General introduction

History, diagnosis and prognosis of neuroendocrine tumor syndromes

Based on

Effect of hormone secretory syndromes on neuroendocrine tumor prognosis

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Role of biomarker tests for diagnosis of neuroendocrine tumors

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INTRODUCTION

Neuroendocrine tumors (NETs) are a group of neoplasms that share common characteristics including the production, storage and secretion of amines and peptide hormones. Despite these universal features, NETs can originate at different organs, have distinct genetic signatures and consequently display a wide array of biological behavior. This is illustrated by the benign nature of an appendix NET versus the poor prognosis of patients with small cell lung cancer.[1] NETs arise from specialized cells diffusely spread throughout the body that act as chemo- and mechanosensors of external and internal stressors and secrete signals to the local micro-environment and circulation in order to preserve homeostasis during (patho-)physiological fluctuations.[2-4] These cells are termed neuroendocrine (NE) due to their underlying trait to combine the uptake of amino acids, decarboxylation and storage of peptides and amines beneath the plasma membrane.[5] Although ubiquitously present, the majority of these cells are restricted to derivatives of the embryologic gut, which includes the pulmonary and gastrointestinal tracts. In contrary to previous beliefs that these NE cells had an ectodermal origin, they originate from local stem cells in the gut.[6]

Although tumors with NE differentiation can arise in many types of cancer, including breast and prostate carcinoma, these are commonly considered separate from NETs from the gut. In the gastrointestinal system neoplasms arising from NE cells are termed gastroenteropancreatic NETs (GEP-NET). These tumors have retained their ability to secrete peptides, amines and other molecules that could overflow into the systemic circulation and be utilized as biomarkers. NET markers were first evaluated at the tissue level where several proteins involved in hormone secretion, including synaptophysin[7] and chromogranin A (CgA),[8] were found to be specific for the NE phenotype. These findings have been instrumental to the further development and consequent clinical implementation of circulating biomarkers.

General biochemical markers

As NE cells share the basic machinery to effectively sense extracellular molecules and communicate with their environment there are commonalities between the different tumor subtypes. These shared characteristics allow the use of general biomarkers as a means to diagnose all NET subtypes. Alternatively, the different original cell types all have dedicated functions and as such secrete unique sets of peptides, proteins and amines. Consequently, the measurement of biomarkers for hormonal sequelae and biological behavior should also be tailored according to type of origin and accompanying clinical syndrome (Figure 1). Clinicians should remain vigilant for symptoms and signs associated with hormonal syndromes in GEP-NET patients as these require distinctive treatment (Table 1).[9] The diagnosis of a secreting or functional NET is based on the measurement of a hormone level that is inappropriately elevated in a particular clinical setting as stimulated circulating concentrations may also occur in response to physiological states or other diseases. Thereby the diagnosis

of a secreting NET is often made using specific endocrine function tests. In rare NET cases, a group of ectopically secreted hormones can be identified as biomarkers. The presence of ectopic hormone secretion is a negative prognostic sign due to the severity of the accompanying syndrome. These symptoms should be promptly recognized, hormones should be confirmed by measurement and treatment should be ensued.

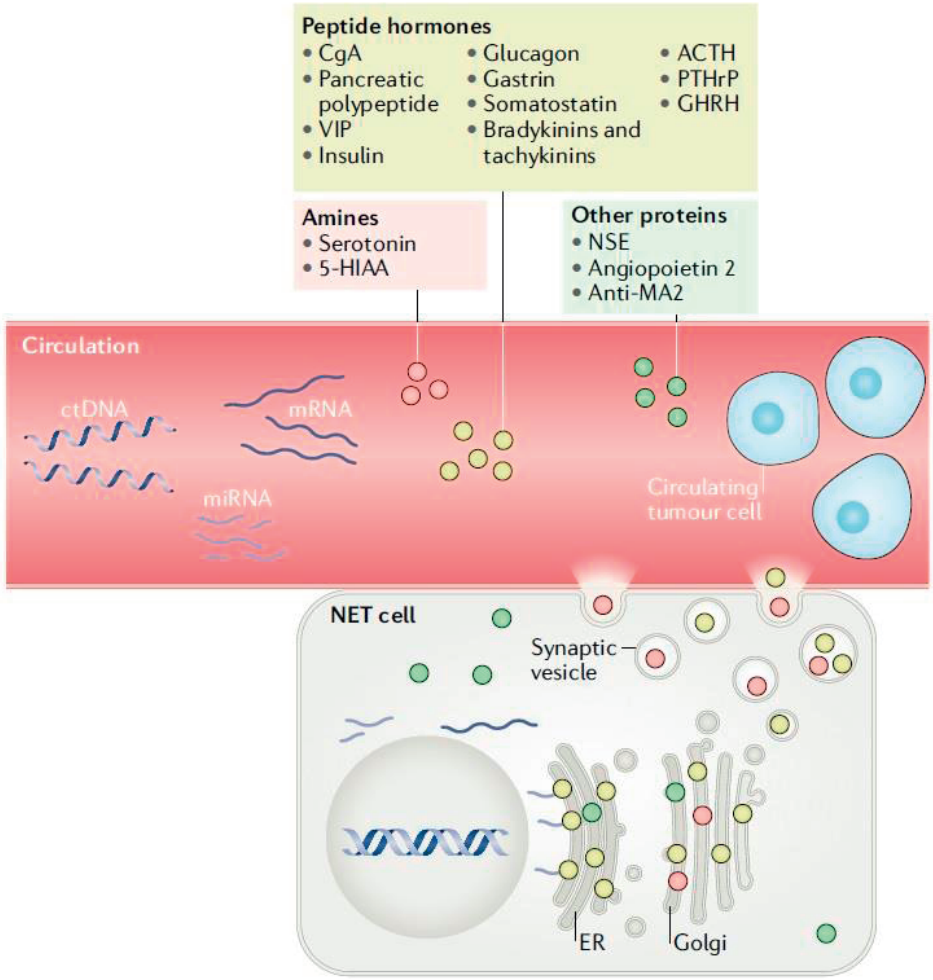

Figure 1: Overview of common GEP-NET biomarkers
The neuroendocrine cell of the gastrointestinal system produces a specific set of transcripts, amines, polypeptide hormones and associated proteins that can be measured in the circulation or urine as biomarkers for NET patients. Also, circulating tumor cells themselves can be evaluated in blood.

Table 1: GEP-NET-associated hormonal syndromes and their biomarkers

Syndrome	Symptoms	Biomarkers	Cut-off	Specific treatment
Carcinoid syndrome	Skin flushing, diarrhea, bronchospasm and cardiac valve fibrosis	Urine 5-HIAA	40-50 µmol per day[57,113]	Somatostatin analogues, telotristat
		Plasma 5-HIAA	118 nmol/l[63]	
		Platelet serotonin	5.4-9.3 nmol/ 10^9 platelets[54]	
		NT-proBNP	24-31 pmol/l[114]	
Insulinoma	Hypoglycemia	Insulin[a]	18 pmol/l[73]	Diazoxide, somatostatin analogues, everolimus
		C-peptide	0.2 nmol/l	
		pro-insulin	5 pmol/l	
Glucagonoma	Diabetes mellitus, wasting, glossitis, necrolytic migratory erythema	Fasting glucagon	500 pg/ml[115]	Insulin, somatostatin analogues
Zollinger-Ellison	Gastroesophageal reflux, recurrent peptic ulcer disease	Fasting gastrin[b]	1000 pg/ml[90]	High-dose proton pump inhibition
VIPoma	Severe diarrhea, electrolyte disturbances	VIP	20-60 pmol/l[111]	Loperamide, electrolyte suppletion, somatostatin analogues
Cushing syndrome	Weight gain, opportunistic infections, diabetes mellitus, hypertension, muscle atrophy, easy bruising, hypokalemic alkalosis	Cortisol after 1mg dexamethasone overnight	50 nmol/l[116]	Bilateral adrenalectomy, steroidogenic enzyme inhibitors (ketoconazole, metyrapone) or GR antagonist (mifepristone)
		urinary cortisol excretion	Upper reference of normal	
		midnight salivary cortisol	4 nmol/l	
		ACTH	Normal or elevated	
Acromegaly	Acral growth, frontal bossing, sweating, cardiomegaly	IGF-1	Upper reference of normal[117]	somatostatin analogues, pegvisomant
		GH suppression test (OGTT)	1 µg/L	
		Growth-hormone-releasing hormone	Detectable[118]	
Humoral hypercalcemia of malignancy	Hypercalcemia (with suppressed Parathyroid hormone level)	Parathyroid hormone-related peptide	Upper reference of normal[119]	Hydration, somatostatin analogues, bisphosphonates, denosumab

Upper reference limit of normal depends on the assay used. 5-HIAA , 5-hydroxyindoleacitic acid; ACTH, adrenocorticotropic hormone; GH, growth hormone; GR , glucocorticoid receptor ; NET, neuroendocrine tumor ; NT- proBNP, amino- terminal pro- brain natriuretic peptide; OGTT, oral glucose tolerance test; VIP, vasoactive intestinal peptide.

a All measured during symptomatic hypoglycaemia with glucose ≤2.1 mmol/l.

b Measured without the use of proton- pump inhibitors and in the presence of gastric acid hypersecretion; pH ≤2 or basal acid output >15 mEq/h. For levels between the upper limit of normal and 1,000 pg/ml, a secretin test is advised.

Chromogranin A

CgA is a water-soluble acidic glycoprotein contained in the secretory vesicles of neurons and NE cells. It is part of a family of granins which also includes chromogranin B and chromogranin C and can be cleaved in several smaller peptides as pancreastatin and vasostatin.[10] A variety of NE-derived tumors beside NETs can secrete CgA, including medullary thyroid carcinoma and pheochromocytoma.[11] CgA is involved in the constitution of dense-core secretory granulae through which it is co-secreted with polypeptide hormones. This makes CgA a non-specific marker for secretion which constitutes one of its diagnostic weaknesses. Increased secretion from NE cells can cause a falsely elevated CgA. This occurs mainly in patients with increased gastrin secretion secondary to atrophic gastritis and treatment with proton-pump inhibitors (PPIs).[12,13] However CgA is still the most used liquid biomarker in the follow-up of NETs as it correlates with the number of liver metastases and tumor burden[14-16] as well as with progressive disease and response to therapy.[17,18]

For the detection of NETs, CgA demonstrates high specificity if all interfering conditions are excluded, but in a general population specificity is lower than 90%.[19,20] In a population of patients with inflammatory bowel disease, renal failure or gastric disorders, specificity is less than 50%, raising the question if CgA is discriminatory where it is most needed.[21] The sensitivity of CgA is dependent on the type of NET, secretory status and tumor burden and varies between 50-90%; the pooled sensitivity for NETs according to a recent meta-analysis is only 73%.[19]

Neuron-specific enolase

Neuron-specific enolase (NSE) is a glycolytic enzyme predominantly detected in the cytoplasm of neurons and NE cells.[22] It is expressed in various tumors with NE differentiation, but is mostly found in small cell lung cancer and poorly differentiated NETs.[15,23] An elevated serum NSE constitutes a negative predictor for overall survival in NET patients, but the diagnostic performance is limited.[24] Sensitivity for the detection of NETs is only 31-47%, while the addition of serum NSE to CgA can increase detection rates as some poorly differentiated NETs lose expression of CgA.[15,23]

Circulating transcripts

Several transcriptomic studies have investigated NET expression profiles in tissue biopsies or resections.[25-27] Tumor transcripts can however also be detected in the circulation and measured by quantitative polymerase chain reaction (qPCR). Individual circulating messenger RNA (mRNA) studies in GEP-NET patients have been lacking[28], but an innovative approach has been the combination of multiple transcripts termed NETest as a readout of NET biology. This multianalyte biomarker encompasses simultaneous measurement of 51 different NET-related transcripts that cover a multiverse of NE and tumor biology and gives a single read-out through an undisclosed algorithm.[29] Conceptually this multianalyte analysis

would more faithfully represent the wide variety in NET subtypes and biological behavior. Initial studies indeed reveal superior biomarker metrics compared to CgA, pancreastatin and neurokinin A[30] with sensitivity and specificity above 90% across varying NET subtypes and stages. Moreover, the NETest predicted treatment efficacy in series of patients treated with surgery,[31] somatostatin analogues (SSA)[32] and peptide receptor radionuclide therapy (PRRT).[33] Compared to anatomical imaging NETest could detect progressive disease one year in advance.[34] Although these outcomes in cross-sectional and retrospective series certainly appear promising, the outcomes of current prospective trials should be awaited to envision the role, availability and costs of this NET biomarker in clinical practice. Also, the specificity of the NETest in patient populations with gastrointestinal diseases or other malignancies remains to be determined.

Tumor-derived microRNA molecules (miRNAs) can also be detected in the circulation by qPCR. Despite that several studies have described miRNAs as possible biomarkers in GEP-NET tissues,[35-40] studies on circulating miRNA levels in NET patients are scarce and predominantly focused on siNET. In three separate studies the serum levels of miR-96, miR-182, miR-196a, miR-200a[41], miR-21-5p, miR-22-3p[42] and miR-7-5p[43] were significantly higher in NET patients compared to controls,[42] but there was a large degree of overlap between groups for individual miRNAs. Further studies are needed to ascertain test metrics of these biomarkers, but clinical implementation of circulating miRNAs as tumor biomarkers could be hampered by the lack of standardization of measurement.[44]

Specific biomarkers: history, diagnosis and prognosis of neuroendocrine tumor syndromes

Carcinoid syndrome

Enterochromaffin (EC) cells, mainly localized in the small intestine, secrete the amine derivative serotonin (5-hydroxytryptamine) to regulate gastrointestinal motility.[3,45] SiNETs arise from these EC cells and have the potential to overproduce serotonin. Serotonin from gastrointestinal NETs is completely metabolized in the liver after delivery by the portal system. Elevated serotonin levels occur only in metastatic disease or when the portal vein is bypassed, for instance in the case of ovarian lesions. Therefore, the systemic sequelae of increased serotonin levels termed carcinoid syndrome is predominantly diagnosed in patients with metastases, particularly in the liver.[46] These symptoms include flushing, diarrhea, bronchospasm and on the long-term mesenteric and cardiac valvular fibrosis.

The first cases of carcinoid syndrome were described from 1927 onward.[47-49] Post-mortem examination revealed tumors in the ileum, liver metastases and tricuspid valve stenosis, but the link connecting these findings remained unknown.[50,51] In the 1950s several discoveries were made, significantly advancing the knowledge of the carcinoid syndrome. Serotonin was identified by *Page* and in a case series published in 1954, *Thorson* et al. linked flushing, diarrhea and right sided heart failure to carcinoids in the small intestine and identified sero-

tonin secretion as a possible cause of the syndrome.[52,53] Survival varied from over ten years when patients first complained of abdominal pain or flushing, to weeks when presenting with heart failure.

The carcinoid syndrome is diagnosed by demonstrating increased serotonin secretion. 5-hydroxyindoleacitic acid (5-HIAA) is the main metabolite of serotonin and can be measured in plasma and urine. Studies that include localized, non-secretory or non-small intestinal NETs report varying urinary 24-hour 5-HIAA excretion levels with a limited sensitivity of 38-73%.[17,54-61] Only several studies have included a control or disease-free population, but they all report high specificity of 89-100% for the detection of NET using urinary 5-HIAA levels, also in control subjects with flushing and diarrhea.[17,54,56-58] Specificity is decreased if patients do not abstain from tryptophan-rich food or use interfering medications.[62] As an alternative, plasma 5-HIAA has now been shown to be well correlated with the 24-hour urinary excretion.[63,64] Nearly all circulating serotonin is stored in platelets. Platelet serotonin concentrations have been compared to urinary 5-HIAA excretion with favorable results: it is has a higher sensitivity and is not influenced by diet, but this has only been tested in a limited number of studies.[54,62,65]

Few studies have exclusively compared survival of functional and non-functional midgut NETs. Mostly urinary 5-HIAA excretion is used as marker for the carcinoid syndrome, but this does not always correlate with the clinical symptoms which are used to define carcinoid syndrome.[66] Only limited number of studies are published on the effect of carcinoid syndrome on survival (on the basis of clinical symptoms) (Table 2). Halperin and colleagues and the group of Janson have demonstrated a shorter survival for functional NETs in respectively a cohort-study (SEER-database) and a center-based study, respectively.[14,67] However, after correction for liver burden and other biomarkers in the study by Janson and colleagues survival did not longer differ between patients with and without carcinoid syndrome. Halperin and colleagues, could not correct for tumor burden, due to the limitations is the data collection. Against these studies are also two studies who do not demonstrate a significant influence of carcinoid syndrome on survival.[61,68]

Insulinoma

The first patient with the typical presentation of an insulinoma was described in 1927 by *Wilder.*[69] This patient turned out to have a malignant insulinoma with liver metastases. Insulinomas present mainly with hypoglycemia resulting in episodes of confusion, loss of consciousness, sweating or dizziness and body weight increases.[70,71] The diagnosis of an insulinoma is based on Whipple's triad: neuroglycopemia with a proven hypoglycemia and elevated insulin with resolving of symptoms after normoglycemia is established.[72] At the time of a confirmed hypoglycemic event with a blood glucose level of ≤2.1 mmol/L, either spontaneous or during a 72-hour fast, measurements of insulin, C-peptide, pro-insulin and oral hypoglycemic agents should be executed.[73] These values help differentiate between

Table 2: Peri-operative mortality: mortality rate the first 30 days after surgery for carcinoid heart disease

	Overall Survival	Peri-operative mortality	Number of patients
Robiolio [120]	5 year: 25%	62.5% (<1995)	(n=8)
Møller [121]	Median survival: 2.6 years	25% (1981-89)	(n=12)
		9% (1995-2000)	(n=43)
Mokhles [122]	5 year: 43%	5.7% (1993-2010)	(n=19)
Bhattacharyya [123]	2 year: 44%	18% (2006-2010)	(n=22)
Connolly [124]	5 year: 35 %	20% (<1990)	(n= 10)
		16.4% (1990-99)	(n=61)
		7.2% (2000-09)	(n-97)
		3.7% (2010-12)	(n=27)
Edwards [125]	2 year: 69 %	13% (2005-2015)	(n=32)

endogenous hyperinsulinism (insulin >18 pmol/L and C-peptide ≥0.2 nmol/L) or other causes of hypoglycemia like exogenous insulin, oral hypoglycemic drugs or autoimmunity. In the case of low insulin and C-peptide levels an IGF-II producing non-islet cell tumor should also be considered. The sensitivity of the supervised 72-hour fast for the detection of insulinomas was found to be 100% in several studies, with most patients already fulfilling Whipple's triad in the first 48 hours.[74-77] Limiting the sensitivity can be the underdiagnosis of neuroglycopenic symptoms thereby making a false negative diagnosis.[74,77] Nevertheless, the near 100% sensitivity and specificity make the 72-hour fast an effective gold standard.

Almost 90% of patients present with localized disease with tumors smaller than 5 cm restricted to the pancreas. Prognosis is excellent in these patients. Overall survival and curation rates are often near 100% after enucleation or (partial) pancreatectomy, higher than most series on non-functioning pNETs.[78,79] As metastasized insulinoma's are rare, no large series are available on prognosis. The few series with more than 10 patients report a median survival of approximately 2 to 3 years, but survival of over 30 years has been described in single patients.[80-82] All these series have been published before PRRT or tumor-targeting therapy was available and thereby probably underestimate current prognosis as for example *van Schaik and colleagues* report a median progression-free survival of 27 months in five patients after treatment with PRRT, which is a vast improvement compared to these historical cohorts.[83] Median survival of metastatic non-functioning pNET in the period before 2005 is 2 to 3 years as well. [84-86]

Gastrinoma

Gastrin secreted in large amounts by a gastrinoma causes severe peptic ulcer disease through acid hypersecretion and is known as the Zollinger-Ellison Syndrome (ZES).[87] Fasting gastrin can be physiologically elevated in cases of atrophic gastritis, *Helicobacter Pylori* infection or due to the effects of PPIs. Therefore, theoretically, fasting gastrin should be measured in the

presence of gastric acid hypersecretion (pH ≤2 or basal acid output >15mEq/h) without interference of PPI. For patients on PPIs, it is advised only to stop PPIs if the gastroscopy shows no sign of mucosal disease, because the interruption of PPIs in ZES patients is not without risk of peptic complications.[88] An approach can be to switch PPIs for histamine type 2 receptor (H2) blockers 1-2 weeks before gastrin measurement and to replace the H2 antagonist for antacids for 24-48 hours before testing.[10,89] A fasting gastrin of more than 1000 pg/mL is diagnostic for a gastrinoma, whereas a secretin test should be performed for fasting gastrin levels between the upper limit of normal and 1000 pg/mL.[90] The secretin test is positive if gastrin rises with more than 120 pg/mL, with a sensitivity of 94% and specificity of 100%.[91]

Gastrinoma's are most often localized in the duodenum or the pancreas (gastrinoma triangle), but are not always found with pre-operative imaging. Fortunately this does not influence outcome and should not withhold patients from surgery.[92,93] A sharp decrease in peptic complications in ZES has been established since the introduction of PPI's leading to a discussion if surgery is indicated for ZES.[94,95] Treatment strategy is also highly dependent on the presence or absence of the Multiple Endocrine Neoplasia 1 (MEN-1) syndrome. Several studies have shown the benefit of surgical resection for sporadic gastrinoma. A large amount of patients have lymph node metastases at time of first resection, so removal of peritumoral nodes is advised.[93,96] This results in curation of approximately half of patients after surgery and an excellent 10-year survival of over 90% in patients with a localized gastrinoma, higher than non-functional pNETs.[93,97-99] For MEN-1 associated gastrinomas only medical treatment with PPI's can be started in most cases. Due to the multifocal nature of gastrinoma's in MEN-1 curation rates are much lower in MEN-1 patients but on the other hand prognosis is better, also justifying an observational strategy.[97,100] While local lymph node metastases don't seem to influence prognosis too much, survival does decrease once liver metastases occur. Then 5-year survival decreases to 30-46% with 10 year survival of 16-30%.[97,101] This seems to be slightly better in MEN-1 with reported 15-years survival of over 50%. Mainly when diffuse liver metastases are diagnosed survival is significantly reduced in MEN-1.[101]

Glucagonoma

Patients with a glucagonoma usually present with diabetes mellitus and typical skin lesions named negrolytic migratory erythema. Other clinical features include glossitis, anemia, weight loss and venous thrombosis.[102] First described in 1966 by McGravan, current incidence is estimated to be 0.02-0.06 per million.[103-105] Tumors are localized in the pancreatic body or tail in 80% of patients and more than half of patients present with liver metastases.[102] The diagnosis of a glucagon-secreting NET or glucagonoma is based on the fasting glucagon levels. In patients with a glucagonoma these levels are often more than 10-20 times elevated above the upper reference value and the diagnosis is quiet clear. However, the glucagonoma syndrome has also been diagnosed in patients with glucagon levels of

only 4 times elevated.[106,107] In these patients it is key to correlate this finding with the typical symptoms of glucagonoma.

The largest series of patients has been described by *Soga and colleagues.* Describing 407 cases of glucagonoma, they report a 10-year survival of 100% in localized disease (not including peri-operative mortality) and 51% in case of metastatic glucagnoma.[102] Other smaller series report 5-year survival of 70% for all stages of glucagonoma combined.[106,108,109]

Vasoactive intestinal peptide

The syndrome caused by hypersecretion of vasoactive intenstinal peptide (VIP) is known under multiple synonyms, namely VIPoma, Verner-Morrison syndrome, pancreatic cholera or Watery Diarrhea Hypokalemia Achlorhydria (WDHA) syndrome. Currently VIPoma syndrome is mostly used, but supplied with all these names one already knowns a lot about VIPoma's. First described by Verner and Morrison in 1958, hardly all patients present with diarrhea, sometimes so severe it causes hypokalemia and metabolic acidosis trough bicarbonate depletion.[110] In normal conditions levels of VIP are very low (<20 pmol/L) and in large series VIP was found to be 100% specific in patients with diarrhoea: in a case series of nearly 1000 patients all patients with elevated VIP above 60 pmol/L turned out to have a VIPoma.[111] However a normal VIP level does not rule out a VIPoma as especially in small VIPomas levels can still be normal.

The primary tumor is localized in the pancreas in 81% of patients and these tumors behave more malignant than the approximately 20% neurogenic tumors.[112] As one of the rarest syndromes in pNETs (estimated incidence of 0.1-0.6 per million) few large series on epidemiology and survival are available. Once again, localized disease has an excellent prognosis when resection is feasible (5 year survival 94%), but 5-year survival declines to 60% in the presence of liver metastases.[112]

Aim of this thesis

1. Evaluation of the prognostic value of 5-hydroxyindoleactic acid in small intestinal and pancreatic NET
2. Evaluation of the treatment of secreting neuroendocrine tumors with PRRT (^{177}Lu-DOTATATE)
    a. Paragangliomas and pheochromocytomas
    b. Insulinomas, VIPomas, gastrinomas and glucagonomas
    c. Small intestinal NET (carcinoid syndrome)
3. Evaluation of quality of care for neuroendocrine tumor patients
    a. Pathology reporting
    b. Expert centers: multidisciplinary team

Outline of this thesis

Chapter 2 describes the prognostic value of urinary 5-hydroxiindoleacitic acid (5-HIAA) excretion in patients with ENETS stage IV small intestinal neuroendocrine tumors and compares its value with NSE and CgA.

In **Chapter 3**, incidence of serotonin secretion and carcinoid syndrome in pancreatic NET patients is determined. In these patients the prognostic value of urinary 5-HIAA excretion is also studied.

Chapter 4 gives an overview of the work-up and treatment of NET, critically reviewing current guidelines.

Chapters 5 to 7 review the results of PRRT with ^{177}Lu-DOTATATE for the treatment of several clinical neuroendocrine tumor syndromes including paragangliomas, carcinoid syndrome and functioning pancreatic NET syndromes.

In the following chapters the quality of care for patients with neuroendocrine tumors is studied. First, the effect of implementations of pathology guidelines of the quality of pathology reports is reported in **Chapter 8.** Similarly, the yield of reviewing the pathology specimens of NET in expert centers is studied in **Chapter 9.**

Chapter 10 describes the effect of the multidisciplinary tumor board decisions on patient care.

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