Endotext

GASTROINTESTINAL NEUROENDOCRINE TUMORS AND THE CARCINOID SYNDROME

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ABSTRACT

Neuroendocrine neoplasms originating from the gut are increasingly diagnosed as a result of the rise in radiological and endoscopic procedures, improved pathological classification, and likely an increase in true incidence. The diffuse neuroendocrine gastrointestinal system can trigger cancer formation into a wide variety of neoplasm subtypes, ranging from well-differentiated tumors to poorly differentiated carcinomas. All gastrointestinal neuroendocrine neoplasms have the potential to metastasize and ultimately impair patient survival. In recent years, changes have occurred in the pathophysiological understanding, nomenclature, pathological grading, molecular imaging, and management options for these neuroendocrine neoplasms. This chapter will focus on well-differentiated neuroendocrine tumors of gastrointestinal origin, which find their origin at separate primary locations, all characterized by their specific clinical behavior. A minority of patients suffer from hormonal syndromes due to the secretion of peptides or amines from the neuroendocrine tumor. The carcinoid syndrome is the quintessential hormonal syndrome in gastrointestinal neuroendocrine tumors, particularly those of midgut origin. Patients suffering from the carcinoid syndrome have a reduced survival and quality of life, due to debilitating symptoms of flushing and diarrhea as well as fibrotic complications. We provide an overview of the background of gastrointestinal neuroendocrine tumors as well as the carcinoid syndrome and discuss the diagnostic pathways as well as treatment possibilities for patients presenting with this disease.

INTRODUCTION

Enteroendocrine cells constitute approximately 1-2% of all cells within the gastrointestinal tract. Quite similarly, neuroendocrine neoplasms (NEN) of the digestive tract form 1-2% of all malignancies in this organ system. When grouped together with pancreatic NEN (panNEN), gastroenteropancreatic (GEP) NEN are the second most common malignancy in the gut, surpassing esophagus, gastric, and pancreatic carcinomas in incidence rates (1). These tumors can arise anywhere along the primitive gut, but are most commonly detected in the small intestine or rectum. Based on histology, NENs are grouped into well-differentiated neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinomas (NEC) (2). The former group was previously termed carcinoid tumors, based on the original observation by Siegfried Obendorfer (1876-1944) in 1907 that NETs of the small bowel displayed “carcinoma-like” or “carcinoid” features (3). As this term has led to the common misconception that carcinoid tumors are

benign or always indolent, current correct nomenclature of this gastrointestinal malignancy solely uses the term NEN.

This chapter focuses on the clinical features, diagnosis, and management of the different well-differentiated NET along the gastrointestinal tract. The reader is referred to chapter “Diffuse hormonal systems” for lung NEN (4), where well-differentiated tumors are still termed typical or atypical carcinoids, and to chapter “Pathophysiology and treatment of pancreatic neuroendocrine tumors” for panNEN (5).

EPIDEMIOLOGY

NEN are historically considered a rare cancer type with an incidence of all subtypes combined of 5-10 per 100,000 persons per year (6). Two registry studies have shown that the incidence of NEN is rising several fold over the last decades. In the United States of America, NEN incidence increased 6.4-fold from 1.09 to 6.98 per 100,000 population per year between 1973 and 2012 (7), while in the United Kingdom rates rose 3.7-fold from 2.35 to 8.61 per 100,000 population per year between 1995 and 2018 (8). Within the GEP subtypes, small intestinal, pancreatic, and rectal NEN are most prevalent and have seen the clearest rising incidence rates. Part of the increased detection rate is caused by the rise in the absolute number of endoscopy procedures and radiological imaging, shifting the diagnosis more often towards incidentalomas. On the other hand, increased awareness among pathologists and improved classification likely also plays a role. The striking rise of NEN incidence compared to the stable incidence of all other malignant neoplasms in recent decades (7, 8) might suggest that a currently unknown epigenetic or environmental risk factor could stimulate NEN carcinogenesis.

The combination of increased detection as well as improved survival leads to an overall increase in NEN prevalence. The recent epidemiological data in the United Kingdom (8) suggest that NEN should not be considered a rare form of cancer anymore, as it comprised the 10th most prevalent cancer.

PATHOPHYSIOLOGY

Much is unknown about the pathogenesis of gastrointestinal NET (9). Besides the driver function of gastrin in two subtypes of gastric NET (see below), the causative factors for NET formation in the gut remain elusive. Genetic mutations have been identified as driving carcinogenesis across a wide array of malignancies, but – even in late, advanced stages of disease – NET remains among the tumor types with the lowest amount of tumor mutational burden or driver mutations (10). Contrarily, NEC show a high tumor mutational burden with gene mutations in well-known oncogenes or tumor suppressor genes, such as *TP53*, *KRAS*, *RB1* (11). Dedicated studies of small intestinal NET genotypes with next generation sequencing have failed to detect prevalent mutations. The most commonly mutated gene in small intestinal NET, *CDKN1B* encoding cyclin-dependent kinase inhibitor p27, was found to be mutated in 10% of cases (12). Germline mutation in *CDKN1B* also cause the rare endocrine tumor syndrome multiple endocrine neoplasia type 4 (MEN4), which predisposes to the occurrence of gastric, duodenal, and pancreatic NET among other tumor types (13). Whole genome sequencing of synchronous multifocal small intestinal NET also failed to detect common genetic drivers, but instead observed clonal independency of tumors within individuals (14). No clear driver mutations have been identified for the other subtypes of gastrointestinal NET as well. Multiple endocrine neoplasia type 1 (MEN1) is besides primary hyperparathyroidism and pituitary NET primarily associated with the occurrence of pancreatic,

bronchial, and thymic NET (15). However, duodenal NET can also arise within the context of MEN1 and these have a predilection to secrete gastrin, leading to gastrinoma or Zollinger-Ellison syndrome. This in turn stimulates secondary gastric NET formation (16). A genome-wide association study of 405 patients compared to more than 600,000 control subjects in two cohorts revealed an association between the occurrence of small intestinal NET and single nucleotide polymorphisms in 6 genes (17). The most interesting locus was of a missense mutation in the intestinal stem cell factor LGR5, suggesting a role for aberrant cellular differentiation in the development of small intestinal NET. Contrary to DNA mutations, chromosomal aberrations are prevalent in gastrointestinal NET. For small intestinal NET copy number variations have been frequently detected. The most prominent observed change is loss of chromosome 18 in up to 70% of cases, followed by losses in chromosomes 9, 11 and 16 and gains in chromosomes 4, 5, 14 and 20 (18). Whether these changes have a causative role in the development of small intestinal NET is currently unknown.

Due to the lack of obvious DNA changes contributing to NET pathogenesis, studies have investigated the role of epigenetics, e.g. changes to the chromatin that affect gene transcription without changing the DNA code (19). In the largest study to date in 97 patients with small intestinal NET, integrated genetic, epigenetic, and transcriptomic analysis detected 3 molecular subtypes, that differed in their survival outcome (20). DNA methylation analysis found that small intestinal NET were highly epigenetically dysregulated. The prognostically favorable molecular subgroup was associated with loss of chromosome 18, while another subgroup displayed no copy numbers alterations. NET in the molecular subgroup with inferior survival outcome displayed multiple copy number variations.

Because of the link between enteroendocrine cells and the bowel content, there have been speculations on carcinogenic factors in the bowel content. This could include but is not limited to dietary factors, microbial species, and microplastics. Further research is needed before a clear role can be identified for these factors.

COMMON FEATURES

NET of the gastrointestinal tract share many features owing to their collective origin from enteroendocrine cells. Originally described as APUD (amine precursor uptake and decarboxylation) tumors or APUDomas by Anthony Pearse (1916-2003) these neoplasms retain the potential to produce and secrete several hormonal substances in the form of amines and peptides (3, 21). These secretagogues are stored in intracellular dense-core secretory granules, which are released upon fusion with the plasma membrane. Gastrointestinal NET, like other types of NET, express markers specific for their neuroendocrine phenotype. The two most prevalent markers, synaptophysin and chromogranin A, form the basis for a immunohistochemical diagnosis of a NEN cell (22).

Stage

Similar to other cancers, NET are staged according to the TNM classification, which signifies key therapeutic and prognostic information (2), Table 1. Whereas stage I and II indicate local disease confined to the presence of the primary tumor (T1-4 N0 M0), stage III signifies the presence of regional spread to lymph node metastases (T1-4 N1 M0). Distant metastases (T1-4 N0-1 M1) are classified as stage IV disease.

Table 1. TNM staging of gastrointestinal neuroendocrine neoplasms according to the 8th edition of the AJCC Cancer Staging Manual (2018)						
	Stomach	**Duodenum**	**Small intestine**	**Appendix**	**Colon and rectum**	
Tx	Primary tumor cannot be assessed					
T0	No evidence of primary tumor					
T1	Invades the lamina propria or submucosa and is ≤ 1 cm in size	Invades the lamina propria or submucosa or confined within the sphincter of Oddi and is ≤ 1 cm in size	Invades the lamina propria or submucosa and is ≤ 1 cm in size	Tumor ≤ 2 cm in size	Invades the lamina propria or submucosa and is ≤ 2 cm in size	
T1a					Tumor ≤ 1 cm in size	
T1b					Tumor > 1 and ≤ 2 cm in size	
T2	Invades the muscularis propria or is > 1 cm in size			Tumor > 2 but ≤ 4 cm in size	Invades the muscularis propria or is > 2 cm in size	
T3	Invades into the subserosa	Growth into the pancreas or peripancreatic adipose tissue	Invades into the subserosa	Tumor > 4 cm in size or invades into the subserosa or mesoappendix	Invades into the subserosa	
T4	Invades into the (visceral) peritoneum or adjacent organs or structures					
Nx	Regional lymph nodes cannot be assessed					
N0	No regional lymph node metastasis has occurred					
N1	Regional lymph node metastasis		Regional lymph node metastasis in < 12 nodes	Regional lymph node metastasis		
N2			Large mesenteric masses (> 2			

			cm) or extensive nodal deposits (≥ 12)			
M0	No distant metastasis					
M1	Distant metastasis					
M1a	Metastasis confined to liver					
M1b	Metastasis in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone)					
M1c	Both hepatic and extrahepatic metastasis					
Stage I	T1 N0 M0					
Stage II	T2-3 N0 M0					
Stage IIA					T2 N0 M0	
Stage IIB					T3 N0 M0	
Stage III	Any T N1 M0 or T4 N0 M0					
Stage IIIA					T4 N0 M0	
Stage IIIB					Any T N1 M0	
Stage IV	Any T any N M1					

Grade

The biological behavior of the individual NEN is classified according to the tumor grade. NEN can display a wide array of biological behavior from generally very indolent taking years to significantly grow (e.g., appendix NET) to very aggressive inevitably leading to death (small cell lung NEC) (23). In order to predict prognosis and guide management all gastrointestinal NEN should be examined histologically for differentiation (well versus poorly differentiated), mitotic index (per 10 HPF), and ki67 index. The latter encompasses staining of the nuclear proliferation marker ki67 by the MIB1 antibody. Different grading cut-offs have been used in the past (24), but the WHO 2019 classification of digestive system tumors and 2022 classification of (neuro)endocrine tumors separate well-differentiated NET from poorly differentiated NEC on the basis of the histological phenotype (2, 25). In cases of an ambiguous entity, molecular analysis or staining of

Rb1 and p53 can point towards the presence of a NEC (26).

NET are divided into grade 1, 2 and 3, whereas NEC by definition are grade 3. NET grading is discerned through the combination of mitotic and ki67 index, with the highest value counted (Table 2) (2, 25). Due to the differences in biological behavior, tumor grading is key to management of GI NET, especially in cases of metastatic and consequently incurable disease.

Table 2. Classification of gastrointestinal neuroendocrine neoplasms, according to 2022 WHO classification of endocrine and neuroendocrine tumors and 2019 WHO classification of tumors of the digestive system

Well-differentiated NEN	**Ki67 proliferation index**	**Mitotes per 2 mm^2**
NET Grade 1	<3%	<2
NET Grade 2	3–20%	2–20
NET Grade 3	>20%	>20
Poorly differentiated NEN Small cell NEC Large cell NEC	>20%	>20

HORMONAL SYNDROMES IN NET

Due to their endocrine heritage, gastrointestinal NET can produce and secrete excessive amounts of hormonal substances, that can elicit clinical syndromes in patients (22). All patients presenting with a gastrointestinal NET should be examined by history taking and physical exam for the presence of a hormonal syndrome, as this has important therapeutic and prognostic consequences. In case of a suspected hormonal syndrome, appropriate biochemical analysis should be performed for the elevation of the causative hormonal peptides or amines (27).

Carcinoid Syndrome

The carcinoid syndrome is the most common hormonal syndrome encountered in gastrointestinal NET and even NEN in general. Estimations fluctuate that around 20% of patients with stage IV midgut NET suffer from carcinoid syndrome (28). It is mainly characterized by symptoms of secretory diarrhea and vasodilatory flushes. Occasionally, bronchospasms can also occur (29). In severe and long-standing cases carcinoid heart disease (CHD) can arise, characterized by plaque-like depositions in mainly right-sided heart valves and endocardium (30). Following acute stressors, some NET associated with carcinoid syndrome are able to secrete massive amounts of vasoactive compounds, leading to hemodynamic instability. This type of vasodilatory shock, also known as carcinoid crisis, can be defined as an acute onset of stressor-induced hemodynamic instability in patients with carcinoid syndrome and can be observed during the induction of anesthesia and after tumor lysis following embolization or peptide receptor radionuclide therapy (31).

The principal effector of carcinoid syndrome is thought to be the amine serotonin (5-hydroxytryptamine) (32), which is also secreted physiologically by several subtypes of neuroendocrine cells in the gut and lungs. A variety of preclinical and clinical studies support a

central role of serotonin in the pathophysiology of carcinoid syndrome-related diarrhea and CHD, while its role in flushing in carcinoid syndrome patients is still controversial. Other hormonal substances postulated to contribute to the carcinoid syndrome include tachykinins, catecholamines, kallikrein and histamine (33).

Carcinoid syndrome predominantly arises in NET of midgut origin, comprised of jejunum, ileum, cecum, and ascending colon. This location specificity is presumably due to carcinogenesis within the enterochromaffin (EC) cell, which uses serotonin as its main secretagogue to communicate with the autonomous nervous system and influence bowel motility (4). This hormonal syndrome can also be encountered in bronchial NET (typical or atypical carcinoid) or NET of other origin (e.g., ovarian, pancreatic, unknown primary). Importantly, tumor seeding beyond the portal circulation is a prerequisite for carcinoid syndrome, as its causative hormones are inactivated by hepatocytes (34). For midgut NET, carcinoid syndrome thus hallmarks spread beyond locoregional disease, with liver metastases being present in more than 90% of cases. Alternatively, the tumor sites may secrete through the retroperitoneal or ovarian/testicular venous drainage, effectively bypassing the portal circulation and drain directly on the inferior caval vein.

The presence of carcinoid syndrome is a negative prognostic indicator, which is likely caused by its association with tumor bulk (28, 35). Within this spectrum, CHD is also associated with decreased survival in patients in univariate analyses (36). Because of these features carcinoid syndrome should be diligently investigated in all patients with NET and actively managed alongside antiproliferative therapy (see management section below).

Other Functioning Syndromes

Besides carcinoid syndrome, other NEN-associated hormonal syndromes are predominantly encountered in patients with a panNEN. Duodenal NET can in rare cases elicit hormonal syndromes that are also seen in pancreatic NET, such as gastrinoma (16), VIPoma (37), and somatostatinoma (38). Ectopic hormonal production has also been described in gastrointestinal NET in limited case reports. However, these functioning syndromes are more frequented encountered in pancreatic (ACTH, PTHrP, GHRH) or lung NET (SIADH, ACTH), see the Endotext chapter on Paraneoplastic syndromes related to Neuroendocrine Tumors (39).

PRIMARY NET LOCATIONS

Esophagus

Well-differentiated NET of the upper alimentary tract are extremely rare. The esophagus is a predilection place for the occurrence of NEC (40). Alternatively, mixed neuroendocrine-non neuroendocrine neoplasms (MiNEN) can be encountered in the esophagus, similar to other gastrointestinal sites. Formerly these tumors were designated as Mixed adeno-neuroendocrine carcinoma (MANEC). This aggressive tumor entity is comprised of both a NEN component (NET or NEC) as well as an adenocarcinoma component, with the latter being responsible for the prognostic outcome (2).

Stomach

The neuroendocrine cells in the stomach can give rise to several NEN subtypes, depending on the underlying pathophysiology. Central to understanding gastric NEN is the dependency of the histamine-producing enterochromaffin-like (ECL) cells on gastrin stimulation. Chronic hypergastrinemia due to several

causes can lead to ECL cell hyperplasia and gastric NET formation, so called ECLoma. When an ECLoma occurs during compensatory gastrin elevations this is termed a type I gastric NET (41), accounting for 75-80% of gastric NEN. This is most commonly caused by atrophic gastritis due to antibodies against intrinsic factor or parietal cells, which is also causative for pernicious anemia. Alternatively, type I gastric NET have been described following Helicobacter pylori infection, chronic use of proton pump inhibitors, or mutations in the proton pump gene (*ATP4A*) and resulting hypergastrinemia (42-45). When ECLoma arise due to a gastrin-producing NET in the pancreas or duodenum (Zollinger-Ellison syndrome), these are termed type 2 gastric NET, which is responsible for 5% of all gastric NET cases. This pathology is generally restricted to patients with MEN-I and a duodenal gastrinoma (46). A well-differentiated gastric NET arising in the presence of normal fasting gastrin levels is termed a type 3 NET and accounts for approximately 15-20% of gastric NET. Some authors have proposed the rare gastric NEC as the type 4 gastric NEN (9), Table 3.

Table 3. Subtypes of Gastric Neuroendocrine Neoplasm

	Hypergastrinemia, ECL cell hyperplasia	**Growth**	**Features**
Gastric NET type 1	Yes	Indolent	Secondary to atrophic gastritis, helicobacter pylori infection, proton pump inhibition or *ATP4A* mutation
Gastric NET type 2	Yes	Indolent	Secondary to gastrinoma (Zollinger Ellison syndrome)
Gastric NET type 3	No	Intermediate	Sporadic
Gastric NEC type 4	No	Aggressive	Sporadic

Biological behavior of the gastric NEN subtypes differs widely with generally indolent course for type 1 and 2 NET, which are predominantly grade 1 and can be characterized by multiplicity (47-49). Only a few metastatic cases have been reported in the literature, without clear evidence of impaired survival (50). Type 3 gastric NET and type 4 gastric NEC were previously considered as a single subtype, which was accompanied by a high rate of metastases and poor survival outcome. However, recent analyses show lower grade, metastatic potential, and better outcome of type 3 gastric NET than previously assumed (51, 52).

The vast majority of gastric NET is clinically non-functional, although ghrelin production has been described in NET presumably derived from gastric H cells, see Endotext chapter on Ghrelinoma (53).

Duodenum

A rare subtype of gastrointestinal NET, duodenal NET are often incidentally discovered during esophagogastroduodenoscopy (Figure 1A). They are characterized by intramural lesions which might sometimes only be visible on endoscopic ultrasound.

Bleeding or ulceration is rare, but can be a presenting symptom (54). The majority of duodenal NET are localized and grade 1-2, particularly for tumors smaller than 1.0 cm. Metastatic potential increases with size and can be present at diagnosis or occur during follow-up (55, 56). Due to the nature of the neuroendocrine cells in the duodenum several hormonal syndromes can be encountered, such as gastrinoma or VIPoma. Somatostatin-expressing NET near the ampulla of Vater have been described as part of neurofibromatosis type 1 (57). Some of the larger duodenal NET cannot be effectively localized as originated from either duodenum or pancreas due to the overlapping anatomy.

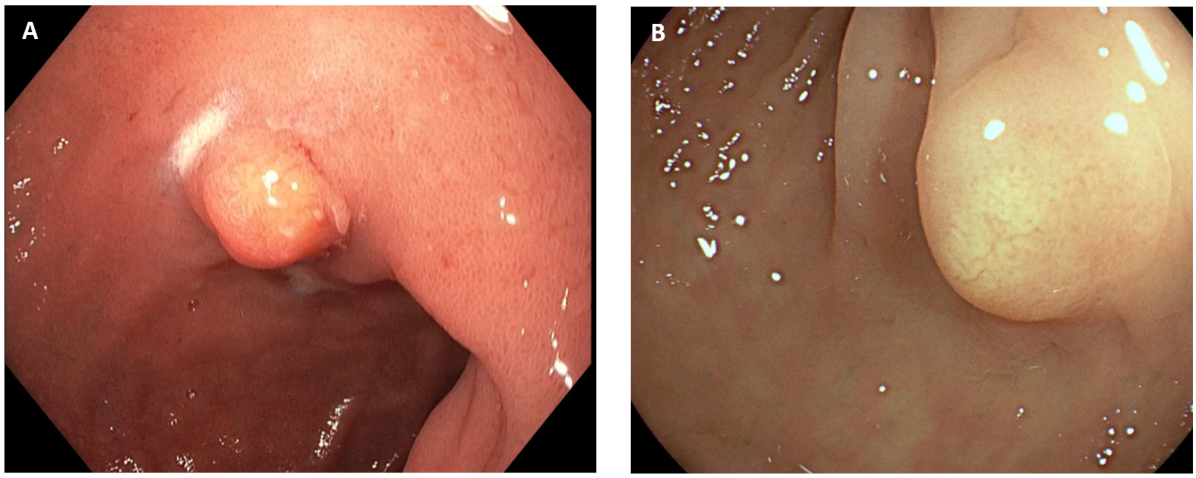

Figure 1. Endoscopy in gastrointestinal NET. (A) Endoscopic image of a 5 mm submucosal lesion in the duodenal bulb. Fine needle aspiration confirmed a grade 1 duodenal NET, which was subsequently removed by endoscopic mucosal resection. (B) Endoscopic view of an 8 mm rectal NET, grade 1, which was successfully resected by endoscopic submucosal dissection.

Small Intestinal (Jejunum and Ileum)

The classic site for well-differentiated NET in the gastrointestinal tract is the small intestine, particularly the terminal ileum. NET are the most common malignancy in the small intestine, followed in incidence by adenocarcinoma and lymphoma (58). Almost all small intestinal NET are low to intermediate grade and can potentially show indolent growth (59). NEC of the small intestine are extremely rare. As EC cells are the predominant neuroendocrine cell in the small intestine, metastatic small intestinal NET are most often associated with the carcinoid syndrome (60).

At presentation, the majority of small intestinal NET are metastasized, with a predilection for lymph node and liver metastases (59). In some cases, the primary tumor cannot be visualized despite modern imaging techniques, such as PET/CT. Lymphogenic spread of small intestinal NET occurs locally within the mesentery. The finding of NET accompanied by a mesenteric mass hints towards a small bowel origin of the NET. Unique to small intestinal NET, mesenteric metastases can develop extensive fibrosis (Figure 2). This is seen on cross-sectional imaging as fibrotic strand radiating from a solid mesenteric mass, in a spoke-wheel pattern (61). This pathognomonic feature

of small intestinal NET can lead to chronic bowel ischemia due to compression of venous drainage, leading to intermittent abdominal cramps or colicky pain, particularly after a large meal. Ultimately, ileus or bowel perforation can occur. In one study of 530 patients with small intestinal NET, mesenteric fibrosis was found to be progressive in 13.5% of cases with a median time to growth of 40 months, signifying slow progression (62). Although mesenteric fibrosis can lead to fatal complications and is associated with overall survival in univariate analysis, it was not associated with a worse overall survival in multivariate analysis (63).

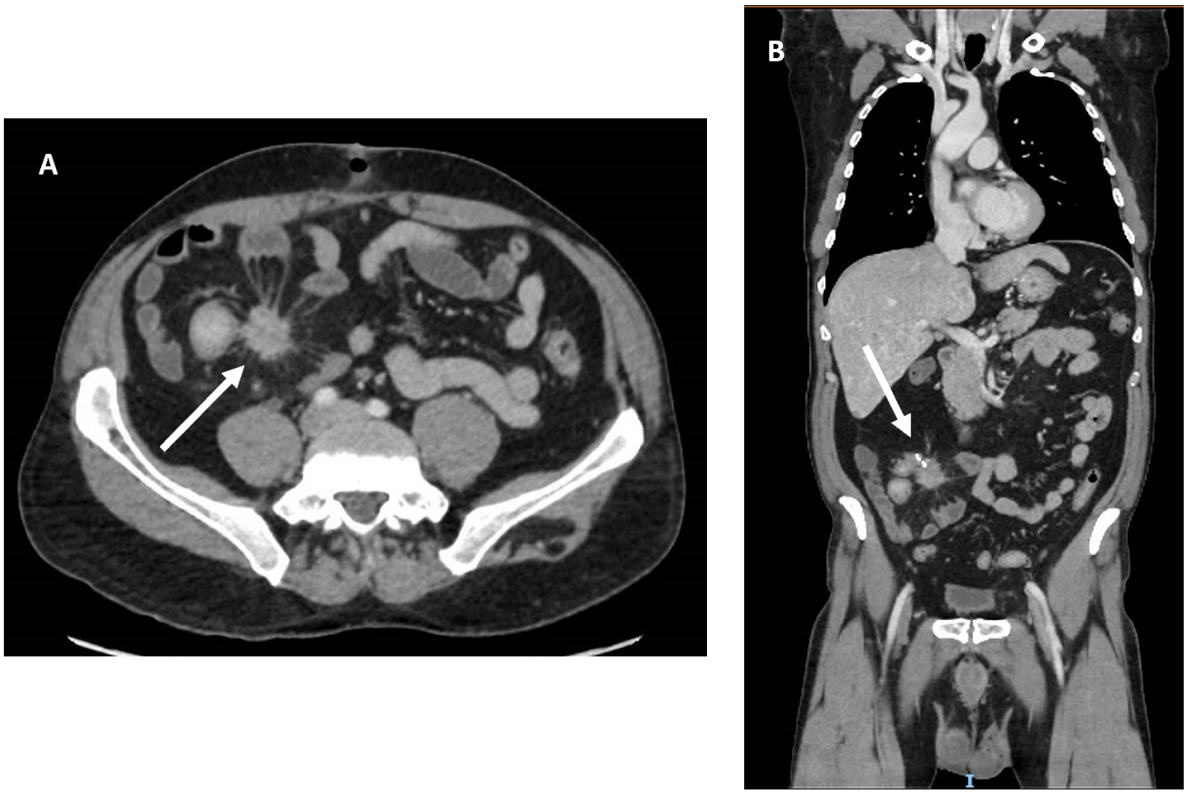

Figure 2. Mesenteric fibrosis in midgut NET. (A) Transversal and (B) coronal plane contrast-enhanced CT images of a patient with a cecal NET and a mesenteric metastasis (arrow). A desmoplastic reaction consisting of fibrotic strands can be seen radiating from the mesenteric tumor mass, which can compromise venous blood flow from the bowel. The mass is partly calcified.

Hepatic metastases of small intestinal NET can be much larger than the primary tumor or lymph nodes. Even in the presence of extensive bilobar metastases, the function of the liver is often preserved, although isolated hyperammonemia due to shunting has been described in selected cases (64).

Appendix

In the majority of cases, appendix NET are incidentally encountered during appendectomy because of appendicitis. A contributory role of the potentially obstructive tumor has been attributed to the occurrence of appendicitis, but this has not been

proven to date. Because of its association with appendicitis, appendix NET have a peak incidence in adolescents and young adults (65). Most appendix NET cases are confined to the appendix and have a favorable proliferation index (grade 1 or low 2). Development of lymph node metastases can be seen in up to 25% of appendix NET patients, whereas distant metastases are rare (66). Contrary to origin NET within the midgut, carcinoid syndrome is rarely encountered in appendix NET patients, potentially due to other cell of origin and limited metastatic spread and tumor bulk.

Colon

NET arising in the caecum and ascending colon generally show a biological behavior that is similar to that of small intestinal NET. Together these are termed midgut NET due to their common embryological origin and vascularization by the superior mesenteric artery and vein. Consequently, cecal and ascending colonic NET are often low-grade tumors, can be associated with carcinoid syndrome when metastasized beyond the portal circulation, and give rise to fibrotic complications (67).

Contrarily, NEN in the transverse and descending colon are more aggressive with a predilection for the occurrence of NEC. These NEC share common features with adenocarcinomas of the colon, like molecular background (11). Hormonal syndromes are seldomly encountered in these colon NEC.

Rectum

Unlike the distal colon, NEN in the rectum show a preference for well-differentiated NET (68). Most rectal NET are incidentally discovered during colonoscopy (Figure 1B). A rise in rectal NET incidence rates has been detected that coincided with the increased use of diagnostic colonoscopy (69). At the time of detection, tumor size is often small (< 1 cm) signifying indolent behavior and small risk of metastatic spread (70). However, a subset of rectal NET can present in locally advanced stages and be associated with metastatic spread. Although their venous drainage is not connected to the portal vein, rectal NET are rarely associated with hormonal syndromes, presumably due to their neuroendocrine cell type of origin.

DIAGNOSIS

Histopathology

Obtaining histology for evaluation and confirmation of diagnosis remains essential in the work-up of a gastrointestinal NEN, even in the setting of modern imaging techniques and circulating biomarkers. The diagnosis of a NEN can be suggested through histological findings on H&E staining, such as an organoid pattern, absence of necrosis, low nucleus to cytoplasm ratio, and salt and pepper chromatin. Ultimately, the histological diagnosis requires positive immunohistochemical staining of neuroendocrine markers (71). Most commonly used neuroendocrine markers include synaptophysin and chromogranin A, although N-CAM (CD56) has also been advocated as such in the past. Staining with either synaptophysin or chromogranin A should be positive, with the former having a higher positivity rate in gastrointestinal NEN (72). Expert pathological examination is advised in uncertain cases, for instance in neoplasms with overlap with other malignancies, such as carcinomas with neuroendocrine differentiation, amphicrine carcinoma and MiNEN (25, 73).

Besides for confirming the diagnosis, histopathological evaluation is required for tumor grading according to the WHO classification. First, the distinction between a poorly differentiated NEC and a well-differentiated

NET is crucial as shown above. This distinction is made on the basis of cellular morphology (74). Second, each pathological evaluation of a NET specimen should include grading through evaluation of differentiation, ki67 (MIB1) proliferation index and mitotic index (Table 2). Importantly, tumor grade can be heterogenous within or between tumor lesions as well as change over time (75, 76). The disease course over many years in patients can be accompanied by an increase in proliferation indices and grade over time, providing rationale for repeat biopsies in selected patients with disease progression. Altogether, grading provides key information for clinical decision making across all stages and primary locations of gastrointestinal NET. The subclass of grade 3 well-differentiated gastrointestinal NET was only introduced as recent as 2019 (2), which limits the clinical studies and experience on the management of this rare subtype.

Immunohistochemical analysis can also helpful in cases of an unknown primary tumor. Although the prevalence of an unknown primary tumor has decreased due to contemporary PET imaging, up to 5% of NET can present with an unknown primary (77). Positive staining for the following immunohistochemical marker is specific for different primary origins of NET: TTF-1 for foregut tumor, ISL-1 or PAX8 for pancreatic tumor, CDX-2 for midgut tumor, and SATB2 for hindgut tumor (78-81).

Biochemistry – General

Historically, elevated levels of biochemical markers have been directly linked to the diagnosis of a NET. While this can be true for certain hormones eliciting clinical syndromes when taken under controlled conditions, the vast majority of NET cannot be diagnosed through the use of a circulating biomarker. At most, a biomarker can be used during follow-up when it is elevated in a particular patient as a marker of disease recurrence or activity (27, 82).

Chromogranin A (CgA) has been extensively studied since the 1990s as a diagnostic and prognostic biomarker for gastrointestinal and other NET. This acid glycoprotein is stored within the secretory vesicles of neuroendocrine cells and co-secreted with the hormones upon stimulation. In a meta-analysis of 13 studies including 1260 patients with a NET sensitivity of CgA was 73%. In healthy controls, CgA levels were elevated in less than 5%, securing an excellent specificity. However, when compared to subjects with other gastrointestinal, renal, or oncological disease the specificity can drop to ranges of 50-60% (83), making CgA a poor diagnostic marker in patients presenting with abdominal complaints or a tumor. Measurement of CgA for this indication has led to many unnecessary clinical investigations, e.g., endoscopy, cross-sectional and functional imaging, into the cause of an elevated CgA (84) and should be discouraged.

Circulating CgA levels are associated with tumor bulk and consequently are correlated to a worse prognostic outcome (85). Because of its link to tumor bulk, CgA can be used during follow-up to track disease activity, although it should never replace imaging due to insufficient sensitivity and specificity of detecting progressive disease.

Neuron-specific enolase (NSE) represents another circulating marker on neuroendocrine cells. Mostly studied in small cell lung cancer, NSE is also elevated in a subset of gastrointestinal NET patients. Its sensitivity and specificity for the diagnosis of NET is approximately 40% and 60%, respectively (85, 86), and thereby inferior to that of CgA. Importantly, NSE levels tend to be more increased in aggressive disease. Consequently, a sudden rise in NSE could herald the occurrence of dedifferentiation in a NET.

Other circulating neuroendocrine markers, like pancreatic polypeptide and neurokinin A, have been used as diagnostic biomarkers in the past, but due to their overall lack of sensitivity or specificity their use in clinical practice has disappeared (27).

Because of the inferior diagnostic characteristics of the peptides described above an mRNA transcript-based marker called the NETest was developed. Through multiplex PCR and a machine learning-based algorithm, the NETest provides a number on a 100-point scale, where an outcome above 20 has been used for optimal diagnostic cut-off (87). In a meta-analysis of 6 studies the sensitivity and specificity of the NETest was 89-94% and 95-98%, respectively (88). An independent study employing serial sampling in 132 patients with gastroenteropancreatic NET showed a high rate of fluctuation in the NETest despite stable disease during follow-up (89). This technique is of interest to the field, but as of yet there are restrictions regarding the availability in clinical practice, costs, and reimbursement. Hopefully, these developments will lead the way towards more superior multianalyte diagnostic biomarkers for gastrointestinal NET in the future.

Biochemistry – Specific

When patients present with features compatible with a NET-associated functioning syndrome dedicated analysis should be performed. The reader is referred to other Chapters in Endotext for hormonal analysis of Gastrinoma (16), Insulinoma (90), VIPoma (37), Glucagonoma (91), Somatostatinoma (38), Ghrelinoma (53), and Paraneoplastic Syndromes (39). The latter included the hormonal work-up of NET-associated hypercalcemia, hyponatremia, Cushing's syndrome, acromegaly and hypoglycemia.

Although the majority of gastrointestinal NET are not accompanied by a hormonal syndrome, the carcinoid syndrome is the most common hormonal complication. Because patients can be asymptomatic but still at risk for complications such as carcinoid crisis or CHD, all patients with advanced gastrointestinal NET should undergo biochemical evaluation for the carcinoid syndrome at baseline and when clinical suspicion arises during follow-up (29).

Serotonin (5-hydroxytryptamine) is the main but not exclusive culprit in the carcinoid syndrome. Upon secretion it is mainly stored in platelets, but a proportion freely circulates in the blood. It is metabolized by hepatocytes to 5-hydroxyindolaceticacid (5-HIAA), which is more stable than serotonin and excreted in the urine. 24-hour urine 5-HIAA levels are the best-established biomarker for the carcinoid syndrome, with 50 µmol/24h used as the optimal diagnostic cut-off (29, 92). Urinary 5-HIAA levels correlate with tumor bulk and multiple studies have described an association in univariate analyses with survival in CS patients, which did not persist in multivariate analyses (93-95). 5-HIAA level associate with the risk of developing CHD, with levels above 300 µmol/24h conferring a 2.7-fold increased risk of the development of CHD (36). Alternatively, 5-HIAA can be measured in plasma or serum, resulting in a slightly lower sensitivity/specificity compared to 24h urine collection (96, 97). Venous sampling saves on the cumbersome collection of 24h urine, but its availability is currently limited. Similarly, platelet serotonin levels are associated with carcinoid syndrome, but few labs can perform the assay (98). Although several other peptides, including neurokinin A, bradykinin, and histamine, have been associated with the occurrence of carcinoid syndrome, these markers have no utility in the diagnostic workup in clinical practice.

NT-proBNP is u useful biomarker to screen for the presence of CHD in patients with established carcinoid

syndrome (99). An NT-proBNP level below 260 ng/mL (31 pmol/L) has a negative predictive value of 97%, thereby effectively ruling out the presence of CHD (100). Patients with NT-proBNP levels above 260 mg/mL should be referred for echocardiography to confirm or exclude the presence of CHD.

Cross-Sectional Imaging

Despite the developments in biochemistry and functional imaging, cross-sectional imaging remains the cornerstone of follow-up of NET. Furthermore, as more NET are incidentally discovered on imaging, it is important to be aware of typical or even pathognomonic radiological features of NET. On contrast-enhanced computer tomography (CT) scan gastrointestinal NET typically present as hypervascular lesions in the bowel wall (101). The majority of NET have enhanced intravenous contrast uptake in arterial phase, making it relevant to include an early arterial scan phase next to a venous or portal phase in case of a suspicion of a NET (102). Primary NET lesions in the small intestine tend to be small and can easily be missed, whereas lymph node or distant metastases can be extensive. Fibrosis can occur in mesenteric NET metastases, leading to pathognomonic fibrotic strands radiating from the mesenteric mass (61) (Figure 2). Gastrointestinal NET predominantly metastasize to the liver, where single, multiple or extensive metastases can be found. Again, these are hypervascular and enhancing on arterial phase in the majority of cases (103) (Figure 3).

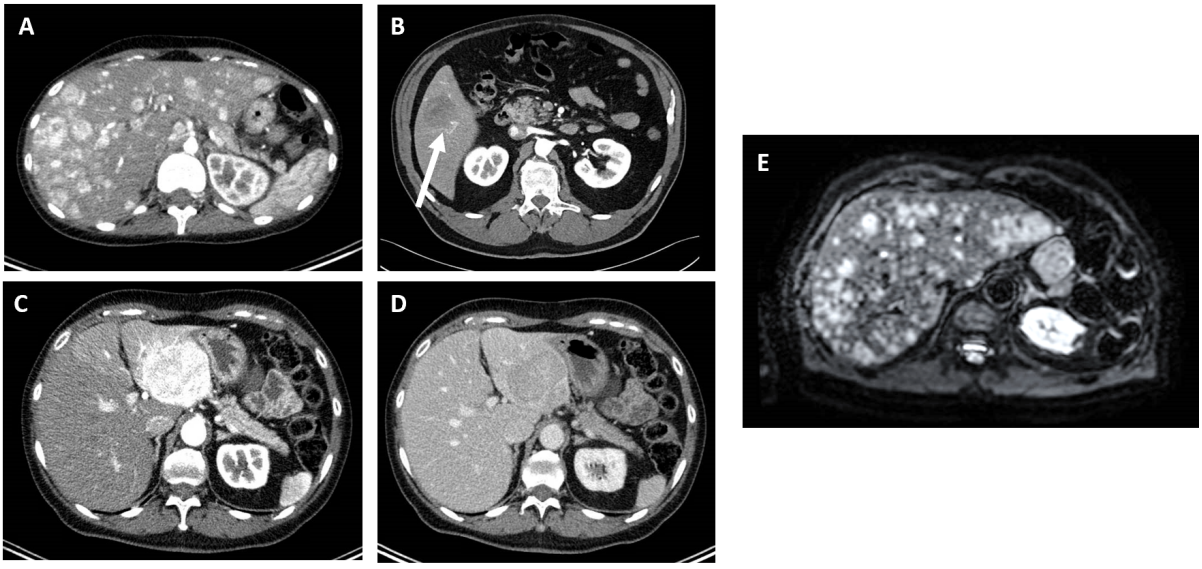

Figure 3. Cross-sectional imaging in gastrointestinal NET. Due to their hypervascular nature, NET primary lesions and metastases can be enhancing in early arterial phase. In case (A) diffuse hypervascular liver metastases of a small intestinal NET are visible. Not all NET (metastases) are hypervascular, as shown in case (B) with a single non-enhancing liver metastasis of small intestinal NET during arterial phase (arrow). The added value of including an early arterial phase after contrast injection (C) op top of venous phase imaging (D) is illustrated within a patient with a small intestinal NET, where visibility of a segment 3 NET metastasis is improved during arterial scan. MRI, particularly diffusion weighted imaging (DWI), can improve the detection rate of small liver NET metastases (E).

Magnetic resonance imaging (MRI) is superior to CT with regard to liver and bone metastases, particularly with contrast enhancement and diffusion-weighted imaging (DWI) (104, 105) (Figure 3). For small liver neuroendocrine metastases, MRI even has a higher lesion-based sensitivity than contemporary SSTR-based PET imaging (see below) (106). In rectal NET, MRI is also helpful to stage local growth and lymph node metastases (107). MRI has caveats in the detection of the primary tumor of the bowel, mesenteric, or peritoneal metastases.

Endoscopy

Endoscopy is often the modality used leading to the incidental detection of a gastrointestinal NET, particularly within primary locations in the stomach or rectum (Figure 1). Primary tumors of gastroduodenal or rectal origin can also be missed on cross-sectional imaging, providing rationale for performing endoscopy or endoscopic ultrasound (EUS) to stage locoregional disease (67, 108). The added value of endoscopy in advanced disease is generally of limited value, unless the aim is to obtain histology. Alternatively, obtaining histology from metastases could be more informative as these can have a higher grade than the primary tumor and ultimately determine the patient prognosis (76).

Nuclear Imaging

Over 90% of well-differentiated NET express somatostatin receptors, which can be used for functional imaging. Somatostatin is a hormone, whose physiological actions are to inhibit hormonal production and release from neuroendocrine cells, for instance in the pituitary, pancreas, and intestine (109). It binds to one or more of five somatostatin receptor subtypes expressed on the cell membrane. Radiolabeled somatostatin analogues (SSA) were developed in the 1980s to image gastrointestinal and pancreatic NET. First, Octreoscan® with gamma-emitter ^{111}In-pentreotide was shown superior to cross-sectional imaging in NET using planar and SPECT imaging (110). In the recent ten years, ^{68}Gallium-labeled SSA (^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, ^{68}Ga-DOTANOC) suitable for PET imaging have replaced ^{111}In-pentreotide as the preferred imaging modality. Importantly, ^{68}Ga-DOTA-SSA PET changes clinical management in 40-50% of cases, according to two meta-analyses (111, 112), and as such constitutes a key diagnostic modality in the NET armamentarium (Figure 4). The PET can be combined with diagnostic, contrast-enhanced CT (PET/CT) or MRI (PET/MRI) for hybrid imaging. Pitfalls include PET-positive granulomatous disease, meningioma, renal cell cancer, and lymphoma. Expression of the somatostatin receptors decreases with increasing proliferative capacity in NET, making it very useful in low-to-intermediate grade NET but less sensitive in higher grade NET or NEC. Recently, ^{64}Cu-DOTA-SSA PET/CT and ^{18}F-AIF-NOTA-SSA have been introduced with similar or slighter superior diagnostic capability compared to ^{68}Ga-DOTA-SSA PET (113, 114).

Alternatively, ^{18}F-DOPA PET has been advocated by several centers as superior to ^{68}Ga-DOTA-SSA PET, particularly for midgut NET (115). Although this may vary between patients and mostly pertain to tumor count rather than to change in management, ^{68}Ga-DOTA SSA also has therapeutic consequences for theranostics using unlabeled (‘cold’) SSA and peptide receptor radionuclide therapy (PRRT) with radiolabeled (‘hot’) SSA (see below).

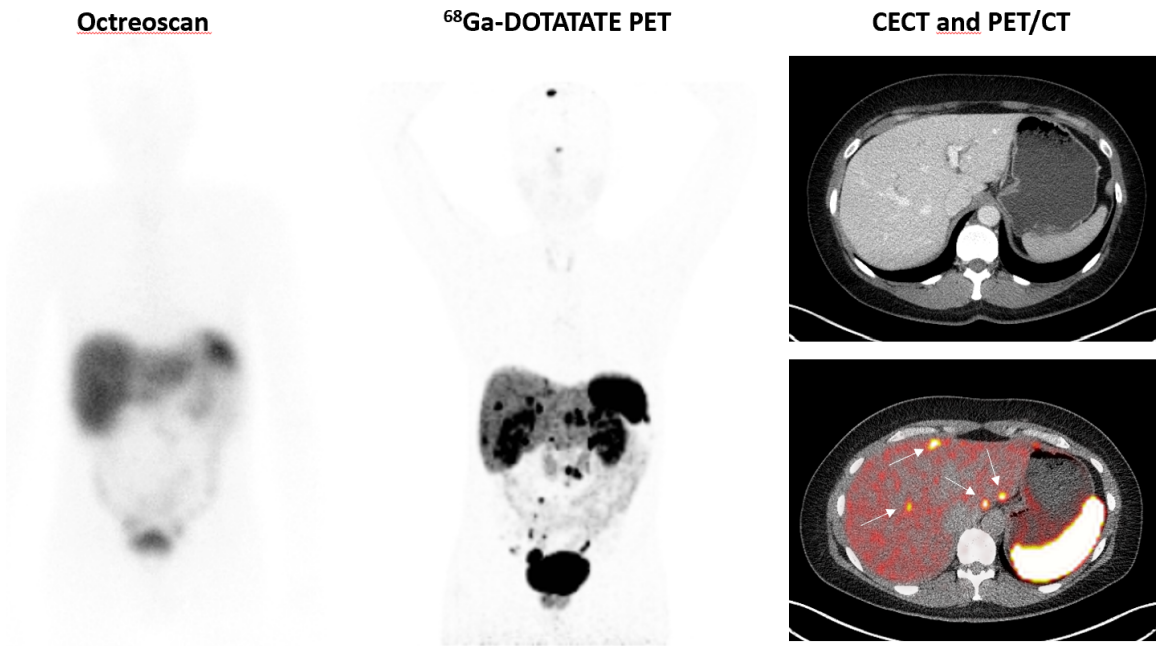

Figure 4. 68Ga-DOTA-SSA PET imaging. 68Ga-DOTA-SSA PET staging is superior to anatomical imaging and 111In-pentreotide SPECT (Octreoscan). In this case of a patient with stage IV small intestinal NET, PET imaging detected more lesions than Octreoscan, scanned within 3-month timeframe without anatomical progression. In the same patient, multiple liver metastases are detected on hybrid PET/CT imaging (arrow), which were not visible on contrast-enhanced CT (CECT).

Similar to other malignancies, a subset of NET metabolize increased amounts of glucose, which makes them amenable to imaging with ^{18}F-fluorodeoxyglucose (FDG) PET. Uptake of ^{18}F-FDG PET in NET increases with aggressiveness, making it the preferred imaging modality in NEC and higher-grade NET (116, 117). Positive FDG uptake of NET is associated with growth potential and consequently several studies have established that FGD uptake constitutes a prognostic marker for a worse survival outcome (118).

MANAGEMENT

Surgery

Radical resection remains the cornerstone in the management of locoregional stages of gastrointestinal NET. Metastatic spread is dependent on the location and size of the primary tumor and adequate staging should be performed accordingly, preferably through hybrid cross-sectional and ^{68}Ga-DOTA-SSA PET imaging (102). If the disease is confined to the local tumor (stage I-II) or locoregional lymph nodes (stage III), the option of a surgical oncological resection should be evaluated. If the NET can be radically resected the outcome is very favorable with 10-years survival outcomes of >90% for all primary sites. A large registry series from Canada did find that recurrence rates can increase up to 60% for small intestinal NET and 40-50% for other NET in a 15-year postoperative period (119). Given the retrospective nature of this series and contemporary preoperative

imaging it remains uncertain whether recurrence rates of current therapeutic interventions are still this high.

For stage I gastroduodenal NET, metastatic spread is limited and endoscopic resection of the NET can be considered (108). This pertains to gastric type I and type II NET up to 2 cm without muscle invasion and duodenal NET localized at safe distance from the Vater's ampulla. Similarly, an endoscopic resection can be performed in stage I rectal NET, as the risk of lymph node metastases is limited to less than 3% (67). Resection from both tumor subtypes should be performed by endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), or endoscopic full thickness resection (eFTR) rather than snare polypectomy due to the submucosal growth pattern of NET. Successful removal of type I gastric NET or stage I rectal NET is are high (>85%) with slight superiority of ESD over EMR, while eFTR might approach 100% radical resection rates (120-122). In cases of an inadequate endoscopic resection further imaging should be performed and a step-up endoscopic approach or surgical resection should be considered.

Patients with oligometastatic disease might also benefit from an upfront surgical approach. As the liver is the predominant site for metastatic disease, concomitant surgical resection and/or interventional tumor ablation should be considered in patients with limited liver involvement (123). This can potentially cure the patient, but it should be noted that modern imaging techniques detect approximately one-third of liver metastases compared to histological evaluation (124, 125). The presence of micrometastases should be factored into the management process. Despite this, long-term outcomes can be excellent in cases of upfront surgery in oligometastatic disease. A potential advantage of tumor debulking in this setting could be the delay of the need to start systemic therapy. Several series have also described survival benefits of extensive liver metastases resection (126-129), but these concern mostly retrospective series, which might introduce selection bias, and data was often collected before the advent of currently available molecular therapies.

Resection of the primary tumor in the context of stage IV or metastatic disease is controversial. Whereas retrospective studies have supported a survival benefit in patients whose primary tumor was resected compared to those that were not operated (130-132), this was later refuted in other series or after propensity score-matched controls (63, 133). Importantly, the disease course locoregionally can be indolent, and in one series only 13% of mesenteric masses showing significant progression after a median follow-up time of 40 months (62). Patients with advanced midgut NET and recurrent complaints from the primary tumor or (fibrotic) mesenteric mass should undergo operation to explore the possibility of a palliative resection or alternatively, an intestinal bypass.

Palliative Management

Patients with unresectable or advanced gastrointestinal NET are in a palliative setting and the different treatment modalities should be weighed in terms of efficacy and toxicity. Given the wide range of gastrointestinal NET subtypes, the treatment chosen should align with the biological behavior of the tumor as well as the characteristics of the individual patient (Figure 5). Factors to consider in the management of gastrointestinal NET include: tumor grade, growth rate and location(s), symptoms, presence of a hormonal syndrome, performance score, comorbidities, previous therapies, availability of treatments and patient preference.

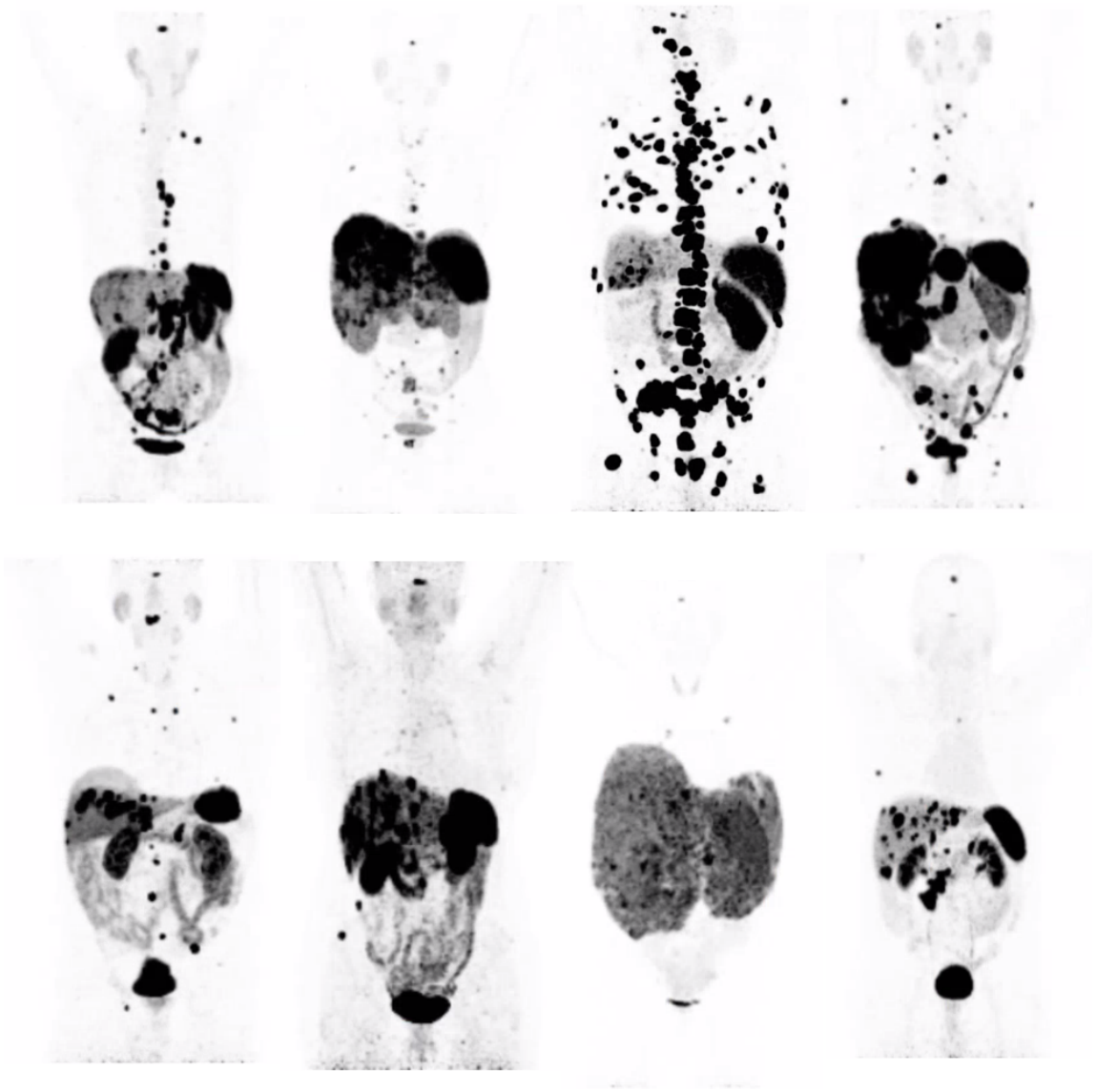

Figure 5. Stage IV gastrointestinal NET. There is a wide heterogeneity in clinical presentation of gastrointestinal NET in advanced or metastatic setting. On these maximal intensity projections of 68Ga-DOTATATE PET, there are 8 different clinical scenarios of stage IV gastrointestinal NET. Despite the similar disease stage, all these patients deserve personalized management of their disease according to several patient- and tumor-specific factors. For optimal management, choice of treatment should be discussed in an experienced multidisciplinary setting.

Active Surveillance

One potential option to consider is to perform active surveillance in asymptomatic patients with advanced, grade I or low-grade II NET with limited tumor bulk. Evidence for this strategy can be found in placebo-controlled trials. First, the median time to progression in placebo-treated patients was 6 months in the phase

III randomized PROMID trial in midgut NET patients (134). Second, in the phase III randomized CLARINET trial in patients with nonfunctioning GEP NET, patients randomized to placebo had a median progression-free survival (PFS) of 18 months (135). Consequently, not all tumors show clear growth potential over time and selected patients can thus safely refrain from costly and potentially toxic medication. This strategy should not be adopted in patients with symptomatic, functioning, high-grade, quickly progressive, or high tumor volume disease. Follow-up cross-sectional imaging every 3-6 months is advised for gastrointestinal NET patients undergoing active surveillance.

Somatostatin Analogs

Before their role in imaging, SSA were developed for their potential antihormonal effects. The SSA octreotide was found to effectively reduce serotonin production in patients with carcinoid syndrome and other NEN-associated functioning syndromes (136). Following its long-term application in functioning NET, antitumoral efficacy was tested in the PROMID and CLARINET trials. The German multicenter PROMID study randomized 85 midgut NET patients to 4-weekly 30 mg octreotide long-acting release (LAR) injections or placebo injections (134). These patients were in the beginning of their disease course with a median time from diagnosis of 4 months and had on average limited liver tumor load and grade I. In an intention to treated (ITT) analysis median time to progression was 14.3 months in octreotide LAR-treated patients versus 6.0 months in the placebo group (P=0.000072). Overall survival (OS) was not different between the groups. The effect of SSA is predominantly stabilization of disease as only one patient in both treatment groups experienced a partial response. Overall, octreotide LAR treatment was well tolerated, although diarrhea, flatulence, and bile stones were more frequently observed in the SSA-treated group.

The international multicenter CLARINET trial randomized 204 patients with advanced nonfunctioning GEP NET to 4-weekly injections of 120 mg lanreotide autogel or placebo injections (135). Tumors were grade I and II with ki-67 index up to 10% and mostly from pancreas or midgut origin. Over 80% of patients had not received previous antitumoral treatment and tumor progression before randomization was only shown in 4-5% of patients. ITT analysis revealed that PFS was significantly longer in lanreotide-treated patients compared to placebo (median not reached versus 18.0 months, P<0.001). The benefit of lanreotide persisted in most predefined subgroups across primary origin, tumor grade, and liver involvement. Safety of lanreotide was good, with known side effects of gastrointestinal complaints, exocrine pancreas insufficiency, and hyperglycemia. Interestingly, the open label extension study of the CLARINET showed a median PFS of 33 months in those continuing lanreotide, while patients in the placebo group – with a median PFS of 14 months - who crossed over to lanreotide after progression had a median second PFS of 18 months (137). This again supports the possibility of considering active surveillance in a subset of patients with indolent disease. Overall survival (OS) in the core CLARINET study was not significantly different between treatment groups, but was also biased by crossover from placebo to lanreotide.

Together these landmark trials have positioned SSA as first-line antiproliferative treatment for well-differentiated gastrointestinal NET, particularly in patients without signs of high tumor volume or aggressive disease course. Injections with octreotide LAR or lanreotide are every 4 weeks in the gluteal area intramuscularly or deep subcutaneously, respectively. Overall tolerability is excellent, although patients should be counselled on the potential gastrointestinal adverse effects, e.g., diarrhea, flatulence, nausea,

stool discoloration, after the first administration, which tend to dissipate after repeated injections. Long-term concerns include hyperglycemia and bile stones. Although preventive cholecystectomy has been advocated in the past, this practice has been abandoned in most expert centers (138).

Several retrospective series and clinical experience supported the use of SSA dose escalation in patients with mild progressive disease (139). These studies suggest that increasing the injected dose or injection frequency might be accompanied by improved antiproliferative control. First prospective evidence of this effect came from the NETTER-1 study designed to investigate the effect of peptide receptor radionuclide therapy (PRRT) with ^{177}Lutetium-DOTA-octreotate (^{177}Lu-DOTATATE) (140). Patients enrolled in this study had advanced, progressive midgut NET on regular dose of SSA and were randomized between PRRT and an escalated dose of 60 mg of octreotide LAR every four weeks. Patients in the high-dose SSA control group had a medium PFS of 8.4 months, supporting some antiproliferative effect of SSA dose escalation after disease progression on a regular dose of SSA. The CLARINET forte single-arm, phase II trial was designed to study the efficacy of lanreotide dose escalation in midgut and pancreatic NET patients with disease progression on standard lanreotide dose in the previous 2 years (141). In the midgut NET cohort, 51 patients were included with grade 1-2 disease and 57% of patients had – generally limited - hepatic metastases. After dose escalation to lanreotide 120 mg every 2 weeks median PFS in this cohort was 8.3 months, while disease control rate (partial response or stable disease as best outcome) was 73%. Importantly, no deterioration of quality of life and no additional treatment-related safety concerns were observed in patients treated with high-dose lanreotide.

SSA treatment should be given lifelong in patients with carcinoid syndrome and other SSA-responsive functioning syndromes for which these drugs are registered and approved (29, 142). This includes continuation of treatment after radiological or clinical progression and initiation of a second-line of treatment. Whether SSA should be continued in nonfunctioning gastrointestinal NET disease is a matter of controversy and no prospective data is available to guide this. Intriguingly, 50% of panelists in the NANETS guideline supported continuing SSA treatment, while 50% supported stopping treatment upon progression (143).

The pan-somatostatin receptor agonist pasireotide has been investigated in NET based on the hypothesis that targeting more somatostatin receptor subtypes might have an additive antiproliferative effect compared to octreotide and lanreotide, which predominantly target the somatostatin receptor subtype 2 (144). However, early phase clinical trials provided insufficient grounds to pursue further clinical development of this drug in NET (145, 146).

Peptide Receptor Radionuclide Therapy

Similar to the diagnostics and therapeutics of thyroid disease with radioactive iodine, the discovery of molecular somatostatin receptor imaging also heralded the advent of targeted somatostatin receptor-based radionuclide therapy. Following initial developments with ^{111}In-pentreotide and ^{90}Yttrium-DOTATATE, the short-range beta-emitter ^{177}Lutetium coupled to DOTATATE (^{177}Lu-DOTATATE) was introduced in 2000 (147). This technique of targeting the somatostatin receptor on tumor cells with internal radiation was termed PRRT.

Individual phase II trials at several centers showed promising antitumoral effects on somatostatin

receptor-positive NET, including gastrointestinal subtypes (148). The multinational phase III randomized NETTER-1 trial established PRRT with 4 cycles of ^{177}Lu-DOTATATE as an effective therapy for advanced, somatostatin receptor-positive midgut NET (140). In this trial, 229 patients were randomized between PRRT, including 30 mg octreotide LAR between cycles and 4-weekly after the fourth cycle, and 60 mg octreotide LAR every four weeks. Patients had a grade 1-2 midgut NET that was progressive on SSA before enrollment. The median PFS in the PRRT group was not reached compared to 8.4 months in the high-dose SSA group. Benefit in PFS prolongation was evident across all pre-specified subgroups. Risk of progression or death was 79% and decreased in the patients treated with PRRT. The study confirmed known side effects of ^{177}Lu-DOTATATE, including nausea, fatigue, abdominal pain, and diarrhea. Two percent of patients experienced grade 3 or higher thrombocytopenia, while 2 patients (1.8%) developed myelodysplastic syndrome following PRRT. In a meta-analysis of 28 studies comprising 7334 patients treated with ^{90}Y-DOTATOC or ^{177}Lu-DOTATATE, the combined incidence of myelodysplastic syndrome and acute myeloid leukemia after PRRT was 2.6% (149). Final analysis of the NETTER-1 study revealed that the median OS in the PRRT group was 48.0 months compared to 36.3 months in the high-dose SSA group, which was not significantly different (150). Crossover of 37% of the patients randomized to high-dose SSA, long-term survival with multiple other treatment lines and insufficient statistical power could have contributed to the failure of reaching this secondary endpoint. Another key secondary endpoint was reached: time to deterioration of quality of life was significantly longer in patients treated with PRRT compared to those treated with high-dose SSA (151).

Although the NETTER-1 only included midgut NET patients, the phase II Erasmus MC Rotterdam data were used to obtain regulatory approval of ^{177}Lu-DOTATATE for all gastrointestinal (and pancreatic) NET subtypes (152). Importantly, PRRT also induced tumor response in 18% of midgut NET patients in the NETTER-1 study and 39% of various NET patients in the Rotterdam study, which makes it a potential cytoreductive therapy. Standard protocol of PRRT included four infusions of 7.4 GBq ^{177}Lu-DOTATATE spaced 8 (range 6-12) weeks apart. PRRT should preferably be administered in the absence of long-acting SSA (4-6 weeks) or short-acting SSA (24 hours) due to competition at the receptor level. An amino acid solution of 2.5% lysine and arginine is co-infused with ^{177}Lu-DOTATATE in order to saturate the renal reuptake of radioactive peptide and prevent radiation-induced nephrotoxicity. This limits the incidence of severe renal insufficiency after PRRT to less than 1% (152). Special considerations should be applied to patients with pre-existing cytopenia or clonal hematopoiesis, impaired renal function or hydronephrosis, massive liver tumor bulk, mesenteric fibrosis, or nervous system involvement (153). Patients with a severe functioning syndrome are at risk of an exacerbation of symptoms or hormonal crisis following temporary SSA withdrawal or tumor lysis with PRRT. Although the risk is minor at 1% incidence in retrospective series and limited to patients with severe hormonal hypersecretion (154, 155), adequate management through supportive measures and swift re-introduction of SSA should be employed to prevent a hormonal crisis.

There is a possibility for salvage PRRT when progressive disease (re-)occurs after a period of disease control following 4 cycles of PRRT. Several retrospective series have described renewed disease control or even response after additional cycles with ^{177}Lu-DOTATATE after progression. In the largest series to date of 181 patients with gastrointestinal, pancreatic, bronchopulmonary, or unknown origin NET, salvage PRRT with two cycles was administered if disease progression occurred after a period of at

least 18 months after the first cycle of the initial PRRT (156). The median PFS after salvage PRRT was 14.6 months and thereby approximately 50% of the initial PRRT, while disease control was observed in 75% of patients. Salvage PRRT was not associated with increased rates of myelotoxicity or nephrotoxicity. In patients that respond favorably to salvage PRRT, future cycles can be considered when progressive disease once again arises, although clinical outcome data of additional treatments are scarce.

Targeted Therapy

The mammalian target of rapamycin (mTOR) protein is a central proliferative factor in many cancer cells. Inhibition of the mTOR pathway has been investigated for several malignancies, including NEN. The RADIANT-2 multicenter phase III trial investigated whether the oral mTOR inhibitor everolimus had efficacy in patients with advanced NET and carcinoid syndrome (157). In total, 429 patients with progressive and advanced grade 1-2 disease were randomized between everolimus 10 mg q.d. plus octreotide LAR 30 mg every 4 weeks or placebo plus octreotide 30 mg every 4 weeks. Primary sites included among others small intestine (52%), lung (10%), colon (6%), and pancreas (6%). Baseline characteristics between the groups were not well balanced with regard to WHO performance status, primary sites, and prior use of chemotherapy. The median PFS was 16.4 months in the everolimus combination group compared to 11.3 months in the placebo combination group (p=0.026). This analysis encompassing central review of radiological images did not reach the pre-specified cut-off for superiority. Median OS was 35.2 months in the placebo-octreotide LAR group compared to 29.2 months in the everolimus-octreotide LAR group, which was not a statistically significant difference, but more deaths related to respiratory or cardiac disease were observed in the everolimus arm.

In the RADIANT-4 phase III trial, patients with advanced, progressive, grade 1-2, nonfunctioning NET of gastrointestinal or lung origin were included (158). Here, 302 patients were randomized 2:1 to everolimus 10 mg q.d. or placebo. Approximately 60% of patients had a gastrointestinal NET, while 80% had liver metastases, generally with limited liver tumor bulk. Median PFS was longer in the everolimus-treated patients at 11.0 months versus 3.9 months in the placebo group. This difference was significant after central radiology review as well as after local review ($P<0.00001$). Despite a 36% reduction in the risk at death in the everolimus group, overall survival was not significantly improved. Partial response was obtained in 2% of patient treated with everolimus, while stable disease was observed in 81%. Given the outcomes of the RADIANT-2 and RADIANT-4 trials, everolimus appears to be better suited for nonfunctioning NET than functioning NET.

Everolimus use is associated with a high rate of side effects, such as stomatitis, rash, diarrhea, fatigue, diabetes, infections, and non-infectious pneumonitis. Dose reductions or interruptions are necessary in up to two-thirds of NET patients taking everolimus (158). No benefit in terms of quality of life has been proven for everolimus (159), with potentially a decrease in quality of life in patients with extrapancreatic NET (160).

Multitarget tyrosine kinase inhibitors (MTKI) are another form of targeted therapy that can exert potent anti-cancer effects. Sunitinib is an oral multireceptor MTKI which has been investigated in panNET patients. In a phase II study, suninitib showed encouraging antitumoral activity in 61 pancreatic NET with partial response observed in 17% (161). While the median time to progression of 10.2 months in 41 patients with gastrointestinal and lung NET treated with sunitinib exceeded the 7.7 months observed in panNET patients, further development of sunitinib in

gastrointestinal NET was not pursued due to the low response rate of 2.4%. A subsequent phase III trial in panNET patients showed that sunitinib improved PFS and OS in panNET patients (162), which led to registration of this drug for NET of pancreatic origin only.

Another MTKI surufatinib was tested in two phase III studies in China in pancreatic and extrapancreatic NET, respectively (163, 164). In the multicenter, randomized SANET-ep trial 198 patients with advanced, grade 1-2, progressive NET of gastrointestinal (47%), thoracic (24%), or other origins were randomized 2:1 to oral surufatinib 300 mg or placebo once daily (164). The median PFS after central review in the surufatinib group was 7.4 months compared to 3.9 months in the placebo group (P=0.037), which appeared to be independent of the subgroups studied. There was a large difference with the local radiology review, which tended to overexaggerate the effect of surufatinib on PFS. OS was not different between the groups at the time of the interim analysis. Partial response and stable disease were observed in 10 (8%) and 88 (70%) out of 126 patients, respectively, in the surufatinib arm. Relevant treatment-related side effects included hypertension, proteinuria, anemia and elevated liver enzymes. Quality of life did not improve in the surufatinib arm, while surufatinib-treated patients experienced more diarrhea than those in the placebo arm (165). Based on the SANET-ep study and its partner SANET-p study in panNET patients, surufatinib is registered in China for the treatment of nonpancreatic and pancreatic NET. Surufatinib is thus far not registered for these indications by the FDA or EMA.

Several other MTKI have shown potential for antiproliferative activity in NET patients. These include pazopanib (166), lenvatinib (167), and axitinib (168). Further phase III data are necessary before these MTKI can be considered in gastrointestinal NET.

Immunotherapy: Interferon-Alpha and Immune Checkpoint Inhibitors

In the 1980s, the advent of interferon as a novel cancer drug was also investigated in NEN. Several uncontrolled series supported antiproliferative and antihormonal effects of interferon alpha in mostly small intestinal NET (169, 170). The proinflammatory effects of interferon alpha however led to side effects of flu-like symptoms, myalgia, asthenia, auto-immune diseases, and diarrhea, limiting its tolerability in patients. Compared to SSA, interferon alpha had comparable antiproliferative effects (171). Long-acting interferon alpha appears to be better tolerated and was shown to produce antitumor effect in a single retrospective series in 17 patients (172).

Immunotherapy with immune checkpoint inhibitors has revolutionized treatment of several malignancies, including melanoma and non-small cell lung cancer. However, infiltration of immune cells, like T-cells, is a rare occurrence in NET samples (173-175). In line with these preclinical findings, immune checkpoint inhibition in clinical (basket) trials have failed to show positive effects in well-differentiated NET (176-178).

Chemotherapy

In contrast to panNET there are no phase III clinical data to support the use of chemotherapy in gastrointestinal NET. Presumably in part through their well-differentiated nature, response rates to chemotherapy have been disappointing and further clinical development halted (179). Consequently, ENETS 2016 and NANETS 2017 guidelines do not support the use of chemotherapy in gastrointestinal NET (143, 180). The EMSO 2021 guideline does advocate the use of either FOLFOX (5-fluorourical, oxaliplatin) or TEMCAP (temozolomide, capecitabine) in selected cases with high grade 2 gastrointestinal

NET in third-line or higher setting, although this is not supported by prospective clinical data (181).

Supportive Therapy

Due to the primary tumor and metastasis locations as well as the sequalae of hormonal overproduction and therapeutic interventions, patients with gastrointestinal NET can be in a poor clinical condition. Inadequate nutrient intake and uptake in these patients leads to increased incidence rates of weight loss, muscle atrophy, and decreased performance status (182). Consequently, all gastrointestinal NET patients should be screened on dietary intake and referred to dieticians if they are at risk of weight loss. High-protein, high-calorie supplements should be prescribed if regular dietary advice is insufficient to prevent weight loss. In cases of suspected reduced calorie uptake due to exocrine pancreatic insufficiency, often encountered during SSA treatment, or bile acid diarrhea, due to bowel resection, a trial of pancreatic enzyme supplements or bile acid sequestrants can be considered.

In some cases, patients can be refractory to these interventions and escalation should be considered. This is particularly true for patients with extensive bowel resections leading to short bowel syndrome and those with severe desmoplastic reaction surrounding mesenteric metastases of small bowel NET. Food intake in the latter group might also be compromised by intermittent venous ischemic pain precipitated by meals. Tube feeding through nasogastric tube should be considered in selected cases. In case enteral feeding fails to improve the clinical situation, total parenteral nutrition can serve as a last resort for these refractory cases. Treatment with total parenteral nutrition up to 5 years has been successfully implemented in severe cases of NET (183).

Besides nutritional support, physical therapy should also be offered to patients in order to improve their clinical performance status. Finally, given the impact of an incurable disease and its complaints psychosocial support should be discussed with patients and made accessible, if needed (184).

MANAGEMENT OF CARCINOID SYNDROME

Patient with gastrointestinal NET and the carcinoid syndrome require dedicated management of their hormonal symptoms. Quality of life in these patients is severely decreased, even when compared to patients with other – generally more aggressive – cancers (185). Prompt recognition of symptoms of flushing and diarrhea is key to specific management, while the complications of mesenteric fibrosis and CHD should also be screened and treated adequately (29).

The cornerstone of the management of the carcinoid syndrome is SSA. Since the 1980s octreotide and later lanreotide have been shown to lead to biochemical and clinical responses in patients with the carcinoid syndrome. In a meta-analysis comprising 1945 interventions in 33 studies, SSA significantly decreased 5-HIAA excretion in 45-46% of patients, while flushing and diarrhea were decreased in 69-72% and 65%, respectively (186). Also given its favorable tolerability, all patients should be started on SSA soon after a confirmed diagnosis of carcinoid syndrome.

Although patients with carcinoid syndrome in the majority of cases have widespread disease, the option of cytoreductive therapy by surgical resection or ablation or intra-arterial liver embolization can be considered in selected cases. If the vast majority of tumor bulk can be resected or embolized, this can lead to biochemical responses and clinical benefit for the patient (186). These options should be weighed also considering the level of serotonin overproduction,

tumor growth rate, and efficacy of SSA. Importantly, SSA should be initiated before interventional therapy is commenced in order to reduce the risk of a carcinoid crisis (187).

Patients with persistent symptoms despite label doses of SSA are designated as having refractory carcinoid syndrome. Several systemic options are available for treatment and these should be weighed on an individual basis guided by tumor bulk, rate of progression, severity of symptoms, and availability. Dose escalation of SSA can be attempted and leads to symptomatic improvement in 72-84% of patients (186). Alternatively, a randomized controlled trial has proven efficacy of the oral drug telotristat ethyl in controlling diarrhea in patients with refractory carcinoid syndrome (188). This serotonin synthesis inhibitor, dosed at 250 mg t.i.d., decreased bowel movements in approximately half of the cases and with a mean reduction of 0.8 bowel movements per day, whilst having no significant effect on flushing. A drug trial of three months is generally advised with stopping of telotristat ethyl if no benefit has been obtained after this time. Clinical symptoms improved in patients treated with PRRT in the NETTER-1 trial (140), although no sub-analysis was performed for carcinoid syndrome patients. In a retrospective series of 24 patients with stable disease or severe, refractory carcinoid syndrome, PRRT with four cycles of ^{177}Lu-DOTATATE effectively reduced flushes and diarrhea in 67% and 47% of patients, respectively (155). Therefore, PRRT constitutes a viable option for refractory carcinoid syndrome patients with aggressive or progressive disease. In the past, interferon-alpha injections have been shown to diminish diarrhea and flushing resulting from carcinoid syndrome. Its antihormonal effect on top of SSA was limited (189), however, and given its poor tolerability interferon-alpha is reserved to selected cases, refractory to the above-mentioned options. Anecdotal reports support the use of serotonin receptor antagonists, like granisetron or ondansetron, and antihistamines (H1 and H2 receptor blockers) in refractory carcinoid syndrome.

Importantly, the patient should be counselled on supportive therapy, which could include the use of antidiarrheals, like loperamide or morphine, adaptation of dietary intake, including avoidance of alcohol, tryptophan-containing or spicy foods, and the avoidance of stressors (29). Patients with severe carcinoid syndrome are at a high risk of a catabolic state and vitamin deficiencies. Patients should be referred to a dietician and adequately monitored and supplemented for vitamin deficiencies, particularly for vitamin B3 or niacin and fat-soluble vitamins.

Patients suffering from CHD should be evaluated by cardiologists experienced in right-sided cardiac pathology. Dedicated echocardiographic evaluations should be performed, preferably through standardized protocols (190). Fluid and salt restriction comprise first-line treatment of right-sided heart failure due to tricuspid valve regurgitation or pulmonary valve regurgitation or stenosis in the context of CHD. Alternatively, loop diuretics can be prescribed to treat fluid overload and edema. Severe symptomatic patients should be discussed in a multidisciplinary team for evaluation of surgical valve replacement (191).

PROGNOSIS AND FOLLOW-UP

Resection is the only potential cure for gastrointestinal NET. Recurrence is however frequently observed in NET patients operated on with curative intent (119). Exceptions that are associated with excellent curation rates after local resection include T1-T2 appendiceal, gastric, duodenal, or rectal NET. Long-term imaging follow-up is mandated for the other subtypes of

gastrointestinal NET after resection of localized, locoregional, or oligometastatic disease.

In a US registry study of almost 100,000 NET patients, median overall survival was 112 months and 62% of patients died of disease-related causes (192). All-cause mortality was 4.3-fold higher in all NET patients, compared to the general population, while patients with stage IV disease had 35-fold elevated risk of mortality. Whereas patients with localized disease still have an elevated standardized mortality ratio, the risk of non-cancer death is higher than cancer-related death in patients with non-metastatic gastrointestinal NET (193). Primary site, stage or grade are tumor-specific prognostic markers, while age, sex, comorbidities and socio-economic status constitute patient-specific factors that are associated with overall survival (7, 8, 192-194). Over the last few decades, NET management has improved considerably with the advent of superior classification, imaging, and biochemical diagnostics and treatment modalities. These developments, combined with expert multidisciplinary team care in dedicated NET centers, have likely contributed to the observed improvement in overall survival in patients with gastrointestinal NET (7, 8). However, survival of gastrointestinal NET patients is still limited, particularly in those with advanced disease, prompting the need for future innovation in the fields of early detection of disease (recurrence), novel druggable targets, and personalized management for NET.

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