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GEP-NET : rare tumour connections. Pathophysiological aspects of gastroenteropancreatic neuroendocrine tumours

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Chapter 2

An Overview of the Current Diagnosis and Recent Developments in Neuroendocrine Tumours of the Gastroenteropancreatic Tract: the Diagnostic Approach

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Abstract

Neuroendocrine tumours of the gastroenteropancreatic tract (GEP-NETs) comprise a group of very heterogeneous neoplasms, which are considered 'rare diseases'. Epidemiological studies on the incidence of GEP-NETs worldwide have reported a remarkable increase in the detection of these tumours.

In a recent study, based on pathology reports (PALGA) to investigate the incidence of pancreatic and duodenal neuroendocrine tumours in The Netherlands from 1991 until 2009, we also noticed a significant increase in the incidence of these tumours. In particular, the incidence of non-functioning neuroendocrine tumours had significantly increased over this period. Remarkably, a substantial discrepancy was observed between the numbers of neuroendocrine tumours diagnosed in the clinical as opposed to the pathological setting, emphasizing that these tumours provide a real diagnostic challenge. To improve the diagnosis of GEP-NETs, we advocate that these complex neoplasms should receive more specialized attention.

In this mini-review we provide an overview of the current diagnostic approach of GEP-NETs, and added the recent developments in establishing the diagnosis of these tumours, in order to increase the intelligibility and awareness of GEP-NETs among clinicians and pathologists. Early detection in order to prevent morbidity of GEP-NETs is advocated.

Main text

Introduction

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are considered to be rare, heterogeneous and complex neoplasms¹. They include the pancreatic (PNETs) and gastrointestinal (GI) neuroendocrine tumours (GI-NETs) or carcinoids, which share their origin of cells of the diffuse neuroendocrine system, but further show many differences regarding pathogenesis, clinical behaviour and prognostic outcome^{2,3}. Characteristic for GEP-NETs is their ability to produce bioactive substances (Table 1)⁴. Based on the clinical symptoms and syndrome caused by these peptides, they can be divided into functioning (F-NETs) and non-functioning tumours (NF-NETs). Due to their heterogeneity, GEP-NETs often provide a diagnostic challenge to physicians. Although GEP-NETs are generally more indolent than carcinomas, the majority are malignant, showing aggressive tumour behaviour and presenting with metastases at diagnosis¹. GEP-NETs can occur sporadically, or as part of a hereditary syndrome like Multiple Endocrine Neoplasia syndrome type 1 (MEN-1), von-Hippel Lindau Disease (vHLD), neurofibromatosis type 1, or tuberous sclerosis⁵.

In 2007, a summit meeting on the major clinical, pathological and scientific challenges in the field of GEP-NETs was held to debate on potential solutions⁶. There was consensus between the participants that there is a worldwide substantial lack of knowledge, experience and reliable research concerning GEP-NETs. In line with these observations, we feel that also in our country, GEP-NETs indeed present a relatively unknown and underdeveloped subject with fairly limited knowledge under most physicians. However, since several epidemiological studies have shown an increase in the incidence of GEP-NETs worldwide, in combination with the fact that these tumours, when accurately managed, provide a relatively good prognosis for the patients, we feel that it can be worth to increase the awareness for and knowledge about GEP-NETs among clinicians and pathologists, in order to further increase the early detection and prevent morbidity of GEP-NETs⁷⁻¹⁰.

In this mini-review, we describe the current diagnostic approach of GEP-NETs, in combination with several common pitfalls and some recent developments to improve the diagnosis of these tumours. In addition, we provide a diagnostic algorithm to facilitate their diagnostic approach.

Epidemiology

Based on pathology information from PALGA the nationwide network and registry of histo- and cytopathology in The Netherlands, we calculated incidence of GEP-NETs from 2000 till 2008 in The Netherlands^{8,11}. For both pancreaticoduodenal NETs and GI-NETs a significant increase in incidence over time was noticed (Figure 1).

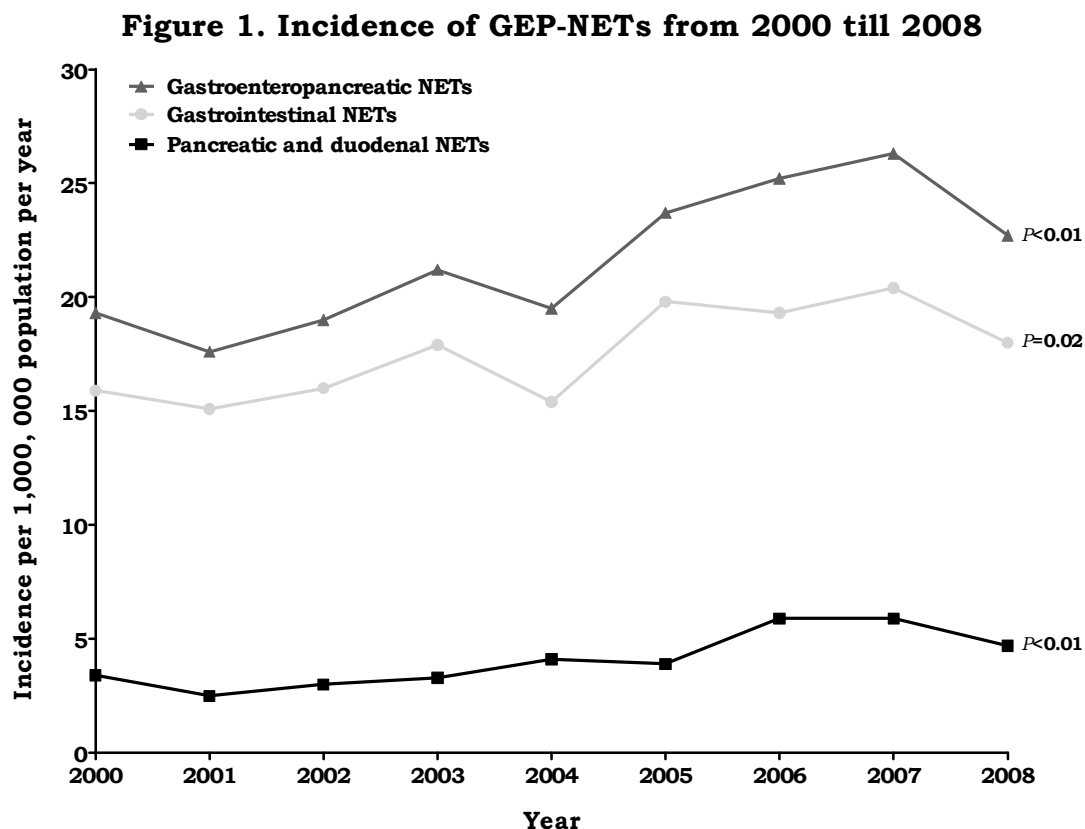


Figure 1. Current incidence of GEP-NETs in The Netherlands from 2000 till 2008. Using linear regression, trends in annual incidence rates over 2000 till 2008 were analyzed. A statistically significant increase was observed in the overall annual incidence of all GEP-NETs, and GI-NETs and pancreaticoduodenal NETs separately, over the study period.

However, these calculated incidence rates are based on pathology information only and therefore might represent an underestimation. In our study, we found that this was approximately 25%, due to the fact that some patients with clinically

diagnosed gastrinomas were not included in the PALGA database, because they had not undergone any surgery, biopsy and/or other pathological evaluation for their tumour⁸. This discrepancy between clinical and pathology incidence of GEP-NETs is an important issue concerning these tumours, which will be discussed later. Nonetheless, this pattern of increasing incidence rates indicates and confirms that GEP-NETs might not be as rare as previously thought. Whether this increase is due to improved detection methods rather than to a true rise in existence of these tumours is debatable. In that context it is important to note that we observed that 4% and 14% of the GI-NETs and pancreaticoduodenal NETs respectively, were found by incidence at autopsy, which indicates that, despite of improved detection methods, some GEP-NETs still do remain undetected.

Current diagnostic procedure for GEP-NETs

Symptoms of patients with GEP-NETs are in general related to the localization and hormonal production of the tumour¹. Frequently, symptoms are vague and aspecific, although symptoms associated with a clinical syndrome may arise suspicion for a F-PNET (Table 1)¹.

Next to standard medical history and physical examination, laboratory analyses are crucial in the diagnosis^{12,13}. To diagnose NETs, chromogranin A (CgA) levels can be determined in plasma/serum, or immunohistochemically^{14,15}. Increased plasma/serum levels of CgA have been reported to correlate with a worse prognosis in these patients. Increased levels of 5-hydroxyindoleacetic acid (5-HIAA, the breakdown product of serotonin) can be determined in a 24-hours urine sample collection, and indicate the presence of a serotonin-producing tumour. Increased levels of hormones like insulin, indicate the presence of a hormone-secreting functioning PNET.

Table 1. Symptoms and syndromes associated with GEP-NETs ¹⁴	
Gastrointestinal neuroendocrine tumours	
Functioning neuroendocrine tumours	Non-functioning neuroendocrine tumours
<u>Carcinoid</u> Flushing, diarrhoea, and wheezing	Abdominal pain, weight loss, anorexia, jaundice, nausea and vomiting, intra-abdominal haemorrhage
Pancreatic neuroendocrine tumours	
Functioning neuroendocrine tumours	
<u>Insulinoma</u> Neuroglycopenic symptoms like headache, blurred vision, confusion, dizziness, lethargy, and amnesia. Autonomic nervous system symptoms like sweating, weakness, anxiety, tremor, palpitations, and nausea	
<u>Gastrinoma</u> Diarrhoea, abdominal pain, heartburn, weight loss, nausea and vomiting, faecal blood loss	
<u>Glucagonoma</u> Necrolytic Migratory Erythema, Diabetes Mellitus, cachexia	
<u>VIPoma</u> Watery diarrhoea, hypokalemia, achlorhydria, hyperglycaemia, hypercalcemia, flushing	
<u>Somatostatinoma</u> Diabetes Mellitus, cholelithiasis, steatorrhea, anaemia, weight loss	
Other (rare) pancreatic functioning neuroendocrine tumours	
<u>ACTHoma</u> Cushing's syndrome	
<u>GRFoma</u> Acromegaly	
<u>PTH-RP tumour</u> Hypercalcemia	
Non-functioning neuroendocrine tumours	
Abdominal pain, weight loss, anorexia, jaundice, nausea and vomiting, intra-abdominal haemorrhage	

Table 1. Overview of all symptoms and syndromes associated with GEP-NETs.

Imaging of GEP-NETs includes endo- or gastroscopy, octreoscan, computerized tomography (CT) scan, or magnetic resonance imaging (MRI) scan¹⁶.

Pathological examination of biopsies or surgical specimens reveal the verification of the neuroendocrine nature of the tumour by immunohistochemistry, for pan-neuroendocrine markers like keratin, CgA, neuron specific enolase (NSE), synaptophysin, grimeius, and CD56. A proliferation marker (Ki67 or MIB1) must

be used to assess the degree of differentiation and proliferation, to grade the tumours according the World Health Organization (WHO) classification¹⁷. Tumour characteristics like localization, size, composition, relationship to anatomic structures, resection margins, and the presence of metastases, should be assessed in order to classify the tumour along the TNM stage classification⁴.

Pitfalls in the diagnosis of GEP-NETs

One of the major pitfalls in the nomenclature of neuroendocrine tumours is the use of the term 'carcinoid'. In 1907, Oberndorfer introduced this term for neuroendocrine tumours with a relatively 'benign' course¹⁸. Increasing knowledge about these tumours, however, had led to the conclusion that carcinoids also encompasses low-grade and high grade malignant tumours. Therefore, Soga *et al.* called the term 'carcinoid' a 'misnomer'¹⁹. In fact, this term has been used for different goals; whereas pathologists label all tumours with neuroendocrine features as a 'carcinoid', clinicians use 'carcinoid' for serotonin-producing tumours that lead to the carcinoid syndrome. Therefore, Capella *et al.* suggested replacing 'carcinoid' by 'neuroendocrine tumour' to include all tumours with neuroendocrine features, but also realized that abandoning this term completely would be too confusing, and therefore proposed to utilize it for the specification of a NET with serotonin production or producing any other substance which may lead to the carcinoid syndrome²⁰. As a consensus in the use of the GEP-NETs nomenclature is highly desirable, we propose that henceforth 1) the term 'carcinoid' should be used solely in the clinical setting, and only for those tumours that lead to the carcinoid syndrome as a result of the hypersecretion of serotonin, prostaglandins, or tachykinins by the tumour, characteristic of symptoms like flushing, diarrhoea and wheezing; 2) pathologists distinguish the various types of neuroendocrine tumours; neuroendocrine tumours should be defined according to the classification of the WHO, thereby replacing 'carcinoid' by 'neuroendocrine tumour' for well-differentiated low-grade malignant carcinoids, whereas malignant carcinoids should be defined as 'neuroendocrine carcinomas'.

Another misunderstanding among pathologists and clinicians has arisen due to the lack of a standardized definition of functioning and non-functioning tumours, as pointed out by Halfdanarson *et al.* Although non-functioning tumours are characterized by the lack of a clinical syndrome, they might secrete hormonal peptides as well, but only those tumours leading to clinical symptoms are referred to as functioning⁷. For example, increased blood levels of pancreatic polypeptide or neurotensin can be found in NF-PNETs²¹. Warner *et al.* already reported that plasma hormone levels not always correlate with the presence of a clinical syndrome²². For example, in case of the Zollinger-Ellison syndrome, fasting serum gastrin levels may be non-diagnostic (i.e., <1000 ng/L), or symptoms might be masked by the use of proton pump inhibitors or histamin receptor antagonists, or pernicious anaemia. Furthermore, it is reported that the hormonal secretion by the tumour is not always reflected in immunohistochemical staining for this hormone at pathology²³. For a standardized approach, we recommend that the clinical diagnosis is superior to the pathological observations concerning the designation of the tumour as 'functioning' or 'non-functioning'. In other words, in the absence of immunohistochemical positivity for a certain hormone in combination with increased serum levels of that particular hormone and/or the presence of a clinical syndrome, the tumour should be defined as 'functioning'. In the opposite situation, i.e., a positive staining at pathology, but absence of increased serum levels and/or a clinical syndrome, the clinical presentation should be decisive, and the tumour should be defined as 'non-functioning'.

Next, the existence of 'benign' GEP-NETs is disputed. Whereas the majority of GEP-NETs are considered to be malignant, insulinomas and appendiceal carcinoids are not. However, we believe that all GEP-NETs have malignant potential, and that early diagnosis of these tumours, because of the symptoms they cause, leads to the assumption that they are benign. Namely tumour size and/or invasion, and the presence of metastases, all characteristics which can be 'prevented' by early detection, makes a tumour to be referred to as malignant.^{17,20} The fact that the majority of NF-NETs have a poor prognosis underlines that

absence of clinical symptoms leads to a delay in diagnosis and a consequently more progressed tumour.

Another difficulty in diagnosing GEP-NETs arises as these tumours show a relative high frequency of 'ectopic occurrence'. For example, gastrinomas, which are usually located in the pancreaticoduodenal region and lymph nodes, have been reported on ectopic locations such as ovaries, biliary tract, kidneys, stomach and liver²⁴. Recently, we reported on a patient with recurrent hepatic gastrinomas, in whom no pancreatic, duodenal or other primary tumour could be detected despite of an intensive, 20-year lasting follow-up²⁵. In literature, primary hepatic gastrinomas were described in about 20 patients, but real evidence for their primary origin (rather than being metastatic) was lacking. We believe that it is therefore uncertain whether these ectopic locations comprise primary gastrinomas rather than metastases of occult primaries. Furthermore, GEP-NETs have been reported on rare locations like oesophagus, gallbladder and biliary ducts, Meckel's diverticulum, ampulla of Vater, genital tract and skin^{26,27}. Lack of awareness that neuroendocrine lesions can also occur on these unusual sites results in the consequence that these tumours are frequently misdiagnosed or overlooked²⁷. Therefore, we recommend that when imaging is not successful to detect a neuroendocrine tumour in usual sites, an intensive search for occult tumours at ordinary sites should be started.

Additionally, it is important to realize that GEP-NETs frequently occur as or together with a second primary malignancy²⁸. The presence of a simultaneous second primary or metastatic malignancy must be thoroughly examined, as several case reports describe the existence of a second tumour synchronous with a carcinoid lesion²⁸⁻³². For example, gastrointestinal stromal tumours (GIST) are frequently seen in combination with (gastric) carcinoids^{29,31}. Furthermore, patients suffering from hereditary syndromes like MEN-1, vHL-disease, neurofibromatosis type 1 or tuberous sclerosis, are at increased risk for a gastroenteropancreatic NET. Therefore, alertness for synchronous (neuroendocrine) tumours among clinicians is advocated. Furthermore, members from hereditary GEP-NET disorder families should be checked for such tumours preferably by genetic counselling, and, if

possible, DNA profile, or by measurement of markers for these or associated tumours.

Recent developments in the diagnosis of GEP-NETs

As CgA is produced by all types of neuroendocrine cells, it serves as a highly sensitive neuroendocrine cell marker^{14,15}. In 2006, Kidd *et al.* demonstrated that also CgA mRNA and protein levels were useful in the detection of gastrointestinal carcinoids and metastases³³. Recently, Modlin *et al.* showed that measurement of circulating mRNA of CgA (and other markers such as Tph1 and NSE) provides a promising new diagnostic method for NETs³⁴. Next to CgA, several studies to other markers have been reported. In particular, investigators are interested to find markers which can discriminate between the diverse GEP-NET subtypes. Long *et al.* demonstrated that PAX8 might be a useful immunohistochemical marker in the discrimination of pancreatic and ileal NETs, as the latter lack expression of this transcription factor³⁵. However, Hosoda *et al.* found that immunohistochemistry on EUS-biopsy specimens using a selected panel of markers, including CK-7, CDX-2, synaptophysin, CgA, and the KRAS mutational status, could be used to discriminate endocrine tumours from two other major types of pancreatic cancers (i.e., invasive ductal carcinoma and acinar cell carcinoma)³⁶. A comparable study was performed by Burford *et al.*, who found that strong immunohistochemical expression for E-cadherin and B-catenin were characteristic for PNETs, and could be used to discriminate from solid pseudopapillary neoplasm, in which staining is absent³⁷. Another selected panel, including CDX-2, NESP-55, TTF-1 and PDX-1, was described to be useful to discriminate between metastatic NETs of pancreatic, gastrointestinal and pulmonary origin, in a study of Srivastava *et al.*³⁸. In contrast, Fendrich *et al.* found that PDX-1 expression was present in pancreatic but not duodenal gastrinomas, and PDX-1 expression in combination with Shh and PP expression in resected metastases might aid to locate undetected or occult primary gastrinomas³⁹. However, all above mentioned studies are non-conclusive, and further research and validation studies are needed before these diagnostic tools can be used in

practice. Based on a literature review and analysis to the utility of plasma/serum CgA measurements in NETs, Modlin *et al.* concluded that CgA still serves as the most specific (86%) and sensitive (68%) biomarker in plasma/serum to diagnose NETs that is currently available⁴⁰.

The improvement of imaging techniques is one of the most probable explanations for the incidence increase of GEP-NETs. For example, in a study of Ishikawa *et al.*, endoscopic ultrasound combined with contrast enhancement showed the best results in the preoperative localization of PNETs in comparison with other imaging techniques, like CT and US⁴¹. Prasad *et al.* reported that occult primary NETs could be detected by PET/CT using 68Ga-DOTA-NOC receptor in 59% of patients with confirmed NETs on biopsies from metastatic lesions, which was approximately three times higher than with CT alone⁴².

Also on the field of genetic and molecular pathology, research is ongoing. Previously, three detailed review articles that describe recent advances in the molecular genetics of sporadic and familial GEP-NETs, were reported^{5,43,44}. Therefore, this review will not discuss this subject into detail.

Diagnostic algorithm

The algorithm comprises a clinical and a pathological part. Although the pathological evaluation is important in the diagnosis, the clinical presentation largely determines the definition of a NET. However, we advocate an interdisciplinary cooperation between clinicians and pathologists in the diagnostic approach of GEP-NETs.

Although research to specific biomarkers to detect GEP-NETs is ongoing, studies are still inconclusive. Therefore, we recommend CgA as a highly specific and sensitive neuroendocrine marker in the diagnosis of NETs. CgA measurement in plasma/serum, and immunostaining for this marker on biopsy or surgical specimens, should be performed routinely by clinicians and pathologists, respectively, in order to adequately diagnose (or exclude) a NET.

Imaging techniques to detect NETs are improving. The use of various imaging tools combined is advocated. In specialized centres, relatively new imaging

modalities including PET-scan can be used in the localization of a NET. Repeatedly negative imaging results in detecting a primary NET should raise the suspicion of a physician for an ectopic localized NET. Furthermore, the presence of a secondary tumour should be investigated, in particular when a hereditary syndrome is present.

For standardized documentation and in order to determine the therapeutic approach, tumours should be categorized according the WHO and TNM classification.

Conclusion

GEP-NETs compose a complex and heterogeneous tumour entity, which form a diagnostic challenge to physicians. In this review, we aimed to provide a clear overview of current diagnostic procedures and common pitfalls for GEP-NETs. Taking some recent diagnostic developments in account, we propose a diagnostic algorithm for GEP-NETs, to generate a more standardized diagnostic approach, facilitate the diagnosis, and eventually improve the early detection of these tumours.

Figure 2. Diagnostic algorithm for GEP-NETs. Based on the current diagnostic approach, and inclusion of several pitfalls and various recent developments in the diagnosis of GEP-NETs, we provided a diagnostic algorithm to adequately diagnose these tumours.

I. CLINICAL DIAGNOSIS

1. Detailed personal history and physical examination

See Table 1 for an overview of symptoms related to the various types of GEP-NETs.

2. Determine localization if possible, using;

- EUS or endoscopy in combination with CT-scan or MRI-scan
- Somatostatin Receptor Scintigraphy or Octreoscan

→ Positive imaging: Continue with 3

→ Negative imaging: Thorough search for occult tumours at unusual locations, continue with 3

3. Measure plasma or serum CgA levels

To verify the neuroendocrine nature of tumour

4. Measure hormone levels in serum

To detect possible peptide production by the tumour in order to define the tumour as 'functioning' or 'non-functioning'.

Note: Only define a tumour as a 'carcinoid' in case of increased serotonin serum levels and/or urinary 5-HIAA elevations, and/or the presence of the classical 'carcinoid syndrome' (Table 1).

5. Confirm diagnosis with a specific diagnostic test

Positive test: Diagnosis confirmed, continue with II

Negative test: consider non-functioning tumour and/or differential diagnosis, continue with II

6. Investigate the presence of a hereditary syndrome

- Detailed family history
- Investigation for associated tumours and/or lesions
- Gene testing

Note: Consider the presence of synchronous tumours in case of gastric carcinoids (GISTs) or the presence of a hereditary syndrome.

II. PATHOLOGICAL DIAGNOSIS

1. Immunostaining

-Staining for general NE markers including chromogranin A, synaptophysin, neuron specific enolase (NSE), keratin and grimalius, to determine the neuroendocrine nature of the tumour.

Note: For the definition of a neuroendocrine tumour, at least one of above mentioned general neuroendocrine markers should show a positive staining

-In case of a clinical (diagnosis or suspicion for) functioning tumour;
Stain for specific hormones including serotonin, gastrin, insulin, glucagon, somatostatin, and/or VIP

Note: Be aware that, also in case of a clinical functioning tumour, immunohistochemical staining for the particular hormone can be absent. Immunohistochemical staining should aid in determining the diagnosis, and determine the actual diagnosis.

2. Determine WHO-classification

-Determination of proliferation index by Ki67 or MIBG1

-Determination of mitotic count

-Investigate tumour characteristics;

*size

*histological pattern

*relation to other structures/invasion

*angioinvasion

*metastases

Note: Define the tumour as NET or NEC, not carcinoid. The term carcinoid should only be designed (by clinicians) to tumours with serotonin production and/or in the presence of the classical carcinoid syndrome (Table 1).

3. Determine TNM stage

-Determine tumour localization

-Determine tumour size

-Determine invasion of the tumour into surrounding organs/structures

-Determine the presence of lymph node metastases

-Determine the presence of distant metastases

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