Symptomatic and radiological response to ^{177}Lu-DOTATATE for the treatment of functioning pancreatic neuroendocrine tumors

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ABSTRACT

Introduction: Peptide receptor radionuclide therapy (PRRT) with the radiolabeled somatostatin analogue [Lutetium-177-DOTA^{0}-Tyr^{3}]octreotate (^{177}Lu-DOTATATE) is widely applied for inoperable metastatic small intestinal and non-functioning pancreatic neuroendocrine tumors (pNETs). The aim of this study is to describe the safety and efficacy of the treatment of functioning pNETs.

Methods: Patients were treated with up to four cycles of ^{177}Lu-DOTATATE with an intended dose of 7.4 Gbq per cycle. Radiological (RECIST 1.1), symptomatic and biochemical response were analyzed retrospectively for all patients with a functioning pNET (insulinoma, gastrinoma, VIPoma and glucagonoma) treated with ^{177}Lu-DOTATATE. Quality of life (QOL) was assessed with the EORTC QLQ-C30 questionnaire.

Results: Thirty-four patients with a metastatic functioning pNET (ENETS grade 1 or 2) were included: 14 insulinomas, 5 VIPomas, 7 gastrinomas and 8 glucagonomas. Subacute hematological toxicity, grade 3 or 4 occurred in 4 patients (12%) and a hormonal crisis in 3 patients (9%). PRRT resulted in partial or complete response in 59% of patients and the disease control rate was 78% in patients with baseline progression. 71% of patients with uncontrolled symptoms had a reduction of symptoms and a more than 80% decrease of circulating hormone levels was measured during follow-up. After PRRT, median progression-free survival was 18.1 months (IQR: 3.3-35.7) with a concurrent increase in QOL.

Conclusion: Treatment with ^{177}Lu-DOTATATE is a safe and effective therapy resulting in radiological, symptomatic and biochemical response in a high percentage of patients with metastatic functioning pNETs. Hormonal crises occur relatively frequent and preventive therapy should be considered before and/or during PRRT.

INTRODUCTION

Pancreatic neuroendocrine tumors (pNET) are rare neoplasms with an estimated incidence of 0.3-0.4 cases per 100.000 person years.[1] A large majority of pNETs is non-functioning, meaning they do not secrete hormones or only secrete inactive amines.[2] However, a small percentage of patients presents with a functioning tumor like an insulinoma, glucagonoma, VIPoma or gastrinoma with distinct symptoms which can be attributed to hypersecretion of the specific hormone.

Patients with an insulinoma present with hypoglycemia due to hyperinsulinism (characterized by elevated plasma insulin and C-peptide) and 90% of patients turn out to have a pNET smaller than 5 cm for which surgery is indicated.[3,4] Glucagonomas are characterized by new onset diabetes mellitus, weight loss, glossitis and typical skin lesions called necrolytic migratory erythema and 50% of patients have metastatic disease at presentation.[5] Gastrinomas cause the Zollinger-Ellison syndrome (ZES), which is defined as inappropriate high gastrin secretion when gastric acid secretion is present (gastric pH <2). A diagnostic problem can be the use of proton-pump inhibitors (PPIs), which also increases gastrin secretion, but these should not be abruptly discontinued in patients with ZES as peptic complications can swiftly develop.[6,7] VIPomas cause a cholera-like secretory diarrhea resulting in loss of electrolytes and therefore the syndrome is also known as Watery Diarrhea, Hypokalemia and Achlorhydria (WDHA), or Verner Morrison syndrome.[8]

For all functioning pNETs, surgery should be considered: 5-year survival is estimated to be more than 90% in patients with localized disease.[3-5,7,9,10] This decreases to around 30-60% 5-year survival in the setting of metastatic functioning pNET.[11] The evidence for palliative treatment of functioning pNET is limited and is often extrapolated from trials with non-functioning pNETs or from small numbers of functioning pNETs within trials studying predominantly non-functioning NETs. First line treatment for inoperable metastatic functioning pNET is a somatostatin analogue (SSA). There are proven anti-proliferative effects in non-functioning pNETs and case series describing significant decreases of hormone secretion and remission of hormone hypersecretory syndromes.[12] Other treatments include everolimus, sunitinib and cytotoxic chemotherapy.[13-16] Another promising systemic therapy is peptide receptor radionuclide therapy (PRRT) with [Lutetium-177-DOTA^{0}-Tyr^{3}]octreotate (^{177}Lu-DOTATATE). In a recent randomized controlled trial (NETTER-1), ^{177}Lu-DOTATATE controlled tumor growth in patients with inoperable, progressive, metastatic non-functional small intestinal NETs. Other large institutional series including pNETs have revealed high tumor control rates following the administration of PRRT.[17,18] For insulinomas and gastrinomas, PRRT has also been shown to give symptomatic control in small patient series.[19-23]

The aim of this study is to describe toxicity and efficacy (symptomatic, biochemical and radiological response) of PRRT with ^{177}Lu-DOTATATE in rare functioning pancreatic NETs, namely insulinomas, glucagonomas, gastrinomas and VIPomas.

METHODS

Patients

For this retrospective analysis, all Dutch patients treated with PRRT with ^{177}Lu-DOTATATE at our center for an insulinoma, glucagonoma, VIPoma or gastrinoma were selected. Patients were eligible if they underwent PRRT between the introduction of ^{177}Lu-DOTATATE in 2000 and June 2017. The hypersecretory syndromes were defined as having symptoms fitting the specific syndrome in combination with an (inappropriately) elevated hormone measured in plasma. For an insulinoma this requires an elevated insulin, and/or pro-insulin, and C-peptide during spontaneous or provoked hypoglycemia.[24] In three cases an insulinoma was diagnosed without demonstrating hyperinsulinism when a hypoglycemia was confirmed in a patient with a pNET after exclusion of all other likely causes like liver disease, hypoglycemic drugs or adrenal insufficiency.

A gastrinoma was diagnosed if a patient presented with acid-peptic disease and concurrently elevated fasting gastrin. Ideally gastrin is measured without the patient taking PPIs, but due to the risks and complications which can occur after discontinuation of PPI's not all patients could be diagnosed according to these guidelines. However, in this series all patients had a gastrin level of more than ten times elevated above the upper reference limit. Glucagonomas and VIPomas were diagnosed when the specific hormone was elevated in combination with symptoms: glucagonomas presented with necrolytic migratory erythema, excessive weight loss or diabetes mellitus and VIPomas with severe secretory diarrhea.

For treatment with PRRT a hemoglobin $\geq$ 5.5 mmol/L, white blood cell count $\geq$ 2x10^9/L, platelet count $\geq$ 75x10^9/L, and Karnofsky performance status $\geq$ 50 was required. Creatinine clearance was required to be $\geq$ 40 mL/min in patients treated until 2007 and 50ml/min after 2007 (assessed in 2x 24-hour urine collection). Also, adequate tumor somatostatin receptor expression as evaluated on planar scintigraphy with ^{111}In-DTPA-octreotide (Octreoscan) was required (grade 2 or higher).

PRRT Protocol

The preparation and administration of ^{177}Lu-DOTATATE was described earlier.[18,25] The intended interval between treatments was 6–10 weeks. Patients were treated with 4 cycles of ^{177}Lu-DOTATATE up to a cumulative intended dose of 27.8–29.6 GBq. Thirty minutes before the administration of ^{177}Lu-DOTATATE, an infusion of 2.5% arginine and 2.5% lysine in 1L of 0.9% NaCl was started during 4 hours. Standard protocol included one night clinical observation after administration of ^{177}Lu-DOTATATE. Selected cases were admitted earlier for the treatment of the hormonal syndrome or, if indicated, for prolonged observation after PRRT.

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. Follow-up imaging with computed tomography (CT), or

magnetic resonance imaging (MRI) was performed within 3 months before the first therapy, and at every follow-up visit.

MEASUREMENTS AND OUTCOMES

Uptake on the OctreoScan was scored with 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 liver burden and whole-body extent of disease were scored by experienced nuclear medicine physicians as: limited, moderate or extensive on OctreoScan as described previously.[26] Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) criteria.[27] Disease control was defined as patients with a complete response (CR), partial response (PR) or stable disease (SD) in patients with progressive disease (PD) at baseline. Progression-free survival (PFS) was defined as the time from first cycle of PRRT until objective progression, new line of treatment or death from any cause. Toxicity was scored with the Common Terminology Criteria for Adverse Events 4.03 (CTCAE) scoring system.

Levels of VIP, glucagon and gastrin were included as biomarker in plasma for cases in which they were elevated at baseline. These were not measured regularly per protocol but were measured at discretion of the treating physician. Insulin was not considered a biomarker as there is no upper limit of normal (ULN) during normoglycaemia. Hormone levels were registered if available at baseline, and 6 months after last treatment. All hormones were measured using commercially available assays according to instructions. At all visits patients completed the European Organisation for Research and Treatment of Cancer (EORTC) quality of life (QOL) questionnaire (QLQ)–core module (C30).[28] The EORTC QLQ-C30 scores were transformed to 0–100 scales and the scores three months after last treatment were compared to baseline.[29]

Statistics

Data were presented as mean and 95% confidence interval (95% CI) or median and interquartile range (IQR: 25^{th}-75^{th} percentiles) as appropriate. For comparison of continuous variables (biomarkers and QOL) a paired t-test was used for normally distributed variables. The Wilcoxon signed-rank test was used for non-normally distributed variables. Progression-free survival was analyzed with the Kaplan-Meier method, with Log Rank testing to determine significant differences between groups. A p-value of <0.05 was considered statistically significant. Calculations were performed using SPSS for Windows software, (version 23.0, SPSS Inc.)

RESULTS

For this retrospective analysis 34 patients with a functioning pNET could be included. Of these, 14 patients had an insulinoma, 7 patients a gastrinoma, 5 patients a VIPoma and 8 patients a glucagonoma (Table 1). Patients had an average age of 59.0 ± 11.3 years and 50% were female. All patients presented with a metastatic NET (ENETS stage IV) with liver metastases (97%), bone metastases (21%) or lung metastases (6%) and with ENETS grade 1 or 2 tumors. One patient with an insulinoma had distant lymph node metastases only. The majority of patients was previously treated with a SSA (65%). At baseline 65% of patients had radiological PD. Progression was unknown in 27% of patients as they were treated before any follow-up scans were made. Indications for treatment were reduction of symptoms (27%), solely because of tumor progression (41%) or a combination of both (24%). Three patients (9%) were treated directly with PRRT, because of high tumor burden.

Two patients were treated concomitantly with capecitabine in a trial. Capecitabine treatment (1650mg/m^2/day in 2 doses) started on the morning of the day of administration of every PRRT cycle and lasted for two weeks.

Safety and toxicity

A total of 125 cycles with ^{177}Lu-DOTATATE were administered. Nausea occurred after 18% of administrations, pain in 8% and vomiting only occurred after 5% of administrations (Table 2). Nausea and vomiting can commence at the time of amino acid infusion and mostly subsides within 48 hours. Pain is usually encountered within the first days after treatment. Occasionally, it can also occur several weeks after administration of PRRT.

Table 1: Baseline characteristics

	All	Insulinoma	Gastrinoma	VIPoma	Glucagonoma
N.	34	14	7	5	8
Male, *n (%)*	17 (50.0)	6 (42.9)	4 (57.1)	0	7 (87.5)
Age (mean ± SD)	59.0 ± 11.3	59.2 ± 11.9	57.1 ± 15.3	56.7 ± 9.2	61.6 ± 8.6
Location of Metastases, *n (%)*					
Liver	33 (97.1)	13 (92.9)	7 (100.0)	5 (100.0)	8 (100.0)
Lungs	2 (5.9)	2 (14.3)	0	0	0
Bones	7 (20.6)	2 (14.3)	2 (28.6)	0	3 (37.5)
Liver Burden, *n (%)*					
0%	1 (2.9)	1 (7.1)	0	0	0
1-25%	13 (38.2)	4 (28.6)	3 (42.9)	2 (40.0)	4 (50.0)
25-50%	13 (38.2)	6 (42.9)	4 (57.1)	1 (20.0)	2 (25.0)
>50%	7 (20.6)	3 (21.4)	0	2 (40.0)	2 (25.0)

Table 1: Baseline characteristics (continued)

	All	Insulinoma	Gastrinoma	VIPoma	Glucagonoma
Extent of Disease (SRS), *n (%)*					
Limited	5 (14.7)	2 (14.3)	1 (14.3)	2 (40.0)	0
Moderate	25 (73.5)	11 (78.6)	5 (71.4)	2 (40.0)	7 (87.5)
Extensive	4 (11.8)	1 (7.1)	1 (14.3)	1 (20.0)	1 (12.5)
ENETS Grade, *n (%)*					
Grade 1	6 (17.6)	1 (7.1)	2 (28.6)	1 (20.0)	2 (25.0)
Grade 2	18 (52.9)	6 (42.9)	3 (42.9)	3 (60.0)	6 (75.0)
Unknown	10 (29.4)	7 (50.0)	2 (28.6)	1 (20.0)	0
Treatment indication, *n (%)*					
PD	14 (41.2)	6 (35.7)	4 (57.1)	1 (20.0)	4 (50.0)
Symptom reduction	9 (26.5)	6 (42.9)	1 (14.3)	2 (40.0)	0
PD and symptoms	8 (23.5)	2 (14.3)	0	2 (40.0)	4 (50.0)
High tumor burden	3 (8.8)	1 (7.1)	2 (28.6)	0	0
Baseline disease status, *n (%)*					
Progressive disease	22 (64.7)	7 (50.0)	4 (57.1)	3 (60.0)	8 (100.0)
Stable disease	3 (8.8)	2 (14.3)	0	1 (20.0)	0
Unknown	9 (26.5)	5 (35.7)	3 (42.9)	1 (20.0)	0
Previous Treatments, *n (%)*					
Surgery	10 (29.4)*	5 (35.7)*	4 (57.1)	1 (20.0)	0
Chemotherapy	3 (8.8)	2 (14.3)	0	1 (20.0)	0
Somatostatin analogue	22 (64.7)	8 (57.1)	5 (71.4)	5 (100.0)	4 (50.0)
Other†	7 (20.6)	3 (21.4)	1 (14.3)	3 (50.0)	0
Nr. previous treatments, *n (%)*					
0	8 (23.5)	3 (21.4)	1 (14.3)	0	4 (50.0)
1	14 (41.2)	6 (42.9)	2 (28.6)	2 (40.0)	4 (50.0)
2	9 (26.5)	4 (28.6)	4 (57.1)	1 (20.0)	0
≥3	3 (8.8)	1 (7.1)	0	2 (40.0)	0
Uptake on somatostatin receptor imaging, *n (%)*					
grade 3	12 (35.3)	6 (42.9)	3 (42.9)	2 (40)	1 (12.5)
grade 4	22 (64.7)	8 (57.1)	4 (57.1)	3 (60)	7 (87.5)
Cumulative dose, GBq					
7.4	3 (8.8)	3 (21.4)	0	0	0
18.5	1 (2.9)	0	0	0	1 (12.5)
22.2	2 (5.9)	0	0	2 (40.0)	0
25.9	4 (11.8)	1 (7.1)	1 (14.3)	0	2 (25.0)
29.6	24 (70.6)	10 (71.5)	6 (85.7)	3 (60.0)	5 (62.5)

* 1 patient with liver transplantation

† other therapies include everolimus, interferon, embolization, radiotherapy

Subacute hematological toxicity (grade 3 or 4) occurred in 4 patients (12%). No therapy-related related kidney failure occurred. One patient developed myelodysplastic syndrome (MDS) with excess blasts subtype 2, 2.5 years after the first administration of PRRT. He was not previously treated with chemotherapy and did not have bone metastases. He was treated with a combination of cytarabine and idarubicine in preparation of a bone marrow transplant. However, a relapse was found in the bone marrow aspirate one month after start of chemotherapy and patient was discharged for palliative care.

Table 2: Toxicity (n(%))

Acute Toxicity (per treatment)	
Nausea	22 (17.6%)
Vomiting	6 (4.8%)
Pain	10 (8.0%)
Subacute Toxicity (per patient)	
Anaemia	
grade 3	1 (2.9%)
grade 4	0 (0.0%)
Thrombocytopenia	
grade 3	1 (2.9%)
grade 4	0 (0.0%)
Leukopenia	
grade 3	3 (8.8%)
grade 4	0 (0.0%)
Hormone crisis	3 (8.8%)
Late toxicity	
Myelodysplastic syndrome	1 (2.9%)

The complete therapy of 29.6 GBq was administered to 70.6% of patients. Five patients (14.7%) were administered a reduced dose (18.5-25.9 GBq) because of earlier hepatotoxicity. Three patients with an insulinoma were only administered 1 cycle: one patient was known with schizophrenia and symptomatic, severe hypoglycemias. He was treated with PRRT for symptom relief and a possible association between the hypoglycemias and the psychiatric disorder. During the first PRRT cycle, the patients' non-compliance caused multiple spills of radioactive urine. Because of the anticipated high risk of persistent non-compliance with the next cycle and thus for radiation safety reasons, no second cycle was given. A second patient developed unexplained progressive cognitive decline after 1 cycle and further therapy was stopped. A third patient discontinued PRRT after the first cycle on her own request.

In three patients (9%) an acute complication associated with hormone secretion occurred after treatment with PRRT, requiring direct medical treatment, which were all classified as hormonal crises. One patient with a gastrinoma developed a stomach perforation after the first PRRT for which emergency surgery was performed. The patient was able to complete all remaining cycles and follow-up imaging showed PR. One patient with a VIPoma required multiple readmissions due to diarrhea and concurrent electrolyte disturbances for which intravenous administration of fluids and potassium was required. Diarrhea increased despite treatment and PRRT was stopped after 3 cycles because of clinical progression. Of the nine patients with a symptomatic insulinoma, seven patients were admitted for extended clinical observation after the regular PRRT protocol for prevention of hypoglycemia. Three patients were treated with glucose infusion and four patients started with octreotide subcutaneously directly after PRRT. The remaining two symptomatic patients were safely discharged after routine overnight observation because hypoglycemias were prevented with the administration of short-acting octreotide subcutaneously. Only one patient developed severe hypogly-

cemias for which octreotide was administered intravenously, which was also classified as hormonal crisis. If no hypoglycemias occurred after the first cycle of PRRT no hypoglycemias occurred after the next cycles. Patients not requiring octreotide or glucose infusion to prevent hypoglycemias, were all safely discharged directly after regular overnight observation.

Efficacy

In all 34 patients, best radiological response according to RECIST 1.1 was partial response (PR) in 56% of patients and stable disease (SD) in another 24% of patients (Table 3). One patient with an insulinoma had a complete response. In patients with radiological baseline PD (n=23), disease control (SD and PR) was seen in 78% of patients. Disease control rates seemed higher in gastrinomas (100%) and glucagonomas (100%) than in insulinomas (50%) and VIPomas (67%). Two patients had PD at the first follow-up CT and a third patient with a VIPoma had clinical progression (severe dehydration due to increase of diarrhea) during therapy and PRRT was discontinued after 3 cycles. For the three patients with an insulinoma who only completed 1 cycle, no follow-up CT was evaluable and thus were regarded to have PD as outcome.

Table 3: Treatment outcomes

	All (n=34)	**Insulinoma (n=14)**	**Gastrinoma (n=7)**	**VIPoma (n=5)**	**Glucagonoma (n=8)**
Best Tumor Response, n(%)					
Complete response	1 (2.9)	1 (7.1)	0	0	0
Partial response	19 (55.9)	6 (42.9)	5 (71.4)	4 (80.0)	4 (50.0)
Stable disease	8 (23.6)	3 (21.4)	1 (14.3)	0	4 (50.0)
Progressive disease	6 (17.6)*	4 (28.6)*	1 (14.3)	1 (20.0)	0
Symptomatic response, n(%)	17 (70.8)	6 (66.7)	2 (66.7)	4 (80.0)	5 (71.4)
Disease control (baseline PD)	**All (n=23)**	**Insulinoma (n=8)**	**Gastrinoma (n=4)**	**VIPoma (n=3)**	**Glucagonoma (n=8)**
	18 (78.3)	4 (50.0)	4 (100.0)	2 (66.7)	8 (100)

* includes 3 patients with unknown response due to withdrawal from therapy

During a median follow-up of 39.3 months 31 patients had a primary event. Primary events included 24 patients with PD, 2 deaths and 5 patients underwent a new therapy without RECIST progression. Median PFS was 18.1 months (IQR: 3.3-35.7) after the first treatment with ^{177}Lu-DOTATATE (Figure 1). In this small cohort, only disease burden assessed with Octreoscan was predictive for PFS (HR 5.9, 95% CI 1.3-26.4, limited versus extensive disease). PFS seemed equal across all syndromes (figure 2).

Additionally, PRRT with ^{177}Lu-DOTATATE resulted in a symptomatic response in 17 patients (71%) out of 23 patients with uncontrolled symptoms at baseline. Specifically, there was a decrease in hypoglycemic events in 6 (67%) metastatic insulinomas and a decrease of diar-

rhea in 4 (80%) patients with a metastatic VIPoma. Treatment resulted in decrease of skin lesions or increase of weight in 5 (71%) glucagonomas and decrease of pyrosis or diarrhea in 2 out of 3 (67%) symptomatic gastrinoma patients. This was also reflected in the follow-up of hormone levels in plasma (Figure 3). In 53% of patients with symptomatic response positive effects were already noted after 2 cycles of PRRT. Mean VIP (-80%), glucagon (-87%) and gastrin (-98%) levels decreased after PRRT, but this was only significant in patients with glucagonomas (p=0.04). Symptomatic response was highly associated with radiological response. All symptomatic patients with a PR or CR (n=14) also had a symptomatic response versus only 30% of patients with SD or PD (relative risk: 5.6, 95% CI: 2.02-15.8). At the time of radiological progression, symptoms were still well controlled in 78% of patients with a symptomatic response. In this series, the symptomatic recurrence occurred after or concurrently with radiological progression in all patients.

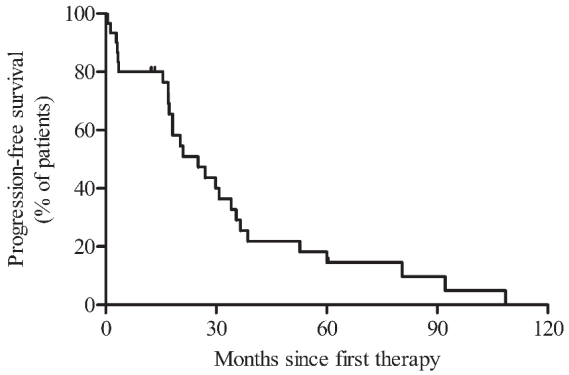

Figure 1: Progression-free survival of all patients after PRRT with ^{177}Lu-DOTATATE

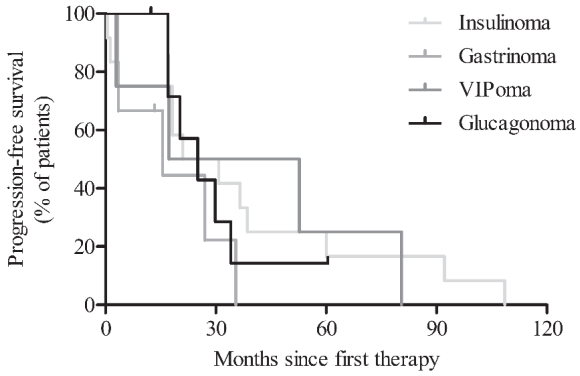

Figure 2: Progression-free survival after PRRT with ^{177}Lu-DOTATATE, stratified for syndrome (NS)

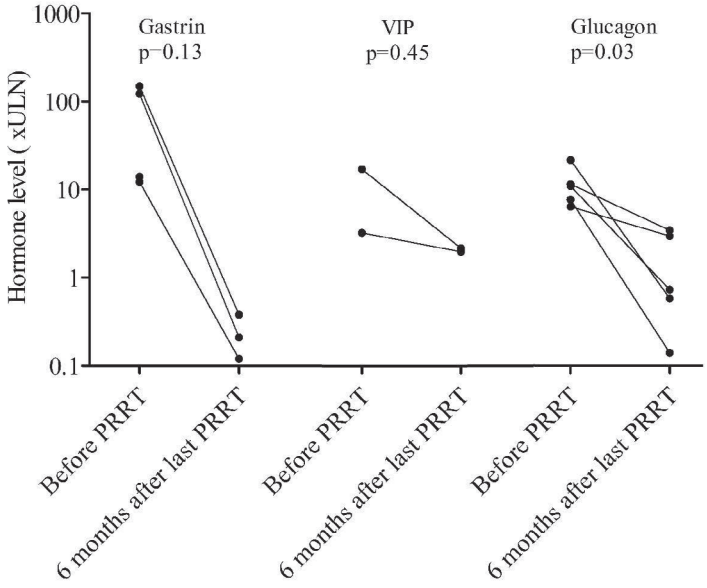

Figure 3: Plasma hormone levels, average at time point ± SD: baseline and 6 months after last therapy; (y-axis: log-10 scale)
- Plasma gastrin: measured sequentially in 4 patients, Upper limit of normal 114ng/L
- Plasma glucagon: measured sequentially in 5 patients, Upper limit of normal 80ng/L
- Plasma VIP: measured sequentially in 2 patients, Upper limit of normal 20ng/L

Quality of life

Follow-up with EORTC QLQ-C30 was available for 22 patients. These selected patients reported a significant increase in QOL three months after the final PRRT cycle (figure 4). The global health score/QOL increased from 61.7 at baseline to 79.5 at follow-up (p=0.002). Also significant increases in physical functioning (79.7 vs 90.0, p=0.008), role functioning (62.7 vs 90.3, p=0.006), emotional functioning (74.1 vs 84.5, p=0.002) and social functioning (77.3 vs 85.6, p=0.047) were reported. Of all symptom scales, only a significant decrease of fatigue was reported (27.3 vs 17.2, p=0.02).

DISCUSSION

PRRT with ^{177}Lu-DOTATATE has a prominent role in the treatment of metastatic NETs. As a second-line therapy, it has been demonstrated to increase PFS when compared to high dose octreotide LAR in patients with inoperable metastatic small intestinal NETs.[17] Furthermore, radiological PR has been observed in the majority of patients with a pNETs in multiple studies.[18,30,31] The outcomes of these studies are often driven by a large cohort of non-functioning pNETs, including small numbers of functioning pNETs. Therefore, in this retrospective study

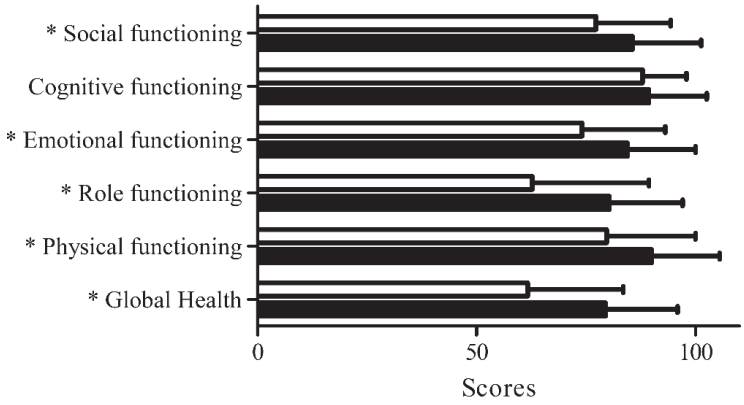

Figure 4: Mean scale scores of EORTC QLQ-C30 before PRRT (white bar) and three months after therapy (black bar)
* $p<0.05$

we focused on the safety and efficacy of ^{177}Lu-DOTATATE in patients with metastatic insulinoma, gastrinoma, glucagonoma or VIPoma.

PRRT was well-tolerated with nausea and pain occurring after 18% and 8% of administrations. However, three patients (9%) had an increase of hormonal symptoms, which had to be managed medically and therefor were classified as a hormonal crises. This risk might be underestimated as seven (50%) insulinoma patients were admitted for prevention of hypoglycemia with glucose infusion or octreotide. Previously, hormonal crises have been described in only 1% of patients,[32] but this study also included non-functioning NETs. In the current study we describe a selected cohort with relatively high hormone secretion and symptomatic burden resulting in a larger percentage of patients with hormonal crises. Only in patients with a glucagonoma, hormonal crises did not occur. Therefore, prevention of hormonal crises should be considered in all patients with an insulinoma, VIPoma and gastrinoma. This implies high dose proton-pump inhibitors for patients with gastrinomas. For patients with a VIPoma, diarrhea inhibitors should be prescribed as needed or in severe cases intravenous administration of fluids and electrolytes is required. In this cohort all insulinoma patients not using octreotide or continuous glucose infusion were all safely discharged after the standard overnight admission. A severe hypoglycemia only occurred in a patient already requiring octreotide besides the usual dietary instruction to prevent hypoglycemia. For safe treatment of patients with insulinomas it is essential to initiate therapy to prevent hypoglycemias before starting PRRT. This starts with dietary instructions and diazoxide.[33] As a second step, short-acting octreotide can be started. Short-acting octreotide should be discontinued 24 hours before PRRT and octreotide can be safely restarted directly after the amino acid infusion. Pasireotide can also be considered if octreotide proofs ineffective.[34] A majority of patients can then safely be treated with only a single night of observation. Lastly,

either continuous enteral tube feeding or intravenous glucose can be started. The patient dependent on enteral tube feeding is at largest risk for hypoglycemia as in selected cases vomiting disrupts feeding. A prolonged admission should be considered in these patients.

The response of functioning pNETs to ^{177}Lu-DOTATATE seems comparable with non-functioning NETs. Several studies report an objective response of 52-57 % in patients with non-functioning pNET, compared to 58% in this cohort.[18,30,31] Therefore, it seems reasonable to extrapolate radiological response from studies with PRRT for non-functioning pNETs to the treatment of their functioning counterparts. Median PFS in this cohort was 18 months which is shorter than earlier studies reporting median PFS of approximately 30 months for non-functioning pNET.[18,35] It remains unclear if this related to response, tumor biology or patient selection. Other second-line treatment options include everolimus, sunitinib and systemic chemotherapy. Treatment with everolimus or sunitinib seldom results in an objective response in trials including small numbers of functioning pNET.[15,36] Symptomatic response does occur with these therapies: treatment with everolimus decreases incidence of hypoglycemia in a high percentage of patients with an insulinoma.[14] This is probably caused by everolimus directly suppressing insulin secretion.[37] Sunitinib has been described to successfully decrease VIP and with that, diarrhea in 2 patients with a VIPoma.[13] The place of chemotherapy (streptozotocin and/or 5-fluoruracil) in the modern treatment of functioning well-differentiated pNET is difficult to assess, because of different response criteria and the lack of reporting of the symptomatic response in past publications.[16]

Besides radiological response, the increase in QOL and the high symptomatic response rates make PRRT a valuable second-line therapy. The increase in QOL of life has been reported in the NETTER-1 trial on small intestinal NET[38] and in GEP-NETs in general.[39] In functioning pNET, treatment with PRRT also resulted in an increase of QOL and several functioning scores. Furthermore, 71% of patients noted a decrease of syndrome-specific syndromes after PRRT. This improvement lasted past the occurrence of radiological progression in a majority of patients. Also in the treatment of other endocrine tumors with PRRT, like paragangliomas, pheochromocytomas and small intestinal NET, a decrease of hormonal symptoms has been described.[39,40]

The retrospective design of this study and the absence of a control group limit the interpretation of results. While we present the largest series of PRRT for functioning pNET to date, the number of patients included is still small due to the rare nature of functioning pNET. Also, while response to PRRT seems very promising, there is no head-to-head comparison with other therapies. As symptomatic response was associated with radiological response it not unlikely that tumor reduction with for example liver-directed therapy or surgery might yield equal or even better results.

However, in combination with previous evidence for the safety and effectiveness of PRRT and in light of the high symptomatic and radiological response rates, PRRT with ^{177}Lu-

DOTATATE currently seems preferable over the other current available second-line therapies for metastatic functional NET.

CONCLUSION

PRRT with ^{177}Lu-DOTATATE for the treatment of functioning pancreatic NET is safe, but prevention of hormonal crises should be considered. Furthermore, it results in a symptomatic response in a high percentage of patients with a significant increase of the quality of life. Radiological response seems comparable with non-functioning pNET.

REFERENCES

1. Fraenkel M, Kim MK, Faggiano A, Valk GD. Epidemiology of gastroenteropancreatic neuroendocrine tumours. *Best Pract Res Clin Gastroenterol* 2012; **26**(6): 691-703.
2. Halfdanarson TR, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (pNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol* 2008; **19**(10): 1727-33.
3. Tsutsumi K, Ohtsuka T, Fujino M, et al. Analysis of risk factors for recurrence after curative resection of well-differentiated pancreatic neuroendocrine tumors based on the new grading classification. *Journal of hepato-biliary-pancreatic sciences* 2013; **21**(6): 418-25.
4. Mehrabi A, Fischer L, Hafezi M, et al. A systematic review of localization, surgical treatment options, and outcome of insulinoma. *Pancreas* 2014; **43**(5): 675-86.
5. Soga J, Yakuwa Y. Glucagonomas/diabetico-dermatogenic syndrome (DDS): a statistical evaluation of 407 reported cases. *Journal of hepato-biliary-pancreatic surgery* 1999; **5**(3): 312-9.
6. Poitras P, Gingras MH, Rehfeld JF. The Zollinger-Ellison syndrome: dangers and consequences of interrupting antisecretory treatment. *Clin Gastroenterol Hepatol* 2012; **10**(2): 199-202.
7. Falconi M, Eriksson B, Kaltsas G, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. *Neuroendocrinology* 2016; **103**(2): 153-71.
8. Verner JV, Morrison AB. Islet cell tumor and a syndrome of refractory watery diarrhea and hypokalemia. *Am J Med* 1958; **25**(3): 374-80.
9. Norton JA, Fraker DL, Alexander HR, Jensen RT. Value of surgery in patients with negative imaging and sporadic Zollinger-Ellison syndrome. *Ann Surg* 2012; **256**(3): 509-17.
10. Soga J, Yakuwa Y. Vipoma/diarrheogenic syndrome: a statistical evaluation of 241 reported cases. *J Exp Clin Cancer Res* 1999; **17**(4): 389-400.
11. Zandee WT, Kamp K, van Adrichem RC, Feelders RA, de Herder WW. Effect of hormone secretory syndromes on neuroendocrine tumor prognosis. *Endocr Relat Cancer* 2017; **24**(7): R261-R74.
12. Caplin ME, Pavel M, Ruszniewski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014; **371**(16): 1556-7.
13. de Mestier L, Walter T, Brixi H, Lombard-Bohas C, Cadiot G. Sunitinib achieved fast and sustained control of VIPoma symptoms. *Eur J Endocrinol* 2014; **172**(1): K1-3.
14. Bernard V, Lombard-Bohas C, Taquet MC, et al. Efficacy of everolimus in patients with metastatic insulinoma and refractory hypoglycemia. *Eur J Endocrinol* 2013; **168**(5): 665-74.
15. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364**(6): 501-13.
16. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. *N Engl J Med* 1980; **303**(21): 1189-94.
17. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med* 2017; **376**(2): 125-35.
18. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-Term Efficacy, Survival, and Safety of [(177)Lu-DOTA(0),Tyr(3)]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. *Clin Cancer Res* 2017; **23**(16): 4617-24.
19. Grozinsky-Glasberg S, Barak D, Fraenkel M, et al. Peptide receptor radioligand therapy is an effective treatment for the long-term stabilization of malignant gastrinomas. *Cancer* 2011; **117**(7): 1377-85.
20. van Schaik E, van Vliet EI, Feelders RA, et al. Improved control of severe hypoglycemia in patients with malignant insulinomas by peptide receptor radionuclide therapy. *J Clin Endocrinol Metab* 2011; **96**(11): 3381-9.

21. Costa R, Bacchi CE, Almeida Filho P. Metastatic insulinoma managed with radiolabeled somatostatin analog. *Case reports in endocrinology* 2014; **2013**: 252159.
22. Magalhaes D, Sampaio IL, Ferreira G, et al. Peptide receptor radionuclide therapy with (177)Lu-DOTA-TATE as a promising treatment of malignant insulinoma: a series of case reports and literature review. *J Endocrinol Invest* 2018.
23. Dumont RA, Seiler D, Marincek N, et al. Survival after somatostatin based radiopeptide therapy with 90Y-DOTATOC vs. 90Y-DOTATOC plus 177Lu-DOTATOC in metastasized gastrinoma. *Am J Nucl Med Mol Imaging* 2015; **5**(1): 46-55.
24. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2009; **94**(3): 709-28.
25. Kwekkeboom DJ, Bakker WH, Kooij PP, et al. [177Lu-DOTAOTyr3]octreotate: comparison with [111In-DTPAo]octreotide in patients. *Eur J Nucl Med* 2001; **28**(9): 1319-25.
26. Kwekkeboom DJ, Teunissen JJ, Bakker WH, et al. Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3] octreotate in patients with endocrine gastroenteropancreatic tumors. *J Clin Oncol* 2005; **23**(12): 2754-62.
27. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**(2): 228-47.
28. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**(5): 365-76.
29. Fayers PM, Aaronson NK, Bjordal K, Grønvold M, Curran D, Bottomley A. EORTC QLQ-C30 Scoring Manual. European Organisation for Research and Treatment of Cancer; 2001.
30. Bodei L, Cremonesi M, Grana CM, et al. Peptide receptor radionuclide therapy with (1)(7)(7)Lu-DOTATATE: the IEO phase I-II study. *Eur J Nucl Med Mol Imaging* 2011; **38**(12): 2125-35.
31. 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**(5): 925-33.
32. 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**(4): 749-55.
33. de Herder WW, van Schaik E, Kwekkeboom D, Feelders RA. New therapeutic options for metastatic malignant insulinomas. *Clin Endocrinol (Oxf)* 2011; **75**(3): 277-84.
34. Hendren NS, Panach K, Brown TJ, et al. Pasireotide for the treatment of refractory hypoglycaemia from malignant insulinoma. *Clin Endocrinol (Oxf)* 2017; **88**(2): 341-3.
35. Sansovini M, Severi S, Ambrosetti A, et al. Treatment with the radiolabelled somatostatin analog Lu-DOTATATE for advanced pancreatic neuroendocrine tumors. *Neuroendocrinology* 2013; **97**(4): 347-54.
36. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364**(6): 514-23.
37. Suzuki L, Miyatsuka T, Himuro M, et al. Everolimus Directly Suppresses Insulin Secretion Independently of Cell Growth Inhibition. *Journal of the Endocrine Society* 2018; **2**(7): 589-96.
38. Strosberg J, Wolin E, Chasen B, et al. Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With (177)Lu-Dotatate in the Phase III NETTER-1 Trial. *J Clin Oncol* 2018: Jco2018785865.
39. Khan S, Krenning EP, van Essen M, Kam BL, Teunissen JJ, Kwekkeboom DJ. Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [177Lu-DOTA0,Tyr3] octreotate. *J Nucl Med* 2011; **52**(9): 1361-8.

40. Kong G, Grozinsky-Glasberg S, Hofman MS, et al. Efficacy of Peptide Receptor Radionuclide Therapy for Functional Metastatic Paraganglioma and Pheochromocytoma. *J Clin Endocrinol Metab* 2017; **102**(9): 3278-87.