Imaging and therapy of neuroendocrine tumors with radiolabeled somatostatin analogs

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Imaging and Therapy of Neuroendocrine Tumors with Radiolabeled Somatostatin Analogs

Beeldvorming en therapie van neuro-endocriene tumoren met radioactief gelabelde somatostatine analogen

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CHAPTER 1

General introduction

General Introduction

The German pathologist Siegfried Oberndorfer was in 1907 the first to describe a neuroendocrine tumor (NET) in a patient with a tumor in the small intestine and named this a "Karzinoide tumor" or carcinoid (1). Although the World Health Organization (WHO) has replaced the term carcinoid in the classification for this type of tumor (2), the term carcinoid is still frequently used for NETs of the small intestine and the lungs in particular. NETs can arise from neuroendocrine cells, which are present throughout the whole body. Therefore, these tumors can develop anywhere in the body. NETs are a rare type of cancer. The most frequent primary locations are in the gastrointestinal tract and in the lungs (3).

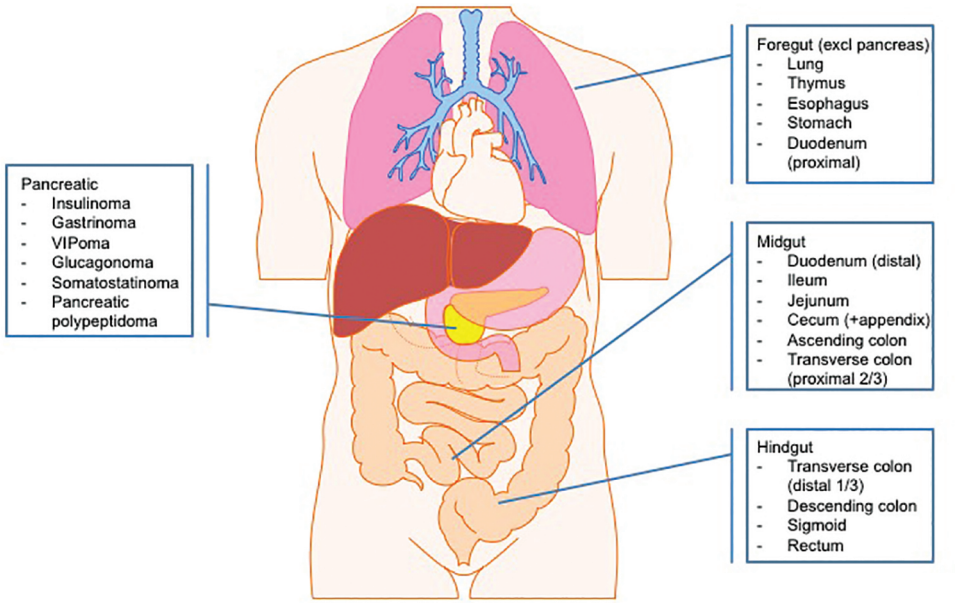

Figure 1. Classification of NETs based according to their embryonic origin

A commonly used classification is based on their embryonic origin (Figure 1). Foregut tumors are tumors from the respiratory tract, stomach, esophagus, proximal duodenum, thymus and pancreas. Midgut tumors arise from the distal duodenum, small bowel, cecum (+ appendix), ascending colon and proximal 2/3 of the transverse colon. Hindgut tumors originate from the distal 1/3 of the transverse colon, descending colon, sigmoid and rectum. Pancreatic NETs are tumors arising from the foregut and they are frequently named after the hormone they produce in excess.

Neuroendocrine tumor cells have in common that the majority express somatostatin receptors on their cell membranes. These receptors are targets for endogenous somatostatin and its synthetic analogs. Somatostatin analogs (SSA) are used for symptom control and tumor growth inhibition (4,5). Radiolabeled somatostatin analogs can be used for imaging and peptide receptor radionuclide therapy (PRRT) (6,7). The cells that produce endogenous somatostatin are located throughout the whole body, but especially in the gastrointestinal tract. In the gastrointestinal tract, somatostatin can inhibit different gastrointestinal processes (8). The somatostatin receptors are G protein-coupled receptors. Currently, there are five known subtypes of this receptor (9). The different commercially available somatostatin analogs have a different affinity for the five subtypes of the receptor. It is known that neuroendocrine tumor cells express especially the high-affinity subtype 2(a) receptors on their surface. After binding of the somatostatin analog to the receptor, the peptide-receptor complex internalizes in the cell. After internalization, the receptor recycles to the cell membrane and is again available for peptide binding (Figure 2). With this process of internalization, high concentrations of radiolabeled somatostatin analogs can enter the cell and this mechanism is used for receptor imaging and PRRT.

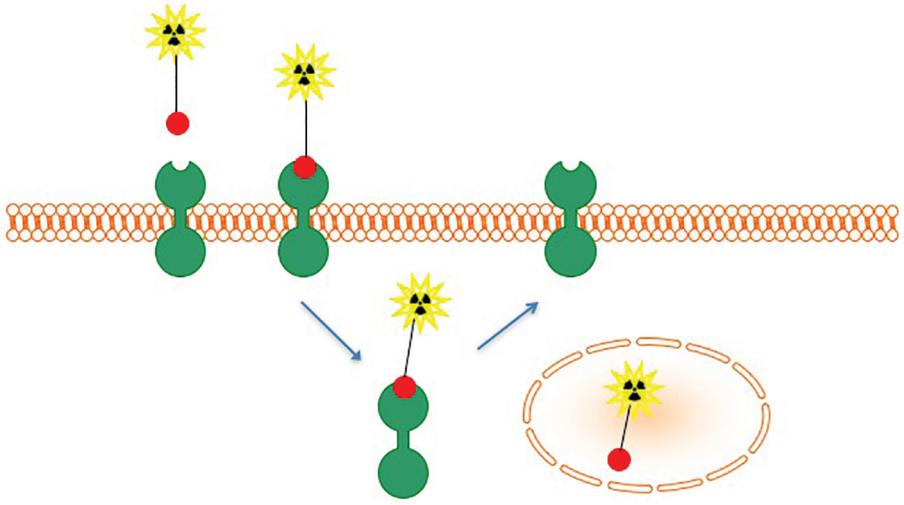

Figure 2. Internalization of radiolabeled somatostatin analogs

Epidemiology

Neuroendocrine tumors are a rare type of cancer. The incidence of NETs in The Netherlands was 4.9/100,000 in 2010. Over the past decades, the incidence has been increasing. In 1990, the incidence of NETs in the Netherlands was 2.1/100,000 (10). Tumor grading depends on the expression of the Ki67 antigen, which can be demonstrated in tumor cells using the MIB-1 antibody (see later). WHO grade 1-2 gastrointestinal tumors (Ki67 index < 20%) are most frequently localized in the appendix and small bowel, followed by the colon, rectum and pancreas. In 10-13% of NET patients, no primary tumor can be found with extensive diagnostic work-up (10,11). However, after the introduction of the new Gallium-68 labeled somatostatin analogs for PET imaging, a primary tumor localization could be found in more than half of these patients (12). Unfortunately, the majority of NET patients have metastatic disease at the time of diagnosis. At that point, curative therapy is generally not feasible anymore, since the main curative option is surgery. Metastatic disease is demonstrated at diagnosis in 24% of WHO grade 1, 35% of grade 2 and 61% of grade 3 NETs (10). The five-year survival rate is higher for localized and low-grade (grade 1-2) NETs, then for metastasized or high-grade tumors. After the recent introduction of new therapeutic options, the five-year survival rate for all patients has significantly improved, particularly for patients with metastatic disease. In 1990-2000, the five-year survival rate was 30%, this has improved to 47% between 2001 and 2010 (10).

Pathologic Classification

Currently, neuroendocrine tumors are staged and graded according to the WHO classification (2). This system is based on mitotic count and proliferative activity (Ki67) (Table 1). The WHO presented the most recent classification of NETs of the digestive system in 2010. Grade 3 tumors are currently named neuroendocrine carcinomas. Grade 3 tumors can be divided in large cell neuroendocrine carcinomas and small cell neuroendocrine carcinomas. The behavior of these grade 3 carcinomas is much more aggressive than that of low-grade tumors and survival rates are lower. Recently, a new tumor category has been introduced: grade 3 neuroendocrine tumors. These will be included in the new WHO 2017 classification.

Table 1. 2010 WHO classification of neuroendocrine tumors

	Grade 1	Grade 2	Grade 3
Ki67 index	≤2	3-20	>20
Mitotic count (MC)	<2	2-20	>20

The ENETS and the AJCC have designed a classification system for gastrointestinal NETs based on size and invasion of the primary tumor (T), lymph node involvement (N) and distant metastases (M) (Table 2). Besides, different classifications are defined according to the primary localization of the tumor (13).

Table 2. ENETS/AJCC TNM classification of neuroendocrine tumors

	ENETS/AJCC Classification criteria GI NETs		
Stage I	T1	N0	M0
Stage IIa	T2	N0	M0
Stage IIb	T3	N0	M0
Stage IIIa	T4	N0	M0
Stage IIIb	Any T	N1	M0
Stage IV	Any T	Any N	M1

Clinical Symptoms

The presence and severity of clinical symptoms depends on the primary localization of the tumor and its potency to produce hormones. In general, all different type of tumors can cause non-specific symptoms, such as pain, weight loss, fatigue and loss of appetite.

Most neuroendocrine tumors of the small bowel are asymptomatic and are found incidentally. Sometimes they can induce obstruction or intussusception of the small intestine. If a midgut tumor produces hormones the carcinoid syndrome may develop, but this usually only occurs in the presence of distant metastases (see later). Colorectal tumors are most often asymptomatic until they cause obstruction, leading to an altered stool pattern and gastrointestinal bleeding. Usually these tumors don't produce hormones (14,15). The type of symptoms caused by neuroendocrine tumors of the pancreas depends on the type of hormone they produce. Larger tumors of the pancreas may cause obstruction of bile ducts and, therefore, jaundice.

Metastatic disease in the liver can cause hepatomegaly and jaundice as well. A mesenteric mass, which is often present in patients with metastatic small bowel NETs, can cause retraction of the mesentery, leading to venous congestion, or arterial obstruction causing edema, or ischemia of the bowel. Bone metastases may cause localized pain. These metastases are especially found in the axial skeleton.

Neuroendocrine tumors can produce up to 40 different bioactive products, which can lead to symptoms (16). The liver inactivates most bioactive products if they are transported via the portal circulation. Tumors in the digestive tract that bypass the portal circulation are more likely to cause endocrine problems. Therefore, tumors of the small bowel most often produce hormonal symptoms when metastases in the liver are present and bioactive products can reach the systemic circulation. The hypersecretion of these bioactive products can result in a carcinoid syndrome. This syndrome includes different symptoms, such as flushing, diarrhea and carcinoid heart syndrome caused by fibrosis of the right sided heart valves. If a patient presents with the carcinoid syndrome, it is very likely that a metastasized NET of the small intestine (or lungs) will be diagnosed (17).

A small proportion of pancreatic (or lung) NETs are associated with familiar hereditary syndromes. These syndromes include: multiple endocrine neoplasia type 1 (MEN-1), von Hippel Lindau syndrome, neurofibromatosis type 1 and tuberous sclerosis (18).

Biochemical Markers

The most frequently used biomarkers for NETs are chromogranin A (CgA), 5-hydroxy indole acetic acid (5-HIAA), and neuron specific enolase (NSE). CgA is a protein that is located in the neurosecretory vesicles of neuroendocrine tumor cells (19,20). Its levels can be elevated in the blood of patients harboring all kinds of NETs, but also non-producing tumors. An elevated level of CgA is associated with a more extensive tumor load and, therefore, also with a worse prognosis (21,22). CgA can be a very useful marker for the follow-up of NETs during and after therapy (23). Unfortunately, CgA is a non-specific marker and it can be elevated in a variety of other conditions. False-positive results are reported with the use of proton pump inhibitors, atrophic gastritis and renal and liver failure. CgA is, therefore, not useful as a diagnostic screening tool for NETs.

5-HIAA is a metabolite of serotonin and it is a very specific marker for serotonin-producing tumors. 5-HIAA is mainly used for detection and follow-up of metastatic midgut tumors and the carcinoid syndrome. Since tumors arising from the foregut and hindgut rarely produce serotonin, this diagnostic test is not useful for patients with these kinds of tumors (24). Healthy persons excrete 5-HIAA's as well in their urine and the reference ranges differ between persons and between laboratories. This marker can be elevated in different malabsorption syndromes and with some diets. Also, the ingestion of large amounts of tryptophan- or serotonin-rich foods and the use of different kind of drugs may increase the urinary excretion of 5-HIAA. It is therefore also difficult to use the 5-HIAA excretion as a diagnostic tool. Recently, a plasma 5-HIAA assay was introduced. This single measurement of the fasting plasma 5-HIAA correlates with the 24-hour urinary 5-HIAA excretion in patients with midgut neuroendocrine tumors (25).

NSE is present in the cytoplasm of neuroendocrine cells. It is mainly elevated in patients with high-grade, or poorly differentiated tumors (26). Due to a poor sensitivity of approximately 38% in neuroendocrine tumors, this marker is not frequently used in the daily practice in the follow up of patients with low-grade tumors (27).

Bronchial Carcinoids

Bronchial carcinoids are NETs of the foregut and include a spectrum of histologically different tumors. These tumors are also classified based on the mitotic count (MC). Typical carcinoids have <2 MC per 2 mm^2 and show no signs of necrosis. Atypical carcinoids have 2-10 MC per 2 mm^2, or foci of necrosis. Poorly differentiated tumors (MC >10 per 2 mm^2 and extensive necrosis) are divided into large cell neuroendocrine carcinomas and small cell neuroendocrine tumors (28). The majority of patients with poorly differentiated lung tumors have metastatic disease at time of presentation and have a very poor prognosis (10). The incidence of bronchial carcinoids is 0,2-2 per 100,000 population/year (29). Approximately 25% of all low-grade NETs are localized in the respiratory tract (3). These tumors can develop in patients who have never or only incidentally smoked, whereas poorly differentiated tumors are strongly associated with smoking (29). Patients may present with non-specific symptoms, such as coughing, pneumonia or hemoptysis. Bronchial carcinoids can be hormonal active and, therefore, patients can present with a so-called atypical carcinoid syndrome or Cushing's syndrome. This atypical carcinoid syndrome, which includes diarrhea and flushing, occurs in approximately 8% of patients. Cushing's syndrome, due to the ectopic production of ACTH, occurs in about 6% (30). Up to 40% of patients with an ectopic Cushing's syndrome appears to have a bronchial carcinoid. There is an association between bronchial and thymic carcinoids and the MEN-1 syndrome. However, the MEN-1 syndrome is diagnosed in less than 5% of patients presenting with a bronchial carcinoid.

Radiological Imaging

The majority of patients with NETs have metastatic disease at the time of presentation. For the detection of the primary tumor, mainly CT and MRI are used. NETs can be very small and multifocal, so detection of the primary tumor can be a challenge. Most tumors are highly vascularized and therefore best visible on the arterial phase of the CT/MRI. If CT and/or MRI don't reveal the primary tumor, nuclear medicine imaging techniques are indicated. Also for optimal (whole body) staging and detection of recurrent disease, nuclear medicine imaging plays a pivotal role (31).

A very distinguished feature of small intestinal NETs is a mesenterial mass, which may cause a desmoplastic reaction, resulting in a spoke wheel phenomenon due to traction on the mesentery.

Since the majority of patients have metastases in the liver, the detection of metastases is focused on the liver. The vascularity of metastases may vary, therefore it is necessary to make a CT in both the arterial and portovenous contrast phase. The majority of liver metastases are highly vascularized, however the vascularity can differ, even within the same patient. Besides, in a quarter of patients there is some necrosis visible within the metastases. MRI can be used for detection and further characterization of liver metastases, since the sensitivity of MRI is better than that of CT (32).

Detection of primary tumors in the pancreas can be challenging. These tumors can be multifocal and may have some calcifications. The most sensitive method for detection of pancreatic NETs is endoscopic ultrasound (EUS). However, a disadvantage of ultrasound is the interobserver variability. Therefore, MRI is used for detection of pancreatic NETs as well, with comparable sensitivity as with EUS.

Nuclear Medicine Imaging

Imaging with nuclear medicine techniques will be extensively described in chapter 2 of this thesis.

Medical Therapy

Somatostatin Analogs

Somatostatin analogs (SSAs) are used for symptom control and inhibition of tumor growth of NETs (4,5). The literature on the treatment of the different subtypes of NETs is emerging and these SSAs are now used for all kinds of somatostatin receptor-positive tumors. Synthetic SSAs can inhibit the secretion of bioactive products and, therefore, therapy with these pharmaceuticals can completely, or partially inhibit the symptoms of the carcinoid syndrome. The most important studies that have demonstrated that SSAs can prolong time to progression (TTP) and progression free survival (PFS) are the PROMID and CLARINET trials. The PROMID study investigated the effect of octreotide LAR in patients with metastatic midgut NETs. TTP was 14.3 months with octreotide LAR 30 mg / month versus 6 months for placebo (4). The other large randomized study was the CLARINET study. Comparison between 120 mg lanreotide autogel / month and placebo in patients with advanced GEP and pulmonary NETs was made. At the end of this study, the PFS for the

lanreotide autogel group was not reached and it was 18 months for the placebo group (5). These different PFS data in the control groups of both studies also demonstrate the differences between study groups used for clinical trials and, therefore, the need for controlled studies. The recent results of the NETTER-1 trial, comparing high dose octreotide LAR therapy (60 mg / month) to 4 cycles of ^{177}Lu-DOTATATE in combination with octreotide LAR 30 mg / month, have demonstrated the superiority of PRRT with ^{177}Lu-DOTATATE as compared to high dose octreotide therapy (33).

Molecular Targeted Therapy

Everolimus and Sunitinib are approved by the US Food & Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of patients with advanced low-grade pancreatic NETs. Everolimus is also approved for the treatment of other GEP-NETs and bronchial NETs. Everolimus is an inhibitor of the mammalian target of rapamycin (mTOR) and sunitinib is a receptor tyrosine kinase (RTK) inhibitor. The RADIANT-3 and 4 studies have compared everolimus to placebo in a group of patients with NETs of the pancreas and the lungs, or gastrointestinal tract, respectively. The PFS in the groups receiving 10 mg everolimus daily was 11 months. This was better as compared to the placebo group with a PFS of 4.6 months for pancreatic NETs and 3.9 months for lung and gastrointestinal NETs (34,35). The other targeted pharmaceutical is sunitinib. The SUN-1 study, studying patients with advanced, progressive pancreatic NETs treated with 37.5 mg sunitinib daily, demonstrated a PFS of 11.4 months as compared to a PFS of 5.5 months in the placebo group (36).

Chemotherapy / Interferon-Alpha

In oncology, chemotherapy is the cornerstone in the treatment of patients with metastatic cancer. However, for low grade NETs the role of chemotherapy is limited. The most frequently used chemotherapy regimen for metastatic inoperable pancreatic NETs is the combination of Streptozotocin (STZ) and 5-Fluorouracil (5-FU). This combination demonstrated an objective response of approximately 16% with a PFS of 5 months (37). Also the combination Temozolomide/Capecitabine, or Temozolomide monotherapy can be used as a fist line treatment for pancreatic low grade NETs. A recent meta-analysis did not demonstrate any difference in PFS, or OS when comparing STZ/5-FU to Interferon-Alpha (IFN-alpha), or other chemotherapeutic regimes (38). IFN-alpha treatment was associated with higher hematological toxicity and less renal toxicity. Currently, no large randomized studies are available comparing different chemotherapeuticals and SSAs, or targeted therapies. IFN-alpha can be used as a second line therapy for patients who can't tolerate SSAs, or who are refractory to SSAs. Besides, it can be used for the treatment of somatostatin receptor-negative tumors. Interferon receptors can be expressed on NETs and are, there-

fore, a potential target for therapy with IFN-alpha. Due to more and severe side-effects this therapy is not frequently used in daily practice (39).

For high grade NEC, chemotherapy with the combination of Cisplatin and Etoposide is the therapy of first choice. For low-grade tumors this regimen is not indicated, due to a limited effect and severe side-effects.

PRRT

Peptide receptor radionuclide therapy will be extensively described in chapter 4 of this thesis.

Other (Liver-Directed) Therapeutic Options

External beam radiotherapy (EBRT) of liver metastases or other liver-directed therapies, such as radiofrequency ablation (RFA), are not frequently used for therapy of liver metastases. In most patients these metastases are multiple and distributed throughout the whole liver and, therefore, these specific localized therapies are not very useful. EBRT can be helpful as pain relief in patients with bone metastases, or to lower the risk of pathological fractures. It is also used for treatment of brain metastases.

New therapies with microspheres made of glass or resin filled with Yttrium-90 administered directly in a hepatic artery are a good treatment option for patients with dominant disease in the liver. A recent meta-analysis reported an objective response rate of 50% (95% CI 38-62%) in patients with liver-dominant metastatic neuroendocrine tumors (40). Unfortunately, this is not a therapeutic option for patients with extra-hepatic disease.

Aims and Outlines of this Thesis

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

1. Evaluate the efficacy and toxicity of ^{177}Lu-DOTATATE in patients with inoperable and/or metastatic GEP and bronchial NETs
2. Identify several pitfalls in imaging and therapy of patients with NETs
3. Evaluate the best way to detect progression after PRRT with ^{177}Lu-DOTATATE

Chapter 2 gives an overview on the nuclear medicine imaging techniques, which are currently used for the imaging of neuroendocrine tumors. In chapter 3, the incidence and mechanism of physiological uptake in the pancreatic head on scintigraphy with ^{111}In-DTPA-octreotide are described. Chapter 4 gives an overview on the current literature on PRRT in patients. Chapter 5 describes a large prospective study, which evaluates the effect of ^{177}Lu-DOTATATE in patients with inoperable and/or metastatic GEP and bronchial NETs In the same chapter different factors that can predict the overall survival are discussed. In chapter 6, several pitfalls which can occur during and direct after therapy with ^{177}Lu-DOTATATE are identified. Pitfalls in biochemical markers and imaging are discussed. Chapter 7 describes different ways to detect progression after PRRT with ^{177}Lu-DOTATATE and evaluates the best way to detect progressive disease.

References

1. Oberndorfer S. Karzinoide Tumoren des Dünndarmes. Fr Z Pathol. 1907;(1):426–9.
2. Bosman, F T, World Health Organization, International Agency for Research on Cancer. WHO classification of tumours of the digestive system. 4th ed. Lyon : IARC Press, 2010; (World Health Organization classification of tumours ; 3).
3. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003 Feb 15;97(4):934–59.
4. Rinke A, Muller H-H, Schade-Brittinger C, Klose K-J, Barth P, Wied M, et al. Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group. J Clin Oncol. 2009 Aug 24;27(28):4656–63.
5. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Anti-tumour effects of lanreotide for pancreatic and i ntestinal neuroendocrine tumours: the CLARINET open-label extension study. Endocr Relat Cancer. 2016 Mar;23(3):191–9.
6. Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WA, Kooij PP, Oei HY, et al. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. Eur J Nucl Med. 1993 Aug;20(8):716–31.
7. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment With the Radiolabeled Somatostatin Analog [177Lu-DOTA0,Tyr3]Octreotate: Toxicity, Efficacy, and Survival. J Clin Oncol. 2008 Apr 29;26(13):2124–30.
8. Lamberts SW, van der Lely AJ, de Herder WW, Hofland LJ. Octreotide. N Engl J Med. 1996 Jan 25;334(4):246–54.
9. Reubi JC, Schär J-C, Waser B, Wenger S, Heppeler A, Schmitt JS, et al. Affinity profiles for human somatostatin receptor subtypes SST1–SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med. 2000;27(3):273–82.
10. Korse CM, Taal BG, van Velthuysen M-LF, Visser O. Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: Experience of two decades of cancer registry. Eur J Cancer. 2013 May;49(8):1975–83.
11. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One Hundred Years After "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States. J Clin Oncol. 2008 Jun 20;26(18):3063–72.
12. Alonso O, Rodríguez-Taroco M, Savio E, Bentancourt C, Gambini JP, Engler H. (68)Ga-DOTATATE PET/CT in the evaluation of patients with neuroendocrine metastatic carcinoma of unknown origin. Ann Nucl Med. 2014 Aug;28(7):638–45.
13. Klöppel G, Rindi G, Perren A, Komminoth P, Klimstra DS. The ENETS and AJCC/UICC TNM classifications of the neuroendocrine tumors of the gastrointestinal tract and the pancreas: a statement. Virchows Arch Int J Pathol. 2010 Jun;456(6):595–7.
14. Mignon M. Natural history of neuroendocrine enteropancreatic tumors. Digestion. 2000;62 Suppl 1:51–8.
15. Kulke MH. Clinical Presentation and Management of Carcinoid Tumors. Hematol Oncol Clin North Am. 2007 Jun;21(3):433–55.

16. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current Status of Gastrointestinal Carcinoids. Gastroenterology. 2005 May;128(6):1717–51.
17. Feldman JM. Carcinoid tumors and syndrome. Semin Oncol. 1987 Sep;14(3):237–46.
18. Öberg K. The Genetics of Neuroendocrine Tumors. Semin Oncol. 2013 Feb;40(1):37–44.
19. O'Connor DT, Deftos LJ. Secretion of chromogranin A by peptide-producing endocrine neoplasms. N Engl J Med. 1986 May 1;314(18):1145–51.
20. Deftos LJ. Chromogranin A: its role in endocrine function and as an endocrine and neuroendocrine tumor marker. Endocr Rev. 1991 May;12(2):181–7.
21. Campana D, Nori F, Piscitelli L, Morselli-Labate AM, Pezzilli R, Corinaldesi R, et al. Chromogranin A: is it a useful marker of neuroendocrine tumors? J Clin Oncol Off J Am Soc Clin Oncol. 2007 May 20;25(15):1967–73.
22. Modlin IM, Gustafsson BI, Moss SF, Pavel M, Tsolakis AV, Kidd M. Chromogranin A—Biological Function and Clinical Utility in Neuro Endocrine Tumor Disease. Ann Surg Oncol. 2010 Sep;17(9):2427–43.
23. Nehar D, Lombard-Bohas C, Olivieri S, Claustrat B, Chayvialle J-A, Penes M-C, et al. Interest of Chromogranin A for diagnosis and follow-up of endocrine tumours. Clin Endocrinol (Oxf). 2004 May;60(5):644–52.
24. Kanakis G, Kaltsas G. Biochemical markers for gastroenteropancreatic neuroendocrine tumours (GEP-NETs). Best Pract Res Clin Gastroenterol. 2012 Dec;26(6):791–802.
25. Tellez MR, Mamikunian G, O'Dorisio TM, Vinik AI, Woltering EA. A Single Fasting Plasma 5-HIAA Value Correlates With 24-Hour Urinary 5-HIAA Values and Other Biomarkers in Midgut Neuroendocrine Tumors (NETs): Pancreas. 2013 Apr;42(3):405–10.
26. Isgrò MA, Bottoni P, Scatena R. Neuron-Specific Enolase as a Biomarker: Biochemical and Clinical Aspects. Adv Exp Med Biol. 2015;867:125–43.
27. Baudin E, Gigliotti A, Ducreux M, Ropers J, Comoy E, Sabourin J, et al. Neuron-specific enolase and chromogranin A as markers of neuroendocrine tumours. Br J Cancer. 1998 Oct;78(8):1102–7.
28. Travis W, Colby T, Corrin B, Shimosato Y, Brambilla E. World Health Organization International Histological Classification of Tumours. Histological Typing of Lung and Pleural Tumours. 1999.
29. Caplin ME, Baudin E, Ferolla P, Filosso P, Garcia-Yuste M, Lim E, et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. Ann Oncol. 2015 Aug;26(8):1604–20.
30. Soga J, Yakuwa Y. Bronchopulmonary carcinoids: An analysis of 1,875 reported cases with special reference to a comparison between typical carcinoids and atypical varieties. Ann Thorac Cardiovasc Surg Off J Assoc Thorac Cardiovasc Surg Asia. 1999 Aug;5(4):211–9.
31. Sundin A. Radiological and nuclear medicine imaging of gastroenteropancreatic neuroendocrine tumours. Best Pract Res Clin Gastroenterol. 2012 Dec;26(6):803–18.
32. Sundin A, Wills M, Rockall A. Radiological Imaging: Computed Tomography, Magnetic Resonance Imaging and Ultrasonography. Front Horm Res. 2015;44:58–72.

33. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of ^{177} Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017 Jan 12;376(2):125–35.
34. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):514–23.
35. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. The Lancet. 2015;(387):968–77.
36. Raymond E, Dahan L, Raoul J-L, Bang Y-J, Borbath I, Lombard-Bohas C, et al. Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors. N Engl J Med. 2011 Feb 10;364(6):501–13.
37. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG, Eastern Cooperative Oncology Group. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. J Clin Oncol Off J Am Soc Clin Oncol. 2005 Aug 1;23(22):4897–904.
38. Wong MH, Chan DL, Lee A, Li BT, Lumba S, Clarke SJ, et al. Systematic Review and Meta-Analysis on the Role of Chemotherapy in Advanced and Metastatic Neuroendocrine Tumor (NET). Stemmer SM, editor. PLOS ONE. 2016 Jun 30;11(6):e0158140.
39. Pavel M, Kidd M, Modlin I. Systemic Therapeutic Options for Carcinoid. Semin Oncol. 2013 Feb;40(1):84–99.
40. Devcic Z, Rosenberg J, Braat AJA, Techasith T, Banerjee A, Sze DY, et al. The Efficacy of Hepatic 90Y Resin Radioembolization for Metastatic Neuroendocrine Tumors: A Meta-Analysis. J Nucl Med. 2014 Sep 1;55(9):1404–10.


1

PART I

IMAGING

CHAPTER 2

Nuclear Medicine Imaging of Neuroendocrine Tumors

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Abstract

An important role is reserved for nuclear imaging techniques in the imaging of neuroendocrine tumors (NETs). Somatostatin receptor scintigraphy (SRS) with ^{111}In-DTPA-octreotide is currently the most important tracer in the diagnosis, staging and selection for peptide receptor radionuclide therapy (PRRT). In the past decade, different positron-emitting tomography (PET) tracers have been developed.

The largest group is the ^{68}Gallium-labeled somatostatin analogs (^{68}Ga-SSA). Several studies have demonstrated their superiority compared to SRS in sensitivity and specificity. Furthermore, patient comfort and effective dose are favorable for ^{68}Ga-SSA. Other PET targets like β-[^{11}C]-5-hydroxy- L -tryptophan (^{11}C-5-HTP) and 6-^{18}F-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) were developed recently. For insulinomas, glucagon-like peptide-1 receptor imaging is a promising new technique. The evaluation of response after PRRT and other therapies is a challenge. Currently, the official follow-up is performed with radiological imaging techniques. The role of nuclear medicine may increase with the newest tracers for PET. In this review, the different nuclear imaging techniques and tracers for the imaging of NETs will be discussed.

Introduction

Nuclear imaging techniques play a pivotal role in the diagnosis and staging of neuroendocrine tumors (NETs). Furthermore, selection of patients for peptide receptor radionuclide therapy (PRRT) can only be done by scintigraphy with radiolabeled somatostatin analogs. Besides the above-mentioned indications, nuclear imaging can play an important role in follow-up after therapy and in the evaluation of therapy response.

In general, two different imaging modalities in nuclear medicine are used to image NETs. With the gamma camera, both planar (two-dimensional) and single-photon emission computed tomography (SPECT; three-dimensional) images can be made. A relative new image modality, the positron emission tomography (PET) camera can be used after the injection of a positron-emitting radionuclide-based tracer. The emitted positrons annihilate with a surrounding electron in the tumor or normal tissue, two gamma rays with an energy of 511 KeV in opposite directions. In this way, imaging with a PET camera ensures a better sensitivity and higher spatial resolution compared to the gamma camera. Currently, most PET cameras are combined with computed tomography (CT), allowing hybrid imaging in a single imaging procedure.

The CT is used for attenuation correction, which improves the image quality. Furthermore, the CT can be used for anatomical correlation. This will improve the accuracy and makes it possible to distinguish between physiological and pathological activity, resulting in less false-positive findings (1, 2). This review will focus on the different imaging modalities which nuclear medicine has to offer for the diagnosis and staging of NETs. Furthermore, selection for PRRT and the imaging options for the evaluation of therapy response will be discussed.

Imaging of Neuroendocrine Tumors

NETs are a heterogeneous group of tumors that can differ in location, function and growth. Variations in these characteristics make the presentation of a NET diverse and, therefore, the optimal diagnostic path for patients may be different. In order to perform the right type of diagnostic imaging, knowledge of the most recent World Health Organization (WHO) classification of gastroenteropancreatic NETs, as published in 2010 (3), is essential. This classification defines three tumor categories or grades, irrespective of their site of origin, based on the mitotic count (MC) and the number of cells positively staining with the proliferation marker Ki-67: low-grade (grade 1; G1) NETs with <2 mitoses/10 HPF (high-power field) and Ki-67 <3%; intermediate (grade 2; G2) NETs with 2–20 mitoses/10 HPF or Ki-67 3–20%, and highgrade (grade 3; G3) neuroendocrine carcinomas with >20 mitoses/10 HPF or Ki-67 >20%. This grading is important since there is an inverse association be-

tween grade and prognosis (4). Besides the prognosis, the classification plays a role in the choice of imaging and/or subsequent therapy.

Somatostatin Receptor-Based Imaging

One of the characteristics of NETs is that they may express somatostatin receptors (SSTRs) on the cell surface. This receptor can be used to image tumors by using radiolabeled somatostatin analogs. In vivo visualization of somatostatin-positive tumors with radioiodine-labeled somatostatin analogs was first described in 1989 (5). In the following years, somatostatin analogs labeled with different radionuclides were developed. These compounds have different affinities for the five subtypes of the SSTR (table 1) (6).

Table 1. Affinity profiles (IC50) for human sst1-sst5 receptors of a series of somatostatin analogs

	hsst1	**hsst2**	**hsst3**	**hsst4**	**hsst5**
SS-28	5.2±0.3	2.7±0.3	7.7±0.9	5.6±0.4	4.0±0.3
Octreotide	>10,000	2.0±0.7	187±55	>1,000	22±6
DTPA-octreotide	>10,000	12±2	376±84	>1,000	299±50
In-DTPA-octreotide	>10,000	22±3.6	182±13	>1,000	237±52
DOTA-TOC	>10,000	14±2.6	880±324	>1,000	393±84
Ga-DOTA-TOC	>10,000	2.5±0.5	613±140	>1,000	73±21
In-DTPA-octreotate	>10,000	1.3 ±0.2	>10,000	433 ±16	>1,000
Ga-DOTATATE	>10,000	0.2±0.04	>1,000	300±140	377±18

All values are IC50±SEM in nM.
Modified from Reubi et al. (5)

Most radiolabeled somatostatin analogs, which are currently available for imaging, have good affinity for the subtype 2 receptor, which is most frequently expressed by NETs. In SSTR-positive NETs, unlabeled somatostatin analogs (e.g. octreotide or lanreotide) can be used for therapy. In case patients have NETs that produce hormones, which lead to specific symptoms or syndromes (e.g. carcinoid syndrome), treatment with somatostatin analogs results in a reduction of hormonal overproduction and, therefore, relief of these symptoms. Furthermore, it can lengthen the time to tumor progression compared to placebo in patients with midgut NETs (7). Currently, many patients with NETs are treated with somatostatin analogs. This cold octreotide can compete for binding to the SSTR with the radiolabeled somatostatin analogs. This may influence the sensitivity of the imaging and effect of PRRT. To obtain the best quality of imaging, it is therefore advised to discontinue somatostatin analogs before SSTR-based imaging and PRRT. With the proper patient prepara-

tion and imaging acquisition SSTR imaging is very helpful in the optimal staging of the patient.

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

Currently, the only registered radiopharmaceutical for SSTR scintigraphy (SRS) is [^{111}In-DTPA^{0}]octreotide (OctreoScan; Covidien, Petten, The Netherlands). The SNM guideline (8) recommends an administered activity of 222 MBq and 10 μg of pentetreotide. Furthermore, SPECT(-CT) of at least the upper abdomen is mandatory for optimal imaging and staging. Due to a relative long half-life of 2.8 days, it is possible to image at 24 h and an optional 48 h after injection. Normal tissues, such as thyroid, spleen and the pituitary gland, express SSTR. Furthermore, the liver and kidneys excrete the tracer, so accumulation of radioactivity is seen in these organs as well (9). More specifically, approximately 2% of the administered dose leaves the body by hepatobiliary excretion. Therefore, laxatives should be considered when visualizing tumors in the abdomen. In the last decade, many studies have evaluated the sensitivity and specificity of ^{111}In-DTPA-octreotide for the detection of NETs, and the results vary considerably due to variations in the size and location of the tumor and different acquisition protocols. A large review of 1,200 patients with gastrointestinal NETs showed a median detection rate of 89% (range 67–100%) and sensitivity of 84% (range 57–93%) (10). Besides the presence of unlabeled somatostatin or therapeutic use of somatostatin analogs blocking the SSTR, SRS can have a negative result due to high glucocorticoid levels, which has a downregulatory effect on tumoral SSTR expression. De Bruin et al. (11) described 2 patients with a negative SRS caused by hypercortisolism due to ectopic ACTH secretion. After treatment with the glucocorticoid receptor antagonist mifepristone, the SRS pointed towards the diagnosis of an ACTH-producing bronchial carcinoid in both patients.

Furthermore, imaging of NETs with ^{111}In-DTPA-octreotide is used to select patients for PRRT. PRRT is performed with somatostatin analogs labeled with a β-emitting radionuclide such as Yttrium-90 or Lutetium-177 (e.g. [^{90}Y-DOTA^{0},Tyr^{3}]octreotide and [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate). The level of accumulation in the tumor on the pretherapeutic SRS is an important prognostic factor for the prediction of tumor regression. The uptake is expressed using a semiquantitative score, comparing the accumulation in the tumor to physiological accumulation in the liver and kidneys/spleen. In general, a high accumulation in the tumor will result in a good response to therapy (12).

^{99m}Tc-Labeled Somatostatin Analogs

As an alternative to ^{111}In-DTPA-octreotide, somatostatin analogs can be labeled with ^{99m}Technetium (^{99m}Tc). Currently, the most commonly used ^{99m}Tc-labeled somatostatin analogs are ^{99m}Tc-depreotide and ^{99m}Tc-EDDA/HYNIC-Tyr^3-octreotide (^{99m}Tc-EDDA/HYNIC-TOC). The latter is available under the commercial name ^{99m}Tc-Tektrotyd and most frequently used in (Eastern) Europe. The main advantage of ^{99m}Tc-labeled somatostatin analogs is the wide availability of ^{99m}Tc, which can be produced by the majority of nuclear medicine departments with the use of a ^{99m}Tc generator. This makes the production of this radionuclide relatively inexpensive. Another advantage is that the radiation burden is lower (13). However, a disadvantage of ^{99m}Tc is the short half-life of 6 h. Because of this short half-life, it is not possible to image at 24 h after injection. On the other hand, imaging can be performed on the day of the administration of the tracer and therefore disturbing bowel uptake is less of an issue. Still, it is recommended that an imaging protocol with ^{99m}Tc-EDDA/HYNIC-TOC should include acquisitions 2 and 4 h after injection, complemented with SPECT(-CT) of the upper abdomen. Using this protocol, a sensitivity of 80% and specificity of 94% could be achieved in 88 patients with NETs of the gastroenteropancreatic tract (14). In a direct comparison between ^{111}In-DTPA-octreotide and ^{99m}Tc-EDDA/HYNIC-TOC SRS, both modalities performed similarly, with a slightly higher sensitivity for ^{99m}Tc-EDDA/HYNIC-TOC. However, the latter showed more false-positive results due to nonspecific abdominal tracer accumulation (15). In summary, although ^{99m}Tc-EDDA/HYNIC-TOC is not widely used and only few studies have been performed with this tracer, somatostatin scintigraphy with ^{99m}Tc-EDDA/HYNIC-TOC seems a reasonable alternative for ^{111}In-DTPA-octreotide.

Somatostatin Receptor PET/CT

Imaging with a positron-emitting radionuclide-labeled compound allows imaging with a PET camera, which results in a better image quality compared to imaging with a gamma camera including SPECT. To image NETs with PET, most somatostatin analogs are labeled with the positron emitter Gallium-68 (^{68}Ga). The most commonly used somatostatin analogs labeled with ^{68}Ga are [^{68}Ga-DOTA^0,Tyr^3]octreotide (^{68}Ga-DOTATOC), [^{68}Ga-DOTA, 1-nal^3]octreotide (^{68}Ga-DOTANOC) and [^{68}Ga-DOTA^0,Tyr^3]octreotate (^{68}Ga-DOTATATE). These ^{68}Ga-labeled somatostatin analogs (^{68}Ga-SSA) all have a different affinity profile for the different subtypes of the SSTR, but have in common that each analog can bind to SSTR2. ^{68}Ga-DOTATATE has the highest affinity for SSTR2. Despite the differences in the affinity profile, the different ^{68}Ga-SSAs perform similarly with regard to sensitivity and specificity (16). Recently, the European Association of Nuclear Medicine (EANM) published the first guideline for imaging with ^{68}Ga-labeled somatostatin analogs. In order to obtain the best imaging quality, an administered activity of at least 100 MBq

and less than 50 µg of ^{68}Ga-DOTA-conjugated peptide is recommended. Image acquisition shouldbe done at 60 min after injection (17). A recent meta-analysis in which studies were included using various somatostatin analogs labeled mainly with ^{68}Ga with a total of 2,105 patients with NETs in the thorax and abdomen showed a pooled sensitivity of 93% and specificity of 91% (16). It is to be expected that the ^{68}Ga-labeled somatostatin analogs will become more widely available in the near future.

Comparison between ^{68}Ga-SSA and non-PET SRS

Several studies have compared ^{68}Ga-SSA to SRS, including ^{111}In-DTPA-octreotide, ^{111}In-DOTATOC and ^{99m}Tc-EDDA/HYNIC-TOC [18–20]. Overall, ^{68}Ga-SSA have many advantages over non-PET SRS. Firstly, as mentioned before, ^{68}Ga is a positron emitting radionuclide, which ensures a higher spatial resolution with PET imaging. Therefore, it is not surprising that, in a direct comparison, ^{68}Ga-SSA imaging shows a significantly higher detection rate compared to non-PET SRS [18]. Especially for the detection of metastatic lesions in the bones and lungs, ^{68}Ga-SSA is superior to ^{111}In-DTPA-octreotide (19). Due to the higher detection rate, the clinical management can change. Secondly, imaging with a ^{68}Ga-SSA is performed 60 min after injection in contrast to imaging with ^{111}In-DTPA-octreotide after 24 h. Due to the short time between injection and image acquisition it is not necessary to use laxatives when performing PET with ^{68}Ga-SSA, which is an advantage as patients often experience the use of these laxatives as burdensome. Other advantages are that ^{68}Ga-SSA is performed in 1 day, and the radiation burden for a whole-body scan is lower compared to ^{111}In-DTPA-octreotide (21). For these reasons, the ^{68}Ga-SSA is better tolerated by the patients than ^{111}In-DTPA-octreotide (20). Furthermore, one cost-effectiveness study comparing ^{68}Ga-DOTATOC and ^{111}In-DTPA-octreotide demonstrated that ^{68}Ga-DOTATOC was less expensive with respect to materials and personnel costs (22). Due to the higher sensitivity and specificity fewer additional examinations were needed. A disadvantage of ^{68}Ga-SSA is the increase in false-positive results especially due to findings of high uptake in the pancreatic head (18, 23), which can be explained by the higher density of SSTRs in this area of the pancreas (24). These false positive findings did not occur with ^{111}In-DTPA-octreotide, probably because of the lower sensitivity and resolution of the gamma camera. Another disadvantage remains the limited availability of ^{68}Ga-SSA. Currently, the most frequently used radiopharmaceutical for imaging of NETs is ^{111}In-DTPA-octreotide. This tracer is available in almost every nuclear medicine department and there is considerable shared experience with the interpretation of the images. Moreover, most literature is based on SRS with ^{111}In-DTPA-octreotide. Currently, the uptake on SRS can be used to assess whether a patient is eligible for PRRT. If the tumor shows less uptake than the physiological liver uptake on the SRS (grade 1 uptake), PRRT is not a suitable therapy. Such a scale is not available for ^{68}Ga-SSA and further studies are needed to translate the semiquantitative ‘Krenning’ score on SRS to quantitative uptake on a PET scan with ^{68}Ga-SSA.

In summary, PET imaging with ^{68}Ga-SSA performs better with regard to sensitivity and detection rate than ^{111}In-DTPA-octreotide. The discomfort for patients is lower, due to a 1-day protocol and there being no need to use laxatives. However, SRS has the advantage of better availability and larger clinical experience. It is expected that ^{68}Ga-SSA PET imaging will replace SRS in the daily practice of imaging NETs.

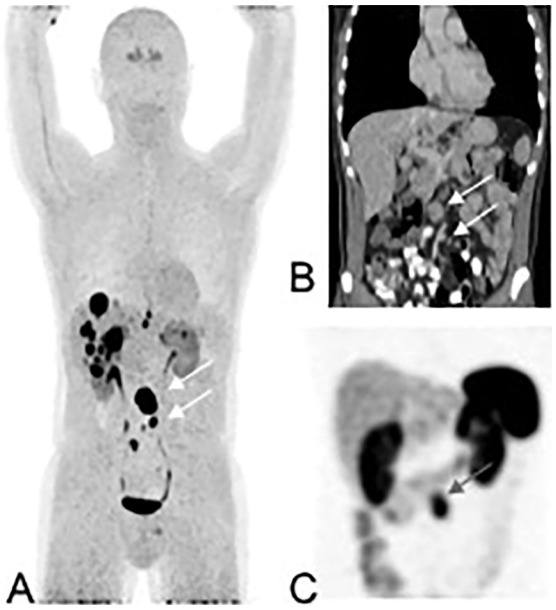

Figure 1. Patient with liver and mesenteric lymph node metastases from a small bowel neuroendocrine tumor grade 1. A. Maximum intensity projection of whole body ^{18}F-DOPA PET showing multiple liver lesions and metastases in the mesenterium. Physiologic uptake is seen in the striata. Physiological excretion is via the kidneys and ureters to the bladder. B. Abdominal CT showing large and smaller (white arrows) malignant mesenteric lymph nodes. C. On the ^{111}In-DTPA-octreotide SPECT scan 24 h after injection only the large mesenteric lymph node could be visualized (grey arrow).

Other Imaging Modalities

^{123}I-Metaiodobenzylguanidine

Metaiodobenzylguanidine (MIBG) labeled with radioactive iodine (^{123}I) can be used to image NETs with planar and/or with SPECT(-CT) imaging. MIBG is structurally similar to norepinephrine and therefore utilizes the vesicular monoamine transporters and is incorporated into vesicles or neurosecretory granules in the cytoplasm of neuroendocrine cells (25). For imaging of pheochromocytoma and paraganglioma, ^{123}I-MIBG scintigraphy has been the investigation of first choice with a high sensitivity and specificity of 87 and 99%, respectively (26). However, new PET tracers (e.g. ^{18}F-DOPA), which will be discussed in the next paragraphs, may perform better in sensitivity and specificity, but their availability is limited. For the detection of NETs, the sensitivity of MIBG scintigraphy is lower than SRS with ^{111}In-DTPA-octreotide. In a large review, the median detection rate was 50% and the sensitivity 76% (27). Therefore, MIBG has a limited role in the diagnosis of NETs. However, ^{123}I-MIBG scintigraphy can be used when other imaging modalities fail to detect the tumor and for the selection of therapy with ^{131}I-MIBG.

^{18}F-Fluorodeoxyglucose

^{18}F-fluorodeoxyglucose (^{18} F-FDG) is the most frequently used PET tracer in oncology. FDG is a glucose analog that accumulates in tumor cells with a high expression of glucose transporters. The FDG undergoes phosphorylation by hexokinase and is trapped intracellularly. However, in contrast to the wide use of ^{18} F-FDG in numerous types of tumors, it has a limited role in the imaging of NETs. Poorly differentiated tumors (G3) with a high proliferative activity have an increased glucose metabolism (28). The majority of the more differentiated tumors (G1/G2) have a normal or slightly increased glucose metabolism. For these tumors, imaging with ^{18}F-FDG should not be the first choice of imaging technique for staging. However, some G2 tumors do have an increased glucose metabolism. For these tumors, the uptake on ^{18} F-FDG PET can predict the prognosis. Overall, a high FDG uptake predicts a poorer prognosis (29, 30). Only a few studies have compared ^{18}F-FDG to ^{68}Ga-SSA (31, 32). Kayani et al. (31) found a significant correlation between uptake of ^{68}Ga-DOTATATE and ^{18}F-FDG and tumor grade on histology. Low-grade tumors had a higher accumulation of ^{68}Ga-DOTATATE than ^{18}F-FDG. The reverse was true in high-grade tumors. The overall sensitivity in this study for ^{68}Ga-DOTATATE was 82%, and for ^{18}F-FDG was 66%. The highest sensitivity of 92% was achieved when combining these two different PET tracers (31). SSTR imaging and glucose metabolism imaging seem to have a complementary role (32). Although ^{18}F-FDG-PET seems to have no additional value for the staging of patients with low-grade tumors (G1/G2), positive findings on an ^{18}F-FDG PET might define specific NET subgroups. However, it is currently not common practice to perform both imaging modalities for staging or to use this functional or metabolic information as a guidance before starting the therapy. Additional clinical studies have to be performed to gain more insight.

$^{1\,8}$F-L-3,4-Dihydroxyphenylalanine

The radiopharmaceutical 6-^{18}F-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) is one of the PET tracers for imaging NETs which makes use of the capability of neuroendocrine (tumor) cells to synthesize various hormones via amine precursor uptake and decarboxylation. In the catecholamine pathway, active in many NETs, phenylalanine and intermediate products such as L -DOPA are taken up via system L large amino acid transporters. Once inside the cell, decarboxylation to dopamine takes place via the enzyme AADC (aromatic amino acid decarboxylase). Dopamine is then transported into intracellular storage vesicles through the vesicular monoamine transporter. From these vesicles, the resulting end products can be released in the extracellular environment. Nowadays, more and more PET centers are capable of producing ^{18}F-DOPA, and it is commercially available in several European countries. Usually, images are made 60–90 min after injection, although earlier images are advocated for some indications (33, 34). Physiological variants and pitfalls have been described (34, 35). Practices differ regarding premedicating patients with carbidopa for NET imaging. Carbidopa is an inhibitor of AADC, and it prevents early decarboxylation of

^{18}F-DOPA to ^{18}F-dopamine outside the brain. This results in decreased renal excretion and increased ^{18}F-DOPA uptake in NET cells, thus increasing image quality and sensitivity (36, 37). However, carbidopa pretreatment is not recommended for the evaluation of pancreatic pathology, such as congenital hyperinsulinism/nesidioblastosis or insulinomas (38, 39).

Most studies with ^{18}F-DOPA PET have been performed for diagnosing and the (re-)staging of NET patients. Its superior role has been established in the following, more common subtypes of NETs: well-differentiated NETs of midgut origin, pheochromocytoma/paraganglioma and medullary thyroid carcinoma. In these NET types, ^{18}F-DOPA PET/CT can serve as the initial imaging technique, provided that it is available (40). In well-differentiated NETs of midgut origin, overall (n = 76 patients) patient- and lesion-based sensitivity for ^{18}F-DOPA is 89 and 97%. This is significantly higher when compared to SRS with ^{111}In-DTPA-octreotide (80 and 49%, respectively; fig. 1), and is equal compared to CT/MRI (89% patient based) or higher (65% lesion based) (40). Furthermore, in these patients, the extension of ^{18}F-DOPA uptake on the whole-body PET scan reflects the total tumor load, and was correlated with various urinary and plasma hormonal products, but not with serum chromogranin A (41). Thus far, patient series directly comparing ^{18}F-DOPA and ^{68}Ga-SSA in NET patients are small. Preliminary results suggest that they perform equally well (40). An example is given in figure 2. There are differences of opinion as to whether or not ^{18}F-DOPA should be advised as a first-choice functional imaging technique in patients with pancreatic NETs. Other functional imaging techniques such as ^{111}In-DTPA-ocetreotide SRS, ^{68}Ga-SSA PET or ^{11}C-5-HTP PET may be considered as well (35, 39, 40, 42).

β-[^{11}C]-5-Hydroxy-L-Tryptophan

PET imaging with β-[^{11}C]-5-hydroxy-L-tryptophan (^{11}C-5-HTP) PET can visualize the serotonin pathway, which is active in many NETs. The precursors tryptophan and 5-HTP are taken up via the L-amino acid transporter, and subsequently decarboxylated by aromatic

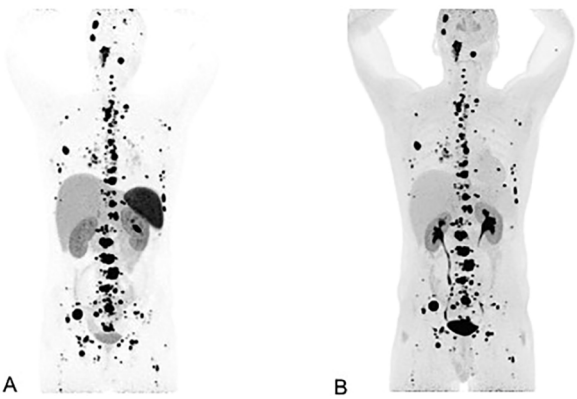

Figure 2. Patient with paraganglioma with widespread (bone) metastases. A. Maximum intensity projection (MIP) of whole body ^{68}Ga-DOTATATE PET B. MIP of whole body ^{18}F-DOPA PET. Note the similarity of uptake of ^{68}Ga-DOTATATE and ^{18}F-DOPA in the lesions. Only some lesions only take up ^{68}Ga-DOTATATE (e.g. axillary regions), but this might be due to progressive disease (the acquisition 6 months after the ^{18}F-DOPA PET).

L-amino acid decarboxylase (DOPA decarboxylase, tryptophan decarboxylase) ADCC. This results in serotonin, which is then also stored in vesicles through the vesicular monoamine transporter. When released into the extracellular environment, serotonin is thereafter degraded and eventually excreted as urinary 5-hydroxyindole acetic acid (5-HIAA).

^{11}C-5-HTP is produced in only a few centers worldwide, since the tracer synthesis is very complex. It is advised for the pretreatment of patients with carbidopa (43). Whole-body imaging usually starts 10–20 min after injection of the tracer. Based on the limited studies that have been published, it can be concluded that ^{11}C-5-HTP is a universal NET tracer for all tumors arising from the fore- to hindgut (44, 45). It has been suggested that ^{11}C-5-HTP performs better compared to ^{18}F-DOPA, especially in foregut (e.g. bronchial) NETs, but this needs further confirmation (33). In a recent study, Orlefors et al. (46) reported for ^{11}C-5-HTP PET a sensitivity of 83% and specificity of 100% in 38 patients with abdominal NETs, confirmed by surgery and histopathology results. An example of a ^{11}C-5-HTP PET is given in figure 3. Based on a study by Koopmans et al. (47), it was concluded that ^{11}C-5-HTP PET outperforms ^{18}F-DOPA PET both in a patient- and a tumor lesion-based analysis in patients with predominantly advanced pancreatic islet cell tumors. However, as stated earlier, there are different opinions regarding the choice for a functional imaging PET tracer in this patient group. Not only for pancreatic NETs, but also for other (subsets) of NETs, further research is needed to define more precisely the role of both metabolic pathway

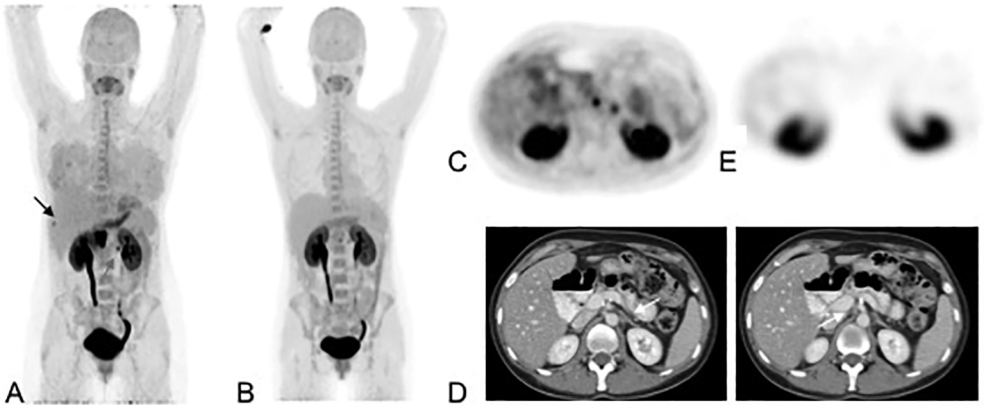

Figure 3. Patient with insulinoma grade 2 of the pancreas, pT3N1M1. A. Maximum intensity projection of whole body ^{11}C-5-HTP PET before surgery. The primary tumor is seen in the head of the pancreas. Also, a liver metastasis (black arrow) and a locoregional lymph node metastasis were detected. All were surgically removed. Physiological uptake is seen in salivary and mammary glands, mucosa of the oesophagus and bone marrow. Physiological excretion is via the kidneys and ureters to the bladder. B. Six months later during follow-up with ^{11}C-5-HTP PET and a diagnostic CT of the abdomen, two small new locoregional metastatic lymph nodes were detected. C. Transverse slices of ^{11}C-5-HTP PET/CT showing the two new lesions, para-aortic right and left-sided. D. Transverse slices of the diagnostic CT of the abdomen (venous phase), also showing the two new lymph node metastases. E. A follow-up ^{111}In-DTPA-octreotide SPECT scan (transverse slice) failed to detect these small metastases.

tracers, ^{18}F-DOPA and ^{11}C-5-HTP, also in relation to other new functional PET tracers that are currently being developed or are already in use.

Glucagon-Like Peptide-1 Receptor

A rare type of NET is the insulinoma. The great majority (more than 90%) of insulinomas are benign, but they can be life threatening due to increased excretion of insulin and induction of episodes of hypoglycemia. Approximately 10% of the insulinomas are multiple, mainly in genetic polyendocrine syndromes. Insulinomas are the most common cause of endogenous hyperinsulinemic hypoglycemia in adults. Virtually all insulinomas are located in the pancreas, but 10–27% remain undetected even after surgery (48). Preoperative localization is therefore essential to facilitate and optimize surgery. The sensitivity of ^{111}In-DTPA-octreotide for detection of insulinomas is only 50–60% (49). Because of this relatively poor sensitivity, other imaging targets such as the glucagon-like peptide-1 receptor (GLP-1R) have been recently developed. GLP-1R is expressed at very high density in almost all benign insulinomas (50). The first studies with GLP-1R agonists demonstrated very promising results (51, 52) with a high detection rate compared to conventional imaging. However, these agonists are not commercially available. Unlike benign insulinoma, malignant insulinomas often lack GLP1-R. In contrast, the malignant insulinomas often express SSTR type 2, which can be visualized by SRS (53).

Imaging Response after Therapy

Adequate assessment of response after therapy is important in NET patients. Not only will it predict the prognosis of the patient, but it will also influence the decision to continue the current therapy or to switch to other alternative therapies. The most frequently used assessment method during follow-up is the response evaluation criteria in solid tumors (RECIST). This assessment is based on the number and size of the lesions measured on CT and, in certain situations, MRI or chest X-ray. The latest guideline version was published in 2009 (54). A partial response (PR) is defined as a decrease of at least 30% in the sum of the diameters of target lesions. Progressive disease (PD) is defined as a 20% increase in the sum of the diameters of target lesions. Stable disease is every change that is not sufficient for PD or PR. Another response evaluation assessment method is the Southwest Oncology Group (SWOG) solid tumor response criteria. The SWOG criteria use a slightly different method for tumor measuring and different definitions for PD and PR. In a direct comparison between the RECIST and SWOG criteria in patients treated with [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate, there were no significant differences in the evaluation of responses (55). In general, NETs are slow-growing tumors and most therapies do not lead to shrinkage of

tumors, but stable disease instead. Therefore, the RECIST criteria using morphological volume characteristics may not be the ideal response criteria for relatively slow-growing NETs (i.e. G1/G2 tumors). Different groups have tried to develop new criteria for response evaluation based on nuclear imaging techniques. A small study with 4 patients found a more appropriate evaluation with the tumor-to-nontumor ratio (T/nT) on SRS with ^{99m}Tc-EDDA/HYNIC-TOC in combination with volume and attenuation changes on CT (56). With the newest ^{68}Ga-SSA, it is easier to measure the change in standardized uptake value (SUV). Haug et al. (57) measured the tumor-to-spleen SUV ratio and maximum SUV ratio at baseline and 3 months after the first cycle of PRRT. They found a significant correlation with improvement in clinical symptoms. Moreover, the decrease in tumor uptake predicted a longer time to progression. On the other hand, Gabriel et al. (58) found that an SUV analysis of individual lesions did not have an additional value in the prediction of individual responses to therapy compared with conventional anatomical imaging with CT. It is clear that further investigation is needed. A disadvantage of somatostatin-based imaging is that NETs may lose their receptors and become negative on these images. Therefore, it would be very interesting to measure the response with metabolic tracers like ^{18}F-DOPA or ^{11}C- 5-HTP, which demonstrate metabolism within the tumor rather than expression of receptors. Unfortunately, there are so far no data available on the use of these tracers for response evaluation, but this type of response evaluation will become paramount within the next decade.

Conclusion

The initial diagnosis of NETs is made with radiological and histological methods.
Nuclear imaging techniques are essential to estimate the total disease burden. Currently, the gold standard for the imaging of NETs is SRS with ^{111}In-DTPA-octreotide. It is almost certain that in the near future this will be replaced by ^{68}Ga-SSA PET imaging. ^{18}F-FDG PET has a limited role in the imaging of NETs, but may play a role in predicting the prognosis in G2/G3 tumor patients. ^{11}C-5-HTP and ^{18}F-DOPA PET show very promising results but are more difficult to produce and/or not widely available. ^{18}F-DOPA is commercially available in several European countries and its use may increase in the coming years. Besides, ^{18}F-DOPA has broader imaging applications than only NETs. Currently, selection for PRRT is based on SRS; further research needs to be done to translate the uptake on SRS to accumulation in the tumor on ^{68}Ga-SSA imaging. Subsequently, changes in tumor accumulation after therapy using metabolic tracers can have an additional value to the existing response criteria based on CT/MRI.

References

1. Townsend DW. Positron Emission Tomography/Computed Tomography. Semin Nucl Med. 2008 May;38(3):152–66.
2. Cohade C, Wahl RL. Applications of positron emission tomography/computed tomography image fusion in clinical positron emission tomography—clinical use, interpretation methods, diagnostic improvements. Semin Nucl Med. 2003 Jul;33(3):228–37.
3. Bosman, F T, World Health Organization, International Agency for Research on Cancer. WHO classification of tumours of the digestive system. 4th ed. Lyon : IARC Press, 2010;
4. Araujo PB, Cheng S, Mete O, Serra S, Morin E, Asa SL, Ezzat S. Evaluation of the WHO 2010 Grading and AJCC/UICC Staging Systems in Prognostic Behavior of Intestinal Neuroendocrine Tumors. Lo AWI, editor. PLoS ONE. 2013 Apr 19;8(4):e61538.
5. Krenning EP, Breeman WAP, Kooij PPM, Lameris JS, Bakker WH, Koper JW, Ausema L, Reubi JC, Lamberts SWJ. Localisation of endocrine-related tumours with radioiodinated analogue of somatostatin. The Lancet. 1989 Feb 4;(Vol. 333, Issue 8632):Pages 242–244.
6. Reubi JC, Schär J-C, Waser B, Wenger S, Heppeler A, Schmitt JS, Macke HR. Affinity profiles for human somatostatin receptor subtypes SST1–SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med. 2000;27(3):273–82.
7. Rinke A, Muller H-H, Schade-Brittinger C, Klose K-J, Barth P, Wied M, Mayer C, Aminossadati B, Pape U-F, Blaker M, Harder J, Arnold C, Gress T, Arnold R. Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group. J Clin Oncol. 2009 Aug 24;27(28):4656–63.
8. Balon HR, Brown TLY, Goldsmith SJ, Silberstein EB, Krenning EP, Lang O, Dillehay G, Tarrance J, Johnson M, Stabin MG. The SNM Practice Guideline for Somatostatin Receptor Scintigraphy 2.0. J Nucl Med Technol. 2011 Nov 8;39(4):317–24.
9. Kwekkeboom DJ, Kam BL, van Essen M, Teunissen JJM, van Eijck CHJ, Valkema R, de Jong M, de Herder WW, Krenning EP. Somatostatin receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. Endocr Relat Cancer. 2009 Dec 8;17(1):R53–R73.
10. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. Current Status of Gastrointestinal Carcinoids. Gastroenterology. 2005 May;128(6):1717–51.
11. De Bruin C, Hofland LJ, Nieman LK, van Koetsveld PM, Waaijers AM, Sprij-Mooij DM, van Essen M, Lamberts SWJ, de Herder WW, Feelders RA. Mifepristone Effects on Tumor Somatostatin Receptor Expression in Two Patients with Cushing's Syndrome due to Ectopic Adrenocorticotropin Secretion. J Clin Endocrinol Metab. 2012 Feb;97(2):455–62.
12. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, Feelders RA, van Aken MO, Krenning EP. Treatment With the Radiolabeled Somatostatin Analog [177Lu-DOTA0,Tyr3]Octreotate: Toxicity, Efficacy, and Survival. J Clin Oncol. 2008 Apr 29;26(13):2124–30.

13. Bombardieri E, Coliva A, Maccauro M, Seregni E, Orunesu E, Chiti A, Lucignani G. Imaging of neuroendocrine tumours with gamma-emitting radiopharmaceuticals. Q J Nucl Med Mol Imaging Off Publ Ital Assoc Nucl Med AIMN Int Assoc Radiopharmacol IAR Sect Soc Radiopharm Chem Biol. 2010 Feb;54(1):3–15.
14. Gabriel M, Muehllechner P, Decristoforo C, Guggenberg E von. 99-mTc-EDDA/HYNIC-Tyr (3)-octreotide for staging and follow-up of patients with neuroendocrine gastro-entero-pancreatic tumors. Q J Nucl Med Mol Imaging. 2005;49(3):237–44.
15. Gabriel M, Decristoforo C, Donnemiller E, Ulmer H, Rychlinski CW, Mather SJ, Moncayo R. An intrapatient comparison of 99mTc-EDDA/HYNIC-TOC with 111In-DTPA-octreotide for diagnosis of somatostatin receptor-expressing tumors. J Nucl Med. 2003;44(5):708–16.
16. Geijer H, Breimer LH. Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2013 Jul 20;40(11):1770–80.
17. Virgolini I, Ambrosini V, Bomanji JB, Baum RP, Fanti S, Gabriel M, Papathanasiou ND, Pepe G, Oyen W, Cristoforo C, Chiti A. Procedure guidelines for PET/CT tumour imaging with 68Ga-DOTA-conjugated peptides: 68Ga-DOTA-TOC, 68Ga-DOTA-NOC, 68Ga-DOTA-TATE. Eur J Nucl Med Mol Imaging. 2010 Jul 2;37(10):2004–10.
18. Gabriel M, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, Kovacs P, Von Guggenberg E, Bale R, Virgolini IJ. 68Ga-DOTA-Tyr3-Octreotide PET in Neuroendocrine Tumors: Comparison with Somatostatin Receptor Scintigraphy and CT. J Nucl Med. 2007 Apr 1;48(4):508–18.
19. Buchmann I, Henze M, Engelbrecht S, Eisenhut M, Runz A, Schäfer M, Schilling T, Haufe S, Herrmann T, Haberkorn U. Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2007 May 23;34(10):1617–26.
20. Krausz Y, Freedman N, Rubinstein R, Lavie E, Orevi M, Tshori S, Salmon A, Glaser B, Chisin R, Mishani E, Gross DJ. 68Ga-DOTA-NOC PET/CT Imaging of Neuroendocrine Tumors: Comparison with 111In-DTPA-Octreotide (OctreoScan®). Mol Imaging Biol. 2010 Jul 22;13(3):583–93.
21. Walker RC, Smith GT, Liu E, Moore B, Clanton J, Stabin M. Measured Human Dosimetry of 68Ga-DOTATATE. J Nucl Med. 2013 Mar 20;54(6):855–60.
22. Schreiter NF, Brenner W, Nogami M, Buchert R, Huppertz A, Pape U-F, Prasad V, Hamm B, Maurer MH. Cost comparison of 111In-DTPA-octreotide scintigraphy and 68Ga-DOTATOC PET/CT for staging enteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2011 Sep 17;39(1):72–82.
23. Castellucci P, Pou Ucha J, Fuccio C, Rubello D, Ambrosini V, Montini GC, Pettinato V, Malizia C, Lodi F, Fanti S. Incidence of Increased 68Ga-DOTANOC Uptake in the Pancreatic Head in a Large Series of Extrapancreatic NET Patients Studied with Sequential PET/CT. J Nucl Med. 2011 May 13;52(6):886–90.
24. Wang X, Zielinski MC, Misawa R, Wen P, Wang T-Y, Wang C-Z, Witkowski P, Hara M, Shi X. Quantitative Analysis of Pancreatic Polypeptide Cell Distribution in the Human Pancreas. Shi X, editor. PLoS ONE. 2013 Jan 31;8(1):e55501.

25. Teunissen JJM, Kwekkeboom DJ, Valkema R, Krenning EP. Nuclear medicine techniques for the imaging and treatment of neuroendocrine tumours. Endocr Relat Cancer. 2011 Oct 17;18(S1):S27–S51.
26. Öberg K, Eriksson B. Nuclear medicine in the detection, staging and treatment of gastrointestinal carcinoid tumours. Best Pract Res Clin Endocrinol Metab. 2005 Jun;19(2):265–76.
27. Modlin IM, Latich I, Zikusoka M, Kidd M, Eick G, Chan AK. Gastrointestinal carcinoids: the evolution of diagnostic strategies. J Clin Gastroenterol. 2006;40(7):572–82.
28. Adams S, Baum R, Rink T, Schumm-Dräger P-M, Usadel K-H, Hör G. Limited value of fluorine-18 fluorodeoxyglucose positron emission tomography for the imaging of neuroendocrine tumours. Eur J Nucl Med. 1998;25(1):79–83.
29. Garin E, Le Jeune F, Devillers A, Cuggia M, de Lajarte-Thirouard A-S, Bouriel C, Boucher E, Raoul JL. Predictive Value of 18F-FDG PET and Somatostatin Receptor Scintigraphy in Patients with Metastatic Endocrine Tumors. J Nucl Med. 2009 Jun 1;50(6):858–64.
30. Severi S, Nanni O, Bodei L, Sansovini M, Ianniello A, Nicoletti S, Scarpi E, Matteucci F, Gilardi L, Paganelli G. Role of 18FDG PET/CT in patients treated with 177Lu-DOTATATE for advanced differentiated neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2013 Jun;40(6):881–8.
31. Kayani I, Bomanji JB, Groves A, Conway G, Gacinovic S, Win T, Dickson J, Caplin M, Ell PJ. Functional imaging of neuroendocrine tumors with combined PET/CT using68Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and18F-FDG. Cancer. 2008 Jun 1;112(11):2447–55.
32. Naswa N, Sharma P, Gupta SK, Karunanithi S, Reddy RM, Patnecha M, Lata S, Kumar R, Malhotra A, Bal C. Dual Tracer Functional Imaging of Gastroenteropancreatic Neuroendocrine Tumors Using 68Ga-DOTA-NOC PET-CT and 18F-FDG PET-CT: Competitive or Complimentary? Clin Nucl Med. 2014 Jan;39(1):e27–34.
33. Jager PL, Chirakal R, Marriott CJ, Brouwers AH, Koopmans KP, Gulenchyn KY. 6-L-18F-Fluorodihydroxyphenylalanine PET in Neuroendocrine Tumors: Basic Aspects and Emerging Clinical Applications. J Nucl Med. 2008 Mar 14;49(4):573–86.
34. Chondrogiannis S, Cristina Marzola M, Al-Nahhas A, Venkatanarayana TD, Mazza A, Opocher G, Rubello D. Normal biodistribution pattern and physiologic variants of 18F-DOPA PET imaging: Nucl Med Commun. 2013 Oct;1.
35. Rufini V, Baum RP, Castaldi P, Treglia G, Gaetano AM, Carreras C, Kaemmerer D, Hommann M, Horsch D, Bonomo L, Giordano A. Role of PET/CT in the functional imaging of endocrine pancreatic tumors. Abdom Imaging. 2012 Mar 16;37(6):1004–20.
36. Brown WD, Oakes TR, DeJesus OT, Taylor MD, Roberts AD, Nickles RJ, Holden JE. Fluorine-18-fluoro-L-DOPA dosimetry with carbidopa pretreatment. J Nucl Med. 1998;39:1884–91.
37. Timmers HJLM, Hadi M, Carrasquillo JA, Chen CC, Martiniova L, Whatley M, Ling A, Eisenhofer G, Adams KT, Pacak K. The Effects of Carbidopa on Uptake of 6-18F-Fluoro-L-DOPA in PET of Pheochromocytoma and Extraadrenal Abdominal Paraganglioma. J Nucl Med. 2007 Oct 1;48(10):1599–606.

38. Kauhanen S, Seppänen M, Nuutila P. Premedication with carbidopa masks positive finding of insulinoma and β-cell hyperplasia in [18F]-dihydroxy-phenyl-alanine positron emission tomography. J Clin Oncol. 2008;26(32):5307–8.
39. Kauhanen S, Seppanen M, Minn H, Nuutila P. Clinical PET imaging of insulinoma and beta-cell hyperplasia. Curr Pharm Des. 2010;16(14):1550–60.
40. Balogova S, Talbot J-N, Nataf V, Michaud L, Huchet V, Kerrou K, Montravers F. 18F-Fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type. Eur J Nucl Med Mol Imaging. 2013 Feb 16;40(6):943–66.
41. Fiebrich H-B, Jong JR, Kema IP, Koopmans KP, Sluiter W, Dierckx RAJO, Walenkamp AM, Links TP, Brouwers AH, Vries EGE. Total 18F-dopa PET tumour uptake reflects metabolic endocrine tumour activity in patients with a carcinoid tumour. Eur J Nucl Med Mol Imaging. 2011 Jun 23;38(10):1854–61.
42. Tessonnier L, Sebag F, Ghander C, De Micco C, Reynaud R, Palazzo FF, Conte-Devolx B. Henry JF, Mundler O, Taieb D. Limited Value of 18F-F-DOPA PET to Localize Pancreatic Insulin-Secreting Tumors in Adults with Hyperinsulinemic Hypoglycemia. J Clin Endocrinol Metab. 2010 Jan;95(1):303–7.
43. Orlefors H, Sundin A, Lu L, Oberg K, Långström B, Eriksson B, Bergstrom M. Carbidopa pretreatment improves image interpretation and visualisation of carcinoid tumours with 11C-5-hydroxytryptophan positron emission tomography. Eur J Nucl Med Mol Imaging. 2006 Jan;33(1):60–5.
44. Orlefors H. Whole-Body 11C-5-Hydroxytryptophan Positron Emission Tomography as a Universal Imaging Technique for Neuroendocrine Tumors: Comparison with Somatostatin Receptor Scintigraphy and Computed Tomography. J Clin Endocrinol Metab. 2005 Mar 15;90(6):3392–400.
45. Orlefors H, Sundin A, Ahlström H akan, Bjurling P, Bergström M, Lilja A, Langstrom B, Oberg K, Eriksson B. Positron emission tomography with 5-hydroxytryprophan in neuroendocrine tumors. J Clin Oncol. 1998;16(7):2534–41.
46. Orlefors H, Sundin A, Eriksson B, Skogseid B, Oberg K, Akerström G, Hellman P. PET-Guided Surgery - High Correlation between Positron Emission Tomography with 11C-5-Hydroxytryptophane (5-HTP) and Surgical Findings in Abdominal Neuroendocrine Tumours. Cancers. 2012;4(1):100–12.
47. Koopmans KP, Neels OC, Kema IP, Elsinga PH, Sluiter WJ, Vanghillewe K, Brouwers AH, Jager PL, de Vries EGE. Improved Staging of Patients With Carcinoid and Islet Cell Tumors With 18F-Dihydroxy-Phenyl-Alanine and 11C-5-Hydroxy-Tryptophan Positron Emission Tomography. J Clin Oncol. 2008 Mar 20;26(9):1489–95.
48. Grant CS. Insulinoma. Best Pract Res Clin Gastroenterol. 2005 Oct;19(5):783–98.
49. De Herder WW, Kwekkeboom DJ, Valkema R, Feelders RA, van Aken MO, Lamberts SWJ, van der Lely AJ, Krenning EP. Neuroendocrine tumors and somatostatin: imaging techniques. J Endocrinol Invest. 2005;28(11 Suppl International):132–6.
50. Reubi JC, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumours: molecular basis for in vivo multireceptor tumour targeting. Eur J Nucl Med Mol Imaging. 2003 Apr 18;30(5):781–93.

51. Christ E, Wild D, Forrer F, Brandle M, Sahli R, Clerici T, Gloor B, Martius F, Maecke H, Reubi JC. Glucagon-Like Peptide-1 Receptor Imaging for Localization of Insulinomas. J Clin Endocrinol Metab. 2009 Oct 9;94(11):4398–405.
52. Sowa-Staszczak A, Pach D, Mikołajczak R, Mäcke H, Jabrocka-Hybel A, Stefańska A, Tomaszuk M, Janota B, Gilis-Januszewska A, Malecki M, Kaminski G, Kowalska A, Kulig J, Matyja A, Osuch C, Hubalewska-Dydejczyk A. Glucagon-like peptide-1 receptor imaging with [Lys40(Ahx-HYNIC-99mTc/EDDA)NH2]-exendin-4 for the detection of insulinoma. Eur J Nucl Med Mol Imaging. 2012 Dec 7;40(4):524–31.
53. Wild D, Christ E, Caplin ME, Kurzawinski TR, Forrer F, Brandle M, Seufert J, Weber WA, Bomanji J, Perren A, Ell PJ, Reubi JC. Glucagon-Like Peptide-1 Versus Somatostatin Receptor Targeting Reveals 2 Distinct Forms of Malignant Insulinomas. J Nucl Med. 2011 Jun 16;52(7):1073–8.
54. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228–47.
55. Van Vliet EI, Krenning EP, Teunissen JJ, Bergsma H, Kam BL, Kwekkeboom DJ. Comparison of Response Evaluation in Patients with Gastroenteropancreatic and Thoracic Neuroendocrine Tumors After Treatment with [177Lu-DOTA0,Tyr3]Octreotate. J Nucl Med. 2013 Oct 1;54(10):1689–96.
56. Sowa-Staszczak A, Chrzan R, Pach D, Stefańska A, Tomaszuk M, Buziak-Bereza M, Kolodziej M, Przybylik-Mazurek E, Hubalewska-Dydejczyk A. Are RECIST criteria sufficient to assess response to therapy in neuroendocrine tumors? Clin Imaging. 2012 Jul;36(4):360–4.
57. Haug AR, Auernhammer CJ, Wangler B, Schmidt GP, Uebleis C, Goke B, Cumming P, Bartenstein P, Tiling R, Hacker M. 68Ga-DOTATATE PET/CT for the Early Prediction of Response to Somatostatin Receptor-Mediated Radionuclide Therapy in Patients with Well-Differentiated Neuroendocrine Tumors. J Nucl Med. 2010 Aug 18;51(9):1349–56.
58. Gabriel M, Oberauer A, Dobrozemsky G, Decristoforo C, Putzer D, Kendler D, Uprimny C, Kovacs P, Bale R, Virgolini IJ. 68Ga-DOTA-Tyr3-Octreotide PET for Assessing Response to Somatostatin-Receptor-Mediated Radionuclide Therapy. J Nucl Med. 2009 Aug 18;50(9):1427–34.

2

CHAPTER 3

Physiological uptake in the pancreatic head on SRS using [^{111}In-DTPA^{0}] octreotide; Incidence and Mechanism

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Abstract

Purpose

Physiological uptake in the uncinate process or pancreatic head has been described with ^{68}Ga-labeled PET tracers for somatostatin receptor imaging. ^{111}In-DTPA-octreotide is the only registered radiopharmaceutical for the imaging of neuroendocrine tumors. We studied the uptake in this region of the pancreatic head on somatostatin receptor scintigraphy (SRS) using ^{111}In-DTPA-octreotide in a large group of patients. Furthermore, known physiological and clinical characteristics are discussed in an attempt to elucidate this phenomenon.

Methods

Four hundred seven patients underwent SRS using ^{111}In-DTPAoctreotide in our department in 2014. After excluding patients with a known malignancy in or close to the pancreas, as well as all scans without SPECT/CT of the upper abdomen, we reviewed 178 scans in total. The uptake was graded on a 4-point scale that correlates the uptake in the pancreatic head to physiological uptake in the liver.

Results

Uptake in the region of the pancreatic head, including the uncinate process, was seen in 46 (26%) of 178 patients on SPECT/CT and in 12 patients (7%) on planar imaging. On SPECT/CT, uptake was lower than the liver in 26 patients (15%), equal to the liver in 17 patients (10%), and higher than the liver in 3 patients (2%). In patients with diabetes mellitus (DM), the incidence of uptake in the pancreatic head was 50% on SPECT/CT.

Conclusions

Physiological uptake in the pancreatic head is seen on SPECT/CT with ^{111}In-DTPA-octreotide in 26% of patients, and the incidence is doubled in patients with DM. Previous case reports showed uptake in the pancreatic head due to histologically proven pancreatic polypeptide (PP) cell hyperplasia. Also, patients with DM have elevated serum PP concentrations, which is likely due to PP cell hyperplasia. Because 90% of PP cells are present in the pancreatic head, PP cell hyperplasia is the most likely explanation for visualization of the pancreatic head on SRS in a substantial number of patients.

Introduction

Neuroendocrine tumors (NETs) are heterogeneous. However, these tumors have in common that in the vast majority the somatostatin receptor (SSTR) is overexpressed on their cell surface. This receptor can be used for imaging with radiolabeled somatostatin analogs. This type of imaging was first described in humans in 1989 (1). Although different somatostatin analogs linked to different radionuclides have been used in the past decades, the only registered radiopharmaceutical for SSTR scintigraphy (SRS) is [^{111}In-DTPA]octreotide (OctreoScan; Covidien, Petten, the Netherlands). Currently, SRS plays a pivotal role in the diagnosis and staging of patients with NETs. Besides, it is the only validated imaging method to select patients for peptide receptor radionuclide therapy. Neuroendocrine tumors are not the only malignant tumors that overexpress the SSTR, and therefore other malignant diseases can be detected with SRS. Furthermore, non neoplastic diseases, such as autoimmune diseases, granulomas, and infections, can be visualized with SRS. False-positive findings have been described in patients with gastritis, splenosis, radiation fibrosis, and inflammatory bowel disease (2–4). This nonspecific uptake can be difficult to distinguish from tumor-related pathology but is important knowledge for optimal reading.

Although new PET tracers have become available in the past years, SRS using ^{111}In-DTPA-octreotide is most widely available and frequently used for imaging of NETs. However, the new ^{68}Ga-labeled somatostatin analogs that are used in PET/CT imaging have many advantages over SRS, such as better image quality, patient comfort, and a lower radiation dose. A disadvantage is the uptake by the pancreatic head or uncinate process, which can lead to false-positive findings. This physiological uptake in the region of the pancreatic head has been described for [^{68}Ga-DOTA^{0}, Tyr^{3}]octreotide (^{68}Ga-DOTATOC), [^{68}Ga-DOTA,1-nal^{3}]octreotide (^{68}Ga-DOTANOC), and [^{68}Ga-DOTA^{0}, Tyr^{3}]octreotate (^{68}Ga-DOTATATE) (5–10) (Table 1). These 3 tracers all have a different affinity for the

Table 1. Frequency of visualization of physiological uptake in the pancreas.

Reference	Ligand	Imaging modality	Localisation	Incidence
Al-Ibraheem et al (2011) (5)	^{68}Ga-DOTATOC	PET/CT	Pancreatic head	20/43 (47%)
Castellucci et al (2011) (6)	^{68}Ga-DOTANOC	PET/CT	Pancreatic head	31/100 (31%)
Kunikowska et al (2012) (7)	^{68}Ga-DOTATATE	PET/CT	Uncinate process	41/250 (16%)
Jacobssen et al (2012) (8)	^{68}Ga-DOTATOC	PET/CT	Uncinate process	35/50 (70%)
Krausz et al (2012) (9)	^{68}Ga-DOTANOC	PET/CT	Head/uncinate process/body	38/103 (37%)
Mapelli et al (2014) (10)	^{68}Ga-DOTATATE	PET/CT	Head/uncinate process	10/38 (26%)
Yamaga et al (2015) (13)	^{99m}Tc-HYNIC-TOC	SPECT/CT	Uncinate process	7/36 (19%)

5 known subtypes of the SSTR, but have in common a high affinity for the subtype 2 receptor. It is known that SSTR subtypes 1, 2, 3, and 5 are present in the endocrine pancreas (12). ^{111}In-DTPA-octreotide also has a high affinity for the subtype 2 receptor, followed by subtypes 3 and 5. Therefore, also with ^{111}In-DTPA-octreotide imaging, uptake in the pancreatic head in some patients can be expected.

Materials and Methods

Patients

This retrospective study included a total of 407 consecutive ^{111}In-DTPA-octreotide imaging studies that were obtained in our department in 2014. Imaging was performed for diagnostic workup, staging, or follow-up. Patients without an SPECT/CT of the upper abdomen or with a known NET in the pancreas were excluded from analysis. Other exclusion criteria were prior surgery of the pancreas and lymph node metastases close to the pancreas (eg, lymph nodes in the hilum of the liver or retroperitoneal metastases of paragangliomas) to minimize the possibility of false-positive uptake in the pancreatic head. If a patient had multiple imaging studies in 2014, only the first was included. All patients who did have uptake in the pancreas, but had no contrast enhanced CTor MRI to correlate with, were excluded as well. After exclusion, 178 patients were available for analysis. The indications for SRS are listed in Table 2.

Image Acquisition and Analysis

Patients were injected intravenously with a mean activity of 225 MBq (range, 203–241 MBq) ^{111}In-DTPA-octreotide. Patients were prepared according to the European Association of Nuclear Medicine guidelines (13). Somatostatin analog therapy was discontinued if clinically feasible. Oral laxatives were administered on the day before and after the injection. Images were acquired 24 hours after injection using a Siemens Symbia T16 SPECT/CT scanner (Siemens Healthcare, Erlangen, Germany). Spotviews of the head, thorax, upper abdomen, and pelvis were made 15 minutes per view (256x256 matrix, MELP collimator), followed by an SPECT/CT of the upper abdomen. A low-dose CTwas acquired for attenuation correction and anatomical localization. The CT parameters were as follows: 110 kV, 40 mAs, a 0.6-second tube rotation, and a 5-mm slice thickness. SPECT parameters were 128x128 matrix, 60 views/detector, 30-second time per view. If indicated, extra images of the abdomen 48 hours after injection were made. A nuclear medicine physician examined the images without knowledge of the medical history. Uptake in the pancreatic head was graded on a 4-point scale: 0, no uptake; 1, intensity less than the physiological uptake in the liver; 2, intensity identical to the liver; and 3, intensity greater than the liver. Uptake was scored both on planar and SPECT/CT imaging. Positive findings were compared with diagnostic abdominal CT or MRI obtained within 12 months of SRS.

Table 2. Indications for ^{111}In-DTPA-octreotide imaging including planar imaging and SPECT/CT of the upper abdomen.

Indication	Number of patients
NET - Small intestine	107
- Rectum	12
- Unknown primary	11
- Bronchus	9
- Ovarian	4
- Kidney	2
- Stomach / esophagus	2
- Appendix	1
- Clinical suspicion	3
Paraganglioma	17
Common variable immunodeficiency	3
Pheochromocytoma	2
Cushing's syndrome	1
Meningioma	1
Hurthle cell carcinoma	1
Castleman's disease	1
Malignant lymphoma	1
Total	178

Results

In 46 (26%) of 178 patients, uptake in the pancreatic head was found on SPECT/CT. Twelve patients (7%) also demonstrated uptake on the planar imaging. On planar imaging, uptake was lower than the physiological uptake in the liver in 7 patients (4%) and equal to the liver in 5 patients (3%). On SPECT/CT, uptake was lower than the liver in 26 patients (15%), equal to the liver in 17 patients (10%), and higher than the liver in 3 patients (2%) (Table 3). An example of a patient with uptake grade 3 in the pancreatic head is given in Figure 1. Of the 178 patients, 20 patients were on antidiabetic drugs (metformin, glimepiride, and/

or insulin), as evidenced by their medical history in patient files. Of these 20 patients, 10 had uptake in the pancreatic head (50%), whereas in the patients without known diabetes, 36 (23%) of 158 had uptake in this area. The correlating diagnostic CT or MRI that was performed within 12 months after ^{111}In-DTPA-octreotide did not show any pathology in this area.

Table 3. Number of patients with uptake in the pancreatic head.

Uptake grade	Planar	SPECT/CT
0	166 (93%)	132 (74%)
1	7 (4%)	26 (15%)
2	5 (3%)	17 (10%)
3	0 (0%)	3 (2%)

Uptake grade: 0, no uptake; 1, intensity less than physiological uptake in the normal liver parenchyma; 2, intensity identical to the liver and 3, intensity greater than the liver

Discussion

In patients imaged with PET-CT with ^{68}Ga-labeled somatostatin analogs (^{68}Ga-SSA), uptake in the area of the pancreatic head or uncinate process is a known pitfall and can result in false-positive findings. In the era before the availability of SPECT/CT, uptake in the upper abdomen was mostly attributed to physiological activity in the intestine. However, with the use of SPECT/CT, it is possible to localize the exact anatomical structure and prove that this activity is located in the pancreatic head. It has been postulated that detection of uptake in the pancreatic head with ^{68}Ga-SSA PET/CT imaging is due to the higher imaging quality and spatial resolution of this type of imaging. We retrospectively demonstrated that the pancreatic head is visible on SRS using ^{111}In-DTPA-octreotide as well. A previous report on SRS with ^{99m}Tc-HYNIC-TOC showed similar results of uptake in the uncinate process on SPECT/CT in 19% of studies without any evidence of a malignancy on the CT or MRI (11). In previous reports, it was postulated that physiological uptake in the uncinate process was due to the presence of SSTR subtypes 2, 3, and 5 on islet cells, and therefore a higher density of islet cells in this area was suggested. However, Ionescu-Tirgoviste et al (14) showed that the numbers of islets found in the head of the pancreas are similar or less compared with other parts of the pancreas. Also, the total islet volume is lower in the head of the pancreas compared with the body and tail. Wang et al (15) demonstrated that the pancreatic head, or more specifically the uncinate region, is very rich in pancreatic polypeptide (PP) cells. Moreover, the vast majority of PP cells (90%) are located in the uncinate process of the pancreas, whereas the number of α and β cells are significantly decreased in this area of the pancreas. The PP cells express SSTR subtypes 1 to 4 on their surface and can therefore be visualized on SRS (Fig. 2). Because of a lack of histological

confirmation in our study, it is difficult to prove that the high number of PP cells in the uncinate region attributes to the demonstrated uptake in this area. On the other hand, there are 2 case reports in which high uptake in the posterior part of the pancreatic head on ^{111}In-DTPA-octreotide scintigraphy was demonstrated because of histologically proven hyperplasia of the PP cells (16,17). This may suggest that the PP cells are responsible for the uptake in the pancreatic head in our study. Interestingly, we found a significantly higher percentage of physiological uptake in the head of the pancreas in patients who were on antidiabetic drugs. It is known that the number and distribution of islet cells change in patients with diabetes mellitus (DM).

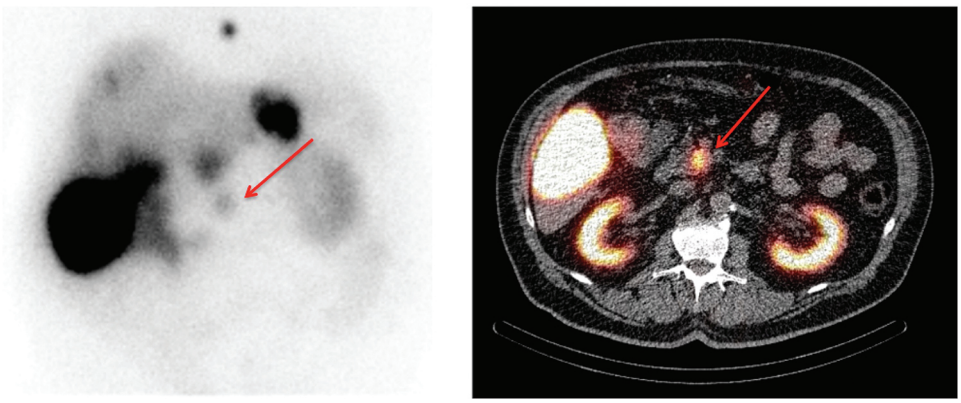

Figure 1. Planar imaging of the abdomen (left image) and axial slice of the SPECT/CT of the upper abdomen (right image). The patient was diagnosed with a NET of the small intestine and multiple metastases in the liver. Images show an intense, focal uptake in the pancreatic head (red arrow). The contrast enhanced CT that was made in the same period did not demonstrate any evidence of a malignancy in this area.

The number of β cells decreases, and the α cells show an increase in number (18). Furthermore, the total islet tissue mass is lower in patients with DM compared with patients with no DM. It was reported in several studies that the level of serum PP is higher in patients with DM compared with patients with no DM (19,20). Such higher serum concentrations of PP might be due to hyperplasia of the PP cells in the pancreatic head. Studies that quantified the changes in PP cell population in patients with DM have produced conflicting reports of increased or unaltered numbers (21–24). It seems likely that the reported elevated serum concentration of PP in patients with DM is due to PP cell hyperplasia. This PP cell hyperplasia as such would then explain the higher frequency of visualization of the pancreatic head on SRS in patients with DM. The elevation of serum PP levels is not specific for DM. It has been described in other disease states, such as infections and inflammatory disorders (25). Because some patients with (a suspected) inflammatory disorder or infection undergo SRS at our department, this may be the explanation for the uptake in patients with no DM. Alternatively, PP cell hyperplasia may be present in such patients and signify a prodromal phase of diabetes.

A different explanation for the increased frequency of visualization of the uncinate process in patients with DM might be the infiltration of lymphocytes in the diabetic pancreas. Previous analyses demonstrated that CD4+ and CD8+ T cells were more frequent in the islets of patients with DM compared with healthy donors (26,27). Also, the proportion of B lymphocytes was significantly elevated in patients with DM type 2 (28). Both T and B lymphocytes in the peripheral blood express SSTR subtype 3. Upon stimulation, monocytes express SSTR subtype 2a as well (29). These subtypes can be visualized by SRS and therefore may lead to a higher uptake during SRS in patients with DM. However, the infiltration of lymphocytes is not limited to the pancreatic head. Therefore, this hypothesis cannot explain our findings on SRS.

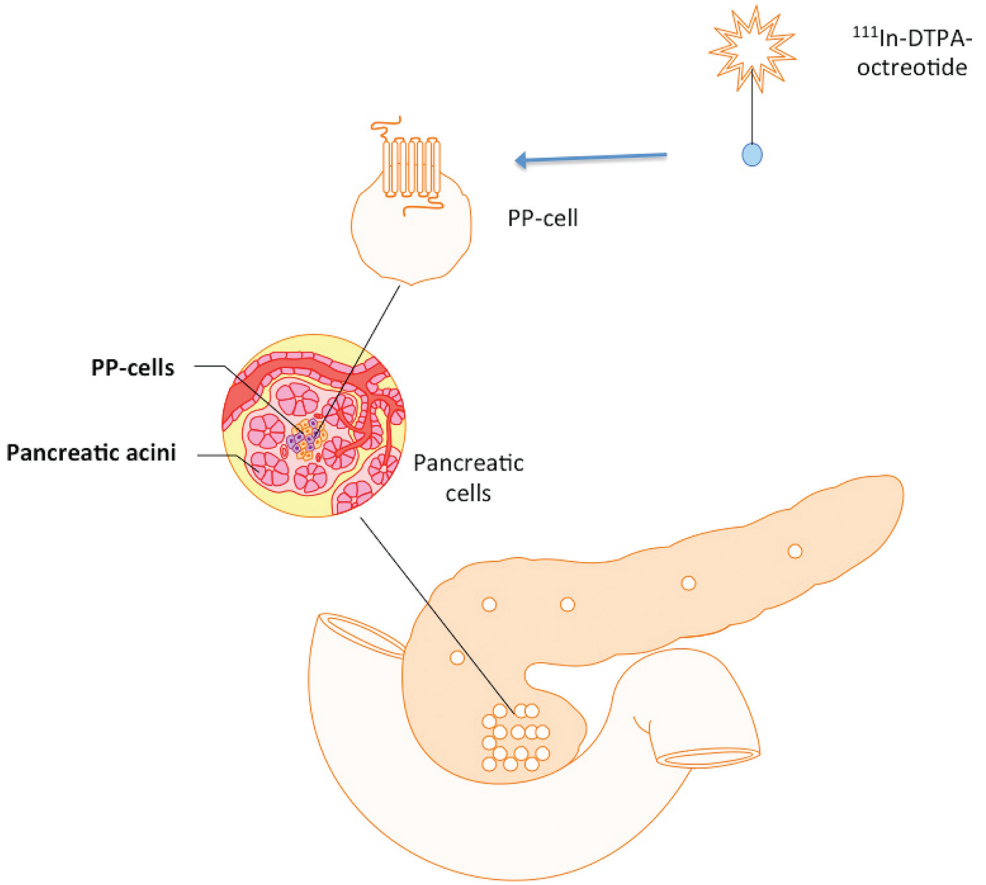

Figure 2. Diagram illustrating the proposed role of the PP-cell in visualization of the pancreatic head on SRS. The head of the pancreas has a high density of pancreatic polypeptide cells. These PP-cells express the somatostatin receptor, which is a member of the family of G-protein-coupled receptor and can bind ^{111}In-DTPA-octreotide.

The main limitation of this study is the lack of a criterion standard, which is histological confirmation of the state of the pancreatic head. None of the patients had a biopsy or surgery in the area of high uptake on SRS. We think, however, that we well argued and discussed the likely role of PP cell hyperplasia as mechanism to explain the visualization of the pancreatic head in approximately a quarter of patients undergoing SRS with ^{111}In-DTPA-octreotide.

Conclusions

In this study, visualization of physiological uptake in the area of the pancreatic head on ^{111}In-DTPA-octreotide SPECT/CT was demonstrated in 26% of patients without any evidence of a malignancy on CT or MRI. These results are consistent with previous studies using ^{68}Ga-SSA in PET/CT and ^{99m}Tc-HYNIC-TOC scintigraphy. The uptake can vary between patients from very low to higher than the uptake in normal liver parenchyma. The uptake is seen more frequently in patients with DM. Previous case reports showed uptake in the pancreatic head due to histologically proven PP cell hyperplasia. Also, patients with DM have elevated serum PP concentrations, which is likely due to PP cell hyperplasia. Because 90% of PP cells are present in the pancreatic head, PP cell hyperplasia is the most likely explanation for visualization of the pancreatic head on SRS in a substantial number of patients. Awareness of the possibility of this physiological uptake in the pancreatic head should be taken into account when evaluating and reporting SRS with ^{111}In-DTPA-octreotide.

References

1. Krenning EP, Breeman WH, BreemanWA, et al. Localisation of endocrinerelated tumours with radioiodinated analogue of somatostatin. Lancet. 1989; 1:242–244.
2. Lebtahi R, Cadiot G, Marmuse JP, et al. False-positive somatostatin receptor scintigraphy due to an accessory spleen. J Nucl Med. 1997;38:1979–1981.
3. Marko J, Lamba R, Miller F, et al. OctreoScan positive Crohn's disease mimicking an ileal carcinoid tumor. J Clin Gastroenterol. 2008;42: 66–68.
4. Rahman S, Raja S, Ehni BL. False-positive indium 111 pentetreotide scan for recurrent meningioma due to radiation fibrosis. Clin Nucl Med. 2011; 36:43–44.
5. Al-Ibraheem A, Bundschuh RA, Notni J, et al. Focal uptake of 68Ga-DOTATOC in the pancreas: pathological or physiological correlate in patients with neuroendocrine tumours? Eur J Nucl Med Mol Imaging. 2011; 38:2005–2013.
6. Castellucci P, Pou Ucha J, Fuccio C, et al. Incidence of increased 68Ga-DOTANOC uptake in the pancreatic head in a large series of extrapancreatic NET patients studied with sequential PET/CT. J Nucl Med. 2011;52:886–890.
7. Kunikowska J, Królicki L, Pawlak D, et al. Semiquantitative analysis and characterization of physiological biodistribution of (68)Ga-DOTA-TATE PET/CT. Clin Nucl Med. 2012;37:1052–1057.
8. Jacobsson H, Larsson P, Jonsson C, et al. Normal uptake of 68Ga-DOTATOC by the pancreas uncinate process mimicking malignancy at somatostatin receptor PET. Clin Nucl Med. 2012;37:362–365.
9. Krausz Y, Rubinstein R, Appelbaum L, et al. Ga-68 DOTA-NOC uptake in the pancreas: pathological and physiological patterns. Clin Nucl Med. 2012; 37:57–62.
10. Mapelli P, Tam HH, Sharma R, et al. Frequency and significance of physiological versus pathological uptake of 68Ga-DOTATATE in the pancreas: validation with morphological imaging. Nucl Med Commun. 2014;35:613–619.
11. Yamaga LY, Neto GC, da Cunha ML, et al. 99mTc-HYNIC-TOC increased uptake can mimic malignancy in the pancreas uncinate process at somatostatin receptor SPECT/CT. Radiol Med (Torino) [Internet]. 2015;121: 225–228.
12. Unger N, Ueberberg B, Schulz S, et al. Differential expression of somatostatin receptor subtype 1–5 proteins in numerous human normal tissues. Exp Clin Endocrinol Diabetes. 2012;120:482–489.
13. Bombardieri E, Ambrosini V, Aktolun C, et al. 111In-pentetreotide scintigraphy: procedure guidelines for tumour imaging. Eur J Nucl Med Mol Imaging. 2010;37:1441–1448.
14. Ionescu-Tirgoviste C, Gagniuc PA, Gubceac E, et al. A 3D map of the islet routes throughout the healthy human pancreas. Sci Rep. 2015; 5:14634.
15. Wang X, Zielinski MC, Misawa R, et al. Quantitative analysis of pancreatic polypeptide cell distribution in the human pancreas. PLoS One. 2013; 8:e55501.
16. Bunning J,Merchant SH, Crooks LA, et al. Indium-111 pentetreotide uptake by pancreatic polypeptide cell hyperplasia: potential pitfall in somatostatin receptor scintigraphy. Pancreas. 2007;35:372–375.

17. Albers MB, Maurer E, Klöppel G, et al. Pancreatic polypeptide-rich islets in the posterior portion of the pancreatic head—a tumor mimic in somatostatin receptor scintigraphy. Pancreas. 2014;43:648–650.
18. Portela-Gomes GM, Grimelius L, Westermark P, et al. Somatostatin receptor subtypes in human type 2 diabetic islets. Pancreas. 2010;39: 836–842.
19. Floyd JC, Fajans SS, Pek S, et al. A newly recognized pancreatic polypeptide; plasma levels in health and disease. Recent Prog Horm Res. 1976;33: 519–570.
20. Floyd JC. Human pancreatic polypeptide. Clin Endocrinol Metab. 1979;8:379–399.
21. Gepts W, DeMey J,Marichal-PipeleersM. Hyperplasia of "pancreatic polypeptide"cells in the pancreas of juvenile diabetics. Diabetologia. 1977;13:27–34.
22. Stefan Y, Orci L,Malaisse-Lagae F, et al. Quantitation of endocrine cell content in the pancreas of nondiabetic and diabetic humans. Diabetes. 1982;31:694–700.
23. Rahier J, Wallon J, Loozen S, et al. The pancreatic polypeptide cells in the human pancreas: the effects of age and diabetes. J Clin Endocrinol Metab. 1983;56:441–444.
24. Clark A,Wells CA, Buley ID, et al. Islet amyloid, increased A-cells, reduced B-cells and exocrine fibrosis: quantitative changes in the pancreas in type 2 diabetes. Diabetes Res. 1988;9:151–159.
25. Hällgren R, Lundqvist G. Elevated levels of circulating pancreatic polypeptide in inflammatory and infectious disorders. Regul Pept. 1980;1:159–167.
26. Sarikonda G, Pettus J, Phatak S, et al. CD8 T-cell reactivity to islet antigens is unique to type 1 while CD4 T-cell reactivity exists in both type 1 and type 2 diabetes. J Autoimmun. 2014;50:77–82.
27. Rodriguez-Calvo T, Ekwall O, Amirian N, et al. Increased immune cell infiltration of the exocrine pancreas: a possible contribution to the pathogenesis of type 1 diabetes. Diabetes. 2014;63:3880–3890.
28. ButcherMJ, Hallinger D, Garcia E, et al. Association of proinflammatory cytokines and islet resident leucocytes with islet dysfunction in type 2 diabetes. Diabetologia. 2014;57:491–501.
29. Lichtenauer-Kaligis EG, Dalm VA, Oomen SP, et al. Differential expression of somatostatin receptor subtypes in human peripheral blood mononuclear cell subsets. Eur J Endocrinol. 2004;150:565–577.

PART II

THERAPY

CHAPTER 4

Peptide Receptor Radionuclide Therapy of Neuroendocrine Tumors

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Abstract

In the past decades, the number of neuroendocrine tumors that are detected is increasing. A relative new and promising therapy for patients with metastasized or inoperable disease is peptide receptor radionuclide therapy (PRRT). This therapy involves an infusion of somatostatin analogs linked to radionuclides like Yttrium-90 or Lutetium-177. Objective response rates are reported in 15-35%. Response rates may vary between type of tumor and radionuclide. Besides the objective response rate, overall survival and progression free survival increase significantly. Also, the quality of life improves as well. Serious side-affects are rare. PRRT is usually well tolerated, also in patients with extensive metastasized disease. Recent studies combined PRRT with other types of therapies. Unfortunately, no randomized trials comparing these strategies are available. In the future, more research is needed to evaluate the best therapy combinations or sequence of therapies.

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors. These tumors can induce a number of symptoms (e.g. carcinoid syndrome) or can be asymptomatic for a long time. Unfortunately, more than 50% of the patients have metastatic disease at time of presentation. When NETs are metastasized, no curative treatment option is available. Surgery, the only therapeutic option with a curative intent, is reserved for limited disease (no or few metastases). For the large group of patients with metastatic disease different types of treatment were developed in the last decades. One of the most promising is Peptide Receptor Radionuclide Therapy (PRRT). This therapy is based on the fact that the majority of neuroendocrine tumors express the somatostatin receptor (SSTR) on their surface. This receptor is the target for somatostatin analogs (SSA), which is an effective first line treatment for especially midgut NETs in terms of time to progression (1). In the nineties of the past century, the first research groups started with PRRT using SSA labeled with Indium-111 (^{111}In-DTPA-Octreotide) (2,3). This radiopharmaceutical, which emits y-rays, can be used for imaging of neuroendocrine tumors. It also emits Auger electrons, which can be used for therapy. The results of PRRT with ^{111}In-DTPA-Octreotide were reasonable, however the number of patients with a complete or partial response (CR, PR) was low. In the following years, radiolabeled somatostatin analog therapy became more advanced, with the introduction of PRRT with analogs labeled with the β-emitting radionuclides Lutetium-177 or Yttrium-90. In general, PRRT with radiolabeled somatostatin analogs is used mostly for NETs, but can also be used for other somatostatin receptor positive disease such as paragangliomas, meningiomas and iodine refractory thyroid cancer (4-6).

Efficacy in vivo stability of the radiolabeled peptide is an important factor that contributes to its success. For the Yttrium-90 and Lutetium-177 based PRRT, the stable binding of the somatostatin analogs linked to the radionuclide is established via the chelator 1,4,7,10-tetraazacyclotetradecane-1,4,7,10-tetraacetic acid (DOTA). With the use of DOTA, these radionuclides can bind to different somatostatin analogs, such as octreotide or octreotate.

The results of several phase 1/2 studies have been published in the last decade. Different somatostatin analogs with different affinity profiles to the five known subtypes were labeled with Yttrium-90 or Lutetium-177. Although in most studies Yttrium-90 is linked to the analog [Tyr^3]octreotide and Lutetium-177 to the analog [Tyr^3]octreotate, different combinations of analogs and chelators have also been tested. Considering the radionuclides used, there are some differences in physical properties between Yttrium-90 and Lutetium-177. The half-life of Lutetium-177 is 6.7 days versus 2.7 days for Yttrium-90. Furthermore, the tissue penetration of Yttrium-90 is 12 mm and of Lutetium-177 is 2 mm. This longer tissue penetration of Yttrium-90 is especially beneficial in tumors with a heterogeneous receptor expression. The shorter tissue penetration of Lutetium-177 makes this radionuclide probably more suitable to treat also smaller tumors (7). Besides beta-emission, Lutetium-177

Table 1. Efficacy of PRRT

Reference	No. of patients	Tumor type	Reported Response						Criteria of Tumor Response
			CR (%)	PR (%)	MR (%)[a]	SD (%)	PD (%)	CR + PR (%)	
[90Y-DOTA0,Tyr3]octreotide									
Waldherr et al. 2001 (8)	41	GEP and bronchial NET	2	22	N/I	49	15	24	WHO
Valkema et al. 2006 (51)	58	GEP-NET	0	9	12	50	29	9	SWOG
Forrer et al 2006 (52)	116	Metastatic NET	4	23	N/I	62	11	27	WHO
Imhof et al 2011 (9)	1,109	SSTR+	0.6	34.1	N/I	5.2	60.1	34.7	RECIST
Bushnell et al 2010 (53)	90	GEP and bronchial NET	0	4	N/I	70	17	4	SWOG
[90Y-DOTA0,Tyr3]octreotate									
Cwikla et al 2010 (10)	60	GEP-NET	0	23	N/I	77	5	23	RECIST
[177Lu-DOTA0,Tyr3]octreotate									
Kwekkeboom et al. 2008 (14)	310	GEP-NET	2	28	16	35	20	30	SWOG
Bodei et al. 2011 (54)	51	SSTR+	2	27	N/I	26	18	29	RECIST
Ezziddin et al 2014 (55)	68	pNET	0	60	12	12	15	60	SWOG
Sabet et al 2015 (56)	61	Midgut NET	0	13.1	31.1	47.5	8.2	44.2	SWOG

[a], modification of the Southwest Oncology Group (SWOG) criteria including MR (minor remission), between 25 and 50% reduction of tumor size
* SWOG: PR (partial remission), ≥ 30% reduction of tumor size; MR (minor remission), 30% reduction or increase of SD (stable disease), < 30% reduction or increase of < 20% of tumor size; PD (progressive disease), ≥ 20% increase of tumor size or new lesion(s), measurements: bidimensional
* World Health Organization (WHO): PR,≥50% reduction of tumor size; SD, <50% reduction or increase of <25% of tumor size; PD, ≥25% increase of tumor size or new lesion(s). Bidimensional
* Response Evaluation Criteria In Solid Tumors (RECIST): PR, ≥ 50%reduction of tumor size; SD, < 25% reduction or increase of tumor size; PD, > 50% increase of tumor size. Unidimensional
* NA, Not Applicable or Non-Available

also emits y-rays that can be used for imaging in the days after therapy. Therefore, these images can be used to verify the targeted delivery of the radiopharmaceutical and to calculate absorbed dose in organs/tissues and SSTR positive tumors.

Yttrium-90

One of the first studies with PRRT other than ^{111}In-DTPA-Octreotide was published in 2001 by Waldherr et al. (8). Patients with gastroenteropancreatic (GEP-NETs) and bronchial NETs were included and treated with [^{90}Y-DOTA^{0},Tyr^{3}]Octreotide (^{90}Y-DOTATOC). The overall response (complete and partial remission) was 24%. For pancreatic NETs the response was 36%. Since then numerous reports from several research groups involved in PRRT were published (Table 1). The number and type of SSRT positive tumors that were treated varied between the studies. Therefore, interstudy comparison of the outcome reported within these studies remains difficult. The largest group of patients studied (9) (1109 patients) showed a morphological response in 34% of patients. However, it was a mixed group with different types of SSTR positive tumors and patients were treated with different amounts of radioactivity and different kinds of radiolabeled SSA. Cwikla et al. (10) treated 60 patients with GEPNETs with ^{90}Y-DOTATATE. An objective tumor response was observed in 23% and stable disease (SD) in the remaining 77%. Other studies with ^{90}Y-DOTATOC showed comparable results (Table 1).

Lutetium-177

Kwekkeboom et al. were the first to describe PRRT with [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate (^{177}Lu-DOTATATE) in 2003 (11) and reported the outcome of PRRT in a large group of patients in 2005 (12). The reported 131 patients were treated with a cumulative dose of 22.2-29.6 GBq (600-800 mCi). Complete response was reported in 2% of the patients, PR in 26% and minor response (MR) in 19%. Overall the tumor response rate for pancreatic tumors was higher than for other types of SSTR positive tumors.

Figure 1 shows a patient with a good result after PRRT with ^{177}Lu-DOTATATE. Like with ^{90}Y-based PRRT, the published clinical studies on ^{177}Lu-based therapies were conducted in patients with different types of SSTR tumors (see Table 1). Although a randomized trial comparing ^{90}Y- and ^{177}Lu-based PRRT is lacking, it is generally accepted that the tumor responses are more or less similar. Unfortunately, a direct randomized comparison between Yttrium-90 and Lutetium-177 is currently not available. Only one non-randomized study compared PRRT with ^{90}Y-DOTATOC and ^{177}Lu-DOTATOC, and no significant difference in median overall survival was found with either radiolabeled peptide (13). One important

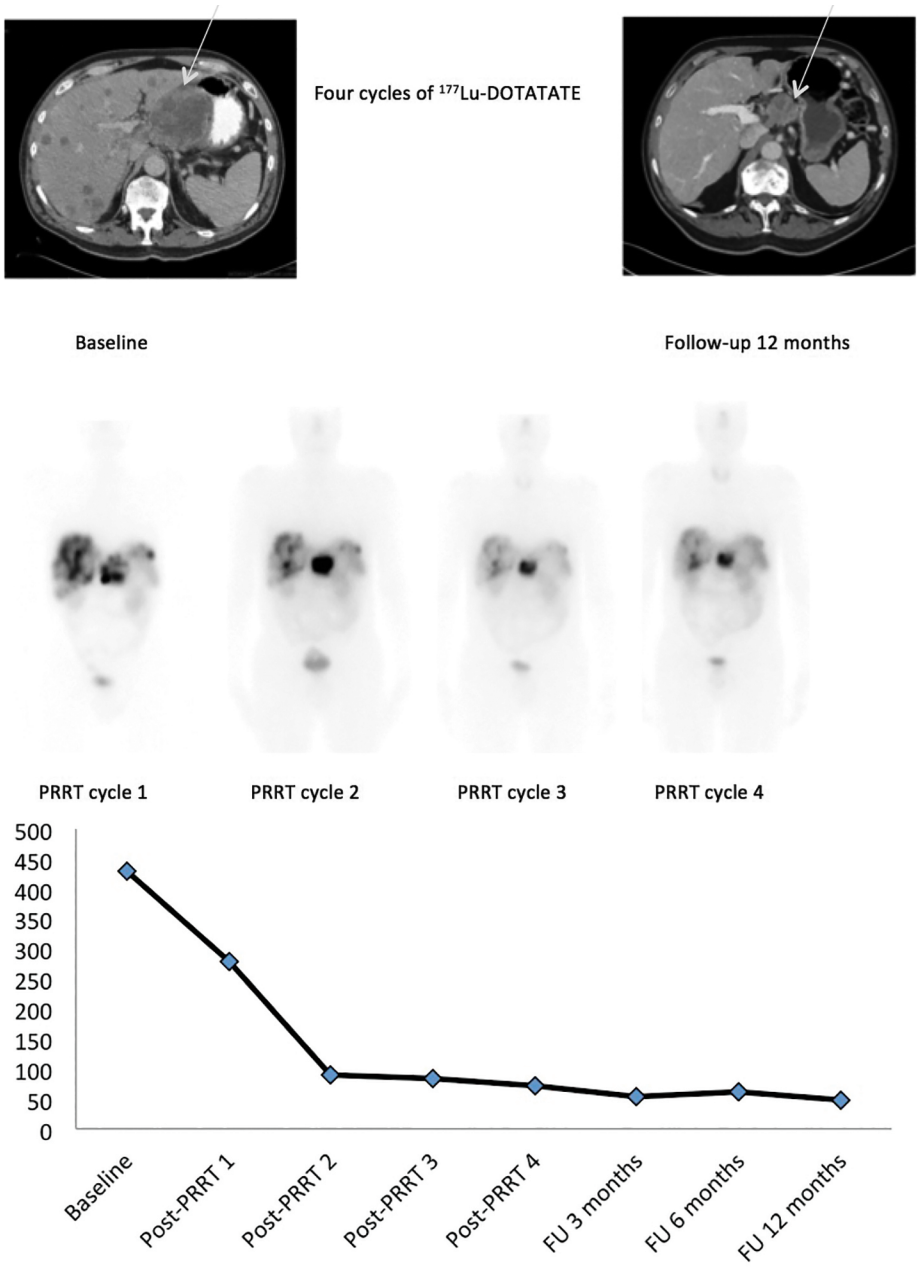

Figure 1. A 60-year-old patient with an insulinoma and liver metastases. A. Upper row: Transverse slices of the diagnostic CT of the abdomen at baseline and 12 months after therapy, showing a large tumor in the pancreas (grew arrow) and liver metastases. Lower row: Planar scintigraphy performed 24 hour postinjection demonstrated high uptake in the pancreatic tumor and liver metastases. During treatment, the intensity in the tumor decreases, indicating tumor response. B. Plot depicts serum chromogranine A (CgA) at baseline, 6 weeks after each administration of PRRT and during follow-up. After therapy, the patient was without any hypoglycemic episodes.

difference between the two studied groups of advanced NET patients, was that patients treated with ^{177}Lu-DOTATOC suffered from less hematological toxicity during follow-up. Other outcome measures, such as progression free survival (PFS) and overall survival (OS), are only reported in a limited number of studies. Median PFS varied from 16 to 33 months and median OS varied from 22 to 53 months (Table 2).

Comparison with the effectiveness of unlabeled SSA is logical since most patients with symptoms of the hormone producing tumors are treated already with unlabeled somatostatin analogs (e.g. octreotide or lanreotide). Besides symptomatic relief, these 'cold' analogs can lengthen the time to tumor progression compared to placebo in patients with midgut NETs as well (1). A large randomized study comparing PRRT (^{177}Lu-DOTATATE) to high-dose Sandostatin LAR in patients with progressive inoperable or metastasized midgut NETs (NETTER-1) was recently concluded in Europe and the USA. The outcome of this unique phase 3 randomized clinical trial is anticipated in the fall of 2015 and will be used to determine the position of PRRT with ^{177}Lu-DOTATATE more clearly in the therapeutic algorithm for this specific patient category. Several clinical factors can predict whether a tumor will respond after therapy with ^{177}Lu-DOTATATE. High uptake on the pretherapeutic somatostatin receptor scintigraphy with ^{111}In-DTPA-octreotide is associated with a good response after therapy. Also, patients without extensive metastases in the liver will respond better than patients with extensive liver metastasis. Conversely, an extensive tumor load and a poor clinical condition are associated with a higher chance of progressive disease (14). PRRT with ^{177}Lu-DOTATATE is mainly used for GEP- NETS, but can be used to treat other somatostatin receptor positive tumors as well, such as paragangliomas, meningiomas and well-differentiated thyroid carcinoma. A limited number of studies showed that the therapy can be effective in such patients. However, the number of patients studied

Table 2. Survival after PRRT

Reference	No. of patients	Tumor type	Median PFS (months)	Median OS (months)
[90Y-DOTA0,Tyr3]octreotide				
Valkema et al 2006 (51)	58	GEP-NET	29	37
Bushnell et al 2010 (53)	90	GEP-NET	16	27
[90Y-DOTA0,Tyr3]octreotate				
Cwikla et al 2010 (10)	58	GEP-NET	17	22
[177Lu-DOTA0,Tyr3]octreotate				
Kwekkeboom et al. 2008 (14)	310	GEP-NET	33	46
Ezziddin et al 2014 (55)	68	pNET	34	53
Sabet et al 2015 (56)	61	Midgut NET	33	61

was limited and therefore further research is needed to evaluate the effectiveness in these tumors (4-6).

Quality of life

Treatment with PRRT is very encouraging in terms of tumor shrinkage, progression free survival and overall survival, but improvement of quality of life (QOL) may be just as important in patients with extensive metastatic disease. A group of Dutch patients completed different questionnaires before and 6 weeks after the last cycle of PRRT, unaware of treatment outcome. After therapy with ^{177}Lu-DOTATATE, insomnia, appetite loss and diarrhea improved significantly (15,16). Besides these symptoms, the global health status/QOL improved significantly as well. Especially patients with bone metastasis had a relief of pain. A similar effect was seen in a small group of 13 patients treated with ^{90}Y-DOTA-TOC or ^{90}Y-DOTA-lanreotide (^{90}Y-DOTALAN) (17). Despite 9 out of the 13 patients had metastasized NETs, patients with SD experienced an improvement in weight, appetite, Karnofsky score and general wellbeing.

Side-effects

Acute side-effects

In general, PRRT is well tolerated. Acute side-effects with ^{177}Lu-DOTATATE as reported in the study by Kwekkeboom et al. (14) are mild and include nausea (in a minority of patients accompanied with vomiting) and mild abdominal pain. These effects are probably caused by the concomitant infusion of amino-acids and occur mostly in the first 24-hours after therapy. Often these side effects are selflimiting or can be treated with anti-emetics. An other sub-acute side-effect is increased hair loss (WHO toxicity grade 1). This was noticed in 64% of the patients treated with ^{177}Lu-DOTATATE. It has not been reported for ^{90}Y-DOTATOC. An other severe but rare complication is a carcinoid crisis. This can be caused by the excessive release of metabolically active amines or peptides. De Keizer et al. [18] described a hormonal crisis in 6 of 479 patients (1%) after treatment with ^{177}Lu-DOTATATE. Three of the six patients developed the crises during or directly after infusion. The other three patients developed the crisis 48 h after infusion. All patients eventually recovered after adequate treatment.

Sub-acute and long-term side-effects

The kidneys and bone marrow are the critical or dose limiting organs due to sub-acute and/or long-term radiation toxicity (Table 3). Radiation-induced bone marrow suppression is

observed frequently at 4-6 weeks after PRRT. This sub-acute hematological toxicity causing a decrease of the platelet count, white blood cell (WBC) count and hemoglobin (Hb), is usually mild and reversible. Most susceptible for the radiation-induced decrease of cell count are the platelets, followed by the white blood cells and Hb level (12). WHO Grade 3/4 toxicity in any of the blood counts occurred in <15% of the treated patients (Table 3). Furthermore, Sierra et al. (19) reported a mild transient toxicity in WBC count in 63%. Grade 2-3 lymphocyte reduction was observed in 88% of treated patients. Fortunately, all toxicity was resolved after 60 days. Although the blood count will recover in the first months of therapy in the majority of patients, some patients will have more severe hematological side-effects resulting in cessation of further cycles of PRRT. Lutetium-177 has a shorter tissue penetration than Yttrium-90 and may therefore, cause less toxicity on the bone marrow (19).

Table 3. Toxicity of PRRT

Reference	No. of patients	Median Follow-up(months)	Severe renal (%)	Hematological Grade 3/4	MDS	AL
[^{90}Y-DOTA^{0},Tyr^{3}]octreotide						
Imhof et al 2011 (9)	1,109	31	9.2	11.3	<1	<1
Bodei et al 2015 (20)	360	30	2.8	14.1	2.35*	1.1*
[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate						
Kwekkeboom et al. 2008 (14)	504	19	<1	3.6	<1	N/A
Gupta et al 2012 (57)	47	6	N/A	4.3	N/A	N/A
Sabet et al 2013 (58)	203	31	0	11.3	1.4	0
Bodei et al 2015 (20)	290	30	0	3.1	2.35*	1.1*

* in the total group patients treated with Y and/or Lu.

Indeed, different studies showed less severe hematological toxicity with PRRT using ^{177}Lu-DOTATATE (Table 3). Grade 3/4 toxicity is reported in approximately 12% of the patients treated with ^{90}Y-DOTATOC, whereas this was observed in 4% of the patients treated with ^{177}Lu-DOTATATE. Serious long-term hematological side-effects are myelodysplastic syndrome (MDS) and acute leukemia (AL). MDS is reported in 1-2% and AL in less than 1% of the patients. A risk factor for the development of MDS is prior treatment with chemotherapy, tumor invasion in the bone marrow and previous use of myelotoxic therapies (20). Also, chemotherapy can cause hematological toxicity and it is impossible to relate the MDS in some patients directly to one of the therapies, since they were treated with multiple cytoreductive therapies. Another risk factor for developing hematological toxicity is an impaired renal function at baseline. Such patients were exposed to a higher renal dose and subsequently were more likely to develop a higher grade of hematological toxicity (14,21).

Another potential clinical problem to take into account is renal toxicity. To decrease the radiation dose on the kidney specific amino-acids are co-administered. Infusion of these positively charged amino acids can reduce the kidney dose up to 40% via the inhibition of tubular reabsorption of the radiopeptide (22-24). Despite the absorbed dose to the kidneys in each patient the development of renal failure after PRRT is extremely rare. However, a retrospective study in 807 patients demonstrated renal toxicity in 35% of the patients. Severe (Grade 3/4) occurred in 1.5% (20). Similar to hematological side-effects, renal toxicity is observed more frequently after therapy with Yttrium-90 and after therapy with the combination of Yttrium-90 and Lutetium-177 than after treatment with Lutetium-177 labeled somatostatin analogs. Especially patients that have a poor renal function before therapy are at risk for severe renal toxicity or renal failure. Other established risk factors include hypertension, diabetes, age (>60 years), renal morphological abnormalities, transarterial chemoembolization and previous chemotherapy with nephrotoxic agents (25).

Alternative PRRT strategies

Despite the fact that the results of PRRT in a monotherapeutic setting are very promising, several groups tried to improve the results by combining PRRT with chemotherapy or using two different radionuclides. The possible synergistic effect of combining two or more therapies to increase the efficacy is supported by the evidence of the successful integration of capecitabine in chemoradiation regimens (26).

Combination of different radionuclides

A combination of ^{177}Lu- and ^{90}Y-labeled somatostatin analogs might be more effective than PRRT with Lutetium-177 or Yttrium-90 alone. The rationale for the usage of the combination is the relatively short pathlength of the medium energy β-emission of Lutetium-177 and the longer pathlength of the high energy of β-emission of Yttrium-90, which may have a maximal impact on small and large tumors, respectively. The first proof of concept was demonstrated in PRRT animal studies in which the combination was superior compared to PRRT with one of the radionuclides (7). Villard et al. (27) treated a large group of 486 patients either with ^{90}Y-DOTATOC monotherapy or with the combination of ^{90}Y-DOTATOC and ^{177}Lu-DOTATOC. Patients who were able to complete three or more treatment cycles of the combination therapy had a significantly longer survival than patients receiving 90Y-DOTATOC alone. However, as it was not a randomized clinical trial, evidence of a real advantage with the combinationtherapy remains to be elucidated (28). Reported severe hematological and renal toxicity were comparable in the two groups.

Combination with chemotherapy

External beam radiotherapy can be combined with 5-fluorouracil (5-FU). In patients with rectal cancer this combination of radiotherapy and 5-FU (or with the prodrug capecitabine) has shown improvement of survival rates (26). It seems obvious that radiosensitising chemotherapy has the potential to enhance the effect of PRRT as well. Increased toxicity could be the major limitation for this combination of PRRT and chemotherapy. However, the first small clinical studies did not show an increase of serious side-effects (29,30). Furthermore, these preliminary studies demonstrated a better response rate compared to PRRT alone. Still, the results of randomized studies have to be awaited before this approach can be adapted as a standard treatment for our patients. Such a study is currently running at Erasmus MC.

Other non-PRRT, combinational therapies have been studied. The combination of capecitabine and temozolomide is used as a first line chemotherapy for metastatic neuroendocrine tumors with reasonable effects (31). In patients with pancreatic NETs an objective response was found in 21 patients (70%). There is not much experience for the combination of these two chemotherapeutic agents and PRRT. Only one study demonstrated a favorable result with a complete response rate in 15%, a partial response in 38% and stable disease in 38%. This study was conducted in a small group of 34 patients and no serious side-effects were reported (32). Nonetheless, these were promising results, but more substantial research is necessary. A potential problem could be an increased hematological toxicity, as both therapies can induce suppression of bone marrow. However, Kesavan et al. (33) monitored patients who were treated with ^{177}Lu-DOTATATE in combination with capecitabine and temozolomide for five years. No significant increased hematological toxicity, including MDS and/or AL, was observed.

Neoadjuvant PRRT

Neoadjuvant PRRT is used mainly for inoperable pancreatic neuroendocrine tumors. Currently, surgery is the only potential curative option for neuroendocrine tumors of the pancreas. Due to metastases or vascular involvement many patients are inoperable at time of diagnosis. If the tumor can be reduced in size by PRRT or limited tumor-load in the liver can be resolved, a curative treatment with surgery might become feasible. There is not much experience with this specific indication for PRRT. However, the few case reports available show promising results (34,35), even in patients with limited metastatic disease. Data from Van Vliet et al. (36) showed successful surgery in 9 of 29 patients treated with neoadjuvant PRRT.

PRRT intra-arterial/loco-regional liver

It is not uncommon for patients with neuroendocrine tumors to have metastases predominantly or solely located in the liver. The disadvantage of 'normal' PRRT administered intravenously is the high radiation dose delivered to healthy tissue or organs. In theory, administration of the radiopharmaceutical directly into the hepatic artery should enable an increase of uptake of the radiolabeled peptide in the liver (the so called "first-pass" effect), and thereby reduce the dose to the remainder of the body. Pool et al. (37) demonstrated a two-fold higher tumor uptake of ^{111}In-DTPA-octreotide after intraarterial (i.a.) administration than after intravenous (i.v.) administration. The renal dose, however, was not significantly lowered. A small group of 17 patients from Greece (38) were treated with ^{111}In-DTPA-octreotide i.a. as well. Complete response was achieved in one patient (5.9%) and partial response in eight (47%). These results are much better than was published with the first PRRT studies with ^{111}In-DTPA-octreotide administrated i.v. (2,3). The next logical step was to use beta-emitting radionuclides to treat this category NET patients intra-arterially. McStay et al. (39) treated 23 patients with ^{90}Y-DOTA-Lanreotide i.a. Partial responses were achieved in three (16%) and stable disease in 12 (63%) of 19 patients. Hematological toxicity occurred in three patients, but was reversible. Furthermore, Kratochwil et al. (40) treated a small group of patients with intra-arterial ^{90}Y-DOTATOC or ^{177}Lu-DOTATOC and found a complete response in one patient (7%) and a partial response in 8 (53%). Overall, the results of i.a. administration are promising, but only pilot studies with limited number of patients have been published. More research in larger groups of patients and in a randomized setting is warranted before this alternative option in this specific group of NET patients to introduce this novel approach into the standard of clinical care.

PRRT salvage therapy

Unfortunately most patients will become progressive after a favorable response induced by the initial series of cycles of PRRT. Currently, when progressive disease becomes evident only few proven effective therapeutic options are available. One alternative treatment option may be treatment with additional cycles of PRRT, if initial PRRT showed benefit in a patient. Reports on studies with only a limited number of retreated patients showed that it is not only feasible to retreat these patients with PRRT in terms of safety and toxicity, but is a serious option to consider when better alternatives are not available. In this 'salvage' therapy setting, Forrer et al. (41) retreated 27 patients after an initial favorable response to therapy with ^{90}Y-DOTATOC with ^{177}Lu-DOTATOC. Patients received only one additional cycle of 7.4 GBq of ^{177}Lu-DOTATOC. Only 8 (30%) patients had PD 8-12 weeks after therapy. No significant changes in hemoglobin and creatinine were observed. Van Essen et al. (42) reported the results in 33 patients who had PD and were retreated with two additional cycles of ^{177}Lu-DOTATATE (7.4-14.8 GBq). After a median follow-up of 16 months 18 (55%) patients had a response or stable disease. Sabet et al. (43) found comparable results

in a group of 33 patients treated with a median two treatment courses per patient. In 67% of patients the salvage therapy resulted in a response or stable disease of after a median follow-up of 27 months from the start of salvage PRRT. Overall, the response rate was not as good as after the initial cycles of PRRT. However, to compare the response rates mentioned within these PRRT salvage studies to the PRRT studies reporting the outcome of initial PRRT cycles is not appropriate. Differences can be found in the number of patients who had PD, since all included patients in the salvage setting had PD at the time of inclusion. Furthermore, patients were treated with less cycles of PRRT. In the initial treatment, the majority of patients received either two or three cycles of ^{90}Y-DOTATOC and either three or four cycles of ^{177}Lu-DOTATATE. These differences might be responsible for the fact that the results of additional cycles of PRRT are not as encouraging as the initial series of PRRT cycles in terms of objective tumor response and PFS. Nonetheless, as there are no good alternative treatments, PRRT as a salvage therapy should be considered in patients who are progressive and responded well to the initial cycles of PRRT.

Future developments

More research is necessary to improve PRRT further with the goal of higher response rates and more durable response. An important goal to achieve this is to induce higher uptake of the radiopharmaceutical and thereby a higher absorbed dose in the tumors. Studies with the previously mentioned method of i.a. administration of the radiopharmaceutical are promising, although no randomized studies are available.

A new strategy to increase the tumor dose is the use of somatostatin antagonists. Since the introduction of PRRT it was generally accepted that an ideal peptide for PRRT has to be internalized to increase its residence time. However, surprisingly, Ginj et al. (44) found significant higher doses of radioactivity in vivo in tumors in mice with the somatostatin antagonists ^{111}In-DOTA-sst3-ODN-8 and ^{111}In-DOTA-sst2-ANT compared to agonists. Also, when coupled to Lutetium-177 a higher dose could be accomplished in vitro in SST2R-expressing human tumor samples (45). A recent pilot study in 4 patients showed a 1.7-10.6 times higher tumor dose using the antagonist ^{177}Lu-DOTA-JR11 compared to ^{177}Lu-DOTATATE. Only minor reversible adverse effects were observed.

A different promising new technique is the use of alpha emitting radiolabeled somatostatin analogs. Alpha emitting radionuclides such as Bismuth-213 have a shorter tissue path-length in comparison with β-emitting radionuclides. The path-range of an alpha particle is approximately 50-100 mm, about two or three cell diameters. Within this short path range all energy is absorbed by the tissue and more DNA damage will be induced compared to beta-emitters. Another advantage is a limited absorbed dose on other, healthy tissue. A pilot study was conducted in seven patients who had PD after initial ^{90}Y/^{177}Lu-DOTATOC

therapy and who were treated with intra-arterial infusion of ^{213}Bi-DOTATOC (46). One patient was treated with ^{213}Bi-DOTATOC intravenously. The results of this study are very promising with an objective response or stable disease in all patients after a follow-up of at least 12 months. Acute hematotoxicity was even less pronounced than PRRT using β-emitting radionuclides. The alkylating agent temozolomide followed by PRRT is also an interesting therapeutic approach. Preclinical studies by Bison et al. (47) demonstrated that a pre-treatment for 14 days with temozolomide resulted in an increase in tumor perfusion as measured by MRI. Subsequently, this increase in perfusion resulted in a significant higher uptake in the tumor. Therefore, temozolomide treatment prior to PRRT might be a good option to increase the tumor response in NET patients.

In the last decade, new targeted therapies such as sunitinib (a tyrosine kinase inhibitor) and everolimus (an inhibitor of mammalian target of rapamycin (mTOR)) were registered for (metastatic) neuroendocrine tumors of the pancreas. In a recent systematic review the different non-surgical treatments for pancreatic NETs were evaluated (48). Unfortunately, there are only a few randomized clinical trials (RCT's) and the included group of patients within these trials are very heterogeneous. Therefore, it is impossible to compare the results of different studies. Overall, the targeted therapies result in a longer PFS of 11.4 months compared to placebo 5.5 months for sunitinib and 11.0 versus 4.6 months for everolimus (49,50). In the future it is important to compare targeted therapies to PRRT in a RCT. Besides a direct comparison, a combination of PRRT with one of these compounds is also an interesting topic for future research.

Summary

PRRT is a good treatment option for patients with metastasized neuroendocrine tumors. Reported response rates for the different β-emitting radionuclides Lutetium-177 and Yttrium-90 are similar, but a slightly higher toxicity is reported in patients treated with Yttrium-90. Beside the reported favorable responses and increased survival rate, PRRT increases the quality of life of patients. In the last decade variants have been proposed to optimize the treatment and increase the response and survival rates. The combination of PRRT and radiosensitising chemotherapy may be very promising. For patients with a predominance of liver metastases, the possibility to administer the radioactivity directly in the hepatic artery in an attempt to optimize dose-delivery has been studied. This localized procedure increases the tumor uptake in the liver metastases and therefore may show better results in terms of tumor response. Large, randomized studies are necessary to compare PRRT to the new targeted therapies, such as sunitinib and everolimus for NET patients. Meanwhile, research is on-going to develop PRRT that is superior to the current PRRT available in terms of objective response and survival, such as PRRT with the use of somatostatin agonists, with alpha emitting radionuclides, or radiolabeled somatostatin antagonists. For patients

who had a favorable response after the initial cycles of PRRT but progressed, salvage therapy is a feasible option in terms of therapeutic efficacy and safety.

PRACTICE POINTS

- PRRT using somatostatin analogs labeled with β-emitting radionuclides, such as Yttrium-90 or Lutetium-177 can induce tumor shrinkage.
- Radiation-induced toxicity is rare; severe hematological toxicity and kidney failure is seen in less than 5% of patients.
- Patients with a favorable outcome after PRRT are likely to have their quality of life improved
- PRRT can be applied successfully in the neo-adjuvant setting.
- Patients with PD after a good initial response can benefit from salvage therapy with additional cycles of PRRT.

RESEARCH AGENDA

- Use of somatostatin analogs labeled with alpha emitting radionuclides.
- Increasing the tumor uptake by replacing the somatostatin agonists with antagonists.
- Intra-arterial administration of radiolabeled somatostatin analogs for patients with a predominance of liver metastases.
- The combination of targeted therapies, such as sunitinib and everolimus, and PRRT.

References

1. Rinke A, Muller H-H, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009;27:4656e63. http://dx.doi.org/10.1200/JCO.2009.22.8510.
2. Valkema R, de Jong M, Bakker WH, et al. Phase I study of peptide receptor radionuclide therapy with [In-DTPA0] octreotide: the Rotterdam experience. Semin Nucl Med 2002;XXXII:110e22.
3. Anthony LB, Woltering EA, Espenan GD, et al. Indium-111-pentetreotide prolongs survival in gastroenteropancreatic malignancies. Semin Nucl Med 2002;XXXII:123e32.
4. Van Essen M, Krenning EP, Kooij PP, et al. Effects of therapy with [177Lu-DOTA0, Tyr3] octreotate in patients with paraganglioma, meningioma, small cell lung carcinoma, and melanoma. J Nucl Med 2006;47:1599e606.
5. Marincek N, Radojewski P, Dumont RA, et al. Somatostatin receptor-targeted radiopeptide therapy with 90Y-DOTATOC and 177Lu-DOTATOC in progressive meningioma: long-term results of a phase II clinical trial. J Nucl Med 2015;56:171e6. http://dx.doi.org/10.2967/jnumed.114.147256.
6. Teunissen JJM, Kwekkeboom DJ, Krenning EP. Staging and treatment of differentiated thyroid carcinoma with radiolabeled somatostatin analogs. Trends Endocrinol Metab 2006;17:19e25. http://dx.doi.org/10.1016/j.tem.2005.11.005.
7. De Jong M, Breeman WAP, Valkema R, et al. Combination radionuclide therapy using 177Lu- and 90Y-labeled somatostatin analogs. J Nucl Med 2005;46(Suppl. 1):13Se7S.
8. Waldherr C, Pless M, Maecke HR, et al. The clinical value of [90Y-DOTA]-D-Phe1-Tyr3-octreotide (90Y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study. Ann Oncol 2001;12:941e5.
9. Imhof A, Brunner P, Marincek N, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol 2011;29:2416e23. http://dx.doi.org/10.1200/JCO.2010.33.7873.
10. Cwikla JB, Sankowski A, Seklecka N, et al. Efficacy of radionuclide treatment DOTATATE Y-90 in patients with progressive metastatic gastroenteropancreatic neuroendocrine carcinomas (GEP-NETs): a phase II study. Ann Oncol 2010;21:787e94. http://dx.doi.org/10.1093/annonc/mdp372.
11. Kwekkeboom DJ, Bakker WH, Kam BL, et al. Treatment of patients with gastro-entero-pancreatic (GEP) tumours with the novel radiolabelled somatostatin analogue [177Lu-DOTA(0),Tyr3] octreotate. Eur J Nucl Med Mol Imaging 2003;30:417e22. http://dx.doi.org/10.1007/s00259-002-1050-8.
12. Kwekkeboom DJ. Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]Octreotate in patients with endocrine gastroenteropancreatic tumors. J Clin Oncol 2005;23:2754e62. http://dx.doi.org/10.1200/JCO.2005.08.066.
13. Romer A, Seiler D, Marincek N, et al. Somatostatin-based radiopeptide therapy with [177Lu-DOTA]-TOC versus [90YDOTA]-TOC in neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2014;41:214e22. http://dx.doi.org/10.1007/s00259-013-2559-8.

14. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177Lu- DOTA0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008;26:2124e30. http://dx.doi.org/10.1200/JCO.2007.15.2553.
15. Teunissen JJM, Kwekkeboom DJ, Krenning EP. Quality of life in patients with gastroenteropancreatic tumors treated with [177Lu-DOTA0,Tyr3]octreotate. J Clin Oncol 2004;22:2724e9. http://dx.doi.org/10.1200/JCO.2004.10.016.
16. Khan S, Krenning EP, van Essen M, et al. Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0,Tyr3]octreotate. J Nucl Med 2011;52:1361e8. http://dx.doi.org/10.2967/jnumed.111.087932.
17. Traub-Weidinger T, Uffmann M, Kurtaran A, et al. Improved quality of life in patients treated with peptide radionuclides. World J Nucl Med 2011;10:115. http://dx.doi.org/10.4103/1450-1147.89779.
18. De Keizer B, van Aken MO, Feelders RA, et al. Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [177Lu-DOTA0,Tyr3]octreotate. Eur J Nucl Med Mol Imaging 2008;35:749e55. http://dx.doi.org/10.1007/s00259-007-0691-z.
19. Sierra ML, Agazzi A, Bodei L, et al. Lymphocytic toxicity in patients after peptide-receptor raionuclide therapy (PRRT) with 177Lu-DOTATATE and 90Y-DOTATOC. Cancer Biother Radiopharm 2009;24.
20. Bodei L, Kidd M, Paganelli G, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging 2015;42:5e19. http://dx.doi.org/10.1007/s00259-014-2893-5.
21. Svensson J, Berg G, W€angberg B, et al. Renal function affects absorbed dose to the kidneys and haematological toxicity during 177Lu-DOTATATE treatment. Eur J Nucl Med Mol Imaging 2015. http://dx.doi.org/10.1007/s00259-015-3001-1.
22. Rolleman EJ, Valkema R, de Jong M, et al. Safe and effective inhibition of renal uptake of radiolabelled octreotide by a combination of lysine and arginine. Eur J Nucl Med Mol Imaging 2003;30:9e15. http://dx.doi.org/10.1007/s00259-002-0982-3.
23. Jamar F, Barone R, Mathieu I, et al. 86Y-DOTA0)-D-Phe1-Tyr3-octreotide (SMT487)ea phase 1 clinical study: pharmacokinetics, biodistribution and renal protective effect of different regimens of amino acid co-infusion. Eur J Nucl Med Mol Imaging 2003;30:510e8. http://dx.doi.org/10.1007/s00259-003-1117-1.
24. Bodei L, Cremonesi M, Zoboli S, et al. Receptor-mediated radionuclide therapy with 90Y-DOTATOC in association with amino acid infusion: a phase I study. Eur J Nucl Med Mol Imaging 2003;30:207e16. http://dx.doi.org/10.1007/s00259-002-1023-y.
25. Bodei L, Cremonesi M, Ferrari M, et al. Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with 90Y-DOTATOC and 177Lu-DOTATATE: the role of associated risk factors. Eur J Nucl Med Mol Imaging 2008;35:1847e56. http://dx.doi.org/10.1007/s00259-008-0778-1.
26. Glynne-Jones R, Dunst J, Sebag-Montefiore D. The integration of oral capecitabine into chemoradiation regimens for locally advanced rectal cancer: how successful have we been? Ann Oncol 2006;17:361e71. http://dx.doi.org/10.1093/annonc/mdj052.

27. Villard L, Romer A, Marincek N, et al. Cohort study of somatostatin-based radiopeptide therapy with [90Y-DOTA]-TOC versus [90Y-DOTA]-TOC plus [177Lu-DOTA]-TOC in neuroendocrine cancers. J Clin Oncol 2012;30:1100e6. http://dx. doi.org/10.1200/JCO.2011.37.2151.
28. Kwekkeboom DJ. Therapy: neuroendocrine cancereare two radionuclides better than one? Nat Rev Endocrinol 2012;8: 326e8. http://dx.doi.org/10.1038/nrendo.2012.64.
29. Van Essen M, Krenning EP, Kam BL, et al. Report on short-term side effects of treatments with 177Lu-octreotate in combination with capecitabine in seven patients with gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2008;35:743e8. http://dx.doi.org/10.1007/s00259-007-0688-7.
30. Claringbold PG, Brayshaw PA, Price RA, et al. Phase II study of radiopeptide 177Lu-octreotate and capecitabine therapy of progressive disseminated neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2011;38:302e11. http://dx.doi.org/10.1007/s00259-010-1631-x.
31. Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer 2011;117:268e75. http://dx.doi.org/10.1002/cncr.25425.
32. Claringbold PG, Price RA, Turner JH. Phase I-II study of radiopeptide 177Lu-octreotate in combination with capecitabine and temozolomide in advanced low-grade neuroendocrine tumors. Cancer Biother Radiopharm 2012;27:561e9. http://dx.doi.org/10.1089/cbr.2012.1276.
33. Kesavan M, Claringbold PG, Turner JH. Hematological toxicity of combined 177Lu-octreotate radiopeptide chemotherapy of gastroenteropancreatic neuroendocrine tumors in long-term follow-up. Neuroendocrinology 2014;99:108e17. http://dx.doi.org/10.1159/000362558.
34. Kaemmerer D. Neoadjuvant peptide receptor radionuclide therapy for an inoperable neuroendocrine pancreatic tumor. World J Gastroenterol 2009;15:5867. http://dx.doi.org/10.3748/wjg.15.5867.
35. Stoeltzing O, Loss M, Huber E, et al. Staged surgery with neoadjuvant 90Y-DOTATOC therapy for down-sizing synchronous bilobular hepatic metastases from a neuroendocrine pancreatic tumor. Langenbeck's Arch Surg 2010;395:185e92.http://dx.doi.org/10.1007/s00423-009-0520-x.
36. Van Vliet EI, van Eijck CH, de Krijger RR, et al. Neoadjuvant treatment of nonfunctioning pancreatic neuroendocrine tumors with [177Lu-DOTA0,Tyr3]octreotate. J Nucl Med 2015. http://dx.doi.org/10.2967/jnumed.115.158899.
37. Pool SE, Kam BLR, Koning GA, et al. [111in-DTPA]octreotide tumor uptake in GEPNET liver metastases after intra-arterial administration: an overview of preclinical and clinical observations and implications for tumor radiation dose after peptide radionuclide therapy. Cancer Biother Radiopharm 2014;29:179e87. http://dx.doi.org/10.1089/cbr.2013.1552.
38. Limouris GS, Chatziioannou A, Kontogeorgakos D, et al. Selective hepatic arterial infusion of In-111-DTPA-Phe1-octreotide in neuroendocrine liver metastases. Eur J Nucl Med Mol Imaging 2008;35:1827e37. http://dx.doi.org/10.1007/s00259-008-0779-0.
39. McStay MKG, Maudgil D, Williams M, et al. Large-volume liver metastases from neuroendocrine tumors: hepatic intraarterial 90Y-DOTA-lanreotide as effective palliative therapy. Radiology 2005;237:718e26. http://dx.doi.org/10.1148/radiol.2372041203.

40. Kratochwil C, Lopez-Benitez R, Mier W, et al. Hepatic arterial infusion enhances DOTATOC radiopeptide therapy in patients with neuroendocrine liver metastases. Endocr Relat Cancer 2011;18:595e602. http://dx.doi.org/10.1530/ERC-11-0144.
41. Forrer F, Uusij€arvi H, Storch D, et al. Treatment with 177Lu-DOTATOC of patients with relapse of neuroendocrine tumors after treatment with 90Y-DOTATOC. J Nucl Med 2005;46:1310e6.
42. Van Essen M, Krenning EP, Kam BLR, et al. Salvage therapy with 177Lu-Octreotate in patients with bronchial and gastroenteropancreatic neuroendocrine tumors. J Nucl Med 2010;51:383e90. http://dx.doi.org/10.2967/jnumed.109.068957.
43. Sabet A, Haslerud T, Pape U-F, et al. Outcome and toxicity of salvage therapy with 177Lu-octreotate in patients with metastatic gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2014;41:205e10. http://dx.doi.org/10.1007/s00259-013-2547-z.
44. Ginj M, Zhang H, Waser B, et al. Radiolabeled somatostatin receptor antagonists are preferable to agonists for in vivo peptide receptor targeting of tumors. Proc Natl Acad Sci U S A 2006;103:16436e41. http://dx.doi.org/10.1073/pnas.0607761103.
45. Cescato R, Waser B, Fani M, et al. Evaluation of 177Lu-DOTA-sst2 antagonist versus 177Lu-DOTA-sst2 agonist binding in human cancers in vitro. J Nucl Med 2011;52:1886e90. http://dx.doi.org/10.2967/jnumed.111.095778.
46. Kratochwil C, Giesel FL, Bruchertseifer F, et al. 213Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience. Eur J Nucl Med Mol Imaging 2014;41:2106e19. http://dx.doi.org/10.1007/s00259-014-2857-9.
47. Bison S, Haeck J, Koelewijn S, et al. Optimization of combination of peptide receptor radionuclide therapy (PRRT) and temozolomide therapy using SPECT/CT and MRI in mice. Eur J Nucl Med Mol Imaging;40(Supp. l2):S290. (abstract) n.d.
48. Valle JW, Eatock M, Clueit B, et al. A systematic review of non-surgical treatments for pancreatic neuroendocrine tumours. Cancer Treat Rev 2014;40:376e89. http://dx.doi.org/10.1016/j.ctrv.2013.08.007.
49. Raymond E, Dahan L, Raoul J-L, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501e13. http://dx.doi.org/10.1056/NEJMoa1003825.
50. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514e23. http://dx.doi.org/10.1056/NEJMoa1009290.
51. Valkema R, Pauwels S, Kvols L, et al. Survival and response after peptide receptor radionuclide therapy with [90YDOTA0, Tyr3]octreotide in patients with advanced gastroenteropancreatic neuroendocrine tumors. Semin Nucl Med 2006;36:147e56. http://dx.doi.org/10.1053/j.semnuclmed.2006.01.001.
52. Forrer F, Waldherr C, Maecke HR, et al. Targeted radionuclide therapy with 90Y-DOTATOC in patients with neuroendocrine tumors. Anticancer Res 2006;26:703e7.
53. Bushnell DL, O'Dorisio TM, O'Dorisio MS, et al. 90Y-edotreotide for metastatic carcinoid refractory to octreotide. J Clin Oncol 2010;28:1652e9. http://dx.doi.org/10.1200/JCO.2009.22.8585.
54. Bodei L, Cremonesi M, Grana CM, et al. Peptide receptor radionuclide therapy with 177Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging 2011;38:2125e35. http://dx.doi.org/10.1007/s00259-011-1902-1.

55. Ezziddin S, Khalaf F, Vanezi M, et al. Outcome of peptide receptor radionuclide therapy with 177Lu-octreotate in advanced grade 1/2 pancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2014;41:925e33. http://dx.doi.org/10.1007/s00259-013-2677-3.
56. Sabet A, Dautzenberg K, Haslerud T, et al. Specific efficacy of peptide receptor radionuclide therapy with (177)Luoctreotate in advanced neuroendocrine tumours of the small intestine. Eur J Nucl Med Mol Imaging 2015. http://dx.doi.org/10.1007/s00259-015-3041-6.
57. Gupta SK, Singla S, Bal C. Renal and hematological toxicity in patients of neuroendocrine tumors after peptide receptor radionuclide therapy with 177Lu-DOTATATE. Cancer Biother Radiopharm 2012;27:593e9. http://dx.doi.org/10.1089/cbr.2012.1195.
58. Sabet A, Ezziddin K, Pape U-F, et al. Long-term hematotoxicity after peptide receptor radionuclide therapy with 177Lu-Octreotate. J Nucl Med 2013;54:1857e61. http://dx.doi.org/10.2967/jnumed.112.119347.

4

CHAPTER 5

Long-term efficacy, survival and safety of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors

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Abstract

Purpose

Bronchial and gastroenteropancreatic neuroendocrine tumors (NETs) are slow-growing tumors, which frequently express somatostatin receptors on their cell membranes. These receptors are targets for therapy with Lutetium-177-labeled somatostatin analogs. We have treated over 1200 patients with peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-DOTATATE) since the year 2000 and present the results on efficacy, survival and toxicity of this therapy.

Patients and methods

For safety analysis, 610 patients treated with a cumulative dose of at least 100 mCi (3.7 GBq) ^{177}Lu-DOTATATE were included. A subgroup of 443 Dutch patients who were treated with a cumulative dose of at least 600 mCi (22.2 GBq) ^{177}Lu-DOTATATE before 2013 was further analyzed for efficacy and survival.

Results

The objective response rate (ORR) of the total group of patients was 39%. Stable disease (SD) was reached in 43% of patients. Progression free survival (PFS) and overall survival (OS) for all NET patients were 29 months (95% CI 26-33 months) and 63 months (95% CI 55-72 months). Long-term toxicity included acute leukemia in 4 patients (0.7%) and myelodysplastic syndrome in 9 patients (1.5%). No therapy-related long-term renal or hepatic failure occurred.

Conclusion

PRRT with ^{177}Lu-DOTATATE is a favorable therapeutic option in patients with metastatic bronchial and gastroenteropancreatic NETs that express somatostatin receptors. PRRT with ^{177}Lu-DOTATATE is safe with few side-effects and shows a good response rates with PFS of 29 months and OS of 63 months.

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors. A subset of this slow-growing tumor type are the gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and bronchial NETs (1). Unfortunately, the majority of GEP-NET patients have metastatic disease at time of presentation (2). Over the past decades, the incidence of GEP-NETs is rising. After the introduction of new therapies, the 5-years survival has significantly improved (3). This improvement is partly due to first-line therapy with long-acting somatostatin analogs (Octreotide LAR, Lanreotide Autogel) and targeted therapies (e.g. everolimus and sunitinib), which are approved second-line therapies for patients with progressive inoperable GEP NETs (sunitinib only being approved in pancreatic NET) (4,5). For gastroenteropancreatic and bronchial NETs, Peptide receptor radionuclide therapy (PRRT) with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-DOTATATE) has yielded very promising results. This therapy is based on the fact that the majority of these NETs express a high number of high affinity somatostatin receptors on their cell membranes. These receptors can be used for both imaging and therapy with radiolabeled somatostatin analogs (6). For therapy, the beta-emitting radionuclide Lutetium-177, with a half-life of 6.7 days and a maximum beta range of 2 mm in tissue, can be used. These parameters makes Lutetium-177 the ideal radionuclide for PRRT. Treatment with beta-emitting radiolabeled somatostatin analogs results in impressive percentages of tumor regression (7–10). Also, success monitored as time to progression (TTP), progression free survival (PFS) and overall survival (OS) has been reported in uncontrolled studies (8,11). With the recent publication of the promising results of the NETTER-1 trial (12), the first phase III trial comparing ^{177}Lu-DOTATATE to high dose Octreotide LAR therapy in patients with inoperable metastatic midgut NETs, it may be expected that the use of this therapy will increase in the coming years. We have previously reported on the treatment with the radiolabeled somatostatin analog ^{177}Lu-DOTATATE (8), and have compared the side-effects and the results of this treatment with other treatment modalities and historical controls. Righteously, critical commentary arose, as to the validity of the comparisons with historical controls. Also, the high number of foreign patients that we have treated, and of whom a significant number was lost to follow-up might bias the percentage of reported severe adverse events. We, therefore, present now the long-term results of efficacy, survival and toxicity of PRRT with ^{177}Lu-DOTATATE in a cohort of more than 500 Dutch patients with metastastic GEP-NETs and bronchial NETs, who all had their follow-up at our institution.

Patients and methods

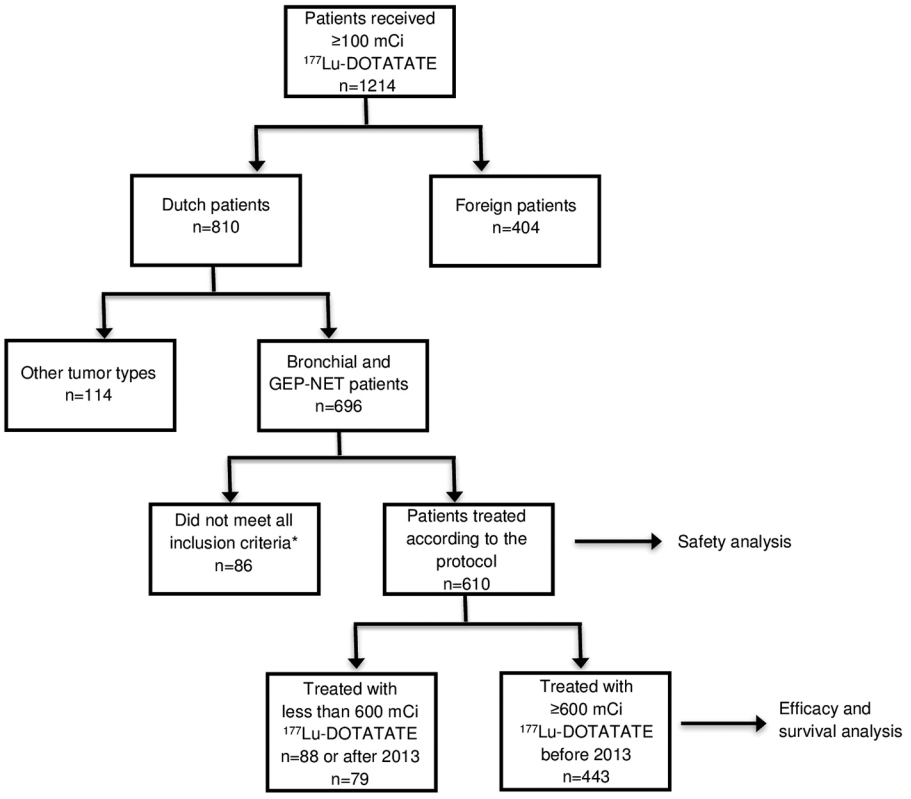
Patients

A total of 1214 patients were treated with ^{177}Lu-DOTATATE from January 2000 to January 2015 in our institution. We selected only Dutch patients with NETs of the midgut, foregut, hindgut and unknown primary that were treated according to a standard protocol, because of the very limited loss in follow-up in this subgroup. For safety evaluation, all patients who received at least 100 mCi (3.7 GBq) ^{177}Lu-DOTATATE were selected. For the evaluation of efficacy, patients who received at least 600 mCi (22.2 GBq) ^{177}Lu-DOTATATE before 2013 were investigated. Patients treated after 2013 returned to their referring specialist in a different institute after therapy, and imaging was not performed according to our study protocol. For safety analysis 610 patients were available and 443 patients for efficacy and survival analysis (Figure 1). For analysis of efficacy, NET types were divided into bronchial, pancreatic, (other) foregut, hindgut, midgut and NET of unknown origin. Other foregut NETs included: 5 NETs of the stomach, 5 NETs of the proximal duodenum and 2 NETs of the thymus. For comparison with the NETTER-1 study (12) 106 patients with progressive midgut NETs who received a cumulative dose of ≥100 mCi (3.7 GBq) ^{177}Lu-DOTATATE were selected. Patients were treated with ^{177}Lu-DOTATATE if the tumor uptake was at least as high as the uptake in the normal parenchyma of the liver on ^{111}In-DTPA-octreotide scintigraphy (OctreoScan) prior to the therapy. Other inclusion criteria were serum hemoglobin ≥ 6.0 mmol/L (≥ 9.7 g/dL), total white blood cell (WBC) count ≥ $2 \cdot 10^9$/L, platelet count ≥ $75 \cdot 10^9$/L, serum creatinine concentration ≤ 150 umol/L (≤ 1.7 mg/dL) - or creatinine clearance ≥ 40 mL/min until 2007 or 50 mL/min from 2007, serum albumin >30 g/L, Karnofsky performance status (KPS) ≥ 50 and no prior treatment with other radiolabeled somatostatin analogs. Preliminary results in a subgroup of these patients with GEP-NETs were reported previously (8). All patients gave written informed consent to participate in the study, which was approved by the medical ethical committee of our hospital.

Methods

[DOTA^0,Tyr^3]octreotate was obtained from BioSynthema, St Louis, MO. $^{177}LuCl_3$ was distributed by IDB-Holland, Baarle-Nassau, the Netherlands. ^{177}Lu-DOTATATE was locally prepared as described previously (13). Before the infusion of the radiopharmaceutical, Granisetron 3 mg or Ondansetron 8 mg was injected intravenously (iv). To reduce the radiation dose to the kidneys, an iv infusion of amino acids (2.5% arginine and 2.5% lysine in 1L 0.9% NaCl) was started 30 min before the administration of the radiopharmaceutical and lasted for 4 h. The radiopharmaceutical was co-administered iv using a second pump system over 30 min. The intended interval between treatments was 6–10 weeks. The treatment interval could be extended to 16 weeks in patients with longer continuing subacute hematological toxicity. Patients were treated up to a cumulative intended dose of 750 to 800 mCi (27.8–29.6 GBq) ^{177}Lu-DOTATATE.

Routine hematology, liver, and kidney function tests were performed after each therapy cycle and at follow-up visits at 6 weeks, 3 months and 6 months after the last treatment cycle, and thereafter at 6 month intervals. Computed tomography (CT), or magnetic resonance imaging (MRI) was performed within 3 months before the first therapy, and at every follow-up visit. Every patient was seen at the outpatient clinic by one of the investigators and a research nurse. A case report form (CRF) was completed at every follow-up visit.



*Exclusion criteria:

Creatinine >150 umol/L (> 1.7 mg/dL)	n=5
Creatinine clearance <40 ml/min	n=3
Thrombocytes <75x10^9/L	n=4
Albumin <30 g/L	n=13
Uptake Octreoscan <2	n=10
Karnofsky performance status <50	n=2
Data not complete	n=49

Figure 1. Flowchart for the selection of patients.

In Vivo Measurements

Tumor response was assessed on CT or MRI according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) criteria (14). Radiological disease control was defined as all patients achieving objective response (OR) or stable disease (SD) in patients with progressive disease (PD) at baseline. Uptake on the OctreoScan was scored on planar images using a 4-point scale; grade 1: less than the uptake in the normal parenchyma of the liver, grade 2: equal to the liver, grade 3: greater uptake than the liver, grade 4: higher than the uptake in the normal spleen or kidneys. The whole body extent of disease was scored by experienced nuclear medicine physicians as: limited, moderate or extensive on OctreoScan as described previously (15).

Outcomes

PFS was defined as the time from first day of treatment until day of ascertainment of objective progression or death from any cause. The TTP was calculated from the first day of treatment to the day of documented progression. Deaths were censored in the TTP analyses. OS was calculated from the first day of treatment until the day of death, or until the last date of follow-up for patients who were lost to follow-up (16). Toxicity was scored according to the Common Terminology Criteria for Adverse Events 4.0 (CTCAE) scoring system (17).

Statistics

For survival analysis, log-rank tests and Cox regression models were used. PFS and OS analyzes were performed using the Kaplan-Meier method. Comparison between subgroups was made using χ^2-test (or if applicable Fisher exact test), ANOVA or paired t-tests. P-values lower than 0.05 were considered to be significant.

Results

For safety outcome 610 patients who received ≥100 mCi (3.7 GBq) ^{177}Lu-DOTATATE were analyzed. Median follow-up time was 64 months (95% CI 58-70 months). Mean age was 60.4 years (range 23-88). The median TTP was 35 months (95% CI 32-39 months) and the median OS was 58 months (95% CI 52-64 months).

CTCAE grade 3/4 toxicity of the combination of the following hematologic parameters occurred in 61/582 patients (10%(95%CI 8-13%)), grade 3/4 toxicity of platelets occurred in 30/582 patients (5%(95%CI 4-7%)), total WBC count grade 3/4 toxicity in 32/582 patients (5%(95%CI 4-8%), hemoglobin grade 3 toxicity in 22/582 patients (4% (95%CI 2-6%))

Table 1. Patient, treatment and tumor characteristics in patients with gastroenteropancreatic and bronchial NETs (n=443).

	Yes	No	Unknown
Characteristic	**No of patients %**	**No of patients %**	**No of patients %**
Male	230 (52)	213 (48)	
Median age (range)		60 years (30-83)	
Pretreatment			
surgery	190 (43)	252 (57)	1 (0)
chemotherapy*	28 (6)	415 (94)	0 (0)
radiotherapy	30 (7)	412 (93)	1 (0)
somatostatin analogs	271 (61)	172 (39)	0 (0)
Bone metastases	70 (16)	367 (83)	
Liver metastases	346 (78)	93 (21)	
Functional pancreatic NET**	21 (5)		
Median time since diagnosis (range)		14 months (0-371)	
Baseline progression	239 (54)	69 (16)	135 (30)
Extent of disease			
Limited	62 (14)		
Moderate	314 (71)		
Extensive	67 (15)		
Uptake on Octreoscan			
Grade 2	35 (8)		
Grade 3	278 (63)		
Grade 4	130 (29)		

* Including alkylating chemotherapy in 16 patients
** Including Vasoactive Intestinal Peptide-secreting tumor (VIPoma), insulinoma, gastrinoma and glucagonoma.

and no grade 4 hemoglobin toxicity was observed. No data are available on the remaining 28 patients. At first follow-up visit after 3 months, these values normalized in 77% of patients. CTCAE grade 3/4 of the lymphocytes was observed in 288/581 patients (50% (95%CI 46-54%)). At 3 months follow-up 74/287 patients and at 30 months follow-up 6/108 patients had persistent grade 3/4 lymphocyte toxicity and 53/108 patients had grade 1/2 lymphocyte toxicity.

An increase of aminotransferases (aspartate transaminase and/or alanine transaminase) grade 3/4 was observed in 20/581 patients (3% (95%CI 2-5%)). After 3 months follow-up, there were 3 patients with persistent grade 3/4 toxicity of the aminotransferases. Creatinine grade 3/4 toxicity occurred in 2/581 patients (0.3% (95%CI <1-1%)). Serum creatinine levels normalized in all patients at 3 months follow-up.

Acute leukemia (AL) occurred during follow-up in 4 patients (0.7%) after a median follow-up of 55 months after first therapy (range 32-125 months). Three of these patients died after a median follow-up of 7 months after diagnosis of AL. Myelodysplastic syndrome (MDS) occurred in 9 patients (1.5%) after a median follow-up of 28 months (range 9-41 months) after first therapy. Five of these patients died after a median follow-up of 7 months after diagnosis of MDS. Of the remaining patients, no date of death is known, since these patients were referred back to their own local hospital after the diagnosis AL/MDS was made. None of these patients were treated with alkylating chemotherapy prior to PRRT.

Renal failure occurred in 6 patients (1%) during follow-up. The most probable cause of the renal failure was post-renal in one patient (hydronephrosis) and pre-renal in the other patients (hypotension after gastrointestinal bleeding in one patient and in four patients dehydration caused by severe vomiting and diarrhea). No hepatic failure was observed during or after therapy.

Patient characteristics of the 443 patients who received ≥600 mCi (22.2 GBq) ^{177}Lu-DOTATATE and who were evaluated for efficacy and survival are presented in table 1. Median follow-up was 78 months from the first day of treatment. The majority of all patients (61%) were treated with somatostatin analogs at referral.

Best objective response rate (ORR) was defined as the proportion of patients achieving CR and PR at follow-up according to the RECIST 1.1 criteria. Best response rates are presented in table 2. The ORR in the entire patient group was 39%. SD was found in 43% of patients. PD as treatment outcome was observed in 12% of patients and 5% of patients had non-evaluable treatment outcome. In patients with midgut NETs and pancreatic NETs with PD at baseline, radiological disease control was observed in 84% and 81%, respectively.

For the entire group of 443 NET patients, the median OS was 63 months (95% CI 55-72 months). The median PFS was 29 months (95% CI 26-33 months). The median TTP was 36 months (95% CI 32-40 months) (table 2). Patients with a primary NET in the pancreas had the longest OS (figure 2). We identified several risk factors associated with shorter OS (table 3). The OS was significantly shorter in patients with liver or bone metastases at baseline. Also, patients with increased alkaline phosphatase (ALP) levels (>120 IU/L) and patients with extensive disease as scored with the OctreoScan had a worse prognosis (table 3). For the group of 239 NET patients with objective PD at baseline the median PFS was 30

Table 2. Best response, PFS, TTP and OS after therapy with ^{177}Lu-DOTATATE

Primary NET location	Total no of pts	CR No of pts %	PR No of pts %	SD No of pts %	PD No of pts %	NE No of pts %	Median PFS (months)	Medi-an TTP (months)	Median OS (months)
Midgut	181	2 (1)	55 (30)	99 (55)	16 (9)	9 (5)	30	42	60
- non-PD	32	0 (0)	10 (31)	18 (56)	3 (9)	1 (3)	24	45	82
- PD	94	1 (1)	28 (30)	50 (53)	9 (10)	6 (6)	29	40	50
Hindgut	12	0 (0)	4 (33)	6 (50)	1 (8)	1 (8)	29	29	Not defined
Pancreatic	133	6 (5)	66 (50)	40 (30)	17 (13)	4 (3)	30	31	71
- non-PD	21	1 (5)	9 (43)	10 (48)	1 (5)	0 (0)	31	31	Not defined
- PD	66	2 (3)	36 (55)	15 (23)	10 (15)	3 (5)	31	36	71
- Functional	21	1 (5)	12 (57)	4 (19)	3 (14)	1 (5)	30	33	Not defined
- non functional	112	5 (4)	54 (48)	36 (32)	14 (13)	3 (3)	30	31	69
Bronchial	23	0 (0)	7 (30)	7 (30)	6 (26)	3 (13)	20	25	52
Other foregut*	12	1 (8)	4 (33)	5 (42)	2 (17)	0 (0)	25	Not defined	Not defined
Unknown	82	0 (0)	29 (35)	35 (43)	11 (13)	7 (9)	29	37	53
Total	443	9 (2)	165 (37)	192 (43)	53 (12)	24 (5)	29	36	63

*Including 5 tumors of the stomach, 5 of the duodenum and 2 of the thymus.
Abbreviations: NET neuroendocrine tumor; CR complete response; PR partial response; SD stable disease; PD progressive disease; NE not evaluable. PFS progression free survival; TTP time to progression; OS overall survival; Primary NET location "non-PD and PD" means "without PD and with PD" at start of therapy with ^{177}Lu-DOTATATE

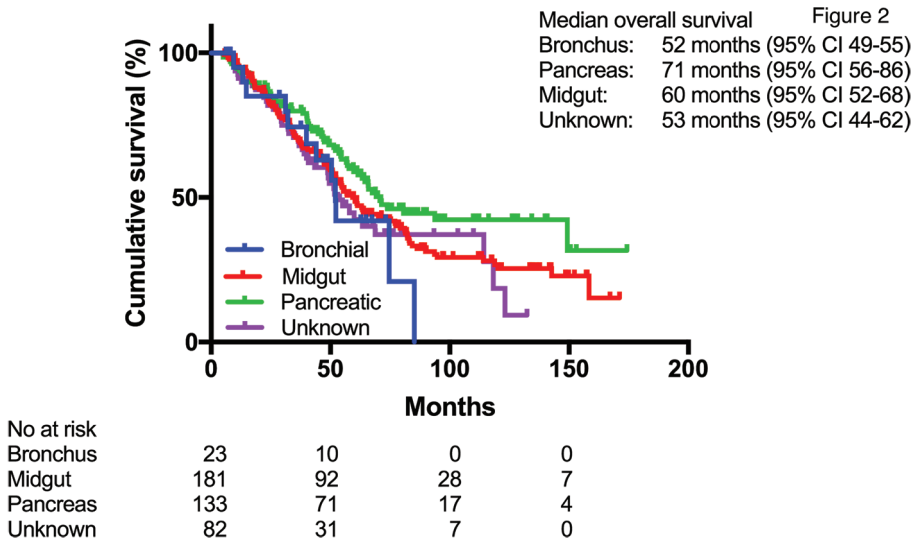


Figure 2. Median overall survival in 419 NET patients treated with ^{177}Lu-DOTATATE according to location of the primary tumor. Not shown are patients with primary tumor of the hindgut (n=12) and other foregut (n=12) due to the small number of patients.

months (95%CI 27-33 months), the median TTP 36 months (95%CI 32-41 months) and the median OS was 58 months (95%CI 52-64 months).

Characteristics of patients with NETs of the midgut and PD at baseline are presented in Table 4. For comparison with the NETTER-1 study, patients that received a cumulative dose of ≥100 mCi (3.7 GBq) ^{177}Lu-DOTATATE were selected. The PFS of patients with progressive midgut NETs was 24 months (95% CI 18-30 months). OS was 46 months (95% CI 32-60 months). The OS was significantly worse for patients with PD at baseline as compared to patients without PD at baseline.

Discussion

The results of this study demonstrate that PRRT with ^{177}Lu-DOTATATE is an excellent therapeutic option for patients with advanced grade 1-2 gastroenteropancreatic and bronchial NETs. This treatment has limited side-effects and is relatively safe. In the last decade various types of targeted therapies have been introduced. After the presentation of the PROMID study (18) in 2009 and the CLARINET study in 2014 (19), the use of somatostatin analogs for progressive, inoperable grade 1-2 GEP-NETs was registered. Rinke and colleagues (18) demonstrated that the median TTP in patients with metastatic midgut tumors is longer (14.3 months) with the use of 30 mg Octreotide LAR per 4 weeks as compared to placebo (6.0 months), although there seemed to be no significant

Table 3. Factors predicting median overall survival in patients with bronchial and gastroenteropancreatic NETs.

Factor	No of patients*	Median OS (months)	Hazard ratio (95% CI)	p-value
ALP				
<120	248	83	0.45 (0.35-0.59)	p<0.01
>120	189	47		
Liver metastases				
Yes	346	57	0.46 (0.34-0.62)	p<0.01
No	93	119		
Bone metastases				
Yes	70	47	0.56 (0.38-0.83)	p<0.01
No	367	69		
Extent of disease				
Limited	62	123		p<0.01
Moderate	314	62		
Extensive	67	46		
KPS				
≤70	35	27		p<0.01
80	103	49		
90	160	65		
100	138	81		
Best response				
CR	9	Undefined		p<0.01
PR	165	82		
SD	192	61		
PD	53	24		

Abbreviations: NET neuroendocrine tumor; OS overall survival; ALP alkaline phosphatase; KPS Karnofsky performance status; CR complete response; PR partial response; SD stable disease; PD progressive disease.
*Number of patients may vary due to missing data.

effect of Octreotide LAR on the overall survival (20). Also for Lanreotide Autogel 120 mg per 4 weeks, Caplin and colleagues have demonstrated that the PFS in GEP-NETs with a Ki67 index < 10% was better (32.8 months) as compared to placebo (18 months) (19,21). Recently, the first results of the NETTER-1 study were published (12). This is the first randomized phase III study comparing ^{177}Lu-DOTATATE to high dose octreotide LAR therapy in patients with inoperable, progressive midgut NETs. The dosing protocol was comparable to our protocol with 4 administrations of 200 mCi (7.4 GBq) ^{177}Lu-DOTATATE every 8 weeks. The PFS for the control group receiving 60 mg Octreotide LAR per 4 weeks was 8.4

months and the PFS was not reached for the patients receiving ^{177}Lu-DOTATATE plus 30 mg Octreotide LAR per 4 weeks. For comparison with the NETTER-1 study, we selected patients with progressive midgut NETs, who received at least the same minimum cumulative dose of ≥100 mCi (3.7 GBq) of ^{177}Lu-DOTATATE. Most patient characteristics were not significantly different from patients in the NETTER-1 study (Table 4). However, tumor regional distribution seemed to be higher and tumor uptake on OctreoScan lower in our patients. The latter may be affected in the NETTER-1 study by the high dose Octreotide LAR pre-treatment (22).

The proliferation marker Ki67 is used for the grading of NETs (23–25). In our study, the results of the Ki67 index labeling was not available in all tumors, because we started to routinely use the Ki67 index for grading of NETs in 2007. In order to have an estimation of the presence of high-grade NETs in our patient cohort, we took a sample of 230 GEP-NET patients who were treated after 2006. Of these 230 patients, 88 patients (38%) had WHO grade 1 NETs, 131 patients (57%) had grade 2 NETs and 11 patients (5%) had grade 3 NETs (23–25). Since mainly grade 1-2 NETs were treated, we can conclude that PRRT is especially a therapeutic option for these tumors. Moreover, the majority of grade 3 tumors are negative on OctreoScan (26) and therefore cannot be treated with PRRT with ^{177}Lu-DOTATATE.

For progressive, metastatic grade 1-2 pancreatic NETs, both Everolimus and Sunitinib are approved therapies. In the RADIANT-3 study (27), comparing 10 mg Everolimus orally daily to placebo, the PFS was 11.0 months for Everolimus. In the study comparing Sunitinib 37.5 mg orally daily to placebo (28), the PFS for Sunitinib was 11.4 months. The PFS for pancreatic NETs with radiological progression at baseline (table 2) after therapy with ^{177}Lu-DOTATATE was 31 months and suggests being longer than with the currently available targeted therapies.

Recently, the results of the RADIANT-4 study (29) have also been published. This study compared everolimus 10 mg orally daily to placebo in patients with advanced grade 1-2 NETs of the lung and gastrointestinal origin. The PFS for Everolimus was 11.0 months and thus comparable to the PFS for Everolimus in the RADIANT-3 study. We found a PFS after PRRT with ^{177}Lu-DOTATATE of 29 months in the total group of patients with primary NETs in the lung or gastrointestinal tract. Although our patients were not randomized at inclusion, the present results can be compared to other studies due to the large number of patients and very long follow-up period. Therefore, not only in patients with pancreatic, but also in patients with bronchial and gastrointestinal NETs, the PFS seems to be better after ^{177}Lu-DOTATATE than the current targeted therapies which are registered for these indications.

A disadvantage of PRRT in general is the potential side-effects, especially on the bone marrow and kidneys. Due to co-infusion of lysine and arginine starting just before therapy, the radiation dose to the kidneys can be lowered and, therefore, the kidney is no longer the

Table 4. Comparison between NETTER-1 study and patients with progressive midgut NETs receiving ≥100 mCi (3.7 GBq) ^{177}Lu-DOTATATE.

Progressive Midgut Carcinoids Characteristic	**NETTER 1 (N = 116)**	**Erasmus MC (N = 106)**	***P*-value**
Sex— no. (%)			
Female	53 (46)	52 (49)	NS
Male	63 (54)	54 (51)	
Mean age (±SD) — yr	63 (±9)	62 (±10)	NS
Mean BMI (±SD) — kg/m^2	25 (±5)	26 (±4)	NS
Mean KPS (±SD)	88.6 (±9.3)	85.8 (±10.2)	p<0.05
Site of metastasis — no. (%)			
Liver	97 (84)	97 (92)	NS
Bone	13 (11)	14 (13)	NS
SRS, uptake scale — no. (%)			
Grade 2	11 (10)	7 (7)	NS
Grade 3	34 (29)	74 (70)	p<0.01
Grade 4	71 (61)	25 (23)	p<0.01
Extent of disease - no. (%)			
Limited	99 (85)	4 (4)	p<0.01
Moderate	13 (11)	82 (77)	p<0.01
Extensive	4 (3)	20 (19)	p<0.01
Previous treatments—no. (%)			
Surgery	93 (80)	60 (57)	p<0.01
Chemotherapy	11 (9)	6 (6)	NS
Radiotherapy	4 (3)	3 (3)	NS
Previous Somatostatin analog therapy (%)	116 (100)	89 (84)	p<0.01
ORR-no.(%)	18 (16)	29 (27)*	p<0.05
PFS rate at 20 months (%)	65	58	NS
Median OS-months	NR	46	

* Best response used for Erasmus MC patients
Abbreviations: BMI body mass index; KPS Karnofsky performance status; CTCAE Common Terminology Criteria for Adverse Events; WBC white blood cell count; ORR objective response rate; PFS progression free survival; OS overall survival; NR not reached.

dose-limiting organ (13). We have observed renal failure in 6 patients during follow-up after this therapy. The cause of this renal failure was probably not related to PRRT, since we found other more plausible causes in all patients. AL and MDS are severe complications related to PRRT and occurred after a median of 28 months after the first cycle of PRRT with ^{177}Lu-DOTATATE for MDS and after a median of 55 months for AL. Although none of our patients who were diagnosed with AL/MDS received prior chemotherapy, recent reports suggest that there might be a higher risk of MDS/AL after alkylating chemotherapy (30–32).

Other therapy-related side-effects are hormone related problems. In this study we did not focus on hormonal crises after PRRT. In a previous study, we have reported on 6/479 patients (1%) with GEP-NETs and pheochromocytomas who developed severe symptoms after PRRT due to a release of bioactive substances (33). When treating patients with hormone-producing tumors, these side-effects should be taken into account as well.

Various centers in Europe use [^{90}Y-DOTA^{0},Tyr^{3}]-octreotide (^{90}Y-DOTATOC) for PRRT. The results of therapy with this radiopharmaceutical have been extensively reported in the last decade (7,11,34–36). Due to the higher energy of Yttrium-90, as compared to Lutetium-177, more side-effects have been reported. Imhof et al (36) reported transient grade 3/4 hematological toxicity in 12,8% of patients and permanent grade 4/5 renal toxicity in 9.2% with ^{90}Y-DOTATOC. In our opinion, ^{177}Lu is therefore the radionuclide of first choice for treating patients with NETs with PRRT because of less renal toxicity.

In 2008, we reported on 310 GEP-NET patients who were treated with ^{177}Lu-DOTATATE (8). Although part of the patients reported in the present paper was included in the 2008 study, we believe that the current results are more distinctive and more unique. In contrast to the former report, in this cohort only Dutch patients with a very long follow-up in our institution were included and results of various subtypes of GEP-NETs are reported. The relative low loss to follow-up makes the present results more solid.

For this study no intention-to-treat analysis was made. We believe that an analysis of all 1214 patients is not reliable. This group includes patients from different countries who were only treated at our institute and all follow-up was conducted in their own country. No data about this follow-up is available. This group also includes patients with different kind of malignancies, e.g. thyroid cancers, paragangliomas and lymphomas. This heterogeneity will make an analysis not reliable and not representative for the investigated group of bronchial and GEPNET patients. The main limitation of this study is the fact that it is a non-randomized study. However, with the selection of patients that were all treated strictly according to the inclusion criteria and an active follow-up during many years make the results very reliable. Also the inclusion of patients with stable disease at baseline is a limitation compared to other studies reporting on NETs. Patients with a very large tumor load or many symptoms of the tumor or its produced hormones were treated, because PRRT was

the best available treatment option at that point in time. However, analysis of the patients with PD at baseline demonstrated only small differences in PFS, TTP and OS compared to all GEPNET patients.

Conclusion

PRRT with ^{177}Lu-DOTATATE produces good tumor response rates for patients with grade 1-2 GEP-NETs and bronchial NETs. The side-effects are limited and in the vast majority of patients reversible on short term. Severe long-term toxicities are AL or MDS, occurring in 2% of patients. No therapy-related long-term renal or hepatic failure was observed. Although this was a non-randomized study, the PFS and TTP for ^{177}Lu-DOTATATE are favorable to all other registered medical options that are currently available for patients with advanced or metastasized G1-G2 GEP-NETs and bronchial NETs.

References

1. Fraenkel M, Kim M, Faggiano A, de Herder WW, Valk GD, On behalf of the Knowledge NETwork. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. Endocr Relat Cancer. 2014;21:R153–63.
2. Korse CM, Taal BG, van Velthuysen M-LF, Visser O. Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: Experience of two decades of cancer registry. Eur J Cancer. 2013;49:1975–83.
3. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One Hundred Years After "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States. J Clin Oncol. 2008;26:3063–72.
4. Kulke MH, Benson AB, Bergsland E, Berlin JD, Blaszkowsky LS, Choti MA, et al. Neuroendocrine tumors. J Natl Compr Canc Netw. 2012;10:724–64.
5. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology. 2016;103:172–85.
6. Krenning EP, Breeman WAP, Kooij PPM, Lameris JS, Bakker WH, Koper JW, et al. Localisation of endocrine-related tumours with radioiodinated analogue of somatostatin. The Lancet. 1989;Pages 242–4.
7. Forrer F, Waldherr C, Maecke HR, Mueller-Brand J. Targeted radionuclide therapy with 90Y-DOTATOC in patients with neuroendocrine tumors. Anticancer Res. 2006;26:703–7.
8. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment With the Radiolabeled Somatostatin Analog [177Lu-DOTA0,Tyr3]Octreotate: Toxicity, Efficacy, and Survival. J Clin Oncol. 2008;26:2124–30.
9. Bodei L, Cremonesi M, Grana CM, Fazio N, Iodice S, Baio SM, et al. Peptide receptor radionuclide therapy with 177Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging. 2011;38:2125–35.
10. Sabet A, Dautzenberg K, Haslerud T, Aouf A, Sabet A, Simon B, et al. Specific efficacy of peptide receptor radionuclide therapy with (177)Lu-octreotate in advanced neuroendocrine tumours of the small intestine. Eur J Nucl Med Mol Imaging. 2015;42:1238-1246.
11. Bushnell DL, O'Dorisio TM, O'Dorisio MS, Menda Y, Hicks RJ, Van Cutsem E, et al. 90Y-Edotreotide for Metastatic Carcinoid Refractory to Octreotide. J Clin Oncol. 2010;28:1652–9.
12. Strosberg JR, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of 177-Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med 2017;376:125-35.
13. Kwekkeboom DJ, Bakker WH, Kooij PP, Konijnenberg MW, Srinivasan A, Erion JL, et al. [177Lu-DOTAOTyr3]octreotate: comparison with [111In-DTPAo]octreotide in patients. Eur J Nucl Med. 2001;28:1319–25.
14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.

15. Kwekkeboom DJ. Radiolabeled Somatostatin Analog [177Lu-DOTA0,Tyr3]Octreotate in Patients With Endocrine Gastroenteropancreatic Tumors. J Clin Oncol. 2005;23:2754–62.
16. Pazdur R. Endpoints for assessing drug activity in clinical trials. The oncologist. 2008;13:19–21.
17. US Department of Health and Human Services, National Institute of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. 2010;
18. Rinke A, Muller H-H, Schade-Brittinger C, Klose K-J, Barth P, Wied M, et al. Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group. J Clin Oncol. 2009;27:4656–63.
19. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. N Engl J Med. 2014;371:224–33.
20. Rinke A, Wittenberg M, Schade-Brittinger C, Aminossadati B, Ronicke E, Gress TM, et al. Placebo Controlled, Double Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors (PROMID): Results on Long Term Survival. Neuroendocrinology [Internet]. 2016 [cited 2016 Jun 8]; Available from: http://www.karger.com/?doi=10.1159/000443612
21. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. Endocr Relat Cancer. 2016;23:191–9.
22. Dörr U, Räth U, Sautter-Bihl M-L, Guzman G, Bach G, Adrian H-J, et al. Improved visualization of carcinoid liver metastases by indium-111 pentetreotide scintigraphy following treatment with cold somatostatin analogue. Eur J Nucl Med. 1993;20:431–3.
23. Rindi G, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch. 2006;449:395–401.
24. Rindi G, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Arch. 2007;451:757–62.
25. Bosman, F T, World Health Organization, International Agency for Research on Cancer. WHO classification of tumours of the digestive system. 4th ed. Lyon : IARC Press, 2010;
26. Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): The NORDIC NEC study. Ann Oncol. 2013;24:152–60.
27. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:514–23.
28. Raymond E, Dahan L, Raoul J-L, Bang Y-J, Borbath I, Lombard-Bohas C, et al. Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors. N Engl J Med. 2011;364:501–13.
29. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. The Lancet. 2015;968–77.

30. Bodei L, Kidd M, Paganelli G, Grana CM, Drozdov I, Cremonesi M, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging. 2015;42:5–19.
31. Brieau B, Hentic O, Lebtahi R, Palazzo M, Ben Reguiga M, Rebours V, et al. High risk of myelodysplastic syndrome and acute myeloid leukemia after ^{177} Lu-octreotate PRRT in NET patients heavily pretreated with alkylating chemotherapy. Endocr Relat Cancer. 2016;23:L17–23.
32. Bodei L, Modlin IM, Luster M, Forrer F, Cremonesi M, Hicks RJ, et al. Myeloid neoplasms after chemotherapy and PRRT: myth and reality. Endocr Relat Cancer. 2016;23:C1–7.
33. de Keizer B, van Aken MO, Feelders RA, de Herder WW, Kam BLR, van Essen M, et al. Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [177Lu-DOTA0,Tyr3]octreotate. Eur J Nucl Med Mol Imaging. 2008;35:749–55.
34. Waldherr C, Pless M, Maecke HR, Haldemann A, Mueller-Brand J. The clinical value of [90Y-DOTA]-D-Phe1-Tyr3-octreotide (90Y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study. Ann Oncol. 2001;12:941–5.
35. Valkema R, Pauwels S, Kvols L, Barone R, Jamar F, Bakker W, et al. Survival and Response After Peptide Receptor Radionuclide Therapy With [90Y-DOTA0,Tyr3]Octreotide in Patients With Advanced Gastroenteropancreatic Neuroendocrine Tumors. Semin Nucl Med. 2006;36:147–56.
36. Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, et al. Response, Survival, and Long-Term Toxicity After Therapy With the Radiolabeled Somatostatin Analogue [90Y-DOTA]-TOC in Metastasized Neuroendocrine Cancers. J Clin Oncol. 2011;29:2416–23.


5

CHAPTER 6

Pitfalls in the response evaluation after peptide receptor radionuclide therapy with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate

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Abstract

Peptide receptor radionuclide therapy (PRRT) with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-DOTATATE) is a treatment with good results in patients with metastatic gastroenteropancreatic neuroendocrine tumors (GEPNETs). However, there are some pitfalls that should be taken into consideration when evaluating the treatment response after PRRT. 354 Dutch patients with GEPNETs who were treated with ^{177}Lu-DOTATATE between March 2000 and December 2011 were retrospectively selected. Liver function parameters and chromogranin A were measured before each therapy and in follow-up. Anatomical imaging was performed before therapy and in follow-up. An increase in aminotransferases by ≥20% compared to baseline was observed in 83 of 351 patients (24%). In patients with an objective response (OR) and stable disease (SD) this increase was observed in 71/297 (24%) and in patients with progressive disease (PD) it was observed in 12/54 patients (22%). An increase in chromogranin A by ≥20% compared to baseline was observed in 76 patients (29%). This was present in 34% of patients who eventually had PD and 27% of patients who had OR/SD. In 70% of patients this tumor marker returned to baseline levels after therapy. An increase in liver enzymes and chromogranin A is not uncommon after PRRT. In the vast majority of patients this will resolve in follow-up. Clinicians should be aware that these changes may occur due to radiation-induced inflammation or disease progression and that repeated measurements over time are necessary to differentiate between the two.

Introduction

Neuroendocrine tumors (NETs) are a rare type of cancer. The overall incidence rate for NETs has increased in the last few decades (1). Unfortunately, the majority of patients have metastatic disease at the time of presentation (2). In the past decade a promising new treatment modality has been developed for inoperable or metastasized NETs. This peptide receptor radionuclide therapy (PRRT) uses radiolabeled somatostatin analogs. Since the majority of NETs express a high number of the somatostatin receptors on their cell membrane, this receptor can be used both for imaging and therapy of NETs with radiolabeled somatostatin analogs.

The most frequently used β-emitting radionuclides for PRRT are Yttrium-90 and Lutetium-177, linked to [DOTA0,Tyr3]octreotide (^{90}Y-DOTATOC) or [DOTA0,Tyr3]octreotate (^{177}Lu-DOTATATE), respectively. The objective response rate in patients with gastroenteropancreatic neuroendocrine tumors (GEPNETs) is 15–35% (3-8). Recently, the results of the multicentre randomized phase III NETTER-1 trial in patients with advanced midgut NETs (9), comparing ^{177}Lu-DOTATATE to high dose octreotide LAR therapy were presented. The progression free survival (PFS) in the group receiving octreotide LAR 60 mg was 8.4 months and was not reached for the group receiving ^{177}Lu-DOTATATE plus 30 mg octreotide LAR (Hazard ratio 0.21; 95% CI 0.13– 0.34). It may be expected that the number of patients treated with ^{177}Lu-DOTATATE will increase in the coming years. Awareness of possible side-effects is important when treating patients with PRRT. The most frequently reported subacute side-effect is hematologic toxicity (4,10,11). This toxicity is mostly mild and reversible. Late severe side-effects are myelodysplastic syndrome (MDS) / acute leukemia (AL). Although 70–90% of patients with disseminated disease have metastases in the liver, reported hepatotoxicity is rare. Between treatment cycles patients undergo different blood tests to detect possible side-effects. These blood tests include hematology, renal and liver function parameters, and measurement of tumor markers. For response evaluation after therapy, imaging is done in addition to these blood tests. In 2013 van Vliet and coworkers demonstrated that there are no differences in the different response methods used in the follow-up of NET patients (12). When interpreting the blood tests and imaging during and directly after therapy some remarkable changes may occur, which are not in line with the final treatment response to therapy. Here, we present several pitfalls that might occur in the response evaluation during treatment and follow-up after PRRT with ^{177}Lu-DOTATATE that the treating physicians should be aware of.

Materials and methods

Patients

354 Dutch patients with GEPNETs who were treated with ^{177}Lu-DOTATATE between March 2000 and December 2011 were selected. Follow-up data was available until 2014. After 2011 most new patients returned to their referring specialist after therapy, so information about follow-up at our institute in these patients was limited. Inclusion criteria for therapy were: histologically proven metastatic or inoperable GEPNETs, tumor uptake at least equal to liver uptake on ^{111}In-DTPA-octreotide scintigraphy, Karnofsky performance score (KPS) of at least 50, creatinine clearance ≥40 mL/min until 2007 or 50 mL/min from 2007, a platelet level of at least 75.109/L, a hemoglobin level of at least 6.0 mmol/L (9.7 g/dL), and a white blood cell count of at least $2.0.10^9$/L. Only Dutch patients were selected, because of the limited loss in follow-up in this patient group. This study was part of the ongoing prospectively designed study in patients with NETs at our department and was approved by the local medical ethical committee. All patients gave their written informed consent to participate in the study.

Treatment

[DOTA0,Tyr3]octreotate was obtained from BioSynthema. $^{177}LuCl_3$ was distributed by IDB-Holland. ^{177}Lu-DOTATATE was locally prepared as described previously (13). 30 min before the infusion of ^{177}Lu-DOTATATE was started, Granisetron 3 mg or Ondansetron 8 mg was injected intravenously. An infusion of amino acids (2.5% arginine and 2.5% lysine, 1 L) was started 30 min before the administration of the radiopharmaceutical as well and lasted for 4 h. The radiopharmaceutical was co-administered, using a second pump system. Cycle doses were 3.7 or 7.4 GBq (100 or 200 mCi), depending on short-term toxicity, injected over 30 min. The intended interval between treatments was 6–10 weeks. Normally, patients undergo 4 treatment cycles. Patients were treated up to an intended cumulative dose of 22.2–29.6 GBq (600–800 mCi).

Anatomical imaging

Computed tomography (CT) or magnetic resonance imaging (MRI) was performed at least 3 months prior to therapy. In follow-up, CT or MRI was performed 6 weeks, 3 months and 6 months after the last treatment and thereafter every 6 months. Tumor response was scored according to the Southwest Oncology Group (SWOG) solid tumor response criteria (14), modified by adding a minor response (MR), pertaining to a decrease of 25–50% of the sum of measurable lesions. Patients were categorized according to confirmative tumor response 3 months after the last therapy.

Groups of patients with limited or extensive metastases in the liver were defined. Extensive liver disease was defined as diffuse metastases throughout the whole liver with hepatomegaly. Examples of patients with limited and extensive disease in the liver are presented in Fig. 1.

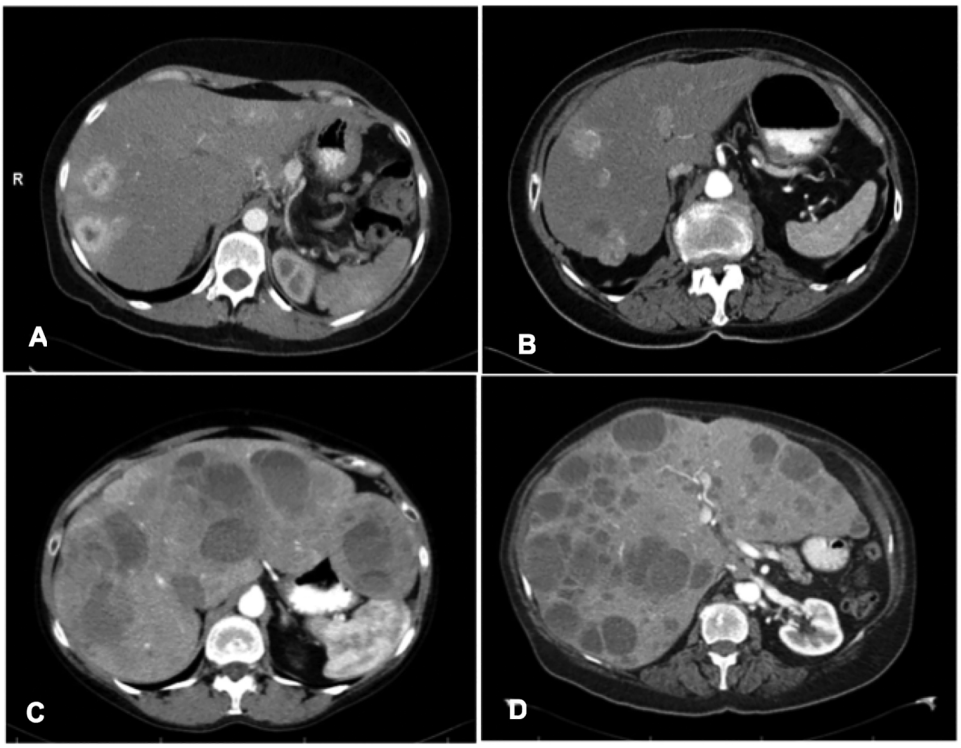

Figure 1. Axial slices of CT's of the upper abdomen in the arterial contrast phase. A and B are examples of patients with limited metastases in the liver. C and D are examples of patients with extensive metastases and enlargement of the liver.

Blood examinations

Routine hematology, liver and kidney function parameters and chromogranin A were determined before each therapy, and at fixed follow-up visits. An increase of ≥20% compared to baseline after the first therapy in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP) or chromogranin A (CgA) was considered clinically significant. ALP was measured as a total of all fractions (including bone and liver fractions).

Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (https://evs. nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_ QuickReference_5x7.pdf).

Statistics

Statistical analysis of the data was performed using Fisher's exact test or chi-square test. A p-value <0.05 was considered to be statistically significant.

Results

354 Dutch patients with GEPNETs were evaluated. Baseline characteristics are presented in Table 1. The most common primary tumor was located in the small intestine (46%), followed by the pancreas (31%). The vast majority of patients (86%) had metastases in the liver. Sixty-one patients (17%) had bone metastases. The mean age was 59 years (range 23–84 years).

Table 1. Baseline characteristics of 354 Dutch patients with a gastroenteropancreatic neuroendocrine tumor.

Characteristic	Number of patients	%
Male	180	51
Female	174	49
Age	59 (range 23-84)	
Primary tumor		
Pancreatic NET	110	31
Non-functional	99	28
Functional	11	3
Small intestine	163	46
Colorectal	14	4
Stomach	7	2
Duodenum	3	1
Unknown primary	57	16
Total	354	
Liver metastases	306	86
Limited	223	63
Extensive	83	23
Bone metastases	61	17

A significant ($p < 0.05$) higher baseline level of the cholestatic liver enzymes GGT and ALP was observed in patients with extensive liver disease compared to patients with limited/no liver metastases. An increase of ≥20% in GGT compared to baseline was observed in a total of 87 patients (25%) (Fig. 2 and Table 2). In patients with an objective response (OR) or stable disease (SD) this increase was seen in 72/293 patients (25%) and in patients with progressive disease (PD) it was seen in 15/54 patients (28%). Of the 87 patients with an increase of GGT, an increase of 1 CTCAE grade was seen in 33 patients (38%) and an increase of 2 grades was seen in 13 patients (15%).

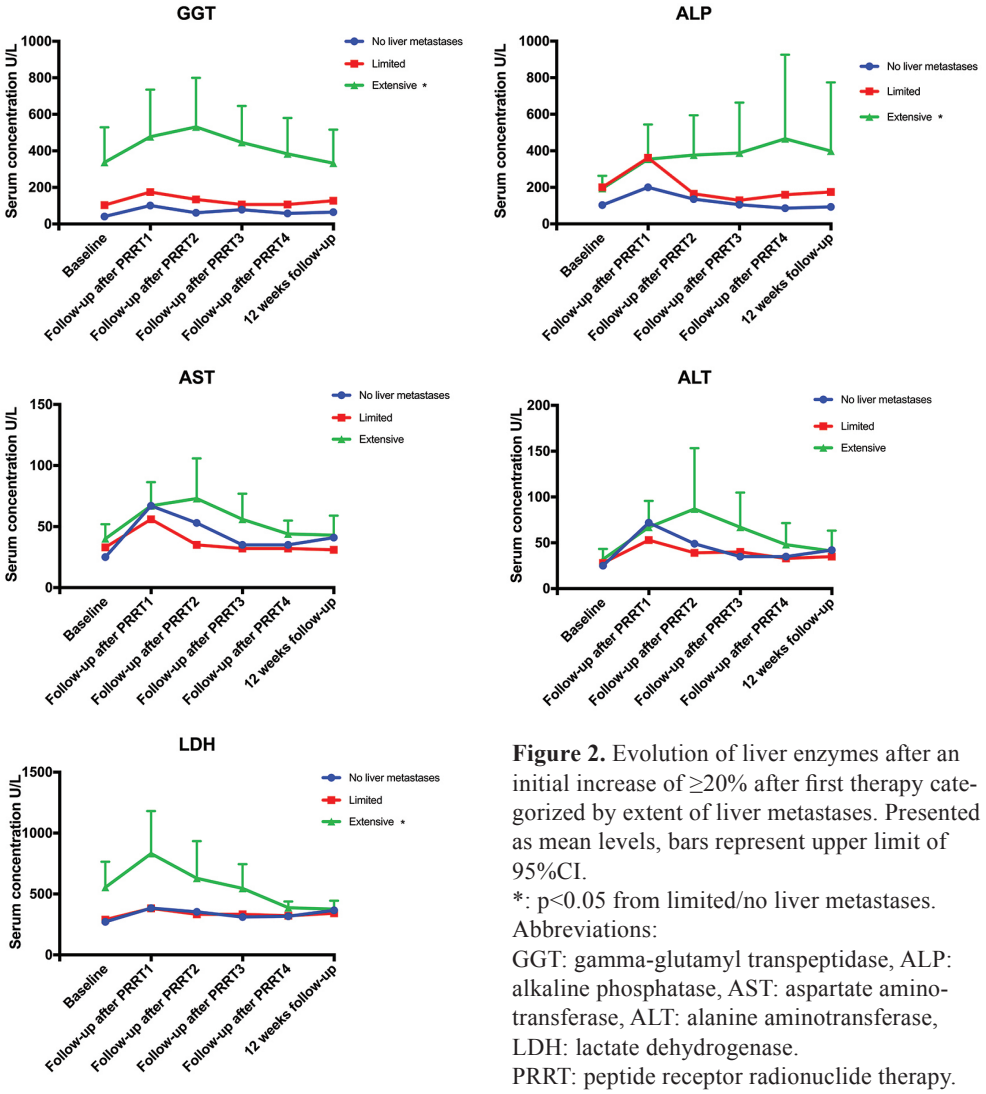

Figure 2. Evolution of liver enzymes after an initial increase of ≥20% after first therapy categorized by extent of liver metastases. Presented as mean levels, bars represent upper limit of 95%CI.
*: $p<0.05$ from limited/no liver metastases.
Abbreviations:
GGT: gamma-glutamyl transpeptidase, ALP: alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase.
PRRT: peptide receptor radionuclide therapy.

An increase of ≥20% in ALP compared to baseline was observed in 36/350 patients (10%). Of these 36 patients, 5 had bone metastases. The incidence of elevation was not significantly different from patients without bone metastases.

An increase in the aminotransferases (AST and/or ALT) by ≥20% compared to baseline was observed in 83 of 351 patients (24%) (Table 2). In patients with OR/SD this increase was observed in 71/297 (24%) and in patients with PD in 12/54 patients (22%). This increase was mild to moderate in all patients, with a maximum of 537 U/L. After an initial increase, the liver enzymes declined and eventually returned to baseline levels in the majority of patients during follow-up. In patients with OR/SD this increase was permanent in 9%, whereas in patients with PD a permanent increase was observed in 43% of patients. The albumin levels of these patients did not change significantly during therapy, bilirubin levels increased ≥20% compared to baseline in 20/83 of these patients (24%). Both patients with and without metastases in the liver showed a similar increase (Fig. 2). In patients without metastases an initial increase in aminotransferases was found in 17/43 patients (40%). This was permanent in 4/17 patients (24%). In 70% of patients with limited or no metastases in the liver, the mean enzyme level declined after the initial increase. In patients with extensive tumor load in the liver this decline was observed after the second therapy (Fig. 2). Of the 66 patients with an increase in AST, 35 (53%) had an increase of CTCAE of 1 grade, 2 patients (3%) had an increase of 2 grades and 3 patients (5%) had an increase of 3 grades. Of the 82 patients with an increase of ALT, 33 (40%) had an increase of 1 grade, 4 patients (5%) had an increase of 2 grades and 3 patients (4%) had an increase of 3 grades. No CTCAE grade 4 toxicity of AST/ALT was observed.

Table 2. Number of patients with an increase of biochemical markers ≥20% after first therapy compared to baseline value.

	OR			SD			PD		
	n	**Increase (%*)**	**Permanent (%**)**	**n**	**Increase (%*)**	**Permanent (%**)**	**n**	**Increase (%*)**	**Permanent (%**)**
ALP	94	6 (6)	1 (17)	202	22 (11)	4 (18)	54	8 (15)	4(50)
GGT	92	16 (17)	2 (13)	205	56 (27)	9 (16)	54	15 (28)	7 (47)
AST	91	16 (18)	1 (6)	205	39 (19)	3 (8)	54	11 (20)	5 (45)
ALT	88	24 (27)	2 (8)	205	46 (22)	5 (11)	54	12 (22)	5 (42)
LDH	88	10 (11)	1 (10)	200	13 (7)	2 (15)	54	5 (9)	1 (20)
CgA	68	14 (21)	1 (7)	147	45(31)	10(22)	50	17(34)	12 (71)

Abbreviations:
ALP: alkaline phosphatase, GGT: gamma-glutamyl transpeptidase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, CgA: chromogranin A.
*Increase: % of n (OR/SD/PD); **Permanent: % of increased n.

An increase of LDH was observed in 28 patients (8%). The baseline level of LDH was significantly higher in patients with extensive disease ($p<0.05$). The hemoglobin levels of these 28 patients did not changed significantly after PRRT. Mean baseline level was 7.6 mmol/L and 12 weeks after PRRT the mean level was 7.3 mmol/L.

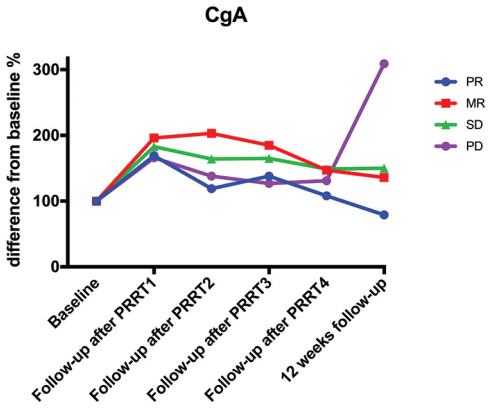

Figure 3. Evolution of chromogranin A after an initial increase of ≥20% after first therapy. Presented as mean levels of CgA.
Abbreviations:
CgA: chromogranin A.
CR: complete remission, PR: partial remission, MR: minor response, SD: stable disease, PD: progressive disease.
PRRT: peptide receptor radionuclide therapy.

CgA was elevated in 265/354 patients. An increase of ≥20% after first therapy compared to baseline was observed in 76/265 patients (29%). This was present in 59/215 patients (27%) who had OR/SD and in 17/50 patients (34%) who eventually had PD. During the treatment cycles no differences of CgA between the response groups was found (Fig. 3). Twelve weeks after the last therapy the mean levels of CgA in patients with an OR/SD continued to decline, whereas the level of CgA in patients with PD showed a strong increase. In 19% of patients with OR/SD and 71% of patients with PD, the initial increase of CgA did not return to baseline levels.

In the group of patients with a complete response (CR) and partial response (PR) at 3 months follow-up, no increase in the tumor size was observed on the first CT in follow-up at 6 weeks after the last PRRT cycle. Of the 206 patients with SD (including MR), 18 patients (9%) had an increase of ≥10% in size at the first follow-up visit at 6 weeks after the last cycle of PRRT. The median increase in size was 18% (range 10–71%). In 16/18 patients this increase was below 50% and in 2/18 patients there was an increase of ≥50%. An example is given in Fig. 4. During follow-up the sum diameter of lesions eventually declined in 50% of patients at 6 months follow-up with a median decrease of 27%. PD as outcome at 3 months follow-up and based solely on an increase in size of measureable lesions of more than 50% occurred in 3 patients out of 54 patients with PD. In the remaining 51/54 patients (94%) new lesions or clear deterioration in clinical condition determined permanent PD.

Discussion

In this study, we identified several pitfalls that should be taken in consideration when evaluating the response to treatment in patients treated with ^{177}Lu-DOTATATE. These temporary changes during and directly after therapy have not been described previously. There are many reports about hematologic and renal toxicity (10, 15-17), while reports about hepatotoxicity after PRRT are rare (18-19). From experience with external beam radiation therapy it is known that radiation-induced liver disease or radiation hepatitis can be a serious problem, which can result in liver failure and even death. Radiation-induced liver disease typically presents 4–8 weeks after therapy (20), especially as increased ALP, but aminotransferases can be elevated as well. The whole liver can recover from a radiation dose of 30 Gy without permanent damage. During treatment with ^{177}Lu-DOTATATE the radiation dose to the liver remains well below 30 Gy (13), explaining the very low radiation-induced liver disease after PRRT. Liver failure after PRRT with ^{90}Y and/or ^{177}Lu labeled somatostatin analogs is reported rarely, and is most commonly due to progressive disease. In patients treated with ^{90}Y microsphere radioembolization, a radiation-induced liver disease grade 2–3 is reported in 0–4% of patients (21). A report from Ezziddin and coworkers found mostly minor (no grade 4) liver toxicity in 23 patients after treatment with ^{90}Y microspheres as a salvage therapy after failed PRRT with ^{177}Lu-DOTATATE (22). We found a mild to moderate (CTCAE grade 1–3) increase in aminotransferases in 24% of patients, which was reversible in most patients. Since the level of albumin did not change, the hepatocyte function seems not to be affected. Both in patients with OR/SD and PD, there was an increase in aminotransferases that was not different between these response groups. Also an increase of serum ALP was observed after the first therapy. An elevated ALP can be indicative of liver toxicity or obstruction, but can also be due to a high bone turnover, caused by bone metastases. However, no differences in ALP between patients with and without bone metastases were found. Also an increase of LDH can have different causes. The hemoglobin level of these patients did not change during therapy, so hemolysis is probably not the cause of this increase. A recent report of Jimenez- Fonseca and coworkers demonstrated that an elevated LDH is associated with a worse prognosis compared to patients with a normal LDH (23). The present results show that patients with extensive metastases in the liver had a higher baseline level of LDH. In 2008 we demonstrated that patients with extensive liver involvement have a shorter survival than patients with limited or no metastases in the liver (4). These findings are concordant with the report by Jimenez-Fonseca and coworkers.

The published reports about hepatotoxicity after PRRT are not consistent. A recent report from Riff and coworkers showed an episode of hepatotoxicity in 59% of patients treated with ^{90}Y-DOTATOC and/or in combination with ^{177}Lu-DOTATOC (19). Besides radiopharmaceuticals, patient features also differ from our study and may explain the difference between the reported hepatotoxicity. A number of patients in the report from Riff and coworkers were treated with radioembolization or other liver-directed therapies before PRRT,

whereas in our study no patient underwent previous radioembolization. Furthermore, the hepatotoxicity in our study was temporary and reversible in 91% of patients with OR/SD and 57% of patients with PD.

Bushnell and coworkers (18) found an increase of one WHO grade in at least one liver enzyme in 9 of 15 patients with liver metastases after the first treatment of ^{90}Y-DOTATOC. In only 4 patients this increase was still present 4–6 weeks after the third and last therapy. In patients without liver metastases one of six patients had an increase after three therapies. No significant relation was found between the extent of hepatic metastases and the increase in liver enzymes. The results from this small study are more consistent with our data than the above-mentioned study from Riff and coworkers (19). None of the patients from the study of Bushnell and coworkers had prior liver-directed therapy.

The pattern of an initial increase followed by normalization in follow-up has also been described for hematologic toxicity after PRRT. Sierra and coworkers reported a grade 2–3 B-cell lymphocyte toxicity after each cycle in 14 of 16 patients (24). All types of lymphocyte toxicity eventually resolved after 90 days. Kulkarni and coworkers described mildly elevated serum creatinine in 5/22 patients directly after PRRT (25). However, serious renal toxicity is very rare after treatment with ^{177}Lu-DOTATATE and occurs in less than 1% of patients (26,27), provided that appropriate renal protection by lysine/arginine infusion is applied.

CgA is a protein that is present in the secretory granules of most neuroendocrine cells (28). In patients with NETs it can be used as a tumor marker, since it is excreted together with the peptide hormones in the neurosecretory granules (29,30). Although CgA is a nonspecific marker for NETs, well-differentiated NETs often have an elevated level of CgA, which is positively correlated with a tumor burden. If elevated, it is a useful marker to evaluate biochemical response to therapy or progression. After the first cycle with ^{177}Lu-DOTATATE an increase of ≥20% in CgA was observed in 29% of our patients. No differences were found between the different response groups. Therefore, this increase did not indicate progression in most patients and may be explained by a release of CgA due to radiation-induced cell damage or lysis. The decline of CgA after the initial peak supports this hypothesis. Also in patients with PD the CgA declined after an initial peak. In follow-up, not until 12 weeks after the last cycle of PRRT, a difference in CgA between PD and non-PD patients occurs. To avoid undertreatment, patients should, therefore, not be considered as progressive based on an increase of CgA during or shortly after PRRT. In a small number of patients the increase in liver enzyme and CgA levels did not return to baseline levels during follow-up. This was seen more often in patients with PD compared to those with OR/SD and this increase is, therefore, more likely to be tumor progression related.

This phenomenon is not unique: in patients with well-differentiated thyroid carcinoma treated with radioactive iodine therapy, a transient increase in the biochemical marker thy-

roglobulin (Tg) directly after radioactive iodine ablation has been described. Similar to PRRT in NETs, it was suggested that this increase is due to tissue destruction/inflammation. During follow-up, the Tg levels fall below baseline levels after 6 months (31). This transient increase of Tg is even considered as a prognostic indicator of the success of the radioactive iodine treatments (32).

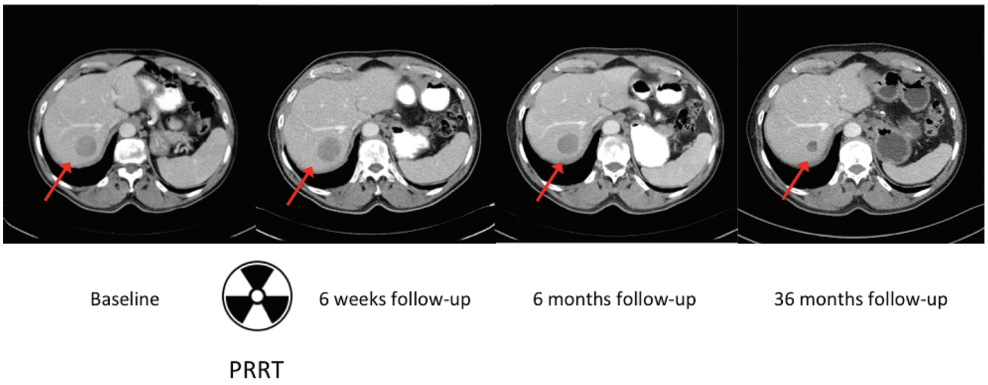

Figure 4. Axial slices of a contrast enhanced CT of the liver before PRRT, 6 weeks, 6 and 36 months after therapy. This 64 year-old patient presented with a NET of the small intestine and metastases in the liver. A well-defined metastasis was visible in segment 7 of the liver (red arrow). Directly after therapy, the metastasis had increase in size and was less demarcated. In follow-up, after 6 and 36 months, the metastasis further decreased in size. Response evaluation after 3 months resulted in a SD.

A change in CgA may also occur after the start and during the use of proton pump inhibitors (PPI), and during the use of somatostatin analogs. A total of 16/76 patients with an increase of CgA used PPIs during PRRT and 33/76 of patients used somatostatin analogs. Three patients started PPIs during therapy, this may have an influence on the evolution of CgA during therapy. Although due to the small number of patients, the potential effect on the increase of CgA is, therefore, limited.

The proliferation marker Ki-67 can be used for the grading of NETs (33,34). In 2007 we started to use Ki-67 routinely for all NETs. This study included patients treated from 2000 and therefore the Ki-67 is not available for all patients. It is, therefore, not possible to correlate the grading to the incidence of increase of CgA and liver enzymes.

An increase of the diameter of lesions of 10% or more on imaging was seen in 9% of patients with SD at 6 weeks post PRRT and was reversible at 6 months follow-up in 50% of patients. This transient increase was probably caused by inflammation causing localized edematous tissue at the site of the metastases and not based on progression. This radiogenic oedema has been described previously for PRRT of brain tumors and external beam radiation (35,36). In studies with cytokines, cancer vaccines and monoclonal antibodies

an increase in tumor burden has been demonstrated in patients with CR, PR or SD as treatment outcome. This phenomenon was described as pseudo-progression and resulted in a new response method, the immune-related response criteria (irRC) (37). This increase in the tumor size after immunotherapy is probably related to infusion of lymphocytes and macrophages in the tumor and new lesions are not always considered as PD. In our study, a temporary increase in tumor size was only observed in NET patients with SD as treatment outcome. Furthermore, it is notable that in 51/54 of the PRRT patients who eventually had PD as treatment outcome, it was based on the finding of new lesions on imaging or clinical deterioration. In 3 of 54 patients who had PD as treatment outcome, it was based solely on an increase of the diameter of the lesions according to SWOG criteria. The irRC are, therefore, not applicable for NET patients. Also, due to the low frequency of radiation-induced inflammation after PRRT, it seems that a new response method for NET patients is not required. However, clinicians should be aware that an increase in size directly after PRRT is more frequently due to radiation-induced inflammation than to permanent disease progression.

Conclusion

In this study we found that a temporary increase in liver function parameters and CgA level is not uncommon after treatment with PRRT, and it is not related to the final response to therapy at 3 months post PRRT. Since CgA may be released during cell damage, this increase does not pertain to progression in most patients. No differences were found between patients with an OR/SD and PD. Therefore, both liver function parameters and CgA should be interpreted with caution during therapy. Lastly, a temporary increase of ≥10% in the size of metastases is not uncommon after the intended cycles of PRRT. Our observations reported in this study indicate that initial permanent progression based on imaging is virtually always reflected by the finding of new lesions and rarely by an increase in tumor size alone. Clinicians should be aware that initial diameter increases are more frequently due to temporary radiation-induced inflammation than due to permanent disease progression, and that repeated imaging over time is necessary to differentiate between the two.

References

1. van der Zwan JM, Trama A, Otter R, Larrañaga N, Tavilla A, Marcos-Gragera R, et al. Rare neuroendocrine tumours: Results of the surveillance of rare cancers in Europe project. Eur J Cancer. 2013 Jul;49(11):2565–78.
2. Korse CM, Taal BG, van Velthuysen M-LF, Visser O. Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: Experience of two decades of cancer registry. Eur J Cancer. 2013 May;49(8):1975–83.
3. Forrer F, Waldherr C, Maecke HR, Mueller-Brand J. Targeted radionuclide therapy with 90Y-DOTATOC in patients with neuroendocrine tumors. Anticancer Res. 2006;26(1B):703–7.
4. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment With the Radiolabeled Somatostatin Analog [177Lu-DOTA0,Tyr3]Octreotate: Toxicity, Efficacy, and Survival. J Clin Oncol. 2008 Apr 29;26(13):2124–30.
5. Bushnell DL, O'Dorisio TM, O'Dorisio MS, Menda Y, Hicks RJ, Van Cutsem E, et al. 90Y-Edotreotide for Metastatic Carcinoid Refractory to Octreotide. J Clin Oncol. 2010 Apr 1;28(10):1652–9.
6. Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, et al. Response, Survival, and Long-Term Toxicity After Therapy With the Radiolabeled Somatostatin Analogue [90Y-DOTA]-TOC in Metastasized Neuroendocrine Cancers. J Clin Oncol. 2011 Jun 10;29(17):2416–23.
7. Bodei L, Cremonesi M, Grana CM, Fazio N, Iodice S, Baio SM, et al. Peptide receptor radionuclide therapy with 177Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging. 2011 Dec;38(12):2125–35.
8. Sabet A, Dautzenberg K, Haslerud T, Aouf A, Sabet A, Simon B, et al. Specific efficacy of peptide receptor radionuclide therapy with 177Lu-octreotate in advanced neuroendocrine tumours of the small intestine. Eur J Nucl Med Mol Imaging. 2015 Jul;42(8):1238–46.
9. Strosberg JR, Wolin E, Chasen B, Kulke MH, Bushnell DL, Caplin M, et al. 177-Lu-Dotatate significantly improves progression-free survival in patients with midgut neuroendocrine tumours: Results of the phase III NETTER-1 trial. European Cancer Congress 2015; 2015; Vienna, Austria.
10. Sabet A, Ezziddin K, Pape U-F, Ahmadzadehfar H, Mayer K, Poppel T, et al. Long-Term Hematotoxicity After Peptide Receptor Radionuclide Therapy with 177Lu-Octreotate. J Nucl Med. 2013 Nov 1;54(11):1857–61.
11. Bodei L, Kidd M, Paganelli G, Grana CM, Drozdov I, Cremonesi M, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging. 2015 Jan;42(1):5–19.
12. van Vliet EI, Krenning EP, Teunissen JJ, Bergsma H, Kam BL, Kwekkeboom DJ. Comparison of Response Evaluation in Patients with Gastroenteropancreatic and Thoracic Neuroendocrine Tumors After Treatment with [177Lu-DOTA0,Tyr3]Octreotate. J Nucl Med. 2013 Oct 1;54(10):1689–96.
13. Kwekkeboom DJ, Bakker WH, Kooij PP, Konijnenberg MW, Srinivasan A, Erion JL, et al. [177Lu-DOTAOTyr3]octreotate: comparison with [111In-DTPAo]octreotide in patients. Eur J Nucl Med. 2001 Sep;28(9):1319–25.

14. Green S, Weiss GR. Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. Invest New Drugs. 1992 Nov;10(4):239–53.
15. Gupta SK, Singla S, Bal C. Renal and Hematological Toxicity in Patients of Neuroendocrine Tumors After Peptide Receptor Radionuclide Therapy with ^{177} Lu-DOTATATE. Cancer Biother Radiopharm. 2012 Nov;27(9):593–9.
16. Svensson J, Berg G, Wängberg B, Larsson M, Forssell-Aronsson E, Bernhardt P. Renal function affects absorbed dose to the kidneys and haematological toxicity during 177Lu-DOTATATE treatment. Eur J Nucl Med Mol Imaging [Internet]. 2015 Feb 6 [cited 2015 Mar 25]; Available from: http://link.springer.com/10.1007/s00259-015-3001-1
17. Bergsma H, Konijnenberg MW, Kam BLR, Teunissen JJM, Kooij PP, de Herder WW, et al. Subacute haematotoxicity after PRRT with 177Lu-DOTA-octreotate: prognostic factors, incidence and course. Eur J Nucl Med Mol Imaging [Internet]. 2015 Sep 30 [cited 2016 Jan 7]; Available from: http://link.springer.com/10.1007/s00259-015-3193-4
18. Bushnell D, Menda Y, Madsen M, O'Dorisio T, Carlisle T, Zehr P, et al. Assessment of hepatic toxicity from treatment with 90Y-SMT 487 (OctreoTher™) in patients with diffuse somatostatin receptor positive liver metastases. Cancer Biother Radiopharm. 2003;18(4):581–8.
19. Riff BP, Yang Y-X, Soulen MC, Pryma DA, Bennett B, Wild D, et al. Peptide Receptor Radionuclide Therapy–Induced Hepatotoxicity in Patients With Metastatic Neuroendocrine Tumors. Clin Nucl Med. 2015;40(11):845–50.
20. Lawrance T, Robertson J, Anscher M, Jirtle R, Ensminger W, Fajardo L. Hepatic Toxicity Resulting from Cancer Treatment. Int J Radiat Oncol. 1995;31(5):1237–48.
21. Kennedy AS, Salem R. Radioembolization (yttrium-90 microspheres) for primary and metastatic hepatic malignancies. Cancer J Sudbury Mass. 2010 Apr;16(2):163–75.
22. Ezziddin S, Meyer C, Kahancova S, Haslerud T, Willinek W, Wilhelm K, et al. 90Y Radioembolization After Radiation Exposure from Peptide Receptor Radionuclide Therapy. J Nucl Med. 2012 Nov 1;53(11):1663–9.
23. Jimenez Fonseca P, Monleon Getino A, Krug S, Fierro Maya F, Tamagno G, de Herder WW, et al. A Univariate Analysis of Factors Influencing Survival in Advanced Pancreatic Neuroendocrine Tumors. Annual Conference of the European Neuroendocrine Tumor Society (ENETS); 2016; Barcelona, Spain.
24. Sierra ML, Agazzi A, Bodei L, Pacifici M, Arico D, De Cicco C, et al. Lymphocytic Toxicity in Patients After Peptide-Receptor Raionuclide Therapy (PRRT) with 177Lu-DOTATATE and 90Y-DOTATOC. Cancer Biother Radiopharm. 2009;24(6).
25. Kulkarni HR, Schuchardt C, Baum RP. Peptide receptor radionuclide therapy with (177)Lu labeled somatostatin analogs DOTATATE and DOTATOC: contrasting renal dosimetry in the same patient. Recent Results Cancer Res Fortschritte Krebsforsch Prog Dans Rech Sur Cancer. 2013;194:551–9.
26. Bodei L, Cremonesi M, Ferrari M, Pacifici M, Grana CM, Bartolomei M, et al. Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with 90Y-DOTATOC and 177Lu-DOTATATE: the role of associated risk factors. Eur J Nucl Med Mol Imaging. 2008 Oct;35(10):1847–56.

27. Sabet A, Ezziddin K, Pape U-F, Reichman K, Haslerud T, Ahmadzadehfar H, et al. Accurate assessment of long-term nephrotoxicity after peptide receptor radionuclide therapy with 177Lu-octreotate. Eur J Nucl Med Mol Imaging. 2014 Mar;41(3):505–10.
28. Deftos LJ. Chromogranin A: its role in endocrine function and as an endocrine and neuroendocrine tumor marker. Endocr Rev. 1991 May;12(2):181–7.
29. O'Connor DT, Deftos LJ. Secretion of chromogranin A by peptide-producing endocrine neoplasms. N Engl J Med. 1986 May 1;314(18):1145–51.
30. Nobels FR, Kwekkeboom DJ, Bouillon R, Lamberts SW. Chromogranin A: its clinical value as marker of neuroendocrine tumours. Eur J Clin Invest. 1998 Jun;28(6):431–40.
31. Stevic I, Dembinski TC, Pathak KA, Leslie WD. Transient early increase in thyroglobulin levels post-radioiodine ablation in patients with differentiated thyroid cancer. Clin Biochem. 2015 Jul;48(10-11):658–61.
32. Bernier M-O, Morel O, Rodien P, Muratet J-P, Giraud P, Rohmer V, et al. Prognostic value of an increase in the serum thyroglobulin level at the time of the first ablative radioiodine treatment in patients with differentiated thyroid cancer. Eur J Nucl Med Mol Imaging. 2005 Dec;32(12):1418–21.
33. Rindi G, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch. 2006 Oct;449(4):395–401.
34. Rindi G, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, et al. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Arch. 2007 Sep 25;451(4):757–62.
35. Kneifel S, Cordier D, Good S, Ionescu MCS, Ghaffari A, Hofer S, et al. Local targeting of malignant gliomas by the diffusible peptidic vector 1,4,7,10-tetraazacyclododecane-1-glutaric acid-4,7,10-triacetic acid-substance p. Clin Cancer Res Off J Am Assoc Cancer Res. 2006 Jun 15;12(12):3843–50.
36. Barani IJ, Larson DA. Radiation therapy of glioblastoma. Cancer Treat Res. 2015;163:49–73.
37. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res. 2009 Dec 1;15(23):7412–20.

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CHAPTER 7

Comparison of biochemical marker response, anatomical and molecular imaging for the detection of progression after therapy with [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate

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Submitted

Abstract

Purpose

Peptide receptor radionuclide therapy (PRRT) is a good therapeutic option for patients with inoperable or metastasized neuroendocrine tumors. In follow-up after PRRT patients undergo routine blood tests, anatomical and molecular imaging to detect progressive disease (PD). We compared the different methods and tried to determine the best diagnostic test to detect PD.

Patients and methods

Seventy-one patients with PD after therapy with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate who all had a CT and somatostatin receptor scintigraphy (SRS) at the moment of PD were retrospectively selected. Chromogranin A (CgA) was elevated in 50 patients and the cholestatic liver enzymes gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) were available in 63 and 65 patients, respectively. Results of CT, SRS and biochemical tests were compared to determine the best diagnostic test to detect progressive disease.

Results

Progression was demonstrated by CT and SRS at the same follow-up visit in 54/71 patients (76%). In 9 patients (13%) SRS detected PD before CT and in 8 patients (11%) CT was the first imaging modality to detect PD. Overall, an increase of ≥25% of CgA level compared to previous measurements as an indication of PD was demonstrated in 37/50 patients (74%), of ALP in 24/65 (37%) and of GGT in 32/63 (51%). An increase of CgA level was observed before imaging in 21/50 (42%) patients.

Conclusion

CT and SRS are complementary in the detection of PD after therapy with ^{177}Lu-DOTATATE. Also biochemical markers are able to detect PD in the majority of patients. However, none of the used diagnostic tests is clearly superior compared to the other and therefore a combination of different diagnostic tests, including imaging, is necessary in every patient.

Introduction

Neuroendocrine tumors (NETs) are a rare and heterogeneous group of tumors. The majority of grade 1-2 tumors express the somatostatin receptor, especially subtype 2 (1). This receptor is a target for somatostatin analogs, which can be labeled with radionuclides for both imaging and therapy. Currently, the most frequently used imaging modalities for NETs are computed tomography (CT), magnetic resonance imaging (MRI) and somatostatin receptor scintigraphy (SRS) with ^{111}In-DTPA-octreotide (Octreoscan, Petten, The Netherlands). For low-grade tumors, SRS is more sensitive for the detection of metastases than CT (2,3). For therapy, the radionuclide Lutetium-177 can be used. This is a β-emitting radionuclide with a half-life of 6.7 days. Linked to the somatostatin analog octreotate ([^{177}Lu-DOTA^{0},Tyr^{3}] octreotate), it is used for the treatment of metastasized or inoperable neuroendocrine tumors. Treatment with these radiolabeled somatostatin analogs results in good tumor response rates and a long time to progression (TTP) and overall survival (OS) (4).

NETs may excrete the tumor marker chromogranin A (CgA) (5). This tumor marker can be elevated in the blood samples of patients with NETs, but is not specific for the disease. Moreover, not every patient with a NET has an elevation of CgA. Especially well-differentiated NETs excrete CgA, while in patients with a poorly differentiated tumor the level of CgA is often not elevated. The level of serum CgA correlates positively with the extent of disease and can also predict the response to therapy (6,7). If a patient has an elevated CgA, this marker can be useful especially in the follow-up after peptide receptor radionuclide therapy (PRRT). Also the metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine of patients with neuroendocrine tumors, may be helpful in the diagnosis and follow-up of patients. The complete response rate in the group of patients treated with PRRT is approximately 2%, so most patients will eventually become progressive during follow-up (4). It is important to confirm progressive disease (PD) in an early stage, since other therapeutic options may be effective and should be started shortly after the detection of PD. In our institute patients undergo CT, SRS and blood sampling in follow-up. We retrospectively selected patients from our department who all had a CT and SRS with PD in the follow-up after PRRT with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-DOTATATE) and tried to determine the best way to detect progression of disease.

Patients and methods

Patients

Dutch patients with a histologically proven neuroendocrine tumor that were treated at our institute with ^{177}Lu-DOTATATE between July 2000 and March 2007 were retrospectively selected. Patients were included if they have had PD and at least 3 CT scans and one SRS in follow-up. For comparison between CT and SRS, patients should have had at least one

SRS. Therefore, the follow-up period must be at least 12 months and only patients with a therapy date before March 2007 were included. Since we previously reported a median TTP of 40 months (4) and patients were referred back to their own referring specialist after 2011, only a limited number of patients treated before March 2007 could be included. Moreover, only Dutch patients were selected, because of the limited loss to follow-up in this patient group.

Inclusion criteria for therapy with ^{177}Lu-DOTATATE were: tumor uptake at least as high as the uptake in the normal parenchyma of the liver on ^{111}In-DTPA-octreotide scintigraphy (Octreoscan, Mallinckrodt, Petten, the Netherlands) prior to the therapy and no previous treatment with other radiolabeled somatostatin analogs. Other inclusion criteria were: serum hemoglobin ≥ 6.0 mmol/L (≥ 9.7 g/dL), WBC count ≥ $2 \cdot 10^9$/L, platelet count ≥ $75 \cdot 10^9$/L, serum creatinine concentration ≤ 150 umol/L (≤ 1.7 mg/dL) or creatinine clearance ≥ 40-50 mL/min and Karnofsky performance status (KPS) ≥ 50.

SRS was performed in the follow-up at 12 months after therapy and thereafter every 18 months. CT or MRI was done in follow-up at 6 weeks, 3 months, 6 months and thereafter every 6 months. Routine blood samples including hematology, liver and kidney function tests and CgA were taken after each therapy cycle and at every follow-up visit.

This study was part of an on-going prospectively designed study on patients with neuroendocrine tumors treated with ^{177}Lu-DOTATATE at our department. The local medical ethical committee approved this study. All patients gave written informed consent to participate in the study.

Methods

[DOTA^0,Tyr^3]octreotate was obtained from BioSynthema, St Louis, MO. $^{177}LuCl_3$ was distributed by IDB-Holland, Baarle-Nassau, the Netherlands. ^{177}Lu-DOTATATE was locally prepared as described previously (8)Tyr3]octreotate has a nine-fold higher affinity for the somatostatin receptor subtype 2 as compared with [DOTA0, Tyr3]octreotide. Also, labeled with the beta- and gamma-emitting radionuclide lutetium-177, this compound has been shown to have a very favorable impact on tumor regression and animal survival in a rat model. Because of these reported advantages over the analogs currently used for somatostatin receptor-mediated radiotherapy, we decided to compare [177Lu-DOTA0,Tyr3] octreotate (177Lu-octreotate. Before the infusion of the radiopharmaceutical, Granisetron or Ondansetron was injected intravenously. To reduce the radiation dose to the kidneys, an infusion of amino acids (2.5% arginine and 2.5% lysine in 1L 0.9% NaCl) was started 30 min before the administration of the radiopharmaceutical and lasted 4 h. The radiopharmaceutical was coadministered using a second pump system over 30 min. The intended interval between treatments was 6–10 wk. Patients were treated up to a cumulative intended

dose of 750 to 800 mCi (27.8–29.6 GBq).

Imaging

Contrast enhanced CT of the abdomen and if applicable also a CT of the thorax were made at every follow-up visit. Additional scanning of the liver in the arterial phase was done if a patient had (suspicion of) liver metastases. SRS was done 24 hours after injection of 220 MBq (± 22 MBq). Planar imaging of the whole body was acquired by spot views of 15 min. Additional SPECT(/CT) of the upper abdomen was done if a patient had a tumor or metastases in the liver or upper abdomen.

Determination of progressive disease

Progressive disease on CT was defined according to the SWOG criteria (9) as ≥50% increase or an increase of 10 cm^2 in the sum of products of all measurable lesions over the smallest sum observed (over baseline if no decrease), or clear worsening of any evaluable disease, or reappearance of any lesion that had disappeared, or appearance of any new lesion. Progressive disease on SRS was defined as reappearance of any lesion that had disappeared, or appearance of any new lesion. Progressive disease based on serum CgA, alkaline phosphatase (ALP) or gamma-glutamyl transpeptidase (GGT) was defined as an increase in serum ≥25% compared to the previous measurement, which was confirmed by a second measurement within 6 months. This second measurement was necessary to avoid any false-positive results. 5-Hydroxyindoleacetic acid (5-HIAA) excretion was tested in 24-hour urine samples. An increase of ≥25% compared to the previous measurement was considered as an indication of PD.

Results

A total of 71 patients were progressive at the time of CT/SRS and available for evaluation. CgA was elevated in 50 patients. Baseline characteristics are presented in table 1. There were 33 men and 38 women. Mean age was 57.2 years (range 32-79). Imaging was done with CT in 70 patients and with MRI in one patient. The median TTP was 37 months (range 22-119 months).

Table 1. Patient and tumor characteristics.

	No patients	%
Male	33	47
Female	38	54
Age	57.2 (range 32-79)	
Primary tumor site		
Small intestine	37	53
Pancreas	20	29
Rectum	5	7
Bronchus	3	4
Stomach	2	3
Kidney	1	1
Unknown	3	4
Liver metastases	66	94
Limited	54	77
Extensive	12	17
Bone metastases	9	13
No. of cycles PRRT	3.9 (range 3-5)	
Median cumulative administered activity	800 mCi (range 600-900)	
Median time to progression	37 months (range 22-119)	

Progression was confirmed on anatomical imaging and SRS at the same follow-up visit in 54/71 patients (76%) (Figure 1). In 9 patients (13%) SRS demonstrated PD before CT. In all patients this was based on new lesions that were not yet visible on CT. In 8 patients (11%) CT was the first imaging modality to detect PD (Figure 1). This was based solely on an increase in size of metastases in one patient and in seven patients based also on new lesions.

CgA was elevated in 50/71 (70%) of the selected patients. Overall, CgA indicated PD in 74% of these patients. An increase of ≥25% compared to the previous measurement confirmed PD at the same follow-up visit as imaging in 16/50 patients (32%). An increase in CgA was observed before imaging in 21/50 (42%) patients (Figure 2). This increase was detected an average of 8 months before PD on imaging. In 13/50 (26%) patients no increase of CgA was observed at the moment of PD on imaging.

5-HIAA was elevated in 27 patients. At the time of progression on imaging 8/27 (30%) patients had an increase of 5-HIAA. In 9/27 (33%) patients an increase of 5-HIAA was observed before the confirmation of PD on imaging. This resulted in a sensitivity for the detection of PD with 5-HIAA of 63%.

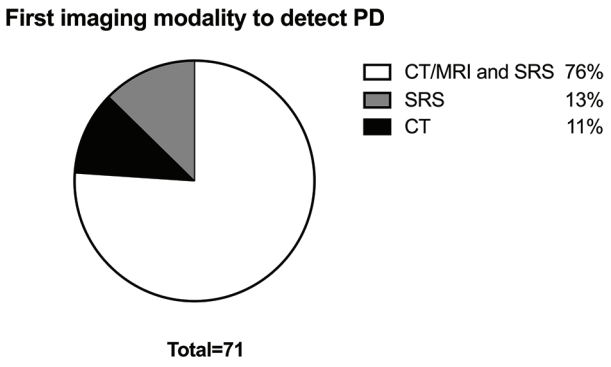

Figure 1. Progression based on different imaging modalities

The cholestatic liver enzymes gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) were available in 63 and 65 patients respectively. ALP was able to indicate PD in 37% and GGT in 51% of patients. An increase ≥25% of GGT compared to the previous measurement was observed in 16/63 (25%) of patients and an increase of ALP in 15/65 (23%) of patients at time of PD on imaging. The cholestatic liver enzymes and CgA showed an increase of ≥25% in the same part of patients at time of PD on imaging (figure 2). An increase of ALP and GGT was observed before imaging in 9/65 (14%) and 16/63 (25%) of patients respectively.

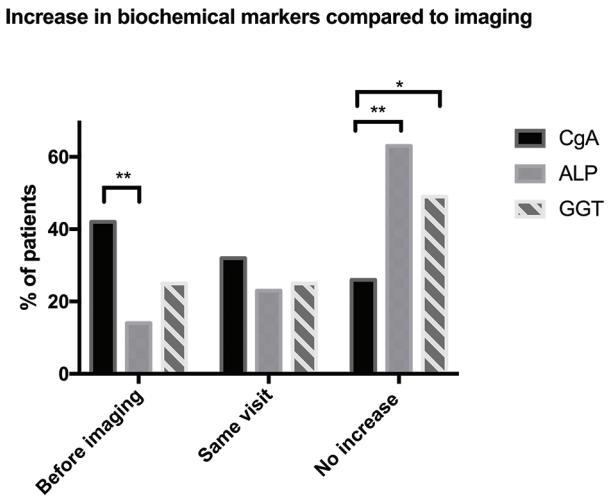

Figure 2. Percentages of patients with PD in relation to the change in biochemical markers.
*: $p<0.05$
**: $p<0.01$

The body weight was measured at every follow-up visit in 59 patients. A decrease of body weight of 3 kg or more was observed in 20/59 patients (34%) at the time of PD (figure 3). The mean weight loss was 6 kg (range 3-19 kg). In 4/59 (7%) patients an increase of body weight of 3 kg or more was found (range 3-6 kg).

In none of these patients the development of ascites or edemas was the cause for the increase in body weight. In the remaining 35/59 patients the body weight was stable.

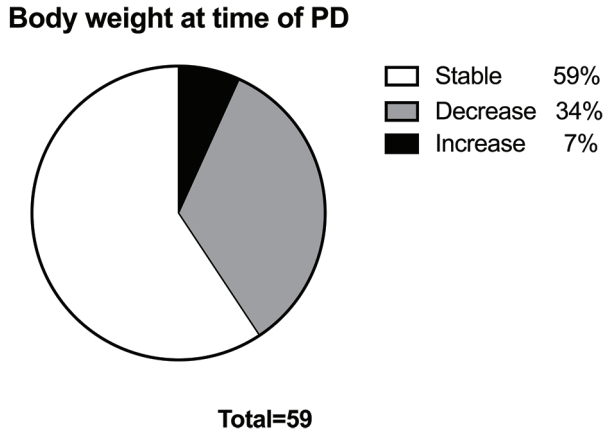

Figure 3. Change in body weight at time of PD

Discussion

In this study, we demonstrated that in the majority of patients (76%) both CT and SRS could detect progressive disease after PRRT with ^{177}Lu-DOTATATE at the same follow-up visit. The tumor marker CgA was able to indicate PD in 74% of patients. In 42% of patients CgA was increased before there was any evidence of PD on imaging. Cholestatic liver enzymes were not very helpful as a method for the detection of PD.

Progressive disease can present as either a deterioration of the clinical condition or an increase of biochemical markers, but the gold standard remains imaging. For low-grade (grade 1 and 2) NET, SRS has a better sensitivity than CT, therefore it is not surprising that new metastases can be detected on SRS at an earlier stage than on CT. However, PD based solely on an increase of size can only be detected with CT. Besides, due to the better spatial resolution of CT, small metastases can be detected before these are visible on SRS. Our results demonstrated that both CT and SRS can detect new lesions before these are recognized on the other imaging modality. Therefore, anatomical and molecular imaging are complementary to each other and not one modality is superior. A disadvantage when frequently imaging is performed is the radiation dose. Both CT and SRS give the patients a significant radiation dose. However, for this specific group of patients this is less relevant, since they receive a significant higher radiation dose during PRRT than with imaging.

With the introduction of somatostatin analogs bound to the positron emitting radionuclide Gallium-68, the sensitivity for the detection of metastases is even better than for SRS

and CT. More metastases can be detected and also a change in clinical management was demonstrated with these new radiopharmaceuticals (10). Due to a higher spatial resolution, it is expected that imaging with ^{68}Ga labeled somatostatin analogs can detect metastases before these are visible on SRS. This imaging modality may be able to detect PD at an earlier stage than CT. Unfortunately, since this technique is only recently introduced in the daily practice, no data is available about results in the follow-up after PRRT in our group of patients.

An increase of CgA is seen in 42% of patients before PD on imaging. Although, in a few of these patients there was an increase in size of the metastases on CT, it did not fulfil the criteria of PD according to the SWOG criteria. Different studies demonstrated that SRS is more sensitive for the detection of NETs than CgA (11–14). A report from Rossi et al demonstrated that CgA can detect PD earlier than radiological imaging (15). This is concordant with our findings. However, the main disadvantage of this tumor marker is the fact that not all tumors produce CgA and in a substantial part of patients there is no increase at the moment of PD on imaging. Moreover, the use of proton pomp inhibitors and somatostatin analogs may cause a fluctuation in the levels of CgA, making it less reliable. To avoid these false-positive results, the confirmation by a second measurement is mandatory. A main advantage of CgA is the low cost compared to imaging.

Other biochemical markers that can be used for detection and follow-up of neuroendocrine tumors are neuron-specific enolase (NSE) and the α-subunit of glycoprotein hormones (α-SU). Unfortunately, the sensitivity for the detection of neuroendocrine tumors is far lower for these markers than for CgA (16). Therefore, these are not frequently used in daily practice.

5-HIAA is a metabolite of serotonin and is typically elevated in patients with a carcinoid syndrome. An increase of this marker may indicate more production of serotonin and thus more tumor activity. Unfortunately, 5-HIAA may show an increase due to other conditions, such as changes in diet. We tried to exclude the false positive results with a confirmation by a second measurement. With these additional measurements a sensitivity of 63% for the detection of PD can be accomplished, which is lower than for CgA.

The cholestatic liver enzymes ALP and GGT may also rise at the time of PD. If a tumor increases in size, it is expected that there will be more obstruction of bile ducts and therefore higher levels of these liver enzymes. Unfortunately, ALP and GGT were only able to predict PD in 37% and 51%, respectively. Besides, the tumor marker CgA was better than the liver enzymes for the overall detection of PD after PRRT. Therefore, these liver enzymes are not very useful for the detection of PD in follow-up.

The most simple and cheapest way to detect PD is body weight. If the body weight is measured at every follow-up visit with the same method, patients with PD had a decrease

in body weight of ≥ 3 kg in 34% of patients. Since this measurement is a very simple and cheap procedure, it should be done at every follow-up visit. Although the sensitivity of body weight for the detection of PD is not very high, an unintended decrease in body weight should always be an indication for further investigations.

Recently, the NETest has been developed (17). This test uses a circulating transcript analysis in NETs and can predict the response after treatment with somatostatin analogs (18). Also, this test can predict the efficacy of PRRT (19). Besides, Bodei et al reported that CgA was non-informative after PRRT compared to NETest. In the near future this might be a promising method to predict response before PRRT and detect progression in follow-up. Unfortunately, this new method is currently used only in studies and not widely performed during and after PRRT.

A limitation of this study is the small number of included patients. Although we analysed more than 300 patients, only 71 patients were suitable for analysis. For a good comparison between SRS and CT, patients were only selected if PD was confirmed at the time of the less frequently performed SRS. Moreover, due to a relative low frequency of imaging with SRS (every 18 months) and long time to progression many patients had to be excluded.

Conclusion

Both CT and SRS are able to detect PD after PRRT with ^{177}Lu-DOTATATE and are complementary to each other. In a relative large part of patients (42%) the tumor marker CgA can detect PD before imaging, however in a substantial part of patients (26%) no increase of this tumor marker was observed at the time of PD. The cholestatic liver enzymes ALP and GGT can detect PD as well, but only in less than half of patients and are therefore not very helpful in the detection of PD after PRRT. In conclusion, there is not one ideal method that can demonstrate PD before the other. Biochemical markers may give an indication, but cannot be leading in the follow-up. The combination of different imaging modalities and biochemical makers is necessary in all patients.

References

1. Reubi JC, Laissue J, Waser B, Horisberger U, Schaer J-C. Expression of Somatostatin Receptors in Normal, Inflamed, and Neoplastic Human Gastrointestinal Tissues. Ann N Y Acad Sci. 1994 Sep;733(1 Molecular and):122–37.
2. Shi W, Johnston CF, Buchanan KD, Ferguson WR, Laird JD, Crothers JG, et al. Localization of neuroendocrine tumours with [111In] DTPA-octreotide scintigraphy (Octreoscan): a comparative study with CT and MR imaging. QJM Mon J Assoc Physicians. 1998 Apr;91(4):295–301.
3. Cwikła JB, Buscombe JR, Mielcarek WA, Caplin ME, Watkinson AJ, Hilson AJ. Comparison of functional imaging and standard CT in evaluation of disease extent in patients with tumours showing neuroendocrine features. Nucl Med Rev Cent East Eur. 2001;4(1):27–33.
4. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment With the Radiolabeled Somatostatin Analog [177Lu-DOTA0,Tyr3]Octreotate: Toxicity, Efficacy, and Survival. J Clin Oncol. 2008 Apr 29;26(13):2124–30.
5. Lawrence B, Gustafsson BI, Kidd M, Pavel M, Svejda B, Modlin IM. The Clinical Relevance of Chromogranin A as a Biomarker for Gastroenteropancreatic Neuroendocrine Tumors. Endocrinol Metab Clin North Am. 2011 Mar;40(1):111–34.
6. Nehar D, Lombard-Bohas C, Olivieri S, Claustrat B, Chayvialle J-A, Penes M-C, et al. Interest of Chromogranin A for diagnosis and follow-up of endocrine tumours. Clin Endocrinol (Oxf). 2004 May;60(5):644–52.
7. Nikou GC, Marinou K, Thomakos P, Papageorgiou D, Sanzanidis V, Nikolaou P, et al. Chromogranin A Levels in Diagnosis, Treatment and Follow-Up of 42 Patients with Non-Functioning Pancreatic Endocrine Tumours. Pancreatology. 2008 Oct;8(4-5):510–9.
8. Kwekkeboom DJ, Bakker WH, Kooij PP, Konijnenberg MW, Srinivasan A, Erion JL, et al. [177Lu-DOTAOTyr3]octreotate: comparison with [111In-DTPAo]octreotide in patients. Eur J Nucl Med. 2001 Sep;28(9):1319–25.
9. Green S, Weiss GR. Southwest Oncology Group standard response criteria, endpoint definitions and toxicity criteria. Invest New Drugs. 1992 Nov;10(4):239–53.
10. Deppen SA, Liu E, Blume JD, Clanton J, Shi C, Jones-Jackson LB, et al. Safety and Efficacy of 68Ga-DOTATATE PET/CT for Diagnosis, Staging, and Treatment Management of Neuroendocrine Tumors. J Nucl Med. 2016 May 1;57(5):708–14.
11. Cimitan M. Somatostatin receptor scintigraphy versus chromogranin A assay in the management of patients with neuroendocrine tumors of different types: clinical role. Ann Oncol. 2003 Jul 1;14(7):1135–41.
12. Namwongprom S, Wong FC, Tateishi U, Kim EE, Boonyaprapa S. Correlation of chromogranin A levels and somatostatin receptor scintigraphy findings in the evaluation of metastases in carcinoid tumors. Ann Nucl Med. 2008 May;22(4):237–43.
13. Rodrigues M, Gabriel M, Heute D, Putzer D, Griesmacher A, Virgolini I. Concordance between results of somatostatin receptor scintigraphy with 111In-DOTA-DPhe1-Tyr3-octreotide and chromogranin A assay in patients with neuroendocrine tumours. Eur J Nucl Med Mol I maging. 2008 Oct;35(10):1796–802.

14. Stokkel MPM, Rietbergen DD, Korse CM, Taal BG. Somatostatin receptor scintigraphy and chromogranin A assay in staging and follow-up of patients with well-differentiated neuroendocrine tumors: Nucl Med Commun. 2011 Aug;32(8):731–7.
15. Rossi RE, Garcia-Hernandez J, Meyer T, Thirlwell C, Watkins J, Martin NG, et al. Chromogranin A as a predictor of radiological disease progression in neuroendocrine tumours. Ann Transl Med [Internet]. 2015 [cited 2016 Jan 25];3(9). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4481369/
16. Nobels FR, Kwekkeboom DJ, Coopmans W, Schoenmakers CH, Lindemans J, De Herder WW, et al. Chromogranin A as serum marker f or neuroendocrine neoplasia: comparison with neuron-specific enolase and the α-subunit of glycoprotein hormones. J Clin Endocrinol Metab. 1997;82(8):2622–8.
17. Kidd M, Drozdov I, Modlin I. Blood and tissue neuroendocrine tumor gene cluster analysis correlate, define hallmarks and predict disease status. Endocr Relat Cancer. 2015 Aug;22(4):561–75.
18. Ćwikła JB, Bodei L, Kolasinska-Ćwikła A, Sankowski A, Modlin IM, Kidd M. Circulating Transcript Analysis (NETest) in GEP-NETs Treated With Somatostatin Analogs Defines Therapy. J Clin Endocrinol Metab. 2015 Nov;100(11):E1437–45.
19. Bodei L, Kidd M, Modlin IM, Severi S, Drozdov I, Nicolini S, et al. Measurement of circulating transcripts and gene cluster analysis predicts and defines therapeutic efficacy of peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumors. Eur J Nucl Med Mol Imaging. 2016 May;43(5):839–51.

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CHAPTER 8

Summary and general discussion

NETs are a heterogeneous group of tumors, but they generally express high numbers of high affinity somatostatin receptors on their cell membranes. These receptors are a target for SSAs, which can be labeled with radionuclides for both imaging and therapy. Treatment with "cold" long-acting SSAs is now widely used for suppression of NET-related symptoms, but also for inhibition of tumor growth (1,2). The expression of the somatostatin receptor subtypes can be used for imaging by SSAs labeled to different radionuclides. Currently, the most frequently used radiopharmaceutical is ^{111}In-DTPA-octreotide (OctreoScan). However, recently developed PET tracers will replace OctreoScan. For PET imaging, three different combinations of SSAs and Gallium-68 are used; ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE. These Gallium-68 labeled SSAs all have different affinity profiles for the different subtypes of the somatostatin receptor, but have in common that each SSA has a high affinity to the somatostatin receptor subtype 2. Despite their different affinities, there are no big differences in the sensitivity for the detection of NETs (3).

For therapy, SSAs can be labeled to the beta-emitting radionuclides Yttrium-90 or Lutetium-177. Although no direct comparison between these two radionuclides is available, reports about PFS/OS are more or less the same (4). The main disadvantage of Yttrium-90 labeled SSAs is the more frequently reported and more severe side-effects due to the high energy of this radionuclide, specifically related to the renal function.

In this thesis, several aspects regarding the imaging and therapy of NETs with radiolabeled SSAs are discussed.

Chapter 1 is a general introduction on NETs and gives an overview about the different imaging and treatment options, which are currently available for NETs.

Chapter 2 is a review of the literature on nuclear imaging techniques of NETs. The different results of imaging with radiolabeled SSAs are discussed. Currently, ^{111}In-DTPA-octreotide and ^{68}Ga-labeled SSAs are most frequently used. Besides these tracers, also other PET targets like ^{11}C-5-HTP and ^{18}F-DOPA were developed. For the localization of insulinomas, glucagon-like peptide-1 receptor (Exendin-4) imaging is a promising new sensitive technique.

In chapter 3, incidence and mechanism of physiological uptake in the pancreatic head on ^{111}In-DTPA-octreotide scintigraphy is described. 178 scans with a SPECT/CT of the upper abdomen were analyzed. Uptake in the pancreatic head (uncinate process) was seen in 46/178 patients on SPECT/CT and in 12 patients uptake was seen on planar imaging. In patients with diabetes mellitus, the incidence of uptake in the pancreatic head was doubled. Since previous case reports showed uptake in the pancreatic head due to histology proven PP cell hyperplasia and 90% of these cells are located in the pancreatic head, PP cell hyperplasia is the most likely explanation for this visualization. Also, patients with diabetes

mellitus may have elevated serum PP concentrations, explaining the high incidence of uptake in the pancreatic head in these patients.

Chapter 4 is a review of the literature on PRRT. The results and side-effects of the different radiolabeled SSAs are discussed. The ORRs that are reported vary between 15-35%. The results may differ for different radionuclides and type of primary tumor. Compared to historical controls and other currently available therapeutic options for metastasized and inoperable NETs, the PFS, TTP and OS are favorable for PRRT. Severe long-term side-effects are rare and the incidence of side-effects differ between the radionuclides. Especially for Yttrium-90 severe long-term renal toxicity is reported in up to 9% of all patients. Other long-term side-effects are MDS and AL. These occur in approximately 2-3% of all patients.

In chapter 5, the long-term efficacy, survival and side effect of treatment with ^{177}Lu-DOTATATE in patients with GEP and bronchial NETs is described. Since 2000, a large group of more than 1200 patients were treated and followed at our department. ORR in 443 patients receiving ≥ 600 mCi ^{177}Lu-DOTATATE was 39% and SD was observed in 43% of patients. PFS was 29 months, TTP was 36 months and OS was 63 months. Long-term toxicity included AL in 4 patients (0.7%) and MDS in 9 patients (1.5%). No therapy-related renal or hepatic failure was observed. Compared to studies with the other therapeutic options that are currently registered for patients with inoperable or metastasized NETs, PRRT with ^{177}Lu-DOTATATE has a better PFS and TTP.

Chapter 6 describes the pitfalls in the response evaluation after PRRT with ^{177}Lu-DOTATATE. An increase of the aminotransferases was observed in 24% of all patients. Also, an increase of CgA was observed in 29% of patients. There was no difference in the tumor marker increase between patients with an OR or PD as treatment outcomes. On imaging, patients with SD as treatment outcome can have a temporary increase in tumor size, which is not related to progression. An increase in tumor size of ≥10% was observed in 9% of patients with SD. Clinicians should be aware that these changes are probably due to radiation-induced inflammation and not related to the treatment response. Repeated measurements are necessary to differentiate between these two and to confirm progression.

In chapter 7, the best ways to detect progression after therapy with ^{177}Lu-DOTATATE are described. Patients underwent biochemical markers tests, molecular and anatomical imaging at follow-up. A definite answer to the question, which is best way to detect progressive disease cannot be given. If we compare the different biochemical tumor markers and cholestatic liver enzymes, CgA has the best sensitivity for the detection of progressive disease. Unfortunately, a subgroup of patients didn't show any increase of this biochemical marker at the time of progression on imaging. Therefore, the combination of biochemical markers and imaging is the only way to not miss any patients with progressive disease. It can be expected that tests using molecular markers (like the NETest) in the future will provide better sensitivities.

Future aspects of PRRT

With the recent publication of the excellent results of the NETTER-1 trial in patients with advanced midgut NETs, it is expected that ^{177}Lu-DOTATATE will become available for the treatment of more NET patients around the world. The NETTER-1 study demonstrated a longer PFS and higher response rates for ^{177}Lu-DOTATATE combined with octreotide LAR in a direct comparison to high-dose octreotide LAR treatment alone (5). The targeted therapies that are currently registered for pancreatic NETs are everolimus and sunitinib. A direct comparison between one of these targeted therapies and ^{177}Lu-DOTATOC is currently being studied for both drugs.

To improve the efficacy of PRRT, the combination of PRRT with chemotherapy has been investigated by different research groups (6–9). These reports have shown better response rates with combined therapies than PRRT alone, but unfortunately no randomized studies are available at this moment. The results of a randomized trial comparing ^{177}Lu-DOTATATE with ^{177}Lu-DOTATATE in combination with capecitabine (Xeloda,) are currently being analyzed in our institute.

NETs of the pancreas may be inoperable due to involvement of the vascular structures. In our study we found the best ORR of 48% in patients with pancreatic NETs. After a significant reduction of tumor size after therapy with ^{177}Lu-DOTATATE, some pancreatic NET patients can become eligible for surgery. Therefore, therapy with ^{177}Lu-DOTATATE can be used in a neo-adjuvant setting. A publication by van Vliet and colleagues (10) indeed demonstrated successful pancreatic surgery after therapy with ^{177}Lu-DOTATATE in 9/29 patients (31%) with inoperable pancreatic NETs at baseline.

Since the majority of NET metastases are located in the liver, intra-arterial/loco-regional administration of PRRT in the liver via the hepatic artery may result in a higher response rates as compared to systemic PRRT (11-13). Pool et al (13) demonstrated a two-fold higher uptake in the liver after intra-arterial administration of ^{177}Lu-DOTATATE via the hepatic artery as compared to intravenous administration in a preclinical model. Also, imaging studies with ^{68}Ga-DOTATOC PET demonstrated an average 3.75 fold higher SUV in liver metastases after intraarterial injection via the hepatic artery than after systemic administration of this radiopharmaceutical (14). Other clinical studies demonstrated better therapeutic results after loco-regional therapy than after systemic therapy in NET patients with dominant metastases in the liver. However, randomized studies are still lacking (11,12).

Unfortunately, most NET patients will become progressive again after initial successful therapy with ^{177}Lu-DOTATATE. If patients tolerated the first PRRT cycles well and if there was an objective response or clinical improvement to the initial PRRT, it is feasible to retreat patients with additional cycles of ^{177}Lu-DOTATATE. PRRT as a salvage therapy has

been described with reasonable results and limited side-effects (15–17). Results of larger studies with a long follow-up are necessary to demonstrate long-term safety.

A different strategy to improve uptake of PRRT in the tumor is the use of somatostatin receptor antagonists instead of agonists. In the past, it was widely accepted that a radiolabeled peptide should internalize into the cell to increase the residence time. The antagonists do not internalize into the cell, but only bind to the receptors on the cell surface. Surprisingly, in a preclinical model comparing the effects of one of these somatostatin receptor antagonists, ^{177}Lu-DOTA-JR11, and ^{177}Lu-DOTA-octreotate a five-times higher uptake of the antagonist as compared to the receptor agonist was demonstrated (18). The first human study with ^{177}Lu-DOTA-JR11 demonstrated that this treatment is feasible in patients and showed a 1.7-10.6 higher tumor uptake than ^{177}Lu-DOTATATE (19). However, no large studies, or direct comparisons with somatostatin receptor agonists are currently available and the (long-term) toxicity of these antagonists is currently unknown.

A different approach to improve the response of PRRT is the use of alpha-emitting radionuclides. Alpha-emitting radionuclides have a shorter tissue path-length than beta-emitting radionuclides. However, all energy is absorbed in the tissue and therefore more DNA-damage will be induced by these alpha-emitting radionuclides. Also, the absorbed dose in other (healthy) organs will be limited due to the shorter path-length. The first study in NET patients using ^{213}Bi-DOTATOC was promising with an objective response or stable disease obtained 12 months after therapy in all 7 patients (20).

A new way to predict the response after PRRT is the NETest (21). This test uses a circulating transcript analysis in NETs and can predict the efficacy of PRRT (22,23). In the near future, this test might prove to be promising with regard to predict response at baseline or to detect progression at follow-up. Unfortunately, this new test is currently only used in clinical studies and not routinely performed during and after PRRT.

In conclusion, PRRT with radiolabeled SSAs is an effective and safe therapy for NETs. The response rates are high and PFS is longer than with the other currently available therapies. With new developments in the fields of imaging and PRRT, hopefully more patients will receive the most appropriate treatment at the best moment (theranostics) and in the end more patients will achieve disease control.

References

1. Rinke A, Muller H-H, Schade-Brittinger C, Klose K-J, Barth P, Wied M, et al. Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group. J Clin Oncol. 2009 Aug 24;27(28):4656–63.
2. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. N Engl J Med. 2014 Jul 17;371(3):224–33.
3. Geijer H, Breimer LH. Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2013 Jul 20;40(11):1770–80.
4. van der Zwan WA, Bodei L, Mueller-Brand J, de Herder WW, Kvols LK, Kwekkeboom DJ. GEPNETS UPDATE: Radionuclide therapy in neuroendocrine tumors. Eur J Endocrinol. 2014 Nov 24;172(1):R1–8.
5. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of ^{177} Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017 Jan 12;376(2):125–35.
6. van Essen M, Krenning EP, Kam BL, de Herder WW, van Aken MO, Kwekkeboom DJ. Report on short-term side effects of treatments with 177Lu-octreotate in combination with capecitabine in seven patients with gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2008 Apr;35(4):743–8.
7. Claringbold PG, Brayshaw PA, Price RA, Turner JH. Phase II study of radiopeptide 177Lu-octreotate and capecitabine therapy of progressive disseminated neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2011 Feb;38(2):302–11.
8. Claringbold PG, Price RA, Turner JH. Phase I-II Study of Radiopeptide ^{177} Lu-Octreotate in Combination with Capecitabine and Temozolomide in Advanced Low-Grade Neuroendocrine Tumors. Cancer Biother Radiopharm. 2012 Nov;27(9):561–9.
9. Kesavan M, Claringbold PG, Turner JH. Hematological Toxicity of Combined ^{177} Lu-Octreotate Radiopeptide Chemotherapy of Gastroenteropancreatic Neuroendocrine Tumors in Long-Term Follow-Up. Neuroendocrinology. 2014;99(2):108–17.
10. van Vliet EI, van Eijck CH, de Krijger RR, Nieveen van Dijkum EJ, Teunissen JJ, Kam BL, et al. Neoadjuvant Treatment of Nonfunctioning Pancreatic Neuroendocrine Tumors with [177Lu-DOTA0,Tyr3]Octreotate. J Nucl Med. 2015 Nov 1;56(11):1647–53.
11. McStay MKG, Maudgil D, Williams M, Tibballs JM, Watkinson AF, Caplin ME, et al. Large-Volume Liver Metastases from Neuroendocrine Tumors: Hepatic Intraarterial ^{90} Y-DOTA-Lanreotide as Effective Palliative Therapy ^{1}. Radiology. 2005 Nov;237(2):718–26.
12. Kratochwil C, Lopez-Benitez R, Mier W, Haufe S, Isermann B, Kauczor H-U, et al. Hepatic arterial infusion enhances DOTATOC r adiopeptide therapy in patients with neuroendocrine liver metastases. Endocr Relat Cancer. 2011 Sep 20;18(5):595–602.

13. Pool SE, Kam BLR, Koning GA, Konijnenberg M, ten Hagen TLM, Breeman WAP, et al. [^{111} In-DTPA]octreotide Tumor Uptake in GEPNET Liver Metastases After Intra-Arterial Administration: An Overview of Preclinical and Clinical Observations and Implications for Tumor adiation Dose After Peptide Radionuclide Therapy. Cancer Biother Radiopharm. 2014 May;29(4):179–87.
14. Kratochwil C, Giesel FL, Lopez-Benitez R, Schimpfky N, Kunze K, Eisenhut M, et al. Intraindividual Comparison of Selective Arterial versus Venous 68Ga-DOTATOC PET/CT in Patients with Gastroenteropancreatic Neuroendocrine Tumors. Clin Cancer Res. 2010 May 15;16(10):2899–905.
15. Forrer F, Uusijärvi H, Storch D, Maecke HR, Mueller-Brand J. Treatment with 177Lu-DOTATOC of patients with relapse of neuroendocrine tumors after treatment with 90Y-DOTATOC. J Nucl Med Off Publ Soc Nucl Med. 2005 Aug;46(8):1310–6.
16. van Essen M, Krenning EP, Kam BLR, de Herder WW, Feelders RA, Kwekkeboom DJ. Salvage Therapy with 177Lu-Octreotate in Patients with Bronchial and Gastroenteropancreatic Neuroendocrine Tumors. J Nucl Med. 2010 Mar 1;51(3):383–90.
17. Sabet A, Haslerud T, Pape U-F, Sabet A, Ahmadzadehfar H, Grünwald F, et al. Outcome and toxicity of salvage therapy with 177Lu-octreotate in patients with metastatic gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2014 Feb;41(2):205–10.
18. Dalm SU, Nonnekens J, Doeswijk GN, de Blois E, van Gent DC, Konijnenberg MW, et al. Comparison of the Therapeutic Response to Treatment with a 177Lu-Labeled Somatostatin Receptor Agonist and Antagonist in Preclinical Models. J Nucl Med Off Publ Soc Nucl Med. 2016 Feb;57(2):260–5.
19. Wild D, Fani M, Fischer R, Del Pozzo L, Kaul F, Krebs S, et al. Comparison of Somatostatin Receptor Agonist and Antagonist for Peptide Receptor Radionuclide Therapy: A Pilot Study. J Nucl Med. 2014 Aug 1;55(8):1248–52.
20. Kratochwil C, Giesel FL, Bruchertseifer F, Mier W, Apostolidis C, Boll R, et al. 213Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience. Eur J Nucl Med Mol Imaging. 2014 Nov;41(11):2106–19.
21. Kidd M, Drozdov I, Modlin I. Blood and tissue neuroendocrine tumor gene cluster analysis correlate, define hallmarks and predict disease status. Endocr Relat Cancer. 2015 Aug;22(4):561–75.
22. Ćwikła JB, Bodei L, Kolasinska-Ćwikła A, Sankowski A, Modlin IM, Kidd M. Circulating Transcript Analysis (NETest) in GEP-NETs Treated With Somatostatin Analogs Defines Therapy. J Clin Endocrinol Metab. 2015 Nov;100(11):E1437–45.
23. Bodei L, Kidd M, Modlin IM, Severi S, Drozdov I, Nicolini S, et al. Measurement of circulating transcripts and gene cluster analysis predicts and defines therapeutic efficacy of peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumors. Eur J Nucl Med Mol Imaging. 2016 May;43(5):839–51.

CHAPTER 9

Samenvatting en algemene discussie

Neuro-endocriene tumoren (NETs) zijn een heterogene groep tumoren, maar over het algemeen brengen ze een groot aantal somatostatine receptoren met een hoge affiniteit tot expressie op hun celmembraan. Deze receptoren kunnen somatostatine analogen (SSAs) binden. Deze SSAs kunnen worden gelabeld met radionucliden voor beeldvorming en therapie. Behandeling met ongelabelde langwerkenden SSAs wordt gebruikt voor het onderdrukken van symptomen, maar ook voor het remmen van tumorgroei (1,2). De expressie van de somatostatine receptoren wordt gebruikt voor beeldvorming door SSAs te labelen met verschillende radionucliden. Op dit moment is het meest gebruikte radiofarmacon ^{111}In-DTPA-octreotide (OctreoScan). Het is echter de verwachting dat dit binnenkort wordt vervangen door radionucliden die positronen uitzenden. Voor beeldvorming met positron emissie tomografie (PET) zijn op dit moment drie verschillende combinaties van SSA en Gallium-68 beschikbaar; ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC en ^{68}Ga-DOTATATE. Deze SSAs gelabeld met Gallium-68 hebben allemaal een andere affiniteit voor de verschillende subtypen van de somatostatine receptor, maar ze hebben overeenkomstig allemaal een goede affiniteit voor receptor subtype 2. Ondanks hun verschillende affiniteiten is de sensitiviteit voor de detectie van NETs min of meer gelijk (3).

Voor therapie kunnen SSAs worden gelabeld met de radionucliden Yttrium-90 en Lutetium-177, welke bèta straling uitzenden. Hoewel er geen directe vergelijking beschikbaar is tussen deze twee radionucliden, zijn de PFS en OS min of meer hetzelfde (4). Het grote nadeel van Yttrium-90 is het optreden van bijwerkingen door de hogere energie van dit radionuclide en dit heeft met name betrekking op de nierfunctie.

In dit proefschrift worden verschillende aspecten van de beeldvorming en therapie van NETs met radioactief gelabelde SSAs besproken.

Hoofdstuk 1 is een algemene introductie over NETs en het geeft een overzicht van de verschillende beeldvorming en therapeutische opties welke op dit moment beschikbaar zijn voor NETs.

Hoofdstuk 2 is een review van de literatuur over beeldvorming van NETs met nucleaire technieken. De verschillende resultaten van beeldvorming met radioactief gelabelde SSAs worden besproken. Op dit moment worden ^{111}In-DTPA-octreotide en Gallium-68 gelabelde SSAs het meest gebruikt. Naast deze tracers, zijn er ook andere PET-tracers zoals ^{11}C-5-HTP en ^{18}F-DOPA ontwikkeld. Voor het lokaliseren van insulinomen is beeldvorming gericht op de glucagon-like peptide-1 receptor (Exendine-4) een veelbelovende nieuwe techniek.

In hoofdstuk 3 worden de incidentie en de mechanismen voor fysiologische uptake in de pancreaskop op ^{111}In-DTPA-octreotide scans beschreven. 178 scans met een single foton

emissie tomografie (SPECT)/CT van de bovenbuik werden geanalyseerd. Opname in de pancreaskop (processus uncinatus) werd gezien bij 46/178 patiënten met SPECT/CT en bij 12 patiënten werd uptake gezien in de pancreaskop met de planaire beeldvorming. Bij patiënten met diabetes mellitus (DM) werd dit twee keer zo vaak gezien. Aangezien eerdere casuïstische beschrijvingen uptake in de pancreaskop hebben aangetoond bij PP-cel hyperplasie en 90% van deze cellen in de pancreaskop gelokaliseerd zijn, is PP-cel hyperplasie de meest waarschijnlijke verklaring voor deze opname. Ook kunnen patiënten met DM een verhoogd serum PP hebben, wat de verhoogde incidentie bij deze patiënten zou kunnen verklaren.

Hoofdstuk 4 is een review van de literatuur over PPRT. De resultaten en bijwerkingen van de verschillende gelabelde SSAs worden besproken. De objectieve respons cijfers die worden gerapporteerd voor PRRT liggen tussen 15-35%. De resultaten kunnen verschillen voor de verschillende radionucliden en soorten primaire tumoren. Vergeleken met historische controlegroepen en de andere beschikbare therapeutische opties voor gemetastaseerde en inoperabele NETs, zijn de PFS, TTP en OS in het algemeen beter voor PRRT. Ernstige lange termijn bijwerkingen zijn zeldzaam en de incidentie hiervan verschilt per radionuclide. Bij Yttrium-90 wordt niertoxiciteit gerapporteerd tot in 9% van de patiënten. Andere ernstige bijwerkingen op de lange termijn zijn het myelodysplatisch syndroom (MDS) en acute leukemie (AL). Dit komt voor bij ongeveer 2-3% van patiënten.

In hoofdstuk 5 wordt de effectiviteit op de lange termijn, overleving en bijwerkingen van de behandeling met ^{177}Lu-DOTATATE van patiënten met gastroenteropancreatische (GEP) en bronchiale NETs beschreven. Vanaf 2000 werd een grote groep van ruim 1200 patiënten behandeld en gevolgd op onze afdeling. De objectieve respons bij 443 Nederlandse patiënten welke minimaal 600 mCi ^{177}Lu-DOTATATE hebben toegediend gekregen was 39% en stabiele ziekte werd gevonden bij 43% van alle patiënten. PFS was 29 maanden, TTP 36 maanden en overleving 63 maanden. Toxiciteit op de lange termijn omvat AL in 4 patiënten (0.7%) en MDS bij 9 patiënten (1.5%). Therapie-gerelateerd nier- of lever falen werd niet gevonden. Vergeleken met alle andere therapeutische opties, welke op dit moment beschikbaar zijn voor de behandeling voor inoperabele en gemetastaseerde NETs, is bij PRRT met ^{177}Lu-DOTATATE de PFS en TTP beter.

Hoofdstuk 6 beschrijft de valkuilen waarmee rekening moet worden gehouden bij de respons evaluatie na PRRT met ^{177}Lu-DOTATATE. Een verhoging van de serum transaminasen wordt gezien bij 24% van alle patiënten. Ook een verhoging van de de tumor marker chromogranine A (CgA) werd gezien bij 29% van de patiënten. Er was geen verschil in de stijging van tumormerkstoffen tussen patiënten met een objectieve respons en progressieve ziekte als uitkomst na therapie. Op beeldvorming kunnen patiënten met stabiele ziekte een tijdelijke toename van de tumorgrootte krijgen, welke niet is gerelateerd aan de uitkomst na therapie. Een toename van de tumorgrootte van minimaal 10% werd gezien bij 9% van de patiënten met stabiele ziekte. Clinici moeten derhalve rekening houden met het feit dat

deze veranderingen waarschijnlijk door stralingsgerelateerde inflammatie veroorzaakt zijn en niet gerelateerd zijn aan de uiteindelijke uitkomst van deze therapie. Meerdere tumor metingen zijn daarom nodig om een onderscheid te maken en om progressie te bevestigen.

In hoofdstuk 7 wordt de beste manier om progressie te bevestigen na therapie met ^{177}Lu-DOTATATE beschreven. In de follow-up krijgen patiënten bloedtesten, nucleaire en radiologische beeldvorming. Een duidelijk antwoord op de vraag wat de beste methode is om progressie te detecteren kan niet worden gegeven. Als we de verschillende biochemische markers en de cholestatische leverenzymen vergelijken, heeft het CgA de hoogste sensitiviteit voor de detectie van progressie. Helaas is bij een deel van de patiënten geen stijging van de biochemische markers zichtbaar op het moment van progressie. Het is daarvoor noodzakelijk om een combinatie van biochemische markers en beeldvorming te maken bij alle patiënten om geen patiënten met progressieve ziekte te missen. Misschien lukt het in de toekomst om hiervoor moleculaire markers, zoals bijvoorbeeld de NETest te gebruiken.

Toekomstvisie

Met de recente publicatie van de uitstekende resultaten van de NETTER-1 studie bij patiënten met vergevorderde middendarm NETs, is het de verwachting dat het ^{177}Lu-DOTATAAT binnenkort wereldwijd beschikbaar komt voor alle patiënten met NETs. De NETTER-1 studie heeft aangetoond dat ^{177}Lu-DOTATAAT gecombineerd met octreotide LAR een langere PFS en een betere tumorrespons geeft dan alleen behandeling met een hoge dosis octreotide LAR (5). De doelgerichte therapieën die op dit moment zijn geregistreerd voor NET van het pancreas zijn everolimus en sunitinib. Een directe vergelijking tussen deze doelgerichte therapieën en ^{177}Lu-DOTATOC wordt op dit moment uitgevoerd.

Om de effectiviteit van PRRT te vergroten is door verschillende onderzoeksgroepen de combinatie met chemotherapie onderzocht (6-9). De studies laten een betere tumorrespons zien dan PRRT alleen, echter op dit moment zijn er nog geen directe vergelijkende studies beschikbaar. De resultaten van een directe vergelijking tussen ^{177}Lu-DOTATAAT en de combinatie van dit middel met capecitabine (Xeloda) worden op dit moment geëvalueerd in ons centrum.

NETs van het pancreas kunnen inoperabel zijn door ingroei in de bloedvaten. In onze studie hebben we gevonden dat tumoren van het pancreas de beste tumorrespons van 48% laten zien op PRRT. Na een significante verkleining van de tumor met therapie met ^{177}Lu-DOTATAAT, kunnen sommige tumoren operabel worden. Daarom wordt therapie met ^{177}Lu-DOTATAAT ook wel gebruikt in de neoadjuvante setting. Een publicatie van van Vliet en collegae (10) laat zien dat succesvolle chirurgie na PRRT mogelijk werd bij 9/29 patiënten (31%) met aanvankelijk inoperabele tumoren van het pancreas.

Aangezien de meeste metastasen van NETs gelokaliseerd zijn in de lever, is het mogelijk dat intra-arteriële, danwel locoregionale toediening van ^{177}Lu-DOTATAAT direct in leverslagader (arteria hepatica) een betere tumorrespons kan geven dan systemische therapie (11-13). Pool en collegae (13) toonden aan dat een twee keer hogere dosis in de lever kon worden bereikt dan na intraveneuze toediening. Ook studies met PET beeldvorming met het ^{68}Ga-DOTATOC liet een 3,75 keer hogere SUV in levermetastasen zien na intra-arteriële toediening in the arterie hepatica ten opzichte van systemische toediening (14). Andere klinische studies hebben betere therapeutische resultaten na locoregionale therapie laten zien dan na systemische therapie bij patiënten met levermetastasering. Directe vergelijkende studies zijn echter niet beschikbaar (11,12).

Helaas wordt de NET ziekte bij het merendeel van de patiënten uiteindelijk weer progressief ondanks een initiële goede reactie op therapie met ^{177}Lu-DOTATAAT. Wanneer patiënten de eerste PRRT cycli goed hebben verdragen en wanneer er een objectieve respons danwel klinische verbetering was, dan is het goed mogelijk om patiënten opnieuw te behandelen met extra cycli met het ^{177}Lu-DOTATAAT. PRRT als herbehandeling geeft redelijk goede resultaten en heeft beperkte bijwerkingen (15-17). Met behulp van grotere studies zal het mogelijk worden om de bijwerkingen op de lange termijn in kaart te brengen.

Een andere strategie om de uptake in de tumoren te verhogen is het gebruik van somatostatine antagonisten in plaats van agonisten. In het verleden werd aangenomen dat radioactief gelabelde peptiden moeten worden geïnternaliseerd in de cel om het effect te vergroten. De antagonisten internaliseren niet in de cel, maar binden alleen aan de receptor op het oppervlak van de cel. Verrassend genoeg bleek bij preklinisch onderzoek dat de somatostatine antagonist ^{177}Lu-DOTA-JR11 een vijf keer hogere uptake had dan het ^{177}Lu-DOTATAAT (18). De eerste studie bij patiënten met ^{177}Lu-DOTA-JR11 liet zien dat het eveneens mogelijk is om dit preparaat toe te dienen bij NET patiënten en dat de opname in de tumor 1,7-10,6 keer hoger was dan met het ^{177}Lu-DOTATAAT (19). Er zijn echter nog geen grote studies of directe vergelijkingen met agonisten verricht en de (lange termijn) bijwerkingen van deze antagonisten zijn nog niet bekend.

Een andere aanpak om de respons op PRRT te verbeteren is het gebruik van alfa emitters. Radionucliden die alfastraling uitzenden hebben een korter cel doordringend vermogen dan bèta emitters. Echter, alle energie wordt geabsorbeerd in het weefsel en daardoor kan er meer DNA-schade plaatsvinden. De geabsorbeerde dosis op andere, gezonde organen is lager door het kortere doordringend vermogen. De eerste studie bij NET patiënten waarbij gebruik gemaakt werd van het ^{213}Bi-DOTATOC liet veelbelovende resultaten zien met een objectieve respons of stabiele ziekte na 12 maanden bij alle 7 patiënten (20).

Een nieuwe diagnostische methode om de respons op PRRT te voorspellen is de NETest (21). Deze test maakt gebruik van circulerende transcript analyses in NETs en kan de effectiviteit van PRRT voorspellen (22,23). In de toekomst is dit een veelbelovende optie om

de respons te voorspellen voor aanvang van de PRRT en om progressie te detecteren. Op dit moment wordt deze test alleen gebruikt in studieverband en nog niet in de dagelijkse praktijk.

Concluderend is PRRT met radioactief gelabelde somatostatine analogen een effectieve en veilige therapie voor NETs. De tumorrespons is goed en de PFS is langer dan met de andere therapieën die momenteel beschikbaar zijn. Met de nieuwe ontwikkelingen op het gebied van beeldvorming zullen hopelijk meer patiënten de juiste behandeling op het juiste moment krijgen en kunnen we bij meer patiënten hun ziekte onder controle krijgen.

References

1. Rinke A, Muller H-H, Schade-Brittinger C, Klose K-J, Barth P, Wied M, et al. Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group. J Clin Oncol. 2009 Aug 24;27(28):4656–63.
2. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors. N Engl J Med. 2014 Jul 17;371(3):224–33.
3. Geijer H, Breimer LH. Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2013 Jul 20;40(11):1770–80.
4. van der Zwan WA, Bodei L, Mueller-Brand J, de Herder WW, Kvols LK, Kwekkeboom DJ. GEPNETS UPDATE: Radionuclide therapy in neuroendocrine tumors. Eur J Endocrinol. 2014 Nov 24;172(1):R1–8.
5. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of ^{177} Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017 Jan 12;376(2):125–35.
6. van Essen M, Krenning EP, Kam BL, de Herder WW, van Aken MO, Kwekkeboom DJ. Report on short-term side effects of treatments with 177Lu-octreotate in combination with capecitabine in seven patients with gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2008 Apr;35(4):743–8.
7. Claringbold PG, Brayshaw PA, Price RA, Turner JH. Phase II study of radiopeptide 177Lu-octreotate and capecitabine therapy of progressive disseminated neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2011 Feb;38(2):302–11.
8. Claringbold PG, Price RA, Turner JH. Phase I-II Study of Radiopeptide ^{177} Lu-Octreotate in Combination with Capecitabine and Temozolomide in Advanced Low-Grade Neuroendocrine Tumors. Cancer Biother Radiopharm. 2012 Nov;27(9):561–9.
9. Kesavan M, Claringbold PG, Turner JH. Hematological Toxicity of Combined ^{177} Lu-Octreotate Radiopeptide Chemotherapy of Gastroenteropancreatic Neuroendocrine Tumors in Long-Term Follow-Up. Neuroendocrinology. 2014;99(2):108–17.
10. van Vliet EI, van Eijck CH, de Krijger RR, Nieveen van Dijkum EJ, Teunissen JJ, Kam BL, et al. Neoadjuvant Treatment of Nonfunctioning Pancreatic Neuroendocrine Tumors with [177Lu-DOTA0,Tyr3]Octreotate. J Nucl Med. 2015 Nov 1;56(11):1647–53.
11. McStay MKG, Maudgil D, Williams M, Tibballs JM, Watkinson AF, Caplin ME, et al. Large-Volume Liver Metastases from Neuroendocrine Tumors: Hepatic Intraarterial ^{90} Y-DOTA-Lanreotide as Effective Palliative Therapy ^{1}. Radiology. 2005 Nov;237(2):718–26.
12. Kratochwil C, Lopez-Benitez R, Mier W, Haufe S, Isermann B, Kauczor H-U, et al. Hepatic arterial infusion enhances DOTATOC r adiopeptide therapy in patients with neuroendocrine liver metastases. Endocr Relat Cancer. 2011 Sep 20;18(5):595–602.

13. Pool SE, Kam BLR, Koning GA, Konijnenberg M, ten Hagen TLM, Breeman WAP, et al. [^{111} In-DTPA]octreotide Tumor Uptake in GEPNET Liver Metastases After Intra-Arterial Administration: An Overview of Preclinical and Clinical Observations and Implications for Tumor adiation Dose After Peptide Radionuclide Therapy. Cancer Biother Radiopharm. 2014 May;29(4):179–87.
14. Kratochwil C, Giesel FL, Lopez-Benitez R, Schimpfky N, Kunze K, Eisenhut M, et al. Intraindividual Comparison of Selective Arterial versus Venous 68Ga-DOTATOC PET/CT in Patients with Gastroenteropancreatic Neuroendocrine Tumors. Clin Cancer Res. 2010 May 15;16(10):2899–905.
15. Forrer F, Uusijärvi H, Storch D, Maecke HR, Mueller-Brand J. Treatment with 177Lu-DOTATOC of patients with relapse of neuroendocrine tumors after treatment with 90Y-DOTATOC. J Nucl Med Off Publ Soc Nucl Med. 2005 Aug;46(8):1310–6.
16. van Essen M, Krenning EP, Kam BLR, de Herder WW, Feelders RA, Kwekkeboom DJ. Salvage Therapy with 177Lu-Octreotate in Patients with Bronchial and Gastroenteropancreatic Neuroendocrine Tumors. J Nucl Med. 2010 Mar 1;51(3):383–90.
17. Sabet A, Haslerud T, Pape U-F, Sabet A, Ahmadzadehfar H, Grünwald F, et al. Outcome and toxicity of salvage therapy with 177Lu-octreotate in patients with metastatic gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2014 Feb;41(2):205–10.
18. Dalm SU, Nonnekens J, Doeswijk GN, de Blois E, van Gent DC, Konijnenberg MW, et al. Comparison of the Therapeutic Response to Treatment with a 177Lu-Labeled Somatostatin Receptor Agonist and Antagonist in Preclinical Models. J Nucl Med Off Publ Soc Nucl Med. 2016 Feb;57(2):260–5.
19. Wild D, Fani M, Fischer R, Del Pozzo L, Kaul F, Krebs S, et al. Comparison of Somatostatin Receptor Agonist and Antagonist for Peptide Receptor Radionuclide Therapy: A Pilot Study. J Nucl Med. 2014 Aug 1;55(8):1248–52.
20. Kratochwil C, Giesel FL, Bruchertseifer F, Mier W, Apostolidis C, Boll R, et al. 213Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience. Eur J Nucl Med Mol Imaging. 2014 Nov;41(11):2106–19.
21. Kidd M, Drozdov I, Modlin I. Blood and tissue neuroendocrine tumor gene cluster analysis correlate, define hallmarks and predict disease status. Endocr Relat Cancer. 2015 Aug;22(4):561–75.
22. Ćwikła JB, Bodei L, Kolasinska-Ćwikła A, Sankowski A, Modlin IM, Kidd M. Circulating Transcript Analysis (NETest) in GEP-NETs Treated With Somatostatin Analogs Defines Therapy. J Clin Endocrinol Metab. 2015 Nov;100(11):E1437–45.
23. Bodei L, Kidd M, Modlin IM, Severi S, Drozdov I, Nicolini S, et al. Measurement of circulating transcripts and gene cluster analysis predicts and defines therapeutic efficacy of peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumors. Eur J Nucl Med Mol Imaging. 2016 May;43(5):839–51.

List of publications

- Brabander T, Kwekkeboom DJ, Feelders RA, Brouwers AH, Teunissen JJM. Nuclear Medicine Imaging of Neuroendocrine Tumors. In: Papotti M., de Herder WW (Eds). Neuroendocrine Tumors. A Multidiscoplinary Approach. Frontiers of Hormone Research. 2015;44:73-87. (Karger, Vol 44, 2015)
- van Vliet EI, van Eijck CH, de Krijger RR, Nieveen van Dijkum EJ, Teunissen JJ, Kam BJ, de Herder WW, Feelders RA, Bonsing BA, Brabander T, Krenning EP, Kwekkeboom DJ. Neoadjuvant Treatment of Nonfunctioning Pancreatic Neuroendocrine Tumors with [177Lu-DOTA0,Tyr3]Octreotate. Journal of Nuclear Medicine. 2015 Nov;56(11):1647-53.
- Brabander T, Teunissen JJM, Van Eijck CH, Franssen GJ, Feelders RA, de Herder WW, Kwekkeboom DJ. Peptide receptor radionuclide therapy of neuroendocrine tumours. Best Practice & Research: Clinical Endocrinology and Metabolism. 2016 Jan;30(1):103-14.
- Brabander T, Schoots IG, Teunissen JJM. Beeldvorming en therapie van neuro-endocriene tumoren. Imago nascholing, februari 2016.
- Brabander T, Teunissen JJM, Kwekkeboom DJ. Physiological uptake in the pancreatic head on SRS using [111In-DTPA0]octreotide; Incidence and Mechanism. Clinical Nuclear Medicine. 2017;42:15-19.
- Brabander T, Van der Zwan WA, Teunissen JJM, Kam BLR, De Herder WW, Franssen GJH, Krenning EP, Kwekkeboom DJ. Long-term efficacy, survival and safety of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. Clinical Cancer Research 2017 Aug;23:4617-4624.
- Brabander T, Van der Zwan WA, Teunissen JJM, Kam BLR, De Herder WW, Krenning EP, Kwekkeboom DJ. Pitfalls in the response evaluation after Peptide Receptor Radionuclide Therapy with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. Endocrine-Related Cancer, 2017;24:243-251
- Brabander T, Graven LH, Teunissen JJM, Kam BLR, De Herder WW, Krenning EP, Kwekkeboom DJ. Comparison of biochemical marker response, anatomical and molecular imaging for the detection of progression after therapy with [^{177}Lu-DOTA^{0},Tyr^{3}] octreotate. Submitted

Oral and Poster Presentations

- Tessa Brabander, Joost Haeck, Harold Groen, Marleen Melis, Sandra van Tiel, Monique Bernsen, Marion de Jong. Magnetic Resonance Imaging (MRI) Contrast Agents Negatively Influences Binding and Internalisation of 111In-DTPA-octreotide into tumour cells in vitro and in vivo in rats. At the Annual Congress of the European Association of Nuclear Medicine, 10/2011 (Poster).
- Joost Haeck, Sandra Tiel, Tessa Brabander, Monique Bernsen, Marion de Jong. Anesthesia and MRI Contrast Agents Affect Organ and Tumor Distribution of SPECT Tracer [Indium-111-DTPA]-Octreotide (Octreoscan) in Vitro and in a Rat Tumor Model. At the Radiological Society of North America 2011 Scientific Assembly and Annual Meeting; 11/2011 (Poster).
- Tessa Brabander, Roelf Valkema, Jaap Teunissen, Wout Breeman, Fred Verzijlbergen. First Experiences with ^{68}Ga-DOTATATE PET/CT, At the NVNG Najaarsbijeenkomst, 11/2014 (Oral)
- Tessa Brabander, Jaap Teunissen, Dik Kwekkeboom. Physiological uptake in the pancreatic head on SRS using 111In-DTPA-octreotide; Incidence and Mechanism. At the Annual Congress of the European Association of Nuclear Medicine and at the North American Neuroendocrine Tumor Society, 10/2016 (2x Poster).
- Tessa Brabander, Wouter van der Zwan, Jaap Teunissen, Boen Kam, Wouter de Herder, Gaston Franssen, Eric Krenning, Dik Kwekkeboom Long-term efficacy, survival and safety of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. At the North American Neuroendocrine Tumor Society, 10/2016 (oral).
- Tessa Brabander, Wouter van der Zwan, Jaap Teunissen, Boen Kam, Wouter de Herder, Eric Krenning, Dik Kwekkeboom. Pitfalls in the response evaluation after Peptide Receptor Radionuclide Therapy with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate. At the North American Neuroendocrine Tumor Society, 10/2016 (Poster) and the European Neuroendocrine Tumor Society, 3/2017 (Poster).
- Tessa Brabander. Long-term safety of Peptide Receptor Radionuclide Therapy. At the European Neuroendocrine Tumor Society breakfast meeting, 3/2017 (Oral).

Curriculum vitae

Tessa Brabander was born on November 7, 1986 in Delft, The Netherlands. She attended secondary school at the “Interconfessionele Scholengemeenschap Westland” in Naaldwijk from which she graduated the VWO in 2005. After that she started her medical training at the Medical Faculty of the Erasmus University in Rotterdam. In 2011 she obtained her medical degree.

After finishing medical school she started as a resident in Nuclear Medicine. As part of this, she worked at the department of Internal Medicine at the Ikazia ziekenhuis and at the department of Radiology at the Erasmus MC. During her residency she started this research project at the department of Nuclear Medicine at the Erasmus MC under supervision of Prof.dr. D.J. Kwekkeboom and Prof.dr. W.W. de Herder. The results of this research project are presented in this thesis. She obtained her registration as a Nuclear Medicine physician in 2016. After that, she combined working as a Nuclear Medicine physician and a resident in Radiology at the department of Radiology & Nuclear medicine of the Erasmus MC.

PhD Portfolio

Summary of PhD training and teaching

Erasmus MC department:	Radiology & Nuclear Medicine
PhD period:	2013-2017
Promotoren:	Prof.dr. D.J. Kwekkeboom, Prof.dr. W.W. de Herder

PhD training

Course ‘Radiation safety, level 5B’	2011	1,5
Course ‘Radiation safety, level 3’	2013	12
Journal club meetings Nuclear medicine	2011-2017	1
Research meetings, dept Nuclear medicine	2011-2017	1

Presentations / posters at conferences

Annual Congress of the European Association of Nuclear Medicine (EANM) Birmingham 2011 (poster)	2011	2
Annual Congress Radiological Society of North America (RSNA) Chicago 2011 (poster)	2011	2
NVNG Najaarsbijeenkomst 2014 (oral)	2014	2
Annual meeting of the North American Neuroendocrine Tumor Society (NANETS) Jackson 2016 (oral and 2 posters)	2016	2
Annual Congress of the European Association of Nuclear Medicine (EANM) Barcelona 2016 (poster)	2016	2
Annual Congress of the European Neuroendocrine Tumor Society (ENETS) Barcelona 2017 (oral and poster)	2017	2

Teaching activities

Supervising practicals medical students 2th year	2011-2016	0,5
Education nuclear medicine at start internships	2011-2016	1
In-hospital teaching for nuclear medicine technologists	2014-2016	0,5
Continuing education for technicians (NVMBR)	2016	2

List of abbreviations

α-SU	α-subunit of glycoprotein hormones
AADC	aromatic amino acid decarboxylase
ACTH	adrenocorticotrophic hormone
AJCC	American Joint Committee on Cancer
AL	acute leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
^{11}C-5-HTTP	β-[11C]-5-hydroxy-L-tryptophan
CgA	chromogranin-A
CI	confidence interval
Ci	Curie
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DM	diabetes mellitus
DOTA	1,4,7,10-tetraazacyclotetradecane-1,4,7,10-tetraacetic acid
DTPA	diethylenetriaminepentaacetic acid
EANM	European Association of Nuclear Medicine
EBRT	external beam radiotherapy
EMA	European Medicines Agency
ENETS	European Neuroendocrine Tumor Society
EUS	endoscopic ultrasound
^{18}F-DOPA	6-18F-L-3,4-dihydroxyphenylalanine
^{18}F-FDG	18-F-fluordeoxyglucose
FDA	Food and Drug Administration (USA)
5-FU	5-fluorouracil
^{68}Ga	Gallium-68
^{68}Ga-DOTANOC	[68Ga-DOTA,1-nal3]octreotide
^{68}Ga-DOTATATE	[68Ga-DOTA0, Tyr3]octreotate
^{68}Ga-DOTATOC	[68Ga-DOTA0, Tyr3]octreotide
^{68}Ga-SSA	68-Gallium labeled somatostatin analogs
G	grade
GBq	gigabequerel
GEP	gastroenteropancreatic
GEPNET	gastroenteropancreatic neuroendocrine tumor

GGT	gamma-glutamyl transpeptidase
GLP-1R	glucagon-like peptide-1 receptor
Gy	Gray
5-HIAA	5-hydroxyindole acetic acid
Hb	hemoglobin
HPF	high-power field
^{123}I	Iodine-123
^{131}I	Iodine-131
^{111}In	Indium-111
i.a.	intra-arterial
IFN-alpha	interferon-alpha
irRC	immune-related Response Criteria
i.v.	intra-venous
KPS	Karnofsky performance score
^{177}Lu	Lutetium-177
^{177}Lu-DOTATATE	[177Lu-DOTA0,Tyr3]Octreotate
LDH	lactate dehydrogenase
MC	mitotic count
mCi	millicurie
MDS	myelodysplastic syndrome
MEN	multiple endocrine neoplasia
MIBG	metaiodobenzylguanidine
min	minutes
MIP	maximum intensity projection
MR	minor response
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamcycin
NEC	neuroendocrine carcinoma
NET	neuroendocrine tumor
NSE	neuron-specific enolase
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease

PET	positron emission tomography
PFS	progression free survival
pNET	pancreatic neuroendocrine tumor
PP	pancreatic polypeptide
PPI	proton pomp inhibitors
PR	partial response
PRRT	peptide receptor radionuclide therapy
QOL	quality of life
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	radiofrequency ablation
RTK	receptor tyrosine kinase
SD	stable disease
SNM	Society of Nuclear Medicine
SPECT	single photon emission computed tomography
SRS	somatostatin receptor scintigraphy
SSA	somatostatin analog
SSTR	somatostatin receptor
STZ	streptozotocin
SUV	standardized uptake value
SWOG	Southwest Oncology Group
^{99m}Tc	Technetium-99m
^{99m}Tc-HYNIC-TOC	99m-Tc-EDDA/HYNIC-Tyr3-octreotide
T/nT	tumor-to-nontumor ratio
TC	thyroid carcinoma
Tg	thyroglobulin
TTP	time to progression
Tyr	tyrosine
VIP	vasoactive intestinal polypeptide
WBC	white blood cell
WHO	World Health Organization
^{90}Y	Yttrium-90
^{90}Y-DOTALAN	90Y-DOTA-lanreotide
^{90}Y-DOTATOC	[90Y-DOTA0,Tyr3]octreotide

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