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**Recent advances in diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms**

Dai M *et al.* Diagnosis and treatment advances for GEP-NENs

Meng Dai, Christina S Mullins, Lili Lu, Guido Alsfasser, Michael Linnebacher

**Meng Dai, Christina S Mullins, Lili Lu, Michael Linnebacher,** Clinic of General Surgery, Molecular Oncology and Immunotherapy, Rostock University Medical Center, 18057 Rostock, Germany

**Guido Alsfasser,** Clinic of General Surgery, Rostock University Medical Center, 18057 Rostock, Germany

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**Corresponding author: Michael Linnebacher, PhD, Academic Fellow, Research Fellow, Research Scientist, Senior Researcher, Senior Scientist,** Clinic of General Surgery, Molecular Oncology and Immunotherapy, Rostock University Medical Center, Schillingallee 35, Rostock 18057, Mecklenburg-Vorpommern, Germany. michael.linnebacher@med.uni-rostock.de

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**Abstract**

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a rare group of tumors originating from neuroendocrine cells of the digestive system. Their incidence has increased over the last decades. The specific pathogenetic mechanisms underlying GEP-NEN development have not been completely revealed. Unfunctional GEP-NENs are usually asymptomatic; some grow slowly and thus impede early diagnosis, which ultimately results in a high rate of misdiagnosis. Therefore, many GEP-NEN patients present with later staged tumors. Motivated hereby, research attention for diagnosis and treatment for GEP-NENs increased in recent years. The result of which is great progress in clinical diagnosis and treatment. According to the most recent clinical guidelines, improved grading standards can accurately define poorly differentiated grade 3 neuroendocrine tumors and neuroendocrine carcinomas (NECs), which are subclassified into large and small cell NECs. Combining different functional imaging methods facilitates precise diagnosis. The expression of somatostatin receptors helps to predict prognosis. Genetic analyses of mutations affecting death domain associated protein (*DAXX*), multiple endocrine neoplasia type 1 (*MEN 1*), alpha thalassemia/intellectual disability syndrome X-linked(*ATRX*), retinoblastoma transcriptional corepressor 1 (*RB 1*), and mothers against decapentaplegic homolog 4 (*SMAD 4*) help distinguishing grade 3 NENs from poorly differentiated NECs. The aim of this review is to summarize the latest research progress on diagnosis and treatment of GEP-NENs.

**Key Words:** GEP-NENs; Functional imaging; Peptide receptor radionuclide therapy; Targeting agents; Immune checkpoint inhibitors; Genetic mutations

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**Core Tip:** Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a group of heterogeneous tumors arising from neuroendocrine cells of the digestive system. Researchers have achieved great improvements in diagnosis and treatment. This includes improved grading, identification of specific genetic mutations, functional imaging, and broad application of peptide receptor radionuclide therapy. Here, we systematically summarized the latest progress in diagnosis and treatment of GEP-NENs, thereby providing guidance for clinicians active in this field.

**INTRODUCTION**

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) originate from neuroendocrine cells of the pancreas or the gastrointestinal tract. They represent the second most common cancer of the digestive system (Figure 1)[1]. The Surveillance, Epidemiology, and End Results (commonly known as SEER) 18 registry (2000-2012) revealed an increased incidence of GEP-NENs in the United States to 3.56/100000 inhabitants in the year 2012[2]. In European countries, the incidence also increased and was reported to be in the range of 1.33 to 2.33/100000 inhabitants[3,4]. Improvements in the detection methods have been identified as the most probable explanation for the increased incidence of GEP-NENs over the last decades[5]. These neoplasms are classified into well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). Moreover, depending on the hormone and amine secretion activity, GEP-NENs can be classified into functional and nonfunctional neoplasms[1,6]. Functional GEP-NENs produce hormones and amines, which cause specific clinical manifestations, such as hypoglycemia, refractory gastric ulcer, flushing, diarrhea, *etc*. However, immunohistochemical hormone staining is not sufficient for diagnosis[7].

Due to the clinical manifestations, functional GEP-NENs can frequently be diagnosed in early stages, what translates into a relatively good prognosis. In contrast, non-functional GEP-NENs are asymptomatic until distant metastases or mass effect cause late symptoms, such as intestinal obstruction[8]. The 2019 World Health Organization (WHO) classification of GEP-NENs consisted of the following categories: Grade 1, Grade 2, Grade 3, and NEC. This grading is based on the mitotic rate and/or the Ki-67 proliferation index, as listed in Table 1 below. The mitotic rate is determined by an immunohistochemistry method, in which 50 fields of 0.2 mm2 are counted. The Ki-67 proliferation index value is determined by counting more than 500 cells in the regions of highest labelling using scanning magnification. The NEN grade is assigned by the proliferation index of the two, which places the neoplasm in the higher-grade according to the classification. Mixed NENs consist of both neuroendocrine and non-neuroendocrine components and are poorly differentiated, and the neuroendocrine component has proliferation indexes in the same range as other NECs. This conceptual category however allows for respect of the fact that one or both components can also be well differentiated; if feasible, every component should be graded separately[9,10]. Surgery is still the mainstay of curative treatment for localized GEP-NENs[11]. Methods of clinical diagnosis and treatment have been continuously updated because of ongoing research and study activities. This review aims at systemically summarizing the latest research advances on diagnosis and treatment of GEP-NENs.

**Clinical presentation**

GEP-NENs present as very heterogeneous, both because of different organs of origin and because of different biological behavior; consequently, clinical symptoms are various. Especially functional GEP-NENs, which secrete specific hormones, cause characteristic clinical syndromes[12]. Insulinomas produce excessive amounts of insulin, thereby causing hypoglycemia. Excessive secretion of gastrin from functional gastrinomas often results in refectory and recurrent peptic ulcerations. Glucagonoma patients regularly present with recent diabetic mellitus as well as migratory necrolytic erythema caused by extremely high glucagon levels, whereas somatostatinoma patients will present with hyperglycemia and steatorrhea. Contrary to that, non-functional GEP-NENs do not cause specific clinical symptoms, and they are often only diagnosed during routine physical examinations[13].

**Diagnosis of GEP-NENs**

Diagnostic improvements over time are shown in Figure 2.

***Biomarkers for diagnosis of NENs***

**Chromogranin-A:** Chromogranin-A (CgA) is a member of the chromogranin glycoprotein family and is physiologically secreted by neurons and neuroendocrine cells[14]. In clinical diagnosis, CgA is established as a universal routine diagnostic biomarker of neuroendocrine neoplasms. Sensitivity of CgA assays varies between 32% and 92%, depending on the NET type, secretory status, and tumor burden. The specificity can approach 100% if other diseases affecting serum CgA levels, such as kidney insufficiency and chronic atrophic gastritis, can be excluded[15].

**Serotonin:** Serotonin isassessed by measuring its degradation product, 5‑hydroxyindoleacetic acid (5-HIAA), in 24-h urine of patients with carcinoid symptoms[16]. A meta-analysis demonstrated that 5-HIAA can be a predictive biomarker for 1-year mortality rate of NEN patients[17]. However, since specific nutritious substances (such as eggplants, bananas, tomatoes, *etc*) and medications (such as nicotine, ephedrine, diazepam, *etc*) can affect 5-HIAA measurement, patients need to be guided to omit these substances.

**Gastrin:** Gastrinomas can result in elevation of serum gastrin levels. With excessive secretion of gastrin, patients will suffer from refractory peptic ulcers. Therefore, serum levels of gastrin are routinely measured in patients suspected to have gastrinomas. Criteria for diagnosis of Zollinger-Ellison syndrome as a result of gastrinomas are: At least 10-fold elevated serum gastrin levels and a gastric pH below 2.1. However, proton pump inhibitors (PPIs) can elevate serum gastrin levels. Patients receiving PPIs need to wean this medication for at least 1 wk before gastrin measurement[18].

**Insulin:** Insulin is measured for diagnosis ofinsulinomas after a 72-h gastric fasting. If, during fasting-induced hypoglycemia, serum insulin levels reach more than 3 mcIU/mL, serum pro-insulin levels rise above 5 pmol/L, and C‑peptide concentrations are at least 0.6 ng/mL, an insulinoma is a probable diagnosis; especially in patients with concurrent pancreatic mass[19].

**Glucagon:** Glucagon is measured in the blood of patients suspected to suffer from glucagonomas and meeting the following criteria: Recently diagnosed with diabetes mellitus, migratory necrolytic erythema, and a positive imaging confirmation of a gastroenteropancreatic mass[20].

In summary, although these serum molecular tests are in standard use for GEP-NEN differential diagnosis, a consensus conference of multinational experts repeated that a single biomarker to diagnose efficaciously and predict prognosis for patients with GEP-NENs would be beneficial[7].

***Imaging for diagnosis of GEP-NENs***

**Computed tomography and magnetic resonance imaging:** Computed tomography and magnetic resonance imaging are conventional techniques used to determine localization and to evaluate neoplasm burden of GEP-NENs. Multiphase computed tomography (CT) or magnetic resonance imaging (MRI) scans are recommended to diagnose distant metastatic lesions[21,22], because GEP-NENs are highly vascularized and thus show the same resolution as the liver in conventional CT scanning. They can, however, be detected by either of these advanced imaging techniques. Similarly, contrast CT chest scanning is recommended for the evaluation of lung metastases. Small peritoneal, liver, and lymphatic metastases < 1 cm cannot be detected by CT analyses[23].

**Functional imaging:** Nowadays, functional somatostatin receptor (SSR) imaging is widely used in clinical diagnosis of NENs. Beside localizing tumors and selecting SSR-positive patients for specific therapies, it can be used to evaluate therapeutic responses[24]. Five subtypes of SSRs (SSR1 to SSR5) have been identified, and their molecular mechanisms of regulation and signaling have been elucidated[25]. The most prominent SSR subtype in GEP-NENs is SSR2, followed by SSR1 and SSR5; SSR3 and SSR4 are less frequently expressed[26]. Moreover, SSR2 and SSR5 are usually expressed in insulinomas[27].

The 68Ga-DOTA somatostatin analogues (SSA) imaging system consists of 68Ga-DOTA-Tyr3-octreotide (68Ga-DOTA-TOC), 68Ga-DOTA-Nal3-octreotide (68Ga-DOTA-NOC), and 68Ga-DOTA-Tyr3-octreotate (68Ga-DOTA-TATE). These different imaging agents display distinct affinities to variable SSRs. Compared to 111In-pentetreotide functional imaging, 68Ga-DOTA-SSA imaging has been shown to improve diagnosis and staging for NENs[28] and has become the imaging method of choice. 68Ga-DOTA-TOC shows a higher affinity to SSR-2, 68Ga-DOTA-NOC towards SSR-2, SSR-3, and SSR-5, whereas 68Ga-DOTA-TATE towards SSR-2 and SSR-5[29]. Clinicians are supposed to select appropriate imaging agents for specific NENs. 18Fluorodeoxyglucose (18FDG), a tracer for glucose metabolism, can indirectly assess metabolic activity of GEP-NENs. The ability of tumor cells to take up glucose is positively correlated with the tumor growth rate[30], which is in turn related to aggressiveness. Combining 18FDG-PET/CT with 18Ga-DOTA-TATE imaging is another functional imaging method for NENs[31]. Even for GEP-NENs with low or negative SSR expression, positive 18FDG PET/CT imaging denotes worse prognosis[32]. For the detection of tumor site and activity, the combination of SSR imaging and 18FDG imaging has proven to be complementary[33,34].

***Endoscopy,******ultrasonography, and endoscopic ultrasonography***

Endoscopy, ultrasonography, and endoscopic ultrasonography are also recommended for the diagnosis and treatment of GEP-NENs. For early-stage and smaller GEP-NENs, endoscopic resection should be taken into consideration when lymphatic metastases have been excluded by endoscopic ultrasonography (US) or imaging[35]. Endoscopic resection should be reserved for GEP-NENs with a diameter < 1 cm, superficial position, and low grading[35]. US can serve as the initial diagnostic approach for liver metastases. Moreover, it can guide the biopsy needle to collect tissues for histopathological assessment. Endoscopic US is currently the most sensitive diagnostic approach for pancreatic NENs and allows biopsy collection at the same time[36], whereas intraoperative US can detect tumors in liver and pancreas, otherwise not detected by imaging methods[37].

***Histopathological examination***

Histopathological examination is the gold standard for GEP-NEN diagnosis; both from biopsies and resected tissues. Hematoxylin and eosin staining is used to determine cytological and histomorphological indices, and immunohistochemical staining of CgA and synaptophysin are mandatory for differential diagnosis in pathological reports[38]. Immunohistochemical Ki-67 index determination and mitotic counts per mm2 are the basis of grade classification for GEP-NENs (see Table 1). According to the latest National Comprehensive Cancer Network (NCCN) guidelines, histological classification, the resection margin status, Tumor, Node, Metastasis (commonly known as TNM) stage, and the presence of vascular invasion are also mandatory in pathological reports, because these factors are significantly associated with patient prognosis[39].

***Somatic mutations***

For WHO grade 3 NENs, somatic mutations in the genes death domain associated protein (*DAXX*), multiple endocrine neoplasia type 1 (*MEN1*), and alpha thalassemia/intellectual disability syndrome X-linked (*ATRX*) are most frequent. Whereas, in NECs, mutations affect the genes retinoblastoma transcriptional corepressor 1 (*RB1*), mothers against decapentaplegic homolog 4 (*SMAD4*), and tumor protein p53 (*TP53*)[40,41]. This difference in the occurrence of somatic mutations can be exploited to discriminate GEP-NECs from WHO grade 3 GEP-NENs in challenging cases[42]. In addition, NECs of the small intestine often show mutations in the cyclin-dependent kinase inhibitor 1B (*CDKN1B*)[43], and lack of *CDKN1B* gene expression has been described as a negative prognostic factor in GEP-NENs[6,44]. Insulinoma-associated protein 1 (*INSM1*) has proven to be a specific and sensitive biomarker for diagnosing NECs[45,46].

**TREATMENT APPROACHES FOR GEP-NENS**

An overview of treatment developments is shown in Figure 3.

***Surgery***

Surgical resection remains the sole curative form of therapy for patients with GEP-NENs[47]. Patients with local or locoregional GEP-NENs should be recommended for curative resection of the primary and the locoregional lymph nodes[48]. For patients with asymptomatic pancreatic NENs < 2 cm, a cautious surveillance with yearly imaging is recommended[49]. Patients with pancreatic NENs > 2 cm should receive pancreatectomy with regional lymphadenectomy[50]. Localized small intestinal NENs are resected radically, including removal of mesenteric lymph nodes[51]. This can also reduce the risk of associated comorbidities, such as intestinal obstruction. A clinical study including 581 patients operated on with metastatic NENs demonstrated that the median overall survival (OS) was 110.4 mo for curative resection. In comparison, resections resulting merely in debulking (OS: 89.2 mo) or performed in a palliative situation (OS: 50.0 mo) had significantly shorter OS rates (*P* < 0.001). Patients receiving cytoreductive surgery survived, in median, 89.2 mo, whereas when all metastatic lesions could be removed, the longest median survival of 112.5 mo could be reached (*P* < 0.001)[52]. Another clinical retrospective analysis of grade 3 GEP-NENs reported a 2-year OS rate after radical surgery of 64.5%, a 2-year progression-free survival (PFS) rate of 44.9%, and a median PFS of 14 mo[53]. Therefore, the 2021 NCCN guidelines6 recommended that, for small (< 2 cm) and low-grade NENs, surgery or close monitoring should be individualized. For large (> 2 cm) and higher-graded NENs, resection with negative margins and removal of regional lymph nodes should be conducted. Cytoreductive or debulking resection for distant metastases is recommended when more than 90% of the lesions can be removed safely, especially if patients present with serious hormonal symptoms[54,55].

***Systemic therapies***

**Somatostatin:** Somatostatin is a general endocrine “off-switch” due to its not only endocrine but also, exocrine, autocrine, and paracrine inhibitory effects. In the digestive system, somatostatin can inhibit bowel movements, decrease the blood flow of mesenteric vessels, inhibit gastrointestinal absorption as well as gallbladder contraction, and suppress hormone secretion[56]. The half-life of somatostatin is only 3 min, thus preventing its pharmacological use. Hence, SSAs with longer half-lives were developed to treat patients with GEP-NENs[57]. SSAs can control hormonal symptoms induced by GEP-NENs[58] by binding to SSRs, thereby preventing the activation. Currently, the most commonly used SSAs for GEP-NENs are octreotide and lanreotide. In the placebo-controlled, double-blind, prospective, and randomized study on the “effect of octreotide long-acting repeatable (LAR) in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID)” clinical trial, it was demonstrated that octreotide significantly delayed tumor progression time (LAR 14.3 mo *vs* placebo 6 mo)[59]. The controlled study of lanreotide anti-proliferative response in NEN (CLARINET) trial confirmed that lanreotide was associated with significantly higher 2-year PFS rates in patients with metastatic enteropancreatic NEN (65.1% in the lanreotide group *vs* 33.0% in the placebo group)[60]. In a phase III trial, pasireotide, a second generation SSA[61], was compared to octreotide. It prolonged the median PFS from 6.8 mo in the octreotide LAR control group to 11.8 mo in the pasireotide LAR group[62]. The guidelines of the European Neuroendocrine Tumor Society (ENETS) and the NCCN guidelines recommended SSAs as first-line therapeutic agents for GEP-NENs. For patients receiving LAR SSAs, cholecystectomy is recommended in case of cholecystitis and gallstones[63].

**Interferon-α:** Interferon-α (IFNα) has been used to inhibit hormone secretion and proliferation in NENs in the past decades[64]. The phase III clinical study of the Southwest Oncology Group compared octreotide LAR plus IFNα with octreotide LAR plus bevacizumab. Antitumor effectiveness was similar with median PFS of 15.4 mo and 16.6 mo, respectively[65]. When other available therapeutic options failed, IFNα could thus be taken into cautious consideration as a rescue antiproliferative therapy[66].

***Molecular targeted agents***

**Mammalian target of rapamycin inhibitors:** When the phosphatase and tension homolog protein is phosphorylated, a negative feedback regulation *via* phosphatidylinositide 3-kinase (PI3K) is normally activated, which inhibits cell proliferation and promotes cell apoptosis. However, the reduction of phosphatase and tension homolog messenger RNA expression stimulates activation of the PI3K-AKT-mammalian target of rapamycin (mTOR) pathway and can trigger tumor formation[67]. The key role of this signaling pathway in GEP-NEN development inspired mechanistic research with the aim to develop drugs targeting PI3K-Akt-mTOR[68,69]. Phase III clinical studies of RAD001 application for patients with advanced NEN (RADIANT)-3 and -4, lead to the approval of everolimus. This targeted inhibitor of mTOR with the capacity to delay NEN progression attained approval for treatment of GEP-NENs[70,71]. Both ENETS and NCCN guidelines recommend everolimus as a second or third-line drug for advanced GEP-NENs. In patients with insulinomas, everolimus showed the positive side-effect of stabilizing glycemic levels[72]. However, low expression of SSR2 in patients with insulinomas results in poor response to SSAs[73]. Even worse, SSA treatment of patients with insulinomas can exacerbate hypoglycemia due to an inhibition of glucagon[56,74]. Therefore, everolimus should be prioritized for patients with insulinomas.

**Vascular endothelial growth factor receptors inhibitors:** Sunitinib, a broadly acting tyrosine kinase inhibitor targeting vascular endothelial growth factor receptors (VEGFRs) and platelet-derived growth factor receptors, has been affirmed to defer progression of pancreatic NENs in a phase III clinical trial75]. Sunitinib was thus included for treatment of advanced pancreatic NENs in the ENETS and NCCN guidelines. However, there is a lack of clinical data for the effects of sunitinib on gastroenteric NENs. The Grupo Espanol de Tumores Neuroendocrinos (GETNE 1509) phase II trial has proven that lenvatinib, another VEGFR inhibitor, achieved an overall response rate of 29.9% (44.2% in pancreatic and 16.4% in gastrointestinal NENs), a median response duration of 21.5 mo (19.9 mo in pancreatic and 33.9 mo in gastrointestinal NENs), a median PFS of 15.7 mo (15.6 mo and 15.7 mo respectively), and a median OS of 32 mo in the pancreatic NEN group. The median OS was not reached in the gastrointestinal NEN group. The phase III trial of surufatinib, a novel VEGFR inhibitor, in advanced extrapancreatic and pancreatic neuroendocrine tumors (SANET-ep and SANET-p) showed a meaningful improvement of PFS to 9.2 mo and 10.8 mo in the surufatinib groups *vs* 3.8 mo and 3.7 mo in the placebo groups for patients with advanced, progressive, well differentiated, extrapancreatic NENs, and advanced pancreatic NENs[76], respectively.

***Immune checkpoint inhibitors***

Immune checkpoint inhibitors, which target for example programmed death protein-1 (PD-1), its receptor programmed death-ligand 1 (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), showed promising antitumor efficacy in various tumor types[77]. In a phase IB study of the anti-PD-1 antibody pembrolizumab in advanced solid tumors (KEYNOTE-028), pembrolizumab monotherapy proved antitumor efficacy in patients with PD-L1-positive carcinoid and pancreatic NENs with high stable disease rates of 60% and 88%, respectively; however, only a disappointing objective response rate (ORR) of 12% and 6.3%, respectively[78]. In a subsequent phase II (KEYNOTE-158) study, pembrolizumab monotherapy had an ORR of only 3.7%, a median PFS of 4.1 mo and a median OS of 24.2 mo in patients with previously treated advanced well-differentiated NENs[79]. Pembrolizumab is also proposed for patients with tumor progression after previous treatment, tumors with high tumor mutational burden and no adequate alternative treatment regimens[80,81]. A phase II clinical trial of dual anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab) inhibition in patients with nonpancreatic NENs reported an auspicious ORR of 44% (18 of 32 patients) with high-grade NENs. This trial demonstrated that dual immunotherapy preferentially plays a role in grade 3 NENs[82]. A similar phase II study (CA209-538) also verified the significant efficacy of combination immunotherapy with ipilimumab and nivolumab in high-grade NEN patients (the median PFS of 4.8 mo and the OS of 14.8 mo in all the patients with NENs)[83].

***Peptide receptor radionuclide therapy***

Peptide receptor radionuclide therapy is actually a kind of systemic and targeted radiotherapy in one[84]. SSAs are structured with a radioisotope [such as Yttrium-90 (90Y) and Lutetium-177 (177Lu)] *via* a chelating agent. The emitted radiation kills the cancer cells that express SSRs on the tumor cells’ surface[85]. 177Lu-DOTA-TATE was approved by the European Medicines Agency for the treatment of patients with GEP-NENs in 2017 and a year later by the American Food and Drug Administration[86,87]. In a comprehensive meta-analysis of 1920 patients with unresectable metastatic NENs receiving 177Lu-DOTATATE therapy from 18 studies, the ORR was between 29.1% and 30.6%, and the disease control rate was 74.1% to 81.1%[88].

***Chemotherapies***

For G1 and G2 pancreatic NENs, SSAs are recommended as first-line therapeutic regimen. When ineffective, however, both NCCN and ENETS guidelines recommend temozolomide combined with capecitabine or streptozotocin-based therapies. To date, there is no recommendation for systematic chemotherapy for G1 and G2 gastroenteric NENs from NCCN and ENETS. Similarly, no standard chemotherapeutic regimens are currently recommended for G3 NETs. The NORDIC NEC study demonstrated that NEC patients with Ki-67 < 55% were less sensitive to platinum-based chemotherapy than those with Ki-67 ≥ 55% (response rate: 15% *vs* 42%, respectively), yet survival times were better for patients with Ki-67 < 55% (14 mo *vs* 10 mo, respectively)[89]. Thus, ENETS and NCCN guidelines do not suggest platinum- but temozolomide-based chemotherapies for patients with Ki-67 < 65%. For grade 3 NEN patients with Ki-67 < 55%, temozolomide-based chemotherapies are recommended; whereas, patients with Ki-67 ≥ 55% should receive platinum-based regimens, such as cisplatin or carboplatin, both in combination with etoposide[90]. These regimens are also recommended for GEP-NEC patients in the 2021 NCCN guideline as first-line chemotherapy.

***Related agents for controlling clinical manifestations***

PPIs can control hypersecretion of gastric acid in patients with gastrinomas. However, related studies have proven that PPIs can lead to hypomagnesemia and vitamin B12 deficiency in patients with long-term use[91], suggesting a cautious use paired with regular control of magnesium and vitamin B12 levels.

Tryptophan hydroxylase is the rate-limiting enzyme for the conversion of tryptophan to serotonin. The tryptophan hydroxylase inhibitor telotristat can reduce the serotonin production. It is thus used in clinical practice to treat patients with refractory diarrhea resulting from a carcinoid syndrome[92] and it has been validated to normalize bowel movements and urinary levels of 5-HIAA[93].

**CONCLUSION**

In summary, the pathogenesis of GEP-NENs is still largely unclear. Multiple classification systems and treatment schedules have been accurately (re)defined thanks to the efforts of GEP-NEN experts. Because of the great improvement of detection technologies, an increasing number of suspicious patients can be diagnosed with GEP-NENs already at an early stage. Novel treatment approaches, including small molecule inhibitors, SSAs, and peptide receptor radionuclide therapy targeting GEP-NENs, have evolved remarkably. However, prospective research still needs to be conducted to confirm their efficacy. Also, many controversies concerning the therapy regimens for specific GEP-NENs of different types remain. Beside identifying and developing novel molecular targeted drugs, the rational combination of targeted, chemo-, and immunotherapy seems to be the future research direction in the field of GEP-NEN therapy.

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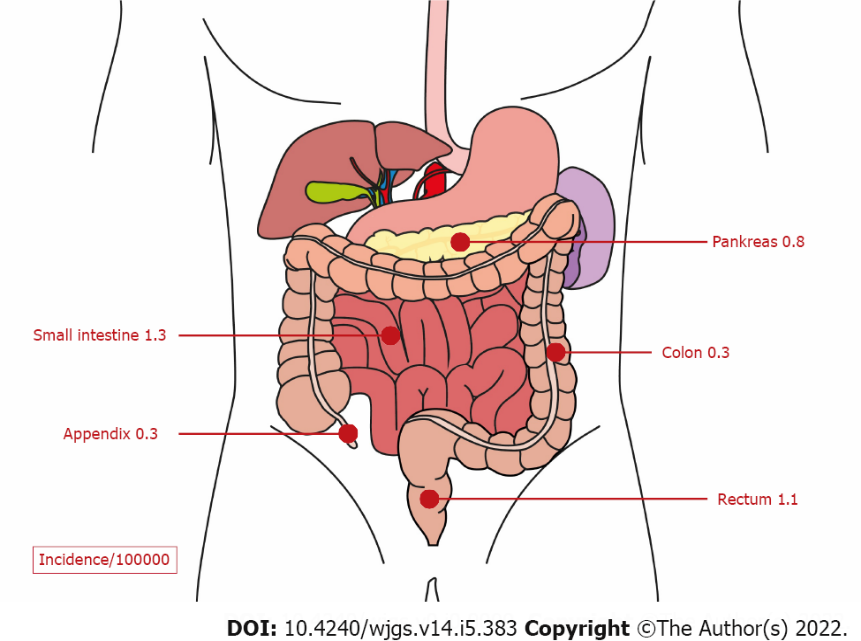
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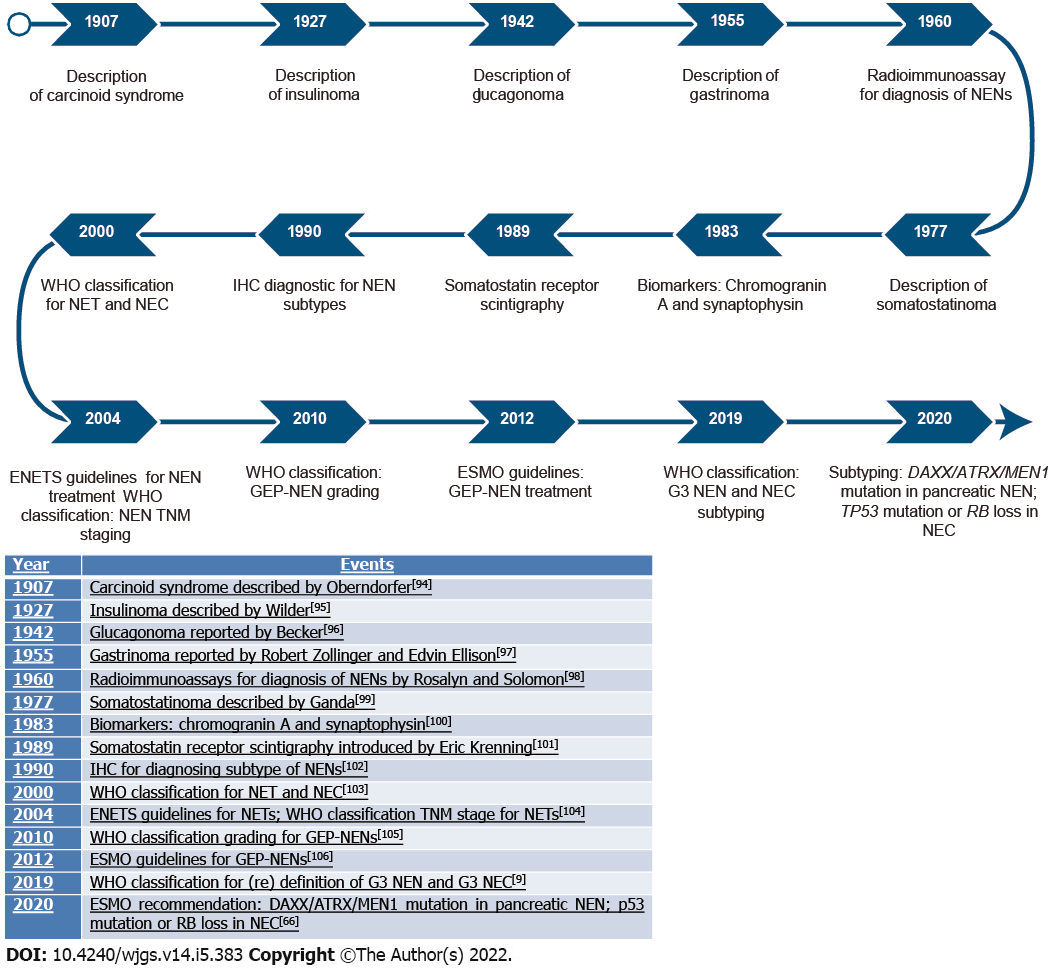
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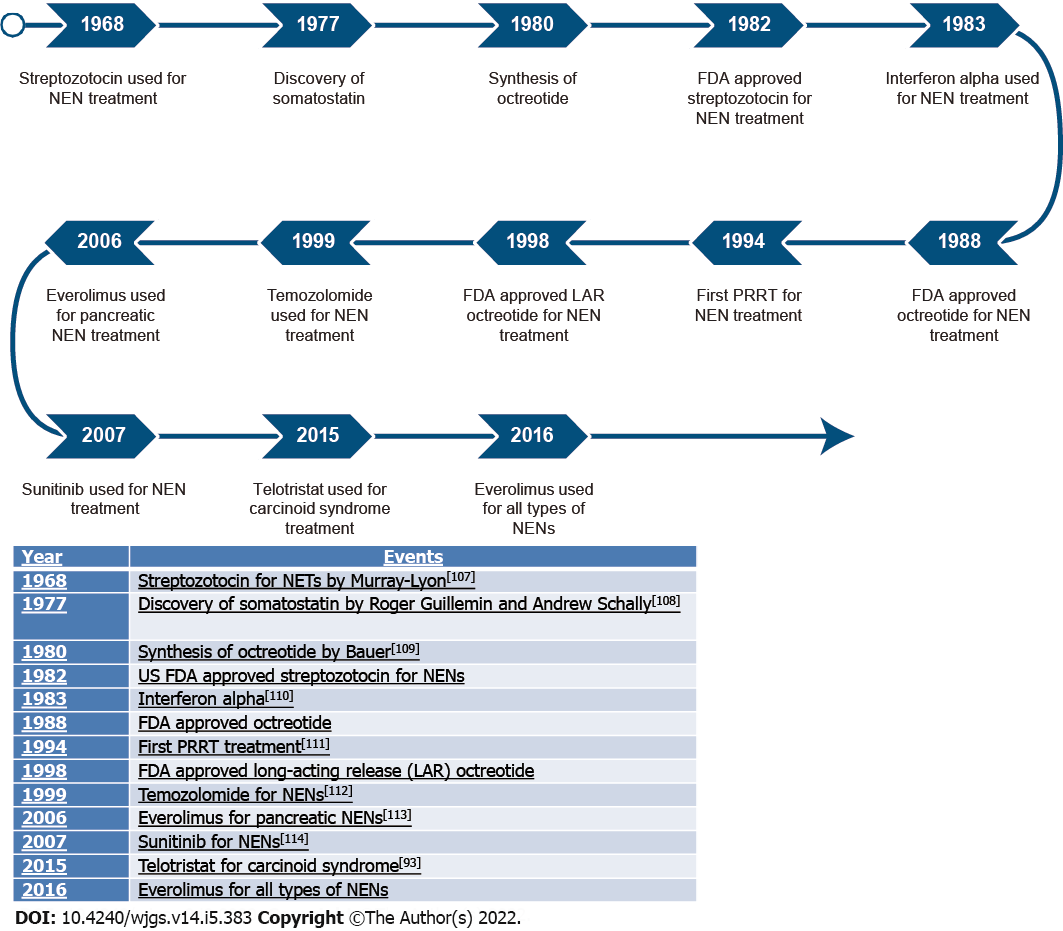
**Figure Legends**



**Figure 1 Incidence in gastroenteropancreatic organs.**



**Figure 2 Milestones in the diagnosis of neuroendocrine neoplasms[94-106].** ENETS: European Neuroendocrine Tumor Society; ESMO: European Society for Medical Oncology; GEP-NEN: Gastroenteropancreatic neuroendocrine neoplasm; IHC: Immunohistochemistry; NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; NEN: Neuroendocrine neoplasm; TNM: Tumor, Node, Metastasis; WHO: World Health Organization.



**Figure 3 Milestones in the treatment of neuroendocrine neoplasms[107-114].** US FDA: United States Food and Drug Administration; NEN: Neuroendocrine neoplasm; LAR: Long-acting repeatable; PRRT: Peptide receptor radionuclide therapy.

**Table 1 The 5th classification system of World Health Organization for gastroenteropancreatic neuroendocrine neoplasms (2019)[10]**

|  |  |  |  |
| --- | --- | --- | --- |
| **Classification** | **Differentiation status** | **Ki-67 index** | **Mitotic rate** |
| Grade 1, NET | Well differentiated | < 3% | < 2 |
| Grade 2, NET | Well differentiated | 3% to 20% | 2 to 20 |
| Grade 3, NET | Well differentiated | > 20% | > 20 |
| Small cell type, NEC | Poorly differentiated | > 20% | > 20 |
| Large cell type, NEC | Poorly differentiated | > 20% | > 20 |
| Mixed NEN | Well or poorly  differentiated | Variable | Variable |

NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; NEN: Neuroendocrine neoplasm.



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