World Journal of
Clinical Cases

World Journal of Clinical Cases

Contents

Contents

Contents

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Yusuf Tutar, PhD, Chairman, Director, Full Professor, Department of Basic Pharmaceutical Sciences, Division of Biochemistry, University of Health Sciences, Istanbul 34668, Turkey. ytutar@outlook.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJCC* as 1.534; IF without journal self cites: 1.491; 5-year IF: 1.599; Journal Citation Indicator: 0.28; Ranking: 135 among 172 journals in medicine, general and internal; and Quartile category: Q4. The *WJCC*'s CiteScore for 2021 is 1.2 and Scopus CiteScore rank 2021: General Medicine is 443/826.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Jin-Lei Wang*.

REVIEW

Molecular factors, diagnosis and management of gastrointestinal tract neuroendocrine tumors: An update

Efstathios Theodoros Pavlidis, Theodoros Efstathios Pavlidis

Efstathios Theodoros Pavlidis, Department of 2nd Surgical Propedeutic, Hippocration Hospital, Aristotle University of Thessaloniki, School of Medicine, Thessaloniki 54642, Greece

Theodoros Efstathios Pavlidis, Department of 2nd Surgical Propedeutic, Aristotle University of Thessaloniki, School of Medicine, Thessaloniki 54642, Greece

Corresponding author: Theodoros Efstathios Pavlidis, Doctor, PhD, Chief Doctor, Director, Full Professor, Surgeon, Department of 2nd Surgical Propedeutic, Aristotle University of Thessaloniki, School of Medicine, Konstantinoupoleos 49, 54642 Thessaloniki, Greece. pavlidth@auth.gr

Abstract

The prevalence of gastrointestinal neuroendocrine tumors (GI-NETs) is increasing, and despite recent advances in their therapy, it remains inadequate in patients with advanced well-differentiated neuroendocrine tumors. These tumors present many challenges concerning the molecular basis and genomic profile, pathophysiology, clinicopathological features, histopathologic classification, diagnosis and treatment. There has been an ongoing debate on diagnostic criteria and clinical behavior, and various changes have been made over the last few years. Neuroendocrine carcinoma of the gastrointestinal system is a rare but highly malignant neoplasm that is genetically distinct from gastrointestinal system neuroendocrine tumors (NETs). The diagnosis and management have changed over the past decade. Emerging novel biomarkers and metabolic players in cancer cells are useful and promising new diagnostic tools. Progress in positron emission tomography-computerized tomography and scintigraphy with new radioactive agents (^{64}Cu-DOTATATE or ^{68}Ga-DOTATATE) replacing enough octreoscan, has improved further the current diagnostic imaging. Promising results provide targeted therapies with biological agents, new drugs, chemotherapy and immunotherapy. However, the role of surgery is important, since it is the cornerstone of management. Simultaneous resection of small bowel NETs with synchronous liver metastases is a surgical challenge. Endoscopy offers novel options not only for diagnosis but also for interventional management. The therapeutic option should be individualized based on current multidisciplinary information.

Key Words: Gastrointestinal neuroendocrine tumors; Neuroendocrine neoplasms; Mixed NEN; Neuroendocrine carcinoma; APUD cells; Carcinoids; Somatostatin analogs

Core Tip: Novel diagnostic modalities, including imaging, biomarkers and molecular factors such as liquid biopsy based on mRNA and NETest index, including 51 genes, have changed diagnosis and follow-up. Current available therapeutic options for gastrointestinal neuroendocrine tumors open new horizons promising better results. Surgery remains the cornerstone for resectable disease, but drug therapies, mainly somatostatin analogs, somatostatin receptor antagonists, molecular-targeted drugs and new chemotherapeutic agents are important in the palliative treatment of inoperable or recurrent cases. Advances in genomic profiling and endoscopic intervention could individualize management options.

INTRODUCTION

Gastrointestinal neuroendocrine tumors (GI-NETs) are a genetically heterogeneous part of neoplasms originating from neuroendocrine cells distributed along the gastrointestinal (GI) tract and exhibit different biological behaviors depending on location[1,2]. They are usually well-differentiated slow-growing lesions and may be functional or nonfunctional without hormone secretion and symptoms[3]. The vast majority of them are sporadic. However, at a rate less than 5%, they are found in genetic syndromes, mainly MEN 1 (multiple endocrine neoplasia), in the form of pancreatic islet cell neoplasms (gastrinoma, insulinoma, glucagonoma, in order) which carry a high rate of malignancy[4].

There is a risk for the coexistence of GI-NETs with adenocarcinoma; also, it has been estimated that in patients with lung neuroendocrine tumors (NETs), there was an increased risk for second primary malignancy compared to the general population[5].

The neuroendocrine cells in general are located throughout the body, *i.e.*, central nervous system, endocrine glands, pancreas, lungs, and gastrointestinal tract and secrete different hormones. These cells have a common embryological origin from the neural crest as well as common physiochemical properties such as amine precursor uptake and decarboxylation (APUD cells) producing amines. The amine precursors include 5-hydroxytryptophan (5-HTP) and dihydroxyphenylalanine (DOPA). The neoplasms of the neuroendocrine cells or APUD cells were previously called APUDomas, but the term NETs now prevails[6]. They were divided into two categories, carcinoids in two-thirds and noncarcinoids in one-third, mainly in the pancreas, named PET (pancreatic endocrine tumors) of islet cell neoplasia. However, the traditional term carcinoids has been replaced widely by the recent term NETs [4].

NETs were derived from the foregut (lungs-bronchi, thymus gland, esophagus, pancreas, stomach and duodenum), midgut (small intestine, vermiform appendix and right colon) and hindgut (distal third of transverse colon, descending colon, sigmoid colon and rectum). The small intestine is the most frequently observed location, usually presenting in an advanced stage[4,7].

Their increasing incidence exhibits a fivefold increase within 30 years in the United States[3]; likewise, an increase has been reported in Japan[8]. The increased incidence may be partially attributed to a better understanding and recognition of the disease and to an improvement in diagnostic modalities [8]. This increase is in parallel with that of metabolic syndrome. It is not yet known whether the latter is involved in the etiology of GI-NETs or influences their consequences[1].

Mixed neuroendocrine neoplasms (MiNEN), neuroendocrine and nonneuroendocrine, are very rare, but with increasing incidence, heterogeneous lesions found in the GI tract, which were previously known as mixed adeno-neuroendocrine carcinomas, present a diagnostic and therapeutic challenge. Their histopathologic differentiation is mainly poor and less commonly well, which determines their biological behavior[9-12]. Neuroendocrine carcinoma (NEC) with poor differentiation represents a more aggressive sub-group located mainly (over one-third) in the GI tract that requires careful assessment for surgical therapeutic excision[13].

The latest 2019 World Health Organization (WHO) classification for gastroenteropancreatic neoplasms clarifies the issue histopathologically, taking into account the differentiation, mitotic rate and KI-67 proliferation index[14]. The diagnosis and management have changed over the past decade. Novel diagnostic tests have contributed to the already promising advances[15].

Positron emission tomography-computerized tomography (PET-CT) combining functional metabolic and anatomical imaging as well as octreotide scintigraphy (Octreoscan), which is also called somatostatin receptor (SSTR) scintigraphy[16-18], are the preferred imaging diagnostic tools, although

no modality alone offers the best results[19]. FDG-PET (fluorine-18-labeled deoxyglucose), gallium PET/CT, ¹⁸F-FDOPA PET/CT (¹⁸F-fluorodihydroxyphenylalanine) and SPECT (single photon emission computerized tomography) scans are several new imaging tools. ¹⁸F-FDOPA PET/CT is the most accurate novel tool for detecting metastasis from small bowel NETs[20].

Surgery is the cornerstone of management followed by interventional endoscopy, but new drugs, chemotherapy, immunotherapy and novel targeted therapy by biological agents provide promising results[21].

GI and pancreatic NETs are quite different in molecular pathology and treatment requiring distinct approach. In this extended narrative review focusing on GI NETs, we evaluate and summarize the modern data on pathogenesis and provide information on available treatments. Current information on contemporary aspects in genomic mutations, diagnosis, classification and therapeutic options will allow gastroenterologists to update their knowledge about gastrointestinal NETs.

MOLECULAR FACTORS – GENOMIC PROFILE

There is a rather familial predisposition for NET and second malignant development.

Pathogenetic variants in the genes *ATM*, *RAD51C*, *MUTYH* and *BLM* have been found in a proportion of 9%-11% of NETs in the small intestine. The variants in these genes are associated with inherited susceptibility for malignancies. However, it is not yet known whether there is an association with NET development[22].

The cytokine *IL-17* (interleukin 17*)* gene that is expressed by the tumor only and the *TNFα* (tumor necrosis factor alpha) gene that is expressed by both the tumor and stroma promote the *pSTAT3* (phosphorylated signal transducer and activator of transcription 3) gene. A possible therapeutic option may be the targeting of these pathways[23].

Small intestine NET is the most common malignant neoplasia of the small bowel. Primary multifocal development arises from clonally independent cells[24].

A familial existence of small intestinal NETs has been reported. In a family with 16 affected individuals, a heterozygous deletion at *7q31.2* (cystic fibrosis locus) was found. The deletion removed the TAP (topologically associating domain) border between *CFTR* (CF transmembrane conductance regulator) by inactivation and *WNT2* (Wnt family members 2) by activation. The predisposing genes were *IPMK* and *MUTYH*. This deletion is an incriminating event for small intestine NET and both small and large bowel adenocarcinoma[25].

Cancer cells develop mechanisms that increase nutrient uptake, since they require a vast amount of nutrients for their survival. Metabolic players could have a potential role in NETs. Specific mechanisms increase nutrient uptake of metabolic players *LAT-1* (amino acid transporter 1) and *GLUT-1* (glucose transporter 1) and perhaps may promote the proliferation and metastatic capacity of NETs. Immunohistochemical *GLUT-1* expression is elevated in GI NETs and is higher in grade 2 tumors than in grade 1 tumors. Additionally, there was a correlation between the *Ki-67 proliferation index* and *GLUT-1* expression. *LAT-1* expression is associated with increased GI NET malignancy and aggressiveness[26].

The correct identification of cell origin and an understanding of the mechanisms of tumorigenesis could open new horizons in prophylaxis and treatment. Currently, cancers are considered to originate from stem cells. Each cell division carries a slight risk of mutation; thus, any stimulation of proliferation has an increased risk of mutation. Some hormones (gastrin, estrogen, testosterone) and growth factors play a pivotal role in tumorigenesis by acting as signaling molecules. For example, increased gastrin levels may promote the growth of enterochromaffin-like (ECL) cells and induce a sequence of hyperplasia, dysplasia, type 4 gastric NETs, and possibly NECs or diffuse adenocarcinomas[27].

Gene expression profiling can be used to classify small intestine NET subtypes and accurately predict metastasis. This might lead to individualized treatment.

Several transcribed genes are implicated in tumor development, metastasis and hormone secretion and can be useful in defining primary small intestine NETs and predicting metastasis occurrence. These genes include *MTA 1* (metastasis associated protein), *Ki-67 proliferation index*, *NAP1L1* (nucleosome assembly protein 1- like), *MAGE-D2* (melanoma antigen family D2), *FZD7* (frizzled homolog 7), *CgA* (chromogranin A), *survivin, NRP2* (neuropilin 2) and *Kiss 1* (Kiss 1 metastasis suppressor)[28].

Important genetic factors, such as the *RET* proto-oncogene and *tumor suppressor menin* and growth factors (VEGF, TGF-β, IGF-1 and PDGF), are associated with cell differentiation regulation, tumor growth and hormone production[29].

GI-NECs are genetically different from GI-NETs. Alterations in the genes *TP53* and *RB1* are common in GI-NECs or in genes *CCNE1* (Cyclin E1) and *MYC* (MYC Proto-Oncogene, BHLH Transcription Factor). Alterations in the Notch gene family are characteristic of nonpancreatic NECs. The transcription factors, mainly the *SOX2* gene, are overexpressed in most GI-NECs[30].

TP53, *RB1, KRAS* mutations have been detected in gastric and colorectal NECs, although *BRAF* mutations have only been reported in colorectal NECs[31]. *BRAF* oncogene is located on chromosome 7q. KRAS or BRAF pathway-related signal transduction is very important in carcinogenesis. Activation of these oncogenes contributes to carcinogenesis. The most common mutation involves the *KRAS*

oncogene on chromosome 12p, which exists in an inactive form. It activates the p21 protein, which causes cell transformation, proliferation, and invasion. Inactivation of tumor suppressor genes, such as the *TP53 (tumor protein)* gene that promotes apoptosis (programmed cell death) and prevents cancer, leads to uncontrolled cell growth, proliferation and carcinogenesis. Additionally, the inactivation of maintenance genes, which regulate DNA damage repair, predisposes patients to cancer. The Notch signaling pathway maintains the required physiological balance among cell proliferation, differentiation and apoptosis. The mammalian target of rapamycin (mTOR) pathway is another cellular signaling pathway that is essential for physiological functions, such as cell growth and proliferation, but its hyperactivation may lead to carcinogenesis. Therefore, it is a target of novel therapeutic biological agents[4,31-33].

Loss in chromosomes was found in midgut carcinoids, such as in *18q22-qter* mainly and *11q-q23* in both primary tumors and metastases but also in *16q21-qter* only in metastases[32]. In ileac carcinoids, the loss of chromosome *18q was reported*, but gain of chromosomes *4q, 5q, 14q, and 20q was also found.* Gain of chromosome *14q* was considered to be a strong predictor for advanced disease and poor survival, and thus, its analysis was recommended in situ by fluorescence[33].

DIAGNOSIS

The diagnosis is based on clinical pictures, biochemical markers, endoscopy, and imaging and confirmed by histopathology[4,15,34,35].

Clinical presentation

The clinical presentation is influenced by hormone secretion or not, therefore defining them as functional or nonfunctional.

Nonfunctional GI tract NETs are usually asymptomatic and revealed incidentally. They do not manifest specific symptoms initially but only display later symptoms that are related to tumor growth or metastases. Among the symptoms, the most common is obstruction and less often bleeding. The obstruction causes dysphagia in the esophagus, vomiting or early satiety in the stomach, incomplete or even complete intestinal obstruction in the small and large bowels with recurrent episodes of diffuse abdominal colicky pain and altered bowel habits (incomplete) or an acute episode of ileus (complete). The appendiceal location mainly on its tip is most commonly asymptomatic and is discovered incidentally by histopathology after appendectomy for acute appendicitis in up to 1% of removed specimens[4,36,37]. It is third in order after the rectum and small bowel and occurs mainly in younkers, which has the most favorable prognosis among the NETs[35]. The location in the Vater's ampoule may cause episodes of acute cholangitis or acute pancreatitis. Metastases usually involving the liver are asymptomatic initially, but later they can present as malaise, nausea, anorexia, weight loss, anemia, jaundice or pain[4,15,35].

In the stomach, the most common type 1 (70% to 80%) occurs in cases of autoimmune atrophic gastritis with multiple small polypoid lesions (1-2 cm in diameter) having less aggressiveness and excellent prognosis. Type 2 (5% to 10%) with multiple small lesions (less than 1 cm in diameter) is associated with gastrinoma, often in the context of MEN 1 syndrome. Type 3 (10% to 15%) with solitary large lesions (more than 2 cm in diameter) by hepatic metastases (50% at the time of diagnosis) has the same prognosis as adenocarcinoma. Type 4 ECL cell NETs have similar characteristics to type 3. However, they are more aggressive and have a worse prognosis. These constitute either poorly differentiated NECs or variably MiNEN[35].

In small bowel locations, regardless of the primary lesion, solitary or multifocal lesions (50%) are usually under 1 cm in diameter, are grade G1 and G2 and grow slowly, with hepatic metastasis presence in approximately 80%-90% of cases at the time of diagnosis; likewise, lymph node metastasis and mesenteric fibrosis are present in approximately 50% of cases[35,38]. The expression of ESR1 (estrogen receptor 1) and AR mRNA (androgen receptor messenger RNA) was increased in primary NETs; likewise, mesenteric fibrosis was increased in men (71%), while mesenteric metastasis was increased with age in women above 70 years (72%). The combined increase in ERα (estrogen receptor alpha) and AR (androgen receptor) protein expression suggests the modulating effect of steroids[38].

Small and large bowel NETs or even stomach NETs may rarely manifest as acute intussusception[39-41].

In large bowel locations, the lesion is often large (more than 2 cm in diameter) with multiple metastases and has poor differentiation (grade 3) and aggressiveness. It manifests as adenocarcinoma, while carcinoid syndrome is extremely rare[35].

The location in the rectum may cause bleeding and tenesmus. Most lesions are small (less than 10 mm in diameter) and are discovered incidentally by colonoscopy between 50-60 years, and they can be managed by endoscopic resection without surgery[42,43].

Functional GI-NETs arise mainly from the most common location, i.e., the small intestine and can produce serotonin (5-hydroxytryptamine) or other vasoactive substances in various (small or large) amounts. The secreted amount beyond the hepatic capacity to metabolize serotonin causes episodes of

carcinoid syndrome (flushing, bronchoconstriction, diarrhea, congestive heart failure, heartbeat feeling and peripheral edema). It usually occurs in extensive metastases and manifests itself in a paroxysmal occurrence that may be exacerbated by ingestion of food (chocolate, cheese) or alcohol (wine)[35].

Biomarkers

Serum CgA (chromogranin alpha) has been the general biomarker for well-differentiated NETs for a long time. It is not associated with the tumor burden. Its diagnostic accuracy is now under debate. However, it is useful in follow-up. False-positive results occur in some circumstances, including drugs, inflammatory bowel disease, heart and renal failure, malignancy or PPI use. Novel biomarkers include circulating tumor cells, circulating tumor DNA, circulating microRNAs, and NETest. Liquid biopsy based on mRNA analysis in the serum is a useful novel biomarker. In particular, the NETest index is a new biomarker in peripheral blood that is based on the simultaneous assay of 51 neuroendocrine-specific marker genes by PCR (polymerase chain reaction). This test expresses the percentage of positivity of the genes involved. The results show a scale from 0% to 100% as an activity index. The cutoff point is 20%. An index between 20% and 40% indicates stable disease, while an index above 40% indicates progressive disease. Its diagnostic accuracy is high (99%) compared to that of CgA (21% to 36%). Additionally, it is very useful for follow-up after therapeutic excision or determining the response to drug therapy. It can reveal recurrence and may predict prognosis. A new immunohistochemical marker is the transcription factor insulinoma-associated protein 1 (INSM1), which is more specific for the differentiation of NETs of the pancreas and rectum[4,35,44,45].

5-HIAA (5-hydroxyindoleacetic acid) is the main metabolic product of serotonin. Its assessment in 24-h urine determines serotonin levels in NETs originating from enterochromaffin cells mainly in the small bowel, secrete serotonin. It is associated with tumor burden. However, it may have false-positive results in some cases (foods, drugs or various diseases)[35].

The serum NT-proBNP (N-terminal-proB-type natriuretic peptide) test, which analyzes the level of this hormone produced by the heart, is a useful biomarker in the case of carcinoid syndrome for the assessment of carcinoid heart disease[46].

Chemokines are a subgroup of cytokines that are secreted from epithelial and stromal cells and act as mediators of cellular functions, including signaling and migration. Chemokyne receptor 4 is expressed in GI-NETs. Its immunohistochemical expression is related to grade 3 and metastatic disease and represents a proper target therapy by antagonists of this receptor[47].

The new monoclonal antibody SP70 differentiates neoplasms of the gastric fundus, including NETs, from nonneoplastic lesions by immunostaining[48].

Ghrelin is secreted mainly by enteroendocrine cells in the oxyntic glands of the stomach. Serum levels are elevated in gastrointestinal tract malignancies and may be a prognostic factor or even a therapeutic target[49].

The very rare inflammatory myofibroblastic tumors are associated with malignancies such as malignant NETs of the small intestine with lymphatic and hepatic metastasis and a mesenteric location of the abovementioned tumor. In this case, TGF β1 Levels are significantly increased, and it is a diagnostic marker, especially for follow-up[50].

Orthotopic liver transplantation for metastatic carcinoid tumors has a high recurrence rate with a poor prognosis. It is important to identify prognostic markers before performing this procedure. MIB-1 (Mindbomb homolog 1) is a recombinant monoclonal antibody that assesses Ki-67 cell proliferative activity by immunohistochemistry. It is a useful prognostic biomarker for such cases detecting tumors with more aggressive biological behavior, thus avoiding unnecessary transplantation[51].

Endoscopy (diagnostic and interventional)

Endoscopy with biopsy is the gold standard for NET diagnosis of the upper GI and colon, including the rectum. For the small intestine, video-capsule endoscopy and double-balloon endoscopy are other options when NETs cannot be detected by conventional imaging. Endoscopic ultrasound is another highly accurate diagnostic tool that, apart from size, echogenicity, and depth of invasion, can reveal lymph node involvement[17]. Additionally, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) or biopsy (EUS-FNB) is performed in submucosal lesions. The accuracy for lesions greater than 21 mm ranges between 49%-78% for the former and 76%-88% for the latter; endoscopic resection is suitable for localized NETs of the upper gastrointestinal tract and for other submucosal lesions of the GI tract less than 2 cm in diameter[52,53]. The ESGE (European Society of Gastrointestinal Endoscopy) guidelines for subepithelial lesions, including NETs, recommend EUS as the best option to determine the features of the lesion; EUS-FNB or MIAB (mucosal incision-assisted biopsy) for tissue diagnosis for lesions equal to or greater than 2 cm in diameter; endoscopic resection for type 1 gastric neuroendocrine neoplasms if they are greater than 10 mm; and endoscopic resection for unknown histology gastric lesions less than 2 cm[54].

A case report of endoscopic submucosal dissection and en bloc removal for a small (< 5 mm), well-differentiated, G3, type 3 gastric NET with a Ki-67 index > 80% has been reported[55].

Endoscopic resection has been recommended for duodenal NETs equal to or less than 10 mm. The outcomes of endoscopic submucosal dissection for duodenal NETs in 20 patients were assessed recently. They were grade 1, except for 3 cases of grade 2; were sized < 15 mm, except for one > 15 mm; and were

located in the bulb except for one that was located in the 2nd part. En bloc removal was feasible in 90% of patients, but endoscopic complete resection was feasible in 95%. R0 resection was achieved in 75%-90% of patients according to size, and R1 resection was achieved in 25%. The complication rate was 25% due mainly to perforation (4 cases) and bleeding (one case). No relapse was seen endoscopically after one year[56].

A recent meta-analysis and meta-regression including 1360 rectal NETs compared endoscopic submucosal dissection (ESD) to endoscopic mucosal resection. Both were equivalent for lesions less than 1 cm. However, ESD was more effective (more complete resection and less microscopic margin invasion) than ESD for lesions equal to or less than 2 cm, despite its longer time and more potential bleeding[57].

Endoscopic submucosal dissection with myectomy for rectal NETs may overcome the risk of vertical margin invasion. Comparison of this new method with ESD alone has proven its safety and effect-iveness for nonmetastatic lesions less than 16 mm[58].

In general, GI tract NETs less than 1 cm in diameter had a potential risk of lymphatic invasion exceeding 10 percent. In such a case, after endoscopic resection, a detailed follow-up and possible additional surgery are required[59].

Imaging

CT is the basic imaging tool commonly used for primary tumors and metastases in detecting lesions more than 0.5 cm[60]. It has difficulties and a limited role in imaging small lesions of the stomach, duodenum and small bowel. Magnetic resonance imaging (MRI) is usually selected for preoperative staging and especially for evaluation of hepatic metastases (sensitivity 91%)[44,61] and their response to chemotherapy[62]. Diffusion weighted MRI and contrast enhanced MRI aid in the detection of small hepatic metastases. High resolution MDCT (multidetector computed tomography) is a new useful modality with a diagnostic accuracy of 90%. Nevertheless, it can localize the bowel NETs, guiding the surgery[63]. SPECT (photon emission computerized tomography) is another imaging option, but its radionuclides are inferior to those of PET[16]. As mentioned in Introduction section the novel diagnostic imaging includes PET-CT, FDG-PET, gallium PET-CT, FDOPA PET-CT (the most accurate) and SPECT [16-20]. Contrast enhanced ultrasound is used for follow-up.

Somatostatin receptor expression has been based since 1994 on the so-called octreoscan (^{111}indium pentetreotide scintigraphy), but in recent years, the novel functional imaging ^{68}Ga-DOTATATE PET/CT (^{68}Gallium) with its excellent detection rate (sensitivity 93%-96% and specificity 85%-100%) has been the method of choice for NETs and metastases. It uses the ^{68}Ga-DOTA-peptides ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC and may possibly change our practice. The newer ^{64}Cu-DOTATATE (^{64}Curium) has higher diagnostic accuracy than ^{68}Ga-DOTATATE[16,44,64,65]. ^{18}F-FDOPA PET/CT (6-[18F]-L-fluoro-L-3,4-dihydroxyphenylalanine) is valuable in the preoperative diagnosis of peritoneal carcinomatosis (possibility of 30%) due to GI-NETs mainly of the small intestine, thus determining the management strategy[20]. The new radiolabeled peptide 99mTcEDDA/HYNIC-TOC has a lower sensitivity (90.5%) than ^{68}Ga-DOTA-peptides but greater specificity and diagnostic accuracy[17,66].

The role of nuclear medicine in diagnostic imaging is essential but has changed sufficiently in recent years. The somatostatin receptor scintigraphy by ^{111}indium pentetreotide (octreoscan) was the most used method for many years in clinical practice[67], but it is no longer the preferred imaging investigation method. However, despite important novel advances, its value may still be useful in some cases[18].

Apart from endoscopy, fluoroscopy is a valuable adjuvant option to assess the lumen of the upper GI tract, especially the duodenum, for NET existence or postoperative complications, obstructions and leakage[68].

The role of diagnostic endoscopic imaging has been mentioned above in detail.

Histopathology staging

The accurate histological assessment includes morphological evaluation, grading and immunohisto-chemistry results[34,69]. To establish the diagnosis of NETs, immunohistochemical staining for chromo-granin A (CgA) and synaptophysin is necessary; another promising new immunohistochemical neuroendocrine marker is the transcription factor INSM1 instead of synaptophysin[44].

The recent histopathology staging is based on the 2019 WHO classification and grading that includes terminology, differentiation, grade, mitotic rate and KI-67 proliferation index[14].

MiNENs are rare aggressive neoplastic lesions in the gastrointestinal system with poor prognosis that usually consist of adenocarcinoma and neuroendocrine carcinoma. They are more frequently located in the colon, including the rectum. MiNENs of the ampulla are extremely rare. The main treatment is radical surgical resection followed by adjuvant chemotherapy[10]. Other locations include the eso-phagus and gastroesophageal junction, stomach, small intestine, appendix pancreas, liver, gallbladder and biliary tree. Currently, MiNENs also include neoplasms in the gastrointestinal system consisting of a nonneuroendocrine component and epithelial neoplasms other than adenocarcinoma. There are 3 main subtypes, *i.e.*, collision, combined and amphicrine lesions. They are derived from a single precursor cell that has the capacity for dual differentiation after the initiation of carcinogenesis. Extensive surgery is not indicated in metastatic disease, especially in high-grade cases. Systemic chemotherapy is advocated in such cases[11].

For pathologic evaluation of small intestine NETs, the established guidelines include CgA and synaptophysin positive stain test as the minimum for making the diagnosis; tumor size more than 1 cm is classified as pT2; mesenteric tumor deposits equal or more than 2 cm are classified as pN2; and metastasis in 7 (from 12 previously) or more lymph nodes is classified as pN2. Findings of a recent study include only one positive test for CgA and synaptophysin[69].

Prognostic factors

For small intestine NETs, tumor size more than 1 cm predicts regional lymph node infiltration; presence of mesenteric tumor deposits predicts distant metastasis; and metastasis in 7 or more lymph nodes predicts disease progression[69].

Independent positive prognostic factors in cases of metastatic (stage IV) small intestine NETs include age less than 60 years, normal C-reactive protein levels, no diarrhea, metastatic liver involvement less than 50% and peptide radioreceptor treatment. Patients treated by both primary tumor resection and peptide radioreceptor treatment had the best survival benefit[45].

Colon NET location in contrast with the rectum has a poor prognosis and is associated with poor survival. A recent large study from China including 1196 patients determined 7 prognostic factors for worse outcome: Age ≥ 68 years, female gender, tumor size ≥ 3.5 cm, grade > 2, without chemotherapy, N1 stage and M1 stage. The location in the vast majority (73.5%) concerned the right colon, and the median tumor size was 4.1 cm[70].

Extramural venous invasion is common in small intestine NETs and is an independent prognostic factor for distant hematogenous metastases, in mainly hepatic as well as colorectal carcinoma[71].

High lymphovascular invasion (24.8%), even in grade 1 cases (22.8%), was found in biopsy for resected GI-NETs. It is a prognostic factor of biological behavior for malignant tendency. Close follow-up is recommended in such cases[59].

The WHO classification has proven adequate in predicting the course of NETs, and the Ki-67 proliferation index is a better prognostic factor for survival than the degree of differentiation[72].

MANAGEMENT

The standard management is surgical therapeutic resection of the primary tumor with wide lymph node clearance[73]. For small, well-differentiated lesions, therapeutic endoscopy has a key role, as mentioned above, that is based on the location[21,34]. For advanced disease, management includes surgical hepatic resection, techniques of local tumor destruction such as radiofrequency or microwave ablation, systemic chemotherapy, targeted therapy by biological agents, immunotherapy and drug therapy, mainly involving somatostatin analogs for symptom alleviation in inoperable lesions or suppressing tumor growth or recurrence after surgery[4,35].

Endoscopic mucosal resection and endoscopic submucosal dissection are indicated for small (≤ 1 cm) and superficial rectal NETs, provided that there is no involvement of muscularis propria or lymph nodes. For lesions above 2 cm in diameter, a low anterior resection or abdominal resection is recommended[4].

Surgical excision

The surgical excision depends on age, location, functional activity, size, grade, staging and sporadic or inherited origin. In general lesions > 2 cm require surgery[35].

The extremely rare esophageal NETs (1.3% of all GI-NETs) mainly in men (4/1) and in the lower third are metastatic in the majority at the time of diagnosis. Small lesions can be managed endoscopically, while large lesions (> 2 cm) require esophagectomy (Ivor Lewis or Mackeown) by wide lymphadenectomy[74].

For stomach location type 3 Lesions (> 2 cm) or type 2 (multiple small lesions) the indication is total or subtotal gastrectomy by wide lympadenectomy. However, since the majority of lesions are type 1, endoscopic excision is the method of first option, preferably by experienced gastroenterologists[21].

For duodenal location apart from bulb location, where endoscopic management is indicated, pancreatoduodenectomy or partial duodenectomy is often required[4,21].

For small intestinal location due to tumor local status a wide enterectomy by lymphadenectomy is indicated. The high rate (up to 50%) of central mesenteric involvement makes the surgical resection more complicated. A systematic review showed overall morbidity 13%, but severe 7% and 30-day mortality 2%[75]. Although, there has been a debate, for small intestine NETs the resection of the primary focus in case of inoperable distant metastases does not have any effect on survival and thus it is not indicated[76]. The opposite conclusion is withdrawn by a recent meta-analysis indicating survival benefit[7].

Colon location in the vast majority is managed as adenocarcinoma by colectomy mainly right or less common left and wide lymphadenectmy[35].

Rectum location in the most cases usually needs endoscopic management (ESD, EMR) as already mentioned[43]; apart from this, TEMS (Transanal Endoscopic Microsurgery) is another resection method. However for rectal lesions greater than 2 cm in size, grade 3, stage T3-T4 or by lymph node invasion low anterior resection or abdominoperineal resection may be necessary[21].

Treatment of appendiceal NETs depends on factors such as Ki-67 proliferation index, tumor size, location, mesoappendix invasion, and lymph node involvement. Ki-67 determines grading; it is in Grade 1 ≤ 2%, Grade 2 between 3% to 20% and Grade 3 > 20%. The vast majority of cases are Grade 1, with tumor size less than 1 cm in which a simple appentectomy is enough. Right hemicolectomy is mandatory for Grade 3 Lesions independently size, in lesions greater than 2 cm, location in basis and invasion of mesoappendix or lymph nodes. In intermediate cases of grey zone a meticulous investigation (imagine, biomarkers) is mandatory and the decision must be individualized[36]. However, given that in up to 18% of appendiceal NETs cases coexist with another neoplasm, colonoscopy is indicated in any case[4].

Nowadays, for liver metastasis hepatectomy is the undoubted management option offering chance of cure and long-term survival, alone or accompanied by adjuvant chemotherapy[77]. With the advances in energy based devices, it is feasible, safe and effective as one stage procedure; the simultaneous hepatectomy along with wide enterectomy for synchronous metastatic disease of small intestine NETs that is present on liver in half of patients, represents a recent achievement. Despite the high recurrence rate (81%), it will achieve prolonged survival, when metastases concern only the liver[78].

In case of functioning liver metastasis and no possibility for curative resection, cytoreduction or debulking surgery by removing the most tumor bulking (> 90%) may alleviate the symptoms due to hormone hyper-secretion. It is recommended in combination with drug and chemotherapeutic agents [79]. Another option for extended bilobar metastases, but only functioning by uncontrolled symptoms or ineffective treatment, is the orthotopic liver transplantation. The 1-year, 3-year and 5-year actuarial survival rate after transplantation reaches 59%, 47% and 36%, respectively for carcinoids tumors; but it is worse and is not indicated for other NETs. Extended lymphadenectomy of the hepatoduodenal ligament during the total hepatectomy is necessary before the implant placement[80].

Radioguided Surgery based on preoperative radionuclides (indium-111 pentetreotide, gallium-68 DOTA-peptides or technetium-99m EDDA/HYNIC-peptides) may improve the intraoperative reveal of GI tract NETs location[81].

Drug therapy- immunotherapy

Somatostatin analogs such as octreotide or lanreotide have been used after surgery to suppress tumor growth or recurrence and in inoperable cases for symptom palliation; also, they are included in the first-line therapy of NETs not amenable to curative surgery[17,35,82,83].

Telotristat is an inhibitor of tryptophan hydroxylases (TPH 1 and TPH2) that limits serotonin biosynthesis and relieves manifestations of carcinoid syndrome. Telotristat together with a long-acting somatostatin analog is currently recommended for uncontrolled carcinoid syndrome diarrhea by the United States National Comprehensive Cancer Network (NCCN)[84].

The NCCN, the North American Neuroendocrine Tumor Society and the Society of Nuclear Medicine and Molecular Imaging guidelines recommend somatostatin analogs as first-line treatment for positive somatostatin receptor grades 1 and 2 gastroenteropancreatic NETs[82].

In such patients with progressive advanced disease, for first-line treatment apart from somatostatin analogs, the therapeutic choices include ^{177}Lu-DOTA-TATE, everolimus, chemotherapy or palliative radiotherapy for painful bone metastases[82].

^{177}Lu-DOTA-TATE is a PRRT (radiolabeled peptide receptor radionuclide therapy) approved by the United States Food and Drug Administration in January 2018 and used for NETs with positive somatostatin receptors[82]. PRRT has superiority over somatostatin analogs (SSAs) and is the first choice of treatment for patients with advanced well-differentiated NETs (effectiveness 96%). PRRT is followed by SSA plus bevacizumab (effectiveness 86%) and SSA plus IFN-α (interferon alpha) (effectiveness 78%); all three have similar serious side effects[85].

There have been five SSTR subtypes, *i.e.*, SSTR1, 2A and 2B, 3, 4, and 5. Somatostatin receptor antagonist therapy targets these subtypes by exerting antineoplastic activity. Peptide receptor radionuclide therapy (PRRT) uses radiolabeled SSA radionucleotides (Y90 or Lu177), which are firmly connected with a transport vehicle that binds directly to tumor cells, similar to a Trojan horse. It may be the most important anti-SSTR2 (most frequently expressed in lung and gastroenteropancreatic NETs) treatment for NETs in recent years[86].

The vast majority of target treatments include the above-mentioned agents against somatostatin receptors and also against paramycin pathways (mTOR) such as everolimus[87]. New drugs (ganitumab or cixutumumab) that increase the efficacy of everolimus have been reported[86].

After failure of standard treatment, targeted therapy by sintilimab, a monoclonal antibody against programmed cell death protein 1 (PD-1), has been assessed with promising results. The response rate was 20.8% for GI tract NETs and 27.8% for NECs[88].

Target therapy by EZH2 (enhancer of zeste homolog 2), which is a histone methyltransferase catalyzing trimethylation of histone H3 Lysine 27 (H3K27me3), represents a novel promising biological agent with an important role in small bowel NETs[89].

Surufatinib, previously known as sulfatinib, is a novel, oral, tyrosine kinase inhibitor that inhibits receptors of VEGF (Vascular Endothelial Growth Factor), FGF (Fibroblast Growth Factor) and CSF (Colony Stimulating Factor 1) and exhibits antineoplastic activity, even in advanced progressive well-differentiated NETs[90].

Sunitinib and everolimus have been used as target therapies for NETs among other uses since they inhibit tumor growth, vasculature and spread capacity[46,91]. Sunitinib is a tyrosine kinase inhibitor approved initially as a target therapy for renal cell cancer and GISTs (gastrointestinal stromal tumors) resistant to imatinib treatment. Everolimus is an inhibitor of mTOR (mammalian target of rapamycin) that was approved as an immunosuppressor, to avoid rejection after transplantation and as a target therapy in renal cell carcinoma and other neoplasms[91].

The combination of the biological agents bevacizumab, an anti-VEGF monoclonal antibody, with atezolizumab, an anti-PD-L1 monoclonal antibody (against the protein programmed cell death-ligand 1), in patients with advanced NETs showed promising results that were compatible with other therapies [92].

Novel monoclonal antibodies as immunotherapy alone or in combination have been investigated for NETs with limited effectiveness and limited data. Several trials are still ongoing. They include pembrolizumab, spartalizumab, toripalimab, avelumab, regorafenib, lenvatinib, tiselizumab and others[93].

Systemic chemotherapy is recommended in cases that worsen despite first-line treatment with somatostatin analogs, or involve increasing tumor burden or rapid growth. Chemotherapy has limited efficacy in extrapancreatic NETs, including GI tract NETs, and thus, it is not indicated routinely. It includes choices such as streptozotocin with 5-fluorouracil or its precursor form capecitabine, temozolomide, which tends to replace streptozotocin, doxorubicin, interferon-α, platinum based agents (oxaliplatin with better safety or cisplatin), dacarbizine and irinotecan. In addition to hepatic artery embolization (spongostan, gel-foam) or preferably chemoembolization by doxorubicin, cisplatin is helpful in hepatic metastases. Chemoembolization in combination with systemic chemotherapy is related to better outcomes[94,95].

Neuroendocrine carcinomas exhibit very aggressive behavior with a median overall survival of up to 12 months. Combination chemotherapy, as in non-small cell lung carcinoma of cisplatin with etoposide (VP-16), has been the classical approach[95].

A recent study from the California Cancer Registry including 154 patients with GI-NETs and liver metastases showed that liver-directed therapy is associated with improved overall and disease-specific survival compared to systemic therapy alone[96].

PROGNOSIS

Appendiceal NETs have the most favorable prognosis[97]. The prognosis of stomach NETs for type 1 is excellent with the 5-year survival rate being greater than 95%, while that for type 2 is good and for type 3 is poor, being equal to or less than 50%. Nonfunctioning duodenal NETs generally have a better prognosis than adenocarcinoma, while high-grade lesions have a worse prognosis. Rectal NETs have the best prognosis among GI-NETs because they are small and without invasion in the majority of cases. In T1, the 5-year survival is 98%-100% for localized lesions, 54%-74% for regional metastases and 15%-37% for distant metastases[21].

Large bowel NETs, in contrast with those of the rectum, have a much worse prognosis and one of the worst survival outcomes among the other GI tract NETs due to their greater size, T stage, grade and lymphatic invasion[70].

Small bowel NETs, as slow-growing lesions, have a rather favorable prognosis in general, but uncommonly, there are some cases with unfavorable prognoses. Overall survival is more favorable than in other cancers. It was estimated that the 5-year survival rate was 67% and the 10-year survival rate was 37%. A meta-regression analysis found that younger age, mainly, or perhaps primary tumor resection is related to better prognosis[98]. The presence of preoperative symptoms determines the prognosis. Those induced by hormone secretion predict advanced disease and poor prognosis[99,100].

It is debatable whether resection of the primary tumor in metastatic small bowel NETs is valuable for improving prognosis. A recent study showed that it does not affect overall survival and thus is not recommended as a standard in such cases[74]. However, a recent meta-analysis supports the opposite, *i.e.*, Noncurative primary site excision offers increased survival (5-year rate of 74%, 10-year rate of 44%) [79].

A NET nomogram (Modlin Score) can be used for prognosis and consists of 15 variables: Age, sex, ethnicity, symptoms, tumor size, invasion, metastasis, histology, Ki-67 index, urinary 5-HIAA, serum HgA, liver function tests, carcinoid heart disease, surgical management or long-acting somatostatin analog therapy[101]. Malnutrition and neoplastic cachexia influence the outcome of cancers affecting survival; they are also associated with the nutritional status of gastrointestinal NETs. Consequently, nutritional assessment or even more precisely ghrelin molecular expression is necessary in such cases to improve the prognosis[102].

NECs (neuroendocrine carcinomas) in the rectum are very uncommon and involve aggressive neoplasms with a dismal prognosis. Treatment options include surgery, chemotherapy and radiotherapy. A large retrospective study including 805 cases confirmed the poor outcome even after radical excision. This indicates cautious and circumspect selection of patients by poor differentiation and high-grade rectal NETs. Systemic chemotherapy may improve the outcome[103].

The biological behavior of MiNENs (mixed neuroendocrine non-neuroendocrine neoplasms) is similar to that of pure NECs, both characterized by poor prognosis[104].

The role of artificial intelligence and machine learning and a deep understanding of the diagnosis and management of NENs of the gastrointestinal system have been recently evaluated. A standard of practice has not yet been established; however, it may serve as a useful adjunct in current practices[105].

CONCLUSION

The gastrointestinal tract and pancreas are the most common locations of NETs. The assessment of NETs includes determining the site, grade, stage and secretion capacity. New imaging techniques, histopathology assessment and classification have been valuable in making the diagnosis and planning therapeutic management. Liquid biopsy and the NETest gene index is a useful novel biomarker in peripheral blood. The somatostatin receptor scintigraphy is no longer the preferred imaging investigation. ^{68}Ga-DOTATATE PET/CT or the newest ^{64}Cu-DOTATATE PET/CT are the preferred imaging. Surgical or endoscopic resection is usually indicated for localized lesions depending on the tumor size (surgery is necessary for tumors 2 cm or more in size). Hepatectomy or even liver transplantation has well-defined indications as well as debulking surgery in secreting NETs. Long-acting release somatostatin analogs is the first-line treatment for inoperable advanced disease, followed in unresponsive cases by chemotherapy or targeted immunotherapy by novel biological agents. Somatostatin receptor antagonist therapy exerts antineoplastic activity. Radiolabeled peptide receptor radionuclide therapy and somatostatin analogs plus bevacizumab or IFN-α are novel therapeutic options. Telotristat treatment is indicated for persistent diarrhea in carcinoid syndrome. The therapeutic option should be individualized based on current multidisciplinary information. The gastroenterologists play an important role in diagnosis and management. Future assessments should be focused on targeted biological agents of the implicated molecular factors, new effective chemotherapy drugs, gene therapy and the use of artificial intelligence in the diagnosis and management of these diseases to open new horizons for therapeutic strategies.

FOOTNOTES

REFERENCES

1   **Natalicchio A**, Faggiano A, Zatelli MC, Argentiero A, D'Oronzo S, Marrano N, Beretta GD, Acquati S, Adinolfi V, Di Bartolo P, Danesi R, Ferrari P, Gori S, Morviducci L, Russo A, Tuveri E, Montagnani M, Gallo M, Silvestris N, Giorgino F. Metabolic disorders and gastroenteropancreatic-neuroendocrine tumors (GEP-NETs): How do they influence each other? *Crit Rev Oncol Hematol* 2022; **169**: 103572 [PMID: 34954047 DOI: 10.1016/j.critrevonc.2021.103572]
2   **Amorim LC**, Ferreira AR, Perez RO, Peixoto RD. Localized Well-Differentiated Rectal Neuroendocrine Tumors - Where

Are We in 2021? *Clin Colorectal Cancer* 2022; **21**: e22-e27 [PMID: 34838461 DOI: 10.1016/j.clcc.2021.10.002]

3   **Şentürk M**, Acar B, Yildirim MA, Çakir M, Küçükkartallar T, Vatansev C. Clinicopathological Characteristics of Gastroenteropancreatic Neuroendocrine Tumors: 10 Years of Experience From a Single Center. *Pancreas* 2022; **51**: 159-163 [PMID: 35404891 DOI: 10.1097/MPA.0000000000001981]

4   **Yin F**, Wu ZH, Lai JP. New insights in diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. *World J Gastroenterol* 2022; **28**: 1751-1767 [PMID: 35633912 DOI: 10.3748/wjg.v28.i17.1751]

5   **Bu X**, Wang X, Wei L, Liu J, Chen M. The Risk of Second Primary Malignancies in Patients With Lung Neuroendocrine Tumors: A Population-Based Study on SEER Database. *Curr Probl Cancer* 2020; **44**: 100613 [PMID: 32563531 DOI: 10.1016/j.currproblcancer.2020.100613]

6   **Elmaaz A**, Kasi A.   APUDoma. 2022 Jul 18. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan- [PMID: 32809382]

7   **Van Den Heede K**, Chidambaram S, Van Slycke S, Brusselaers N, Warfvinge CF, Ohlsson H, Nordenström E, Almquist M. Effect of primary tumour resection without curative intent in patients with metastatic neuroendocrine tumours of the small intestine and right colon: meta-analysis. *Br J Surg* 2022; **109**: 191-199 [PMID: 34941998 DOI: 10.1093/bjs/znab413]

8   **Masui T**, Ito T, Komoto I, Kojima S, Kasai Y, Tanabe M, Hara K, Hirano S, Okusaka T, Ichikawa Y, Kinugasa Y, Kokudo N, Kudo A, Sakurai A, Sugihara K, Date H, Haruma K, Hijioka S, Hirata K, Yamano H, Sakamine M, Kikuchi T, Fukushima M, Imamura M, Uemoto S. Nationwide registry for patients with neuroendocrine neoplasm of pancreas, gastrointestinal tract, lungs, bronchi, or thymus in Japan. *Int J Clin Oncol* 2022; **27**: 840-849 [PMID: 35178624 DOI: 10.1007/s10147-022-02130-y]

9   **Guerrera LP**, Suarato G, Napolitano R, Perrone A, Caputo V, Ventriglia A, Martini G, Della Corte CM, Orditura M, Martinelli E, Ciardiello F, Montella M, Franco R, Troiani T, Napolitano S. Mixed Neuroendocrine Non-Neuroendocrine Neoplasms of the Gastrointestinal Tract: A Case Series. *Healthcare (Basel)* 2022; **10** [PMID: 35455885 DOI: 10.3390/healthcare10040708]

10   **Wang Y**, Zhang Z, Wang C, Xi SH, Wang XM. Mixed neuroendocrine-nonneuroendocrine neoplasm of the ampulla: Four case reports. *World J Clin Cases* 2022; **10**: 2268-2274 [PMID: 35321159 DOI: 10.12998/wjcc.v10.i7.2268]

11   **Elpek GO**. Mixed neuroendocrine-nonneuroendocrine neoplasms of the gastrointestinal system: An update. *World J Gastroenterol* 2022; **28**: 794-810 [PMID: 35317101 DOI: 10.3748/wjg.v28.i8.794]

12   **Pellat A**, Cottereau AS, Terris B, Coriat R. Neuroendocrine Carcinomas of the Digestive Tract: What Is New? *Cancers (Basel)* 2021; **13** [PMID: 34359666 DOI: 10.3390/cancers13153766]

13   **Dasari A**, Shen C, Devabhaktuni A, Nighot R, Sorbye H. Survival According to Primary Tumor Location, Stage, and Treatment Patterns in Locoregional Gastroenteropancreatic High-grade Neuroendocrine Carcinomas. *Oncologist* 2022; **27**: 299-306 [PMID: 35380711 DOI: 10.1093/oncolo/oyab039]

14   **Popa O**, Taban SM, Pantea S, Plopeanu AD, Barna RA, Cornianu M, Pascu AA, Dema ALC. The new WHO classification of gastrointestinal neuroendocrine tumors and immunohistochemical expression of somatostatin receptor 2 and 5. *Exp Ther Med* 2021; **22**: 1179 [PMID: 34475969 DOI: 10.3892/etm.2021.10613]

15   **Fang JM**, Li J, Shi J. An update on the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. *World J Gastroenterol* 2022; **28**: 1009-1023 [PMID: 35431496 DOI: 10.3748/wjg.v28.i10.1009]

16   **Gherghe M**, Lazăr AM, Stanciu AE, Mutuleanu MD, Sterea MC, Petroiu C, Galeş LN. The New Radiolabeled Peptide [99m]TcEDDA/HYNIC-TOC: Is It a Feasible Choice for Diagnosing Gastroenteropancreatic NETs? *Cancers (Basel)* 2022; **14** [PMID: 35681704 DOI: 10.3390/cancers14112725]

17   **Vahidfar N**, Farzanehfar S, Abbasi M, Mirzaei S, Delpassand ES, Abbaspour F, Salehi Y, Biersack HJ, Ahmadzadehfar H. Diagnostic Value of Radiolabelled Somatostatin Analogues for Neuroendocrine Tumour Diagnosis: The Benefits and Drawbacks of [^{64}Cu]Cu-DOTA-TOC. *Cancers (Basel)* 2022; **14** [PMID: 35454822 DOI: 10.3390/cancers14081914]

18   **Inaba Y**, Hijioka S, Iwama I, Asai T, Miyamura H, Chatani S, Hasegawa T, Murata S, Kato M, Sato Y, Yamaura H, Onaya H, Shimizu J, Hara K. Clinical usefulness of Somatostatin Receptor Scintigraphy in the Diagnosis of Neuroendocrine Neoplasms. *Asia Ocean J Nucl Med Biol* 2022; **10**: 1-13 [PMID: 35083344 DOI: 10.22038/AOJNMB.2021.56254.1390]

19   **Ramzan A**, Tafti D.   Nuclear Medicine PET/CT Gastrointestinal Assessment, Protocols, And Interpretation. 2022 Apr 9. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan- [PMID: 35593839]

20   **Morland D**, Jallerat P, Brixi H, Cadiot G, Papathanassiou D, Deguelte S. Performances of 18F-FDOPA PET/CT in the Preoperative Evaluation of the Peritoneal Cancer Index in Small Intestine Neuroendocrine Tumors. *Clin Nucl Med* 2022; **47**: 294-298 [PMID: 35067541 DOI: 10.1097/RLU.0000000000004057]

21   **Carvão J**, Dinis-Ribeiro M, Pimentel-Nunes P, Libânio D. Neuroendocrine Tumors of the Gastrointestinal Tract: A Focused Review and Practical Approach for Gastroenterologists. *GE Port J Gastroenterol* 2021; **28**: 336-348 [PMID: 34604465 DOI: 10.1159/000512089]

22   **Perez K**, Kulke MH, Chittenden A, Ukaegbu C, Astone K, Alexander H, Brais L, Zhang J, Garcia J, Esplin ED, Yang S, Da Silva A, Nowak JA, Yurgelun MB, Garber J, Syngal S, Chan J. Clinical Implications of Pathogenic Germline Variants in Small Intestine Neuroendocrine Tumors (SI-NETs). *JCO Precis Oncol* 2021; **5**: 808-816 [PMID: 34994613 DOI: 10.1200/PO.21.00047]

23   **Rico K**, Duan S, Pandey RL, Chen Y, Chakrabarti JT, Starr J, Zavros Y, Else T, Katona BW, Metz DC, Merchant JL. Genome analysis identifies differences in the transcriptional targets of duodenal versus pancreatic neuroendocrine tumours. *BMJ Open Gastroenterol* 2021; **8** [PMID: 34750164 DOI: 10.1136/bmjgast-2021-000765]

24   **Elias E**, Ardalan A, Lindberg M, Reinsbach SE, Muth A, Nilsson O, Arvidsson Y, Larsson E. Independent somatic evolution underlies clustered neuroendocrine tumors in the human small intestine. *Nat Commun* 2021; **12**: 6367 [PMID: 34737276 DOI: 10.1038/s41467-021-26581-5]

25   **Aavikko M**, Kaasinen E, Andersson N, Pentinmikko N, Sulo P, Donner I, Pihlajamaa P, Kuosmanen A, Bramante S, Katainen R, Sipilä LJ, Martin S, Arola J, Carpén O, Heiskanen I, Mecklin JP, Taipale J, Ristimäki A, Lehti K, Gucciardo E, Katajisto P, Schalin-Jäntti C, Vahteristo P, Aaltonen LA. WNT2 activation through proximal germline deletion

predisposes to small intestinal neuroendocrine tumors and intestinal adenocarcinomas. *Hum Mol Genet* 2021; **30**: 2429-2440 [PMID: 34274970 DOI: 10.1093/hmg/ddab206]

26   **Sampedro-Núñez M**, Bouthelier A, Serrano-Somavilla A, Martínez-Hernández R, Adrados M, Martín-Pérez E, Muñoz de Nova JL, Cameselle-Teijeiro JM, Blanco-Carrera C, Cabezas-Agricola JM, Díaz JÁ, García-Centeno R, Aragones J, Marazuela M. LAT-1 and GLUT-1 Carrier Expression and Its Prognostic Value in Gastroenteropancreatic Neuroendocrine Tumors. *Cancers (Basel)* 2020; **12** [PMID: 33066332 DOI: 10.3390/cancers12102968]

27   **Waldum H**, Mjønes PG. Correct Identification of Cell of Origin May Explain Many Aspects of Cancer: The Role of Neuroendocrine Cells as Exemplified from the Stomach. *Int J Mol Sci* 2020; **21** [PMID: 32796591 DOI: 10.3390/ijms21165751]

28   **Drozdov I**, Kidd M, Nadler B, Camp RL, Mane SM, Hauso O, Gustafsson BI, Modlin IM. Predicting neuroendocrine tumor (carcinoid) neoplasia using gene expression profiling and supervised machine learning. *Cancer* 2009; **115**: 1638-1650 [PMID: 19197975 DOI: 10.1002/cncr.24180]

29   **Grötzinger C**. Tumour biology of gastroenteropancreatic neuroendocrine tumours. *Neuroendocrinology* 2004; **80** Suppl 1: 8-11 [PMID: 15477708 DOI: 10.1159/000080732]

30   **Yachida S**, Totoki Y, Noë M, Nakatani Y, Horie M, Kawasaki K, Nakamura H, Saito-Adachi M, Suzuki M, Takai E, Hama N, Higuchi R, Hirono S, Shiba S, Kato M, Furukawa E, Arai Y, Rokutan H, Hashimoto T, Mitsunaga S, Kanda M, Tanaka H, Takata S, Shimomura A, Oshima M, Hackeng WM, Okumura T, Okano K, Yamamoto M, Yamaue H, Morizane C, Arihiro K, Furukawa T, Sato T, Kiyono T, Brosens LAA, Wood LD, Hruban RH, Shibata T. Comprehensive Genomic Profiling of Neuroendocrine Carcinomas of the Gastrointestinal System. *Cancer Discov* 2022; **12**: 692-711 [PMID: 34880079 DOI: 10.1158/2159-8290.CD-21-0669]

31   **Mafficini A**, Scarpa A. Genetics and Epigenetics of Gastroenteropancreatic Neuroendocrine Neoplasms. *Endocr Rev* 2019; **40**: 506-536 [PMID: 30657883 DOI: 10.1210/er.2018-00160]

32   **Kytölä S**, Höög A, Nord B, Cedermark B, Frisk T, Larsson C, Kjellman M. Comparative genomic hybridization identifies loss of 18q22-qter as an early and specific event in tumorigenesis of midgut carcinoids. *Am J Pathol* 2001; **158**: 1803-1808 [PMID: 11337378 DOI: 10.1016/S0002-9440(10)64136-3]

33   **Andersson E**, Swärd C, Stenman G, Ahlman H, Nilsson O. High-resolution genomic profiling reveals gain of chromosome 14 as a predictor of poor outcome in ileal carcinoids. *Endocr Relat Cancer* 2009; **16**: 953-966 [PMID: 19458023 DOI: 10.1677/ERC-09-0052]

34   **Chen LH**, Chen J. [Interpretation of updated international guidelines for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2021; **24**: 843-848 [PMID: 34674457 DOI: 10.3760/cma.j.cn.441530-20210823-00342]

35   **Fernandez CJ**, Agarwal M, Pottakkat B, Haroon NN, George AS, Pappachan JM. Gastroenteropancreatic neuroendocrine neoplasms: A clinical snapshot. *World J Gastrointest Surg* 2021; **13**: 231-255 [PMID: 33796213 DOI: 10.4240/wjgs.v13.i3.231]

36   **Yıldırım E**, Kegin M, Özdemir M, Bektaş S, Pelen Z, Er M. Neoplasms of the appendix: Single institution and ten-year experiences results. *Ulus Travma Acil Cerrahi Derg* 2022; **28**: 352-360 [PMID: 35485573 DOI: 10.14744/tjtes.2021.86032]

37   **Alkhayyat M**, Saleh MA, Coronado W, Abureesh M, Zmaili M, Qapaja T, Almomani A, Khoudari G, Mansoor E, Cooper G. Epidemiology of neuroendocrine tumors of the appendix in the USA: a population-based national study (2014-2019). *Ann Gastroenterol* 2021; **34**: 713-720 [PMID: 34475743 DOI: 10.20524/aog.2021.0643]

38   **Blažević A**, Iyer AM, van Velthuysen MF, Hofland J, Oudijk L, de Herder WW, Hofland LJ, Feelders RA. Sexual Dimorphism in Small-intestinal Neuroendocrine Tumors: Lower Prevalence of Mesenteric Disease in Premenopausal Women. *J Clin Endocrinol Metab* 2022; **107**: e1969-e1975 [PMID: 34999838 DOI: 10.1210/clinem/dgac001]

39   **Wong L**, Kanthasamy SV, Durairaj G, Thangaratnam RR. Neuroendocrine tumour masquerading as intussusception: A case report. *Int J Surg Case Rep* 2020; **77**: 48-52 [PMID: 33137672 DOI: 10.1016/j.ijscr.2020.10.091]

40   **Morrison JH**, Grzanna R, Molliver ME, Coyle JT. The distribution and orientation of noradrenergic fibers in neocortex of the rat: an immunofluorescence study. *J Comp Neurol* 1978; **181**: 17-39 [PMID: 355267 DOI: 10.1016/j.cgh.2022.04.016]

41   **Zhornitskiy A**, Le L, Tareen S, Abdullahi G, Karunasiri D, Tabibian JH. Gastro-gastric intussusception in the setting of a neuroendocrine tumor: A case report. *World J Clin Cases* 2019; **7**: 3517-3523 [PMID: 31750333 DOI: 10.12998/wjcc.v7.i21.3517]

42   **Cope J**, Srirajaskanthan R. Rectal Neuroendocrine Neoplasms: Why Is There a Global Variation? *Curr Oncol Rep* 2022; **24**: 257-263 [PMID: 35084662 DOI: 10.1007/s11912-021-01172-1]

43   **Glover M**, Caplin M, Leeuwenkamp OR, Longworth L. Use of [¹⁷⁷Lu]Lu-DOTA-TATE in the treatment of gastroenteropancreatic neuroendocrine tumours: Results of a UK cost-effectiveness modelling study. *EJC Suppl* 2021; **16**: 14-23 [PMID: 34912479 DOI: 10.1016/j.ejcsup.2021.06.003]

44   **Takayanagi D**, Cho H, Machida E, Kawamura A, Takashima A, Wada S, Tsunoda T, Kohno T, Shiraishi K. Update on Epidemiology, Diagnosis, and Biomarkers in Gastroenteropancreatic Neuroendocrine Neoplasms. *Cancers (Basel)* 2022; **14** [PMID: 35267427 DOI: 10.3390/cancers14051119]

45   **Maurer E**, Heinzel-Gutenbrunner M, Rinke A, Rütz J, Holzer K, Figiel J, Luster M, Bartsch DK. Relevant prognostic factors in patients with stage IV small intestine neuroendocrine neoplasms. *J Neuroendocrinol* 2022; **34**: e13076 [PMID: 34964186 DOI: 10.1111/jne.13076]

46   **Khan MS**, Pritchard DM. Neuroendocrine tumours: what gastroenterologists need to know. *Frontline Gastroenterol* 2022; **13**: 50-56 [PMID: 34966533 DOI: 10.1136/flgastro-2020-101431]

47   **Popa O**, Tăban SM, Dema ALC, Plopeanu AD, Barna RA, Cornianu M, Dema S. Immunohistochemical expression of chemokine receptor in neuroendocrine neoplasms (CXCR4) of the gastrointestinal tract: a retrospective study of 71 cases. *Rom J Morphol Embryol* 2021; **62**: 151-157 [PMID: 34609417 DOI: 10.47162/RJME.62.1.14]

48   **Luo R**, Huang W, Chen L, Liu Y, Xu L, Zhang X, Xu C, Hou Y. SP70 is a potential biomarker to identify gastric fundic gland neoplasms. *World J Surg Oncol* 2022; **20**: 132 [PMID: 35468832 DOI: 10.1186/s12957-022-02564-8]

49   **Spiridon IA**, Ciobanu DGA, Giușcă SE, Căruntu ID. Ghrelin and its role in gastrointestinal tract tumors (Review). *Mol*

Med Rep 2021; **24** [PMID: 34296307 DOI: 10.3892/mmr.2021.12302]

50   **Udelnow A**, Jechorek D, Wex C, Klose S, Pech M, Reinhold A, Meyer F. Possible role of TGF β1 in inflammatory pseudotumor associated with multiple neuroendocrine tumors of the small intestine. *Pathol Res Pract* 2015; **211**: 805-809 [PMID: 26293797 DOI: 10.1016/j.prp.2015.06.005]

51   **Amarapurkar AD**, Davies A, Ramage JK, Stangou AJ, Wight DG, Portmann BC. Proliferation of antigen MIB-1 in metastatic carcinoid tumours removed at liver transplantation: relevance to prognosis. *Eur J Gastroenterol Hepatol* 2003; **15**: 139-143 [PMID: 12560757 DOI: 10.1097/00042737-200302000-00006]

52   **Papaefthymiou A**, Laskaratos FM, Koffas A, Manolakis A, Gkolfakis P, Coda S, Sodergren M, Suzuki N, Toumpanakis C. State of the Art in Endoscopic Therapy for the Management of Gastroenteropancreatic Neuroendocrine Tumors. *Curr Treat Options Oncol* 2022; **23**: 1014-1034 [PMID: 35511346 DOI: 10.1007/s11864-022-00986-w]

53   **Caillol F**, Meunier E, Zemmour C, Ratone JP, Guiramand J, Hoibian S, Dahel Y, Poizat F, Giovannini M. Efficiency of an endoscopic resection strategy for management of submucosal tumors < 20 mm in the upper gastrointestinal tract. *Endosc Int Open* 2022; **10**: E347-E353 [PMID: 35433227 DOI: 10.1055/a-1783-8675]

54   **Deprez PH**, Moons LMG, O'Toole D, Gincul R, Seicean A, Pimentel-Nunes P, Fernández-Esparrach G, Polkowski M, Vieth M, Borbath I, Moreels TG, Nieveen van Dijkum E, Blay JY, van Hooft JE. Endoscopic management of subepithelial lesions including neuroendocrine neoplasms: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2022; **54**: 412-429 [PMID: 35180797 DOI: 10.1055/a-1751-5742]

55   **Zhu C**, Kawachi H, Lu X. A rare gastric lesion: diminutive, well-differentiated, Grade 3, type 3 gastric neuroendocrine tumor with extremely high ki-67 index removed en bloc under endoscopy. *Gastric Cancer* 2022; **25**: 659-664 [PMID: 35179666 DOI: 10.1007/s10120-022-01277-x]

56   **Nabi Z**, Ramchandani M, Asif S, Basha J, Chavan R, Darisetty S, Reddy N. Outcomes of Endoscopic Submucosal Dissection in Duodenal Neuroendocrine Tumors. *J Gastrointest Surg* 2022; **26**: 275-277 [PMID: 34508292 DOI: 10.1007/s11605-021-05133-8]

57   **Yong JN**, Lim XC, Nistala KRY, Lim LKE, Lim GEH, Quek J, Tham HY, Wong NW, Tan KK, Chong CS. Endoscopic submucosal dissection versus endoscopic mucosal resection for rectal carcinoid tumor. A meta-analysis and meta-regression with single-arm analysis. *J Dig Dis* 2021; **22**: 562-571 [PMID: 34472210 DOI: 10.1111/1751-2980.13048]

58   **Sun P**, Zheng T, Hu C, Gao T, Ding X. Comparison of endoscopic therapies for rectal neuroendocrine tumors: endoscopic submucosal dissection with myectomy versus endoscopic submucosal dissection. *Surg Endosc* 2021; **35**: 6374-6378 [PMID: 34231072 DOI: 10.1007/s00464-021-08622-8]

59   **Miyashita H**, Yamasaki T, Akita Y, Ando Y, Maruyama Y, Nagata Y, Miyazaki R, Noguchi M, Sawada R, Sakurai T, Kato T, Sumiyama K, Suka M, Hamatani S, Saruta M. Small Neuroendocrine Tumors of the Whole Gastrointestinal Tract Performed Endoscopic or Surgical Resections Also Show Positive for Lymphovascular Invasion. *Digestion* 2021; **102**: 921-928 [PMID: 34265770 DOI: 10.1159/000517282]

60   **Pelage JP**, Soyer P, Boudiaf M, Brocheriou-Spelle I, Dufresne AC, Coumbaras J, Rymer R. Carcinoid tumors of the abdomen: CT features. *Abdom Imaging* 1999; **24**: 240-245 [PMID: 10227886 DOI: 10.1007/s002619900488]

61   **Baxi AJ**, Chintapalli K, Katkar A, Restrepo CS, Betancourt SL, Sunnapwar A. Multimodality Imaging Findings in Carcinoid Tumors: A Head-to-Toe Spectrum. *Radiographics* 2017; **37**: 516-536 [PMID: 28287937 DOI: 10.1148/rg.2017160113]

62   **Gualdi GF**, Casciani E, Polettini E. [Imaging of neuroendocrine tumors]. *Clin Ter* 2001; **152**: 107-121 [PMID: 11441522]

63   **Morani AC**, Gupta S, Elsayes KM, Mubarak AI, Khalaf AM, Bhosale PR, Sun J, Jensen CT, Kundra V. Performance of Multidetector Computed Tomography and Negative Versus Positive Enteric Contrast for Evaluation of Gastrointestinal Neuroendocrine Neoplasms. *J Comput Assist Tomogr* 2022; **46**: 333-343 [PMID: 35575649 DOI: 10.1097/RCT.0000000000001291]

64   **Doroudinia A**, Emami H, Hosseini MS. ^{68}Ga-DOTATATE Radioisotope scan to detect neuroendocrine tumors; A Cross-Sectional Study. *Asia Ocean J Nucl Med Biol* 2022; **10**: 14-19 [PMID: 35083345 DOI: 10.22038/AOJNMB.2021.56971.1397]

65   **Raj N**, Reidy-Lagunes D. The Role of 68Ga-DOTATATE Positron Emission Tomography/Computed Tomography in Well-Differentiated Neuroendocrine Tumors: A Case-Based Approach Illustrates Potential Benefits and Challenges. *Pancreas* 2018; **47**: 1-5 [PMID: 29232339 DOI: 10.1097/MPA.0000000000000949]

66   **Danti G**, Flammia F, Matteuzzi B, Cozzi D, Berti V, Grazzini G, Pradella S, Recchia L, Brunese L, Miele V. Gastrointestinal neuroendocrine neoplasms (GI-NENs): hot topics in morphological, functional, and prognostic imaging. *Radiol Med* 2021; **126**: 1497-1507 [PMID: 34427861 DOI: 10.1007/s11547-021-01408-x]

67   **Seregni E**, Chiti A, Bombardieri E. Radionuclide imaging of neuroendocrine tumours: biological basis and diagnostic results. *Eur J Nucl Med* 1998; **25**: 639-658 [PMID: 9618580 DOI: 10.1007/s002590050267]

68   **Johnson LN**, Moran SK, Bhargava P, Revels JW, Moshiri M, Rohrmann CA, Mansoori B. Fluoroscopic Evaluation of Duodenal Diseases. *Radiographics* 2022; **42**: 397-416 [PMID: 35179986 DOI: 10.1148/rg.210165]

69   **Polydorides AD**, Liu Q. Evaluation of Pathologic Prognostic Factors in Neuroendocrine Tumors of the Small Intestine. *Am J Surg Pathol* 2022; **46**: 547-556 [PMID: 35192293 DOI: 10.1097/PAS.0000000000001808]

70   **Xu R**, Zhou B, Hu P, Xue B, Gu D, Li X, Tang Q. Development and validation of prognostic nomograms for patients with colon neuroendocrine neoplasms. *World J Surg Oncol* 2021; **19**: 233 [PMID: 34364382 DOI: 10.1186/s12957-021-02338-8]

71   **Liu Q**, Polydorides AD. Diagnosis and prognostic significance of extramural venous invasion in neuroendocrine tumors of the small intestine. *Mod Pathol* 2020; **33**: 2318-2329 [PMID: 32514164 DOI: 10.1038/s41379-020-0585-1]

72   **Faggiano A**, Mansueto G, Ferolla P, Milone F, del Basso de Caro ML, Lombardi G, Colao A, De Rosa G. Diagnostic and prognostic implications of the World Health Organization classification of neuroendocrine tumors. *J Endocrinol Invest* 2008; **31**: 216-223 [PMID: 18401203 DOI: 10.1007/BF03345593]

73   **Zhang S**, Zheng C, Chen Y, Xu Q, Ma J, Yuan W, Jiang Q, Zhao Y, Zhang J, Che X, Wang C, Huang X, Chen F, Wang N, Ma X, Lan Z. Clinicopathologic features, surgical treatments, and outcomes of small bowel tumors: A retrospective study in China. *Int J Surg* 2017; **43**: 145-154 [PMID: 28583893 DOI: 10.1016/j.ijsu.2017.05.076]

74   **Lee CG**, Lim YJ, Park SJ, Jang BI, Choi SR, Kim JK, Kim YT, Cho JY, Yang CH, Chun HJ, Song SY; Neuroendocrine tumor study group. The clinical features and treatment modality of esophageal neuroendocrine tumors: a multicenter study in Korea. *BMC Cancer* 2014; **14**: 569 [PMID: 25098730 DOI: 10.1186/1471-2407-14-569]

75   **Kaçmaz E**, Chen JW, Tanis PJ, Nieveen van Dijkum EJM, Engelsman AF. Postoperative morbidity and mortality after surgical resection of small bowel neuroendocrine neoplasms: A systematic review and meta-analysis. *J Neuroendocrinol* 2021; **33**: e13008 [PMID: 34235792 DOI: 10.1111/jne.13008]

76   **Yan H**, Yin L, Han H, Jin Y, Liu Z. Relationship between Primary Tumor Resection for Metastatic Small Intestine Neuroendocrine Tumors and Survival: A Propensity Score-Matched Analysis. *J Invest Surg* 2022; **35**: 1239-1247 [PMID: 34991432 DOI: 10.1080/08941939.2021.2024306]

77   **Kraft A**, Croitoru A, Moldovan C, Lupescu I, Tomescu D, Purnichescu-Purtan R, Herlea V, Popescu I, Botea F. Is Long-Term Survival in Metastases from Neuroendocrine Neoplasms Improved by Liver Resection? *Medicina (Kaunas)* 2021; **58** [PMID: 35056330 DOI: 10.3390/medicina58010022]

78   **Addeo P**, Bertin JB, Imperiale A, Averous G, Terrone A, Goichot B, Bachellier P. Outcomes of Simultaneous Resection of Small Bowel Neuroendocrine Tumors with Synchronous Liver Metastases. *World J Surg* 2020; **44**: 2377-2384 [PMID: 32179974 DOI: 10.1007/s00268-020-05467-5]

79   **Concors SJ**, Maxwell JE. Neuroendocrine hepatic metastatic disease: the surgeon's perspective. *Abdom Radiol (NY)* 2022 [PMID: 35476146 DOI: 10.1007/s00261-022-03515-3]

80   **Le Treut YP**, Delpero JR, Dousset B, Cherqui D, Segol P, Mantion G, Hannoun L, Benhamou G, Launois B, Boillot O, Domergue J, Bismuth H. Results of liver transplantation in the treatment of metastatic neuroendocrine tumors. A 31-case French multicentric report. *Ann Surg* 1997; **225**: 355-364 [PMID: 9114793 DOI: 10.1097/00000658-199704000-00003]

81   **Cockburn KC**, Toumi Z, Mackie A, Julyan P. Radioguided Surgery for Gastroenteropancreatic Neuroendocrine Tumours: a Systematic Literature Review. *J Gastrointest Surg* 2021; **25**: 3244-3257 [PMID: 34506015 DOI: 10.1007/s11605-021-05115-w]

82   **Hendifar AE**, Mehr SH, McHaffie DR. Best Practices for the Coordinated Care of Patients With Neuroendocrine Tumors Undergoing Peptide Receptor Radionuclide Therapy. *Pancreas* 2022; **51**: 213-218 [PMID: 35584377 DOI: 10.1097/MPA.0000000000002002]

83   **Li SC**, Martijn C, Cui T, Essaghir A, Luque RM, Demoulin JB, Castaño JP, Öberg K, Giandomenico V. The somatostatin analogue octreotide inhibits growth of small intestine neuroendocrine tumour cells. *PLoS One* 2012; **7**: e48411 [PMID: 23119007 DOI: 10.1371/journal.pone.0048411]

84   **Kulke MH**, Kennecke HF, Murali K, Joish VN. Changes in Carcinoid Syndrome Symptoms Among Patients Receiving Telotristat Ethyl in US Clinical Practice: Findings from the TELEPRO-II Real-World Study. *Cancer Manag Res* 2021; **13**: 7439-7446 [PMID: 34611437 DOI: 10.2147/CMAR.S330429]

85   **Liu T**, Liao J, Dang J, Li G. Treatments for patients with advanced neuroendocrine tumors: a network meta-analysis. *Ther Adv Med Oncol* 2019; **11**: 1758835919853673 [PMID: 31191714 DOI: 10.1177/1758835919853673]

86   **Garcia-Alvarez A**, Hernando Cubero J, Capdevila J. Drug Development in Neuroendocrine Tumors: What Is on the Horizon? *Curr Treat Options Oncol* 2021; **22**: 43 [PMID: 33786683 DOI: 10.1007/s11864-021-00834-3]

87   **Raj N**, Reidy-Lagunes D. Current clinical trials of targeted agents for well-differentiated neuroendocrine tumors. *Pancreas* 2014; **43**: 1185-1189 [PMID: 25333401 DOI: 10.1097/MPA.0000000000000232]

88   **Jia R**, Li Y, Xu N, Jiang HP, Zhao CH, Liu RR, Shi Y, Zhang YY, Wang SY, Zhou H, Xu JM. Sintilimab in Patients with Previously Treated Metastatic Neuroendocrine Neoplasms. *Oncologist* 2022; **27**: e625-e632 [PMID: 35647908 DOI: 10.1093/oncolo/oyac097]

89   **Barazeghi E**, Hellman P, Norlén O, Westin G, Stålberg P. EZH2 presents a therapeutic target for neuroendocrine tumors of the small intestine. *Sci Rep* 2021; **11**: 22733 [PMID: 34815475 DOI: 10.1038/s41598-021-02181-7]

90   **Xu J**. Current treatments and future potential of surufatinib in neuroendocrine tumors (NETs). *Ther Adv Med Oncol* 2021; **13**: 17588359211042689 [PMID: 34484432 DOI: 10.1177/17588359211042689]

91   **Capdevila J**, Argilés G, Mulet-Margalef N, Tabernero J. [Neuroendocrine tumors: the age of targeted therapies]. *Endocrinol Nutr* 2012; **59**: 438-451 [PMID: 22565119 DOI: 10.1016/j.endonu.2012.03.003]

92   **Halperin DM**, Liu S, Dasari A, Fogelman D, Bhosale P, Mahvash A, Estrella JS, Rubin L, Morani AC, Knafl M, Overeem TA, Fu SC, Solis LM, Parra Cuentas E, Verma A, Chen HL, Gite S, Subashchandrabose P, Dervin S, Schulze K, Darbonne WC, Yun C, Wistuba II, Futreal PA, Woodman SE, Yao JC. Assessment of Clinical Response Following Atezolizumab and Bevacizumab Treatment in Patients With Neuroendocrine Tumors: A Nonrandomized Clinical Trial. *JAMA Oncol* 2022; **8**: 904-909 [PMID: 35389428 DOI: 10.1001/jamaoncol.2022.0212]

93   **Xu JX**, Wu DH, Ying LW, Hu HG. Immunotherapies for well-differentiated grade 3 gastroenteropancreatic neuroendocrine tumors: A new category in the World Health Organization classification. *World J Gastroenterol* 2021; **27**: 8123-8137 [PMID: 35068858 DOI: 10.3748/wjg.v27.i47.8123]

94   **Angelousi A**, Kaltsas G, Koumarianou A, Weickert MO, Grossman A. Chemotherapy in NETs: When and how. *Rev Endocr Metab Disord* 2017; **18**: 485-497 [PMID: 28890993 DOI: 10.1007/s11154-017-9432-1]

95   **Espinosa-Olarte P**, La Salvia A, Riesco-Martinez MC, Anton-Pascual B, Garcia-Carbonero R. Chemotherapy in NEN: still has a role? *Rev Endocr Metab Disord* 2021; **22**: 595-614 [PMID: 33843007 DOI: 10.1007/s11154-021-09638-0]

96   **Kessler J**, Singh G, Ituarte PHG, Allen R, Chang S, Li D. A Comparison of Liver-Directed Therapy and Systemic Therapy for the Treatment of Liver Metastases in Patients with Gastrointestinal Neuroendocrine Tumors: Analysis of the California Cancer Registry. *J Vasc Interv Radiol* 2021; **32**: 393-402 [PMID: 33358144 DOI: 10.1016/j.jvir.2020.10.019]

97   **Muñoz de Nova JL**, Hernando J, Sampedro Núñez M, Vázquez Benítez GT, Triviño Ibáñez EM, Del Olmo García MI, Barriuso J, Capdevila J, Martín-Pérez E. Management of incidentally discovered appendiceal neuroendocrine tumors after an appendicectomy. *World J Gastroenterol* 2022; **28**: 1304-1314 [PMID: 35645544 DOI: 10.3748/wjg.v28.i13.1304]

98   **Van Den Heede K**, Chidambaram S, Van Slycke S, Brusselaers N, Warfvinge CF, Ohlsson H, Gustafsson R, Nordenström E, Almquist M. Long-term survival of metastatic small intestine neuroendocrine tumors: a meta-analysis. *Endocr Relat Cancer* 2022; **29**: 163-173 [PMID: 34982042 DOI: 10.1530/ERC-21-0354]

99   **Eriksson J**, Garmo H, Hellman P, Ihre-Lundgren C. The Influence of Preoperative Symptoms on the Death of Patients with Small Intestinal Neuroendocrine Tumors. *Ann Surg Oncol* 2017; **24**: 1214-1220 [PMID: 27904972 DOI: 10.1245/s10434-016-5703-4]

100   **Canakis A**, Lee LS. Current updates and future directions in diagnosis and management of gastroenteropancreatic neuroendocrine neoplasms. *World J Gastrointest Endosc* 2022; **14**: 267-290 [PMID: 35719897 DOI: 10.4253/wjge.v14.i5.267]

101   **Modlin IM**, Gustafsson BI, Pavel M, Svejda B, Lawrence B, Kidd M. A nomogram to assess small-intestinal neuroendocrine tumor ('carcinoid') survival. *Neuroendocrinology* 2010; **92**: 143-157 [PMID: 20733279 DOI: 10.1159/000319784]

102   **Herrera-Martínez Y**, Alzas Teomiro C, León Idougourram S, Molina Puertas MJ, Calañas Continente A, Serrano Blanch R, Castaño JP, Gálvez Moreno MÁ, Gahete MD, Luque RM, Herrera-Martínez AD. Sarcopenia and Ghrelin System in the Clinical Outcome and Prognosis of Gastroenteropancreatic Neuroendocrine Neoplasms. *Cancers (Basel)* 2021; **14** [PMID: 35008278 DOI: 10.3390/cancers14010111]

103   **Erstad DJ**, Dasari A, Taggart MW, Kaur H, Konishi T, Bednarski BK, Chang GJ. Prognosis for Poorly Differentiated, High-Grade Rectal Neuroendocrine Carcinomas. *Ann Surg Oncol* 2022; **29**: 2539-2548 [PMID: 34787737 DOI: 10.1245/s10434-021-11016-8]

104   **Toor D**, Loree JM, Gao ZH, Wang G, Zhou C. Mixed neuroendocrine-non-neuroendocrine neoplasms of the digestive system: A mini-review. *World J Gastroenterol* 2022; **28**: 2076-2087 [PMID: 35664032 DOI: 10.3748/wjg.v28.i19.2076]

105   **Pantelis AG**, Panagopoulou PA, Lapatsanis DP. Artificial Intelligence and Machine Learning in the Diagnosis and Management of Gastroenteropancreatic Neuroendocrine Neoplasms-A Scoping Review. *Diagnostics (Basel)* 2022; **12** [PMID: 35453922 DOI: 10.3390/diagnostics12040874]