Gastroenteropancreatic neuroendocrine tumours (GEP-NETs). A comprehensive review

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Abstract

Neuroendocrine tumours (NETs) are a heterogeneous group of epithelial tumours arising from the diffuse endocrine system throughout the body. NETs are considered to be rare tumours, however their incidence is increasing, while their pathophysiology is yet poorly understood. Moreover, given their heterogeneity, they remain a challenging disease to diagnose and treat. In this review we aim to delineate in a comprehensive way the epidemiology, prognosis, as well as the latest advances in diagnosis and management in the field of NETs, with focus on NETs of the digestive tract, (gastroenteropancreatic NETs, GEP-NETs).

Key words: *Neuroendocrine tumours; somatostatin analogues; octreotide; lanreotide; malignant carcinoid syndrome*

INTRODUCTION

The discovery of neuroendocrine tumours (NETs) dates back to 1870, when the German physiologist Rudolf P.H. Heidenhain identified a group of cells that were different from the enteric, chief, and parietal cells of the gastrointestinal (GI) tract. A few years later, in 1907, the German pathologist S. Oberndofer was the first to use the term "carcinoid" - from the German word for "cancer-like"- to describe NETs of the gastrointestinal tract. In 1995, a revised classification of NETs was published suggesting to avoid the use of the term "carcinoid tumours", as it fails to encapsulate their malignant potential and promotes the misconception that all NETs lead to carcinoid syndrome. Instead, the use of the term "neuroendocrine tumours" for all NETs was established. Throughout this period, physicians have continuously studied neuroendocrine cells in an effort to pinpoint their intricacies, analyse their clinical presentation, and manage their symptoms [1,2].

NETs are a group of heterogeneous epithelial tumours originating from secretory cells of the neuroendocrine system. They are indolent neoplasms that secrete a range of peptide hormones and monoamines [3]. The "neuro" component refers to their dense core granules (DCGs), which are organelles commonly found in serotonergic neurons that store biogenic amines. The "endocrine" component refers to their ability to synthesize and secrete these monoamines [4]. The neuroendocrine system includes the parathyroid, pituitary, and adrenal glands, as well as thyroid and pancreatic endocrine islet cells. The neuroendocrine cells within these glandular organs, together with scattered cells found in the gastrointestinal, respiratory, or genitourinary tracts, constitute the diffuse neuroendocrine system [4].

The most common primary tumour sites for NETs are the lungs, GI tract and pancreas. However, given the extensive distribution of NE cells, NETs can also be found in a plethora of other organs, such as the prostate, breast, skin, thymus, and genitourinary system [5,6].

This review will primarily focus on gastroenteropancreatic NETs (GEP-NETs), which consist of tumours of the GI tract and pancreatic tumours (pNETs). Although

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GI tumours arise from enterochromaffin cells of the gut, pNETs originate from the islet of Langerhans or precursors of the ductal/acinar system [5]. By classifying NETs by their embryonic origin, a distinction can be made between foregut (gastric and duodenal), midgut (jejunal, ileal, and caecal), and hindgut (distal colonic and rectal) tumours [5].

EPIDEMIOLOGY

According to the Surveillance, Epidemiology, and End Results (SEER) program in the United States, the age-adjusted incidence rate of NETs has increased 6.4-fold from 1973 (1.09 per 100000) to 2012 (6.98 per 100000) in all stages, grades, and sites of the disease [7]. The incidence has been increasing in a 3-10% rate depending on the tumour subtype [8]. This increase could be attributed to the advancements in disease detection via imaging and recognition of neuroendocrine histology [9].

GEP-NETs are the second most prevalent gastrointestinal tract cancer [10]. The most common primary site of GEP-NETs is the small intestine (30.8%), with the rectum (26.3%), colon (17.6%), pancreas (12.1%), stomach (8.9%), and appendix (5.7%) following. Small intestinal NETs are more common amongst Caucasians, whereas NETs originating from the rectum are more prevalent in African American, Asian, and Native American populations [7]. Although NETs of the stomach, appendix, and cecum develop more frequently in females, jejunal, ileal, duodenal and rectal NETs are more common amongst the male population [7]. As far as disease progression is concerned, 53% of patients have localized disease, 20% present with locoregional disease, and 27% present with distant metastases at the point of diagnosis [11]. In patients with a family history of NETs in a first-degree relative, the risk of developing NETs increases by 3.6-fold [12].

Although the vast majority of GEP-NETs are sporadic, approximately 10% of pNETs can be found within the context of genetic syndromes such as Multiple-Endocrine-Neoplasia type 1 (MEN-1), von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC). Of those, MEN-1 is the most common one, consisting of hyperparathyroidism (associated with parathyroid adenomas in over 90% of cases), pNETs (in up to 70% of cases) and pituitary adenomas (in 30-40% of cases). Other manifestations of MEN-1, include bronchial NETs and type-II gastric NETs [13].

HISTOPATHOLOGIC FEATURES

The histopathologic morphology and immunohistochemical profile form the basis for the diagnosis of NETs [15]. Depending on their morphology and degree of proliferation, NETs can be categorized into poorly differentiated neuroendocrine carcinomas (NEC) and well differentiated neuroendocrine tumours. Well differentiated NETs are composed of bland, benign looking, monomorphic neoplastic cells. The intermixing of coarse chromatin with finely granulated chromatin gives these cells their characteristic "salt and pepper" appearance. Despite their predictable cytologic and nuclear features, well differentiated NETs demonstrate wide-ranging morphological growth patterns. These include trabecular, glandular, solid or gyriform growth patterns, with tumour cells sometimes arranged in pseudorosettes.

Poorly differentiated neuroendocrine carcinomas (NEC) are particularly aggressive in nature and lack resemblance in morphology, clinical presentation, and genetic makeup to well differentiated NETs. Depending on their nuclear size, they are divided into large and small cell neuroendocrine tumours.

Small cell carcinomas morphologically resemble their well-differentiated NETs counterparts, as they both exhibit the characteristic salt and pepper chromatin. Their cell nuclei are near each other because of their thin cytoplasm, thus giving them the distinctive appearance of nuclear impressions ("nuclear moulding"). Small cell carcinomas commonly demonstrate confluent growth patterns, with cells arranged in solid sheets in a streaming pattern. Single cell necrosis as well as large necrotic areas are frequently identified.

Large cell NETs demonstrate a clumpy chromatin appearance with prominent nucleoli. They consist of highly pleomorphic and hyperchromatic tumour cells with a markedly pronounced cytoplasm. They are characterized by a solid growth pattern, with extensive necrotic areas centrally and palisading peripherally.

The immunohistochemical markers of NETs include synaptophysin, chromogranin A (CgA), cluster of differentiation 56 (CD56), neuron-specific enolase (NSE) and Ki-67. Poorly differentiated tumours are often positive for synaptophysin and NSE expression, whereas well differentiated tumours usually demonstrate high levels of synaptophysin and CgA expression. Thyroid transcription factor 1 (TTF1), caudal type homeobox 2 (CDX2) and insulin gene enhancer protein 1 (ISL1) can be immunohistochemically labelled to track the primary

site of metastatic tumours, as these proteins are typically found in the lung, small intestine, and pancreas respectively. Ki-67 is a proliferation marker used for grading GEP-NETs as well as for predicting the course of the disease [14].

CLASSIFICATION AND STAGING (TABLE 1)

There are several ways of approaching the classification of GEP-NETs. One classification, based on embryonic derivation, distinguishes between foregut (gastroduodenal), midgut (jejunal, ileal, and cecal), and hindgut (distal colic and rectal) tumours. GEP-NETs can be subclassified into two groups: carcinoid tumours of the luminal GI tract and pancreatic NETs. In addition, the grade and degree of differentiation of GEP-NETs are of paramount importance in determining the clinical behaviour of the disease. Grade refers to how rapidly the neoplastic cells divide, proliferate and grow. It is measured by the Ki-67 index or the mitotic rate. Each tumour receives a numerical grade, with grade 1 (G1) tumours having a Ki-67 index from 0% to 2% or a mitotic rate from 0 to 1 per 10 high power fields (HPF), G2 tumours having a Ki-67 index from 3% to 20% and mitotic rate from 2 to 20 per 10 HPF, and G3 tumours having a Ki-67 index over 20% and mitotic count higher than 20 per 10 HPF [15]. Importantly, it is advised that tumour grades should be measured at the areas of the histopathology specimen with the highest levels of mitotic activity, as GEP-NETs are considered to have a high degree of intratumor heterogeneity when it comes to morphology and proliferative rate. Specifically, it is recommended that 40-50 high-power fields should be used for the mitotic count, and at least 2000 cells should be counted in the areas of highest labelling for an accurate measurement of the Ki67 index [16]. Importantly, according to the WHO newest classification (2017), there is a distinction between well-differentiated (G1, G2, or G3) NETs and poorly-differentiated NECs (found primarily in the pancreas), which are considered high-grade by definition [17].

The prognostic significance of the current grading systems has been demonstrated in a study by Karakas et al. [18]. In particular, the 5-year survival rates for G1 and G2 NETs were 97% and 82% respectively; however, the prognostic significance of G3 tumours could not be evaluated due to the low number of patients presenting with G3 tumours. Larger, long-term studies with well-balanced patient populations should be performed to effectively evaluate the prognostic significance of the 2017 WHO classification system.

The TNM staging system for NETs was first introduced by Rindi et al in 2006 and was later adopted by the European Neuroendocrine Tumour Society and the American Joint Committee on Cancer in 2010 [19]. The latest version (2017) features separate staging systems for well-differentiated NETs of the appendix, stomach, colorectal, duodenal, jejunal, and ileal primary sites. A new TNM staging system is also used for pNETs, which is separate from the one used for exocrine pancreatic cancers [20].

Importantly, case reports have also demonstrated that NETs can rarely co-exist with pancreatic and colorectal adenocarcinomas, giving rise to unique therapeutic challenges [21–23]. Accordingly, it is recommended that patients with NET diagnosis should undergo meticulous screening to prevent late-stage diagnosis of synchronous tumours [24].

CLINICAL PRESENTATION AND SYMPTOMS (TABLE 2)

GEP-NETs

GEP-NETs clinical presentation depends greatly on the hormonal status of the tumour. Non-functioning GEP-NETs are usually incidentally discovered during surgery, as they are commonly asymptomatic [25]. Nonspecific symptoms such as abdominal discomfort

Table 1. *Classification of GEP-NENs*

Grade	Differentiation	Ki-67 %	Mitotic rate/10 HPF
G1 NET	Well	<3	<2
G2 NET	Well/moderate	3-20	2-20
G3 NET	Moderate	>20	>20
G3 NEC	Poor	>20	>20

Abbreviations: GEP-NEN, gastroenteropancreatic neuroendocrine neoplasm; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; HPF, high power field.

Table 2: *Secretory syndromes in patients with hormonally active GEP-NENs*

Tumor type	Symptoms/Findings	Substances responsible
Midgut NETs with liver metastases	Carcinoid syndrome (diarrhea, flushing, wheezing, carcinoid heart disease)	Serotonin, bradykinin, histamine, prostaglandins
Insulinoma	Hypoglycemia	Insulin
Gastrinoma	Multiple gastric ulcers, abdominal pain, diarrhea	Gastrin
VIPoma	Watery diarrhea, hypokalemia, achlorhydria (WHDA syndrome)	VIP
Glucagonoma	Diabetes, diarrhea, stomatitis, weight loss, necrolytic migratory erythema	Glucagon

Abbreviations: GEP-NEN, gastroenteropancreatic neuroendocrine neoplasm; NET, neuroendocrine tumor; VIP, vasoactive intestinal peptide.

may also be present, but do not contribute to earlier diagnosis due to their vague nature. As a result, diagnosis may delay up to a decade, and often symptoms are attributed to irritable bowel syndrome or other benign gastroenteric disorders. On the other hand, functioning tumours may present with a variety of symptoms, based on the anatomic location of the tumour, as well as the type of produced hormones [26,27]. For example, small bowel/midgut carcinoids metastatic to the liver are responsible for the carcinoid syndrome, characterized by flushing, diarrhoea, wheezing and carcinoid heart disease, via releasing serotonin and other vasoactive substances in the circulation [5]. Similarly, functioning pNETs (VIPoma, glucagonoma, gastrinoma etc.) are responsible for the development of various clinical syndromes which will be described in detail below.

1. Appendiceal NETs

Appendiceal NETs are usually benign and not associated with any hormonal-related symptoms. They are commonly diagnosed incidentally after examining the specimens of appendicectomies. Women have higher prevalence of appendiceal NETs, possibly due to the fact that pre-menopausal females undergo diagnostic laparoscopies more frequently in order to differentiate between gynaecologic and other reasons of lower abdominal pain [28].

2. Gastric NETs

Gastric NETs are rare and can be subdivided into three categories. Type I gastric NETs have an association with chronic atrophic gastritis and pernicious anaemia. Due to the loss of the gastric glands and long-term achlorhydria, antral G cells are forced to secrete excessive serum gastrin, thus causing hyperplasia of the gastric neuroendocrine cells [Entero-Chromaffin-Like (ECL) cells] and development of multifocal, polypoid NETs [31]. Type II gastric NETs are associated with Zollinger-Ellison and MEN-1 syndrome. They are commonly small in size, multifocal, and relatively unaggressive. Patients usually suffer from symptoms of Zollinger-Ellison syndrome, such as diarrhoea, heartburn, and peptic ulcers. Type III gastric NETs are large, sporadic, solitary tumours that are not associated with gastrin excess. They are more invasive than their Type I and II counterparts and can occasionally present with an "atypical carcinoid syndrome" mainly due to histamine production. This can be clinically distinguished from the typical (serotonin-associated) carcinoid syndrome by the patchy red, serpiginous, highly pruritic flush patients usually present with [29,30].

3. Small bowel NETs

The majority of small bowel NETs are located in the distal ileum [32], with around 25% of patients presenting with multifocal tumours clustered close to each other at the time of diagnosis. Despite the fact that the malignant potential of GEP-NETs is associated with tumour size, even small bowel NETs less than 1cm in size have the ability to metastasize [33]. Common sites of metastases include the liver, mesentery, and peritoneum. Mesenteric desmoplasia and intestinal ischemia can occur when the tumour metastasizes to the lymph nodes at the root of the mesentery [34]. Accordingly, patients may present with colicky or intermittent abdominal pain and intestinal obstruction [34]. Small bowel NETs originating from the duodenum are rarely syndromic. Up to 30-40% of advanced small bowel NETs produce and secrete serotonin and other vasoactive substances, causing "carcinoid syndrome". Carcinoid syndrome occurs due to the hypersecretion of vasoactive amines and

peptides, such as serotonin. Serotonin is synthesized from dietary tryptophan in specialized neuroendocrine cells called enterochromaffin (Kultchisky) cells [35]. The classical "carcinoid syndrome" symptoms include diarrhoea (73%), flushing (65%), and bronchospasm (8%) [5]. Other symptoms include hypotension (as part of "carcinoid crisis") and valvular heart disease ("carcinoid heart disease"). Excess serotonin is primarily responsible for the development of diarrhoea, whereas flushing can be mainly attributed to substance P, kallikrein, and a range of other prostaglandins and tachykinins [36,37]. Flushing may be triggered by alcohol consumption, stress, spices, and tyramine-containing foods. It usually manifests in the face, neck, and thorax. High levels of serum serotonin can also lead to "carcinoid heart disease". In this case, serotonin receptors in the subendocardial cells of heart valves are activated [38], leading to fibrosis of the tricuspid and pulmonary valves and consequently to tricuspid regurgitation and pulmonary stenosis [39] (Figure 1). The left side of the heart is usually unaffected as serotonin is metabolised while passing through the lungs [40]. Similarly, since serotonin is secreted from small bowel NETs, it is drained in the portal circulation and metabolized by monoamine oxidases in the liver before entering the systemic circulation [41]. Thus, carcinoid syndrome only occurs in patients with liver or other distal metastases. Carcinoid syndrome patients also commonly present with hypoproteinaemia, as tryptophan is the precursor for serotonin synthesis [42]. Pellagra-like symptoms like diarrhoea, dermatitis, and dementia can also manifest, as niacin production is reliant on tryptophan [43]. Rarely, carcinoid syndrome can be associated with pancreatic (<1% of pNETs), bronchial, and ovarian NETs [44].

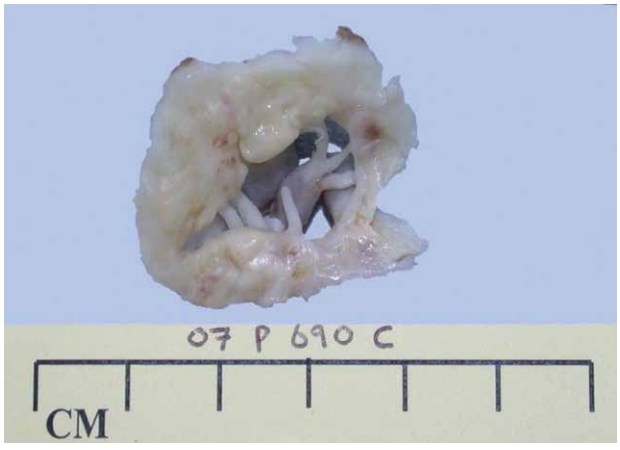

Figure 1. Tricuspid valve, almost replaced by fibrotic plaque ("carcinoid heart disease").

4. Colorectal NETs

Colorectal NETs are rare but have poorer prognosis than adenocarcinomas due to their aggressive clinical course [45]. They can manifest with rectal bleeding, pain, and change in bowel habit. Most colorectal NETs are small, located in the submucosa, and are incidentally discovered during lower endoscopy [46]. In particular, small (<1cm), nonaggressive rectal NETs have low metastatic potential and are often endoscopically or transanally excised. On the other hand, large (>2cm), high-grade rectal NETs present with stage IV disease in more than half of the patients. The tendency of intermediate-size tumours to metastasize depends on the depth of tumour invasion of the muscularis propria [47]. Tumours originating distal to the cecum are more malignant in nature than rectal NETs, as they are commonly poorly differentiated [48].

5. Pancreatic NETs (pNETs)

The vast majority (90%) of pNETs are hormonally non-functioning. Hormonally silent neoplasms appear to have worse prognosis than hormonally active tumours, possibly because they are diagnosed late in the disease progression [49]. Insulinomas are the most common type of hormonally functioning pNETs. They are commonly small (<2 cm), solitary, hypervascular tumours, with low malignant potential. They usually manifest with low blood glucose levels, symptomatic hypoglycaemia, reversal of symptoms after administrating glucose (Whipple triad) [50], and hypokalaemia due to excessive insulin secretion [51]. Gastrinomas commonly present in the pancreas and duodenum and are responsible for the development of Zollinger-Ellison syndrome. Their clinical features include peptic ulceration, heartburn, and diarrhoea. High-dose proton pump inhibitors can help in alleviating these symptoms [52]. VIPomas are another subtype of pNETS. Given that vasoactive intestinal polypeptide (VIP) inhibits electrolyte and water absorption and stimulates intestinal secretion, VIPomas usually present with profuse, watery diarrhoea and electrolyte disturbances, such as hypokalaemia [53]. Glucoganomas, on the other hand, are extremely rare and manifest with hyperglycaemia, weight loss, deep vein thrombosis, dermatitis (necrolytic migratory erythema), and depression [54]. Somatostatinomas are characterized by excessive secretion of somatostatin. Pa-

tients usually present with steatorrhea, hyperglycaemia, cholelithiasis, diabetes, and reduced gastric acid levels. ACTH, PTHrP, growth hormone-releasing hormone, serotonin, and cholecystokinin, may infrequently be secreted by pNETs, leading to the development of the corresponding syndromes [55].

DIAGNOSIS

GEP-NET diagnosis requires a high index of suspicion and is based on their clinical presentation, histopathologic morphology, immunohistochemical profile, and imaging modalities. Traditionally, carcinoid syndrome diagnosis is largely dependent on detection of elevated urinary 5-hydroxyindoleacetic acid (5-HIAA) over 24 hours [56]. Recently, however, it has been found that serum and plasma 5-HIAA can be used as an alternative for the diagnosis and monitoring of carcinoid syndrome [57]. Hormone levels should be measured in patients presenting with symptoms of hormonally functioning pNETs. Hormone concentration can then be monitored and used as a marker of disease progression or treatment response [58]. On the other hand, Chromogranin A (CgA) is the diagnostic biomarker of choice for non-functioning NETs [59]. CgA has a high sensitivity (53%-91%) but low specificity (<50%) [59]. Endoscopic imaging also plays an important in the diagnosis of NETs. In particular, endoscopic ultrasonography is the most sensitive test for the diagnosis of pNETs (sensitivity 82%-93%), especially for detecting tumours smaller than 2 cm and for the localization of insulinoma [60,61]. Colo-rectal NETs are usually identified at colonoscopy. Importantly, the entire colon needs to be examined to detect any potential synchronous tumours [62].

Cross sectional imaging is of paramount importance for the identification of tumour location and the assessment of the extent of invasion of GEP-NETs. In particular, computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen and pelvis are employed for the detection of pNETs and midgut carcinoids respectively. A triple-phase helical CT is recommended for the diagnosis of liver metastasis [63]; however, a RCT by Baudin et al showed that MRI may be superior to CT [64]. Functional imaging modalities also play a key role in the diagnosis of GEP-NETs. Specifically, somatostatin receptor scintigraphy (Octreoscan) is commonly employed, during which a $^{[111]}$indium-labeled somatostatin analog like octreotide is used to detect tumours expressing somatostatin receptors. Lately, gallium-68 (^{68}Ga)-DOTATATE PET/CT has become the preferred imaging modality, due to increased patient satisfaction, high sensitivity (97%), specificity (95.1%) and accuracy (96.6%), as well as decreased radiation exposure (Figure 2) [65]. Gallium-68, is a positron emitter that can be linked to somatostatin analogues and can be localized with positron emission tomography (PET) imaging [66]. (^{68}Ga)-DOTATATE PET/CT contributes to staging the disease, identifying potential lymph node or bone tumour invasion, and detecting previously unknown primary tumours in complex cases [67]. A ^{18}F-fluorodeoxyglucose PET/CT scan is usually employed for imaging of the Grade 3 NETs and poorly differentiated NECs [68]. Combination of (^{68}Ga)-DOTATATE PET/CT and ^{18}F-fluorodeoxyglucose PET/CT at follow-up of GEP-NETs patients is needed, when tumour heterogeneity or co-existence of GEP-NETs with adenocarcinomas is suspected [69].

GEP-NETs: APPROACHES IN MANAGEMENT

The European Society of Medical Oncology [70] and European Neuroendocrine Tumour Society [65–68] have developed an evidence-based approach on the manage-

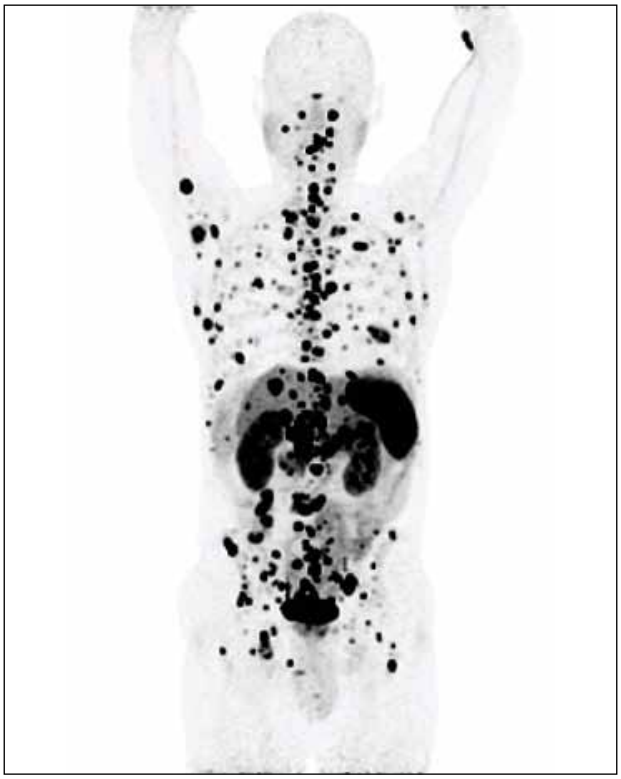

Figure 2. Gallium-68 (68Ga)-DOTATATE PET of a patient with metastatic small bowel NET with multiple hepatic mesenteric and skeletal metastases.

ment of GEP-NETs, including gastric, SI, pancreatic and colorectal NETs which is delineated below. In summary, the main goals of management of GEP-NETs include: a) control of hormonal-related symptoms (in functioning tumours), b) consideration of surgery in localized and sometime in metastatic disease (if technically feasible and clinically appropriate) and c) control of tumour growth with systemic treatments and prolong patients' survival in cases with advanced disease. The selection of treatment is generally affected by the extent of disease (locoregional vs. locally advanced/metastatic) with the latter being the most common presentation, whilst tumour histology and status (stable/progressing), as well as patient's performance status and comorbidities need to be taken into account. Patients should be referred to a Specialized NET Unit. Management decisions should be individualized and made in Multi-Disciplinary-Team meetings, aiming not only to control the disease, but also to improve and maintain patients' quality of life.

1. Management of localized/locoregional disease

Surgery is the treatment of choice for local or locoregional disease in NET G1 and G2. For small bowel NETs (SB-NETs), radical resection in combination with mesenteric lymph node resection is recommended. Surgery may also be considered in cases of locally advanced SB-NETs, for palliative purposes and avoidance of complications like acute/subacute/chronic small bowel obstruction and intestinal ischemia in the presence of a large mesenteric mass [70,71]. For pNETs, surgery is also recommended in locoregional disease, especially in tumours >2cm (standard pancreatectomy, pancreaticoduodenectomy or distal pancreatectomy). Regional lymph node resection should also be considered given high risk for nodal metastases. For non-functioning pNETs <2cm, a conservative watch-and-wait approach may be considered, with yearly imaging [70,71].

In terms of localized gastric NETs, a surveillance approach is recommended for type I, with potential endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) to be considered in tumours ≥10mm. For type II, an individualized treatment approach is recommended, given the possibility of concomitant tumours as part of MEN-1 (e.g. pan-NETs). Local or limited excision can be recommended, however a referral to a NET center of excellence should be strongly considered for further management. For type III, a partial or total gastrectomy with lymph node resection is recommended, given that they are considered to be more invasive than their I and II counterparts [72].

Treatment of colorectal NETs depends on site and size. For colonic lesions of any size, a localized colectomy with lymph node resection should be considered. For rectal NETs, lesions <1 cm can be resected endoscopically, carrying a low risk of developing metastatic disease in the future. Lesions >2cm have a higher metastatic potential and radical surgery (anterior excision) is often recommended. For borderline lesions 1-2cm with unclear metastatic potential, approach is individualized based on certain tumour characteristics like histologic features (e.g. high mitotic index) and disease extent, which can be assessed with a combination of CT/MRI/PET or endoscopic ultrasound (EUS) techniques [73,74].

2. Management of locally advanced/metastatic disease

Management of locally advanced/metastatic disease revolves around the role of systemic treatments with antiproliferative effect and/or symptomatic control of carcinoid syndrome, resection of primary site and/or metastatic deposits, and utilization of locoregional treatments, mainly with palliative intent. Below a summary of ESMO Consensus Guidelines for management of locally advanced/metastatic disease is presented [71].

A. SYSTEMIC THERAPY

Systemic therapy has a dual role in GEP-NETs; it is used not only to inhibit tumour growth (antiproliferative) but also to control symptoms related to hormonal production (antisecretory), and especially carcinoid syndrome (CS) [71].

Antiproliferative treatments

In terms antiproliferative treatment options, SSAs can be considered as first-line especially in slowly-growing G1 and G2 GEP-NETs with Ki-67 up to 10% and demonstrated somatostatin receptor (SSTR) positivity on functional imaging modalities (octreoscan, Ga-Dotatate PET scan). Octreotide and lanreotide are the most commonly utilized SSAs and are mainly used in long-acting formulations, requiring intramuscular administration in 4-week intervals. It should be noted that in patients with stable advanced SB-NETs, low disease burden and very low Ki-67 (<2%) an active surveillance strategy can be considered. Other lines of antiproliferative treatment include IFN-a, which could be considered in patients with midgut NETs, where SSAs have failed or functional imaging shows SSTR-negative

tumours. Everolimus, a selective mTOR inhibitor, is another antiproliferative agent approved by FDA for use on G1 and G2 advanced well-differentiated GEP-NETs and bronchial NETs, progressing on prior treatment lines, based on the results of the RADIANT-1 trial [75]. In addition, sunitinib, a multi-targeted tyrosine kinase inhibitor (TKI), is another option for patients with pNETs progressing on prior lines of treatment, based on the results of SUN 1111. This was a phase 3 randomized control trial comparing sunitinib to placebo in patients with advanced well-differentiated pNETs, with disease progression <12 months before baseline, demonstrating a statistically significant superior median progression-free survival for sunitinib (11.4 months compared to 5.5 months with placebo) [76]. It should be noted that both sunitinib and everolimus are not valid treatment options in G3 tumours.

An important breakthrough regarding the management of advanced GEP-NETs has been the development of peptide-receptor radionuclide therapy (PRRT). PRRT is a targeted form of systemic radiotherapy, utilizing the attachment of a radioactive agent such as Yttrium- 90 or Lutetium-177 to a somatostatin analogue, which then binds to somatostatin receptors of GEP-NETs and directs the radionuclides inside the tumour cells [77]. Based on the results of NETTER-1 trial, a phase 3 randomized controlled trial accruing patients with advanced, progressive, somatostatin-receptor-positive G1 and G2 midgut NETs, 177Lu-DOTATATE plus octreotide LAR demonstrated superior PFS and response rate compared to octreotide LAR alone [78]. 77Lu-DOTATATE is FDA-approved as a second-line therapy for patients with midgut G1 and G2 NETs and disease progression on SSAs. It may also be used in pan-NETs, after failure of approved therapies, as well as in carefully selected patients with NET G3 [71]. Guidelines recommend that PRRT should ideally be used in conjunction with SSAs in patients with functioning NETs and CS to prevent CS flares, which are expected to occur in the setting of PRRT [71].

Systemic cytotoxic chemotherapy is generally advised in NETs G3 of any site. Cisplatin or carboplatin plus etoposide is considered first line in NEC G3. Data on second-line regimens are conflicting and several combinations have been used, mainly extrapolated from the treatment of GI adenocarcinomas [5-FU/leucovorin/irinotecan (FOLFIRI), 5-FU/leucovorin/oxaliplatin (FOLFOX), capecitabine plus temozolomide]. In metastatic disease from G1/G2 pan-NETs regimens like streptozotocin with 5FU can also be considered [71].

Antisecretory treatments

SSAs are the mainstay of antisecretory agents for CS control in GEP-NETs as well as other hormonal syndromes, such as those associated with functional pNETs (VIPomas, glucagonomas). For patients with CS refractory to standard doses of SSAs, next line options include SSA treatment escalation with increased doses or increased frequency of administration, peptide-receptor radionuclide therapy (PRRT) and telotristat ethyl [71]. Telotristat ethyl, a novel inhibitor of tryptophan hydroxylase, which is implicated in the production of serotonin, has been developed, for patients with GEP-NETS and carcinoid syndrome [79]. An international, multicenter, randomized, double-blind, placebo-controlled phase III trial (TELESTAR) reported a reduction of approximately 40% of bowel movements per day using telotristat ethyl doses of 750–1500 mg in those patients [79]. Other antisecretory treatments also specifically target functional pNETs. In the case of insulinoma, which is characterized by excessive production of insulin, diazoxide, a benzothiadiazide derivative that inhibits insulin secretion via ATP-dependent potassium channels in pancreatic β-cells, can be utilized [79]. Similarly, proton pump inhibitors (PPIs) are frequently used to suppress gastric acid hypersecretion in the case of gastrinomas [79].

B. THE ROLE OF SURGERY

Surgery for primary NET site can be considered in the palliative setting for Stage IV NETs, especially in the case of SB-NETs, to prevent or treat complications related to small bowel obstruction and intestinal ischemia. A similar approach can be followed in advanced functional pNETs with uncontrolled hormonal symptoms. On the other hand, surgical removal of metastases has a limited role, and is primarily indicated in the case of liver metastases, in patients with exclusive/predominant liver metastatic disease. Other options for treatment of liver metastases includes liver transplantation, while locoregional liver treatments (e.g. selective internal radiation therapy – SIRT) can be considered a more conservative approach in patients with otherwise rejectable liver deposits, while locoregional liver treatments (as below) can be considered a more conservative approach in patients with otherwise rejectable liver deposits.[71].

C. LOCOREGIONAL TREATMENTS

Locoregional treatments are mainly targeted against liver metastatic deposits, aiming to control liver tumour burden and sometimes also improve symptoms of

carcinoid syndrome. They are divided into two main categories; ablative and transarterial.

Ablative approach

Ablative treatments include radiofrequency, microwave, cryoablation and alcoholization. Of those, radiofrequency ablation (RFA) and microwave ablation are the most commonly utilized in the management of liver metastases. During RFA, liver tumours are ablated with the heat generated from medium-frequency alternating current between 350-500 kHz. Microwave ablation utilizes microwaves, a non-ionizing form of radiation used to generate heat, in order to ablate liver metastatic tissue, and it is an appropriate alternative to RFA [80].

Transarterial approach

Transarterial treatments are directed against highly vascular liver metastases from GEP-NETs, which are mainly perfused by the hepatic artery. The aim is to induce ischemia and necrosis of metastatic liver lesions by occluding their arterial supply. These interventions are performed by accessing the arterial liver circulation via the femoral artery, followed by transarterial embolization (TAE) of the hepatic artery with gelatin beads, often combined with intraarterial administration of cytotoxic chemotherapeutic agents (transarterial chemoembolization, TACE), or drug-eluding beads. (TACE-DEB). Another interesting transarterial approach is the so-called transarterial radioembolization (TARE) with yttrium-90 (Y-90) microspheres which are injected through the hepatic artery to the pre-capillary level of the liver metastases, attaching to the microcirculation and releasing radiation [80].

CONCLUSION

In this review, we delineate in a comprehensive way the latest data on epidemiology, histopathologic features, clinical presentation, diagnosis and management of patients with GEP-NETs. We demonstrated that GEP-NETs are a rather heterogeneous group of tumours with differences as well as many similarities in terms of incidence, diagnostic and therapeutic approach. Patients' management is based on a multi-disciplinary approach and needs to be individualized. Further research is still needed in the field of NETs to further elucidate the pathogenesis of these malignancies as well as define new diagnostic methods and novel treatments in the field.

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