Review paper

Gastroenteropancreatic neuroendocrine tumours – an overview

Guzy neuroendokrynne układu pokarmowego – przegląd

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Abstract

Neuroendocrine neoplasms (NENs) belong to a group of various tumours that can arise on many internal organs. Among NENs a large class of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) can be distinguished, which comprise neoplasms arising from the gastrointestinal tract and pancreas. Therefore, this review provides the current status of the World Health Organization classification of GEP-NETs as well as an overview of their clinical presentation, diagnosis, and treatment methods. GEP-NETs are generally divided into 5 groups: pancreatic NETs (PanNETs), gastric NETs (G-NETs), duodenal NETs (D-NETs), jejunoileal NETs (Je-Ile NETs), and neuroendocrine neoplasms of the large intestine. Moreover, in each group several subtypes have been introduced according to cell differentiation, mitotic rate, and Ki-67 index. Low- and intermediate-grade GEP-NETs are well differentiated, have a mitotic rate under 20, and a Ki-67 index under 20%. High-grade GEP-NETs, however, are characterized by poor differentiation, mitotic rate over 20, and Ki-67 index over 20%.

Streszczenie

Nowotwory neuroendokrynne (NENs) obejmują różnorodne guzy, które mogą powstać w obrębie wielu narządów wewnętrznych. Pośród NENs można wyszczególnić klasę nowotworów neuroendokrynnych trzustki i przewodu pokarmowego, określanych wspólnie jako GEP-NETs. Obecne kryteria klasyfikacji GEP-NETs są nieprecyzyjne i różnią się pomiędzy różnymi źródłami, dlatego celem pracy przeglądowej było opisanie jednoznacznych kryteriów diagnostycznych zaproponowanych przez WHO. Ponadto w artykule zawarto przegląd literatury dotyczący objawów, metod diagnostycznych oraz leczenia GEP-NETs. GEP-NETs zostały podzielone na pięć następujących klas: nowotwory neuroendokrynne trzustki (PanNETs), żołądka (G-NETs), dwunastnicy (D-NETs), jelita cienkiego i krętego (Je-Ile NETs) oraz jelita grubego. W każdej klasie wyróżniono kilka podgrup, opierając się na stopniu zróżnicowania komórek nowotworu, wskaźniku mitotycznym oraz wartości indeksu Ki-67. GEP-NETs niskiego i pośredniego stopnia zaawansowania są dobrze zróżnicowane, mają częstość podziałów poniżej 20, a wartość indeksu Ki-67 to poniżej 20%. GEP-NETs o wysokim poziomie zaawansowania cechują się niskim stopniem zróżnicowania komórek, wskaźnikiem mitotycznym powyżej 20 oraz wartością indeksu Ki-67 powyżej 20%.

Introduction

Neuroendocrine neoplasms (NENs) are a heterogenous group of malignancies originating from cells dispersed throughout the body [1]. Those cells are characterised by 2 properties. The "neuro" property applies to the identification of dense core granules, which are like those in serotonergic neurons, which store monoamines. The "endocrine" property means that they can synthesise and secrete those monoamines [2]. NENs can be well, moderately, or poorly differentiated and have variable metastatic potential. Furthermore, they can be functional or nonfunctional, and if they give symptoms, they can reduce the quality of the patient's life and hence require therapy [3]. Gastroenteropancreatic NETs (GEP-NETs) comprise neoplasms originating from the gastrointestinal tract and pancreatic tissues. GEP-NETs are the second most common tumours among all digestive cancers, and their prevalence is still increasing. The reported annual incidence rate increased from 1.09 per 100,000 in 1973 to 6.98 per 100,000 in 2012 [4, 5]. Because the number of patients who have GEP-NETs is continuously growing, proper diagnostic criteria are needed to perform the correct distinction of GEP-NETs from

Table 1. Classification and grading criteria for neuroendocrine neoplasms of the gastrointestinal tract

Terminology	Differentiation	Grade	Mitotic rate	Ki-67 index
G1 NET	Well differentiated	Low	< 2	< 3%
G2 NET	Well differentiated	Intermediate	2–20	3–20%
G3 NET	Well differentiated	High	> 20	> 20%
SCNEC	Poorly differentiated	High	> 20	> 20%
LCNEC	Poorly differentiated	High	> 20	> 20%
MiNEN	Well or poorly differentiated	Variable	Variable	Variable

Adapted from [13]. MiNEN: Mixed neuroendocrine non-neuroendocrine neoplasm.

other NENs. That is crucial for applying the best treatment to each patient. In this review, we present the current status of the World Health Organization classification of GEP-NETs, as well as an overview of their clinical presentation, diagnosis, and treatment.

Pancreatic neuroendocrine tumours

Epidemiology

Pancreatic neuroendocrine neoplasms (PanNENs) are a heterogeneous group of tumours. They originate from diffuse neuroendocrine cells and account for around 1% to 5% of all pancreatic neoplasms [6]. The incidence of all neuroendocrine neoplasms has increased visibly over the past few decades – for PanNENs it is estimated for 0.8 per 100,000/year [5]. Most PanNENs occur between the fourth and the sixth decade. Up to 7% are related to inherited syndromes, but they mostly arise sporadically. The association between alcohol use and the risk of developing PanNENs is still not clear [7]. Most of the literature suggests that the prevalence of PanNENs is higher in males, but some data show a higher prevalence among females in some regions of the world [7, 8]. A recent increase in incidence seems to be caused by advances in imaging technologies such as positron emission tomography, somatostatin receptor scintigraphy, endoscopic ultrasound, or MRI. Another important reason is the growing awareness of clinicians about PanNENs, which previously caused a lot of confusion [6, 9].

Classification

Proliferation activity is the main aspect used to determine the grade of the tumour. We use mitotic rate and/or Ki-67 proliferation index to grade neuroendocrine tumours (NETs) into well-differentiated NETs and poorly differentiated NECs (neuroendocrine carcinoma). Furthermore, well-differentiated NETs are divided into well-differentiated low-grade NETs (G1), well-differentiated intermediate-grade NETs (G2), or well-differentiated high-grade NETs (G3), whereas NECs are subtyped into small-cell NECs (SCNEC) and large-cell NECs (LCNEC) [10]. The mitotic rate is expressed as the number of mitoses/2 mm^2, and it is assessed by counting in 50 fields of 0.2 mm^2 [11]. Another way to classify PanNENs is to segregate them based on their activity. There are functional PanNENs, able to secrete peptide hormones in amounts leading to clinical syndromes, and it helps to detect them earlier. Functioning PanNENs include insulinoma (35–40% of PanNETs), glucagonoma (5% of PanNETs), somatostatinoma (< 5% of functioning PanNETs), gastrinoma (15% of PanNETs), VIPoma (3% to 5% of functioning PanNETs), serotonin-producing tumours (around 100 cases have been documented), and ACTH-producing tumours (< 150 cases have been documented) [10]. Non-functional PanNENs can secrete some peptides, but they do not give clinical syndromes. In the group of PanNENs there are also mixed ductal–neuroendocrine carcinoma (representing less than 0.5% of all pancreatic ductal adenocarcinomas) and mixed acinar–neuroendocrine carcinoma (account for up to 20% of acinar cell carcinomas) [12, 13] (Table 1).

Clinical presentation

Insulinomas are the most common functional PanNETs. This type of tumour presents itself with hypoglycaemia (plasma glucose < 50 mg/dl), symptoms like weakness, sweating, palpitations, and confusion, and relief after administration of glucose. This set of symptoms is called Whipple's triad [14]. On the other hand, glucagonoma is a rare tumour causing an excess of glucagon. It leads to the typical glucagonoma triad, which includes necrolytic migratory erythema (a rash that most frequently appears during the onset of the disease), diabetes, and weight loss [15]. Somatostatinoma originates from δ cells of the pancreas, which produce somatostatin. Apart from the pancreas, its frequent organ of origin is the duodenum. There is a triad of symptoms, which includes glucose metabolism anomalies, steatorrhoea, and achlorhydria, but it may also present itself with vague symptoms or cholelithiasis [16]. Gastrinoma is the second most common functional PanNET. This tumour is responsible for excessive gastrin production and uncontrolled acid hypersecretion. It causes Zollinger-Ellison syndrome (ZES), which is a severe peptic ulcer disease. Around 25% of cases are associated with multiple endocrine

Table 2. Clinical features of functional pancreatic neuroendocrine tumours

Tumour	Incidence	Secreted hormones	Clinical presentation
Insulinoma	35–40%	Insulin	Whipple's triad
Glucagonoma	5%	Glucagon	necrolytic migratory erythema, diabetes, and weight loss
Somatostatinoma	< 5%	Somatostatin	glucose metabolism anomalies, steatorrhoea, and achlorhydria,
Gastrinoma	15%	Gastrin	Zollinger-Ellison syndrome (ZES)
VIPoma	3–5%	Vasoactive intestinal peptide	Verner-Morrison syndrome, WDHA syndrome
Serotonin-producing tumours	Rare	Serotonin, or other tachykinins	Carcinoid-syndrome
ACTH-producing tumours	Rare	Adrenocorticotropic hormone	Cushing syndrome

neoplasia type 1 (MEN1), an autosomal dominant syndrome caused by a mutation of the MEN1 gene [17]. Vasoactive intestinal peptide tumours (VIPomas) secrete vasoactive intestinal peptide (VIP) in an uncontrolled way leading to a syndrome known as Verner-Morrison syndrome, watery diarrhoea, hypokalaemia, hypochlorhydria or achlorhydria (WDHA) syndrome, and pancreatic cholera syndrome. Because of dehydration and hypokalaemia, lethargy can occur, and in severe cases – cardiac arrhythmias. VIPoma are mostly located in the pancreas but can be found also in other areas, such as the colorectal region or lungs. Five percent of cases are part of MEN1 syndrome [18]. Serotonin-producing tumours originate from either enterochromaffin cells or multipotent precursor cells, which are scattered along the epithelium of pancreatic ducts and among the islet cells. They are extremely rare [19]. This type of tumour may present itself with carcinoid syndrome. Clinical presentation includes mainly diarrhoea, cutaneous flushing, wheezing/asthma-like symptoms, and skin lesions with pigmentation and hyperkeratosis [20]. ACTH-producing tumours are very rare, and they were reported in 15% of patients with ectopic ACTH production. They cause ectopic Cushing syndrome, which presents itself with asthenia and muscle weakness as the expression of proximal myopathy, arterial hypertension and weight gain, centripetal fat distribution, skin striae, and others. Along with ACTH, different hormones like gastrin or insulin can be secreted, leading to manifestations like ZES or insulinoma syndrome [21–23]. Non-functional PanNETs (NF-PanNETs) account for 65% to 90% of PanNETs. They can secrete different products such as chromogranin A, neuron-specific enolase, and pancreatic polypeptide but do not give symptoms. They remain asymptomatic until they lead to metastatic disease or local compression. Then they can manifest with abdominal pain, anorexia, nausea, weight loss, icterus, intraabdominal haemorrhage, or palpable mass. Among non-metastatic NF-PanNETs, up to 50% are diagnosed incidentally. Nearly 10% of NF-PanNETs are associated with genetic syndromes, encompassing MEN1, von Hippel-Lindau disease (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC) [12, 24]. MEN1 is a syndrome inherited in an autosomal dominant manner caused by a mutation of the MEN1 gene. This gene is on chromosome 11q13. It is in general connected with tumours of the parathyroid glands, the pancreatic islet cells, and the anterior pituitary. PanNENs occur in 30–80% of patients with MEN1, and non-functioning PanNETs are among the most common. Gastrinoma is the most common functional PanNET in MEN1 and it may lead to ZES. Insulinomas are the second most common in this category [25]. VHL is an autosomal dominant syndrome, which is caused by the mutation of the VHL gene on chromosome 3. Patients with VHL can develop retinal and central nervous system hemangioblastomas, clear cell renal cell carcinomas (RCC), pheochromocytomas, pancreatic neuroendocrine tumours, and endolymphatic sac tumours (ELSTs). PanNETs are found in 15–56% of VHL patients. Patients with this syndrome can develop different pancreatic lesions, but mostly pancreatic cysts [26]. NF1 is an autosomal dominant condition caused by mutations in the NF1 gene. It is clinically characterised by neurofibromas, café-au-lait spots, Lisch nodules, and freckles in the underarms. PanNETs have been reported in less than 1% of patients with NF1 [27]. TSC is an autosomal dominant multisystemic neurocutaneous genetic condition. Cutaneous manifestations such as hypopigmented macules or facial angiofibromas are most often observed in patients with TSC. However, conditions like epilepsy or renal angiomyolipomas are also frequent [28]. There are few data on the subject, but insulinomas and non-functioning PanNETs have been reported in patients with TSC [27, 29] (Table 2).

Diagnostic work-up

Functional Pan-NETs giving symptoms can be diagnosed by measuring the level of the peptides or hormones they secrete. On the other hand, non-functional tumours are often diagnosed incidentally on cross-sectional imaging [28]. Biomarkers are helpful in the diagnosis of PanNETs. General biomarkers include chromogranin A, neuron-specific enolase, progastrin-releasing peptide, and pancreatic polypeptide. Specific biomarkers are insulin, glucagon, VIP, gastrin, somatostatin, and ectopic hormones. Novel biomarkers are a group created by circulating tumour cells, NETest, microRNAs, and cytokines [30, 31]. Chromogranin A (CgA), considered the most accurate tumour marker in the diagnosis of gastroenteropancreatic NETs (GEP-NETs), is an acidic glycoprotein stored in the dense granules of the NETs, which belongs to the granin family involved in biological pathways controlling protein secretion. It was meant to be a reliable biomarker when it comes to diagnostic value, prognosis prediction, and treatment response evaluation, but it has flaws. Smaller and localized PanNETs tend to exhibit lower plasma CgA levels, and those levels are higher in patients with liver metastases compared with localized disease. However, a direct correlation was reported between the CgA increase and the extent of liver involvement. The specificity and sensitivity depend on factors like the type of assay used, the cut-off value, tumour burden, and organs involved [31, 32]. Neuron-specific enolase (NSE) is an enzyme present in the cytoplasm of neuroendocrine cells and neurons. Elevated NSE levels have been associated with poor tumour differentiation. It has been reported to be elevated in 31–44% of patients with GEP-NETs. Although diagnostic biometrics for NSE is poor, the combination of CgA and NSE in GEP-NETs has a higher sensitivity than either parameter separately [33, 34]. Progastrin-releasing peptide (ProGRP) is a precursor of gastrin-releasing peptide (GRP) that is produced by small cell lung cancer (SCLC). That is why it serves as a biomarker in patients with this type of tumour and is the most sensitive for distinguishing SCLC from other diseases of the lung [35]. In NENs its serum level is associated with tumour grade and provides more information when combined with CgA, NSE, and cytokeratin fragments [30]. NETest is a circulating transcript analysis. It is useful for confirming the disease in blood samples from patients and has proved to be more accurate than CgA in patients with PanNETs [36]. Furthermore, it may be used in the prediction of progression and response to treatment [37]. Circulating tumour cells (CTCs) are released into the bloodstream and are associated with the disease progression and metastases. On the other hand, the absence of CTCs is connected with stable disease [38]. MicroRNAs are non-coding RNAs responsible for the regulation of different biological processes including carcinogenesis. What is particularly important is that in tumour cells they are significantly dysregulated. Overexpression or loss of some miRNAs helps to distinguish PanNETs – they may take part in tumourigenesis [39]. When it comes to cytokines, Interleukin-8, which plays an important role in angiogenesis, is elevated in patients with PanNETs. Furthermore, in patients with a higher level of VEGFR-2 (receptor for vascular endothelial growth factor) overall survival (OS) is decreased [30]. On histological examination well-differentiated PanNETs demonstrate variable one or more organoid growth patterns with nested, trabecular, gyriform, and/or pseudoglandular architecture. The cells can vary in size, and the nuclei are coarse with a 'salt-and-pepper' appearance [40]. Most common genetic alterations are connected with MEN1 (44%), DAXX (death-domain-associated protein), and ATRX (α thalassemia/mental retardation syndrome X-linked) (43%) [41]. Morphologic features that help distinguish PanNECs from well-differentiated PanNETs include expansile large and irregular nests, desmoplastic type fibrosis, and an infiltrative growth pattern with randomly oriented large vascular structures [42]. The most frequently seen genetic alterations include TP53 inactivating mutations in about 60%, mutations in KRAS in 30%, PIK3CA/PTEN in 22%, APC and CTNNB1 in 14%, BRAF in 13%, and RB1 in 8% [41]. Although immunohistochemical examination plays the most important role in the diagnosis of PanNET, imaging can be extremely helpful, especially when it comes to non-functional tumours discovered incidentally. Computed tomography (CT) is the most used procedure, mainly because it is easily available and quick. Magnetic resonance imaging (MRI) has a slightly worse sensitivity in detecting primary PanNETs, at 79% (for CT it is 82%), but it is more sensitive in detecting hepatic metastases – 95.2% for MRI and 78.5% for CT [43, 44]. NETs tend to express somatostatin receptors (SSTRs), which can be targeted by somatostatin analogues for the treatment or localization of the tumour [45]. Radiolabelled somatostatin analogue octreotide (^{111}In-pentetreotide) is used in the visualization of many functional PanNETs and non-functional tumours. ^{111}In-pentetreotide scintigraphy has a sensitivity of 75–100% for the detection of VIPomas, glucagonomas, gastrinomas, and non-functional tumours. The level of expression of somatostatin receptors by insulinomas is not high enough, and they usually remain undetected by this method [14]. 68-Gallium-DOTA peptide positron emission tomography/computed tomography (^{68}Ga-DOTATATE PET/CT) is an imaging modality of high accuracy for NETs when it comes to primary tumours and primary and metastatic GEP-NETs. ^{68}Ga-DOTATATE PET/CT had a detection rate of GEP-NETs of 95.2%, which is significantly greater than ^{111}In- pentetreotide SPECT/CT – 30.9% and anatomic imaging – 45.6%. It is also

Table 3. Genetic syndromes associated with PanNENs

Genetic syndrome	Way of inheritance	Occurrence in patients with PanNENs	Other possible conditions
MEN1	Autosomal dominant	30–80%	Parathyroid tumour, anterior pituitary tumour
VHL	Autosomal dominant	15–56%	Hemangioblastomas, RCC, pheochromocytomas
NF1	Autosomal dominant	< 1%	Neurofibromas, café-au-lait spots, Lisch nodules
TSC	Autosomal dominant	Rare	Hypopigmented macules, facial angiofibromas, epilepsy

better in detecting disease in patients without biochemical evidence of GEP-NETs [45, 46]. Endoscopic ultrasonography (EUS) is the most sensitive modality for detecting small PanNETs. EUS has a pooled sensitivity of 87–97% and a specificity of 98% for detecting a PanNET. When it comes to small lesions it is generally better than CT. It also allows the detection of lymphadenopathy and features of the lesion like depth and invasiveness [47]. It was reported that EUS is more sensitive than MRI. However, the significance of EUS depends on the experience and individual skills of the endosonographer because it is a subjective modality [48] (Table 3).

Treatment

Surgical resection is the only curative option for many patients with PanNETs. In general, it is preferred when there are no contraindications and no diffuse metastatic disease [12]. However, there is still the problem of considerably high morbidity in patients who have undergone pancreatic operations. That is why some tumours should be resected but others not – the main criterium is the size of the tumour. Several studies suggest different margins [49, 50]. Currently, the approach is to resect tumours larger than 2 cm in patients without metastatic disease or any comorbidity that would complicate it. Patients with tumours smaller than 1 cm are under observation with close interval surveillance [51]. Enucleation is a surgical technique preferred for small, superficial, and benign lesions with a particular margin to the pancreatic duct [52]. Central pancreatectomy is an alternative for enucleation, because it decreases the risk of postoperative endocrine and exocrine insufficiency [51]. NETs can lead to metastasis, especially to the liver, and for those patients the only curative option, which prolongs OS, is hepatectomy. A meta-analysis proved that liver resection provides higher 1-, 3-, and 5-year survival rates, postoperative symptom relief rate, and longer median survival [53]. Another option is local ablation. Techniques like radiofrequency ablation, microwave ablation, and cryotherapy have the same effectiveness as surgical resection for lesions smaller than 3 cm [30]. Liver-directed transarterial embolization (TAE), transarterial chemoembolization (TACE), and selective internal radiation therapy (SIRT) are treatment modalities that are useful in patients with diffuse metastases. TACE is reserved for patients with PanNETs [54]. The ability to express SSTRs by NETs is used not only in imaging but also in therapy. Somatostatin analogues (SSAs) (octreotide and lanreotide) are accepted as the first-line treatment in advanced and progressive PanNETs. Based on the two-phase III randomized, double blind, placebo-controlled studies PROMID and CLARINET, National Comprehensive Cancer Network (NCCN) guidelines recommend the use of lanreotide or octreotide LAR in the first line for relief of symptoms and tumour control in patients with PanNETs expressing SSTRs. Both studies suggest prolonged PFS in patients on SSAs therapy [55, 56]. Targeted therapy inhibiting angiogenesis is another approved method of treatment that uses everolimus and sunitinib. The first one is an oral inhibitor of the mammalian target of rapamycin (mTOR). In the randomized, phase III RADIANT-3 study patients with advanced, progressive PanNET were treated with everolimus. This study showed a median OS of 44.0 months and the prolongation of survival by 6.3 months among those patients [57]. Sunitinib is a small-molecule tyrosine kinase inhibitor targeting VEGFRs, PDGFRs, and KIT. In a phase III randomized study a 6.8-month improvement in median PFS was reported with sunitinib compared with placebo in patients with progressive, well-differentiated PanNET. Furthermore, the improvement of OS in the sunitinib arm, compared to the placebo arm, was 9.6 months [58]. Peptide receptor radionuclide therapy (PRRT) is a targeted treatment inducing tumour cell death by using radiation. PRRT agents consist of a chelator that is attached to an SSTR ligand, and the radionuclide, such as Lutetium-177 (^{177}Lu), is bound by the chelator. The ligand will bind to SSTRs on the tumour cells, and β-emission of these PRRT agents effectively targets toxicity to NET [59]. In a study in which patients with PanNETs were treated with [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate (^{177}Lu-DOTATATE) a median PFS and median OS of, respectively, 30 months and 71 months were reported The results of this study suggest that PRRT is an excellent therapy for patients with advanced GEP-NETs [60]. Chemotherapy is an option against more aggressive tumours and those of a heavy tumour burden. Chemotherapy agents include alkylating agents (streptozocin, temozolomide, dacarbazine) and plati-

num agents [56]. Streptozocin is selectively toxic to β cells of the pancreas. In a study conducted on a group of patients (99.1% of them had metastases) the objective response rate (ORR) was best in those with NET G2, whole ORR of NET G1 + G2, and G3 was slightly lower [61]. Temozolomide is another alkylating agent, a prodrug of dacarbazine. A retrospective study on 138 patients with well-differentiated PanNETs has shown a median OS of 47.6 months and a median PFS of 21.4 months [62]. Cisplatin is a platinum agent that appears to be effective only in patients with G3 NETs. On the other hand, the activity of oxaliplatin-based regimens is higher in advanced PanNETs [63]. A multicentre retrospective study evaluated the efficacy of oxaliplatin-based chemotherapy. The ORR was 26%, and specifically for patients where the pancreas was the site of the primary tumour, the median OS was 2.64 years and median PFS was 0.81 years [64]. Cancer immunotherapy is a relatively new strategy. The immune checkpoint-based therapy targeting programmed death protein one (PD-1) and programmed death-ligand 1 (PD-L1) is already used in treating lung, renal cancer, and melanoma, and the growing demand for new therapeutic options for patients with NENs is an encouragement for new research [65]. When it comes to PanNETs, expression of PD-L1 was observed in just 7.4% of them, and expression of PD-1 is also uncommon. In contrast, expression of PD-L2 was observed in 97% of NETs located in the pancreas. Both PD-L2 and PD-L1 bind to the PD-1 receptor, so the expression of PD-L2 is promising, and the use of PD-1 inhibitors may have therapeutic benefit [66].

Gastric neuroendocrine tumours

Epidemiology

Gastric neuroendocrine tumours (G-NETs) arise mainly from enterochromaffin-like cells (ECL) of the gastric mucosa and are responsible for less than 2% of all gastric neoplasms [67]. They have a higher incidence among obese patients, and in contrast to other gastrointestinal NETs, they are typically non-functional neoplasms [68]. Their annual incidence is estimated at 0.5 per 100,000, and it increased 15-fold from 1973 to 2012 [5].

Classification

The classification of gastroenteropancreatic neoplasms (GEP-NENs) presented by the World Health Organisation, including gastric neuroendocrine neoplasms (G-NENs) is presented in Table 1. Furthermore, G-NETs are generally divided into 3 types based mostly on their clinical presentation, pathophysiology, aggressiveness, and prognosis. Moreover, type IV with similar features to type II is described; however, its existence as a separate type is under debate [68].

Clinical presentation

Type I G-NETs are the most common, accounting for about 70–80% of all G-NETs and being more prevalent in women. They are mostly confined to the mucosa or submucosa and are usually small and multiple [69]. This type of G-NET is associated with chronic atrophic gastritis, which leads to progressive loss of parietal cells, which causes achlorhydria. That subsequently stimulates the production of gastrin causing hypergastrinaemia, which is an appropriate reaction to the decreased level of HCl. The excessive amount of gastrin induces hypertrophy and hyperplasia of the ECL cells. It eventually leads to the appearance of numerous small lesions [67, 68]. Reduction of the intrinsic factor leading to the decreased absorption of vitamin B_{12} may cause deficiency of this vitamin and pernicious anaemia [67, 69]. Type II G-NETs are responsible for 5–10% of G-NETs and are mostly found in patients with MEN-1 syndrome, which causes Zollinger-Ellison syndrome [68, 70]. Even though they have features common with type I tumours, they tend to be more aggressive and with higher risk of metastatic disease. Their occurrence is equal in men and women [69]. Similarly, to type I, in type II G-NETs hypergastrinaemia also occurs [68]. Type III G-NETs account for about 10–20% of G-NETs and are more prevalent in men. They are usually singular lesions ranging from 2 to 5 cm in size. As opposed to type I and type II, the prognosis is poor [67, 69]. Another difference is the lack of hypergastrinaemia and normal acid production in type III. They are frequently aggressive and tend to present lympho-vascular invasion or infiltration beyond the submucosal layer [71]. Carcinoid syndrome may also occur with this type [67]. Type IV tumours are poorly differentiated lesions and are thought to be the most aggressive [72]. Most rare G-NETs, in contrast to other types, are of non-ECL cell origin. Hypergastrinaemia is present in one-third of cases. They can be found anywhere in the stomach and are usually greater than 4 cm in size. The prognosis is exceptionally poor [73].

Diagnostic work-up

Esophagogastroduodenoscopy (EGD) with biopsy remains the gold standard in diagnosing G-NETs [74]. Additionally, gastric pH and fasting gastrin levels should be measured in every patient diagnosed with this tumour. This diagnostic scheme helps in subtyping and selecting accurate treatment options [68]. Type I tumours are presented as small, reddish polyps with pale, yellowish, and transparent blood vessels, contrasting with the smooth and red mucosa of regular areas. Atrophy of the mucosa cells, hyperplasia of neuroendocrine cells, and absence of parietal cells are visible on the histological examination. Furthermore, parietal cell antibodies and/or intrinsic factor

antibodies may be present with high gastric pH (≥ 7). When it comes to type II G-NETs, in EGD hypertrophic gastric mucosa is detected. In contrast to type I, the gastric pH is low. Type III tend to be visualised as solitary lesions with normal mucosa [70]. Serum gastrin levels are elevated in both type I and II, whereas in type III they should be normal. Measurement of serum biomarkers such as CgA, histamine, and serotonin can also be helpful in diagnostic workup. CgA is the most used biomarker for the diagnosis of GEP-NETs. However, it can also be elevated in tumours other than NETs, in cardiovascular disease, renal disease, and in patients using drugs such as proton pump inhibitors (PPIs) and others [75]. Imaging techniques are also used in diagnostic procedures. EUS is used in patients with types I and II to estimate the depth of invasion, to decide whether a patient might benefit from endoscopic treatment. In patients with type III EUS is used to assess the presence of regional lymph node involvement [76]. CT scan is a modality recommended for patients with G-NETs type I and II larger than 2 cm, for those with type III, and if the tumour is proven to be invasive on EUS. ^{68}Ga-DOTA PET/CT has already been proven to be superior to other commonly used imaging modalities, and its high sensitivity is particularly useful for identifying patients with metastatic disease [45] (Table 4).

Treatment

The main features that should be taken into account when selecting a proper method of treatment of GNETs are the type of tumour, its size, the number of lesions, the presence of infiltration of the muscular wall, and metastases [77]. Today, staging systems focus more on the size of the tumour, depth of invasion, and metastases, and the importance of the type of tumour is being neglected, even though it is essential in determining the best treatment strategy [78]. In general, for type I G-NETs, endoscopic management is recommended. Tumours smaller than 1 cm are managed by regular endoscopic follow-up or can be removed endoscopically. When there are 6 or fewer lesions measuring 1 to 2 cm, either endoscopic resection or surveillance with EGD is recommended every 3 years. In the case of 6 or fewer tumours greater than 2 cm, the proposed management includes endoscopic resection if possible or surgical resection. Finally, when more than 6 tumours greater than 2 cm are present, surgical resection is the only option [79]. Nonsurgical management requires endoscopic surveillance, which may be a source of discomfort for patients. Antrectomy is an option that, by removing gastrin-producing G-cells, reduces hypergastrinaemia, so it targets the source of the disease. In antrectomy patients the risk of recurrence is lower, and the surveillance does not need to be as frequent as in patients who receive endoscopic resection. However, antrectomy may lead to complications like anastomotic leaks. Strictures can also develop, causing vomiting, nausea, and bloating [80]. As has already been mentioned, type II G-NETs have a higher risk of metastases than type I, which is why all such lesions should be resected. In the case of lymph node involvement or metastases, surgery is preferred, but for localized tumours endoscopic resection is enough [81]. Type III G-NETs, having high risk of metastasis, generally should not be managed endoscopically. Surgical resection including partial or total gastrectomy with nodal dissection is recommended for those tumours. However, it has been reported that type III tumours smaller than 2 cm and small, well-differentiated (G1) type III GNETs could be managed by endoscopic treatment [77]. As for localized type IV G-NETs, partial or total gastrectomy and regional lymph node dissection with subsequent chemotherapy is suggested [73]. Although surgical or endoscopic resection may be the treatment of choice in most cases of G-NETs, there are some situations in which a different approach should be considered. For instance, patients with type I, in cases of recurrent disease, may benefit from SSA treatment. SSAs can decrease ECL cell hyperplasia and inhibit proliferation of the tumour cells. A prospective study conducted on a small group of patients treated with SSAs for

Table 4. Types of gastric neuroendocrine tumours

Variable	Type I	Type II	Type III	Type IV
Distribution	70% to 80% of all G-NETs	5% to 10% of all G-NETs	10% to 20% of all G-NETs	Most rare
Cell of origin	ECL	ECL	ECL in most cases	Non-ECL
Gastrin status	Hypergastrinaemia	Hypergastrinaemia	Normogastrinaemia	Hypergastrinemia – one-third of cases
Concomitant conditions	Pernicious anaemia	Zollinger-Ellison syndrome	Carcinoid syndrome	
Treatment	Endoscopic management, surgical resection, SSAs, netazepide	Endoscopic management, surgical resection	Surgical resection preferred, chemotherapy	Partial or total gastrectomy and nodal dissection, followed by chemotherapy

12 months revealed that it is an effective treatment for recurrent disease. Regression of the tumour was reported in all patients, and this effect persisted after discontinuance of the treatment [82]. Another option for type I is gastrin/CCK2R antagonist netazepide. This drug inhibits a gastrin-regulated signalling pathway causing regression of the tumour [83]. When it comes to type II tumours proton PPIs can be used as a therapy for excessive acid production, which leads to peptic ulcer disease, but long-acting SSAs have also been used [81]. For type III G-NETs, when surgical resection is not possible because of metastases, systemic chemotherapy is recommended [84]. Treatment of advanced NETs can be problematic. One of the strategies is everolimus treatment. In a randomised study conducted on patients with advanced, progressive NETs of lung or gastrointestinal origin, treated with this mTOR, inhibitor median progression-free survival (PFS) was prolonged by 7.1 months compared with placebo, which was a 2.8-fold improvement [85]. In the case of carcinoid syndrome SSA octreotide and lanreotide are used to reduce the symptoms, and they also demonstrate antitumour activity [86]. For metastatic disease, targeted radionucleotide therapies and systemic chemotherapy can also be used [73].

Duodenal neuroendocrine tumours

Epidemiology

Duodenal neuroendocrine tumours (D-NETs) arise from the enterochromaffin cells and comprise about 2–3% of gastrointestinal NETs (GI-NETs) [87]. In the United States the incidence is 0.19 per 100,000. In England the prevalence is 0.04 per 100,000, and in Japan it is 0.17 per 100,000 [77]. They tend to appear around the 6th decade of life and appear slightly more frequently in men than in women [88, 89].

Classification

The classification of D-NETs is given in Table 1. The types of D-NETs include gastrinomas, somatostatinomas, gangliocytic paragangliomas, non-functioning D-NETs, and duodenal carcinomas [90].

Clinical presentation

In general, D-NETs are small lesions without mucosa and submucosa crossing; however, regional lymph node invasion is observed in 40–60% of cases. Less than 10% of patients are reported with liver metastases [91]. D-NETs may be connected with MEN-1, and if functional, they might release excessive levels of gastrointestinal hormones like gastrin [92]. Gastrinomas can be located in various locations of the body, but 70% of them are found in the duodenum. Furthermore, they are the most common among functional D-NETs (48%) [88]. Patients present with gastric acid hypersecretion, which leads to ZES. Features of this syndrome include severe peptic ulcer disease or gastroesophageal reflux disease (GERD) [93]. Another type is somatostatinoma; the duodenum area is involved in 19% of such tumours, and generally it is connected with anaemia and gastrointestinal haemorrhage. In addition, duodenal somatostatinoma is associated with NF1, TSC, and VHL [16]. Gangliocytic paragangliomas are rare tumours mostly occurring in the second part of the duodenum. They can present with gastrointestinal bleeding and subsequent anaemia caused by ulceration, or abdominal pain. Those tumours may also remain asymptomatic [73]. Most D-NETs are non-functional and are usually classified as solitary lesions [79]. Lastly, duodenal carcinomas tend to appear in the ampullary region, and they are known for their poor prognosis [90]. Symptoms include nausea, vomiting, abdominal pain, and gastrointestinal bleeding, although the lesions might develop asymptomatically [73].

Diagnostic work-up

Although D-NETs are mostly diagnosed incidentally, sometimes patients present symptomatic disease [94]. Similarly to gastric neuroendocrine tumours, EGD with biopsy is the best method in detecting D-NETs [79]. They are usually visualised as singular lesions with a mean size of approximately 1.2–1.5 cm, but when multiple, it should suggest the potential presence of MEN-1 in the patient [94]. After gaining the material, a histological examination should be performed. Gangliocytic paragangliomas usually show an admixture with an epithelial endocrine component with gangliocytic and spindle cell components. Gastrinomas are presented with well-defined gyriform trabeculae, often with vascular pseudorosettes. Somatostatinomas show tubular-acinar structures, possibly with intraluminal psammoma bodies. Gastrin cells are frequently present in non-functioning D-NETs [88]. When it comes to biomarkers, chromogranin A is measured as in other gastrointestinal NETs. Despite considerably high sensitivity, the specificity is low, ranging from 10% to 35%, and so it should be used with caution [95]. EUS is a modality used to assess the presence of locoregional lymph node metastases, and thus to check whether endoscopic resection is the correct management [76]. Other options include CT or MRI for patients with advanced disease [77]. ^{68}Ga-DOTATATE PET/CT is used particularly to identify patients with metastatic disease [45].

Treatment

The decision about the management is made mainly based on the tumour size. For non-ampullary D-NETs smaller than 1 cm, endoscopic removal is recommended. Those ranging from 1 cm to 2 cm can be

managed by surgical resection as well. Lesions larger than 2 cm and those with resectable liver metastases or suspected lymph node metastases require formal oncological surgical resection and systematic lymphadenectomy. Ampullary and periampullary tumours are thought to be more aggressive, and pancreaticoduodenectomy (PD) with lymphadenectomy should be performed [96]. After resection, surveillance using EGD every 2 years is recommended [94]. In a study conducted on patients with Pan-NETs and D-NETs who underwent PD, the 5-year OS was 79.5% for the latter. Those with D-NETs were also more likely to recur early (within 2 years) than those with Pan-NETs [97]. Another study has shown that regardless of tumour size, endoscopic, local, or anatomic resection is associated with improvement in OS. The 5-year OS for the whole cohort was 76%, but in patients who underwent resection it was improved [89]. Patients with functional tumours might need drug therapy to manage hormone excess. To control gastric acid hypersecretion in patients with ZES, the drugs of choice are PPIs. SSAs can be used as well to reduce gastrin levels [92]. For patients with advanced metastatic disease, treatment options encompass SSAs, everolimus or sunitinib, interferon-a, PRRT, or chemotherapy [88].

Jejunoileal neuroendocrine tumours

Epidemiology

Jejunoileal neuroendocrine tumours (Je-Ile NETs) are rare neoplasms arising from serotonin-producing enterochromaffin cells [98]. The estimated incidence is 0.67 per 100,000, and men are affected more frequently than women. Furthermore, the black race is more likely to develop this tumour. The median age of diagnosis is 64 years [99].

Classification

The classification of Je-Ile NETs is presented in Table 1.

Clinical presentation

Je-Ile NETs are usually found in the terminal ileum [100]. It is estimated that 11% of them are present in the jejunum and rarely appear in Meckel's diverticulum [101]. These tumours frequently lead to metastases. Patients with primary tumours larger than 2 cm experience lymphatic metastases in 80% of cases. They tend to present with typical desmoplastic reaction in the intestinal mesentery [102]. It may eventually lead to bowel obstruction or bowel ischaemia, and in effect, to abdominal pain [99, 102]. When the superior mesenteric vein is involved, it might cause venous ischaemia leading to cachexia and malnutrition. Other areas may also be affected, leading to different conditions. For instance, in the case of retroperitoneal fibrosis, patients might develop obstructive uropathy, scleroderma, or fibrosis of the bladder [103]. Patients with desmoplastic reaction more frequently show distant metastases, mostly in the liver [102]. It is also associated with significant morbidity and mortality [103]. Furthermore, symptoms can be caused by carcinoid syndrome or the obstruction caused by the tumour itself [99]. It is estimated that 20% of patients with carcinoid syndrome are affected by carcinoid heart disease. It usually leads to fibrosis of the right-sided cardiac valves, causing tricuspid regurgitation, and when pulmonary valve is affected, mixed regurgitation and stenosis [104].

Diagnostic work-up

Imaging plays a pivotal role in the process of diagnosis and selection of the proper treatment. Primary tumours tend to be small and multifocal, which makes them hard to visualise. On the other hand, on CT mesenteric lymph node metastases present as spiculated masses, sometimes with calcifications [105]. MRI can also be used; however, CT more effectively detects anatomical details that are important from a surgical point of view. For better staging of the tumour in terms of metastases, somatostatin receptor scintigraphy (SRS) and ^{68}Ga-DOTATATE PET/CT are needed. Furthermore, even when the patient does not present any symptoms associated with carcinoid syndrome, levels of 24-hour urinary 5-hydroxy indole acetic acid (5-HIAA) should be evaluated [106]. 5-HIAA is a principal metabolite of serotonin, and quantification of its urinary excretion is 73% sensitive and 100% specific for detecting advanced NETs in the small intestine [75]. In the case of carcinoid heart disease, the most common method of evaluation is echocardiographic imaging. Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) is also used to assess heart failure [107].

Treatment

Patients with tumours located in the proximal jejunum and ileum generally undergo segmental small intestinal resection. When the primary tumour is located in the distal ileum close to the ileocecal valve, right hemicolectomy or ileocecal resection is performed [108]. Regarding liver metastases, when unresectable liver disease is present, patients may benefit from surgical debulking [109]. Another appropriate method for metastatic disease is SSA therapy. It inhibits tumour growth and is effective in controlling carcinoid syndrome. For patients with signs of carcinoid heart disease and with high levels of urine 5-HIAA, telotristat ethyl can be considered [107]. Another option for patients with metastases or with locally advanced tumours is ^{177}Lu-Dotatate, which is a peptide receptor radionuclide therapy. In a study the response rate

was 18% in ^{177}Lu-Dotatate group, while in the control group it was 3%, and the OS was longer with ^{177}Lu-Dotatate than with SSA-high-dose octreotide LAR [110].

Large intestine neuroendocrine tumours

Epidemiology

Neuroendocrine carcinoma of the large intestine and rectum accounts for less than 1% of all colorectal cancer cases. In the United States the incidence of colon and rectum NENs is, respectively, 0.3 and 1.1 per 100,000 people, and unfortunately these numbers have been increasing in the past decades. Colonic NENs are more common in women in the United States, and rectal NENs have highest incidence among Asians and black people [111, 112]. NENs of the rectum, appendix, and colon comprise 20%, 16%, and 11%, respectively; thus, NENs of the large intestine represent nearly half of all gastrointestinal NEN cases [73]. Considering NENs of the colon, more than 60% of them are located in the caecum, nearly 8% in the ascending colon, 5% in the transverse colon, and 25% in the descending colon or sigmoid. Rectal NENs are usually positioned in the rectum, but they are also found in the rectosigmoid [113].

Classification

Generally, NENs of the large intestine are partitioned into colorectal tumours and appendiceal neuroendocrine neoplasms (ANENs). The classification of colorectal neuroendocrine neoplasms is presented in Table 1. G1 tumours have light colour, almost no vessels, and they may possess spots on the surface. Neoplasms from G2 are characterized by a darker tint compared to the surrounding tissue and the presence of white structures on their surface. These white structures are encompassed by brown vessels. G3 colorectal tumours have got a dim colouring, disrupted vessels, together with amorphous surface pattern [114, 115]. Colorectal NECs are poorly differentiated and include SCNEC and LCNEC type. Most MiNENs are poorly differentiated, and the neuroendocrine component has a proliferation rate in the same range as other NECs, but one or both of the neuroendocrine and non-neuroendocrine components may also be well differentiated [13].

Clinical presentation

The symptoms of NECs are nonspecific and include haematochezia, abdominal pain, changes in bowel habits, anaemia, weight loss, abdominal distention, and obstruction. The carcinoid syndrome is usually absent because most NECs are nonfunctional. Unfortunately, at the date of diagnosis the tumour is large and advanced in most of cases [116]. Colorectal NETs have similar clinical presentation. Most patients are asymptomatic, which delays diagnosis. Rectal NENs can also cause anorectal discomfort and pruritus ani. About 10% of colorectal NENs induce a carcinoid syndrome, which results in diarrhoea, hot red flushing in the face, palpitations, and asthma attacks [112]. The symptoms of ANENs are acute appendicitis and abdominal pain located in the right lower quadrant [115].

Histopathology

Colorectal neuroendocrine neoplasm cells express CgA and synaptophysin. Colorectal NENs present a mean Ki-67 proliferative index of 21%, and the majority of these tumours are well-differentiated (type 1 and 2). The staining of poorly differentiated neoplasms for synaptophysin or CgA is less intense compared to that of well-differentiated tumours [116, 117]. Colorectal NECs are morphologically similar to neuroendocrine carcinoma of the lung, and they can be large or small cell carcinomas. Small cell NECs arise from the squamous mucosa from the anal canal, and large cell NECs from the glandular mucosa of the large intestine [118]. Small cell NECs possess cells with minimal amounts of cytoplasm as well as granular nuclear chromatin, and these cells form ribbon-like structures. Well-differentiated colorectal NETs form trabecular, insular, or ribbon-like cell clusters, and have no or little cellular pleomorphism and sparse mitoses [119]. Colorectal neuroendocrine carcinomas frequently possess BRAF gene (B-Raf proto-oncogene, serine/threonine kinase gene) mutations, which is associated with a poorer prognosis. NECs also present a high Ki-67 index (> 60%) [120]. Most ANENs are well-differentiated and have a low Ki-67 index, i.e. < 20%. Rare appendiceal neuroendocrine carcinomas present the same histological characteristics as the other gastrointestinal NECs [115].

Diagnostic work-up

CgA and synaptophysin are protein markers used to diagnose patients with colorectal neuroendocrine neoplasms. Patients with this tumour have elevated plasma CgA levels and test positive for synaptophysin [117]. Also, NSE and histochemical stains of Fontana-Masson or Grimelius are also used as markers. To confirm the diagnosis, tumour cells are routinely stained with haematoxylin and eosin as well as immunohistochemical and histochemical stains [121]. Colorectal NECs should be analysed for immunohistochemical expression of mismatch repair (MMR) proteins. It was shown that early-stage MMR-deficient NECs have a better prognosis compared with MMR-proficient NECs. According to the Royal College of Pathologists in the United Kingdom, MMR protein expression status is a core data item of the histopathology report [118]. MicroRNAs are very promising markers in diag-

nosing colorectal NENs. It was found that microRNA *MiR-186* is downregulated in these tumours, and it causes PTTG1 gene (pituitary tumour-transforming 1 gene) overexpression. This leads to a greater invasiveness of colorectal NENs [39]. Colorectal NEN imaging includes CT, which can be useful in differential diagnosis between colorectal NETs and NECs. Compared to colorectal NETs, NECs are large ulceroinfiltrative neoplasms without intact overlying mucosa. Patients with NECs also have enlarged lymph nodes and liver metastasis [122]. Patient with colorectal NETs can be diagnosed by endocytoscopy, which enables real-time endoscopic assessment of the histology [123].

Treatment

Colonoscopy is an effective method for the prevention and early diagnosis of colorectal NENs. The main treatment for local or locoregional gastrointestinal NETs is surgery [3]. Although surgery is performed to treat colorectal NENs, resection of the primary tumour is not associated with improved survival [124]. A combination of surgery and chemotherapy in colorectal NECs treatment is better than using these methods independently; however, the 5-year survival remains low at 37%. Colorectal NEC chemotherapy includes platinum-based agents, and it is associated with better survival for patients with both localized and metastatic disease [125]. First-line chemotherapy contains combinations of cisplatin/carboplatin combined with etoposide or irinotecan/cisplatin and oxaliplatin-based therapies. Second- and third-line NEC treatment with Ki-67 < 50% consists of temozolomide alone or with capecitabine/bevacizumab [126]. Patients with metastatic rectal NENs are cured with everolimus, octreotide, and somatostatin analogues. Appendiceal NEN treatment methods vary with tumour size. Appendectomy is performed when the neoplasm size is less than 1 cm and if the size is 1–2 cm, then, as well as appendectomy, periodic post-operative follow-up is recommended for 5 years. Right hemicolectomy should be used when the tumour measures above 2 cm [73]. Recent studies have shown that the $BRAF^{V600E}$ mutation is a promising target for colorectal NEC therapy. This mutation results in more intense mitogen-activated protein kinase (MEK) phosphorylation, so MEK can also be a target for future treatment [127]. The therapy can also target the tumour microenvironment (TME). GEP-NET therapy destinations include the formation of enrichment vascular supply in TME, the role of tumour stroma, immune cells, and cancer associated fibroblasts [128]. Table 5 presents recent clinical trials of promising colorectal NET treatment options.

Conclusions

In general, GEP-NETs comprise tumours derived from gastrointestinal and pancreatic cells. They constitute a serious problem in healthcare because they are the second most common neoplasms among all digestive cancers, and their prevalence is still increasing [3]. The diagnosis of GEP-NETs is made based on various imaging methods like CT, MRI, and PET, as well as laboratory tests. The latter include measurement of 5-hydroxyindoleacetic acid in urine and evaluation of

Table 5. Clinical trials for colorectal NETs

Sponsor	Treatment	Condition	Results
National Cancer Institute (NCI)	Octreotide acetate in combination with recombinant interferon α-2b or bevacizumab	Colorectal NET G1	Patients who have taken octreotide acetate in combination with bevacizumab had better complete and partial response to the treatment than patients who were treated with octreotide acetate in combination with recombinant interferon α-2b
Sichuan Huiyang Life Science and Technology Corporation	Artificial recombinant super-compound interferon (rSIFN-co)	Colorectal NET	Estimated study completion date is December 2022
University of Sao Paulo	Stereotactic body radiation therapy (SBRT)	Unresectable liver metastases in patients with gastrointestinal NETs	Estimated study completion date is May 2021
Nanfang Hospital of Southern Medical University	Cap endoscopic mucosal resection (EMR-C) versus endoscopic submucosal dissection (ESD)	Rectal NET less than 10 mm	Estimated study completion date is 20 December 2021

chromogranin A levels in the blood. Currently, surgical treatment is the best option for GEP-NET patients [129]. However, recently novel therapeutic approaches have been introduced. Some of them are based on targeted radionuclide therapy, which uses radiolabelled drugs. These medicines include ^{177}Lu-DOTATATE, which was proven to be effective, especially in gastroenteropancreatic NET treatment [130]. The future targets of NEN treatment will also be genome and DNA alterations because many of the neuroendocrine neoplasms present epigenetic changes [131].

Conflict of interest

The authors declare no conflict of interest.

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