REVIEW ARTICLE

Neuroendocrine Neoplasms of the Gastrointestinal Tract

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SUMMARY

Background: Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are complex tumors whose incidence is rising and whose treatment requires precise classification and risk stratification.

Method: Selective review of the relevant literature, including recently published guidelines.

Results: GEP-NENs are initially classified by their degree of histological differentiation and their graded cell proliferation (Ki-67 index). In addition, there are GEP-NEN specific TNM staging protocols. The laboratory assessment includes the measurement of general tumor markers (synaptophysin, chromogranin A) as well as specific ones (hormones). The most important imaging technique for diagnosis is octreotide scintigraphy. The surgical treatment of GEP-NEN is based on oncological resection criteria whose aim is to achieve locally radical resection while preserving as much organ function as possible. Metastases, too, may be amenable to resection. The treatment options for unresectable metastases include radiofrequency ablation and chemoembolization, both of which are palliative methods of reducing tumor volume and hormone production. Other chemotherapeutic and nuclear-medical treatments can be applied depending on the extent of metastatic spread, the proliferation index, and the degree of hormone production by the tumor.

Conclusion: The accurate diagnosis and appropriate treatment of GEP-NET currently gives most patients with this tumor a good prognosis, as long as it is discovered early. Early GEP-NETs have a favorable prognosis. Further advances in the diagnosis and treatment of this disease may result from structural changes in patient care, including the establishment of NET centers.

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Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs), also known as carcinoids and islet cell tumors, arise from the neuroendocrine cells of the gastroenteropancreatic system. This cell system and its tumors are characterized by the expression of cell-type-specific peptide hormones and general markers (synaptophysin, chromogranin A). All GEP-NENs are included in one common classification. The incidence of these tumors, reported to be 1 to 2 per 100 000 head of population per year (for insulinomas, the reported incidence is around 4 per 1 million persons per year) seems to be on the rise, which is probably due to improvements and intensification of efforts in diagnostic endoscopy (1). As the prevalence of GEP-NENs has increased, so have the questions about their prognosis and treatment. This article aims to give general practitioners a general overview of the classification, prognosis, and treatment of GEP-NENs including practical hints for patient management. A selective literature search was carried out and guidelines from, among others, the European Neuroendocrine Tumor Society (ENETS) were taken into account.

Clinical picture and main symptoms

The symptoms of patients with GEP-NETs depend on the hormonal activity (functional status) of the tumors and on their location and extent (*Table 1*).

Recurrent hypoglycemia is typical of insulinomas. These tumors manifest themselves in adrenergic symptoms such as tachycardia, anxiety, sweating, and palpitations, and eventually, unless carbohydrates are consumed, in loss of consciousness as a symptom of neuroglycopenia.

Recurrent duodenal ulcer and gastroesophageal reflux are the primary symptoms of duodenal or pancreatic gastrinoma. Diarrhea is rare.

Necrolytic migratory erythema, marked weight loss, and glucose intolerance are characteristic of glucagonoma. A VIPoma (vasointestinal polypeptide-producing tumor) leads to watery diarrhea, resulting in dehydration (2).

Diarrhea, stomach cramps, and typical flushing, particularly in the face, are symptoms of usually metastasized ileal NETs. As a rule, the flushing starts suddenly and lasts for only seconds to a few minutes, often accompanied by burning sensations in the skin and a

TABLE 1

Gastroenteropancreatic neoplasms and their clinical diagnostic profile

Tumor	Secretion product	Symptoms/syndrome	Diagnostic laboratory tests
Foregut tumors			
Insulinoma	Insulin	Hypoglycemia syndrome	Fasting blood glucose, insulin, and C-peptide concentrations
Gastrinoma	Gastrin	Peptic ulcers, diarrhea	Serum gastrin concentration and gastric pH
Glucagonoma	Glucagon	Diabetes mellitus, exanthema	Serum glucagon concentration
VIPoma	Vasointestinal polypeptide	Watery diarrhea/WDHH	Serum VIP concentration
Nonfunctional tumors	Various hormones	Depend on tumor extent	Serum chromogranin A concentration
Midgut tumors			
Carcinoid	Serotonin	Carcinoid syndrome (diarrhea/flushing)	Concentration of 5-hydroxyindoleacetic acid in 24-hour urine sample
Hindgut tumors			
Nonfunctional tumors	Various hormones	Depend on tumor extent	Serum chromogranin A concentration

VIP, vasointestinal polypeptide-producing tumor; WDHH, watery diarrhea, hypokalemia, hypochlorhydria/achlorhydria; Chromogranin A is another very sensitive tumor marker, especially for monitoring the course of all GEP-NENs

sensation of heat. Forty to 50% of all patients with carcinoid syndrome develop cardiomyopathy with plaque-like fibrosis of the tricuspid valves and pulmonary valves (3, e1).

Classification

In 1963 the GEP-NENs were divided on an embryogenic basis into those of the foregut (lung, stomach, duodenum, upper jejunum, and pancreas), midgut (lower jejunum, ileum, appendix, cecum), and hindgut carcinoids (colon and rectum) (4). However, this classification does not include all the tumor entities that are known today (5). At the end of 2010 a new WHO classification appeared (Table 2). Fundamental criteria of the 2000 WHO classification such as differentiation and proliferation were retained, but location, tumor size, tumor extent, and angioinvasion were transferred into the TNM (Tumor, Node, Metastasis) staging classification. Functional activity and association with hereditary or other diseases are indicated in the description of the individual tumor entities. The 2010 WHO classification starts from the assumption that all GEP-NENs are potentially malignant, but differ in their probability of metastasization (6). Well-differentiated NENs are classified together as neuroendocrine tumors (NETs) G1 or G2. NET G1 can be equated with carcinoid. The term neuroendocrine carcinoma (NEC), unlike NET, refers to all poorly differentiated NENs. NEC is further subdivided into a small-cell and a large-cell variant. In respect of proliferation, all NECs are actively proliferating G3 tumors. Mixed adenoneuroendocrine carcinomas (MANEC) and hyperplastic and preneoplastic lesions are special groups. This classification is complemented by GEP-NEN-specific TNM classifications and a grading system, which improve prognostic and treatment stratification (7, e2, e3).

TABLE 2

Comparison of the WHO classifications of gastroenteropancreatic neuroendocrine neoplasms

WHO 1980	WHO 2000	WHO 2010
Carcinoid	Highly differentiated neuroendocrine tumor	Neuroendocrine tumor G1 (carcinoid)
	Highly differentiated neuroendocrine carcinoma	G2
	Poorly differentiated (small-cell) neuroendocrine carcinoma	(Small- or large-cell) neuroendocrine carcinoma G3
Mucocarcinoid mixed carcinoid-adenocarcinoma	Mixed endocrine-exocrine carcinoma	Mixed adenoneuroendocrine carcinoma
Pseudotumorous lesion	Tumor-like lesion	Hyperplastic and preneoplastic lesion

Figure 1: Well-differentiated neuroendocrine tumor in the gastric body extending into the mucosa and submucosa and with a greatest diameter less than 1 cm. This tumor can be endoscopically resected. (With kind permission of Springer Science and Business Media)

Figure 2: Well-differentiated neuroendocrine tumor of the stomach with infiltration of the mucosa, submucosa, and muscularis propria and with a greatest diameter of 2 cm. This tumor needs to be surgically resected. (With kind permission of Springer Science and Business Media)

Gastric NENs are divided into four types, all of which are functionally (hormonally) inactive (8). Type 1 is by far the most common. This appears as a small (<1 cm), polypous, multifocal NEN in the gastric body in patients with autoimmune chronic atrophic gastritis (CAG) of the body of the stomach. Type 2, which also develops multifocally, arises in association with a type 1 multiple endocrine neoplasm (MEN-1), while type 3 is a solitary sporadic NET and type 4 a solitary sporadic NEC. If the tumors are smaller than 1 to 2 cm and restricted to the mucosa and submucosa, they can be endoscopically resected (*Figure 1*). With tumors larger than 2 cm and/or when the muscularis propria has been infiltrated, regional lymph node metastases are likely (*Figure 2*).

Most neuroendocrine tumors of the duodenum, ileum, appendix, rectum, and pancreas are NETs as opposed to NECs. In the duodenum, many NETs produce gastrin but are nonfunctional (5). Functional gastrin-producing NETs are associated with Zollinger–Ellison syndrome and are called gastrinomas. These occur either as sporadic solitary entities or as multifocal tumors in MEN-1. Even when small (<1 cm), gastrinomas have often led to regional lymph node metastases that can become so big that they are mistaken for the primary tumor (5). Metastasis to regional lymph nodes occurs early, whereas liver metastases appear late. Somatostatin-producing NETs are found in the area of the papilla of Vater. These are nonfunctional but are often associated with type 1 neurofibromatosis.

NETs of the ileum produce serotonin and lie, often as multiple entities, in the terminal ileum (5). At the time of diagnosis, they have usually metastasized to the lymph nodes and, in 20% of patients, the liver. This can result in carcinoid syndrome (*Table 1*), because serotonin is metabolized in the liver and does not appear in the main circulation until after liver metastasization has occurred.

NETs of the appendix produce serotonin but are nonfunctional, and are usually discovered as an incidental finding at appendectomy for appendicitis, and hence (if smaller than 1 to 2 cm) are curatively removed (10).

NETs of the rectum (colon NETs are very rare) are usually small (<1 cm), nonfunctional tumors that are mobile with respect to the underlying musculature and can be endoscopically resected. Metastases are likely only if the tumor is larger than 1 cm (10).

Of NETs of the pancreas, only 50% to 60% are functional. Among these, the most common are insulinomas (*Table 1*) (5). In over 80% of cases these are smaller than 2 cm and are benign. All other tumors, such as gastrinomas, glucagonomas, and VIPomas, and especially the numerous nonfunctional NETs of the pancreas, are usually larger than 2 cm and are malignant.

Diagnosis

Laboratory techniques

When a serotonin-producing NEN of the ileum (“ileum carcinoid”) is suspected on the basis of recurrent diarrhea and cutaneous flushing, increased levels of 5-hydroxyindoleacetic acid, a product of serotonin metabolism, should be tested for in a 24-hour urine sample (9). False positive results may be caused by various foods (e.g., bananas).

To demonstrate the presence of a gastrinoma in a patient with recurrent ulcer, the serum gastrin value must be determined. The combination of a fasting gastrin value higher than 1000 pg/mL and an intragastric pH value below 2.5 is virtually pathognomonic of this disease. However, high gastrin values are also found in patients with chronic atrophic corpus gastritis. If the gastrin concentration is between 150 and 1000 pg/mL in a patient with hyperacidity, the diagnosis must be confirmed by a secretin test and by determining baseline gastric acid secretion. Fasting gastrin values between 150 and 1000 pg/mL are also seen in patients on proton pump inhibitor therapy.

In patients with spontaneous hypoglycemia and suspected insulinoma, a standardized diagnostic fasting test under inpatient conditions is indicated. A fall in plasma glucose concentration below 40 mg/dL without accompanying suppression of insulin and C-peptide values speaks for an insulinoma. However, the blood or urine sulfonylurea concentration should be measured in

Figure 3: Liver metastases from a malignant insulinoma. Arterial-phase abdominal CT shows an arterially hypervascularized hotspot (a, arrow) which pools contrast further during the portal-venous phase (b, arrow). Catheter angiography with selective imaging of the right hepatic artery in the late arterial phase (c) shows two arterial tumor blushes; the one marked with the arrow correlates to the CT slices in (a) and (b). A further metastasis is marked with an arrowhead. In the parenchymal phase (d), both metastases (arrow and arrowhead) are visible as persisting blush. After chemoembolization (e), tumor blush is no longer demonstrated

addition in order to rule out artificially induced hypoglycemia. For the laboratory-chemical diagnosis of so-called nesidioblastosis in the adult with inadequate insulin secretion, an intra-arterial calcium stimulation test is carried out in addition to the fasting test or C-peptide suppression test to identify the region of pathological insulin secretion (10).

In cases where glucagonoma is the cause of necrotizing exanthema with diabetes mellitus, a serum glucagon concentration above 50 pmol/L is found. In patients with watery diarrhea and suspected VIPoma, a fasting serum VIP level above 200 pg/mL is usually found.

Chromogranin A is a very sensitive but relatively nonspecific serum marker of GEP-NENs. False high values are found, for instance, in patients with renal insufficiency or severe malabsorption syndrome. Chromogranin A determination is useful for staging and prognosis, since the serum concentration correlates to the tumor mass.

Imaging techniques

Tumor location and extent have a decisive role in therapy planning. The role of the various diagnostic technique depends strongly on the type and location of the primary tumor (11). A general principle is that no one technique is sensitive enough. For this reason, a multimodal diagnostic approach is recommended that combines computed tomography (CT) and magnetic resonance imaging (MRI) with nuclear medicine imaging. Despite all this, in 20% to 50% of cases of GEP-NENs the primary tumor remains undiscovered.

A standard modality in diagnostic transverse imaging is CT, which allows the primary tumor to be located in 22% to 45% of patients (*Figures 3 and 4*). CT diagnosis of gastrinomas and insulinomas depends largely on the size of the tumor; tumors smaller than 1 cm are rarely discovered. For this reason, endoscopic ultrasound is usually recommended to locate insulinomas and gastrinomas, as in the hands of experienced endosonographers this is regarded as the most sensitive

mode of detection (sensitivity for duodenal NENs 45% to 60%; for pancreatic NENs 90% to 100%) (e4). Liver metastases often show marked arterial hypervascularization in transverse diagnostic imaging. Sensitivity is reported at 79% for CT and 95% for MRI (12).

Another mainstay of tumor localization imaging is somatostatin receptor scintigraphy (octreotide scintigraphy). Nuclear medicine has a number of radiotracers to offer, which vary in the properties of their receptor ligands and labeling nuclides. Many years of experience have been accumulated using ^{111}In -labeled octreotide (12, e5). In positron emission tomography (PET) centers, ^{68}Ga -labeled somatostatin analog (13, e6) is preferred. This PET tracer is undergoing intensive evaluation in certain centers and offers excellent image quality (e7, e8). It must be emphasized that so far it has not been licensed for general use in Germany. Costs are about 2000 euros at present. Positive visualization of the tumors is essential for treatment with radioactive somatostatin receptor analogs.

Surgical therapy

Surgical treatment of GEP-NENs follows oncological resection principles. Because GEP-NENs are rare, there are no evidence-based recommendations for surgical treatment, only expert recommendations. The indication for removal of the primary tumor depends on clinical symptoms, tumor size and location, malignity, and metastatic potential. In general, locally radical resection is aimed at while at the same time preserving maximum function, especially in patients with pancreatic NENs.

For type 1 and type 2 gastric NENs (<2 cm; no angioinvasion; tumor extent limited to the mucosa and submucosa), endoscopic resection with annual follow-ups suffices. A type 3 (>1 cm) gastric NEN is treated with subtotal gastric resection or gastrectomy, depending on its location, and type 4 is resected like gastric adenocarcinoma.

For NENs of the small intestine, resection of the tumor-bearing intestinal loop including the lymphatic pathways is recommended, and for NENs of the colon, standard colon resection including lymph node dissection.

In duodenopancreatic NENs, the requirement for surgical radicality is opposed by the requirement for organ preservation in order to avoid exocrine and endocrine insufficiency. For the more frequent sporadic NENs of the pancreas, organ-preserving resection is recommended, ranging from tumor enucleation, resection of the tail or central segment of the pancreas with an inserted intestinal loop to pylorus-preserving resection of the pancreatic head or multivisceral resection. As first-line therapy, surgical resection of metastases should aim at complete removal (R0). However, reoperations with palliative intent are also justified.

Operative treatment of liver metastases requires expertise in this field. Techniques range from atypical open or laparoscopic approaches to extensive resection. If insufficient healthy liver tissue remains, repeated

Figure 4: Insulinoma in the pancreatic tail. Abdominal CT in the arterial phase (a) shows an 8-mm spherical space-occupying mass in the ventral part of the pancreatic tail, which appears arterially hyperdense (arrow). The maximum intensity projection (b) allows better anatomic characterization of this finding

sessions of portal venous embolization followed by resection are indicated. Liver transplantation is rarely indicated.

In hereditary MEN1-associated GEP-NENs, surgery needs to be tailored to the individual case. These NENs usually appear as multiple entities and, in addition, duodenal NENs metastasize early to lymph nodes and thus have a high rate of recurrence (14). The operative strategy in MEN1-associated pancreatic NETs ranges from enucleation with organ preservation, which is common but carries a higher risk of recurrence, to radical resection, which is much less common and carries the risk of subsequent exocrine and endocrine insufficiency. In MEN1-associated multiple duodenal gastrinomas, with their early metastasization to lymph nodes, early and aggressive radical surgery is recommended (15).

Surgical treatment of insulomatosis (16), which is very rare, and adult nesidioblastosis requires careful judgment, because of the diffuse distribution of the neoplastic and/or hypertrophied insulin-producing cells (10). The difficulty lies in judging the extent of the resection so as to adequately reduce the beta cell mass

while both preventing persistence or recurrence of the disease and avoiding endocrine insufficiency.

Chemoembolization and radiofrequency ablation

Transarterial chemoembolization (TACE) of the liver is a palliative procedure that is only indicated in patients with disseminated liver metastases. There are no comparative studies showing chemoembolization to be superior to alternative systemic therapies. Chemotherapeutic drugs used are doxorubicin, cisplatin, streptozocin, and others. These can be mixed with iodized oil (lipiodol) to form a suspension, and may be combined with embolization particles. Recently, embolization particles to which doxorubicin is bound have become available (response rate: 40% to 80%; therapy-related mortality: 0% to 6%) (e9). Mean time to progression is around 15 months (17). Postembolization syndrome is a regular unwanted effect of the treatment. Errors in patient selection for this treatment can lead to life-threatening complications. The risk of a carcinoid crisis and of liver abscess is markedly reduced by peri-interventional hormonal and antibiotic therapy.

Radiofrequency ablation (RFA) is another palliative procedure. However, since it is impossible, in patients with disseminated metastases, to find and treat every metastasis with the RFA probe, RFA is combined with other procedures, usually liver resection (18).

Medical therapy

Somatostatin analogs are often used as long-term preparations injected monthly. A recently completed placebo-controlled double-blind study proved the tumor proliferation inhibiting effect of somatostatin analogs (19). Mean progression-free survival in the somatostatin group was 14.3 months, versus 6.0 months in the placebo group (median overall survival in the somatostatin analog group has not yet been reached). However, somatostatin analogs are only licensed for functional GEP-NENs. The newer somatostatin analog SOM 230 (pasireotide), which is also very effective, binds especially to the somatostatin receptor subtype 5. This drug is not yet generally available, however.

Combined therapy using a somatostatin analog together with interferon alpha is less effective. Promising new therapies involve, for example, the use of the mTOR inhibitor everolimus and the multikinase inhibitor sunitinib (e10, e11). In two placebo-controlled, recently published studies, the median progression-free interval was increased by 6.4 months with everolimus (e10) and 5.9 months with sunitinib (e11). Sunitinib is now licensed for the treatment of advanced pancreatic NETs, and this has been applied for for everolimus. Trials of cell therapies are continuing.

For the treatment of metastasized pancreatic NENs, even those with a low proliferation (mitotic) index, chemotherapy with streptozotocin is often indicated. Partial remissions are seen in 20% to 35% of cases (20, 21).

In patients with tumors of the midgut with increased mitotic activity, combination therapy with cisplatin and etoposide is recommended (e12). However, hormonal crises can occur during this therapy. This therapy is ineffective in tumors with low mitotic activity.

Nuclear medicine therapies

If curative surgical treatment is not possible, one available alternative is nuclear medicine therapy. Particular guiding factors for this are tumor extent, the Ki-67 index, and any functionality (hormonal activity). For slow-growing GEP-NENs with high octreotide uptake, DOTATOC or DOTATATE therapy should be considered (22, 23). The indication for this is evidence of tumor progression within 3 months in a patient undergoing another established therapy (usually with somatostatin analogs). Partial tumor regression is seen in around 30% of cases and tumor stabilization in more than 50% of cases. Median time to renewed disease progression is 30 to 40 months for DOTATOC therapy (24, 25).

Prognosis

For all GEP-NENs together, if the diagnosis is made before metastasization has occurred, the 10-year survival rate is over 90%; after metastasization it is around 50%. This is largely independent of the primary tumor, but does show a dependence on mitotic index (<5%, 10-year survival 80%; >10%, 10-year survival 20%) (26).

Conclusions

Patients with GEP-NENs need to be managed in specialized centers by an interdisciplinary team. This is because of the very variable behavior of these tumors in terms of mean survival in dependence on various factors such as potential heritability, the size of the primary tumor, mitotic index, metastasization, and so on. These centers coordinate the planning of the diagnostic and therapeutic procedures required, aftercare, and the work of the medical specialties involved. Interdisciplinary collaboration is essential for optimal patient care.

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Conflict of interest statement

The authors declare that no conflict of interest exists.

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KEY MESSAGES

- Symptoms such as recurrent diarrhea, flushing, hypoglycemia, and duodenal ulcers are classic signs of functional (hormonally active) gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs).
- Biopsy with prognostic classification and determination of the general neuroendocrine tumor markers synaptophysin and chromogranin A and the proliferation marker Ki-67 are the mainstays of diagnosis and prognosis.
- Computed tomography, magnetic resonance imaging, and scintigraphy using somatostatin receptor ligands are the methods of choice for determination of tumor location and extent and are important instruments for treatment decisions.
- Depending on the morphological findings, options for therapy include surgical tumor resection including removal of metastases, radiofrequency ablation, systemic chemotherapy including chemoembolization, and experimental therapies such as the use of multikinase inhibitors.
- Because of the complex nature of GEP-NENs, patients with these tumors should be treated by an interdisciplinary team in a center specializing in and hence with extensive experience of treating NENs (see www.net-register.org [in German]).

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