycle dosages were 100 mCi (3.7 GBq) in seven patients, 150 mCi (5.6 GBq) in 16 patients, and 200 mCi (7.4 GBq) in the remaining 108 patients. The treatment doses of 100 mCi were injected in 20 minutes, and the doses of 150 and 200 mCi were injected in 30 minutes. The interval between treatments was 6 to 10 weeks. Patients were treated up to a cumulative dose of 750 to 800 mCi (27.8 to 29.6 GBq; corresponding with a radiation dose to the bone marrow of 2 Gy) [14], unless dosimetric calculations indicated that the radiation dose to the kidneys would then exceed 23 Gy; in these cases, the cumulative dose was reduced to 600 to 700 mCi.

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

In Vivo Measurements

The tumors on CT or magnetic resonance imaging were measured and scored according to the Southwest Oncology Group solid tumor response criteria [16]. The uptake during pretreatment [^{111}In-DTPA^{0}]octreotide scintigraphy was scored visually on planar images using the following 4-point scale: lower than (grade 1), equal to (grade 2), or greater than (grade 3) normal liver tissue; or higher than normal spleen or kidney uptake (grade 4).

Statistics

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

RESULTS

One hundred thirty-one patients with metastasized or inoperable endocrine GEP tumors were treated between January 2000 and September 2003. Two patients were lost to follow-up; in all of the other 129 patients, follow-up data for at least 3 months after the last therapy were available. There were 66 women and 65 men; the mean age was 56 years (range, 19 to 83 years). Eight patients had gastrinoma, two had insulinoma, 33 had nonfunctioning endocrine pancreatic tumors, 18 had endocrine tumors of unknown origin, and 70 had carcinoid tumors (one thymic, one gastric, four bronchial, and 64 small bowel carcinoids). In 18 patients, the liver was the only known site of tumor spread; in two patients, this was the skeleton; and in 11 other patients, sites such as lymph nodes or pancreas were the sole known tumor sites. In the remaining 100 patients, combinations of these tumor sites were present (Figure 1).

Sixty-three patients had previously been operated on, seven had had external-beam radiation, 20 had been treated with chemotherapy, and 66 had used somatostatin analogs (usually Sandostatin; Novartis, Basel, Switzerland). Fifty-two patients used somatostatin analogs in between treatments. In all but three patients, short-acting somatostatin analogs were stopped at least 1 day before the treatment, and long-acting somatostatin analogs were stopped at least 6 weeks before the treatment. In three patients with severe symptoms of carcinoid syndrome, the administration of somatostatin analogs was not stopped; in these three patients, a pretreatment OctreoScan during continued somatostatin analog treatment had shown sufficient uptake of the radiolabeled analog in the tumor sites. Fifty-five (42%) of the 131 patients had documented progressive disease (PD) within 1 year before the start of the therapy, 37 patients (28%) had stable disease (SD), and in 39 patients (30%), information on disease progression was absent.

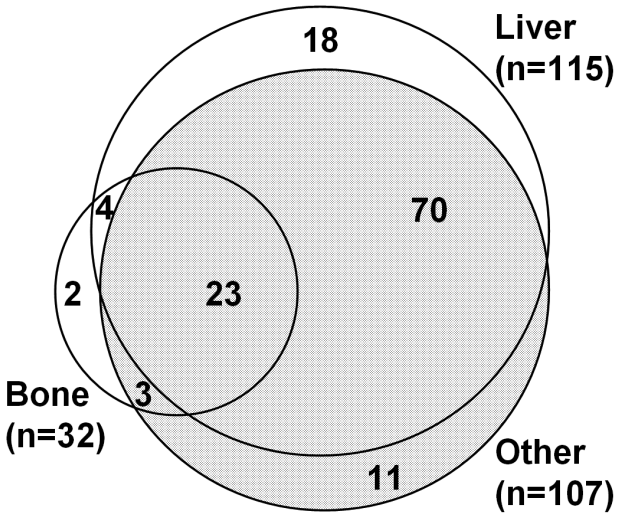

Figure 1. The distribution of known tumor sites in 131 patients. Venn diagram is shown in which circle diameters are proportional to total numbers of patients with certain localizations. Overlapping areas represent patients with lesions in both categories.

Treatment intervals were 6 to 10 weeks, except in four patients who had persistent thrombocytopenia and in 13 other patients because of reasons unrelated to the treatment. In 116 patients, the final intended cumulative dose of 600 to 800 mCi was administered. Ten of the 15 remaining patients died of PD before completing their treatment; two elderly patients stopped treatment after having received 600 mCi because they felt the treatment was too tiring; one patient stopped early because of developing kidney failure; one patient stopped early because a colorectal carcinoma was diagnosed; and one patient stopped early because of social reasons.

Nausea and vomiting (WHO toxicity grade 1 to 2) within the first 24 hours after the administration were present in 31% and 14% of the administrations, respectively. Mild abdominal pain was noticed by 12% of the patients, especially those with liver enlargement. Increased hair loss (WHO toxicity grade 1) was noticed by 64% of the patients; hair regrowth occurred within 3 months after the last administration.

Serious side effects occurred in two patients. One patient in whom, in the year preceding the therapy, serum creatinine concentrations had risen from 60 to 70 µmol/L to 90 to 100 µmol/L and who had a urinary creatinine clearance of 41 mL/min when entering the study eventually developed renal insufficiency 1.5 years after receiving her last treatment (cumulative dose, 600 mCi). A kidney biopsy demonstrated tubular depositions and microangiopathy. Eventually, the patient refrained from hemodialysis and died shortly thereafter. In another patient who

had diffuse liver metastases from an endocrine pancreatic tumor that had grown rapidly in the months preceding the therapy, an increase in upper abdominal pain and a deterioration of liver functions occurred in the days and weeks after the first administration. The patient developed hepatorenal syndrome and died after 5 weeks.

WHO toxicity grade 3 or 4 anemia (Hb, 4.0 to 4.9 or < 4.0 mmol/L, respectively), leukocytopenia (WBC, 1.0 to 1.9 or <1.0 x 10^9/L, respectively), and thrombocytopenia (platelets, 25.0 to 49.9 or < 25 x 10^9/L, respectively) occurred after 0.4% and 0.0%, 1.3% and 0.0%, and 1.5% and 0.2% of the administrations, respectively. Patients who had been treated with chemotherapy had significantly more frequent thrombocytopenia toxicity grade 2, whereas patients older than 70 years had a significantly higher frequency of WHO toxicity grade 2 leukocytopenia, especially neutropenia (Fisher's exact test, $P < .01$). Mean Hb, leukocytes, and platelets decreased significantly during treatment but were not significantly different from pretreatment values 18 to 24 months after the last therapy (Figure 2).

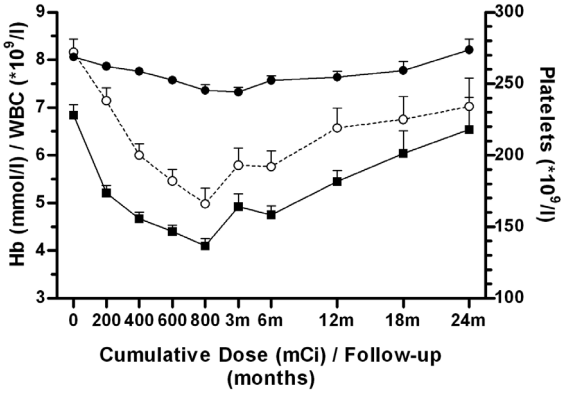

Figure 2. Mean (± SEM) serum hemoglobin (Hb; closed circles, solid line), WBC (closed squares, solid line), and platelets (open circles, dotted line) during and after therapy with [^{177}Lu-DOTA^0,Tyr^3]octreotate.

Serum creatinine, creatinine clearance, and serum HbA1c did not change significantly. Excluding five patients who were hypothyroid before the treatment and in whom, subsequently, replacement therapy was started and also excluding another six patients who already used thyroid medication, serum thyrotropin levels did not change significantly during or after treatment, whereas free thyroxine concentrations were significantly lower (mean, 18.3 pmol/L before therapy; and 15.5 to 17.5 pmol/L 3 to 24 months after therapy).

In women, serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and inhibin-B concentrations did not change significantly. In men, serum testosterone concentrations decreased significantly in the follow-up period (from a mean of 14.4 nmol/L before treatment to 10.4 nmol/L 24 months after the last treatment; $P < .01$, analysis of variance, Bonferroni tests), whereas serum LH concentrations did not change significantly. Serum inhibin-B concentrations decreased significantly (from a mean of 179 ng/L before treatment to a nadir of 23 ng/L 3 months after the last treatment) accompanied by a rise in serum FSH concentrations, but both returned to values not significantly different from pretreatment levels 18 to 24 months after the last treatment (Figure 3).

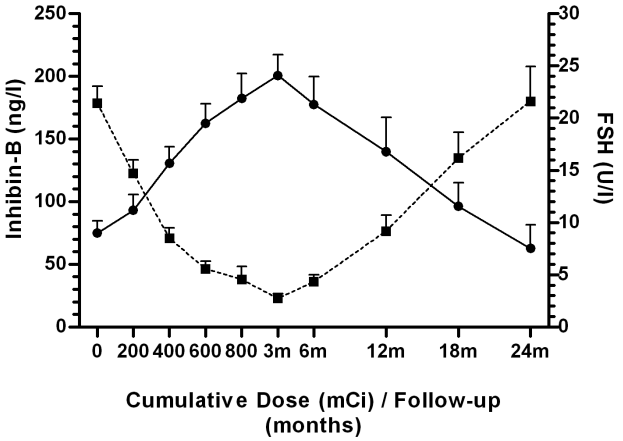

Figure 3. Mean (± SEM) serum inhibin-B (squares, dotted line) and follicle-stimulating hormone (FSH; circles, solid line) concentrations in men during and after therapy with [^{177}Lu-DOTA°,Tyr^3]octreotate.

Tumor size could be evaluated in 125 patients (two patients were lost to follow-up, and in four patients, no measurable disease was documented). A CR was found in three patients (2%), PR was found in 32 patients (26%), minor response (MR) was found in 24 patients (19%), SD was found in 44 patients (35%), and PD was found in 22 patients (18%), including the 10 patients who died before the intended cumulative dose was reached (Table 1; Figure 4).

Higher remission rates were positively correlated with high uptake during pretherapy [^{111}In-DTPA°]octreotide scintigraphy and a limited number of liver metastases, whereas PD was significantly more frequent in patients with a low KPS and extensive disease (logistic regression, Table 2, Figures 5 and 6). A high tumor uptake during [^{111}In-DTPA°]octreotide scintigraphy and gastrinoma tumor type were significantly correlated; also, a low KPS and weight loss and extensive liver involvement were also significantly correlated (Pearson's correlation test, $P < .05$).

Table 1. Tumor responses in 125 patients 3 months after the last administration of ^{177}Lu-octreotate

Tumor Type	CR		PR		MR		SD		PD		Total patients (No.)
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. Of patients	%	
Carcinoid	-	-	13	20	13	20	28	42	12	18	66
NE pancreas	3	9	7	22	7	22	11	34	4	13	32
NE unknown origin	-	-	6	35	2	12	4	24	5	29	17
Gastrinoma	-	-	5	63	2	25	1	12	-	-	8
Insulinoma	-	-	1	50	-	-	-	-	1	50	2
Total	3	2	32	26	24	19	44	35	22	18	125

NOTE. Ten patients with PD died before reaching their final dose.
Abbreviations: CR, complete remission; PR, partial remission; MR, minor response; SD, stable disease; PD, progressive disease; NE, neuroendocrine; ^{177}Lu-octreotate, [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate.

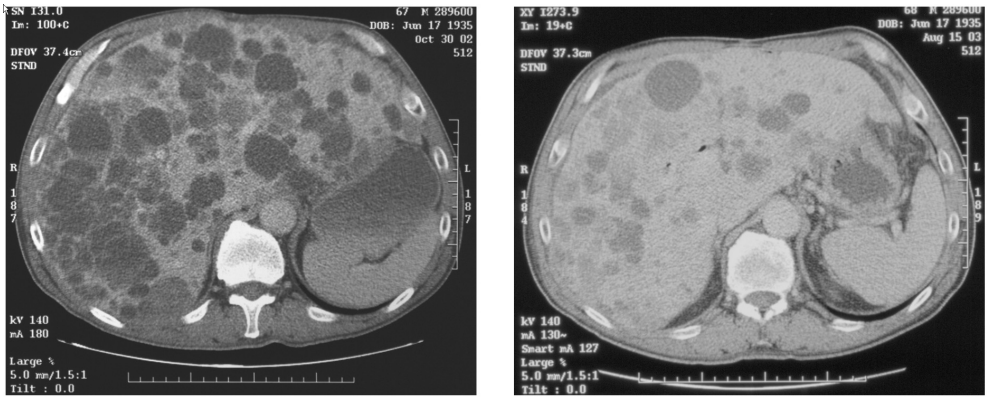

Figure 4. Computed tomography scans in a patient with a metastasized nonfunctioning endocrine pancreatic tumor before treatment (left) and 3 months after the last treatment (right). Notice the decrease in number of cystic liver lesions and the decrease in total liver size. The patient had a minor response.

On the posttherapy scans after the third or fourth treatment, if compared with the scan after the first treatment, a reduced tumor uptake was frequently seen in patients who eventually experienced a tumor regression (Figures 7 and 8).

Table 2. Results of the analysis of factors that may predict the chances of tumor regression or progression, tested with χ^2 tests and logistic regression for multivariate analysis

Factor	No. Patients	Remission				PD			
		No.	%	*P* (χ^2)	*P* (logistic)	No.	%	*P* (χ^2)	*P* (logistic)
[^{111}In-DTPA°]octreotide scintigraphy uptake									
≈ Liver	4	1	25	.008	.002	0	0	NS	NS
> Liver	97	40	41			21	22		
>> Liver	24	18	75			1	4		
Tumor type									
Gastrinoma	8	7	88	.018	NS	0	0	NS	NS
Other	117	52	44			22	19		
Tumor mass									
Limited	21	14	67	NS	NS	0	0	.045	.028
Moderate	78	35	45			15	19		
Extensive	26	10	38			7	27		
Liver metastases									
None/moderate	91	48	53	.042	.017	11	12	.008	NS
Extensive	34	11	32			11	32		
Bone metastases									
Absent	94	48	51	NS	NS	15	16	NS	NS
Present	31	11	36			7	23		
Weight loss									
Absent	103	50	49	NS	NS	12	12	.000	NS
Present	22	9	41			10	46		
KPS									
>70	104	53	51	NS	NS	10	10	.000	.000
≤70	21	6	29			12	57		
Progressive at baseline									
No	34	16	47	NS	NS	4	12	NS	NS
Yes	53	26	49			13	25		

NOTE: Remission includes CR, PR, and MR. All tumor characteristics listed in the first column pertain to baseline observations. Tumor mass was judged on [^{111}In-DTPA°]octreotide scintigrams, and liver involvement was judged on CT/MRI. Weight loss was scored positive if it at least amounted to 1 kg per month, existing for at least 3 months.

Abbreviations: PD, progressive disease; ≈, Liver, approximately equal to liver uptake; > Liver, more than liver uptake; >> Liver, very high uptake; KPS, Karnofsky performance score; NS, not significant; CR, complete remission; PR, partial remission; MR, minor response; CT, computed tomography; MRI, magnetic resonance imaging.

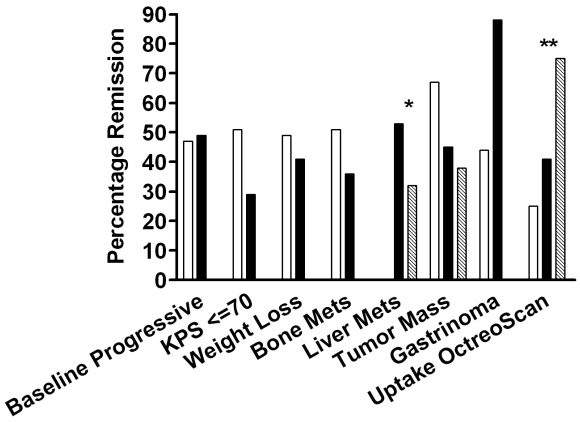

Figure 5. Analysis of factors that may predict tumor remission (minor response, partial remission, or complete remission). (*) $P < .05$; (**) $P < .01$, logistic regression. KPS, Karnofsky performance score.

Median follow-up time in the 103 patients who had either SD or tumor regression was 16 months (range, 7 to 44 months). Median time to progression was more than 36 months; in the eight patients who had gastrinoma, median time to progression was 20 months ($P < .01$, log-rank test; Fig 9). Also, in patients with extensive liver involvement, the median time to progression was significantly shorter at 26 months ($P < .05$, log-rank test). Neither initial tumor response nor any other of the factors listed in Table 2 were significant in predicting the time to progression when tested separately.

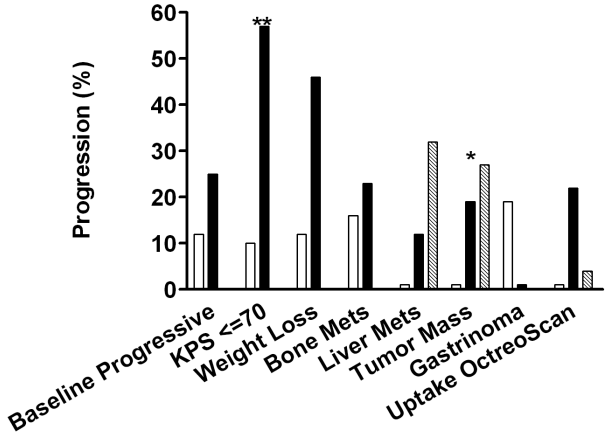

Figure 6. Analysis of factors that may predict tumor progression (progressive disease). (*) $P < .05$; (**) $P < .01$, logistic regression. KPS, Karnofsky performance score.

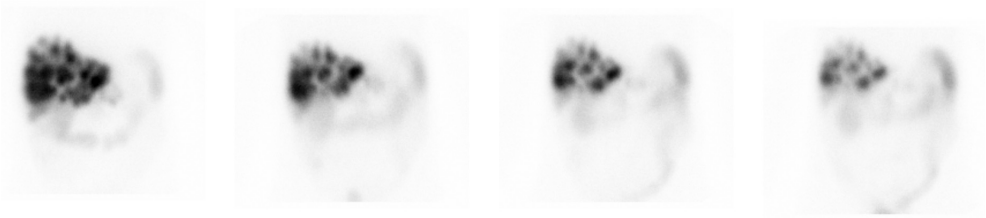

Figure 7. Posttherapy scans after 200 mCi of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (first to last therapy, left to right) in a patient with gastrinoma who eventually had partial remission. Notice the decreasing uptake in the liver metastases.

In a multivariate model, however, gastrinoma tumor type and the presence of bone metastases were the factors that indicated a significantly shorter time to progression (Cox regression, $P < .004$ and $P < .037$, respectively).

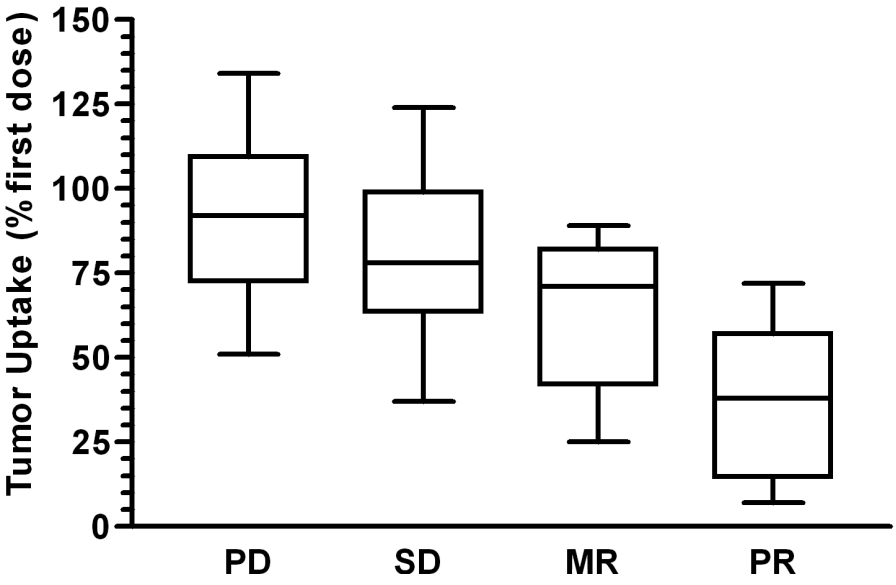

Figure 8. The uptake in tumor sites after the last (third or fourth) therapy, expressed as percentage of the uptake after the first treatment, according to treatment outcome (x-axis). Boxes show medians and 25th to 75th percentiles; whiskers indicate ranges. PD, progressive disease; SD, stable disease; MR, minor response; PR, partial response.

DISCUSSION

In this study in a large number of patients with endocrine GEP tumors who were treated with ^{177}Lu-octreotate, we found a favorable effect on tumor size (MR, PR, or CR) in 47% of patients. Serious side effects that were potentially treatment related were found in only two patients. Renal insufficiency occurred in one of our patients.

It has also been reported in patients who were treated with [^{90}Y-DOTA^{0}, Tyr^{3}]octreotide, especially if no amino acids were coadministered to reduce the kidney radiation dose [7,10,17]. Therefore, our protocol, which used amino acid coinfusion and limited the estimated cumulative dose to the kidneys to 23 Gy or less, seems adequate in reducing the chances of therapy-related kidney failure. One patient who had extensive and diffuse liver metastases developed lethal hepatic failure. This grave complication, which was probably a result of a much higher radiation dose to the relatively limited number of viable hepatocytes than in patients with a limited tumor burden in the liver, has also been reported in three patients who were treated with [^{111}In-DTPA^{0}]octreotide [5] and one patient who was treated with [^{90}Y-DOTA^{0}, Tyr^{3}]octreotide [10], all of whom also had extensive liver disease. Therefore, in such patients, extra caution, in terms of additional testing for liver-synthesizing capacity and, if necessary, lowering the cycle dose, seems well advised.

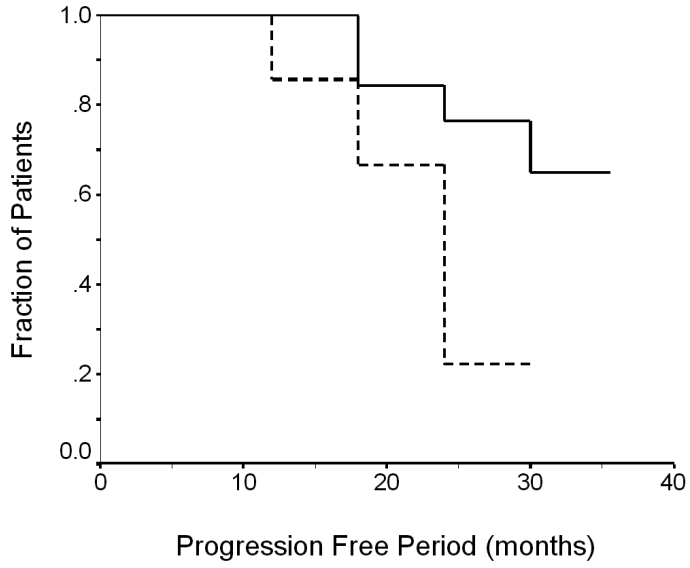

Figure 9. Progression-free period in patients with gastrinoma (dotted line) and patients with other tumors (solid line). The time to progression was significantly shorter in the eight patients with gastrinomas.

In previous studies with ^{111}In- and ^{90}Y-labeled somatostatin analogs, myelodysplastic syndrome and leukemia have been reported as infrequent side effects, especially in patients treated with high cumulative doses [4,10]. In the present study, none of the patients had this grave complication, and this is probably because of the fact that we limited our maximum cumulative dose to a relatively safe upper value, which corresponds to a bone marrow radiation absorbed dose of 2 Gy.

Transient and relatively mild bone marrow suppression was found in a minority of patients and in a lower percentage than reported in most studies with ^{111}In- and ^{90}Y-labeled somatostatin analogs [4,5,9,10,17]. Transient hair loss, but no turning bold, was present in two thirds of the patients; this is probably a result of the fact that ^{177}Lu-octreotate has a slower urinary excretion rate than [^{111}In-DTPA^{0}]octreotide [14], thus causing a longer retention of radioactivity in the whole body. To date, there are no reports on the presence of somatostatin receptors in, for instance, hair follicles.

The pituitary gland possesses somatostatin receptors. Therefore, theoretically, treatment with ^{177}Lu-octreotate could impair pituitary function. In our patients, we saw no decrease in serum gonadotroph or thyrotroph hormone concentrations, so obviously the absorbed radiation dose to the pituitary was low. In men, a transient significant decrease in serum inhibin-B concentrations and a concomitant increase in serum FSH levels were found during and after therapy. This radiation effect on the testicular Sertoli cells has also been described after therapy with ^{131}I in patients with thyroid cancer [18]. Longer lasting, significant decreases of testosterone in men and of free thyroxine in the whole patient group were also found. These were not accompanied by significant increases in serum LH or TSH concentrations, and therefore, although statistically significant, the decreases were clinically not significantly relevant. It can also be hypothesized that these minor decreases in testosterone and thyroid hormone concentrations were caused by chronic illness as well.

We found antitumor effects (CR, PR, or MR) in 47% of our patients. The reasons to categorize tumor size reductions of 25% to 50% as MRs and to regard these as favorable therapeutic effects are that endocrine GEP tumors usually grow slowly and also because many of these tumors are cystic, which makes it unlikely that their response to therapy is comparable to that of fast-growing solid tumors. CR and PR occurred in 28% of the patients. With [^{90}Y-DOTA^{0},Tyr^{3}]octreotide, remission rates of 7% to 33% in GEP tumor patients have been reported [6,7,9-11]. The differences in remission rates may, in part, be a result of differences in study design and dosages used, but the differences may also be a result of patient selection. In our patients, we found that a high uptake during [^{111}In-DTPA^{0}]octreotide scintigraphy and limited liver involvement were predictive factors for a favorable tumor response, whereas a low

KPS and, to a lesser extent, a high tumor load were significant factors in predicting tumor progression. In the studies using [^{90}Y-DOTA^{0},Tyr^{3}]octreotide, which were performed in relatively small patient groups, insufficient data on these important factors are available. This lack of comparable data underscores the need for randomized trials comparing [^{90}Y-DOTA^{0},Tyr^{3}]octreotide and ^{177}Lu-octreotate. Indeed, we plan to perform such a study comparing ^{90}Y- and ^{177}Lu-labeled somatostatin analogs.

We treated both patients who had PD at baseline and those who were stable or in whom disease progression was not documented. The reason for this was that, in many of these patients, waiting for disease progression would have implied a serious deterioration of their clinical condition. As the present analysis shows, this would also have implied diminished chances of a successful therapy. Unfortunately, we did not have a control group of untreated patients. However, Faiss *et al*. [19] recently reported tumor remissions in four (5%) of 80 GEP tumor patients who had PD at study entry and were treated with somatostatin analogs and/or interferon alfa. By contrast, we found tumor remissions in 47% of our patients, whether or not they had PD at study entry. 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 endocrine GEP tumors are as high as 40% to 60% for well-differentiated pancreatic tumors and poorly differentiated tumors of any origin, whereas success rates for midgut tumors rarely exceed 20% in recent studies (Table 3, [20-29] see review in 30). High response rates have been reported in older series [20-22] (Table 3), 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 and Saltz [23] who maintained 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 less than 18 months. In this respect, our treatment with ^{177}Lu-octreotate performed considerably better, with a median time to progression of more than 36 months. However, some caution in the interpretation of these data is warranted because the median follow-up in this ongoing study is 16 months. Also, cardiac and renal toxicity, as well as vomiting and hematologic toxicity, are much more frequent with chemotherapy than with treatment with ^{177}Lu-octreotate (Table 3).

Unexpectedly, we found that patients with gastrinomas had a shorter time to progression than other patients who had, for instance, carcinoids or nonfunctioning endocrine pancreatic tumors. In theory, this could be caused by a faster growth pattern of gastrinomas. There are only a few reports in relatively small numbers of neuroendocrine tumor specimens on proliferative markers like Ki-67. To date, there are reports that evidence that a high Ki-67 proliferative index correlates with a fast tumor growth and short survival in vivo for both functioning and nonfunctioning endocrine GEP tumors [31-33], but as far as the authors are aware, there is no direct evidence that proliferative indices differ between metastasized gastrinomas and other endocrine GEP tumors. However, an interesting difference is that, on immunostains, gastrinomas, in contrast to other endocrine pancreatic tumors, frequently coexpress neuroendocrine and exocrine markers, such as carcinoembryonic antigen, cytokeratin 19, and epithelial membrane antigen [34]. This could imply the different origins of gastrinomas and, it can be speculated that gastrinomas also have different behavior in vivo.

Tumor remission was positively correlated with a high uptake during [^{111}In-DTPA^{0}]octreotide scintigraphy and a limited number of liver metastases, whereas disease progression was significantly more frequent in patients with a low performance status and a high tumor load. This implies that the chances of a successful treatment are greater 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 [15], the percentage of patients with a remission does not differ significantly between those patients who have disease progression at baseline and those who do not; therefore, to wait for disease progression has no advantage in terms of chances of success. However, firm conclusions on the effect of our therapy on overall survival cannot be drawn from this or any other study with radiolabeled somatostatin analogs because randomized trials comparing treatment with radiolabeled analogs with no additional treatment have not been performed.

Treatment with the radiolabeled somatostatin analog ^{177}Lu-octreotate results in tumor remission in a high percentage of patients with endocrine GEP tumors. Serious side effects are rare. The median time to progression is more than 36 months, which compares favorably with chemotherapy. Results are better in patients with a limited tumor load. Therefore, early treatment, even in patients who have no PD, may be better.

Acknowledgment

We thank all supporting personnel of the Departments of Nuclear and Internal Medicine (Erasmus Medical Center, Rotterdam, the Netherlands) for their expert help and effort.

Table 3. Results and side effects of chemotherapy in patients with neuroendocrine tumors compared with the present study

Regimen	Tumor Types	No. of Patients	PR and CR (%)	Median Response Duration (months)	Hematologic Toxicity Grade 3 and 4 (%)	Nausea and Vomiting (%)	Other Major Side Effects	Study
Doxorubicin	Carc	33	21*	4	NA	NA	—	Moertel [20]
FU	Carc	19	26*	3	NA	NA	—	Moertel [20]
STZ + FU	Carc	43	33*	7	NA	NA	—	Moertel [20]
STZ	NEP	42	36*	17	0	83	Renal toxicity, 29%; liver failure, 2%	Moertel *et al.* [21]
STZ + FU	NEP	42	63*	17	29	85	Renal toxicity, 31%	Moertel *et al.* [21]
STZ + FU	NEP	33	45*	7	25	81	Diarrhea, 33%; renal insufficiency, 7%	Moertel *et al.* [22]
STZ + doxorubicin	NEP	36	69*	20	5	80	Diarrhea, 5%; renal insufficiency, 4%; heart failure, 9%	Moertel *et al.* [22]
STZ + doxorubicin	NEP	16	6	> 18	19	NA	Diarrhea, 19%; cardiac toxicity, 19%	Cheng and Saltz [23]
DTIC	Carc	15	13	4	NA	NA	—	Van Hazel *et al.* [24]
DTIC	Carc	56	16	3	29	88	Diarrhea, 23%	Bukowski *et al.* [25]
DTIC	Carc/NEP	7	14	NA	NA	0	—	Ritzel *et al.* [26]
FU + IFN-A	Carc/NEP	24	21	13	42	NA	Diarrhea, 8%	Andreyev *et al.* [27]
Mitoxantrone	Carc	35	9	14	32	26	—	Neijt *et al.* [28]
Paclitaxel	Carc/NEP	24	4	3	61	63	Diarrhea, 54%; neurologic toxicity, 61%	Ansell *et al.* [29]
^{177}Lu-octreotate	Carc/NEP	131	28	> 36	< 2	31	Renal insufficiency, 1%; liver failure, 1%	Present study

Abbreviations: PR, partial remission; CR, complete remission; DTIC, dimethyltriazenoimidazole carboxamide; FU, fluorouracil; STZ, streptozocin; Carc, carcinoids; NEP, neuroendocrine pancreatic tumors; NA, not available; IFN-A, interferon alpha; ^{177}Lu-octreotate, [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. Response evaluation including biochemical responses and physical examination for evaluation of hepatomegaly.

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3

Quality of Life in patients with gastro-enteropancreatic tumors treated with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate

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Abstract

Purpose

To evaluate the quality of life (QoL) in patients with metastatic somatostatin receptor positive gastroenteropancreatic tumors treated with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate) therapy.

Patients and Methods

Fifty patients who had been treated with 600 to 800 mCi of ^{177}Lu-octreotate and had a follow-up of at least 3 months were studied. The patients completed 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. Overall QoL and specific QoL domains of both the total group of patients and subgroups according to treatment outcome were analyzed. Twenty-four patients had regression, 19 had stable disease, six had progressive disease, and one had nonassessable disease status. Analysis of variance was used for statistical comparison.

Results

A significant improvement in the global health status/QoL scale was observed after therapy with ^{177}Lu-octreotate ($P < .01$). The score increased significantly six weeks after therapy to a mean of 78.2, up from 69.0 (scale range, 0 to 100). Furthermore, significant improvement was observed in the role, emotional, and social function scales. The symptom scores for fatigue, insomnia, and pain were significantly decreased. Patients with proven tumor regression most frequently had an improvement of QoL domains. Unexpectedly, patients with progressive disease also indicated an improvement in their global health/QoL score.

Conclusion

^{177}Lu-octreotate therapy significantly improved the global health/QoL and several function and symptom scales in patients with metastasized gastroenteropancreatic tumors, but especially in those patients with proven tumor regression.

INTRODUCTION

Neuroendocrine gastroenteropancreatic (GEP) tumors, including pancreatic islet-cell tumors, nonfunctioning neuroendocrine pancreatic tumors, and carcinoids, are relatively rare neoplasms. In comparison with other malignancies, these tumors usually grow slowly [1]. Manifestations of disease in patients are mainly based on symptoms or syndromes caused by the overproduction of bioactive substances or hormones by the tumor, like in carcinoids, gastrinomas, and insulinomas. In nonfunctioning tumors, diagnosis occurs at a relatively late stage of the disease and therefore, widespread metastatic disease is often present. In symptomatic patients, treatment with somatostatin analogs is the therapy of choice and highly effective in these symptoms reduction [2,3]. However, somatostatin analog treatment results in tumor regression in only 4% to 10% of the patients [4-6].

Peptide receptor radionuclide therapy is a promising treatment modality in patients with metastasized GEP tumors [7-9]. Treatment with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-octreotate) resulted in a complete remission (CR) in 3%, partial remission (PR) in 35%, stable disease (SD) in 41%, and progressive disease (PD) in 21% of the patients. Also, reported side effects were few [9]. The therapeutic effect on tumor volume is most frequently used as the primary end point in clinical oncologic trials. However, over the last decades, the effect of therapy on the self-reported quality of life (QoL) has also become an important (secondary) end point. To detect subjective differences in aspects of QoL, many assessment instruments have been developed. Most widely used is the European Organization of Research and Therapy in Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), which is especially designed to assess QoL in clinical cancer trials. This questionnaire has been validated and is accepted as a reliable method for the assessment of QoL [10]. Therefore, we chose this questionnaire to evaluate the impact of treatment with ^{177}Lu-octreotate on QoL in patients with metastasized GEP tumors.

PATIENTS AND METHODS

Study Design

Patients were referred from both tertiary care referral centers and community hospitals throughout the country. During the treatment and thereafter, the patients came for follow-up in our hospital. The most important criteria for inclusion were histologically proven metastatic GEP tumor(s) and good tumor uptake on somatostatin receptor scintigraphy. Also, patients had to have a Karnofsky performance status score (KPS) ≥ 50 [9,11]. Exclusion criteria were: creatinin clearance > 40 mL/min, platelets > 80 x 10^{9}/L, hemoglobin > 9.7 g/dL, and WBC count > 2.0 x 10^{9}/L. A total of 66 patients with metastatic somatostatin receptor positive GEP tumors treated with 600 to 800 mCi ^{177}Lu-octreotate (three to four cycles, 6- to 9-week interval) could

be analyzed. Eight patients were excluded because of missing forms at the 6-week follow-up visit. In these cases, the forms were missing because of administrative reasons. Seven patients were excluded because of follow-up outside the Netherlands, and one because of progressive disease. A total of 50 patients were analyzed.

Outcome Measures

QoL was assessed with the EORTC QLQ-C30 (version 3.0), a patient-based questionnaire which includes a total of 30 items and is composed of scales that evaluate physical (five items), emotional (four items), role (two items), cognitive (two items), and social (two items) functioning, as well as global health status (two items). Higher mean scores on these scales represent better functioning. There are also three symptom scales measuring nausea and vomiting (two items), fatigue (three items), and pain (two items), and six single items assessing financial impact and various physical symptoms. A higher mean value on the symptom scales/single items means more symptomatology. Following the scoring instructions given by the EORTC Quality of Life Study group, the raw EORTC QLQ-C30 scores were linearly transformed to 0-100 scales before statistical analyses were performed [12]. A mean change in score between 0 and 5 was regarded as not clinically important. A change in scores between 5 and 10 was regarded as a "little" subjective change, whereas a change between 10 and 20 was regarded as a "moderate" change, and more than 20 was regarded as an "important" change, as previously described [13]. The different outcome groups were defined as regression (including CR, PR, and minimal regression [MR]; 25% to 50% reduction in tumor size), SD, and PD, and were determined by means of computed tomography (CT) and magnetic resonance imaging (MRI) measurements following the WHO solid tumor response criteria. MR was included in the regression group because of the usually slow growth rate of neuroendocrine tumors, if compared with other carcinomas, and because of the cystic lesions that these tumors often cause.

Timing and Data Collection

In accordance with the requirements from the hospital's Ethics Committee, informed consent was obtained from all the patients. Questionnaires were filled out at fixed points in the treatment scheme in the week before the first treatment and at the first follow-up visit 6 weeks after the last treatment. The treating physician scored their KPS. The patients were carefully instructed how to fill out the questionnaire, but were not assisted in answering the questions. At the 6-week follow-up visit, the patients were unaware of the response as the questionnaires were filled out on the same day the first follow-up CT or MRI was performed. Patients were only informed about outcome of therapy at the next follow-up visit when tumor imaging was evaluated. The first questionnaire was used as baseline.

Missing Data

The questionnaires were collected carefully, but some were not filled out adequately and contained missing values at the time of analysis. The missing items were handled with the method of simple mean imputation as described in the Guidelines for assessing QoL in clinical trials provided by the EORTC [12].

Data Analysis

Analysis of variance (two-sided) was used to compare the patients' ratings before and after treatment. $P < .05$ was considered significant. The linear associations between changes in KPS scores and patients' global health/QoL scores were investigated using Spearman's rank correlation (two-tailed).

RESULTS

Baseline patients' characteristics are listed in Table 1. The questionnaires of 50 patients (mean age, 58 years; range, 30 to 78 years), before and after treatment, were available for analysis.

Of the 50 patients, 26 patients (52%) had carcinoid tumor, 13 (26%) neuroendocrine (NE) pancreatic tumor, seven (14%) had NE tumor of unknown origin, three (6%) had gastrinoma, and one (2%) had insulinoma. Twenty-two patients (44%) had been operated in the past, five patients (10%) had received chemotherapy, and 24 patients (48%) had been treated with somatostatin analogs before the ^{177}Lu-octreotate therapy. Seventeen of the included 50 patients (34%) had documented progressive disease within 1 year before the start of therapy. In the other patients, disease was stable for more than 1 year, or progression had not been documented with CT or MRI within the preceding year. Treatment with ^{177}Lu-octreotate resulted in the following responses 3 months after therapy: 24 patients (48%) had tumor regression (CR, PR, and MR), 19 patients (38%) had SD, and six patients (12%) had PD. In one patient, it was not possible to measure tumor response because evidence of disease before and after therapy could only be visualized with somatostatin scintigraphy.

Eight patients were excluded from the analysis because of missing forms. Two of these had tumor regression, three had SD, two had PD, and in one patient no treatment outcome could be established. These treatment outcomes were not significantly different from the whole patient group (Fisher's exact test [two-sided]; $P < .05$). The total amount of missing items of all the EORTC QLQ-C30 questionnaires was 14 of 3,000, yielding a completion rate of 99.5%. These missing items were randomly distributed and therefore, simple mean imputation was considered appropriate to handle the data without the introduction of significant bias [14].

Table 1. Baseline characteristics at study entry

	No. of patients	%
Total	50	
Sex		
Male	22	44
Female	28	56
Age, years		
Mean	58.3	
Range	30-78	
Karnofsky Performance Score		
Mean	87.2	
Median	90	
Range	50-100	
Type of tumor		
Carcinoid	26	52
NE tumor unknown origin	7	14
NE tumor pancreas	13	26
Gastrinoma	3	6
Insulinoma	1	2
Metastases		
Liver	45	90
Bone	10	20
Prior Therapy		
Surgery	22	44
Chemotherapy	5	10
Somatostatin analogs	24	48

Abbreviation: NE, neuroendocrine.

The mean interval between baseline and first follow-up visit (6 weeks after the last therapy) was approximately 7 months (range, 5 to 12 months). This interval varied because in some patients, treatments had to be postponed as a result of sustained bone marrow suppression, and because the number of treatments varied due to patients reaching their cumulative maximum kidney radiation dose. The latter was calculated for each indiviual patient separately, and varied considerably. All patients received between 600 and 800 mCi of ^{177}Lu-octreotate.

The EORTC QLQ-C30 data indicated that patients assigned high scores to the functional scales at baseline (Table 2).

Table 2. Patients (n=50) mean scores on EORTC QLQ-C30 scales and single items

	At baseline		Follow-up (6 weeks)			
	Mean	SD	Mean	SD	Change	P*
Global quality of life †						
Global health-status/quality of life	69.0	20.8	78.2	16.9	9.2	< 0.01
Functional scales †						
Physical	80.8	19.3	84.6	20.4	3.8	0.07
Role	67.0	31.7	82.0	25.2	15.0	< 0.01
Emotional	77.7	15.7	85.8	15.5	8.1	< 0.001
Cognitive	88.7	16.0	88.3	17.3	-0.4	0.89
Social	80.7	22.7	90.3	21.3	9.6	< 0.01
Symptom scales ‡						
Fatigue	31.9	24.4	22.8	22.5	-9.1	< 0.01
Nausea/Vomiting	6.7	16.5	5.0	11.3	-1.7	0.46
Pain	23.3	28.8	15.0	20.0	-8.3	< 0.05
Single items ‡						
Dyspnea	16.3	23.7	17.3	27.1	1.0	0.71
Insomnia	26.0	30.3	14.3	21.5	-11.7	< 0.01
Appetite loss	10.2	19.5	8.7	21.1	-1.5	0.70
Constipation	8.8	20.2	6.1	16.2	-2.7	0.32
Diarrhea	16.7	26.3	12.2	18.9	-4.5	0.26
Economical impact	5.3	14.1	5.3	15.6	0.0	1.00
Body Weight	71.3	14.5	74.0	15.5	2.7	0.01
Karnofsky Performance Status Scale	87.2	12.3	87.9	12.0	0.7	0.52

NOTE Mean scores and ± SD of the EORTC QLQ-C30 questionnaire before and after (6 weeks follow-up visit) ^{177}Lutetium-octreotate therapy. Body weight and KPS are also shown.
Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; SD, standard deviation.
**: P < .05 was regarded as statistical significant.*
†: Scores ranges from 0 to 100, with a higher score representing a higher level of function.
‡: Scores ranges from 0 to 100, with a higher score representing a higher level of symptoms.

The role and cognitive function scales were given respectively the lowest (67.0) and the highest (88.7) scores. The score for the global health status/QoL scale (69.0) was slightly lower than most of the functional scales. The highest scores of the symptoms scales and single items were assigned to fatigue (31.9), insomnia (26.0), and pain (23.3), as well as diarrhea (16.7) and dyspnea (16.3).

The global health/QoL scale score changed significantly from 69.0 to 78.2 ($P < .01$). Moreover, significant improvements were demonstrated in the emotional function scale (77.7 to 85.8; $P < .001$), the role function scale (67.0 to 82.0; $P < .01$) and in the social function scale (80.7 to 90.3; $P < .01$). In the symptoms scale scores, fatigue and pain decreased from 31.9 to 22.8 ($P < .01$) and 23.3 to 15.0 ($P < .05$), respectively. Only insomnia, as one of the six single items, decreased 11.7 points in score ($P < .01$). At baseline, 17 (34%) of 50 patients had diarrhea as part of a secretory syndrome, versus 16 (32%) of 50 at the first follow-up visit ($P < .05$). However, patients who initially had diarrhea had a significant decrease in diarrhea score from 49.0 to 15.7 ($P < .0001$) after therapy. Only one patient in this group switched to morphine, which probably accounted for the observed decrease of diarrhea in this patient. Mean body weight increase during the average period of 7 months changed significantly from 71.3 to 74.0 kg ($P < .01$).

In the group with tumor regression, the global health/ QoL scale score increased significantly from 70.1 to 80.6 ($P < .05$). The physical, role, emotional, and social scale improved with an increase in score of 6.0, 22.2, 10.0, and 11.1, respectively ($P<.05$). The score of the symptom scale fatigue decreased from 30.3 to 19.2 ($P<.01$) and the single item insomnia decreased from 23.6 to 8.7 ($P < .01$) after therapy. Body weight increased significantly from 72.4 to 77.2 kg ($P <.01$). The KPS did not change significantly (Figure 1).

In the group with stable disease, no significant changes were found in the functional scales. In patients with pain at baseline (13 of 19 patients; 68%), a significant decrease in score was found from 41.0 (baseline) to 17.9 (6 weeks after therapy; $P < .01$). In patients with stable disease (n = 19), no further significant change of any other score was found. In patients with progressive disease (n = 6), only the global health/QoL score increased from 48.6 to 72.2 ($P <.01$; Fig 2).

The change in score of the self-reported global health/ QoL scale between before and after therapy was positively correlated with the change in KPS (Pearson's rank correlation; $\varrho = 0.39$; $P < .01$). Twenty (60%) out of 33 patients who had a lower or equal KPS after therapy reported an increase in global health/QoL scale, and 12 (80%) of 15 patients who had a higher KPS after the therapy also had a higher global health/QoL scale score compared to baseline (Fig 3).

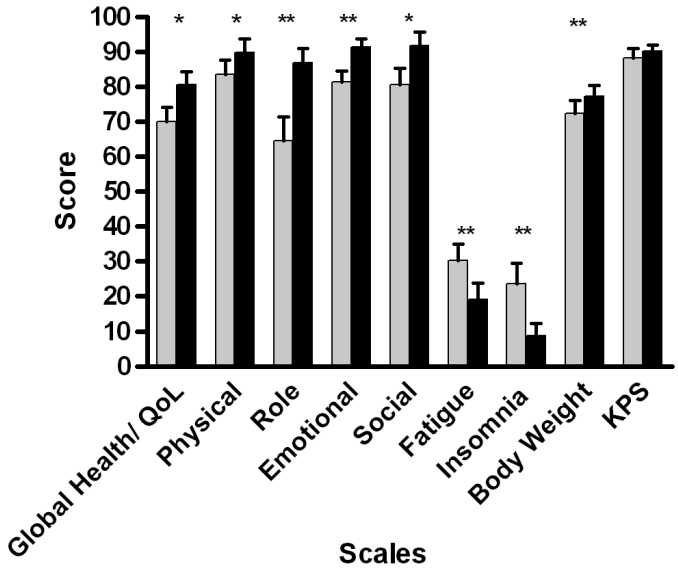

Figure 1. Changes in the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 scales and Karnofsky performance score (KPS) in patients with tumor regression before (baseline) and at 6 weeks follow-up. Only scales that changed significantly are shown. SE to the mean are shown above each bar. Gray bars:before [^{177}Lu-DOTA°,Tyr^3]octreotate therapy; black bars: after therapy.*P < .05 ; **P < .01.

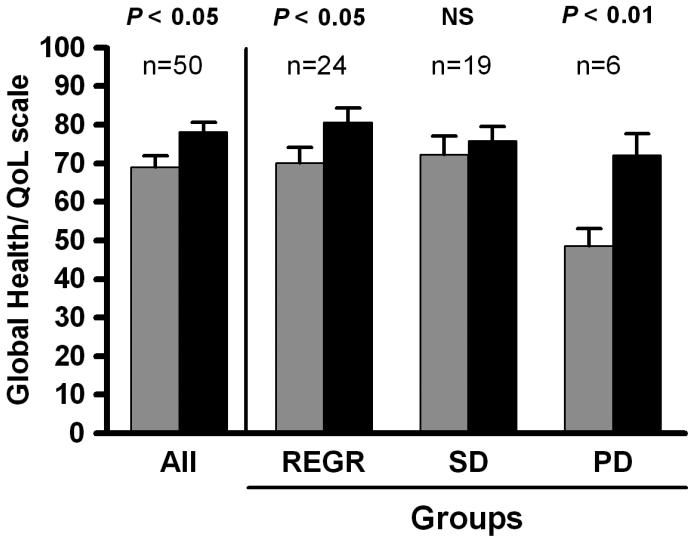

Figure 2. Global health/quality of life (QoL) scale scores of all the patients (N = 50) and the different outcome groups according to tumor evaluation before (gray bars) and after (black bars) [^{177}Lu-DOTA°,Tyr^3]octreotate therapy. SE to the mean are shown above each bar. REGR, regression; SD, stable disease; PD, progressive disease; NS, not significant.

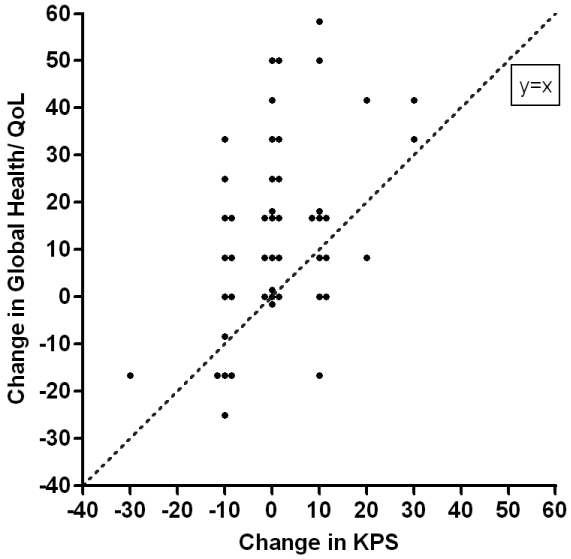

Figure 3. Changes in global health/quality of life (QoL) scores per patient versus changes in Karnofsky performance score (KPS). Values are scores at 6 weeks follow-up minus scores at baseline. The line (y = x) represents equal changes. Note that positive changes in global health/QoL scale are more frequent than positive changes in KPS.

DISCUSSION

Treatment with radiolabeled somatostatin analogs, like ^{177}Lu-octreotate, in patients with metastasized neuroendocrine GEP tumors may be very rewarding in terms of tumor volume reduction [7-9]. Here, we report the outcome of health related quality-of-life (HRQoL) assessment before and after treatment with ^{177}Lu-octreotate. The EORTC QLQ-C30 scores of patients with metastasized GEP tumors at baseline indicated that the patients maintain a relatively good HRQoL. This is in line with a previous study by Larsson *et al.*[15] in which the questionnaire was used to study the general HRQoL in patients with GEP tumors. Assessment of HRQoL data results in detailed information about many aspects of the patients' QoL, including symptoms, specific functional scales, and the overall health/QoL scale. The combined global health/QoL scale is regarded as the most important scale to score, as it gives an overall impression of the experienced HRQoL. Furthermore, it has been shown to be a good predictor of survival [16,17].

To identify aspects of HRQOL in which the patients clearly had gained meaningful improvement, a significant change of more than five points was considered to be clinically important, according to the method described by Osoba *et al.*[13]. The patients in our study experienced such an improvement of their global health/QoL after

therapy with ^{177}Lu-octreotate. In addition, the role, emotional, and social function scale score showed a clinically important improvement. The symptom scales fatigue and pain and the single item insomnia were the only scores that were high at baseline and decreased significantly. Fatigue is the most frequently reported symptom in cancer patients, and its reason is often obscure [18-20]. Also, insomnia is reported in 30% to 50% of patients with cancer [21]. Profound diarrhea is a common symptom in patients with GEP tumors. However, we found no significant change in diarrhea, most probably because most patients with severe diarrhea used somatostatin analogs that resulted in an adequate symptom control. However, patients who still suffered from diarrhea before the start of ^{177}Lu-octreotate therapy did notice an improvement of this symptom.

The change in self-reported global health/QoL was positively correlated with the change in KPS as judged by the physician. Correlation between KPS scores and the different domains of QoL have been reported in other studies [22,23]. In these studies, however, it was concluded that, although associated, both measures are not assessing the same construct. Schaafsma *et al.* [22] stated that the EORTC QLQ-C30 is a more comprehensive measure of QoL than the KPS. This is in line with the greater number of positive changes we found in the global health/QoL scale as reported by the patient, as compared with the changes in the physician-based KPS. Larsson *et al.* [24] stated that patients with GEP tumors rated the physical aspects of life as the most important aspect for experiencing a good HRQoL. In contrast, we found no evidence of significant change in the physical function scale, whereas other scales, including the global health/QoL, did increase significantly. Thus, although reported as the most important aspect of QoL, it appears that, when the level of physical functioning is relatively high as in our patients, aspects of QoL other than physical functioning become important to determine the patients' overall QoL.

In the group with SD, no worsening of symptoms or decrease in functioning scales was found. However, considering the five (26%) of 19 patients who had documented PD in the year before therapy, a stabilization of any aspect of QoL suggests a positive effect of ^{177}Lu-octreotate therapy. Furthermore, patients with pain at baseline had a significant decrease in score with more than 20 points. Waldherr *et al.* [25] reported similar findings of clinical benefit in a group of 21 patients with NE tumors treated with the radiolabeled somatostatin analog ^{90}Y-DOTATOC. However, they used a physician-based method, whereas we preferred to use a more patient-based method with the EORTC QLQ-C30. In contrast to the group of patients with SD, a significant improvement of the global health/QoL scale was found in patients with PD. The difference between the low score at baseline in the latter group, compared with the relatively high score in patients with SD, could explain this contradicting observation. In combination with the absence of any significant change in any other

scale, it suggests that, in patients with PD, even a small change in any other scale could have had a large impact on their overall health/QoL. Because our group with PD represented a small number of patients and, moreover, one patient was lost to follow-up, the accuracy of these observations remains questionable. Also, a placebo effect cannot be ruled out completely.

In conclusion, we found that ^{177}Lu-octreotate therapy improved the QoL in patients with metastasized GEP tumors, especially in the patients with proven regression.

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4

Effects of therapy with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate on endocrine function

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Submitted

Abstract

Purpose

Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues is a novel therapy for patients with somatostatin receptor-positive tumours. We determined the effects of PRRT with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu–octreotate) on glucose-homeostasis and the pituitary-gonadal, -thyroidal and -adrenal axes.

Methods

Hormone levels were measured and adrenal function assessed at baseline and up to 24 months of follow-up.

Results

In 35 men, mean serum inhibin B levels were decreased at 3 months posttherapy (205±16 to 25±4 pg/ml; $P<0.05$) and FSH levels increased (5.9±0.5 to 22.7±1.4IU/L; $P<0.05$). These levels returned to near baseline levels. Total testosteron and SHBG levels decreased (15.0±0.9 to 10.6±1.0 nmol/L and 61.8±8.7 to 33.2±3.7 nmol/L; $P<0.05$), respectively, whereas non-SHBG-bound-T did not change. An increase (5.2±0.6 to 7.7±0.7I IU/L; $P<0.05$) of LH levels was found 3 months of follow-up returning to baseline levels thereafter. In 21 postmenopausal women, decrease in FSH (74.4±5.6 to 62.4±7.7 IU/L; $P<0.05$) and LH levels (26.8±2.1 to 21.1±3.0 IU/L; $P<0.05$) were found.

Two out of 66 patients developed persistent primary hypothyroidism. FT4 levels decreased (17.7±0.4 to 15.6±0.6pmol/L; $P<0.05$), whereas TSH and T3 levels did not change. rT3 levels decreased (0.38±0.03 to 0.30±0.01 nmol/L; $P<0.05$). Before and after therapy ACTH-stimulation tests showed an adequate response (>550 nmol/L; n=18). Five patients developed elevated HbA_{1c} levels (>6.5%).

Conclusion

In men ^{177}Lu–octreotate therapy induced transient inhibitory effects on spermatogenesis, but, non-SHBG-bound-T levels remained unaffected. In the long-term, gonadotropin levels decreased significantly in postmenopausal women. Only few patients developed hypothyroidism or elevated levels of HbA_{1c}. Therefore, PRRT with ^{177}Lu–octreotate can be regarded as a safe treatment modality with respect to short-and long-term endocrine function.

INTRODUCTION

Treatment with radiolabelled somatostatin analogues, or peptide receptor radionuclide therapy (PRRT), is a new treatment modality in patients with metastasised or inoperable somatostatin receptor-positive tumours. Recent reports on the effectiveness of PRRT with the radioligands [^{90}Y-DOTA^{0},Tyr^{3}]octreotide (^{90}Y-octreotide) or [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu–octreotate) in patients with neuroendocrine tumours, report 20-30% partial remissions[1-3]. Short-term side-effects included mild nausea, vomiting and abdominal pain [4,5]. Serious side-effects are related to tissue specific radiation exposure and radiation sensitivity. Radiation absorbed doses to bone marrow and kidneys are dose limiting. So far, reported serious complications include 2 cases of myelodysplastic syndrome [5] and several cases of radiation-induced renal failure [6-8], especially in patients who did not receive amino-acid co-infusion, which is currently used to reduce renal absorbed radiation dose [9].

Additional non-intended targets of PRRT are endocrine organs. Many of these, such as the anterior pituitary gland, endocrine pancreas, adrenal medulla and thyroid are known to express somatostain receptors (SSTRs), especifically SSTR subtype 2[10-13]. The radiopharmaceuticals currently used in PRRT target especially this SSTR subtype, followed by subtype 5 and 3 [14].

Until recently, limited data regarding the effect of PRRT on endocrine function was available. In a previous report on the therapeutic effect of ^{177}Lu-octreotate in a large group of patients with gastroenteropancreatic neuroendocrine tumours, we briefly reported on the short-term effects of PRRT on endocrine function [5]. In the present study, we focused on both the short- and long-term effects of PRRT on the anterior pituitary, gonadal, thyroid, endocrine pancreas and adrenal function.

SUBJECTS AND METHODS

Patients and study design

Seventy-nine patients who were treated with 600-800 mCi ^{177}Lu-octreotate (three to four cycles with 6 to 9-week interval) between January 2000 and December 2004 and with a follow-up period of 12-24 months, were selected for analysis. Only local (Dutch) residents were analysed, because these had their follow-up at our institution. All patients had tumour uptake on SSTR scintigraphy that was at least as high as the physiological uptake in normal liver tissue on planar imaging preceding therapy. Hormone measurements, routine haematology, liver and kidney function tests were performed before each administration of ^{177}Lu-octreotate and at each follow-up visit. Outcome of therapy was assessed by computed tomography or magnetic resonance

imaging and performed within 3 months before the first therapy, at 6 to 8 weeks, at 3 and 6 months after the last treatment, and thereafter every 6 months.

Inclusion criteria were: Karnofsky performance score ≥ 50, creatinin clearance ≥ 40 ml/min, haemoglobin > 9.7 g/dL, platelet count > $75x10^9$/L and WBC > $2.0x10^9$/L. All patients gave written informed consent before inclusion in the study, which was approved by the medical ethics committee of the hospital. ^{177}Lu-octreotate preparation and administration of therapy were performed as described earlier [5].

Hormone measurements

Blood samples were processed within 2 hours after withdrawal. Serum was stored at –20 °C until assayed.

Gonadotropins, gonadal hormones and cortisol

Serum levels of LH, FSH, SHBG and cortisol were measured using luminescence-based immunometric assays (Immulite 2000, Diagnostic Products Corp., Los Angeles, CA, USA) Serum estradiol (E2), and total testosterone (TT) levels were measured using nonextraction coated-tube radioimmunassay (Coat-a-Count, Diagnostic Products Corp., Los Angeles, CA, USA). Sensitivities of the assays were 0.1 IU/L for FSH and LH, 10 pmol/L for E2 and 0.1 nmol/L for TT. Interassay coefficients of variation for LH and FSH, were <7%, <5% for SHBG, 5% for cortisol, <10% for E2 and <9% for TT. Non-SHBG-bound-T levels were calculated by using the mass action equation as described by Södergard [15] using a variable albumin concentration. The affinity constants used for the binding of testosterone to SHBG or albumin were $5.97x10^8$ L/mol and $4.06x10^4$ L/mol, respectively. Dimeric inhibin B levels were assessed using an immunoenzymometric assay Oxford BioInnovation, (Oxford, UK), The detection limit of the assay was 10 ng/L. Interassay coefficients of variation were <15% and 21% at concentrations of 215 and 19 ng/L, respectively.

Thyroid hormones

Serum FT4 and T3 were measured by chemoluminescence assays (Vitros ECi Immunodiagnostic System; Ortho-Clinical-Diagnostics Inc., Rochester, NY, USA). Serum levels of TSH were measured using the Immulite 2000 system. Reverse T3 (rT3) was measured by RIA as previously described [16]. Interassay coefficients of variation amounted to 4% for TSH, 5% for FT4, 3.3% for T3, and 10% for rT3.

HbA_{1c}

Percentage of glycolysated hemoglobin (HbA_{1c}) was determined by HPLC measurement.

Hypothalamo-pituitary-adrenal (HPA)-axis assessment

The 1 μg (low-dose) ACTH stimulation test (LDST) was used to test the integrity of the HPA axis. The LDST was performed in thirty-nine patients before therapy. Eighteen patients also had an LDST 12-18 months after therapy. Cortisol was measured 0, 20, 30 and 60 minutes after the injection of 1 μg tetracosactrin (Synacthen, Novartis Pharma) intravenously. The solution of 1 μg ACTH/ml was used immediately after preparation. The intravenous line used was flushed with saline after the administration and after each time a blood sample was taken. A stimulated peak cortisol concentration of at least 550 nmol/L was considered to be an adequate response.

Statistical Analyses

All results are expressed as mean concentrations ± standard error of the mean (SEM). Hormones were analysed using repeated-measures analysis of variance (ANOVA) with Bonferroni's correction for multiple comparisons. For the HPA-axis analysis paired student *t*-tests was used. *P*-values <0.05 (2-tailed) were considered significant.

RESULTS

Patients' characteristics are listed in Table 1. Data from thirty-five men were available for analysis. Three were excluded at baseline: one had severe chemotherapy-induced hypogonadism, one had testicular atrophy and one had high levels of FSH and LH suggestive of a co-existing gonadotropin-secreting pituitary adenoma, which was not further analysed.

At baseline, one patient had combined low TT (<8.1 nmol/L) and inhibin B (<150 pg/ml) levels, 2 patients had isolated low TT levels, 2 other patients had low non-SHBG-bound-T (<5.9 nmol/L) and another 10 patients had isolated low inhibin B levels.

Mean inhibin B level decreased significantly from 205±16 pg/ml to a nadir level of 25±4 pg/ml at 3 months after ^{177}Lu-octreotate therapy *(P*<0.05) and returned to near pre-treatment levels in the follow-up period thereafter. At 24 months posttherapy, although marginal, the inhibine B level was significantly decreased (Figure 1a). Mean FSH levels had a mirrored course with a transient increase from 5.9±0.5 IU/L to a maximum of 22.7±1.4 IU/L 3 months after the last therapy. Twenty-four months after the last therapy, the mean FSH level was not significantly different from baseline.

Table 1. Baseline patient characteristics

	No. of Patients	Mean (range)	%
Total	79		
Gender			
Male	38		48
Age		58.4 (30-83)	
Female	41		52
Age		54.8 (20-74)	
Age at diagnosis (yr)		56.7 (20 – 83)	
Weight (kg)		74.3 (43 – 142)	
BMI (kg/m^2)		25.0 (15.6 - 45.1)	
Height (cm)		172 (152-196)	
Karnofsky Performance Score		89.4 (50-100)	
Diagnosis			
Carcinoid	49		62
NE of unknown origin	8		10
NE pancreas	15		20
Gastrinoma	1		1
Insulinoma	1		1
Hürthle cell Thyroid Carcinoma	3		4
Medullary Thyroid Carcinoma	1		1
Paraganglioma	1		1
Metastases			
Liver	66		84
Bone	18		23
Prior therapy			
Surgery	36		46
Chemotherapy	6		8
External Radiotherapy	3		4
Somatostatin analog therapy	36		46

Abbreviations: BMI, body mass index; NE, neuroendocrine

Mean TT level decreased significantly from 15.0±0.9 nmol/L at baseline to 12.3±0.7 nmol/L at 3 months *(P*<0.05) with a further decline to 10.6±1.0 nmol/L at 24 months after therapy (Figure 1b). Mean LH level from 5.2±0.6 IU/L to 7.7±0.7 IU/L at 3

months of follow-up and returned to levels not significantly different from baseline at 6 months.

Concomitant with the decrease of TT, the mean SHBG level decreased significantly from baseline level of 61.8±8.7 nmol/L to a nadir of 33.2±3.7 nmol/L at 24 months after the last therapy *(P*<0.05). The calculated levels of non-SHBG-T did not change significantly (Figure 1c).

Based on the levels of FSH, LH, inhibin B and E2, and age before therapy, three groups of women (41 patients in total) could be distinguished. Eight women had hormonal changes during follow-up which were suggestive for menopausal transition and were therefore excluded. Since no menstrual data was available from six premenopausal women, these women were also excluded from analysis.

Gonadotropin analysis was performed in 21 postmenopausal women. Five women were excluded because of hormonal changes due to concomitant disease (n=3), previous cranial external beam radiation because of meningeoma (n=1) and temporary use of high dose opioid medication (n=1). One 39-year-old woman was excluded because of bilateral oophorectomy, followed by hormone replacement therapy.

In the postmenopausal women, both mean inhibin B and E2 were at low levels, <10 ng/L and <50 pmol/L, respectively, at baseline and did not change significantly thereafter. Before therapy, the mean FSH concentration was 74.4±5.6 IU/L. During follow-up it decreased significantly to 62.4±7.7 IU/L, at 24 months of follow-up. The mean LH concentration, which was 26.8±2.1 IU/L before therapy, decreased significantly to 21.1±3.0 IU/L at 24 months *(P*<0.05). (Figure 2).

Sixty-six patients were included for analysis of thyroid hormone status. Excluded were ten patients with thyroid associated conditions before therapy including primary hypothyroidism (n=4), TSH suppressive therapy for thyroid carcinoma (n=4), hyperthyroidism (n=1) and combined neck surgery and external beam radiotherapy (n=1). Furthermore, 3 patients were excluded because they had either undetected hypothyroidism (n=1) or subclinical hypothyroidism (n=2) before ^{177}Lu-octreotate therapy and were subsequently started on thyroxine therapy. After the third cycle of therapy one patient developed anti-TPO antibody-positive hypothyroidism. Another patient gradually developed primary hypothyroidism after therapy and was eventually started on substitution therapy 3.5 years after ^{177}Lu-octreotate therapy. Thyroid hormone levels from these patients were included in the analyses until hypothyroidism was evident.

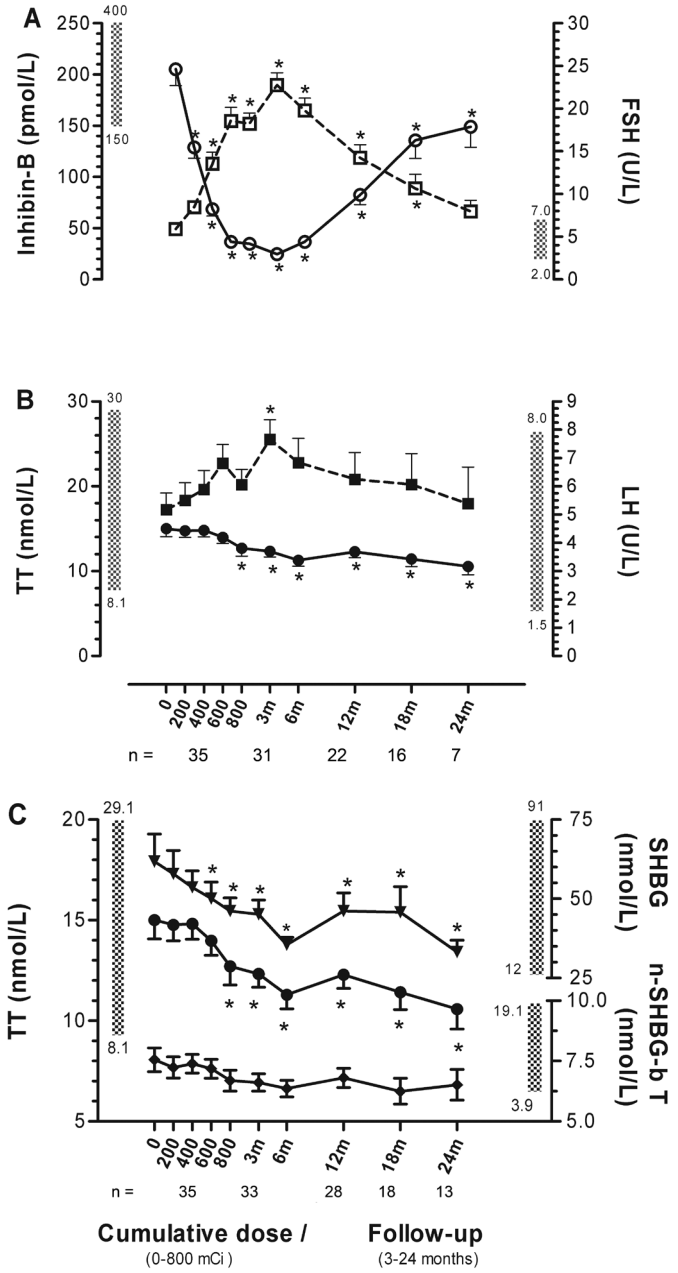

Figure 1. Longitudinal analyses of mean (± SEM) serum levels of (**A**) FSH (dotted line with open squares), Inhibin B (black line with open circles), (**B,C**) LH (dotted line with filled squares) total testosterone (TT; black line with filled circles), sex hormone binding globuline (SHBG; dotted line with filled triangles), and non-SHBG-bound testosterone (n-SHBG-bound T; black line with filled diamonds) in 35 men with SSTR positive tumors before, during and up to 24 months after 600-800 mCi ^{177}Lu-octreotate therapy. Bars along both y-axes represent the reference range (4 SD) values; *, P <0.05.

The course of the mean thyroid hormone levels of the included patients is shown in Figure 3. Mean FT4 decreased significantly from 17.7±0.4 to 15.6±0.6 IU/L pmol/L (reference range 11-25 pmol/L; *P*<0.05); TSH and T3 levels did not change significantly. Mean rT3 concentration of 0.38±0.03 nmol/L was above the reference range (0.14-0.34 nmol/L) before therapy. During therapy a significant 18% decrease of mean rT3 level with a nadir of 0.30±0.01 nmol/L after a cumulative dose of 400 mCi was found *(P*<0.05). Thereafter the mean rT3 level increased slowly to 0.32±0.03 nmol/L, 24 months after therapy. The ratio of T3 over rT3 (T3/rT3), with a T3/rT3 of 6.24±0.03 at baseline was significantly elevated with a maximum of 7.54±0.33 after a cumulative dose of 400 mCi *(P*<0.05) after which it returned to levels not significantly different from baseline.

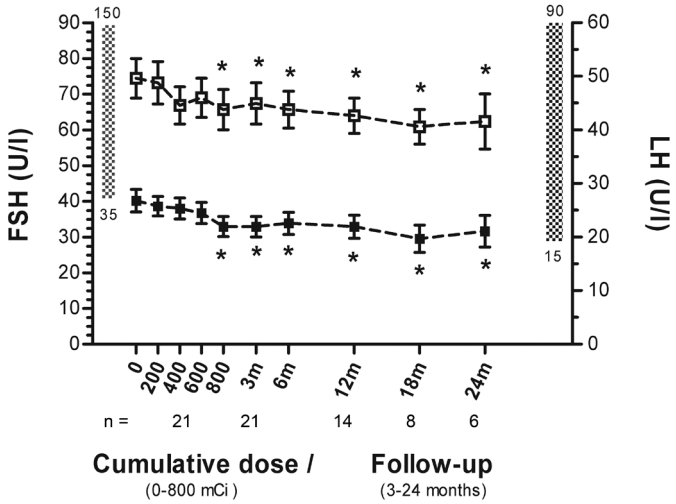

Figure 2. Longitudinal analysis of mean (± SEM) serum levels of FSH (dotted line with open squares) and LH (dotted line with filled squares) in 21 postmenopausal women with SSTR positive tumors before, during and up to 24 months after 600-800 mCi ^{177}Lu-octreotate therapy. Mean inhibin B and E2 level not shown as these were at normal low postmenopausal levels(<10 ng/L and <50 pmol/L, respectively). Bars along both y-axes represent the reference range (4 SD) values; *, *P* < 0.05

In a subanalysis, in which 3 groups of patients were analysed according to their outcome of tumour assessment at 3 months of follow-up (progressive disease, PD; stable disease, SD;. minor or partial remission, MR or PR) a significant decrease of mean rT3 *(P*<0.05) level during therapy was demonstrated in the groups with SD and MR or PR whereas in the PD group no significant change was observed (Figure 4).

An LDST was performed before therapy in 39 patients, which showed stimulated cortisol values higher than the cut-off value of 550 nmol/L in all patients. The mean

peak level after LDST was 822±28 nmol/L. The LDST was repeated 12-18 months after the last therapy in 18 patients (8 men, 10 women). All patients again had stimulated cortisol values higher than 550 nmol/L after ^{177}Lu-octreotate therapy. The mean peak cortisol response before therapy was significant higher than after therapy (909±57 nmol/L vs. 822±35 nmol/L; P<0.001, n=18) (Figure 5).

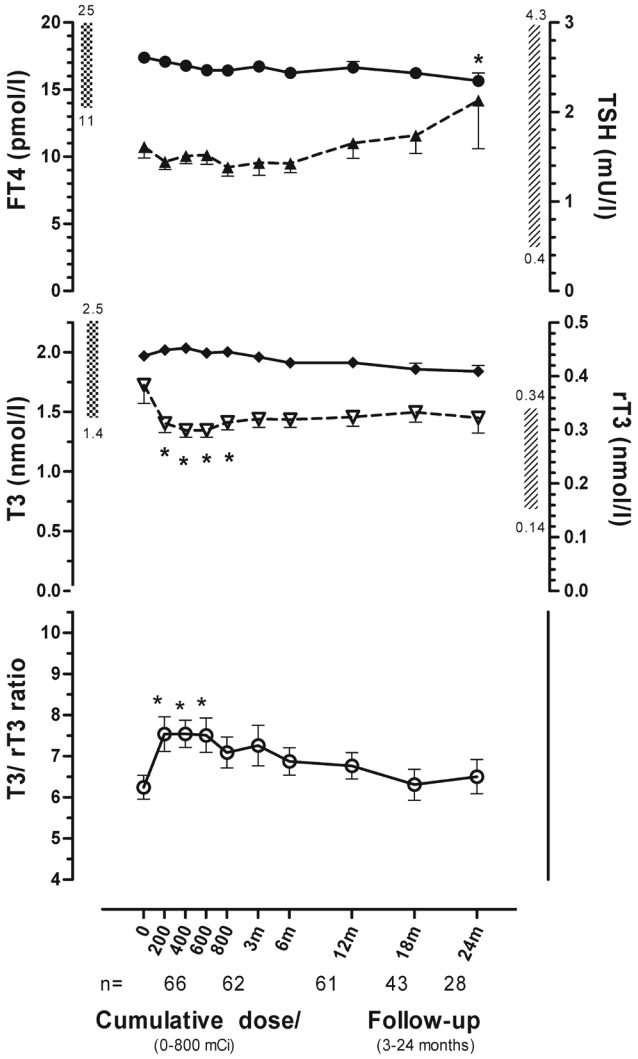

Figure 3a-c. Longitudinal analysis of mean (± SEM) serum levels of TSH (dotted line with filled triangles), FT4 (black line with filled cirlces), T3 (black line with filled diamonds), rT3 (dotted line with open triangles), and T3/ rT3 ratio (line with open circles), of 66 patients with SSTR positive tumors before, during and up to 24 months after 600-800 mCi ^{177}Lu-octreotate therapy. Bars along y-axes represent the reference range (4 SD) values; *, P <0.05.

Nine out of 79 patients had diabetes mellitus diagnosed before treatment and were either on subcutanous insulin therapy (n=4) or oral antihyperglycemic agents (n=5). Furthermore, one patient had an insulinoma and another patient had an abnormal hemoglobin pattern and therefore serum unfit for HbA_{1c} measurement. Five patients had elevated HbA_{1c} (>6.5%) before ^{177}Lu-octreotate therapy of whom 3 were started on oral antihyperglycemic drugs during or after ^{177}Lu-octreotate therapy. Six patients developed high levels of HbA_{1c} after PRRT. In one patient this occurred after pancreatic surgery. In the other 5 patients, elevated HbA_{1c} levels occurred after 2-30 months from study inclusion (Table 2). Analysis in 69 patients demonstrated a decrease of HbA_{1c} from 5.7±0.1 to 5.5±0.1% (*P*<0.05) during therapy, but an increase to 6.0±0.1% (*P*<0.05) thereafter.

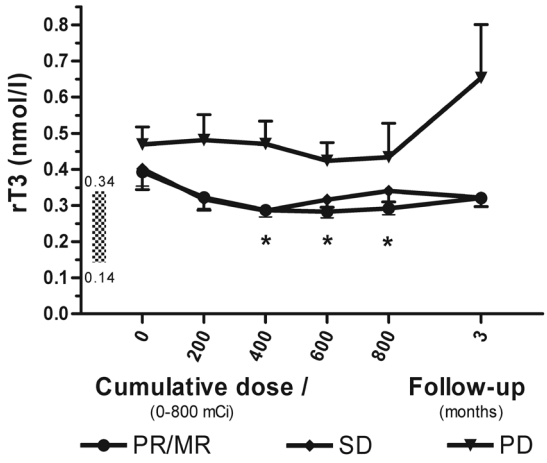

Figure 4. Longitudinal analysis of mean (± SEM) serum levels of rT3 in patients with SSTR positive tumors before, during and at 3 months of follow-up after 600-800 mCi ^{177}Lu-octreotate therapy grouped according to their therapy outcome (partial remission and minor remission, PR/MR; filled circles; stable disease, SD, filled diamonds; progressive disease, PD, filled triangles) at 3 months of follow-up. Bar along the y-axis represent the reference range values. *, $P < 0.05$.

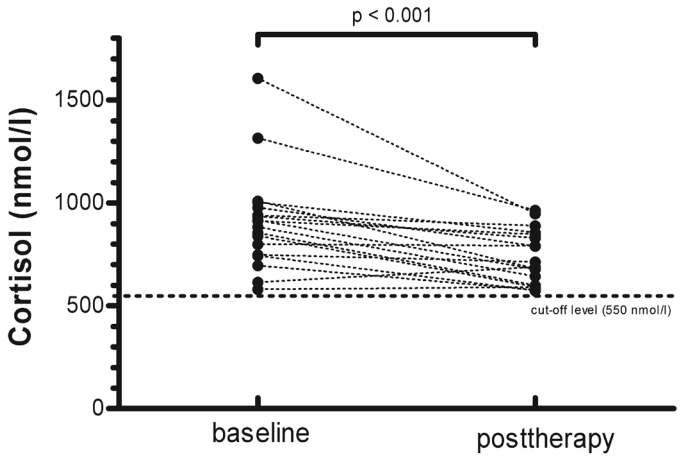

Figure 5. Mean peak cortisol response with the low dose (1 µg) ACTH stimulation test in 18 patients before and 12-18 months after ^{177}Lu-octreotate therapy are shown. Each dotted line connects one individual patient.

Table 2. Number of patients(n) who were evaluable for HbA_{1c} percentages based on their HbA_{1c} percentage at baseline and after ^{177}Lu-octreotate therapy. Patients excluded at baseline were medically treated patients with diabetes (n=9), one patient who had an insulinoma and one patient had with an abnormal hemoglobin pattern.

	Posttherapy			
	HbA_{1c} (in %)	n ≤ 6.5	n > 6.5	Total
Baseline	n > 6.5	0 (0%)	5 (100%)	5
	n ≤ 6.5	57 (90%)	6* (10%)	63
	Total	57	11	68

**, one patient developed elevated levels of HbA_{1c} after Whipple surgery*

DISCUSSION

Besides the currently known complications and adverse effects due to the non-specific radiation absorbed doses to the bone marrow and kidneys, specific receptor-related effects on non-tumourous tissue by PRRT have not been studied in detail. SSTRs are expressed in most hormone secreting organs, such as pituitary gland, pancreas, thyroid and adrenals, as evidenced by *in vitro* studies as well as by the physiological uptake *in vivo* during somatostatin receptor scintigraphy[10, 17-20]. Although the receptor density of SSTRs in normal, non-pathologic hormone secreting organs is not as high as observed in neuroendocrine tumours, the presence of SSTRs implicates the possibility of specific receptor-mediated targeting by radiolabelled somatostatin analogues. Furthermore, as the radiopharmaceuticals used in PRRT are systemically administered, all organs will receive an additional non-specific dose, including those organs that are known to be radiosensitive (e.g. the gonads).

Fifteen out of 35 (43%) of our male patients had evidence of hypogonadism prior to PRRT. Gonadal dysfunction in patients with disseminated cancer prior to chemotherapeutic treatment has been reported by Chlebowski *et al.* [21]. A relationship between markedly decreased gonadal function and weight loss was also observed. Furthermore, other factors, including age, history of alcohol intake, and liver disease have been reported to have effects on the TT levels in male patients [22]. As there are many factors that may cause decreased TT levels, a specific or common cause of the high percentage of hypogonadism within our group of patients before PRRT is difficult to point out. Because of the very similar patterns of hormonal changes observed after PRRT in men with normal or low levels of TT before therapy (data not shown), it is likely that these additional factors did not contribute to the observed change in hormone levels in our study.

Decrease of mean TT level coincided with a decrease of SHBG level, whereas the mean non-SHBG-bound-T remained stable after PRRT. These observations are in line with findings of de Ronde *et al.* [23] who demonstrated a strong positive relationship between SHBG and TT levels and no or only a weak positive association between SHBG and circulating non-SHBG-bound-T levels. Because SHBG correlates negatively with BMI [24], a possible explanation for the decrease of SHBG is the significant increase of body mass index (BMI) in our patients from 24.0±0.7 $kg.m^{-2}$ to a maximum of 25.3±0.8 $kg.m^{-2}$ at 12 months of follow-up. Furthermore, we found a weak positive, but significant correlation (Spearman's rho = 0.29, p=0.01) between FT4 and SHBG (data not shown). Correlation between FT4 and SHBG was demonstrated during thyroid hormone replacement therapy in hypothyroid men by Cavaliere *et al.* [25]. However, whether the relatively small increase of mean BMI or the limited decline in mean FT4 level observed in our study is responsible for the marked decline of SHBG is questionable. In theory, impaired liver function after therapy can also cause

decreased SHBG levels. This is unlikely, however, because of unchanged albumin levels and stable or decreased serum levels of gamma-GT, alkaline fosfatase, ASAT and ALAT throughout the whole study period (data not shown).

Our data indicate that transient impairment of spermatogenesis occurs following PRRT. A significant decrease of mean serum inhibin B levels with a concomitant increase in FSH levels was observed, with recovery to almost pretreatment levels after 24 months. This is in line with several studies in patients with differentiated thyroid carcinoma who received radioiodine therapy [26-29]. Inhibin B is produced in the Sertoli cells of the testis and is the major feedback regulator of FSH [30, 31]. It has been demonstrated that serum inhibin B levels are positively correlated with spermatogenic status and sperm count [32, 33]. Therefore, although we did not perform semen analyses, our results likely indicate temporarily impaired spermatogenesis. Both the gonadal and pituitary gland function are potentially at risk after PRRT. Effects on gonadotroph levels after ^{177}Lu-octreotate therapy was demonstrated in postmenopausal women. A significant decrease in both FSH and LH was found. The observed decrease in mean FSH and LH level of approximately 12.5% and 8.2% per year, respectively, was higher than could be expected because of ageing as such. In a study of 680 postmenopausal women, the decrease of gonadtropin levels between the ages of 55 and 75 years was less than 1% per year [34].

Two out of 66 (3%) patients developed primary hypothyroidism after treatment. One patient had hypothyroidism with the development of anti-TPO antibodies suggesting autoimmune induced hypothyroidism. The other patient had slowly progressive primary hypothyroidism and was put on substitution therapy 3.5 years after ^{177}Lu-octreotate therapy. Thyroid hormone analyses of the total group demonstrated a significant decrease of FT4 at the end of the study period. This is in line with a significant decrease of FT4 levels we reported earlier [5]. The decline of FT4 was not accompanied by a significant increase of TSH or T3, though trends towards an increase and decrease, respectively, were noticed. Of interest, analysis excluding the two hypothyroid patients revealed no significant change in FT4, TSH or T3. Since chronicity and severity of disease might have an impact on the thyroid hormone status and even can induce non-thyroidal illness (NTI), the observed changes of thyroid hormones in the long-term could reflect the development of NTI rather than the effect of PRRT. Signs of NTI were observed at baseline with an increased mean level of rT3. Specific changes in thyroid hormone levels were reported to correlate with the severity of illness or even to be prognostic for survival in critically ill patients [35]. Directly after the first cycle of PRRT, rT3 returned to reference range values. Thereafter, rT3 slowly increased but remained within the normal reference range. The active over inactive thyroid hormone (T3/rT3) ratio had a similar, but inverse pattern. These changes suggest a rapid change to a more favorable disease

state directly after initiation of PRRT and which persists during follow-up. A sub-analysis of patients according to therapy outcome indicated that patients who had PD had a no significant change in rT3 level, whereas the other patients had a significant decrease, returning to the normal range during therapy. Therefore, in our group of patients, the change in rT3 and T3/rT3 ratio probably reflected changes in the disease status.

The hypothalamo-pituitary-adrenal (HPA) axis is not affected by PRRT in terms of intact adrenal reserve. All patients had adequate responses with the LDST before therapy. Additionally, adequate responses in eighteen patients after therapy indicated no apparent primary or secondary adrenal insufficiency. The LDST is a valid replacement for the commonly used short synacthen test and the insulin tolerance test (ITT), of which the latter is widely regarded as the gold standard test for the integrity of the HPA axis [36]. Unfortunately, the ITT is not completely safe, costly and difficult to perform in an outpatient setting, thus hampering its clinical use. An LDST peak cortisol response higher than 550 nmol/L was observed in all patients and was regarded as a sufficient response indicating sustained integrity of the HPA-axis. In a recent meta-analysis on the diagnosis of adrenal insufficiency, it was concluded that a cut-off value between 500 and 600 nmol/L cortisol is necessary to achieve reasonable sensitivity for the detection of both primary and secondary adrenal insufficiency [37].

Interestingly, mean peak cortisol level after PRRT was significantly lower than before therapy. Whether this subtle difference in LDST response after therapy reflects radiation-induced mild partial adrenal insufficiency or simply a less stressful state of the patients is not clear. However, Schmiegelow *et al*., reported similar findings in 73 patients treated with radiotherapy and chemotherapy for childhood brain tumours with a mean follow-up of 15 years [38]. Nineteen percent of the patients had insufficiency of the HPA axis, whereas the remainder of patients, even though an adequate response to an ACTH test or ITT, had lower peak cortisol levels compared with controls. The external beam radiotherapy, not chemotherapy, was regarded as the main factor that had contributed to the observed adrenal insufficiency. It was concluded that this latter group might be potentially at risk of becoming HPA axis insufficient in the future. Life-long follow-up was recommended in these patients. Although it is difficult to compare ^{177}Lu-octreotate therapy with external beam radiation therapy in terms of dose-tempo, exposure area and period of follow-up, these studies indicate that despite the adequate LDST responses found in our patients, awareness of a radiation-induced disturbance of the HPA-axis is important in the long-term follow-up.

Five patients out of 62 (8%) developed increased levels of HbA_{1c} after ^{177}Lu-octreotate therapy without any obvious cause, such as subsequent pancreatic surgery. Pancreatic islets express somatostatin receptors, especially the subtype SSTR2a [39]. However, 46% of our patients used somatostatin analogues, such as octreotide, during and/or after therapy. Therefore, besides the possibility of a direct radiation effect as the cause of the observed subtle, but significant increase of mean HbA_{1c} after therapy, long-term treatment with somatostatin analogues, could have contributed as well.

In conclusion, in men ^{177}Lu–octreotate therapy induced transient inhibitory effects on spermatogenesis, but, non-SHBG-bound-T levels remained unaffected. In the long-term, gonadotropin levels decreased significantly in postmenopausal women. Only few patients developed hypothyroidism or elevated levels of HbA_{1c}. No clinically apparent relevant effects was observed on pituitary-adrenal function. Despite temporary and minor hormonal changes, PRRT with ^{177}Lu–octreotate can be regarded as a safe treatment modality with respect to the short and long-term endocrine function.

We conclude that patients who are treated with ^{177}Lu-octreotate therapy may develop radiation-induced hormone disturbances, some of which have been proven to be temporary, and which are in general mild. No severe hormone inbalance was observed and, therefore, ^{177}Lu-octreotate therapy, in terms of endocrine sequelae, can be regarded as safe. However, awareness of the possibility of changes in, and thereby surveillance of, the endocrine status, is important and implicates the necessity of future studies.

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Comparison of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate and [^{177}Lu-DOTA^{0},Tyr^{3}]octreotide: which peptide is preferable for PRRT?

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Abstract

Purpose

Patients with somatostatin receptor subtype 2-positive metastasised neuroendocrine tumours can be treated with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. Some use octreotide as the peptide for peptide receptor radionuclide therapy (PRRT). We compared in seven patients [^{177}Lu-DOTA^{0},Tyr^{3}]octreotide (^{177}Lu-DOTATOC) and [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-DOTATATE), to see which peptide should be preferred for PRRT with ^{177}Lu.

Methods

In the same patients, 3,700 MBq ^{177}Lu-DOTATOC and 3,700 MBq ^{177}Lu-DOTATATE was administered in separate therapy sessions. Amino acids were co-administered. Whole-body scanning was performed on days 1, 4 and 7 posttherapy. Blood and urine samples were collected. We calculated residence times for tumours, spleen and kidneys.

Results

All patients had longer residence times in spleen, kidneys and tumours after use of ^{177}Lu-DOTATATE ($p=0.016$ in each case). Comparing ^{177}Lu-DOTATATE with ^{177}Lu-DOTATOC, the mean residence time ratio was 2.1 for tumour, 1.5 for spleen and 1.4 for kidneys. Dose limiting factors for PRRT are bone marrow and/or kidney dose. Although the residence time for kidneys was longer when using ^{177}Lu-DOTATATE, the mean administered dose to tumours would still be advantageous by a factor of 1.5, assuming a fixed maximum kidney dose is reached. Plasma radioactivity after ^{177}Lu-DOTATATE was comparable to that after ^{177}Lu-DOTATOC. Urinary excretion of radioactivity was comparable during the first 6 h; thereafter there was a significant advantage for ^{177}Lu-DOTATOC.

Conclusion

^{177}Lu-DOTATATE had a longer tumour residence time than ^{177}Lu-DOTATOC. Despite a longer residence time in kidneys after ^{177}Lu-DOTATATE, tumour dose will always be higher. Therefore, we conclude that the better peptide for PRRT is octreotate.

INTRODUCTION

One of the new treatment modalities for metastasised neuroendocrine gastro-entero-pancreatic (GEP) tumours— taking its place alongside surgery, (chemo)embolisation, chemotherapy and treatment with somatostatin analogues —is peptide receptor radionuclide therapy (PRRT). Since 2000 we have treated patients with somatostatin receptorpositive pathology with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate; in most cases these patients have had metastasised neuroendocrine tumours (NETs). An analysis of 131 of the more than 400 treated patients with so-called GEP tumours was performed after obtaining all results following completion of treatment. A decrease in tumour size was found in 47%, stable disease in 35% and tumour progression despite treatment in 18% [1]. A significant improvement in quality of life in those patients with tumour regression was also noted [2]. The average duration of the effect of therapy was more than 36 months, calculated from the start of therapy. From these figures it seems that PRRT is a promising choice of treatment for metastasised neuroendocrine GEP tumours. Some research groups use radiolabelled octreotide for PRRT [3,4] whereas we use radiolabelled octreotate as the peptide, this approach being supported by evidence from different sources. Reubi *et al*. reported that octreotate has a higher affinity than octreotide for somatostatin receptor subtype sst2 [5]. De Jong *et al*. compared in vitro and in vivo ^{111}In-labelled somatostatin analogues for tumour scintigraphy and radionuclide therapy in the same somatostatin receptor-positive rat CA20948 pancreatic tumour. DTPA-chelated octreotate had the highest uptake in the target organs [6]. Further, the same authors investigated [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in biodistribution and radionuclide therapy experiments using Lewis rats bearing the CA20948 tumour and reported excellent results of radionuclide therapy, especially in animals bearing smaller tumours [7]. Capello and co-workers evaluated the therapeutic effects of somatostatin analogues chelated with DOTA and labelled with ^{90}Y or ^{177}Lu in an in vitro colony-forming assay using the rat pancreatic tumour cell line CA20948. They concluded that [DOTA^{0},Tyr^{3}]octreotate labelled with ^{177}Lu or ^{90}Y is the most promising analogue for PRRT [8]. Nilsson *et al*. studied the biokinetics and therapeutic effect of radiolabelled somatostatin analogues on a midgut carcinoid (GOT1) grafted to nude mice. They tested [^{111}In-DTPA-*D*-Phe^{1}]octreotide and [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate, and concluded that octreotate is the most promising peptide for use in treatment [9]. Schmitt *et al*. compared the biodistribution of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate, [^{111}In-DTPA]octreotide and ^{99m}Tc-depreotide in nude mice bearing tumours from the human SCLC cell line NCI-H69. [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate gave the highest tumour activity concentration [10]. Kwekkeboom *et al*. found in a comparison with [^{111}In-DTPA^{0}]octreotide in patients a three- to fourfold higher tumour uptake with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate [11]. In summary, all these studies showed that octreotate might be the better candidate for PRRT. However, recently Forrer *et al*. could not find a significant difference when comparing ^{111}In-DOTATOC and ^{111}In-DOTATATE in five patients with metastasised NETs [12]. So far, however, no comparison between

[^{177}Lu-DOTA°,Tyr^{3}]octreotide (^{177}Lu-DOTATOC) and [^{177}Lu- DOTA°,Tyr^{3}]octreotate (^{177}Lu-DOTATATE) has been published. Therefore we decided to compare octreotide with octreotate in therapeutic doses in the same patients to investigate which is the preferable peptide for PRRT. Randomly, we selected patients who came for PRRT and divided the usual first therapeutic dose of 7,400 MBq (200 mCi) into two separate doses/treatments, each of 3,700 MBq (100 mCi) ^{177}Lu. In order to exclude possible therapeutic effects, one group started with octreotide as the peptide and one group with octreotate, then switching to the other peptide for the second therapy.

MATERIAL AND METHODS

Patients

Four male patients (age 44–64, mean 59 years) and three female patients (age 43–67, mean 56 years) with known NETs were injected with 3,700 MBq ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC. Four patients received ^{177}Lu-DOTATOC for the first treatment and three, ^{177}Lu-DOTATATE; as already mentioned, the second treatment was with the other peptide. Three patients had NETs of the pancreas, two a midgut carcinoid, one a carcinoid of unknown primary and one a carcinoid of the lung. All except one patient with a NET of the pancreas had metastases. The interval between the two therapies was 8 weeks. Long-acting somatostatin analogues were stopped at least 6 weeks before treatment and short-acting analogues were stopped at least 24 hours before treatment. All patients had a histologically proven NET and had never previously had PRRT. Tumour sites were confirmed by CT or MRI together with a positive OctreoScan. All patients gave informed consent to participation in the study, which was approved by the hospital's ethics committee.

Radiopharmaceuticals

Both somatostatin analogues, [DOTA°,Tyr^{3}]octreotide (DOTATOC) and [DOTA°,Tyr^{3}]octreotate (DOTATATE), were synthesised according to previously published procedures [11] and labelled with ^{177}Lu (obtained from NRG, Petten, the Netherlands and distributed by IDB-Holland, Baarle Nassau, the Netherlands).

Infusion

To prevent nausea, first granisetron 3 mg was injected i.v.; thereafter an infusion of amino acids (lysine 2.5%, arginine 2.5% in 1 l 0.9% NaCl: 250 ml/h) was started 30 min before the administration of the radiopharmaceutical and lasted in total for 4 h. The radiopharmaceutical was co-administered in 30 min via a second pump system.

Imaging

All imaging was done on a Picker Prism 2000 XP dual-head gamma camera. Counts from both gamma peaks of ^{177}Lu (208 and 113 keV) were collected in separate windows (width 20%). Parallel-hole, medium-energy general-purpose collimators were used. Whole-body scans of 40 min were obtained 24 h and 4 and 7 days post therapy. A known aliquot of radioactivity was placed between the patients' knees to enable calculation of the uptake in spleen, kidneys and tumours.

Measurement of radioactivity in blood and urine

Blood samples were taken 10 min after the infusion of the radiopharmaceutical had been completed and 30 min, 60 min, 4 h, 24 h, 4 days and 7 days thereafter. Urine was collected in four intervals: 0–3, 3–6, 6–12 and 12–24 h after infusion. Radioactivity in these samples was measured with a gamma counter (LKB-Wallac 1282 Compugamma, Turku, Finland) and a dose calibrator (VDC-202, Veenstra instrumenten B.V., Joure, the Netherlands).

Methods

Regions of interest (ROIs) were drawn manually on the whole-body scans over kidneys, spleen and tumours. Regions were placed close to the ROIs for background correction. Organs showing superimposition of tumour were excluded for evaluation of organ residence time. No attenuation correction was performed because every patient was his/her own control. Instead, the ratio of residence time in the organs and tumours between the two therapies was considered most important. The dose measured before infusion minus the residual radioactivity in the infusion system after administration was defined as 100%. All data were expressed as percentage of this 100%.

Statistics

Analysis of variance (ANOVA) and Sign tests were used for statistical analysis. P values <0.05 were considered significant.

RESULTS

As can be seen in Figure 1, for both peptides there was fast clearance from the blood expressed as percentage of injected activity (%IA), resulting in a decrease to less than 10% within the first 3 h. During the first day the blood clearance of ^{177}Lu-DOTATOC was slightly faster than that of ^{177}Lu-DOTATATE, but the difference did not reach significance (ANOVA test $P>0.05$). Thereafter the blood clearance for both peptides was nearly the same.

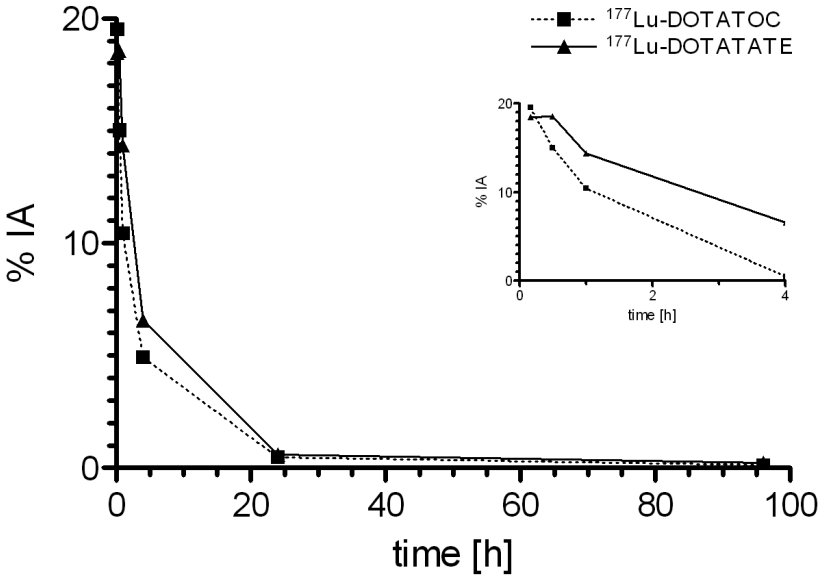

Figure 1. Serum radioactivity expressed as mean percentage injected activity (%IA)

The cumulative excreted activity in the urine was higher for ^{177}Lu-DOTATOC than for ^{177}Lu-DOTATATE, at 81% versus 71% (Figure 2). This was significant for the time periods 0–12 h (ANOVA *P*=0.045) and 0–24 h (ANOVA *P*=0.026).

The biodistribution pattern for the two peptides was nearly the same. However, the residence time of radioactivity in the tumours was significantly longer in all patients after ^{177}Lu-DOTATATE (Table 1; Sign test, *P*=0.016). Comparing ^{177}Lu-DOTATATE with ^{177}Lu-DOTATOC, the mean ratio of the tumour residence time was 2.1 (Figure 3). Similarly, the residence times in the spleen and the kidneys were significantly longer after ^{177}Lu-DOTATATE (Sign test, *P*=0.016 for both spleen and kidneys). Comparing ^{177}Lu-DOTATATE with ^{177}Lu-DOTATOC, the mean ratio of the residence time was 1.5 for spleen and 1.4 for kidneys.

DISCUSSION

Treatment options for inoperable, metastasised NETs are limited. Usually, treatment with somatostatin analogues is started if patients suffer from syndromes caused by hormonal overproduction by the tumours. Although usually very rewarding in terms of symptom control, such treatment seldom results in tumour growth remission. If the tumour is progressive, chemo-embolisation or embolisation of liver metastases may be effective if the bulk of the tumour is situated within the liver [13,14]. Radiological expertise in this procedure has to be available, however.

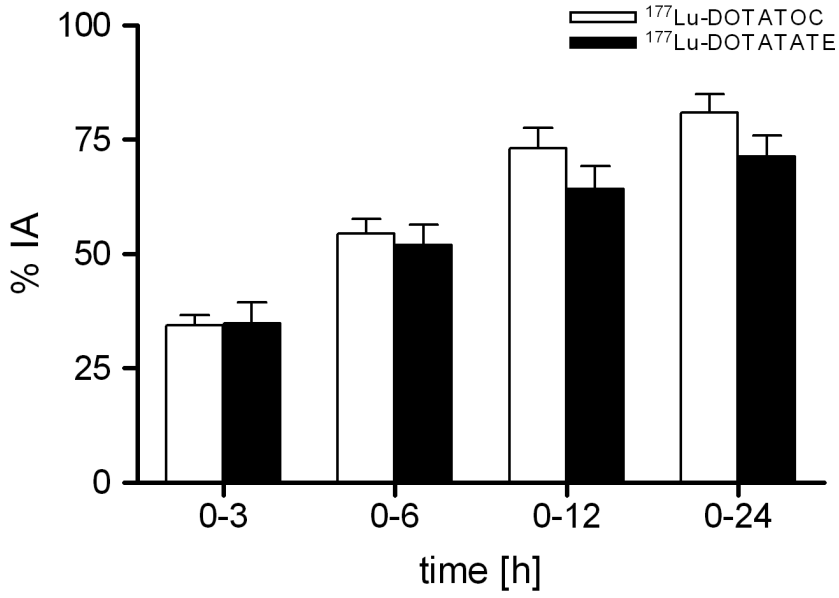

Figure 2. Cumulative radioactivity excreted in urine, expressed as mean (±SEM) percentage injected activity (%IA)

Another option is chemotherapy. O'Toole *et al*. reviewed the use of chemotherapy for GEP tumours and found that the published series evaluating chemotherapy for midgut endocrine tumours were outdated and had yielded disappointing results. Thus the objective response rates with combination chemotherapy (including 5-fluorouracil and/or streptozotocin) rarely exceeded 20%. These authors reported that only for the relatively rare poorly differentiated GEP tumours is chemotherapy, using cisplatin and etoposide, the reference treatment: objective response rates of >50% were achieved in such patients, but despite the chemosensitivity of these tumours, disease control was limited (8–10 months) [15]. Öberg also reviewed chemotherapy and biotherapy in the treatment of NETs. He reported that streptozotocin-based combinations including 5-fluorouracil and doxorubicin resulted in partial remissions in 40–60% of the patients, with a median survival of about 2 years in patients with advanced disease. Cisplatin plus etoposide demonstrated significant anti-tumour effects in anaplastic endocrine pancreatic tumours and lung carcinoids. However, for classical midgut carcinoids, the same combination of cytotoxic agents resulted in short-lasting responses in only 10% of patients [16]. Summarising, the results of chemotherapy are disappointing in the most common NETs, the midgut carcinoids. Although results are somewhat better for pancreatic NETs, the reported time to progression and the duration of survival are relatively short. Therefore, chemotherapy is best reserved for patients with relatively rare undifferentiated or anaplastic NETs.

A relatively new treatment modality is radiolabelled somatostatin analogues. Various peptides and radionuclides have been used. The most commonly used peptides are [DOTA°,Tyr^3]octreotide (DOTATOC) and [DOTA°, Tyr^3]octreotate (DOTATATE), labelled with either ^{90}Y or ^{177}Lu. We compared ^{177}Lu-DOTATOC and ^{177}Lu-DOTATATE in a therapeutic setting and within the same patients.

Our assumption that octreotate is the preferable peptide when labelling it with ^{177}Lu was confirmed. We found a longer residence time in the tumours in all our patients after ^{177}Lu-DOTATATE treatment compared with ^{177}Lu-DOTATOC, leading to a higher absorbed tumour dose. The mean difference was statistically significant (P=0.016). A longer residence time is especially of interest when using radionuclides with a longer half-life (6.7 days for ^{177}Lu compared with 2.7 days for ^{90}Y).

Reubi *et al*. evaluated the in vitro binding characteristics of different somatostatin radiotracers, among which were labelled and unlabelled DOTATOC and DOTATATE. They showed a higher binding affinity to somatostatin receptor subtype 2 (sst2) for ^{90}Y-DOTATATE than for ^{90}Y-DOTATOC [5]. Our findings are in concordance with those of Reubi *et al*.: we found a significantly longer residence time in the tumours and in the spleen using DOTATATE. We also found that ^{177}Lu-DOTATATE shows higher affinity for sst2 compared with ^{177}Lu- DOTATOC.

Forrer *et al*. [12] compared ^{111}In-DOTATOC and ^{111}In- DOTATATE. They used ^{111}In as a surrogate for ^{90}Y and found comparable data for the two peptides with regard to tumour-to-kidney ratios. Therefore they concluded that they would continue with therapy using ^{90}Y-DOTATOC.

The assumption that ^{111}In is comparable to ^{90}Y is disputable. In 2000, Reubi *et al*. tested the affinity of different somatostatin radiotracers. There was a marked difference in affinity after small structural changes in the radioligand molecule, the introduction of a metal, the replacement of one metal by another or the replacement of one chelator by another [5].

Forrer *et al*. also assumed that a diagnostic investigation with 222 MBq ^{111}In could be translated to a therapeutic session [12]. They used only 10 µg peptide to predict the outcome of a therapeutic dose with a significantly higher peptide concentration. For our evaluation we used 200 µg of peptide with 3,700 MBq of activity. The amount of peptide that we typically use when administering ^{177}Lu-DOTATATE is 130–210 µg, depending on the specific activity of the radionuclide; therefore, we think that our setup is far more comparable to the usual therapeutic conditions.

Table 1. Residence time (h) and ratio between both peptides, not corrected for attenuation

	Tumour			Kidney			Spleen		
Patient	DOTATOC	DOTATATE	TATE:TOC	DOTATOC	DOTATATE	TATE:TOC	DOTATOC	DOTATATE	TATE:TOC
1	0.53	0.57	1.1	0.37	0.56	1.5	0.81	1.16	1.4
2	0.05	0.11	2.2	0.42	0.56	1.3	0.78	1.05	1.3
3	1.21	1.81	1.5	0.34	0.45	1.3	0.25	0.31	1.2
4	0.03	0.07	2.3	0.47	0.61	1.3	0.85	1.28	1.5
5	0.11	0.26	2.4	0.46	0.72	1.6	2.1	3.17	1.5
6	0.55	1.2	2.2	0.34	0.41	1.2	0.97	1.32	1.4
7	0.07	0.22	3.1	0.21	0.28	1.3	0.45	0.89	2.0
Mean ± SEM	0.36 ± 0.16	0.60 ± 0.25	2.1	0.37 ± 0.03	0.51 ± 0.06	1.4	0.89 ± 0.22	1.31 ± 0.34	1.5
P value		0.016			0.016			0.016	

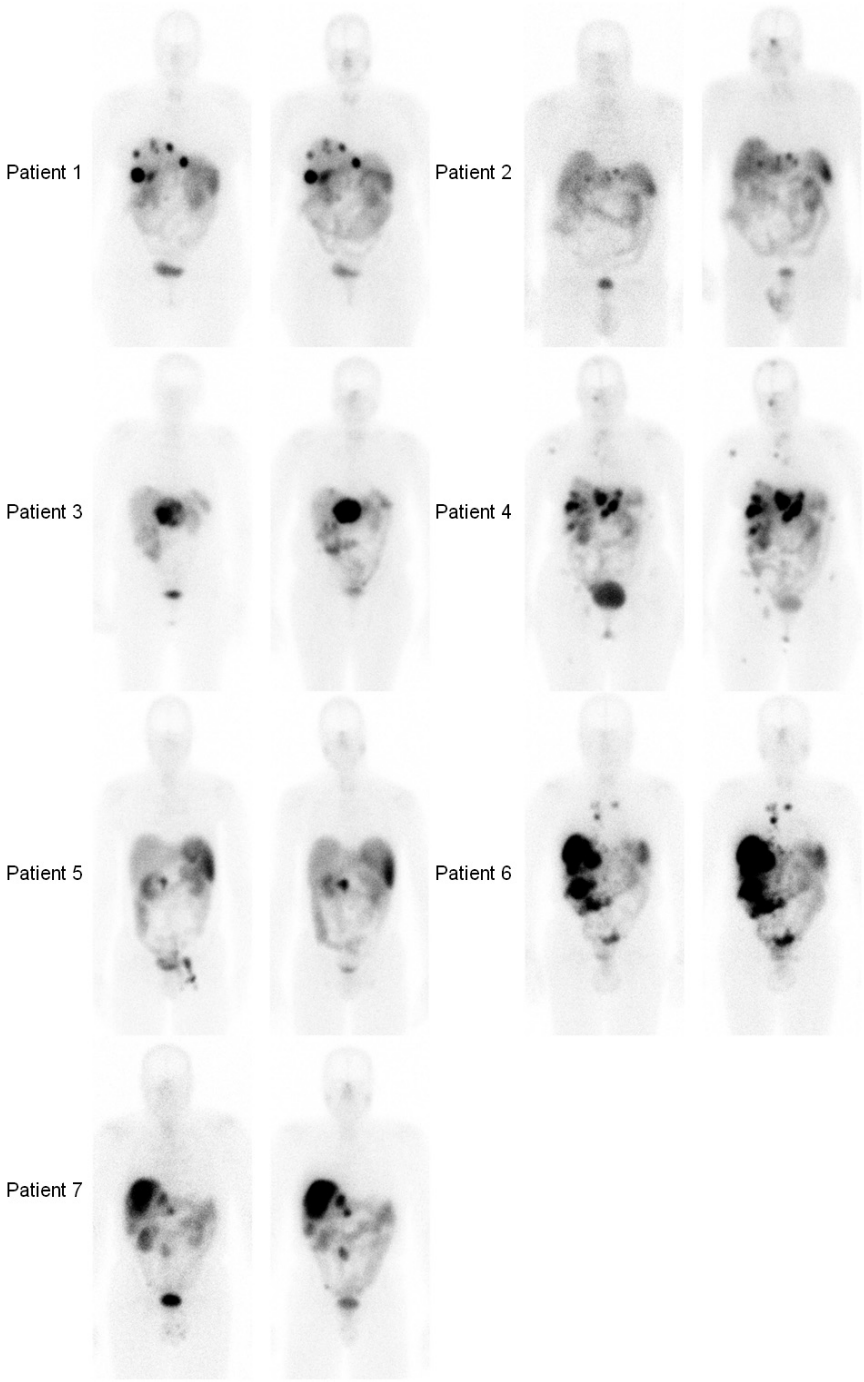

Figure 3. Planar anterior whole-body scans 1 day post therapy, after ^{177}Lu-DOTATOC (*left*) and after ^{177}Lu-DOTATATE (*right*). Patient numbers correspond to those in Table 1.

The pharmacokinetics of ^{177}Lu-DOTATOC and ^{177}Lu-DOTATATE in our study, such as urinary excretion and blood clearance, were nearly the same compared to the results of Forrer *et al*. One of the dose-limiting factors for PRRT can be the total kidney dose. Comparing ^{177}Lu-DOTATATE with ^{177}Lu-DOTATOC, we found a 2.1 times longer tumour residence time of the radioactivity after ^{177}Lu-DOTATATE, leading to a higher absorbed tumour dose. The residence time ratio for the kidneys (1.4) was lower than that for tumours. Consequently, in general one can say that tumours treated with ^{177}Lu-DOTATATE will always receive a higher total dose of radioactivity than those treated with ^{177}Lu-DOTATOC. Even if one assumes that a certain maximum total dose can be given that is determined by the maximum radiation absorbed dose to the kidneys, there will still be a higher radiation absorbed dose to the tumour after ^{177}Lu-DOTATATE, given that division of the mean tumour residence time ratio (2.1) by the mean kidney residence time ratio (1.4) yields a factor of 1.5 in favour of ^{177}Lu-DOTATATE. Furthermore, we know from our own unpublished data, obtained in more than 400 patients, that in 70% of patients treated with ^{177}Lu-DOTATATE, the maximum dose allowed for a presumed bone marrow absorbed dose of 2 Gy, i.e. 29,600 MBq or 800 mCi, determines treatment cessation, and not the maximum allowed kidney dose of 23 Gy. Therefore, in most patients, the mean tumour residence time ratio of 2.1 in favour of ^{177}Lu-DOTATATE will apply.

In conclusion, [^{177}Lu-DOTA°,Tyr^3]octreotate demonstrated a significantly longer tumour residence time than[^{177}Lu-DOTA°,Tyr^3]octreotide in patients with sst2 receptor-positive metastasised NETs. Therefore, when labelled with ^{177}Lu, octreotate is the preferred peptide for PRRT.

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6

Radiolabelled somatostatin analogues and differentiated thyroid carcinoma

6.1

Peptide receptor radionuclide therapy for non–radioiodine-avid differentiated thyroid carcinoma

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Abstract

In patients with progressive metastatic (or recurrent) differentiated thyroid carcinoma (DTC) who do not respond to radioiodine therapy or do not show uptake on radioiodine scintigraphy, treatment options are few. Because these tumors may express somatostatin receptors, peptide receptor radionuclide therapy might be effective. We evaluated the therapeutic efficacy of the radiolabeled somatostatin analog ^{177}Lu-1,4,7,10-tetraazacyclododecane-*N,N′,N″,N‴*-tetraacetic acid° (DOTA), Tyr^3-octreotate (^{177}Lu-DOTATATE) in patients with DTC. The uptake of radioactivity in tumors was also studied in relation to treatment outcome.

Methods

Five patients with DTC (3 with Hürthle cell thyroid carcinoma [HCTC], 1 with papillary thyroid carcinoma [PTC], and 1 with follicular thyroid carcinoma [FTC]) were treated with 22.4–30.1 GBq of ^{177}Lu-DOTATATE. Response to therapy was evaluated with CT. Uptake on ^{177}Lu-DOTATATE scintigraphy (24 h after treatment), expressed as percentage of injected dose, was compared with uptake on pretherapy ^{111}In-octreotide scintigraphy (24 h after injection).

Results

After the last treatment with ^{177}Lu-DOTATATE, 1 patient with HCTC had stable disease as a maximum response, 1 patient with HCTC had minor remission (tumor shrinkage between 25% and 50%), and 1 patient with HCTC had partial remission (shrinkage > 50%). The responses in PTC and FTC were stable disease and progressive disease, respectively. A decrease in serum thyroglobulin level was found in patients with HCTC. Patients with minor and partial remissions had the highest ^{177}Lu-DOTATATE–to–^{111}In-diethylenetriamine pentaacetic acid°-octreotide (^{111}In-octreotide) uptake ratios (3.2 and 2.4, respectively) whereas the other patients had uptake ratios smaller than 1.5.

Conclusion

^{177}Lu-DOTATATE therapy can be effective in patients with progressive DTC who have no therapeutic options and sufficient uptake of ^{111}In-octreotide in tumor lesions as shown on ^{111}In-octreotide scintigraphy. This finding is especially important in patients with HCTC, because they cannot benefit from radioiodine therapy because of non–iodine-avid lesions at diagnosis.

INTRODUCTION

Standard therapy in patients with differentiated (follicular and papillary) thyroid carcinoma (DTC) involves total or near-total thyroidectomy, followed by ablation of the thyroid remnant with ^{131}I. Although long-term prognosis with this combination of surgery and radioiodine therapy is generally quite good, tumor recurrences occur in about 20% of patients, sometimes decades after initial therapy [1,2]. Follow-up in these patients is based on a combination of serum thyroglobulin (Tg) monitoring and radioiodine whole-body scans (WBSs). Whenever recurrence or metastatic disease is evident on the WBS, patients are retreated with radioiodine. However, in 20%–30% of these patients, additional ^{131}I therapy is not effective because of the lack of radioiodine uptake in tumors [3,4]. In addition, Hürthle cell thyroid carcinomas (HCTCs), which are assigned to the group of follicular thyroid carcinoma (FTC), are known to rarely take up iodine, even at the time of diagnosis [5].

Alternative treatments in patients with no uptake of radioiodine are few. Dedifferentiation is associated with a worse prognosis, which is largely because these patients cannot be treated with radioiodine [6]. Patients with iodine-concentrating pulmonary metastases have a 5-yr survival rate of 60% compared with 30% for patients with tumors that do not concentrate radioiodine [4,7]. Therefore, any effective therapy would be welcome. As most of these patients have widespread metastatic disease, surgery is not an option. External beam radiotherapy can provide only regional control of localized recurrences. Studies on the effectiveness of chemotherapy have been disappointing [8,9].

In patients with elevated serum thyroglobulin levels with no evidence of disease on radioiodine scintigraphy, scintigraphy with the somatostatin analog ^{111}In-diethylenetriaminepentaacetic acid° (DTPA°)-octreotide (^{111}In-octreotide, OctreoScan; Mallinckrodt) can be an alternative imaging modality. Several reports have demonstrated uptake of ^{111}In-octreotide in metastatic or recurrent disease in the majority of these patients [10–13]. As a consequence, the use of high doses of radiolabeled somatostatin analogs as targeted therapy in peptide receptor radionuclide therapy (PRRT) has become the focus of major interest as an alternative therapy. Patients with progressive DTC and tumor uptake on ^{111}In-octreotide scintigraphy have been treated with various radiolabeled somatostatin analogs, including ^{111}In-octreotide, ^{90}Y-1,4,7,10-tetraazacyclododecane-*N,N',N",N"'*-tetraacetic acid° (DOTA)-*D*-Phe^{1},Tyr^{3}-octreotide (^{90}Y-DOTATOC), and ^{90}Y-DOTA-lanreotide [14–17]. In this study, we report the results of treatment with the novel radiolabeled somatostatin analog ^{177}Lu-DOTA°,Tyr^{3}-octreotate (^{177}Lu-DOTATATE) in 5 patients with DTC.

MATERIALS AND METHODS

Patients

Five patients with recurrent or metastatic differentiated thyroid carcinoma were treated with ^{177}Lu-DOTATATE. Patient characteristics are summarized in Table 1. All patients had visible tumor uptake on ^{111}In-octreotide scintigraphy before therapy. None of the patients had been treated with other radiolabeled somatostatin analogs in the past. All patients were on thyroid-stimulating hormone (TSH) suppressive thyroxin therapy. Prerequisites for treatment were: hemoglobin > 5.5 mmol/L; white blood cell count >2 x 10^9/L; platelets > 75 x 10^9/L; creatinine <150 μmol/L; Karnofsky performance status > 50. All patients gave written informed consent to participate in the study, which was approved by the medical ethical committee of the hospital.

Imaging

^{111}In-octreotide. Planar spot imaging was performed with a double-head γ-camera (Prism 2000XP; Philips Medical Systems). Windows with a 20% width were centered over each of the 2 ^{111}In photon peaks (245 and 172 keV). Fifteen-minute spot images were obtained 24 h after injection of 222 MBq of ^{111}In-octreotide. A standard with a known aliquot of the injected dose was measured for dosimetry.

^{177}Lu-DOTATATE. Planar spot images of the chest, neck, and upper abdomen were obtained 24 h after injection of the therapeutic dose of ^{177}Lu-DOTATATE. Upper abdomen images were also obtained on 2 occasions in the following days for kidney dosimetry. Counts (20% window width) from the 208 keV γ-peak were collected. The acquisition time was 15 or 7.5 min/view. For dosimetry, a standard with a known aliquot of the injected dose was also measured.

Therapy

DOTATATE was obtained from Mallinckrodt. $^{177}LuCl_3$ was obtained from NRG and the Missouri University Research Reactor, distributed by IDB. ^{177}Lu-DOTATATE was prepared as described in a previous publication [18]. Three milligrams of granisetron were injected intravenously and an infusion of amino acids (2.5% lysine and 2.5% arginine in 1 L 0.9% NaCl at 250 mL/h) was started 30 min before administration of the radiopharmaceutical and lasting up to 3.5 h afterwards. The radiopharmaceutical was coadministered through a second pump system. Treatment doses of 1.9 and 3.7 GBq were injected over 20 min and those of 5.6 GBq and 7.4 GBq were injected over 30 min. The interval between treatments varied from 6 to 15 wk. The number of treatments varied from 3 to 8. Some patients were included in the early phase of therapy with ^{177}Lu-DOTATATE, when dose escalation was among the objectives.

Table 1. Patient characteristics

				Pre ^{177}Lu-octreotate Therapy						^{177}Lu-octreotate Therapy	
Patient	Gender	Age (yrs)	Tumor Classification *	Prior Therapy †	Tg (µg/ml) ‡	TSH (mU/l) §	^{131}I /^{123}I scan ||	^{111}In-octreotide **	PD"	Cumulative dose (GBq)	No. of Treatments
1	M	52	PTC	TT, ND, RIT (16.7 GBq) ¶, R	49.1	0.168	-	2	Yes	25.7	8
2	F	73	FTC	TT, RIT (10.6 GBq), R, C	5665	< 0.01	-	2	Yes	22.4	3
3	F	52	HCTC	TT, ND, RIT (1.9 GBq)	1110	0.02	-	3	Yes	27.4	8
4	F	74	HCTC	TT, RIT (12.9 GBq)	126	N/A	+	2	No	30.1	4
5	F	52	HCTC	TT, RIT (13,0 GBq), R	237	0.24	+/-	1	No	22.7	3

** PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; HCTC, Hürthle cell thyroid carcinoma; † TT, total thyroidectomy; ND, neck dissection; ¶ RIT, ^{131}I therapy (cumulative dose); C, chemotherapy; R, external radiation; ‡ serum thyroglobuline (Tg) level during levothyroxine treatment prior to ^{177}Lu-octreotate therapy; § TSH, thyroid stimulating hormone during levothyroxine treatment; || outcome of radioiodine scan; +/-, mixed ^{131}I positive and negative lesions; N/A, not available, ** tumor uptake score on ^{111}In-octreotide scintigraphy: 1; uptake in lesion less than the liver, 2; equal to the liver, 3; higher than the liver as described previously [19]; " PD, documented progressive disease within one year before therapy*

As a result of the time schedule, completion of all treatments varied from 3 to 12 months for any individual. All patients were allowed to receive up to a cumulative dose of 30 GBq, which corresponded to a calculated bone marrow dose of 2 Gy, except in those individual cases in which kidney dosimetry indicated less (maximum allowed kidney dose was 23 Gy). Routine hematology, liver and kidney function tests, hormone measurements, and serum tumor markers were measured 1 wk before each therapy, as well as at follow-up visits. CT or MR imaging was performed within 3 months before the first therapy, and 6–8 weeks, 3 months, and 6 months after the last treatment. Thereafter follow-up continued every 6 months.

In Vivo Measurements

CT- or MRI-assessed tumor measurements were scored according to the following criteria: progressive disease (PD), increase in measurable tumor mass volume ≥25%; stable disease (SD), tumor mass volume increase or decrease ≤25%; minor remission (MR), decrease of tumor mass volume between 25% and 50%; and partial remission (PR), decrease of tumor mass volume ≥50%. Time to progression (TTP) was defined as the time interval between the first treatment and the earliest date of disease progression based on CT or MR imaging measurements. The amount of uptake on pretherapy ^{111}In-octreotide and posttherapy ^{177}Lu-DOTATATE scintigraphy was scored visually on planar images on a 4-point scale according to criteria previously described by Krenning *et al*. [19]: lower than (grade 1), equal to (grade 2), or greater than (grade 3) normal liver tissue; and grade 4, higher than normal spleen/kidney uptake.

RESULTS

Five patients with metastatic DTC (3 with HCTC, 1 with papillary thyroid carcinoma [PTC], and 1 with FTC) were treated with 22.4–30.1 GBq of ^{177}Lu-DOTATATE. The patients were either negative on ^{131}I scintigraphy after therapy or proven unresponsive to ^{131}I therapy. Metastatic disease was present in all patients based on conventional imaging (CT/MR imaging or sonography), pathologic uptake of ^{111}In-octreotide, and elevated serum Tg levels. Tumor response after therapy was monitored by CT/MR imaging and serum Tg levels (Table 2).

Patient 1 was diagnosed in 1995 with PTC with supraclavicular metastases. Initial treatment consisted of total thyroidectomy followed by radioiodine ablation. In April 1996, the patient was treated with radioiodine for recurrent disease. Because of a newly developed sarcomatoid carcinoma of the vocal chord, a total laryngectomy and bilateral nodal neck dissection was performed later that year. Lymph nodes were positive for DTC, and a third dose of ^{131}I was given. In 1998, a fourth treatment of ^{131}I was given because of a third recurrence. However, no uptake of ^{131}I was visible on posttherapy scintigraphy. In contrast, ^{111}In-octreotide scintigraphy showed uptake

in the mediastinum. Subsequently, ^{177}Lu-DOTATATE therapy was initiated. Eight treatments were given with a cumulative treatment dose of 25.7 GBq, which resulted in SD. TTP was documented 18 months after the first treatment, with gradually increasing serum Tg levels. Thereafter, CT measurements showed PD. Four years after the first treatment, the patient died of the disease.

Patient 2 was diagnosed in 1990 with FTC. Within 1 yr after total thyroidectomy and ablation, CT assessment showed lung metastases, which were treated with a therapeutic dose of ^{131}I. However, posttherapy ^{131}I scintigraphy did not reveal any uptake in tumor. Therefore, additional treatment consisted of local external radiotherapy and chemotherapy with adriamycine. However, the patient had PD, and her clinical condition worsened. In 2000, tumor progression led to airway obstruction, which was complicated with pneumonia and severe stridor, necessitating emergency tracheostomy. At that time, ^{111}In-octreotide scintigraphy revealed numerous lesions in the chest, and, subsequently, ^{177}Lu-DOTATATE therapy was started. Three treatments of ^{177}Lu-DOTATATE with a total dose of 22.4 GBq could not stop tumor progression, which was obvious from both symptomatology and increased serum Tg levels. Two weeks after the last therapy, the patient died of tumor progression.

Patient 3 was diagnosed with HCTC and had undergone total thyroidectomy combined with a neck dissection. However, complete removal of the tumor mass was not possible because of intraoperative identification of tumor growth into the trachea. Surgery was followed by radioiodine therapy. Eighteen months later, an ultrasound of the neck revealed continued growth of the (para)tracheal mass, which did not accumulate any ^{123}I. ^{111}In-octreotide scintigraphy, however, showed uptake in the lower neck region. ^{177}Lu-DOTATATE therapy was initiated, and the patient received 8 treatments with a cumulative dose of 27.4 GBq. Six months after the last therapy, the patient was found to be in MR. Two years later progression was demonstrated. After an initial rise in serum Tg level after treatment, this decreased to a nadir of 46.6 μg/L, which reflected decrease of tumor mass volume (Figure 1a).

Patient 4 initially had a left-sided hemithyroidectomy for HCTC. Sixteen years later, 3 lung metastases were detected, and she had a right-sided hemithyroidectomy followed by ^{131}I therapy with 3.7 GBq, after which the serum Tg levels decreased from 150 to 18 μg/L. However, no change in tumor size was found. One year later no accumulation during ^{123}I scintigraphy was found. Despite the absence of radioiodine uptake, she was retreated with 3.7 GBq of ^{131}I, with no effect on tumor mass or serum Tg levels. In 1999, the serum Tg level increased to 507 μg/L and 5.5 GBq of ^{131}I was administered. Despite a positive lesion in the right upper lobe of the lung on ^{131}I scintigraphy after therapy, again no effect was found.

Table 2. Results of ^{177}Lu-DOTATATE therapy

	Tumor uptake score *		Best Response after Therapy †		
Patient	Pre-Therapy ^{111}In-octreotide	Post ^{177}Lu-octreotate Therapy	Tumor volume	Tg	TTP (months) ‡
1	2	1	SD	increase	18
2	2	3	PD	increase	4
3	3	3	MR	decrease	43
4	2	2	SD	decrease	24+
5	1	3	PR	decrease	22+

** tumor uptake score according to somatostatin receptor scintigraphy visual scoring system as described previously [19]; † SD (stable disease), < 25% reduction or increase of tumor size; PD (progressive disease), > 25% increase of tumor size; MR (minor remission), between 25% and 50% reduction of tumor size; PR (partial remission), > 50% reduction of tumor size; Tg = thyroglobulin; ‡ TTP=time to progression in months since start of therapy.*

Because of positive lesions detected on ^{111}In-octreotide scintigraphy, the patient received 4 treatments with a total dose of 30.1 GBq ^{177}Lu-DOTATATE. The serum Tg levels, which were measured before each treatment, increased up to a maximum of 1,730 µg/L. After the last treatment, the serum Tg levels decreased, with a nadir of 746 µg/L 14 months later (Figure 1b). On CT, no difference in tumor size was found. However, the radiology report mentioned an inhomogeneous aspect that suggested tumor necrosis.

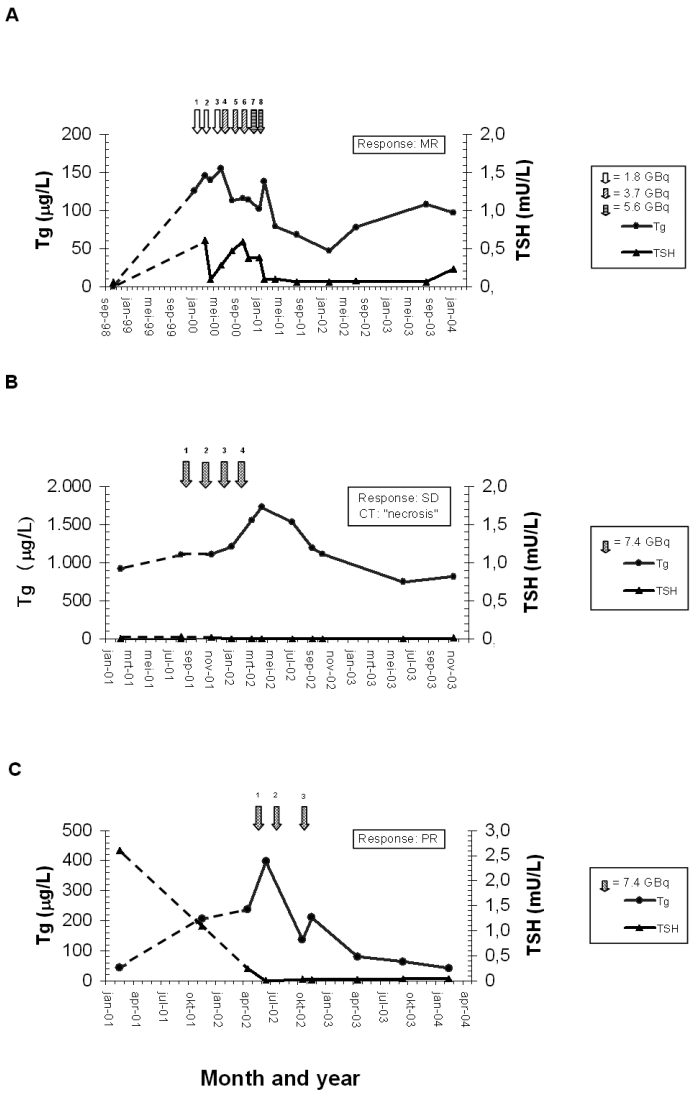

Figure 1a-c. Time course of serum Tg and TSH levels in patient 3, 4, and 5 treated with ^{177}Lu-DOTATATE. Broken lines represent pretherapy levels.

Patient 5 with an HCTC was diagnosed in 1997 and subsequently underwent a total thyroidectomy followed by radioiodine ablation therapy. Because of local recurrences in the surgical bed and low cervical region, she was retreated with radioiodine in 2000 and 2001. Persistent uptake near the jugulum was seen on ^{131}I scintigraphy after therapy. In 2001, additional imaging was performed because of persistent elevated serum Tg levels and progressive pain in the left leg. In addition to the neck lesion seen on ^{131}I scintigraphy, both ^{18}F-FDG-PET and MRI showed lesions in the spine (L3 and L5-S1). Lack of radioiodine accumulation in the latter lesions suggested dedifferentiation, and, therefore, external radiation was given. Because of the growth of the neck lesion, which compressed the trachea, the patient developed a stridor. ^{111}In-octreotide scintigraphy showed uptake in all tumor lesions as previously seen on ^{18}F-FDG-PET and MRI. The patient received 3 treatments with a cumulative dose of 22.7 GBq of ^{177}Lu-DOTATATE. After the second treatment, serum Tg levels began to decrease (Figure 1c). At the same time, the CT scan showed regression of the tracheal lesion with a shrinkage of 50% 12 months after the last therapy.

A comparison between pretherapy ^{111}In-octreotide and posttherapy ^{177}Lu-DOTATATE scintigraphy in patients 1 and 3 is shown in Figure 2.

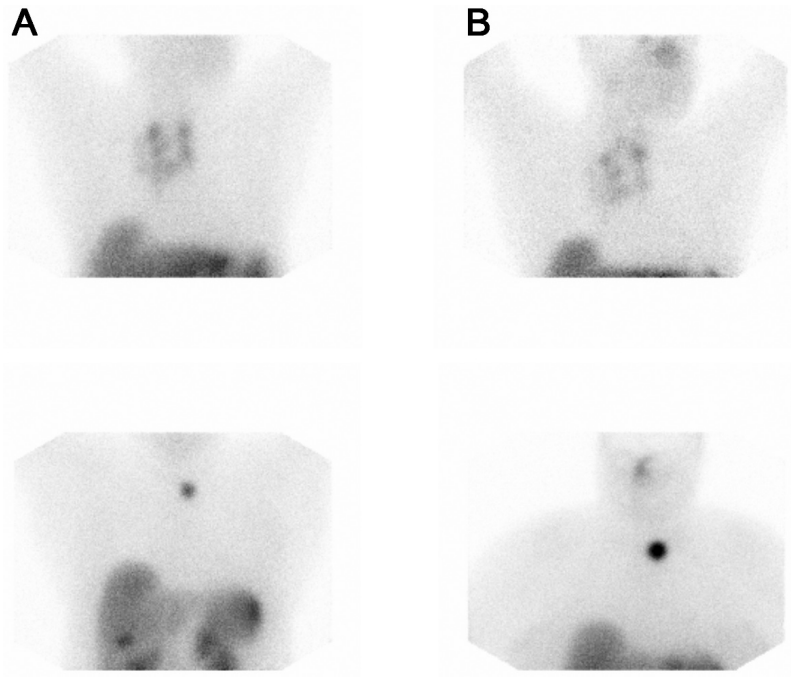

Figure 2. Images comparing pretherapy ^{111}In-octreotide scintigraphy (**A**) and posttherapy ^{177}Lu-DOTATATE scintigraphy at 24 h (**B**). Top row shows corresponding images of tumor sites in patient 1 with metastatic PTC. Bottom row shows corresponding images of patient 3 with HCTC.

In patient 1, the uptake of both somatostatin analogs was about the same. In contrast, more uptake was shown in the tracheal lesion of patient 3 on ^{177}Lu-DOTATATE scintigraphy than on ^{111}In-octreotide scintigraphy. Calculated ^{177}Lu-DOTATATE/^{111}In-octreotide tumor uptake ratios in the tumor lesions of all patients varied from 1.1 to 3.2. Two patients with HCTC, in whom tumor shrinkage was demonstrated, had the highest ratios (Figure 3).

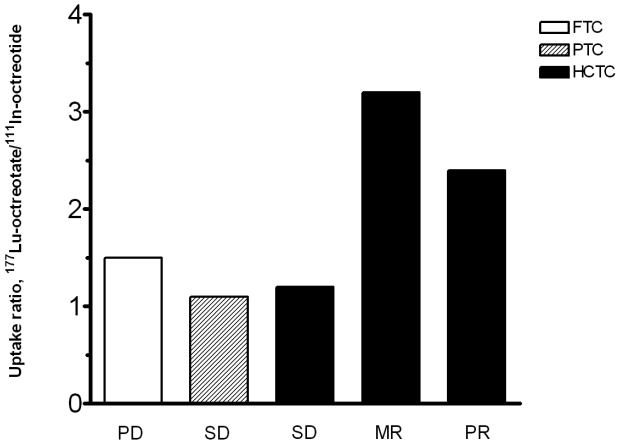

Figure 3. Ratios of ^{177}Lu-DOTATATE and ^{111}In-octreotide uptake in tumor sites. Uptake was expressed as percentage of administered dose. Note differences in uptake between patients with HCTC who responded with MR and PR and those who did not respond with tumor shrinkage.

DISCUSSION

Therapeutic options in patients with recurrent or metastatic DTC that cannot concentrate radioiodine are limited. Also, the loss of iodine-trapping ability, or dedifferentiation, is associated with a more aggressive behavior [6].

In this paper we describe the results of therapy with ^{177}Lu-DOTATATE in 5 patients with DTC, who had no other treatment available. CT-assessed tumor shrinkage was found in 2 patients with HCTC. Concomitantly, a decrease in serum Tg levels was observed in both patients. In the other patient with HCTC the serum Tg levels decreased significantly, whereas CT-assessed tumor volume did not change. However, the aspect of the lesions changed, which suggested necrosis. Disease stabilization was achieved in one patient with clearly progressive PTC before therapy, whereas the patient with FTC progressed despite treatment. These results suggest that in some patients with DTC, who have no treatment options left, ^{177}Lu-DOTATATE therapy can be effective.

The reason to treat these patients with ^{177}Lu- DOTATATE, was found in the successful treatment with this compound in patients with somatostatin receptor–positive gastroenteropancreatic (GEP) tumors. Objective tumor shrinkage was demonstrated in up to 38% of patients [20]. In addition, reports in which other somatostatin analogs were labeled with different radionuclides, such as ^{111}In or ^{90}Y, showed similar therapeutic benefit in patients with GEP tumors [16,17,21,22]. Apart from GEP tumors, other results of therapy in patients with DTC were reported (Table 3). Patients with DTC were treated because they had progressive disease, somatostatin receptor–positive lesions on ^{111}In-octreotide scintigraphy, and no other treatment option available.

Krenning *et al.* [19] reported the first 2 DTC patients treated with radiolabeled somatostatin analogs. Both had PTC and were treated with ^{111}In-octreotide, which was available for therapy. One patient, who had a total cumulative dose of at least 20 GBq, showed disease stabilization, whereas the other patient, who had received <20 GBq, was lost to follow-up. In a review that summarized the use of ^{111}In-octreotide therapy in a total of 50 patients in a single institution, 40 patients were evaluated after cumulative doses of at least 20 GBq up to 160 GBq. Within this group, 5 patients had DTC, including 4 patients with PTC and 1 with FTC [17]. Four patients were progressive despite treatment, whereas 1 patient, who was reported earlier to have SD for some time, ultimately progressed. In a recent report, 11 patients with progressive iodine nonresponsive thyroid carcinoma were treated with high, fixed doses of ^{111}In-octreotide [23]. Nine patients were evaluable, because 2 patients died during follow-up of causes unrelated to their disease. Six months after the last therapy, 4 patients had SD and 5 patients had PD. Stablilization of disease was accompanied with a stable Tg level, whereas 3 out of a group of 5 patients with radiologic progression had increasing levels of Tg. Interestingly, the mean Tg value in the latter group was higher than in the group with stabilization of disease (mean Tg value 180,432 vs. 275 µg/L). It was suggested that low Tg values could be used as selection criteria for ^{111}In-octreotide therapy.

Waldherr *et al.* [15] treated 8 DTC patients (3 FTC, 4 PTC, and 1 anaplastic thyroid carcinoma) with ^{90}Y-DOTATOC. Two patients, who were treated with 9.1 and 14.8 GBq, had SD and documented TTP of 8 months, whereas the other patients had PD. Chinol *et al.* [21] also used ^{90}Y-DOTATOC to treat 2 patients with PTC. Unfortunately, the efficacy of therapy in these 2 patients was difficult to determine from this study, because results were presented as the effect of treatment in the whole group of somatostatin receptor (SSTR) positive tumors. Three patients had regressive disease (>25% reduction of tumor size), 11 had SD, and 11 had PD. In a very recent report, 5 patients with DTC were treated with ^{90}Y-DOTATOC with a dose range of 5.6 GBq to 7.4 GBq [24].

Table 3. Peptide receptor radionuclide therapy in patients with differentiated thyroid carcinoma

References	Tumor classification*	Radiopharmaceutical			Cumulative Dose	Response / (TTP[mo]) †	Criteria ‡
		Radionuclide	Chelator	Peptide			
Gorges et al. 2001 (14)	3x HCTC	^{90}Y	DOTA	TOC	1.7-9.6 GBq	1x SD (21); 2x PD	N/A
Waldherr et al. 2001 (15)	3x FTC; 4x PTC; 1x ATC	^{90}Y	DOTA	TOC	1.7-14.8 GBq	2x SD (8,8); 6x PD	WHO
Virgolini et al. 2002 (16)	25x TC	^{90}Y	DOTA	Lanreotide	0.9-7.0 GBq	3x RD (N/A); 11x SD(N/A); 11x PD	WHO
Valkema et al. 2002 (17)	1x FTC; 4x PTC	^{111}In	DTPA	TOC	3.0-8.3 GBq	4x PD; 1x SD (N/A)	SWOG
Chinol et al. 2002 (21)	2x PTC	^{90}Y	DOTA	TOC	>7.4 GBq	N/A	SWOG
Christian et al. 2003 (12)	1x HCTC	^{90}Y	DOTA	TOC	N/A	N/A	N/A
Gabriel et al. 2004 (24)	4x FTC; 1x PTC	^{90}Y	DOTA	TOC	5.6-7.4 GBq	5x SD (5)	N/A
Stokkel et al. 2004 (23)	4x FTC; 5x PTC	^{111}In	DTPA	TOC	14.3-33.1 GBq	4x SD (N/A); 5x PD	N/A

‡ *WHO, World Health Organization Criteria: RD (regressive disease)= >25% reduction of tumor size; SD (stable disease)= <25% reduction or increase of tumor size; PD (progressive disease)= >25% increase of tumor size.*
SWOG, Southwest Oncology group criteria: PR (partial remission)= >50% reduction of tumor size; SD (stable disease)= <50% reduction or <25% increase of tumor size; PD (progressive disease)= >25% increase of tumor size
** TC, undefined thyroid carcinoma; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; HCTC, Hürthle cell thyroid carcinoma; ATC, anaplastic thyroid carcinoma; †, TTP=time to progression (months); N/A, not available*

The authors reported that patients who responded under this therapy regimen had SD for at least 5 months. Especially interesting in comparison with our results is the report by Gorges *et al.* [14], who described the courses of disease of the first 3 patients with HCTC treated with ^{90}Y-DOTATOC (total dose, 1.7–9.6 GBq). The patient with the highest dose responded with a period of SD of 9 months, whereas the other 2 patients had progressive disease despite treatment. They concluded that the protocol was not ideal, because tumor radiation dose was suboptimal.

To draw conclusions from all the studies concerning the therapeutic efficacy of PRRT in patients with non–radioiodine-avid or unresponsive thyroid cancer is difficult. The number of treated patients in the reported studies was low. Furthermore, different radiolabeled somatostatin analogs were used with individually variable administered doses. Clearly, PRRT in DTC seems to be less effective than in GEP neuroendocrine tumors.

One reason for this difference in efficacy might be the expression profile of SSTR subtypes by tumors. Reubi *et al.* [25], who intensively studied the SSTR subtype profile of numerous human tumors, reported a predominance of SSTR2 or SSTR1 in GEP tumors. In contrast, in vitro studies with thyroid cancer cell line monolayers and xenografts showed a predominant expression of SSTR3 and SSTR5, whereas SSTR2 mRNA was only faintly detectable [26]. In another report, in which the receptor subtype expression in biopsied DTC tumor tissue was investigated by Northern Blot analyses, SSTR1, SSTR3, SSTR4, and SSTR5 were expressed in all tumors, whereas SSTR2 was not detected in any FTC or PTC tumors. In line with these observations, Forssell-Aronsson *et al.* [27] also demonstrated that the highest tumor-to-background ratio and expression of high-affinity SSTR2, was found in medullary thyroid carcinoma and Hürthle cell neoplasia. In the latter, the expression of SSTR2 was irregular. These findings suggest that the SSTR subtype expression profile found in DTC cells is different and more variable than that in GEP tumors.

Most radiolabeled somatostatin analogs available for therapy share the high binding affinity for the SSTR2 receptor. It was reported that, in comparison with DTPA°, Tyr^3-octreotide, DTPA°,Tyr^3-octreotate showed improved binding to SSTR positive tissues in animal experiments [28]. Furthermore, the somatostatin analog DOTATATE has a 9-fold higher affinity for the SSTR2 than does DOTATOC, whereas the affinity to SSTR3 and SSTR5 were found to be lower [29]. In line with the higher affinity for the SSTR2, our biodistribution studies on ^{111}In-octreotide and ^{177}Lu-DOTATATE scintigraphy, reported previously, showed a 3- to 4-fold higher tumor uptake in 4 out of 5 patients [18]. The presence of SSTR subtypes other than SSTR2 was suggested as an explanation for equivalent tumor uptake of both somatostatin analogs in 1 patient with PTC, who is also described in this article (patient 1). Interestingly, the

^{177}Lu-DOTATATE/^{111}In-octreotide uptake ratios calculated in the 5 patients demonstrated that the 2 HCTC patients with the highest uptake ratios responded with tumor shrinkage, whereas the others had ratios <1.5. Thus, in patients with PTC or FTC with tumors that probably exhibit a different and variable SSTR expression profile with predominantly SSTR5 and SSTR3 instead of SSTR2, there is no clear advantage of Tyr^3-octreotate over Tyr^3-octreotide.

For the better tumor targeting and increase in uptake required for better therapeutic efficacy of PRRT in DTC, SSTR subtype-specific analogs with higher affinity for SSTR3 and SSTR5 are necessary. Most promising is the recent study by Wild *et al.* [30], who reported the first preclinical data on ^{111}In- and ^{90}Y-labeled DOTA-1-Nal^3- octreotide (DOTA-NOC), which has, apart from high affinity to SSTR2, a favorable affinity for SSTR3 and SSTR5. In addition, they briefly mentioned excellent images of thyroid cancer patients in clinical studies with [^{111}In]DOTA-NOC. It was assumed that DOTA-NOC labeled with either ^{90}Y or ^{177}Lu will have similar favorable properties, so that it might become available for therapy in patients with DTC in the near future.

In our opinion, the best candidates for PRRT with ^{177}Lu-DOTATATE in non–iodine-avid metastatic and radioiodine unresponsive DTC are patients with HCTC. The combination of a large percentage of HCTC patients with positive lesions on ^{111}In-octreotide scintigraphy, relatively high tumor uptake of ^{177}Lu-DOTATATE compared with PTC or FTC, and the favorable outcomes observed in our patients suggest that especially in these patients ^{177}Lu-DOTATATE may induce tumor shrinkage or prolonged disease stabilization.

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6.2

Staging and treatment of differentiated thyroid carcinoma with radiolabeled somatostatin analogs

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Abstract

In patients with progressive metastatic (or recurrent) differentiated thyroid carcinoma that either do not take up radioioidine or are unresponsive to continued radioiodine therapy, staging is difficult and treatment options are few. However, in most of these patients uptake of radiolabeled somatostatin analogs is evident on somatostatin-receptor scintigraphy (SRS). Using SRS, patients with sufficient uptake of radiolabeled somatostatin analogs can be selected for high-dose peptide receptor radionuclide therapy (PRRT) as an alternative targeted-treatment option. PRRT with the β-particle-emitting radionuclides ^{90}Yttrium (^{90}Y) and ^{177}Lutetium (^{177}Lu) gives the best results in terms of objective tumor response. Promising, novel, radiolabeled somatostatin analogs that have a broader receptor affinity profile and, thus, a potentially wider therapeutic range are being tested clinically.

INTRODUCTION

Standard therapy in most patients with non-medullary differentiated (papillary, follicular and Hürthle cell) thyroid carcinoma (DTC) involves either total or near-total thyroidectomy followed by ablation of the thyroid remnant with radioiodine. With a reported overall 10- year-survival rate of 75–95%, DTC is regarded as a malignancy with a relatively good prognosis [1-3]. However, tumors recur in ~20% of patients [2, 3]. Long-term follow-up after initial therapy, which is based primarily on measurements of serum thyroglobulin (Tg) in combination with radioiodine whole-body scans (WBSs), is, therefore, obligatory. Additional treatment with radioiodine can be initiated when recurrence and/or metastases are evident and imaged by radioiodine WBS. However, radioiodine therapy is no longer an option in the 20–30% of patients who have recurrences and/or persistent metastases caused by dedifferentiation with a lack of radioiodine uptake (non-radioiodine-avid) within the tumors (4–6% of patients diagnosed with DTC) [4, 5].

Patients with dedifferentiated DTC have a worse prognosis, largely because they cannot be treated with radioiodine [2, 5, 6]. Therefore, alternative, accurate imaging methods for diagnosis, and therapeutic modalities are of interest. Hürthle cell thyroid carcinoma (HCTC), an uncommon form of thyroid cancer that is usually classified as a variant of follicular thyroid carcinoma (FTC), is of special interest because these carcinomas rarely take up radioiodine, even at the time of diagnosis [7]. In this review, we focus on both the staging and the therapeutic potential of radiolabeled somatostatin analogs in patients with non-radioiodine-avid DTC.

SOMATOSTATIN RECEPTOR SCINTIGRAPHY

Over ten years ago, we published the first results of patients with DTC who were imaged by somatostatin receptor scintigraphy (SRS) [8, 9]. The potential value of SRS in patients with non-radioiodine-avid DTC was clear because, in some patients, either new or more tumor localizations were detected compared with radioiodine WBS. Furthermore, in some patients with a negative radioiodine WBS, SRS showed tumor uptake of the radiolabeled somatostatin analog ^{111}Indium-diethylene triamine pentaacetic acid (DTPA) octreotide (^{111}In-octreotide). The finding that SRS visualizes tumors in patients with DTC whose tumors do not take up radioiodine has great potential for staging the disease and treating it with somatostatin analogs.

The value of SRS in clinical practice

Most reported studies on SRS focus on the clinical value of this image modality in patients with non-radioiodine-avid DTC with progressive disease. Tenenbaum *et al.* [10] studied four patients with DTC of whom three showed no uptake on radioiodine WBS. Two patients, one with papillary thyroid carcinoma (PTC) and one with

poorly differentiated thyroid carcinoma (insular; PDTC), showed ^{111}In-octreotide uptake on SRS. In a larger study of 25 DTC patients (16 with radioiodine-negative tumors and nine with radioiodine-positive tumors), 20 out of 25 (80%) showed uptake during SRS with ^{111}In-octreotide [11]. In the patients with radioiodine-negative tumors, 12 out of 16 (75%) showed uptake on SRS. All patients had elevated serum levels of Tg, which reflected the presence of disease. It was concluded that SRS is a useful, additional image and staging modality for follow-up in patients with elevated serum Tg levels and negative radioiodine WBS. Several studies have confirmed these findings and reported uptake of ^{111}In-octreotide in either non-radioiodine-avid metastatic or recurrent disease in 74–100% of patients (Table 1) [12-15]. By contrast, Garin *et al.* [16] reported a positive ^{111}In-octreotide scan in only three out of 16 patients (19%) in whom no radioiodine uptake could be demonstrated. Valli *et al.* [17] reported similar results and concluded that octreotide scintigraphy has a lower diagnostic accuracy than conventional imaging modalities, including chest x-ray, ultrasound (US) of the neck, spiral computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy. However, the administration of a low dose of ^{111}In-octreotide and a short acquisition time compared with the other studies might account for the discrepancy in sensitivity observed. Giammarile *et al.* [18], who performed ^{111}In-octreotide scintigraphy with the largest group of patients with no detectable radioiodine uptake and elevated serum Tg levels, reported an overall sensitivity of 51% which was clearly lower than that of both conventional imaging, such as US of the neck and abdomen, CT and/or MRI, and bone scintigraphy, and the relatively new technique of positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG). With the large number of patients studied, factors that might influence diagnostic accuracy of SRS, were discussed. The first of these is the anatomical localization of the tumors. The sensitivity of SRS was high for the detection of mediastinal lesions (93%), whereas most false-negative results were observed in patients who, at follow-up, were proved to have had undetectable, small, neck and lung metastases at the time of SRS.

In addition to anatomical location, a high serum Tg level (>50 ng ml^{-1}) in patients who had thyroxine substitution therapy (Tg-on) was associated with significantly increased sensitivity. Furthermore, Görges *et al.* [19] reported a clear distinction between the detected lesions within the group of patients with low serum Tg-on levels (<10 ng ml^{-1}, n=11) and those from the group with high serum Tg-on levels (>10 ng ml^{-1}, n=39). In the latter group, 85% of patients had a positive SRS whereas in the group with low serum Tg-on levels only 27% of patients had a positive SRS. Garin *et al.* [16] reported that all their studied patients with a positive SRS had a serum Tg-on level >5 ng ml^{-1}. Patients without uptake had low serum Tg-on levels (<5 ng ml^{-1}). These results indicate a positive correlation between the serum Tg level and/or thyroid-stimulating hormone (TSH) and visualization on SRS.

Table 1. ^{111}In-octreotide scintigraphy in non-radioiodine-avid differentiated thyroid carcinoma [a]

Study year	Number of patients	Tumor classification	Serum Tg level range (ng ml^{-1})		Imaging	Refs
			Tg-on [b] (number of patients)	Tg-off [b] (number of patients)	Number of patients with radioiodine negative but SRS positive scans	
1995	3	2 PTC; 1 insular TC	120-60 000 (3)		2 out of 3 (67%)	[10]
1996	16	11 FTC; 5 PDTC	2-42 500 (16)		12 out of 15 (75%)	[11]
1996	6	5FTC;1PTC	NA	NA	6 out of 6 (100%)	[12]
1998	16	15 PTC; 1 vesicular TC	< 0.2-1440 (11)		3 out of 16 (19%)	[16]
1999	15	14 PTC; 1 HCTC	10-65 000 (15)	1670/ 2030 (2)	7 out of 15 (49%)	[17]
2001	29	3 FTC; 4 PTC; 21 HCTC; 1 insular TC	0.48-48 300 (27)		19 out of 29 (66%)	[19]
2001	25	9 FTC; 16 PTC	< 1.5-14 910 (25)		6 out of 8 (75%)	[13]
2003	17	1 FTC; 4 PTC; 12 HCTC	NA	NA	14 out of 17 (82%)	[14]
2004	23	8 FTC; 13 PTC; 2 HCTC	16.6-586 000 (22) [c]		17 out of 23 (74%)	[15]
2004	43	9FTC;20PTC;8HCTC; 6insularTC	0.7-5250 (40)	171-5850 (3)	22 out of 43 (51%)	[18]

[a] *Abbreviations: FTC, follicular thyroid carcinoma; HCTC, Hürthle cell thyroid carcinoma; NA, not available; PTC, papillary thyroid carcinoma; SRS, somatostatin receptor scintigraphy; TC, thyroid carcinoma; Tg, thyroglobulin*

[b] *Tg-off, thyroglobulin levels without TSH suppressive treatment (L-thyroxine); Tg-on, thyroglobulin levels under TSH suppressive treatment*

[c] *excluding one patient with serum Tg of 0.8 ng ml^{-1} who was Tg antibody positive*

To test this hypothesis Haslinghuis *et al.* [13] studied whether withdrawal of thyroxine therapy and the subsequent increase in TSH and serum Tg levels might optimize the information obtained with SRS. Direct comparison of SRS before and after withdrawal of thyroxine therapy was performed in six patients. Essentially, the same clinical information was obtained after withdrawal of thyroxine, and it was concluded that there is no need to withdraw patients from thyroxine to perform SRS. In the case of SRS for purely diagnostic purposes, this conclusion is fair and the benefit for patients is that they do not have to suffer the burden of thyroxine withdrawal before SRS. However, although the same information was obtained, higher pathological uptake was observed in at least two patients in whom thyroxin-substitution therapy

was withdrawn temporarily [13]. In view of therapy with radiolabeled somatostatin analogs (see later), increased uptake in the tumors after thyroxine withdrawal might be beneficial in terms of tumor shrinkage. Such a correlation between uptake on pretherapy SRS and favorable outcome of therapy with radiolabeled somatostatin analogs was reported in patients with neuroendocrine gastroenteropancreatic (GEP) tumors [20]. Further quantitive imaging studies into the effect of thyroxine withdrawal on tumor uptake of radiolabeled somatosatin analogs are warranted to address this issue. In view of a possible correlation of elevated serum Tg level, tumor size and SRS sensitivity, the report by Bachelot *et al*. [21] is of interest. This study demonstrated a close relationship between the serum Tg level after withdrawal of thyroid-hormone treatment and tumor mass/extent of disease. Thus, the reported increased SRS sensitivity in patients with elevated serum Tg levels [16,18,19] might reflect an increase in SRS sensitivity in larger tumors, rather than the elevated serum Tg level.

In summary, these studies indicate that anatomical localization and tumor size/extent of disease are important in determining the outcome of SRS in patients with non-radioiodine-avid DTC.

Somatostatin receptor subtypes

Another important factor in the observed differences in uptake during SRS might be the relative expression of somatostatin receptor subtypes (sstr1–sstr5) and their density on the tumor cell surface. John *et al*. demonstrated that positive ^{111}In-octreotide scintigraphy is caused mainly by sstr2, whereas sstr1, sstr3, sstr4 and sstr5 are less important. Therefore, the presence of sstr2 is essential for imaging tumors with SRS [22]. Reubi *et al*. [23], who used autoradiography to study the sstr profile of numerous human tumors, reported a predominance of sstr2 and/or sstr1 in neuroendocrine GEP tumors. No DTC tissue was studied. In contrast to the high concentration of sstr1 and sstr2 in GEP tumors, in vitro studies with monolayers of thyroid cancer cell lines and xenografts showed predominant expression of sstr3 and sstr5, with sstr2 mRNA detected only faintly [24]. In another report, which investigated sstr expression in biopsies of DTC tumor tissue by northern-blot analyses, sstr1, sstr3, sstr4 and sstr5 were expressed in all tumors, but sstr2 was not detected in either FTC or PTC tumors [25]. The same report demonstrated the highest tumor:background ratio and expression of high-affinity sstr2 in medullary thyroid carcinoma and Hürthle cell neoplasia, including Hürthle cell adenenoma, rather than in the clinically more common, in vitro studied PTC and FTC. In Hürthle cell neoplasia, the expression of sstr2 is irregular, and tumors with high, intermediate and low expression of sstr2 were demonstrated. These findings indicate that the sstr expression profile in DTC cells is different and more variable than in neuroendocrine GEP tumors, which might explain the variation of uptake observed during SRS (Figure 1).

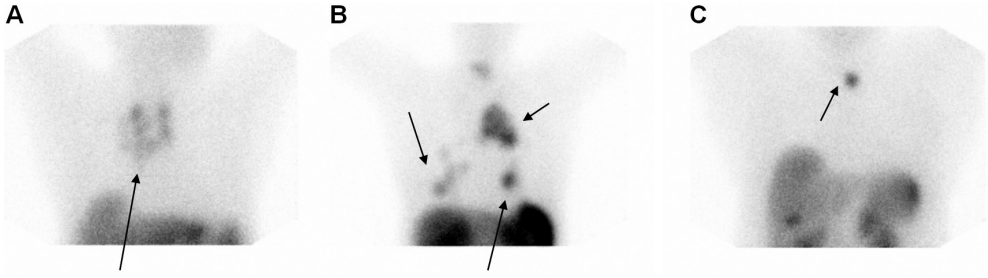

Figure 1. Somatostatin analog scintigraphy images from three patients that illustrate the variable uptake of somatostatin analogs in DTC. 15-min planar spot images were obtained 24 h after injection of 222 MBq ^{111}In-octreotide. Chest and upper abdomen are shown. All patients had pathological uptake of ^{111}In-octreotide in the chest (dark gray–black areas). Normal, physiological uptake of ^{111}In-octreotide by the liver (apparent as the gray organ in the left corner of each image) is used as reference to semi-quantify uptake by chest tumors. (**a**) Patient has PTC metastatic to the lungs (black arrow) with uptake of ^{111}In-octreotide lower than normal liver uptake. (**b**) Patient has FTC with widespread metastatic disease in the lungs (black arrows) with uptake of ^{111}In-octreotide similar to liver uptake. (**c**) Patient has recurrence of HCTC (black arrow) and metastatic lesions in bone (not shown) with uptake of ^{111}In-octreotide higher than liver uptake.

Differences in SRS protocols

In addition to these clinical factors, differences in SRS imaging protocols must also be taken into account. Differences in the amount of injected dose and/or imaging acquisition characteristics can have a significant impact on the interpretation of scintigraphy. The methodology used is, therefore, important because this might lead to differences in the sensitivity of SRS. For optimal and standardized imaging, guidelines for SRS with ^{111}In-octreotide were published in 2001 [26], but only three of the 10 studies in Table 2 have been performed in accordance with these. In some clinical centers, only half of the recommended dose of 222 MBq was used. Furthermore, high-speed whole-body scanning (>3 cm min^{-1}) was performed frequently, rather than the recommended ≥10 min planar-spot imaging, which indicates suboptimal imaging. However, adding single-photon emission computed tomography (SPECT) imaging, which allows a more precise anatomic delineation than planar imaging, resulted in similar sensitivity to the SRS studies that followed the guidelines. This underlines the importance of SPECT and the injection of sufficient radioactive dose in SRS to obtain the best possible imaging with the lowest number of false-negative cases.

Table 2. Differences in the used ^{111}In-octreotide scintigraphy protocols [a]

Study year	Diagnostic ^{111}In-octreotide scintigraphy protocol				Guidelines[b]	Refs
	Dose (MBq)	Images	Acquisition		(Y/N)	
			Scan duration	Time after injection [c]		
1995	110	WBS	NA	4h, 24h and 48h	N	[10]
1996	120-200	WBS; SPECT	10 cm/min	4h, 24h and 48h	N	[11]
1996	220	Planar spot images	15 min	24h and 48h	Y	[12]
1998	137-200	Planar spot images	5 min and 10 min	1h, 4h and 24h	Y	[16]
1999	111	WBS; SPECT	8 cm/min	24h and 48h	N	[17]
2001	110-170	WBS; SPECT	10 cm/min	4h and 24h	N	[19]
2001	222	Planar spot images; SPECT	15 min	24h and 48h	Y	[13]
2003	111	WBS; SPECT	NA	24h and 48h	N	[14]
2004	200	WBS; SPECT	10 cm/min	4h and 24h	N	[15]
2004	110	WBS; Planar spot Images; SPECT	10 cm/min (WBS); 10 min (planar spot images)	4h, 24h and 48h	N	[18]

[a] *Abbreviations: MBq, megabecquerel; NA, not available; SPECT, single-photon emission computed tomography; WBS, whole-body scan;*
[b] *Y = ^{111}In-octreotide scintigraphy following the procedure guidelines for somatostatin receptor scintigraphy as described before [26]; N = different protocol*
[c] *the 48h post injection scan was only performed when high background uptake was present on the 24h post injection scan to increase the sensitivity*

NOVEL RADIOLABELED SOMATOSTATIN ANALOGS IN DTC

Alternative radiolabeled somatostatin analogs are under investigation for SRS [27, 28]. Gabriel et al.[29] studied the use of a new radiolabeled somatostatin analog ^{99m}Tc-EDDA/HYNIC-TOC [^{99m}Tc- labeled hydrazinonicotinyl (HYNIC)-Tyr^3-octreotide (TOC) coupled with ethylene diamine diacetic acid (EDDA) as a co-ligand] in 54 patients with thyroid cancer and no radioiodine uptake during WBS. The rationale for conducting this study were the favorable characteristics of ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy compared with ^{111}In-octreotide scintigraphy, such as wider availability of the radionuclide, shorter acquisition time and higher

spatial resolution [30]. A sensitivity of 66% for ^{99m}Tc-EDDA/HYNIC-TOC scintigraphy in patients with DTC was reported. Furthermore, it demonstrated a positive correlation between true-positive findings and elevated serum Tg levels. In addition, direct comparison of both SRS modalities was performed in eight patients. One discordant finding in favor of ^{99m}Tc-EDDA/ HYNIC-TOC scintigraphy was reported. Although these results indicate that both radiopharmaceuticals have a similar affinity profile for the different somatostatin receptor subtypes, this remains to be proven. Further studies are necessary to assess the affinity profile of ^{99m}Tc-EDDA/HYNIC-TOC and the value of ^{99m}Tc-EDDA/ HYNIC-TOC scintigraphy in clinical practice.

Recently, Rodrigues *et al.* [31] reported results of in vitro binding studies and SRS of two other radiolabeled somatostatin analogs; ^{111}In-coupled to 1,4,7,10-tetraazacyclododecane (DOTA)-lanreotide (^{111}In-DOTA-LAN) and DOTA-*D*-Phe^{1}-Tyr^{3}-octreotide (^{111}In-DOTA-TOC). SRS with both radioligands demonstrated tumor-related uptake in 17 out of 18 patients (94%). Each radioligand demonstrated an equal number of lesions in radioiodine-negative and in radioiodine-positive patients. ^{18}F-FDG PET imaging in the same patients detected fewer tumor lesions in 15 out of 18 (83%) patients.

In addition, the novel radiolabeled somatostatin analog, [^{111}In]DOTA-1-Nal^{3}-octreotide (^{111}In-DOTANOC), which besides high affinity for sstr2, also has high affinity for sstr3 and sstr5, is of interest [28]. Because of this affinity profile, which clearly differs from that of ^{111}In-octreotide, this analog holds promise for better tumor imaging in patients with non-radioiodine-avid DTC.

THERAPY WITH RADIOLABELED SOMATOSTATIN ANALOGS

Despite the differences in sensitivity, and variations in the expression of somatostatin receptor subtypes and uptake during ^{111}In-octreotide scintigraphy, SRS has additional diagnostic value in determining either the extent of metastatic disease or recurrences in DTC. Furthermore, the uptake of ^{111}In-octreotide in tumor sites, imaged by SRS, indicates somatostatin receptors on the tumor-cell surface, which might be a potential therapeutic target for somatostatin analogs such as octreotide in patients with DTC for whom there is no alternative treatment. However, reports on the use of these non-radioactive somatostatin analogs to treat patients with non-radioiodine-avid DTC tumors are scarce and evidence of therapeutic benefit is limited (Box 1).

Another therapeutic approach in patients with uptake on SRS is tumor-targeted therapy with radiolabeled analogs of somatostatin. This approach, called peptide receptor radionuclide therapy (PRRT), is known to be effective in neuroendocrine GEP tumors with several radiolabeled somatostatin analogs (Reviewed in 20).

Box 1. Treatment of DTC with non-radioactive somatostatin analogs

Zlock et al. [32] treated four patients with DTC with relatively high doses (4 mg daily) of non-radioactive octreotide subcutaneously for up to 12 months: each showed progressive disease under therapy. However, the expression of the somatostatin receptor in biopsied tumor tissue and uptake of ^{111}In-octreotide during SRS was not evaluated, which makes it difficult to evaluate the effect of octreotide treatment in this study. In a more recent report, Robbins et al. described two patients with widely metastatic PTC who, because of failure of conventional treatment, were treated with monthly injections of a slow-release form of octreotide (Sandostatin LAR depot®) [33] Both patients had visible uptake in the lungs on SRS. ^{18}F-FDG PET scans before therapy and 3–4 months after the start of the monthly injections of sandostatin LAR showed a reduction of standard uptake values in both patients, which suggested octreotide-induced reduction of metabolic activity in the tumors. However, no effect on tumor size and/or serum Tg levels was reported. Despite the absence of an objective response, one patient showed clear clinical improvement whereas the other experienced no change in clinical signs and symptoms. Alternative explanations for the observed reduced metabolic activity, such as inhibition of inflammatory cells and inhibition of revascularization or angiogenesis, were suggested. These early, limited studies indicate that octreotide is likely to be of limited value in the management of patients with DTC, and no further studies have been published since 2000. Recently, a novel somatostatin analog, SOM230, has been introduced [34]. Compared with octreotide, the binding affinity of SOM230 for sstr1, sstr3 and sstr5 is 30x, 5x and 40x higher, respectively, and 2.5x lower for sstr2 [34]. In addition, the favorable elimination half-life of SOM230 (23 h), makes it suitable for clinical application. Therefore, it is of interest to study the anti-tumor effects of this somatostatin analog with a broader somatostatin receptor profile than the somatostatin analogs that are currently available.

In the first clinical PRRT study, patients with SRS positive tumors, five of whom had DTC, were treated with high doses of ^{111}In-octreotide [35]. PRRT resulted in stable disease in one patient whereas the other four had progressive disease. In patients with neuroendocrine GEP tumors, 2–17% had a partial remission determined by clinical imaging and/or biochemical parameters [35-37]. Although the results were promising, most PRRT studies that followed used β-particle-emitting radionuclides such as ^{90}Y and ^{177}Lu instead of the Auger electron emitting ^{111}In. β-particle-emitting radionuclides have greater therapeutic potential because the emitted particle range exceeds the cell diameter [38-40]. Furthermore, the ability to irradiate neighboring cells is an advantage in tumors, which are characterized by a heterogeneous tissue distribution of somatostatin receptors, with regions of high density next to regions that do not express the receptor [41].

In addition to the introduction of β-particle-emitting radionuclides, structural changes in the analog, such as insertion of tyrosine (Tyr^3-OC or TOC) and replacement of the C-terminal threoninol with threonine (TATE), increased the affinity for the sstr2 [42]. As expected, clinical and pre-clinical studies in which somatostatin analogs were coupled to either ^{90}Y or ^{177}Lu were more successful in terms of tumor shrinkage than somatostatin analogs coupled to ^{111}In [43-46]. The results of treatment with the β-particle-emitting radiolabeled somatostatin analogs ^{90}Y-DOTA-TOC and

^{177}Lu-DOTATATE in patients with neuroendocrine GEP tumors are the most encouraging, with 24–33% of patients experiencing either complete or partial remission [20].

In addition to the use of ^{90}Y- and ^{177}Lu-labeled somatostatin analogs for treating patients with neuroendocrine GEP tumors, patients with non-radioiodine-avid DTC have also been treated. Recently, we have reported the results of the first patients with DTC treated with ^{177}Lu-DOTATATE [47] and reviewed the available clinical PRRT studies that report the outcome of PRRT in patients with DTC [14, 19, 29, 35, 44, 48, 49]. Additionally, Stokkel *et al.* [50] reported their results of high-dose (~15–30 GBq) therapy with ^{111}In-octreotide in patients with progressive radioiodine-non-responsive thyroid cancer. Table 3 summarizes the available reports of PRRT on 62 patients with DTC. In this group, five patients (8%), including two with HCTC (Box 2), had an objective tumor response and 26 patients (42%) had stable disease. Time-to-progression data were either not available or reported for <1 year. Comparing these studies, some of which include only a few patients, is difficult because of differences in the radionuclides, somatostatin analogs and maximum doses administered. Nevertheless, it is clear that the radiolabeled analogs that have been evaluated, PRRT is less effective in DTC than in neuroendocrine GEP tumors.

THE FUTURE OF PRRT IN DTC

Most of the radiolabeled somatostatin analogs that are used for diagnostic and therapeutic purposes bind with high affinity to sstr2 and with lower affinity for the other receptor subtypes. In DTC, studies indicate that the expression of the different somatostatin receptor subtypes is more variable than in neuroendocrine GEP tumors in which sstr2 is expressed predominantly. The ongoing development of somatostatin-based radioligands with a broader receptor subtype profile is, therefore, of interest [51]. Wild *et al.* [28] reported the first preclinical data on the novel radiolabeled (^{111}In and ^{90}Y) somatostatin analog DOTANOC that has high affinity for sstr2, sstr3 and sstr5. They briefly mentioned excellent image quality in the first scintigraphy studies with ^{111}In-DOTANOC in patients with thyroid cancer. It is assumed that DOTANOC labeled with either ^{90}Y or ^{177}Lu will have similar favorable binding properties and, therefore, might become available to treat patients with DTC. Preliminary results of SRS and PRRT with ^{111}In and ^{177}Lu-DOTANOC, respectively, are encouraging [52].

Table 3. Peptide receptor radionuclide therapy in 62 patients with differentiated thyroid carcinoma [a]

Study year	n	Tumor classification	PD before PRRT (Number of patients out of total)	Radiopharmaceutical			Cumulative dose (GBq)	Response [b] (TTP in months)	Refs
				Radionuclide	Chelator	Peptide			
2001	3	3 HCTC	3/3	^{90}Y	DOTA	TOC	1.7 - 9.6	1 SD (21); 2 PD	[19]
2001	7	3 FTC; 4 PTC	7/7	^{90}Y	DOTA	TOC	1.7 - 14.8	2 SD (8,8); 5 PD	[48]
2002	2	2 PTC	NA	^{90}Y	DOTA	TOC	>7.4	NA	[49]
2002	5	1 FTC; 4 PTC	4/5	^{111}In	DTPA	Octreotide	29.5 - 83.2	4 PD; 1 SD [c] (NA)	[35]
2002	25	25 unclassified TC	25/25	^{90}Y	DOTA	LAN	0.9 - 7.0	3 MR (NA); 11 SD (NA)	[44]
2003	1	1 HCTC	NA	^{90}Y	DOTA	TOC	NA	NA	[14]
2003	5	3 FTC; 2 PTC	NA	^{90}Y	DOTA	TOC	5.6 - 7.6	5 SD (5)	[29]
2004	9	4 FTC; 5 PTC	9/9	^{111}In	DTPA	Octreotide	14.3 - 33.1	4 SD (NA); 5 PD	[50]
2005	5	1 FTC; 1 PTC; 3 HCTC	3/5	^{177}Lu	DOTA	TATE	22.4 - 39.1	1 PR (22+); 1 MR (43); 2 SD [d] (18,24+); 1 PD (4)	[47]

[a] *Abbreviations: ^{111}In, ^{111}Indium; ^{90}Y, ^{90}Yttrium; ^{177}Lu, ^{177}Lutetium; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DTPA, diethylenetriamine pentaacetic acid; FTC, follicular thyroid carcinoma; GBq, gigabecquerel; HCTC, Hürthle cell thyroid carcinoma; LAN, lanreotide; n, number of patients; NA, not available; PTC, papillary thyroid carcinoma; TATE, Tyr^3-Thr^8-octreotide; TC, unclassified thyroid carcinoma; TOC, Tyr^3-octreotide; TTP, time to progression;*

[b] *MR, minor remission: between 25% and 50% reduction in tumor size; SD, stable disease: <25% reduction or increase in tumor size; PD, progressive disease: >25% increase in tumor size; PR, partial remission: > 50% reduction in tumor size;*

[c] *patient had progressive disease before therapy*

[d] *one patient had progressive disease before therapy*

Box 2. PRRT in patients with HCTC

In view of their therapeutic options patients with HCTC are of special interest. In general, most patients with HCTC do not accumulate radioiodine and, therefore, are unlikely to benefit from radioiodine therapy. Consequently, local recurrences and/or metastases after the initial therapy are difficult to manage, which gives the diagnosis of HCTC the worst prognosis within DTC. New therapeutic options, such as PRRT, are of interest because analysis of the reports summarized in Table 1 shows that 35 out of 39 (90%) HCTC patients with proven residual disease had detectable uptake of ^{111}In-octreotide during SRS. As suggested previously [47], this is likely to result from higher expression of sstr2 in HCTC, which gives a more favorable profile of the expression of somatostatin receptor subtypes compared with PTC and FTC. However, a large prospective clinical trial of PRRT for HCTC is unlikely because of the rarity of this condition. Thus, substantial evidence of the effectiveness of PRRT in HCTC is unlikely in the near future. Therefore, although the results in HCTC patients treated with PRRT, such as excellent palliation and prolonged stable disease, minor remission or partial remission are anecdotal [14, 19, 47], PRRT must be considered as an alternative therapy when conventional treatment is no longer an option and SRS shows sufficient uptake of ^{111}In-octreotide.

CONCLUDING REMARKS

In patients with recurrent and/or metastatic non-radioiodine-avid DTC, SRS can demonstrate tumor sites in a substantial percentage of patients. Therefore, SRS is useful for imaging and to localize tumor sites in patients in whom disease is suspected because of elevated serum Tg level but who are without apparent uptake during postradioiodine therapy WBS. Localization with SRS might be helpful in the further management of these patients. The sensitivity of SRS is likely to depend on the tumor size, the extent of disease and the expression of the different somatostatin receptor subtypes.

In patients with uptake on SRS who have no alternative therapeutic options, SRS can select potential candidates for PRRT. When conventional treatment is no longer an option and SRS shows sufficient uptake of ^{111}In-octreotide, PRRT should be considered as an alternative therapy.

Research into radiolabeled somatostatin analogs that have high binding affinity to the different sstr subtypes is underway. This might introduce more receptor subtype-specific SRS and, thereby, more effective PRRT for patients with DTC in the future.

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7

Summary and general discussion

The concept of radiolabelled peptide analogues to target cell membrane-bound receptors is subject of an increasing number of research projects and source of inspiration for many researchers throughout the world. The first application of radiolabelled peptides in the human was introduced by Krenning et al. in 1989[1]. The somatostatin analogue Tyr^3-octreotide was labelled with ^{123}I and scintigraphy to localise somatostatin receptor positive tumours was established. However, the use of ^{123}I-Tyr^3-octreotide for scintigraphy had several major drawbacks regarding its metabolic behaviour, preparation difficulties and the relatively short physical half-life of the radionuclide [2]. Therefore, another radiolabelled analogue of somatostatin, ^{111}In-DTPA-*D*-Phe^1-octreotide was introduced which had several advantages such as easy preparation, general availability, appropriate half-life and absence of major interference in the upper abdominal region. In 1994, ^{111}In-DTPA-*D*-Phe^1-octreotide (OctreoScan®) was approved by the U.S. Food and Drug Administration (FDA) and since then OctreoScan® has become a commonly used imaging technique to diagnose neuroendocrine tumours, such as carcinoids and neuroendocrine tumours of the pancreas. These tumours have a high expression of somatostatin receptors, especially the receptor subtype 2, in common [3].

The next logical step in this field, made by Krenning *et al*. was to use radiolabelled somatostatin analogues for therapy in those patients with neuroendocrine tumours, who had somatostatin receptor positive tumours on scintigraphy and inoperable disease [4]. This was an important new approach in these patients since for most of these patients no effective systemic anti-tumour therapy, besides aggressive chemotherapy, was available.

The first radiolabelled somatostatin analogue therapy in patients with advanced stage neuroendocrine tumours was based on the administration of high dosages of the therapeutic Auger electron emitting ^{111}Indium-octreotide. The total cumulative dose varied from 3.1 GBq up to 160 GBq. However, besides encouraging and promising results, such as biochemical reponses and clinical benefit in terms of symptomatic control, only small numbers of patients with an objective morphological response were reported [5-7]. Therefore, several research groups, who initially treated their patients with ^{111}Indium-octreotide, developed somatostatin analogues that could be linked with a β-emitting radionuclide, such as ^{90}Yttrium (^{90}Y) or ^{177}Lutetium (^{177}Lu). For these radionuclides a better efficacy was expected due to the longer radiation path length of the emitted β-particles in comparison with the relatively short range of Auger electrons emitted by ^{111}Indium. Studies with various somatostatin analogues labelled with the β-emitting radionuclide ^{90}Y followed and better efficacy in terms of the percentage of patients with objective tumour responses was demonstrated. Shortly after the start of the clinical studies with ^{90}Y-labelled somatostatin analogues, peptide receptor radionuclide therapy (PRRT) with the β-emitting radionuclide

^{177}Lutetium coupled to the somatostatin analogue octreotate was started in Rotterdam for the treatment of patients with inoperable and or metastasised neuroendocrine gastroenteropancreatic tumours (GEP-NETs).

The aim of this thesis was to evaluate the efficacy of treatment with [^{177}Lu-DOTA°,Tyr^{3}]octreotate (^{177}Lu-DOTATATE) therapy in patients with somatostatin receptor positive GEP-NETs in terms of toxicity, effects on tumour size and number, side-effects and quality of life. Furthermore, it was questioned whether ^{177}Lu-DOTATATE or ^{177}Lu-DOTATOC might be the radiolabelled analogue of choice in this form of PRRT. All these aspects are discussed in chapter 2-5 of this thesis.

Since ^{177}Lu-DOTATATE therapy demonstrated favourable clinical efficacy in GEP-NETs, other somatostatin receptor positive tumours were considered as candidates for this therapy and subsequently patients with non-radioiodine avid differentiated thyroid carcinoma, who had no alternative treatment option left, were treated. Feasibility of PRRT with ^{177}Lu-DOTATATE therapy in these patients is described in chapter 6. In addition, staging with radiolabelled somatostatin analogue scintigraphy and the use of ^{177}Lu-DOTATATE therapy in differentiated thyroid carcinoma is reviewed.

An overview of the management of patients with GEP-NETs is given in **chapter 1.1**. Together with a large number of other therapeutic options currently available, PRRT with radiolabelled somatostatin analogues is put into perspective, addressing important results and findings of each therapy such as toxicity, side-effects, outcome and survival. An extensive overview of PRRT in patients with GEP-NETs, is given in **chapter 1.2**. The aims and outline of this thesis are presented in chapter 1.3.

In **chapter 2.1** the first results of ^{177}Lu-DOTATATE therapy studied in 35 patients with GEP-NETs is presented. Side-effects of and toxicity after treatment with ^{177}Lu-DOTATATE are infrequent and mostly transient, with mild bone marrow depression as the most common finding. Although the main objective of our study was to evaluate the feasibility of the treatment in terms of side-effects and toxicity, the reported effects on tumour size with complete and partial remission in 38% of patients compared favourably with the earlier reported PRRT with [^{90}Y-DOTA°,Tyr^{3}]octreotide (^{90}Y-DOTATOC) and the reported outcome of most trials with chemotherapy. However, inclusion of more patients was necessary to prove these early preliminary findings. The results in a larger number of patients are presented in **chapter 2.2**, in which the favourable objective responses as described in chapter 2.1 were confirmed with minor, partial or complete response in 47% of 125 evaluable patients. Furthermore, we were able to delineate predictive factors

of tumour response. A high uptake on pretherapy ^{111}In-octreotide scintigraphy and limited liver involvement were predictive for a favourable response, whereas, in general, patients with a low Karnofsky Performance Score and, to a lesser extent, a high tumour load before therapy had a higher risk of progressive disease. From these results we concluded that early treatment, even in patients without evidence of progression or symptoms, may be better. Comparison of our results in ^{177}Lu-DOTATATE treated patients with studies in which ^{90}Y-DOTATOC was used, is difficult, as besides differences in study design, protocol and administered dosages, patient selection could have influenced the study outcome. Therefore, until now, it is not proven which radiolabelled somatostatin analogue can be regarded as the most optimal for PRRT in GEP-NET patients.

Another interesting finding described in this chapter was the decrease of uptake on the last posttherapy scan compared with the first posttherapy scan, which was frequently seen in patients who eventually had objective tumour regression on computed tomography. Also, in patients who had stable disease or a tumour size reduction, the median time to progression was more than 36 months. A direct comparison with chemotherapeutic regimens was not performed as chemotherapy is relatively ineffective in patients with inoperable GEP-NETs. Therefore, we compared our results with historical data from earlier studies with, mostly, chemotherapy as the first option of cytoreductive therapy in inoperable GEP-NETs. High variation in reported objective tumour responses made it difficult to make that comparison. However, most studies reported a response duration of less than 18 months, whereas the median time to progression after ^{177}Lu-DOTATATE therapy was longer than 36 months. Furthermore, toxicity of most chemotherapeutic regimens is more severe and more frequent than with ^{177}Lu-DOTATATE therapy. However, since our study is ongoing and the median time of follow-up is 16 months, evaluation at a later time point will provide more definite evidence of these observations.

As described in **chapter 3**, the quality of life of patients treated with ^{177}Lu-DOTATATE therapy improves, especially in patients who have an objective tumour response or stable disease. To our surprise, the quality of life in patients who had progressive disease did also show significant improvement. Beside bias from a placebo effect, another explanation of this unexpected result might be the relatively low number of patients in this group, caused by the fact that patients with highly aggressive tumours were not able to fill out the questionnaire or even died before the last intended therapeutic cycle was given. Therefore, the interpretation of the data in this category of patients is difficult and has to be looked at with caution. In addition to the global health-related quality of life, the scales of role, emotional, and social function as well as the symptom scales fatigue, pain and the single item insomnia improved significantly after PRRT. Finally, we concluded that the favourable objective tumour

responses found in our patients were accompanied by an improvement of their health-related quality of life in most patients.

In **chapter 4**, the short- and long-term effect of ^{177}Lu-DOTATATE therapy on endocrine function is described and discussed. As PRRT is a systemic therapy and many endocrine organs are known to possess somatostatin receptors, these organs are potential unwanted targets of PRRT. In line with the observations in men treated with high doses of radioiodine after thyreoidectomy because of differentiated thyroid carcinoma [8], our male patients demonstrated a temporarily decrease of inhibin B levels and a mirrored course of FSH levels. Although no semen analysis was performed, this indicated a temporarily impaired spermatogenesis. Increased serum levels of gonadotropins and subnormal serum levels of testosterone were also documented in men with rectal carcinoma treated with external beam radiation [9]. Because no direct evidence of the presence of somatostatin receptor protein in the testes is available and because of the similarity of these findings in men treated with high doses of radioiodine or external beam radiation in proximity of the gonads, this observed radiotoxicity is probably not somatostatin receptor related. More obvious reasons are radiation from the circulation and (scattered) radiation in proximity of the radiosensitive gonads such as the bladder urine or faeces from the rectum after PRRT.

Another interesting observation is the decrease of both LH and FSH levels in postmenopausal women. This decrease is more than could be expected from ageing alone[10]. As somatostatin receptors are present in the pituitary and because postmenopausal women lack the premenopausal negative feedback mechanism, a receptor dependent radiation delivery mechanism is likely.

Although remaining within the reference range, the mean FT4 level of the group available for thyroid hormone analyses decreased significantly. Furthermore, two patients developed primary hypothyroidism during and after ^{177}Lu-DOTATATE therapy. Whether the occurrence of the primary hypothyroidism cases in our series of patients is caused by the ^{177}Lu-DOTATATE, or can be regarded as normal incidence of the disease is difficult to determine. However, the observed decrease of the mean FT4 level is suggestive for a somatostatin receptor-mediated, but limited radiation dose to the thyroid gland resulting in the subtle decrease demonstrated, which is probably not clinically important. Furthermore, we demonstrated a decrease of mean rT3 levels directly after ^{177}Lu-DOTATATE therapy, which was elevated at baseline. This decrease is suggestive for a change in disease status according to the observed changes of thyroid hormone levels in patients with chronic disease with the non-thyroidal illness syndrome [11]. No adrenal insufficiency, as was assessed by a low-dose ACTH stimulation test, was observed in patients before and after

^{177}Lu-DOTATATE therapy. Additionally, five patients developed elevated levels of HbA_{1c} without any obvious cause such as pancreatic surgery. Because pancreas islets are known to exhibit somatostatin receptors, a receptor-mediated detrimental effect of ^{177}Lu-DOTATATE therapy on the glucose homeostasis cannot be excluded. Also the effect of chronic 'cold' somatostatin analogue therapy in these patients might have contributed to this observation. Overall we conclude that patients who are treated with ^{177}Lu-DOTATATE therapy may develop radiation-induced hormone disturbances, some of which are temporary, but which in general are mild. Although the treating physician should be aware of the possibility of hormonal changes, such as in young men planning to have children, ^{177}Lu-DOTATATE therapy, in terms of endocrine sequelae, can be regarded as safe.

To date many different somatostatin analogues have been synthesised, which exhibit diverse affinity profiles for the currently known somatostatin receptor subtypes. To evaluate which analogue has the best profile regarding the ideal balance between uptake in the tumour(s) and dose-limiting organs or therapeutic window we compared the two most commonly used somatostatin analogues in PRRT, DOTATATE and DOTATOC, coupled to ^{177}Lu. The results of this study are described in **chapter 5**. A direct comparison between both analogues in a PRRT setting was performed. Residence times of the radioactivity, which are directly related to absorbed tumour dose, within the spleen, kidneys and tumours was longer with the use of ^{177}Lu-DOTATATE than ^{177}Lu-DOTATOC. The ratios of mean residence time of ^{177}Lu-DOTATATE versus ^{177}Lu-DOTATOC were 1.5, 1.4 and 2.1, for spleen, kidneys and tumours, respectively. Consequently, higher absorbed tumour doses are expected to be achievable with ^{177}Lu-DOTATATE than with ^{177}Lu-DOTATOC. The higher kidney residence time with the use of ^{177}Lu-DOTATATE can be a problem in PRRT, as beside the bone marrow, the kidneys are one of the dose limiting organs. However, in any case of PRRT in which the dose is limited because of reached maximum calculated dose to the kidneys (23 Gy) the absorbed dose within the tumour(s) will still be higher since the mean tumour residence time ratio (2.1) exceeds the mean kidneys residence time ratio (1.4) with a factor of 1.5 in favour of ^{177}Lu-DOTATATE. Furthermore, in most of our patients the bone marrow (maximum allowed dose of 2 Gy) is the dose limiting factor instead of the kidneys.

A similar study was performed by Forrer and colleagues in Basel, comparing ^{111}In-DOTATOC with ^{111}In-DOTATATE [12]. It was assumed that for dosimetry purposes ^{111}In could be used as a surrogate for ^{90}Y, frequently used for PRRT at their institution. Three out of five patients demonstrated a better tumour-to-kidney ratio with ^{111}In-DOTATOC compared to ^{111}In-DOTATATE. Based on these data, it was decided that they would continue to use the somatostatin analogue DOTATOC labelled with ^{90}Y for PRRT. However, the assumption that ^{111}In is a useful surrogate for ^{90}Y,

is questionable. Different radionuclides coupled to one somatostatin analogue may have different affinity profiles [13] which subsequently may result in differences in radiopharmacon biodistribution as was shown in a neuroendocrine tumour model in rats [14]. Also, the diagnostic quantity of peptide used in the study by Forrer *et al*. was much less than the quantities used in PRRT. Differences in amount of peptide can introduce different biodistribution patterns as was demonstrated by several authors [15-17]. Breeman *et al*. reported that the uptake of ^{111}In-pentetreotide in somatostatine receptor positive organs when presented as a function of the injected mass of the radiopharmaceutical resembles a tissue specific bell-shaped curve. The same bell-shaped curve was demonstrated in normal tissue as well as in tumours by Bernhardt *et al*. in SSTR positive tumour bearing nude mice [18]. Thus, the biodistribution patterns can have a significant effect on the absorbed kidney dose as well as tumour dose and, thus, on the tumour-to-kidney ratios which were found by Forrer *et al*. [12]. Furthermore and in contrast to the diagnostic setting amino-acid co-infusion is currently used in PRRT at most institutions. Co-infusion of the amino-acids lysine and/or arginine in PRRT results in a significant inhibition of renal radioactivity and, thereby, has its effect on the tumour-to-kidney ratio [19]. Thus, in contrast with the study from the Basel group, our study resembles the therapeutic setting better on several important points. Furthermore, we compared the residence times in the tumour and kidneys, reflecting absolute absorbed tumour dose, instead of the relative uptake method of tumour-to-kidney ratios.

Finally, in ^{177}Lu-DOTATATE and ^{90}Y-DOTATOC based PRRT the critical organs are the kidneys and bone marrow. The corresponding maximal tolerated doses (MTD) for external radiation of these tissues are 23 and 2 Gy, respectively, and are used as dose constraints to avoid radiation-induced nephropathy and severe bone marrow toxicity, such as myelodysplastic syndrome or leukaemia. In approximately 30% of the patients treated with ^{177}Lu-DOTATATE the MTD for the kidneys was reached before the intended cumulative dose of 29.6 GBq, which corresponds with the accepted MTD for the bone marrow of 2 Gy. The remaining 70% of patients received the cumulative dose of 29.6 GBq, which for most patients resulted in a cumulative dose to the kidneys less than 23 Gy. Thus, only in a minority of the patients treated with ^{177}Lu-DOTATATE the tumour-to-kidney ratio plays a role in the maximum cumulative dose of 29.6 GBq given.

In contrast, in patients with ^{90}Y-DOTATOC, the kidneys must be considered as the main, if not, the only dose-limiting organ, since the MTD for the kidney is reached before the bone marrow MTD comes in view [20].

Taken into consideration all of the aforementioned arguments, we concluded that DOTATATE has a better therapeutic window than DOTATOC and therefore is the

preferred somatostatin analogue to be coupled to ^{177}Lu when used in PRRT.

In **chapter 6.1**, we describe the feasibility to treat patients with differentiated thyroid carcinoma, who had proven non-radioiodine avid disease and were inoperable, with ^{177}Lu-DOTATATE. Five patients with metastatic differentiated thyroid carcinoma (3 with Hürthle cell carcinoma, 1 with papillary thyroid carcinoma and 1 with follicular thyroid carcinoma) were treated with 22.1–30.1 GBq ^{177}Lu-DOTATATE. After PRRT, two patients had stable disease, two had tumour shrinkage and one had progressive disease. Besides objective tumour response favourable time to progression was demonstrated. Since these patients had no alternative treatment option left, it was concluded that treatment with ^{177}Lu-DOTATATE can be benificial. Obviously, studies with a larger group of patients are necessary to establish the true potential of this approach. In addition, other radiolabelled somatostatin analogues, such as [DOTA-1-Nal^3]octreotide coupled to either ^{90}Y or ^{177}Lu which exhibit a different affinity profile to the somatostatin receptor [21], are of interest. This somatostatin analogue has in addition to the high affinity to the somatostatin receptor subtype 2, favourable affinity to the subtypes 3 and 5 which is potentially more effective in the treatment of differentiated thyroid carcinoma. This is because the expression profile of somatostatin receptors in differentiated thyroid carcinoma is likely to be different from GEP-NETs, with evidence of (co-) expression of subtypes 3 and 5 [22].

In **chapter 6.2** the current use of somatostatin receptor imaging and therapy in non-radioiodine avid differentiated thyroid carcinoma is reviewed. The overall conclusion regarding scintigraphy is that it can be useful to localize tumor sites in patients in whom disease is suspected because of an elevated serum Tg level but without apparent uptake during postradioiodine therapy whole body scintigraphy. In more than 50% of the cases somatostatin receptor scintigraphy is able to localize disease and hence helpful in the further management of these patients. PRRT in differentiated thyroid carcinoma has been described in only 62 patients up until now. Three different radionuclides (^{111}In, ^{90}Y and ^{177}Lu) coupled to 4 different somatostatin analogues (DOTATOC, [DTPA^o]octreotide, lanreotide and DOTATATE) were used with cumulative dosages in the range of 0.9 to 30.1 GBq. The ^{90}Y and ^{177}Lu coupled somatostatin analogues demonstrated to be the most promising in terms of tumour response compared to ^{111}In, and therefore the usage of the latter is not recommended anymore for PRRT in differentiated thyroid carcinoma which is also true for PRRT in GEP-NET patients.

Final conclusions

PRRT with ^{177}Lu-DOTATATE is the choice of therapy in patients with inoperable, metastasised well-differentiated somatostatin receptor positive GEP-NETs. The outcome of therapy in terms of objective response, quality of life, time to progression

and preliminary survival analysis compares favourably with the historical data of alternative therapeutic approaches, including the currently available chemotherapy. Also, side-effects and toxicity profile are in general favourable. Furthermore, ^{177}Lu-DOTATATE therapy can be an optional therapy in selected patients with non-radioiodine-avid differentiated thyroid carcinoma. Especially in non-radioiodine-avid differentiated carcinoma, radiolabelled somatostatin analogues with a different, more specific, somatostatin receptor profile may be promising.

To increase the effectiveness of PRRT, administration of higher cumulative doses to the individual patient could be one of the methods. This can only be achieved via the introduction of individually assessed dosimetry in order to estimate the exact dose to the dose-limiting organs. However, since this approach is difficult, time-consuming and therefore costly, individual accurate pre-therapy dosimetry is currently not available in any therapeutic institution [23]. Further research towards patient-based dosimetry, including the kidneys and bone marrow, is necessary to provide practical methods for tailored PRRT so that it can be part of patient management in the future. Furthermore, besides individual dosimetry to provide optimal treatment dose, the development of kidney protective agents could widen the therapeutic window. With the use of kidney protective agents, higher dosages can be given which could increase PRRT efficacy.

Besides attempts to widen the therapeutic window of PRRT, new approaches for future studies include the development of new somatostatin analogues with more favourable affinity profiles, combinational therapy with other radionuclides, such as ^{90}Y or ^{111}In, and the use of radiosensitizing agents. A multi-centre randomised controlled trial with ^{177}Lu-DOTATATE therapy in combination with the radiosensitizing agent capecitabine versus monotherapy with ^{177}Lu-DOTATATE has been started at our department in 2007.

Finally, the use of PRRT in patients with somatostatin receptor positive tumours demonstrates that a therapy based on a radionuclide coupled to a peptide can be succesful and holds great promise for future treatment of various other cancers. Frequently, new tumour-specific receptors are discovered that might become potential targets for high affinity radiolabelled peptides and thus PRRT. Therefore, it is not unlikely that PRRT will become an important therapeutic modality in other parts of the challenging field of oncology.

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8

Samenvatting en algemene discussie

Het concept van radioactief gelabelde peptiden die zich kunnen binden aan membraan gebonden receptoren is een inspiratiebron voor veel onderzoekers en resulteerde in een groot aantal interessante onderzoeksprojecten op dit gebied. De allereerste humane toepassing van radioactief gelabelde peptiden werd geïntroduceerd door de groep van Krenning in 1989 [1]. Het somatostatine analoog Tyr^3-octreotide werd gelabeld met Jodium-123 (^{123}I). Door middel van scintigrafie met dit radiofarmacon konden neuroendocriene tumoren, die somatostatinereceptoren tot expressie brengen, worden aangetoond. Het gebruik van ^{123}I-Tyr^3-octreotide had echter een aantal nadelen zoals de hoge fysiologische activiteit in de buik na toediening, de moeizame productiemethode en de relatief korte halfwaardetijd [2]. Om deze problemen te voorkomen werd een ander radioactief gelabeld somatostatine-analoog ontwikkeld, het ^{111}Indium-DTPA-*D*-Phe^1-octreotide (^{111}In-octreotide). Het ^{111}In-octreotide heeft een aantal voordelen zoals de relatief gemakkelijke bereiding, de goede beschikbaarheid, de praktische halfwaardetijd en minimale fysiologische opname in de buik. In 1994 werd ^{111}In-octreotide (OctreoScan®) goedgekeurd door de Amerikaanse Food and Drug Administration. Vanaf die tijd is scintigrafie met OctreoScan® de meest gebruikte methode voor het diagnosticeren van gastro-intestinale neuroendocriene tumoren, zoals het carcinoid en de neuroendocriene tumoren van de pancreas. Deze tumoren hebben in het algemeen een hoge expressie van somatostatinereceptoren, met name van subtype 2 op hun celmembraan [3].

De volgende logische stap op dit gebied, tevens uitgevoerd door de groep van Krenning, was het gebruik van radioactief gelabelde somatostatine-analogen voor therapie bij patiënten met inoperabele, somatostatinereceptor positieve neuroendocriene tumoren, aangetoond op de OctreoScan® [4]. Dit was een belangrijke nieuwe therapeutische benadering voor deze groep patiënten, aangezien er op dat moment geen effectieve systemische therapie beschikbaar was.

De eerste therapie met een radioactief gelabeld somatostatine-analoog was gebaseerd op hoge doses van het ^{111}In-octreotide. De radiotoxiciteit van met name de Auger electronen die door het ^{111}Indium worden uitgezonden zijn van belang voor het eventuele therapeutische effect. Vanwege het experimentele karakter van deze therapie kwamen voornamelijk patiënten met uitgebreid gemetastaseerde neuroendocriene tumoren in aanmerking. De totaal gecumuleerde dosis die aan deze patiënten werd gegeven, varieerde van 3,1 tot en met 160 Gigabecquerel (GBq). Hoewel de resultaten, zoals biochemische en klinische verbeteringen, bemoedigend en veelbelovend waren kon slechts in een klein aantal patiënten een objectiveerbare verkleining van de tumoren (tumorrespons) worden aangetoond [5-7]. Het is dan ook niet verwonderlijk dat verschillende onderzoeksgroepen, die eerst hun patiënten behandelden met ^{111}In-octreotide, somatostatine-analogen ontwikkelden die gekoppeld konden worden aan een radionuclide dat bètastraling uitzendt, zoals het ^{90}Yttrium (^{90}Y) of ^{177}Lutetium

(^{177}Lu). Van deze radionucliden was een betere effectiviteit te verwachten, gezien het langere emissiepad van de uitgezonden bètadeeltjes (2-12 mm) in vergelijking met de relatief korte afstand (≈ 10 μm) die wordt afgelegd door de Auger electronen uitgezonden door het ^{111}Indium (^{111}In). Klinische studies met verschillende somatostatine-analogen gelabeld met ^{90}Y volgden en toonden inderdaad een hoger percentage patiënten met een tumorrespons in vergelijking met ^{111}In-octreotide. Bijna gelijktijdig werd in het Erasmus MC in Rotterdam gestart met de behandeling van patiënten met inoperabele of gemetastaseerde gastro-intestinale neuroendocriene tumoren met ^{177}Lu gelabeld [DOTA^{0},Tyr^{3}]octreotaat (^{177}Lu-DOTATAAT) .

Het doel van dit proefschrift was om de effectiviteit van ^{177}Lu-DOTATAAT therapie bij patiënten met somatostatinereceptor positieve gastro-intestinale tumoren te evalueren. Hierbij komen achtereenvolgens de toxiciteit, bijwerkingen, het effect op de tumorgrootte en de kwaliteit van leven na ^{177}Lu-DOTATAAT therapie aan de orde. Vervolgens is onderzocht welk somatostatine-analoog het meest geschikt is om te gebruiken bij peptide receptor radionuclide therapy (PRRT) met ^{177}Lu; DOTATAAT of [DOTA-*D*-Phe^{1}-Tyr^{3}]octreotide (DOTATOC). Deze onderwerpen komen aan de orde in het eerste gedeelte van dit proefschrift (hoofdstuk 2 t/m 5).

Aangezien ^{177}Lu-DOTATAAT therapie succesvol bleek te zijn in patiënten met gastro-intestinale neuroendocriene tumoren, werd deze therapie mogelijk ook geschikt geacht voor de behandeling van andere somatostatinereceptor positieve tumoren. Mogelijke kandidaten voor ^{177}Lu-DOTATAAT therapie bleken patiënten met gedifferentieerd schildkliercarcinoom, waarbij de tumor niet meer in staat was om radioactief jodium (^{131}I) op te nemen. Voor deze specifieke patiëntengroep bestaat er, naast het gebruikelijke ^{131}I, geen goede alternatieve systemische therapie. Wanneer er wel duidelijke activiteitsstapeling werd gezien op de OctreoScan® werden deze patiënten behandeld met ^{177}Lu-DOTATAAT. De effectiviteit van PRRT met ^{177}Lu-DOTATAAT bij een aantal van deze patiënten is beschreven in het tweede gedeelte van dit proefschrift (hoofdstuk 6.1). Daarnaast is een uitgebreid overzicht van de stagering van gedifferentieerd schildkliercarcinoom met OctreoScan® en het gebruik van PRRT bij deze specifieke patiëntenpopulatie weergegeven (hoofdstuk 6.2).

Hoofdstuk 1.1 geeft een overzicht van de behandelingsmogelijkheden van patiënten met gastro-intestinale tumoren. Een groot aantal therapeutische opties, inclusief PRRT met radioactief gelabelde somatostatine-analogen, is beschreven waarbij uitkomstmaten en bevindingen zoals toxiciteit, bijwerkingen, therapierespons en overlevingsduur ter sprake komen. **Hoofdstuk 1.2** bevat een uitgebreid overzicht van PRRT bij patiënten met gastro-intestinale neuroendocriene tumoren. In **hoofdstuk 1.3** zijn het doel en de opzet van dit proefschrift uiteengezet.

In **hoofdstuk 2.1** zijn de eerste resultaten van ^{177}Lu-DOTATAAT therapie bij 35 patiënten met gastro-intestinale neuroendocriene tumoren beschreven. Het doel van deze studie was in eerste instantie het evalueren van de mogelijkheid van behandeling van patiënten met ^{177}Lu-DOTATAAT met daarbij de nadruk op evaluatie van de mogelijke bijwerkingen en de toxiciteit van de behandeling. Toxiciteit en bijwerkingen na behandeling met ^{177}Lu-DOTATAAT kwamen niet frequent voor en waren meestal kortdurend. Tijdelijke milde beenmergdepressie was de meest voorkomende bijwerking. Naast deze resultaten zijn ook de effecten op tumorgrootte beschreven. Complete en partiële remissie werd gevonden in 38% van de onderzochte patiënten, hetgeen een beter resultaat was dan dat van de eerder beschreven PRRT studies met ^{90}Y-DOTATOC en chemotherapie. Het was echter noodzakelijk om deze eerste veelbelovende bevindingen te bevestigen in een grotere groep patiënten. Deze resultaten bij een grotere groep patiënten zijn beschreven in **hoofdstuk 2.2,** waarin de goede therapierespons, zoals eerder beschreven in hoofdstuk 2.1, werd bevestigd. Minimale, partiële of complete tumorrepons werd gevonden in 47% van de 125 geëvalueerde patiënten. Voorspellende factoren voor een goede respons waren zowel een hoge opname van het radiofarmacon in de tumoren op de OctreoScan® voorafgaande aan de therapie als ook een minimale hoeveelheid metastasen in de lever. Daarentegen hadden patiënten met een lage Karnofsky Performance Score of een hoge tumor load, een hoger risico op progressieve ziekte na therapie.

Uit de resultaten van dit onderzoek concludeerden wij dat vroege behandeling met ^{177}Lu-DOTATAAT therapie, zelfs bij patiënten zonder duidelijk aantoonbare tumorgroei, waarschijnlijk tot betere therapieresultaten leidt. Een goede vergelijking van onze bevindingen omtrent de behandeling met ^{177}Lu-DOTATAAT met de resultaten van ^{90}Y-DOTATOC therapie is moeilijk te geven, aangezien naast de verschillen in studie-opzet, protocol en de hoogte van de gegeven doses, de selectie van bepaalde categoriën patiënten de uitkomsten van ons onderzoek mogelijk heeft beïnvloed. Tot op de dag van vandaag is het op basis van de klinische studies nog niet goed mogelijk om aan te geven welk radioactief gelabeld somatostatine-analoog nu echt beschouwd mag worden als het ideale radiofarmacon om te gebruiken bij PRRT in patiënten met gastro-intestinale neuroendocriene tumoren.

Een andere interessante bevinding beschreven in hoofdstuk 2.2 is de verminderde ^{177}Lu-DOTATAAT opname op het laatste posttherapie scintigram in vergelijking met het eerste posttherapie scintigram. Meerdere malen bleek een vermindering van opname samen te gaan met een objectiveerbare tumorrespons op de CT scan. Ook werd duidelijk dat bij patiënten met stabiele ziekte of regressie als therapierespons, de mediane periode tot progressie meer dan 36 maanden bedroeg. Een direct vergelijk met chemotherapie werd niet verricht, aangezien chemotherapie relatief ineffectief is bij patiënten met inoperabele gastro-intestinale neuroendocriene tumoren. Wel

werden onze resultaten vergeleken met historische data van studies waarbij meestal chemotherapie werd gebruikt als systemische cytotoxische therapie. Een grote variatie in de beschreven objectiveerbare tumorresponsen maakt het echter nog steeds moeilijk om de studies goed met elkaar te kunnen vergelijken. Toch kwam naar voren dat in de meeste studies een responsduur van minder dan 18 maanden werd beschreven, hetgeen duidelijk minder is dan de door ons gevonden mediane periode tot progressie van 36 maanden. Verdere vergelijking bracht naar voren dat de toxiciteit van de gebruikte chemotherapie schema's duidelijk ernstiger is en frequenter werd geconstateerd dan met ^{177}Lu-DOTATAAT therapie. Op dit moment worden er nog steeds patiënten in de studie geïncludeerd en is de mediane periode van follow-up 16 maanden. Waarschijnlijk zal evaluatie op een later tijdstip meer definitief bewijs voor onze huidige bevindingen opleveren.

In **hoofdstuk 3** wordt de kwaliteit van leven van 50 patiënten na ^{177}Lu-DOTATAAT therapie beschreven. De kwaliteit van leven werd bepaald door middel van een gestandaardiseerde en gestructureerde vragenlijst van de European Organisation for Research and Treatment of Cancer (EORTC), de EORTC QLQ-C30. Binnen de gehele patiëntengroep verbeterde de kwaliteit van leven, met name bij patiënten die later ook een goede tumorrespons lieten zien. Tot onze verrassing bleek echter ook de kwaliteit van leven significant te verbeteren bij patiënten die later bewezen progressieve ziekte bleken te hebben. Naast het placebo-effect zal ook het kleine aantal patiënten in deze groep een rol hebben gespeeld bij deze verrassende uitkomst. Het kleine aantal patiënten dat de gestructureerde vragenlijst had ingevuld is te verklaren uit het feit dat patiënten met de meest agressieve tumoren soms fysiek niet in staat waren de vragenlijst in te vullen. Daarom zijn de resultaten in deze categorie patiënten niet erg betrouwbaar en moeten ze met enige terughoudendheid worden geïnterpreteerd.

Naast de algemene kwaliteit van leven was er een significante verbetering van een aantal zogenaamde functioneringsschalen (het emotioneel, rol (gezin, werk) en sociaal functioneren), symptoomschalen (moeheid en pijn) en het single item slapeloosheid.

Tenslotte concludeerden we dat een goede therapierespons meestal gepaard ging met een verbetering van de algemene kwaliteit van leven in de onderzochte patiënten.

In **hoofdstuk 4** wordt ingegaan op de korte- en langetermijneffecten van ^{177}Lu-DOTATAAT therapie op de hormonale functies. Aangezien PRRT een systemisch toegediende therapie is en omdat vele endocriene organen somatostatinereceptoren tot expressie brengen, worden deze organen mogelijk blootgesteld aan een ongewenste hoeveelheid stralenbelasting. We toonden aan dat, net zoals bij mannen

behandeld met hoge doses ^{131}I na thyreoidectomie, er een tijdelijke daling was van de concentratie van het hormoon inhibine B van ongeveer 24 maanden, terwijl de concentratie van het FSH een gelijktijdige tijdelijke stijging liet zien. Hoewel er geen analyse van het sperma van deze mannen was verricht, geven deze waarden aan dat de spermatogenese tijdelijk verminderd moet zijn geweest.

Verder werd duidelijk dat, hoewel de serumconcentratie van zowel het totale testosteron als van het sexhormoonbindend globuline een daling lieten zien na ^{177}Lu-DOTATAAT therapie, de ongebonden testosteronconcentratie niet veranderde. Tegelijkertijd was er sprake van een tijdelijke toename van de concentratie van het luteïniserend hormoon (LH). Dit suggereert dat hormonale feedbackmechanismen hebben gezorgd voor het op peil houden van de ongebonden testosteronconcentratie in het bloed.

Verhoogde serumconcentraties van de gonadotrope hormonen en de subnormale testosteronconcentratie in het serum zijn recent ook gerapporteerd bij mannen met rectumcarcinoom na behandeling met externe radiotherapie [9]. Omdat er geen goed direct bewijs is voor de aanwezigheid van eiwitexpressie van somatostinereceptoren in de testes en vanwege de overeenkomsten met de bevindingen bij mannen behandeld met hoge doses ^{131}I en externe radiotherapie, is de geconstateerde radiotoxiciteit waarschijnlijk niet gerelateerd aan de expressie van somatostatinereceptoren. De meest waarschijnlijke oorzaak hiervoor is dat er bestraling van de radiosensitieve testes vanuit de systemische circulatie plaatsvindt. Daarnaast is er ook een bijdrage van gescatterde straling aanwezig door radioactieve urine in de blaas of ontlasting in het rectum na PRRT te verwachten.

Een andere opmerkelijke bevinding is de daling van zowel LH als FSH concentraties in postmenopauzale vrouwen. Deze daling is duidelijk meer dan verwacht kan worden op basis van veroudering alleen[10]. Aangezien somatostatinereceptoren tot expressie worden gebracht in de hypofyse en omdat postmenopauzale vrouwen het premenopauzale feedback mechanisme missen, is een receptorafhankelijk mechanisme een voor de hand liggende oorzaak.

Daarnaast daalde de gemiddelde serumconcentratie van het schildklierhormoon vrij-T4 in de groep patiënten significant. De waarden bleven echter nog ruim binnen de referentiewaarden. Twee patiënten ontwikkelden een primaire hypothyreoidie tijdens en na ^{177}Lu-DOTATAAT therapie. Het is echter de vraag of deze hypothyreoidie veroorzaakt is door de PRRT of dat het beschouwd mag worden als berustend op variatie binnen de normale populatie. De subtiele, maar significante daling van de gemiddelde vrij-T4 concentratie is echter suggestief voor een beperkt receptorgerelateerde dosiseffect.

Van de geobserveerde subtiele daling mag worden aangenomen dat deze in het algemeen klinisch niet relevant is.

Vervolgens toonden we aan dat er een daling is van de gemiddelde serumconcentratie van het schildkierhormoon reverse T3 (rT3) direct na behandeling met ^{177}Lu-DOTATAAT therapie. De rT3 concentratie was overigens al verhoogd voor de eerste therapie. Een dergelijke daling is ook beschreven bij patiënten met een chronische ziekte, het zogenaamde "non-thyroid illness" syndroom. Een daling van het rT3 correleert met de ernst van de ziekte [11]. De daling van het rT3 bij onze patiënten wijst daarom mogelijk op een verandering in de ernst van de ziekte.

Met behulp van de lage dosis ACTH-stimulatie test werd aangetoond dat na ^{177}Lu-DOTATAAT therapie geen bijnierschorsdeficiëntie ontstaat .

Bij vijf patiënten werden verhoogde HbA_{1c} waarden geconstateerd, zonder dat er sprake was van een aanwijsbare oorzaak, zoals bijvoorbeeld pancreaschirurgie in het verleden. Omdat het bekend is dat de eilandjes van Langerhans somatostatinereceptoren tot expressie brengen is een receptorafhankelijk stralingseffect van ^{177}Lu-DOTATAAT therapie op de glucose huishouding niet uitgesloten. Ook het effect van langdurig gebruik van een "koud" somatostatine-analoog, hetgeen niet ongebruikelijk is bij deze groep patiënten, kan eventueel hebben bijgedragen aan onze bevindingen.

In het algemeen concludeerden we dat patiënten, behandeld met ^{177}Lu-DOTATAAT, stralingsgeïnduceerde hormonale veranderingen kunnen ontwikkelen. Vaak zijn dergelijke veranderingen tijdelijk en klinisch niet relevant. De behandelend arts dient echter rekening te houden met eventuele veranderingen in de hormoonhuishouding, bij bijvoorbeeld jonge mannen met een kinderwens. Desondanks kan ^{177}Lu-DOTATAAT therapie op basis van door ons geobserveerde endocriene effecten als veilig worden beschouwd.

In **hoofdstuk 5** worden de resultaten beschreven van een onderzoek naar welk van de twee meest gebruikte somatostatine-analogen, DOTATAAT of DOTATOC, het meest geschikt is om, gekoppeld aan ^{177}Lu, gebruikt te worden bij PRRT. Beide somatostatine-analogen hebben verschillende affiniteiten voor de bekende somatostatinereceptor subtypen. Voor PRRT is de balans tussen opname in de tumor en in de dosislimiterende organen van belang, aangezien dit de therapeutische breedte van het radiofarmacon bepaalt. Een directe vergelijking van beide analogen in een therapeutische setting werd uitgevoerd. Verblijftijden van radioactiviteit in milt, nieren en aanwezige tumoren, die direct gerelateerd zijn aan de geabsorbeerde tumordosis, waren langer met gebruik van ^{177}Lu-DOTATAAT in vergelijking met ^{177}Lu-DOTATOC. Daarbij waren de ratio's van de gemiddelde verblijftijden van

^{177}Lu-DOTATAAT versus ^{177}Lu-DOTATOC respectievelijk 1,5, 1,4 en 2,1 Dientengevolge is te verwachten dat hogere geabsorbeerde tumordoses worden bereikt met ^{177}Lu-DOTATAAT dan met ^{177}Lu-DOTATOC. De langere verblijftijd in de nieren bij gebruik van ^{177}Lu-DOTATAAT kan echter een probleem vormen bij PRRT. De nieren kunnen namelijk naast het beenmerg ook dosislimiterend zijn. Indien de nieren echter inderdaad de limiterende factor zijn, doordat bij eventuele voortgang van therapie de maximale tolereerbare dosislimiet (MTD) van 23 Gy voor de nieren wordt overschreden, dan zal de geabsorbeerde tumordosis met ^{177}Lu-DOTATAAT altijd hoger zijn dan met ^{177}Lu-DOTATOC. De ratio van de gemiddelde verblijftijd in de tumor(en) (2,1) is namelijk een factor 1,5 hoger dan de gemiddelde verblijftijdratio van de nieren (1,4), in het voordeel van ^{177}Lu-DOTATAAT. Overigens bleek dat bij de meeste patiënten niet de nieren, maar het beenmerg (MTD van 2 Gy) het dosisbeperkende orgaan was.

Een vergelijkbare studie is uitgevoerd door Forrer en zijn collega's in Bazel, waarbij ^{111}In-DOTATOC werd vergeleken met ^{111}In-DOTATAAT [12]. Aangenomen werd dat voor dosimetrie berekeningen ^{111}In gebruikt kon worden als surrogaat for ^{90}Y, het radionuclide dat in Bazel wordt gebruikt voor PRRT. Drie van de vijf patiënten, van wie tweemaal een scintigram werd vervaardigd, hadden een betere tumor/achtergrond ratio op het scintigram na ^{111}In-DOTATOC in vergelijking met ^{111}In-DOTATAAT. Op basis van deze gegevens werd besloten om het gebruik van het somatostatine-analoog DOTATOC gelabeld met ^{90}Y in PRRT te continueren. De aanname dat ^{111}In een bruikbaar surrogaat is voor ^{90}Y, is echter niet helemaal valide. Verschillende radionucliden gebonden aan één somatostatine-analoog kunnen geheel andere affiniteitsprofielen hebben [13]. Dit zou kunnen leiden tot een verschil in biodistributie van de verschillende radiofarmaca, hetgeen is aangetoond in een onderzoeksmodel in ratten met neuroendocriene tumoren [14]. Ook de diagnostische hoeveelheid van het peptide dat gebruikt werd in de studie van Forrer *et al*. was veel kleiner dan de gebruikelijke hoeveelheid bij PRRT. Door verschillende auteurs is aangetoond dat het verschil in de hoeveelheid peptide een verschil in biodistributie kan betekenen [15-17]. Breeman *et al*. beschreven dat indien de opname van ^{111}In-octreotide in somatostatinereceptor positieve organen wordt weergegeven als functie van de hoeveelheid toegediende massa er een weefsel-specifieke klokvormige curve ontstaat. Vervolgens werd het bestaan van dezelfde klokvormige curve aangetoond, zowel in het normale weefsel als in somatostatinereceptor positieve tumoren in zogenaamde naakte muizen door Bernhardt *et al*[18]. De biodistributie kan dus zowel een effect hebben op de geabsorbeerde dosis in de nieren als in tumoren. Het directe gevolg is een effect op de tumor/nieren ratio zoals gevonden door Forrer *et al*. [12]. Tevens is het in de meeste instituten gebruikelijk om, gelijktijdig met radioactief gelabelde somatostatinereceptoren, aminozuren intraveneus toe te dienen. Gelijktijdige toediening van de aminozuren lysine en arginine tijdens PRRT bewerkstelligt een

significante afname van renale radioactiviteit en heeft dus ook een effect op de tumor/nieren ratio [19].

Concluderend is onze studie, in tegenstelling tot de studie uit Bazel, op verschillende punten beter vergelijkbaar met de uiteindelijke therapeutische setting. Daarbij geven de door ons geanalyseerde verblijftijden van radioactiviteit in de tumor en nieren een betere indruk van de absolute geabsorbeerde dosis dan de relatieve uptake methode met tumor/nieren ratio's.

Tenslotte zijn, zoals eerder genoemd, bij PRRT met ^{177}Lu-DOTATAAT of ^{90}Y-DOTATOC, de nieren en het beenmerg de kritische organen. De bijbehorende MTD voor externe bestraling van deze organen zijn respectievelijk 23 en 2 Gy en worden gebruikt als dosisgrens om stralingsgeïnduceerde nefropathie en beenmergtoxiciteit, zoals het myelodysplastische syndroom of leukemie te voorkomen.

Wanneer PRRT met ^{177}Lu-DOTATAAT of ^{90}Y-DOTATOC wordt overwogen, dan is de tumor/nieren ratio bij het gebruik van ^{177}Lu-DOTATAAT niet zo belangrijk als bij het gebruik van ^{90}Y-DOTATOC, aangezien in ongeveer 30% van de patiënten behandeld met ^{177}Lu-DOTATAAT de MTD van de nieren (23 Gy) werd bereikt voordat de MTD van het beenmerg werd bereikt. Dientengevolge ontvingen deze patiënten minder dan de vooraf beoogde 29,6 GBq (4x7400 MBq) ^{177}Lu-DOTATAAT, overeenkomstig met de geaccepteerde MTD van het beenmerg van 2 Gy. Uiteindelijk ontving ongeveer 70% van de patiënten de volledige dosis van 29,6 GBq. Bij PRRT met ^{90}Y-DOTATOC worden de nieren beschouwd als het belangrijkste dosislimiterend orgaan, aangezien de MTD van de nieren vrijwel altijd eerder bereikt is dan de MTD van het beenmerg [20].

De eerder genoemde argumenten in ogenschouw nemend, concluderen we dat het somatostatine-analoog DOTATAAT een betere therapeutische breedte heeft dan DOTATOC en daarom de voorkeur geniet om, gekoppeld aan ^{177}Lu, te worden gebruikt bij PRRT.

In **hoofdstuk 6.1** worden de eerste patiënten met inoperabel en Jodium-131 (^{131}I) negatief gedifferentieerd schildkliercarcinoom die behandeling met ^{177}Lu-DOTATAAT hebben ondergaan, beschreven.

Vijf patiënten met gemetastaseerd gedifferentieerd schildkliercarcinoom (3x Hürthle cel carcinoom; 1x papillair schildkliercarcinoom; 1x folliculair schildkliercarcinoom) werden behandeld met 22,1-30,1 GBq ^{177}Lu-DOTATAAT. Na behandeling met ^{177}Lu-DOTATAAT hadden 2 patiënten stabiele ziekte, 2 patiënten hadden een verkleining van de tumor en 1 patiënt had progressieve ziekte. Naast deze objectieve

therapierespons was er een gunstige periode tot progressie. Aangezien deze patiënten geen alternatieve therapeutische opties meer hadden, werd geconcludeerd dat therapie met ^{177}Lu-DOTATAAT bij deze patiëntengroep een goede behandelingsoptie kan zijn. Vanzelfsprekend is een studie met inclusie van een grotere groep patiënten noodzakelijk om de echte waarde van deze therapeutische benadering vast te stellen. Naast het ^{177}Lu-DOTATAAT zijn andere radioactief gelabelde somatostatine-analogen, zoals het [DOTA-1-Nal^3]octreotide, gelabeld met ^{90}Y of ^{177}Lu, interessant [21]. Deze somatostatine-analogen verschillen met het ^{177}Lu-DOTATAAT in hun affiniteitsprofiel voor de somatostatinereceptor, waarbij er naast een hoge affiniteit voor subtype 2, ook een hoge affiniteit voor de subtypen 3 en 5 bestaat. Behandeling van schildkliercarcinoom met deze gelabelde somatostatine-analogen zou interessant kunnen zijn, aangezien er aanwijzingen zijn dat het somatostatinereceptor expressieprofiel bij schildkliercarcinomen anders is dan bij de gastro-intestinale neuroendocriene tumoren, met hogere expressie van zowel subtype 3 als 5, naast subtype 2 [22].

In **hoofdstuk 6.2** is een overzicht gegeven van het gebruik van somatostatinereceptor scintigrafie en PRRT bij het ^{131}I negatief gedifferentieerd schildkliercarcinoom. De conclusie die getrokken kan worden uit dit literatuuroverzicht is dat somatostatinereceptor scintigrafie behulpzaam kan zijn om de tumoren te localiseren indien er aanwijzingen zijn voor aanwezigheid van ziekte door bijvoorbeeld een verhoogde thyroglobulineconcentratie in het serum, echter zonder duidelijke stapeling van ^{131}I bij totale lichaamsscintigrafie na ^{131}I behandeling. In meer dan 50% van de patiënten is somatostatinereceptor scintigrafie alsnog in staat om de ziekte te localiseren. Op deze wijze speelt somatostatinereceptor scintigrafie een rol bij de stagering en het verder te bepalen behandeltraject.

PRRT bij gedifferentieerd schildkliercarcinoom is beschreven in slechts 62 patiënten. Drie verschillende radionucliden (^{111}In, ^{90}Y and ^{177}Lu) gekoppeld aan 4 verschillende somatostatine-analogen (DOTATOC, [DTPA^0]octreotide, lanreotide and DOTATAAT) zijn gebruikt met cumulatieve doses variërend van 0,9 tot 30,1 GBq. De somatostatine-analogen gekoppeld aan ^{90}Y en ^{177}Lu waren veelbelovender met betrekking tot tumorrespons dan wanneer gekoppeld aan ^{111}In. Het ^{111}In wordt daarom, net zoals bij de behandeling van gastro-intestinale neuroendocriene tumoren, niet meer aanbevolen voor PRRT bij gedifferentieerd schildkliercarcinoom.

Slotconclusies

PRRT met ^{177}Lu-DOTATAAT is de aangewezen therapie bij patiënten met inoperabel, gemetastaseerde, goed gedifferentieerde, somatostatinereceptor positieve gastro-intestinale neuroendocriene tumoren. De uitkomsten op het gebied van objectiveerbare tumorrespons, kwaliteit van leven, gemiddelde periode tot progressie

en de eerste overlevingsduuranalyse laten zien dat in vergelijking met de historische data van andere beschikbare therapeutische benaderingen, inclusief de huidige chemotherapie, PRRT met ^{177}Lu-DOTATAAT beter is. Daarbij zijn de geobserveerde bijwerkingen minder en is het toxiciteitsprofiel gunstig.

Ook kan bij het ontbreken van chirurgische opties bij ^{131}I negatief gedifferentieerd schildkliercarcinoom behandeling met ^{177}Lu-DOTATAAT als therapeutische behandeling overwogen worden. Met name in deze groep zijn de radioactief gelabelde somatostatine-analogen met een ander affiniteitsprofiel veelbelovend.

Een methode om de effectiviteit van PRRT nog verder te vergroten is door toedienen van hogere cumulatieve doses bij de individuele patiënt. Dit is alleen mogelijk door gebruik te maken van dosimetrie bij iedere afzonderlijke patiënt. Door de exacte dosis op de dosis-beperkende organen per behandeling en per patiënt te berekenen kan worden bepaald of er nog (dosis)ruimte is voor verdere behandeling. Omdat deze methode lastig, zeer arbeidsintensief en dus kostbaar is, wordt deze manier van behandelen nog niet in alle instituten toegepast [23].

Verder onderzoek naar deze patiëntgebonden dosimetrie, met name van de nieren en het beenmerg, is essentieel om tot praktische oplossingen te komen voor zogenaamde PRRT op maat, zodat dit in de toekomst toegepast kan worden bij de integrale benadering en behandeling van de patiënten.

Ook de ontwikkeling van zogenaamde nierbeschermende middelen is van belang om de therapeutische breedte te vergroten. Door gebruik te maken van nierbeschermende middelen wordt het mogelijk om hogere doses toe te dienen om zo de effectiviteit van PRRT te vergroten.

Naast het vergroten van de therapeutische breedte bij de bestaande radioactief gelabelde somatostatine-analogen zijn er verscheidene nieuwe benaderingen zoals de ontwikkeling van nieuwe somatostatine-analogen met een gunstiger somatostatinereceptor affiniteitsprofiel, combinatietherapie met andere radionucliden zoals ^{90}Y of ^{111}In of combinatie met radiosensitizers. Een multicentrum gerandomiseerde studie met ^{177}Lu-DOTATAAT in combinatie met de radiosensitizer capecitabine versus monotherapie met ^{177}Lu-DOTATAAT is reeds gestart op de afdeling Nucleaire Geneeskunde in het Erasmus MC (Rotterdam).

Tenslotte laat het gebruik van PRRT bij patiënten met somatostatinereceptor positieve tumoren zien dat een therapie gebaseerd op een radionuclide gekoppeld aan een peptide zeer succesvol kan zijn. PRRT is daarom veelbelovend voor de behandeling van andere vormen van kanker. Nieuwe tumor-specifieke receptoren

worden veelvuldig ontdekt. Deze receptoren zijn in principe allemaal een potentiëel doelwit voor radioactief gelabelde peptiden en dus ook voor PRRT. Het is dan ook niet ondenkbaar dat PRRT in de toekomst ook in andere deelgebieden van de oncologie een belangrijke therapeutische optie zal zijn.

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Abbreviations

5-FU	fluorouracil
5-HIAA	5-hydroxyindoleacetic acid
ACTH	adrenocorticotropic hormone
AML	acute myeloid leukemia
ANOVA	analysis of variance
BMI	body mass index
CARC	carcinoid
CCDP	cisplatin
CNS	central nervous system
CR	complete remission
CT	computed tomography
DOTA	1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetra-acetic acid
DOTALAN	DOTA-lanreotide
DOTANOC	[DOTA°-1-naphthyl^{3}]octreotide
DOTA-OC	DOTA-octreotide
DOTATOC	[DOTA°,Tyr^{3}]octreotide
DOX	doxorubicin (adriamycin)
DNA	deoxyribonucleic acid
DTPA	diethylene triamine penta-acetic acid
DOTATATE	[DOTA°,Tyr^{3}]octreotate
DTC	differentiated thyroid carcinoma
DTIC	dimethyltriazenoimidazole carboxamide
E2	oestradiol
EBRT	external beam radiation therapy
EGFR	epidermal growth factor receptor
ENETS	European Neuroendocrine Tumour Society
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
^{18}F-FDG	^{18}F-fluorodeoxyglucose
FDG-PET	fluorodeoxyglucose-positron emission tomography
FSH	follicle stimulating hormone
FT4	free thyroxine
FTC	follicular thyroid carcinoma
GBq	Gigabecquerel (10^{9} Bq)
GEP	gastroenteropancreatic
GEP-NET	gastroenteropancreatic neuroendocrine tumour
GLP-1	glucagon-like peptide-1
Gy	Gray
HACE	hepatic artery chemoembolisation
HAE	hepatic artery embolisation
HbA1c	haemoglobin A1c or glycolysated hemoglobin

HCTC	hürthle cell thyroid carcinoma
HPA-axis	hypothalamo-pituitary-adrenal axis
HPF	high power field
HRQoL	health related quality-of-life
HYNIC	hydrazinonicotinyl
ICC	islet cell tumour
IFN	interferon
ITT	insulin tolerance test
IU	international unit
keV	kiloelectron volt
KPS	Karnofsky Performance Scale
LAN	lanreotide
LDST	low-dose ACTH stimulation test
LH	luteinizing hormone
LITT	laser induced thermotherapy
MBq	Megabecquerel (10^6 Bq)
mCi	millicurie
MDS	myelodysplastic syndrome
MMC	mitomycin C
MR	minor remission
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NE	neuroendocrine
NEP	neuroendocrine pancreatic tumour
NET	neuroendocrine tumour
NOC	NaI^3-octreotide
NTI	non-thyroidal illness
OLT	orthotopic liver transplantation
OS	overall survival
PD	progressive disease
PDEC	poorly differentiated endocrine carcinoma
PDGF	platelet derived growth factor
PFS	progression free survival
PRRT	peptide receptor radionuclide therapy
PR	partial remission
PRS	peptide receptor scintigraphy
PTC	papillary thyroid carcinoma
QLQ-C30	Cancer 30-item Quality of Life Questionnaire
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	radiofrequency ablation

rT_3	reverse triiodothyronine
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results database
SEM	standard error of the mean
SHBG	sex hormone binding globulin
SPECT	single-photon emission computed tomography
SRS	somatostatin receptor scintigraphy
SS	somatostatin
SSTR	somatostatin receptor
STZ	streptozotocin
SWOG	SouthWest Oncology Group
T	testosterone
T_3	triiodothyronine
TATE	Tyr^3-Thr^8-octreotide
Tg	thyroglobulin
TOC	Tyr^3-octreotide
TPO	thyroid peroxidase
TK	tyrosine kinase
TSH	thyroid-stimulating hormone
TT	total testosterone
TTP	time to progression
Tyr	tyrosine
US	ultrasound
VEGF	vascular endothelial growth factor
VIP	vasoactive intestinal peptide
WBS	whole body scan
WHO	World Health Organization

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Curriculum Vitae

Jaap Teunissen was born on August 25th, 1972 in Arnhem, the Netherlands. In 1990 he graduated from highschool (VWO; Van Lingen College) in Arnhem. In the same year he started his study Biomedical Sciences at the University of Leiden. In 1995 he started his medical training at the Faculty of Medicine at the University of Leiden. From September 1997 till March 1998, he participated in a project called '*An Assessment of Steroid Cover during Pituitary Surgery'* at the department of Internal Medicine, division of Endocrinology, Radcliffe Infirmary, Oxford, UK under the supervision of Prof. dr. J.A.H. Wass. In 1999 he obtained his biomedical degree, followed by his medical degree in 2000. He started to work as a resident in Internal Medicine at the department of Internal Medicine of the Rode Kruis Hospital in The Hague (head: Dr. R.M. Valentijn). From November 2001 till December 2008 he worked as a research fellow at the department of Nuclear Medicine of the Erasmus MC in Rotterdam (supervised by Prof. dr. E.P. Krenning and Dr. D.J. Kwekkeboom) on the research presented in this thesis. In September 2005 he started his clinical nuclear medicine residency in training (AIOS) at the Erasmus MC in Rotterdam (head: Prof. dr. E.P. Krenning). As part of his training, he worked as a resident at the department of Internal Medicine of the Rijnland Hospital in Leiderdorp (head: Dr. F.H.M. Cluitmans), at the department of Radiology of the Erasmus MC in Rotterdam (head: Prof. dr. G.P. Krestin) and at the department of Nuclear Medicine of the The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital in Amsterdam (head: Dr. C. Hoefnagel). At the end of February 2009, he will finish his training period and become a Nuclear Medicine specialist and a staff member of the department of Nuclear Medicine, Erasmus MC, Rotterdam.
Since 2003, he is living happily together with Maaike Schaart in Leiden.

List of publications

Journals

2008

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Radiolabeled somatostatin analogs. Kwekkeboom DJ, **Teunissen JJM**, Kam BLR, Valkema R, de Herder WW, Krenning EP

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Chapter 24: Peptide Receptor Radionuclide Therapy with Lutetium-octreotate. **Teunissen JJM**, Kwekkeboom DJ, de Jong M, Esser JP, Valkema R, Krenning EP