Gastric neuroendocrine neoplasms: A review

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Abstract

Gastric neuroendocrine neoplasms (g-NENs) or neuroendocrine tumors are generally slow-growing tumors with increasing incidence. They arise from enterochromaffin like cells and are divided into four types according to clinical characteristic features. Type 1 and 2 are gastrin dependent, whereas type 3 and 4 are sporadic. The reason for hypergastrinemia is atrophic gastritis in type 1, and gastrin releasing tumor (gastrinoma) in type 2 g-NEN. The diagnosis of g-NENs needs histopathological investigation taken by upper gastrointestinal endoscopy. g-NENs are positively stained with chromogranin A and synaptophysin. Grading is made with mitotic index and ki-67 proliferation index on histopathological analysis. It is crucial to discriminate between types of g-NENs, because the management, treatment and prognosis differ significantly between subtypes. Treatment options for g-NENs include endoscopic resection, surgical resection with or without antrectomy, medical treatment with somatostatin analogues, netazepide or chemotherapy regimens. Follow-up without excision is another option in appropriate cases. The prognosis of type 1 and 2 g-NENs are good, whereas the prognosis of type 3 and 4 g-NENs are close to the prognosis of gastric adenocancer.

Key Words: Gastric neuroendocrine tumors; Gastric neuroendocrine neoplasm; Gastric neuroendocrine carcinoma; Hypergastrinemia; Carcinoid; Somatostatin receptor imaging

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Core Tip: Gastric neuroendocrine neoplasm is an indolent tumor, which is more commonly seen with time. It has 4 subtypes with different clinical characteristics, and diagnostic management and treatment depends on subtypes. This article reviews the
INTRODUCTION

The term “carcinoid” was firstly used in 1907 to define a slowly progressing tumor somewhere between adenoma and carcinoma[1]. When it was first described, the main features of carcinoids were determined as follows: (1) Usually small and multiple; (2) Surrounded by an undifferentiated tissue; (3) Potentially invasive but they do not metastasize; and (4) Grow slowly and therefore considered as harmless[2]. After the first description, various definitions and classifications have been used over years, which illustrates the complex biological nature of these tumors. In 1963 Williams and Sandler classified carcinoid tumors as foregut, midgut and hindgut according to embryological development sites[3]. Later, Soga and Tazawa classified carcinoids according to histological features as A, B, C, D and mixed type[4]. Capella et al[5] stated that the term neuroendocrine tumor (NET) would be more appropriate instead of carcinoid and proposed a new classification system. They classified NETs of the stomach as benign, benign or low-grade malignant, low-grade malignant and high-grade malignant.

The World Health Organization (WHO) classified neuroendocrine neoplasms (NENs) as Grade 1, 2 and 3 according to Ki-67 proliferation index and mitotic activity in 2010[6]. In 2017 this classification was changed and NENs were divided into NET and neuroendocrine carcinoma (NEC) according to tumor grade, independently where the tumor arises[7]. A less common type is mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN), which includes both neuroendocrine tumor and non-neuroendocrine tumor components (each neoplasms constitute more than 30% of the entire tumor)[8].

The proposed classification and staging criteria for NENs of the gastrointestinal tract according to 2017 WHO classification is summarized in Table 1[7].

EPIDEMOLOGY AND TYPES OF NENS OF THE STOMACH

NENs of the digestive system may arise from the pancreas and the digestive tract. Gastric NENs (g-NENs) are uncommon disorders, and represent 5% to 23% of all digestive NENs in various trials[9-14]. The incidence of g-NENs increases nearly 15-fold with time, probable because of the expanding use of upper gastrointestinal endoscopy[9,15]. A recent study showed that the incidence of g-NENs increased from 0.309 to 6.149 per 1000000 persons in the last 40 years[16]. Similar incidence results were reported in a study from Japan with an adjusted incidence of 4.82 per 1000000 population[17].

Rindi et al[18] defined three different subtypes of g-NENs. They showed that some patients had atrophic gastritis and hypergastrinemia along with non-metastatic lesions, some patients had hypertrophic gastropathy and hypergastrinemia due to multiple endocrine neoplasia (MEN) and Zollinger-Ellison syndrome and finally some NENs were sporadic which showed invasion and metastasis[18]. This classification is still in use and with further knowledge the three types of g-NENs may be summarized as followed, along with a newly defined fourth type (Table 2).

Type 1 g-NEN

Type 1 is the most common type and represents 70-80% of g-NENs[9,19]. It is commonly seen in patients with 60-70 years of age and a slight female dominancy is present[20,21]. Chronic atrophic gastritis is present along with elevated gastrin levels. The elevated gastrin level due to chronic atrophic gastritis has a trophic effect on enterochromaffin-like (ECL) cells, with ECL cell hypertrophy and hyperplasia as the
Table 1 Classification of neuroendocrine neoplasms according to World Health Organization criteria

| Classification                                      | Mitotic rate (mitoses/mm²) | Ki-67 index | Differentiation |
|-----------------------------------------------------|----------------------------|-------------|---------------|
| Neuroendocrine tumor, Grade 1                       | < 2                        | < 3%        | Well          |
| Neuroendocrine tumor, Grade 2                       | 2-20                       | 3%-20%      | Well          |
| Neuroendocrine tumor, Grade 3                       | > 20                       | > 20%       | Well          |
| Neuroendocrine carcinoma, small-cell type           | > 20                       | > 20%       | Poor          |
| Neuroendocrine carcinoma, large-cell type           | > 20                       | > 20%       | Poor          |
| Mixed neuroendocrine-non-neuroendocrine neoplasm    | Variable                   | Variable    | Variable      |

Table 2 Characteristics of the subtypes of neuroendocrine neoplasms of the stomach

| Type 1                          | Type 2                          | Type 3                          | Type 4                          |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Approximate proportion         | 70%-80%                         | 5%                              | Rarely                          |
| Pathogenesis                   | Increased gastrin levels due to atrophic gastritis. ECL origin | Increased gastrin levels due to gastrinoma. ECL origin | Not known. Mostly ECL origin Not known. Non-ECL origin |
| Location and characteristics   | Gastric body and fundus. Often small and multiple | Gastric body and fundus. Often small and multiple | Anywhere. Large and solitary Anywhere. Large (often larger than type 3) |
| Gastrin level                   | Increased                        | Increased                        | Normal                          |
| Prognosis                      | Excellent                        | Good                            | Bad                             |
| Treatment                      | Surveillance without resection, Endoscopic resection, surgery | Endoscopic or surgical resection, resection of gastrinoma | Gastrectomy and regional lymphadenectomy, systemic chemotherapy | Gastrectomy and regional lymphadenectomy, systemic chemotherapy |

result[22]. Annual risk of development of g-NENs among patients with chronic atrophic gastritis is around 0.4%-0.7%[23,24]. Most of the lesions in type 1 g-NENs are multiple and are around 1-2 cm. The lymph node metastasis potential of type 1 g-NENs is low and only few cases of distant metastasis have been reported to date[25,26]. The prognosis is good and the expected 5 year survival is over 95%[27,28].

**Type 2 g-NEN**
Type 2 g-NEN constitutes 5% of g-NENs[25,29]. Hypergastrinemia is also present in these patients, but it is due to ectopic gastrin producing neoplasia (gastrinoma), which is also named as Zollinger-Ellison syndrome[25,29,30]. Among patients with MEN 1 and gastrinoma, 20% of patients will develop type 2 g-NEN[31]. Although type 2 g-NENs may present with metastasis for up to 30%, the prognosis is still good with tumor-related deaths under 10%[9,32].

**Type 3 g-NEN**
This type of g-NEN is not associated with hypergastrinemia, and is therefore accepted as sporadic[33]. Type 3 g-NENs represents 15%-25% of g-NENs[9]. The lesion is commonly single and large with a high metastasis potential and high grade compared to type 1 and 2 g-NENs[21,34,35].

**Type 4 g-NEN**
Type 4 g-NEN is a more recently defined type, which is the rarest subtype. They are not originated from ECL cells and their growth is independent from gastrin. Mostly the lesion presents as a large polypoid lesion localized anywhere in the stomach. Type 4 g-NENs are aggressive tumors with high invasion and metastasis potential[36].
Trinh et al[37] investigated patients without atrophic gastritis or gastrinoma according to long term PPI use, and they showed that this group of NENs had some different clinical characteristics than type 3 g-NEN, including better prognosis. They suggested to classify g-NENS arising in moderate hypergastrinemia in patients who were treated continuously for a long period with PPI, without autoimmune chronic atrophic gastritis, gastrinoma, and MEN1 syndrome as a new group of g-NEN[37]. This suggestion needs further investigations.
PATHOGENESIS OF NENS OF THE STOMACH

It is known for years that elevated gastrin levels, which results commonly due to gastric acid inhibition, are associated with the hyperplasia, dysplasia and neoplasia development in ECL cells[38]. Furthermore the gastrin level was found to be correlated with the severity of hyperplasia[39]. Elevated serum gastrin levels are associated with type 1 and 2 g-NENs, with different mechanisms for hypergastrinemia.

Many factors and cells are involved in the physiological acid secretion. After food consumption, G cells which are placed in the gastric antrum release gastrin. Elevated gastrin levels stimulates ECL cells to produce histamine, and histamine stimulates parietal cells to produce acid. Normally, increased acid levels inhibits gastrin levels primarily via somatostatin, which is released from D cells placed in the gastric antrum[25].

Chronic atrophic gastritis is involved in the pathogenesis of type 1 g-NEN. If chronic atrophic gastritis is associated with parietal cell or intrinsic factor antibodies the condition is named as pernicious anemia, and this is commonly present in patients with type 1 g-NEN[25]. Achlorhydria, which occurs in chronic atrophic gastritis, leads to D cell suppression and hypergastrinemia due to G cell hyperplasia. This hypergastrinemia is actually a physiological response to achlorhydria, but has also trophic effect on ECL cells, resulting in ECL cell hypertrophy and hyperplasia[22]. This alteration leads finally to the development of NEN[40]. Long term proton pump inhibitor use enhances the development of g-NEN in animal studies and case reports[41,42], but various studies showed that chronic proton pump inhibitor use or vagotomy has no effect on g-NEN development[29,43]. This fact proves that hypergastrinemia is essential for type 1 g-NEN development but is not sufficient.

Type 2 g-NEN develops similar to type 1 due to hypergastrinemia. Conversely, hypergastrinemia and excess acid production is due to an ectopic gastrin-producing G cell neoplasia (gastrinoma). The neoplasia is located commonly in the duodenum or pancreas. In the case of gastrinoma the normal inhibitory feedback of hyperacidity on gastrin production is inadequate[25,30]. Patients with gastrinomas without MEN may not develop NEN, but they showed nevertheless a 168% increase of ECL cell volume compared to normal population[44]. Gastrinoma may or may not be a component of MEN-1. Compared to non-MEN 1 related gastrinomas, the potential of the development of g-NENs is increased in patients with MEN-1 induced gastrinomas[45].

In patients with type 3 g-NEN the gastrin and acid production are in normal ranges. The exact pathogenesis of type 3 g-NEN is not well known. Mutations of the p53 gene may have probable role in the pathogenesis of type 3 g-NEN[46,47].

The fact that g-NEN develops only in a minority of patients with chronic atrophic gastritis[24] suggests that other pathogenic factors than hypergastrinemia is involved in the development of g-NENs. Expression of glycoprotein hormone alpha-subunit, production of basic fibroblast growth factor and mutations of Reglaalpha gene are examples for accused factors for g-NEN development[48-50]. MEN-1 associated gastrinoma is commonly related to type-2 g-NEN. But even patients with NEN without MEN-1 syndrome may have loss of heterozygosity (LOH) at the MEN-1 gene locus at 11q13. In a study LOH was detected in 50% of patients with type-1 g-NEN, and 75% of patients with type-2 g-NEN without MEN-1 syndrome[51]. Helicobacter pylori (H. pylori) may also have an effect on the development of g-NENs[52,53].

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of g-NENs are not specific and they are usually diagnosed during upper gastrointestinal endoscopy for upper gastrointestinal tract symptoms such as abdominal pain, nausea, bleeding or anemia[19,28]. Bleeding has been reported more commonly in type 3 g-NENs[54]. Carcinoid syndrome may be seen in patients with gastrointestinal NENs, but it is rarely detected in patients with g-NENs[55,56]. If carcinoid syndrome develops in g-NENs, it shows a different presentation than carcinoid syndromes that develop from midgut and hindgut, which is termed as atypical carcinoid syndrome. In this type of carcinoid syndrome, the rashes are more diffuse, the surrounding area is prominent and serpiginous and the lesions are very itchy. Diarrhea and cardiac symptoms are usually absent[19,55,57].

Diagnosis of g-NENs are made by upper gastrointestinal endoscopy. Generally small polyps are detected on endoscopy. Type 1 and 2 Lesions are often located in multiple areas outside the antrum, while type 3 and 4 NENs are usually single and can
be detected in all parts of the stomach[29]. In type 3 g-NENs the gastric mucosa except for polyps is detected normal. It is commonly atrophic in type 1 g-NENs and peptic ulcers may accompany in especially type 2 g-NENs[29].

The definitive diagnosis of g-NEN is made on histopathological examination. Biopsy samples should be obtained from both the gastric mucosa and the polyps in order to examine the condition of the underlying mucosa and to detect microscopic NENs[56]. Four samples from the corpus and two samples from the antrum should be taken for histopathological examination[38]. In histopathological examination of g-NENs, the tumor cells are usually uniform with round-oval nuclei, coarse chromatin and fine granular cytoplasm. On immunohistochemical staining the cells are positively stained with Chromogranin A (CgA) and Synaptophysin[38]. CgA may be absent in type 4 g-NENs[36]. It is crucial to determine the tumor grade during pathological examination with proliferative indices such as mitotic activity and Ki-67 index. Mitotic activity is determined by examining 10 fields at 40× magnification and counting the active cells in these areas. Although the amounts of mitotic activity used in determining the tumor grade level are not clearly defined, mitotic activity of 2 is accepted by WHO to distinguish grade 1 from grade 2, and 20 to distinguish grade 2 from grade 3 NEN. But mitotic activity index may be misleading in determining the grade of the tumor, especially in the distinction in grade 1 from grade 2 NENs. Ki-67 is another proliferation index, which was first described by Gerdes et al[59] in 1991. Studies have shown that Ki-67 is present in proliferation phases of the cell cycle, but not in the quiescent or resting cells, which makes it possible to use as a proliferation marker effectively in many cancers[60]. Different cut-off levels of Ki-67 indexes were suggested for differentiating grade 1 from grade 2 NEN, but the cut-off level of 3% was accepted for this differentiation[61,62]. Although the 10% level was suggested for grade 3 definition, this limit was changed to 20% in the following studies and WHO recommendation[7]. It is not clear whether mitotic index or Ki-67 proliferation index is better in determining the tumor grade. But it is recommended that both indexes should be measured and the higher parameter should be selected if there is a discrepancy between them[7]. Since Ki-67 index is a method that gives the ratio of cells with positive staining, it has the advantage of having the ability to study also in small tissue samples. Whereas the advantage of mitotic index is that it does not need immunohistochemical staining[63].

INITIAL MANAGEMENT OF GASTRIC NENS

After g-NEN is diagnosed, it is necessary to determine the tumor type, spread and stage of the disease, and to detect the presence of metastasis. While upper gastrointestinal endoscopy is performed, the whole mucosa should be examined properly, and the number of the lesions and the size of the largest polyp should be recorded[64]. If gastrinoma is present, the localization of the tumor should also be made.

The discrimination between g-NEN types is of great importance, because the therapy and follow-up differs among types. Serum gastrin levels are elevated in type 1 and 2 g-NENs, whereas it is normal in patients with type 3 and 4 g-NENs. Before the measurement of gastrin, the use of proton pump inhibitors should be withdrawn. But in patients with type 2 g-NENs the withdrawal of antisecretory therapy is with the risk of rebound acid secretion, which may lead to peptic ulcer and bleeding[65]. For differential diagnosis of type 1 and 2 g-NENs, biopsy samples outside the lesions should be investigated to detect whether atrophy is present. Atrophic mucosa indicates type-1 g-NENs, whereas normal mucosa is detected in patients with type 2 g-NEN. Another tool for differential diagnosis may be gastric acid measurement. In cases with hypergastrinemia, gastric pH is generally above 4 in type-1 g-NEN, while it is less than 2 in type 2 g-NEN[29]. If type 2 g-NEN is detected, additional testing for MEN-1 syndrome should be performed. Vitamin B12 Level should be tested along with anti-parietal cell and anti-intrinsic factor antibodies, if indicated. Addison disease and hypothyroidism should also be screened in suspected cases[25]. Serum CgA level is usually elevated in patients with g-NENs, but its specificity is low[66]. Serum CgA measurement may be also used in the follow up to predict response to chemotherapy and predict prognosis[19]. Somatostatin analogues (SSA) and proton pump inhibitors may alter the level of serum CgA, which should be taken into account in interpreting the results[29].

Several imaging modalities are used to evaluate the spread and stage of the disease. Endoscopic ultrasonography (EUS) plays an important role in the diagnostic workup.
of g-NENs. EUS helps to detect tumor invasion to the deeper layers of the gastric wall, and also to determine lymph node metastasis with the advantage of ability of histological confirmation by fine needle aspiration [58, 67]. Cross sectional imaging modalities like computerized tomography (CT) and magnetic resonance imaging (MRI) may be needed to determine disease staging and metastasis for advanced neoplasms and especially type 3 g-NEN [9]. Liver metastases rapidly enhance contrast after contrast material injection on CT and a wash-out is observed in the portal venous phase [68]. Somatostatin receptor imaging (SRI) modalities (somatostatin receptor scintigraphy or 68 Ga-PET-DOTANOC) are rarely useful for type 1 g-NENs which are generally small and indolent, but they can be useful in type 2 and 3 g-NENs as part of the overall staging and perhaps choosing therapy [28, 69, 70].

If smaller than 1 cm type 1 g-NEN is detected, no further evaluation is required. Although the exact cut-off level of lesion size for EUS is not defined, EUS should be performed if the lesion is greater than 1 cm to assess invasion [9, 58]. CT scan and MRI techniques are not indicated in most type 1 g-NENs [58]. SRI techniques do not make extra contribution compared to imaging methods, but they can be performed for treatment response evaluation if SSA therapy is planned [71]. H. pylori should be assessed in these patients. Serum CgA and gastrin levels should be tested, and the patients should also be evaluated for autoimmune diseases with anti-parietal cell and anti-intrinsic factor autoantibodies and anti-thyroid peroxidase antibodies [58].

Because locally advanced disease and metastasis is seen more commonly in type 2 g-NEN compared to type 1, imaging modalities are more commonly used for patients with especially larger type 2 g-NEN lesions. CT, MRI and SRI modalities are used to determine for disease stage and to find the gastrinoma lesions’ origin [58]. SRI modalities and EUS may detect gastrinoma lesions more effectively than CT or MRI [72, 73]. It is recommended to perform genetic testing for MEN-1 and screen for associated tumors in the pituitary gland and pancreas [22]. Serum gastrin and CgA levels should also be tested in these patients [58].

Type 3 and 4 g-NENs behave similar to gastric adenocarcinoma, and the staging and diagnostic modalities should be performed like adenocarcinoma [64]. CT, MRI or SRI modalities (especially 68 Ga-PET-DOTANOC) are needed for disease staging, but SRI tests may be false negative in poorly differentiated patients [9, 64].

### TREATMENT

The treatment options of g-NENs depends on the tumor type, lesion number and size, disease extent and the differentiation of the tumor. Follow up without excision, endoscopic resection, surgical resection and medical therapies are treatment options for g-NENs.

**Type 1**

The metastasis risk of type 1 g-NEN is low, and therefore conservative management strategies are commonly preferred in small lesions [9, 74]. Some authors suggested to resect all visible lesions larger than 5 mm [67, 75], but this approach is not widely accepted. In a study performed by Sato et al. [76], 25 patients were followed up without resection, and after an average of 7 years, no significant rapid growth, metastasis or invasion of the tumor was detected in any patient, and no disease-related death was reported. ENETS suggested to remove all lesions in their guideline in 2013, but they changed this recommendation in 2016 and recommended to remove lesions greater than 10 mm with close follow-up [9, 58]. Similarly, NENs suggest that surveillance without excision and endoscopic removal may be chosen for lesions smaller than 10 mm [74]. They recommended endoscopic resection or close follow up with less than 6 Lesions between 1 to 2 cm diameter, and endoscopic or surgical resection in patients with more than 6 Lesions [74]. Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) may be used for endoscopic resection. ESD has the advantage of en bloc resection for complete histological analysis [9, 77]. Preferably EUS should be performed for lesions greater than 10 mm to assess tumor invasion, and endoscopic resection should be done when it is possible [58, 74].

Surgical treatment is the option for lesions which are predicted to be T2 or lesions with positive margins. Surgical antrectomy may be added to the surgical procedure to suppress gastrin secretion, with questionable efficacy [9]. Although it is stated that performing antrectomy after surgical or endoscopic removal of the lesion provides tumor regression and reduces recurrence [78, 79], there are also publications reporting
that it does not reduce metastasis and recurrence\cite{80}. It has been shown in a study that performing antrectomy requires less often endoscopies in the follow-up time period, lowers the risk of recurrence and it may reduce the anxiety of patients for malignancy development\cite{81}. Another method to suppress gastrin levels is SSAs. SSAs have the advantage of regression of tumors, but this has not been compared to other treatment strategies, and it is not widely accepted for routine use. SSAs may be useful for multiple small lesions which are not possible for endoscopic resection\cite{82}. The use of SSAs (both lanreotide and octreotide) may be an option for inoperable patients and for metastatic diseases\cite{9,83,84}. Netazepide is a gastrin receptor antagonist, which has favorable effects on type 1 g-NENs\cite{85,86,87,88}, but its use needs further studies for clear recommendation. It also should be kept in mind that the tumors will grow after the withdrawal of netazepide\cite{25}.

**Type 2**
The preferred treatment of type 2 g-NEN is local excision\cite{58}. Endoscopic treatment for noninvasive tumors and surgical resection for invasive or metastatic lesions should be chosen. Another important issue is to search for the gastrinoma lesions and perform surgical resection for it\cite{64}. Because the cause of hyperacidity is not antral G cells, antrectomy has no favorable effect. Proton pump inhibitors should be used for hyperacidity and to reduce the risk of peptic ulcer. No evidence is present for the treatment of type 2 g-NEN with netazepide.

**Type 3 and type 4**
If type 3 g-NEN is detected, the optimal treatment strategy is surgical treatment as the procedure for gastric adenocarcinoma (partial or total gastrectomy with lymph node dissection)\cite{9,74}. Although some authors cited that endoscopic resection would be sufficient in small lesions without invasion, this is not a widely accepted approach \cite{89}. Similarly, the treatment of localized type 4 g-NEN is gastrectomy and lymph node dissection.

**Metastatic disease**
Surgery, local methods and systemic treatment are included in the treatment options of liver metastasis due to g-NENs. Treatment options for patients with metastases of g-NENs are not specific for gastric lesions, and the options are based on recommendations for liver metastases of NETs. The appropriate method for liver metastases of grade 1 and 2 g-NENs is surgical removal of the metastatic lesions. Although surgery is not commonly recommended for grade 3 tumors, single and suitable lesions may be surgically removed\cite{90}. Primary tumor resection is suggested in patients with advanced resectable disease, but the role of primary tumor resection in patients with unresectable metastases is debated\cite{74,91}. Recently published studies showed that resection of primary gastrointestinal neuroendocrine tumors among patients with metastases (with and without liver treatment) has survival advantage, but improved survival could not be achieved in patients with g-NENs\cite{92,93}. Liver transplantation may be done after surgical removal of the primary focus, especially in selected low-grade patients with extensive liver metastasis\cite{94,95}. Transarterial embolization, chemoembolization and radioembolization and radiofrequency ablation may be effectively used as local treatment options of liver metastasis\cite{90,96}. Systemic chemotherapy with etoposide and cisplatin is recommended in grade 3 and metastatic patients\cite{58,97}. Peptide receptor radionuclide therapy targeting somatostatin receptors may also be an alternative treatment approach for gastrointestinal NENs, but its use in metastatic g-NEN is not widely studied\cite{98,99}.

**Carcinoid syndrome**
Carcinoid syndrome is seldom seen in patients with g-NENs. But it is more commonly seen in patients with liver metastasis. If carcinoid syndrome is present, it should be treated with SSAs, along with symptomatic treatment if indicated\cite{74}. In addition, SSAs should be given for prophylaxis before surgical and local treatment methods\cite{90}.

**PROGNOSIS**
The prognosis of g-NENs depends on tumor type, grade and tumor stage. In general, tumor size, histological grade, type 3 NEN, mitotic index and Ki-67 index, tumor depth, lymph node involvement and presence of metastasis are defined as poor prognosis criteria for g-NENs. Type 1 g-NENs have usually excellent prognosis with...
around 100% of survival even in untreated patients[27,28,100]. Type 2 g-NENs have almost similar prognosis to type 1 and are generally detected at early stages, which shows good survival rates. But patients with type 2 g-NEN may have MEN-1, and when MEN-1 is present patients may die with metastatic diseases from other organs (especially pancreas and thymus) than the stomach[101]. Type 3 g-NEN shows the worst prognosis with similar survival rates with gastric adenocarcinoma, which displays the crucial role of the differential diagnosis among g-NENs[35]. The tumour-related annual mortality rate of g-NENs was calculated as 1.07%, but this rate gradually increases in grade 2 and 3 and reaches 57% in grade 3 g-NENs[102].

CONCLUSION

G-NENs or neuroendocrine tumors are tumors with increasing incidence. The pathogenesis, clinical characteristics, prognosis and treatment options differs apparently between subgroups of g-NENs. Type 1 and 2 are gastrin dependent, whereas type 3 and 4 are considered as sporadic. The reason for hypergastrinemia is atrophic gastritis and gastrinoma in type 1 and type 2 g-NEN, respectively. New data is emerging recently about new subgroups, which should be evaluated with further studies. It is crucial to differentiate tumors between these subgroups for further management and treatment. Treatment options for g-NENs include endoscopic resection, surgical resection with or without antrectomy, medical treatment with somatostatin analogues, netazepide or chemotherapy regimens. Also follow-up without endoscopic or surgical excision is another option in appropriate cases. The prognosis of type 1 and 2 g-NENs are good, whereas the prognosis of type 3 and 4 g-NENs are worse. Despite it took decades after the definition of carcinoid or NET, new data and evidences still change the management of g-NENs in recent years.

REFERENCES

1. Oberndorfer S. Karzinoid tumoren des dünndarms. Frankfurt Z Path 1907; 1: 426-432
2. Modlin IM, Shapiro MD, Kidd M. Siegfried Oberndorfer: origins and perspectives of carcinoid tumors. *Hum Pathol* 2004; 35: 1440-1451 [PMID: 15619202 DOI: 10.1016/j.humpath.2004.09.018]
3. Williams RA, Whitehead R. Non-carcinoid epithelial tumours of the appendix—a proposed classification. *Pathology* 1986; 18: 50-53 [PMID: 3725433 DOI: 10.3109/030320528000900827]
4. Soga J, Tazawa K. Pathologic analysis of carcinoids. Histologic reevaluation of 62 cases. *Cancer* 1971; 28: 990-998 [PMID: 4106849 DOI: 10.1002/1097-0142(1971)28:4<990::aid-cncr2820280424>3.0.co;2-k]
5. Capella C, Heitz PU, Höfler H, Solcia E, Klöppel G. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. *Virchows Arch* 1995; 425: 547-560 [PMID: 7697211 DOI: 10.1007/BF00199342]
6. Rindi G, Arnold R, Capella C, Klimstra DS, Klöppel G, Komminoth P, Solcia E. Nomenclature and classification of digestive neuroendocrine tumours. In: Bosman FT, editor. WHO Classification of Tumours, Pathology and Genetics of Tumours of the Digestive System. Lyon, France: International Agency for Research on Cancer (IARC) Press, 2010: 10-12
7. Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, Busam KJ, de Krijger RR, Dietel M, El-Naggar AK, Fernandez-Cuesta L, Klöppel G, McCluggage WG, Moch H, Ohgaki H, Rakha EA, Reed NS, Rouz BA, Sasano H, Scarpa A, Scoccaz S, Travis WD, Tallini G, Trouillas J, van Krieken JH, Cree IA. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol* 2018; 31: 1770-1786 [PMID: 30140036 DOI: 10.1038/s41379-018-0110-y]
8. Ishida S, Akita M, Fujikura K, Komatsu M, Sawada R, Matsumoto H, Saegusa J, Ichikawa H, Kakeji Y, Zen Y. Neuroendocrine carcinoma and mixed neuroendocrine–non-neuroendocrine neoplasm of the stomach: a clinicopathological and exome sequencing study. *Hum Pathol* 2021; 110: 1-10 [PMID: 33359239 DOI: 10.1016/j.humpath.2020.12.008]
9. Delie Faye G, O’Toole D, Sundin A, Taal B, Ferolla P, Ramage JK, Ferone D, Ito T, Weber W, Zheng-Pei Z, De Herder WW, Pascher A, Ruszniewski P, Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for Gastroenteroental Neuroendocrine Neoplasms. *Neuroendocrinology* 2016; 103: 119-124 [PMID: 26784901 DOI: 10.1159/000443168]
10. O’Connor JM, Marmisolle B, Bestani C, Pesce V, Bells S, Dominichini E, Mendez G, Price P, Giaconii N, Pairola A, Loria FS, Huertas E, Martin C, Patane K, Polieri C, Rosenberg M, Cabanne A, Kujarac M, Caino A, Zamora V, Mariani J, Dioca M, Parma P, Podesta G, Andriani O, Gondioli G, Rocca E. Observational study of patients with gastroenteropancreatic and bronchial neuroendocrine tumours in Argentina: Results from the large database of a multidisciplinary group clinical
multicenter study. *Mod Clin Oncol* 2014; 2: 673-684 [PMID: 25054030 DOI: 10.3892/mco.2014.332]

11 Niederle MB, Hackl M, Kaserer K, Niederle B. Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. *Endocr Relat Cancer* 2010; 17: 909-918 [PMID: 20702725 DOI: 10.1677/ERC-10-0151]

12 Yau JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vaubhey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for gastric neuroendocrine tumours in 35,825 cases in the United States. *J Clin Oncol* 2008; 26: 3063-3072 [PMID: 18565894 DOI: 10.1200/JCO.2007.15.4377]

13 Hallett J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumours: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* 2015; 121: 589-597 [PMID: 25312765 DOI: 10.1002/cncr.29099]

14 Tsai HJ, Wu CC, Tsai CR, Lin SF, Chen LT, Chang JS. The epidemiology of neuroendocrine tumours in Taiwan: a nation-wide cancer registry-based study. *PLoS One* 2013; 8: e62487 [PMID: 23614051 DOI: 10.1371/journal.pone.0062487]

15 Yang Z, Wang W, Lu J, Pan G, Pan Z, Chen Q, Liu W, Zhao Y. Gastric Neuroendocrine Tumors (G-Nets): Incidence, Progression and Recent Trend Toward Improved Survival. *Cell Physiol Biochem* 2018; 45: 389-396 [PMID: 29402806 DOI: 10.1159/000486915]

16 Hu P, Bai J, Liu M, Xue J, Chen T, Li R, Kuai X, Zhao H, Li X, Tian Y, Sun W, Xiong Y, Tang Q. Trends of incidence and prognosis of gastric neuroendocrine neoplasms: a study based on SEER and our multicenter research. *Gastric Cancer* 2020; 23: 591-599 [PMID: 32026156 DOI: 10.1007/s10120-020-01046-8]

17 Masui T, Ito T, Komoto J, Umemoto S. INETS Project Study Group. Recent epidemiology of patients with gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NEN) in Japan: a population-based study. *BMC Cancer* 2020; 20: 1104 [PMID: 33189127 DOI: 10.1186/s12885-020-07581-y]

18 Rindi G, Luinetti O, Cornaggia M, Capella C, Solcia E. Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. *Gastroenterology* 1993; 104: 994-1006 [PMID: 7681798 DOI: 10.1016/0016-5085(93)90266-7]

19 Borch K, Ahren B, Ahlman H, Falkmer S, Granérus G, Grimelius L. Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. *Ann Surg* 2005; 242: 64-73 [PMID: 15973103 DOI: 10.1097/01.sla.0000167862.52309.7d]

20 Dakin GF, Warner RR, Pomp A, Salky B, Inabnet WB. Presentation, treatment, and outcome of type 1 gastric carcinoid tumors. *J Surg Oncol* 2006; 93: 368-372 [PMID: 16550587 DOI: 10.1002/jso.20468]

21 Rindi G, Bordi C, Rappel S, La Rosa S, Stolte M, Solcia E. Gastric carcinoids and neuroendocrine carcinomas: pathogenesis, pathology, and behavior. *World J Surg* 1996; 20: 168-172 [PMID: 8661813 DOI: 10.1007/s002699000026]

22 Corey B, Chen H. Neuroendocrine Tumors of the Stomach. *Surg Clin North Am* 2017; 97: 333-343 [PMID: 28325190 DOI: 10.1016/j.suc.2016.11.008]

23 Annibale B, Azzoni C, Corleto VD, di Giulio E, Caruana P, D'Ambra G, Bordi C, Delle Fave G. Atrophic body gastritis patients with enterochromaffin-like cell dysplasia are at increased risk for the development of type I gastric carcinoid. *Eur J Gastroenterol Hepatol* 2001; 13: 1449-1456 [PMID: 11742193 DOI: 10.1097/00042737-200112000-00008]

24 Vannella L, Sbrozzi-Vanni A, Lahner E, Bordi C, Pilozzi E, Corleto VD, Osborn JF, Delle Fave G, Annibale B. Development of type I gastric carcinoid in patients with chronic atrophic gastritis. *Aliment Pharmacol Ther* 2011; 33: 1361-1369 [PMID: 21492197 DOI: 10.1111/j.1365-2036.2011.04659.x]

25 Gluckman CR, Metz DC. Gastric Neuroendocrine Tumors (Carcinoids). *Curr Gastroenterol Rep* 2019; 21: 13 [PMID: 30868284 DOI: 10.1007/s11894-019-00684-7]

26 Tsolakis AV, Ragkousi A, Vujasinovic M, Kaltas G, Daskalakis K. Gastric neuroendocrine neoplasms type 1: A systematic review and meta-analysis. *World J Gastroenterol* 2019; 25: 5376-5387 [PMID: 31558880 DOI: 10.3748/wjg.v25.i35.5376]

27 Kim BS, Park YS, Yook JH, Oh ST, Kim BS. Differing Clinical Courses and Prognoses in Patients With Gastric Neuroendocrine Tumors Based on the 2010-WHO Classification Scheme. *Medicine (Baltimore)* 2015; 94: e1748 [PMID: 26554772 DOI: 10.1097/MD.0000000000001748]

28 Thomas D, Tsolakis AV, Grozinsky-Glasberg S, Fraenkel M, Alexanderaki K, Sougioultzis S, Gross DJ, Kaltas G. Long-term follow-up of a large series of patients with type 1 gastric carcinoid tumors: data from a multicenter study. *Eur J Endocrinol* 2013; 168: 185-193 [PMID: 23132699 DOI: 10.1530/EJE-12-0836]

29 Burkitt MD, Pritchard DM. Review article: Pathogenesis and management of gastric carcinoid tumours. *Aliment Pharmacol Ther* 2006; 24: 1305-1320 [PMID: 17059512 DOI: 10.1111/j.1365-2036.2006.01130.x]

30 Schubert ML, Peura DA. Control of gastric acid secretion in health and disease. *Gastroenterology* 2008; 134: 1842-1860 [PMID: 18474247 DOI: 10.1053/j.gastro.2008.05.021]

31 Gibril F, Schumann M, Pace A, Jensen RT. Multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: a prospective study of 107 cases and comparison with 1009 cases from the literature. *Medicine (Baltimore)* 2004; 83: 43-83 [PMID: 14747767 DOI: 10.1016/j.jsb.2010.01.015]
Köseoğlu H et al. Gastric neuroendocrine neoplasms

10.1097/01.md.0000112297.72510.32

32 Gilligan CJ, Lawton GP, Tang LH, West AB, Modlin IM. Gastric carcinoid tumors: the biology and therapy of an enigmatic and controversial lesion. Am J Gastroenterol 1995; 90: 338-352 [PMID: 7872269]

33 Bordi C. Endocrine tumours of the stomach. Pathol Res Pract 1995; 191: 373-380 [PMID: 7479354 DOi: 10.1016/S0344-0338(1)80891-5]

34 Rappel S, Altendorf-Hofmann A, Stolte M. Prognosis of gastric carcinoid tumours. Digestion 1995; 56: 455-462 [PMID: 8536814 DOi: 10.1159/000201276]

35 Panzuto F, Campana D, Massironi S, Faggiano A, Rinzivillo M, Lamberti G, Sciola V, Lahner E, Manuzzi L, Colao A, Annibale B. Tumour type and size are prognostic factors in gastric neuroendocrine neoplasia: A multicentre retrospective study. Dig Liver Dis 2019; 51: 1456-1460 [PMID: 31175013 DOi: 10.1016/j.dld.2019.04.016]

36 Ahmed M. Gastrointestinal neuroendocrine tumors in 2020. World J Gastrointest Oncol 2020; 12: 791-807 [PMID: 32879660 DOi: 10.4251/wjgo.v12.i8.791]

37 Trinh VQ, Shi C, Ma C. Gastric neuroendocrine tumors from long-term proton pump inhibitor users are indolent tumours with good prognosis. Histopathology 2020; 77: 865-876 [PMID: 32702178 DOi: 10.1111/his.14220]

38 Solcia E, Bordi C, Creutzfeldt W, Dayal Y, Dayan AD, Falkner S, Grimalius L, Huvé N. Histopathological classification of nonantral gastric endocrine growths in man. Digestion 1988; 41: 185-200 [PMID: 3072229 DOi: 10.1159/000199786]

39 Bordi C, Annibale B, Azzoni C, Marignani M, Ferraro G, Antonelli G, D’Adda T, D’Ambra G, Delle Fave G. Endocrine cell growths in atrophic body gastritis. Critical evaluation of a histological classification. J Pathol 1997; 182: 339-346 [PMID: 9249238 DOi: 10.1002/(SICI)1096-9896(199707)182:3<339::AID-PATH854>3.0.CO;2-V]

40 Qvigstad G, Falkner S, Westre B, Waldum HL. Clinical and histopathological tumour progression in ECL cell carcinoids (“ECLomas”). APMIS 1999; 107: 1085-1092 [PMID: 10660138 DOi: 10.1111.j.1600-0463.1999.tb01513.x]

41 Tsukamoto H, Mizoshita T, Sasaki M, Mizushima T, Tanida S, Ozeki K, Hirata Y, Shimura T, Kataoka H, Kaniya T, Nojiri S, Tsukamoto T, Joh T. Long-term high-dose proton pump inhibitor administration to Helicobacter pylori-infected Mongolian gerbils enhances neuroendocrine tumour development in the glandular stomach. Am J Gastroenterol 1999; 94: 175-180 [PMID: 10722269 DOi: 10.1111/j.1572-0241.1999.tb07658.x]

42 Nandy N, Manuzzi L, Colao A, Annibale B. Tumour type and size are prognostic factors in gastric neuroendocrine neoplasms. Rev Gastroenterol Mex (Engl Ed) 2019; 84: 52-56 [PMID: 29705524 DOi: 10.1016/j.rgmx.2018.03.002]

43 D’Adda T, Corleto V, Pilato FP, Baggi MT, Robutti F, Delle Fave G, Bordi C. Quantitative ultrastructure of endocrine cells of oxyntic mucosa in Zollinger-Ellison syndrome. Correspondence with light microscopic findings. Gastroenterology 1990; 99: 17-26 [PMID: 2344924 DOi: 10.1016/0016-5085(90)91224-t]

44 Peghini PL, Annibale B, Azzoni C, Milione M, Corleto VD, Gibril F, Venzon DJ, Delle Fave G, Bordi C, Jensen RT. Effect of chronic hypergastrinemia on human enterochromaffin-like cells: insights from patients with sporadic gastrinomas. Gastroenterology 2002; 123: 68-85 [PMID: 12105853 DOi: 10.1053/gast.2002.34231]

45 Peny MO, Donckier V, Gelin M, Haot J, Noel JC. Sporadic carcinoid of the stomach: a highly proliferative disease with a probable role for p53 protein dysregulation. Eur J Gastroenterol Hepatol 1999; 11: 677-679 [PMID: 10418942 DOi: 10.1097/01.cad.0000390767.85658.83]

46 Nandy N, Manuzzi L, Colao A, Annibale B, Azzoni C, Marignani M, Ferraro G, Antonelli G, D’Adda T, D’Ambra G, Delle Fave G. Endocrine cell growths in atrophic body gastritis. Critical evaluation of a histological classification. J Pathol 1997; 182: 339-346 [PMID: 9249238 DOi: 10.1002/(SICI)1096-9896(199707)182:3<339::AID-PATH854>3.0.CO;2-V]

47 D’Adda T, Keller G, Bordi C, Höfler H. Loss of heterozygosity in 11q13-14 regions in gastric neuroendocrine tumors not associated with multiple endocrine neoplasia type 1 syndrome. Lab Invest 1999; 79: 671-677 [PMID: 10378509 DOi: 10.1121/1.424682]

48 Endall R, Thompson M, Parameswaran V, Burgess J. The Relationship of Gastrinoma in MEN 1 to Helicobacter pylori infection. J Clin Endocrinol Metab 2020; 105 [PMID: 31919513 DOi: 10.1210/clinem/dgaat004]

49 Kagawa J, Honda S, Kodama M, Sato R, Murakami K, Fujioka T. Enterocromaffin-like cell tumor
induced by Helicobacter pylori infection in Mongolian gerbils. *Helicobacter* 2002; 7: 390-397 [PMID: 12485127 DOI: 10.1046/j.1523-5378.2002.00115.x].

54 Dallal HJ, Ravindran R, King PM, Phull PS. Gastric carcinoid tumour as a cause of severe upper gastrointestinal haemorrhage. *Endoscopy* 2003; 35: 716 [PMID: 12929078 DOI: 10.1055/s-2003-41506].

55 Gough DR, Thompson GB, Crotty TB, Donohue JH, Kvols LK, Carney JA, Grant CS, Nagorney DM. Diverse clinical and pathologic features of gastric carcinoid and the relevance of hypergastrinemia. *World J Surg* 1994; 18: 473-9; discussion 479 [PMID: 7725731 DOI: 10.1007/BF00353739].

56 Zhang L, Ozao J, Warner R, Divino C. Review of the pathogenesis, diagnosis, and management of type I gastric carcinoid tumor. *World J Surg* 2011; 35: 1879-1886 [PMID: 21559999 DOI: 10.1007/s00268-011-1137-0].

57 Öberg K, Knigge U, Kwiekbeoom D, Perren A; ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; 23 Suppl 7: vii124-vii130 [PMID: 22997445 DOI: 10.1093/annonc/mds295].

58 Delle Fave G, Kwiekbeoom DJ, Van Cutsem E, Rindi G, Kos-Kudla B, Knigge U, Sasano H, Tomassetti P, Salazar R, Ruszniewski P; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with gastroaodenal neoplasms. *Neuroendocrinology* 2012; 95: 74-87 [PMID: 22226004 DOI: 10.1159/000335595].

59 Gerdes J, Li L, Schlueter C, Duchrow M, Wohlenberg C, Gerlach C, Stahmer I, Kloth S, Brandt E, Flad HD. Immunobiochemical and molecular biologic characterization of the cell proliferation-associated nuclear antigen that is defined by monoclonal antibody Ki-67. *Am J Pathol* 1991; 138: 867-873 [PMID: 2012175].

60 Meonon SS, Guruvayoorapann C, Sakhtrive KM, Rasmi RR. Ki-67 protein as a tumor proliferation marker. *Clin Chim Acta* 2019; 491: 39-45 [PMID: 30653951 DOI: 10.1016/j.cca.2019.01.011].

61 Panzuto F, Boninsegna L, Fazio N, Campana D, Pia Brizzi M, Capurso G, Scarpa A, De Braud F, Dogliotti L, Tomassetti P, Delle Fave G, Falconi M. Metastatic and locally advanced pancreatic neuroendocrine carcinomas: analysis of factors associated with disease progression. *J Clin Oncol* 2011; 29: 2372-2377 [PMID: 21555696 DOI: 10.1200/JCO.2010.33.0688].

62 La Rosa S, Klersy C, Uccella S, Dainese L, Albarello L, Sonzogni A, Doglioni C, Capella C, Solcia E. Improved histologic and clinicopathologic criteria for prognostic evaluation of pancreatic endocrine tumors. *Hum Pathol* 2009; 40: 30-40 [PMID: 18715612 DOI: 10.1016/j.humpath.2008.06.003].

63 Capelli P, Fassan M, Scarpa A. Pathology - grading and staging of GEP-NETs. *Best Pract Res Clin Gastroenterol* 2012; 26: 705-717 [PMID: 23582914 DOI: 10.1016/j.bpcg.2013.01.003].

64 Basu Roy R, Srijayaskanthan R, Prachalias A, Quaglia A, Ramage JK. Review article: the investigation and management of gastric neuroendocrine tumours. *Aliment Pharmacol Ther* 2014; 39: 1071-1084 [PMID: 24628519 DOI: 10.1111/apt.12698].

65 Metz DC. Diagnosis of the Zollinger–Ellison syndrome. *Clin Gastroenterol Hepatol* 2012; 10: 126-130 [PMID: 21806955 DOI: 10.1016/j.cgh.2011.07.012].

66 Peracchi M, Gubbio C, Basilisco G, Quattrini M, Tarantino C, Vescarelli C, Massironi S, Conti D. Plasma chromogranin A in patients with autoimmune chronic atrophic gastritis, enterochromaffin-like cell lesions and gastric carcinoids. *Eur J Endocrinol* 2005; 153: 443-448 [PMID: 15757862 DOI: 10.1530/eje.1.10816].

67 Merola E, Shrooz-Vanni A, Panzuto F, D’Ambra G, Di Giulio E, Pilozzi E, Capurso G, Lahner E, Bordi C, Annibale B, Delle Fave G. Type I gastric carcinoids: a prospective study on endoscopic management and recurrence rate. *Neuroendocrinology* 2012; 95: 207-213 [PMID: 21811050 DOI: 10.1159/000329043].

68 Ganesan D, Bhosale P, Yang T, Kundra V. Imaging features of carcinoid tumors of the gastrointestinal tract. *AJR Am J Roentgenol* 2013; 201: 773-786 [PMID: 24059366 DOI: 10.2214/AJR.12.9758].

69 Alexander HR, Fraker DL, Norton JA, Bartlett DL, Tio L, Benjamin SB, Doppman JL, Goebel SU, Serrano I, Gibril F, Jensen RT. Prospective study of somatostatin receptor scintigraphy and its effect on operative outcome in patients with Zollinger-Ellison syndrome. *Ann Surg* 1998; 228: 228-238 [PMID: 9712569 DOI: 10.1097/00000658-199808000-00013].

70 Cavallaro A, Zanghi A, Cavallaro M, Lo Menzo E, Di Carlo I, Di Vita M, Cardi F, Piccolo G, Di Mattia P, Cappellani A. The role of 68-Ga-DOTATOC CT-PET in surgical tactic for gastric neuroendocrine tumors treatment: our experience: a case report. *Int J Surg* 2014; 12 Suppl 1: S225-S231 [PMID: 24862665 DOI: 10.1016/j.ijsu.2014.05.017].

71 Grozinsky-Glasberg S, Thomas D, Strosberg JR, Pape UF, Felder S, Tsalokis AV, Alexandraki KI, Fraenkel M, Saiegh L, Reissman P, Kalthas G, Gross DJ. Metastatic type 1 gastric carcinoid: a real threat or just a myth? *World J Gastroenterol* 2013; 19: 8687-8695 [PMID: 24379587 DOI: 10.3748/wjg.v19.i14.8687].

72 Nikou GC, Toubanakis C, Nikolau P, Giannatou P, Marinou K, Safiolas M, Karamanolis D. Gastrinomas associated with MEN-1 syndrome: new insights for the diagnosis and management in a series of 11 patients. *Hepatogastroenterology* 2005; 52: 1668-1676 [PMID: 16334754 DOI: 10.1002/1098-2744.a.5917].

73 Naswa N, Sharma P, Soundararajan R, Karunamithi S, Nazar AH, Kumar R, Malhotra A, Bal C.
Diagnostic performance of somatostatin receptor PET/CT using 68Ga-DOTANOC in gastrinoma patients with negative or equivocal CT findings. Abdom Imaging 2013; 38: 552-560 [PMID: 22743840 DOI: 10.1007/s00261-012-9925-2]

74 Kunz PL, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, Chen H, Jensen RT, Kim MK, Klimstra DS, Kulike MH, Liu EH, Metz DC, Pan AT, Sippel RS, Strosberg JR, Yao JC; North American Neuroendocrine Tumor Society. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas 2013; 42: 557-577 [PMID: 23591432 DOI: 10.1097/MPA.0b013e31828e344a]

75 Uygun A, Kadayiferi A, Polat Z, Yilmaz K, Gunacl A, Demir H, Bagci S. Long-term results of endoscopic resection for type I gastric neuroendocrine tumors. J Surg Oncol 2014; 109: 71-74 [PMID: 24165913 DOI: 10.1002/jso.23477]

76 Sato Y, Imamura H, Kaizaki Y, Koizumi W, Ishido K, Kuraoka K, Suzuki H, Fujisaki J, Hirakawa K, Hosokawa O, Ito M, Kaminishi M, Furuta T, Chiba T, Haruma K. Management and clinical outcomes of type I gastric carcinoid patients: retrospective, multicenter study in Japan. Dig Endosc 2014; 26: 377-384 [PMID: 24188531 DOI: 10.1111/den.12197]

77 Kim HH, Kim GH, Kim JH, Choi MG, Song GA, Kim SE. The efficacy of endoscopic submucosal dissection of type I gastric carcinoid tumors compared with conventional endoscopic mucosal resection. Gastroenterol Res Pract 2014; 2014: 253860 [PMID: 24693280 DOI: 10.1155/2014/253860]

78 Hirschowitz BI, Griffith J, Pellegrin D, Cummings OW. Rapid regression of enterochromaffinlike cell gastric carcinoids in pernicious anemia after antrectomy. Gastroenterology 1992; 102: 1409-1418 [PMID: 1551550]

79 Ozao-Choy J, Buch K, Strauchen JA, Warner RR, Divino CM. Laparoscopic antrectomy for the treatment of type I gastric carcinoid tumors. J Surg Res 2010; 162: 22-25 [PMID: 20421108 DOI: 10.1016/j.jss.2010.01.005]

80 Gladwy RA, Strong VE, Cott D, Allen PJ, Gerdes H, Shia J, Klimstra DS, Brennan MF, Tang LH. Defining surgical indications for type I gastric carcinoid tumor. Ann Surg Oncol 2009; 16: 3154-3160 [PMID: 19727959 DOI: 10.1245/s10434-009-0687-3]

81 Jenny HE, Ogando PA, Fujitani K, Warner RR, Divino CM. Laparoscopic antrectomy: a safe and definitive treatment in managing type 1 gastric carcinoids. Am J Surg 2016; 211: 778-782 [PMID: 26992358 DOI: 10.1016/j.amjsurg.2015.08.040]

82 Jianu CS, Fosmark R, Syversen U, Hauso Ø, Fykse V, Waldum HL. Five-year follow-up of patients treated for 1 year with octreotide long-acting release for enterochromaffin-like cell carcinoids. Scand J Gastroenterol 2011; 46: 456-463 [PMID: 21133821 DOI: 10.3109/00365552.2010.539255]

83 Sato Y. Clinical features and management of type I gastric carcinoids. Clin J Gastroenterol 2014; 7: 381-386 [PMID: 26184015 DOI: 10.1007/s13386-014-0528-9]

84 Ryan P, McBride A, Ray D, Pulgar S, Ramirez RA, Elquza E, Favaro JP, Dranitsaris G. Lanreotide vs octreotide LAR for patients with advanced gastroenteropancreatic neuroendocrine tumours in a nonrandomised trial of patients with chronic atrophic gastritis. PLoS One 2013; 8: e76462 [PMID: 24098507 DOI: 10.1371/journal.pone.0076462]

85 Fosmark R, Sordal O, Jianu CS, Qvigstad G, Nordrum IS, Boyce M, Waldum HL. Treatment of gastric carcinoids type 1 with the gastrin receptor antagonist netazepide (YF476) results in regression of tumours and normalization of serum chromogranin A. Aliment Pharmacol Ther 2012; 36: 1067-1075 [PMID: 23072686 DOI: 10.1111/apt.12090]

86 Boyce M, Moore AR, Sagatun L, Parsons BN, Varro A, Pritchard DM. Netazepide, a gastrin receptor antagonist, normalises tumour biomarkers and causes regression of type 1 gastric neuroendocrine tumours in a nonrandomised trial of patients with chronic atrophic gastritis. PLoS One 2013; 8: e76462 [PMID: 24098507 DOI: 10.1371/journal.pone.0076462]

87 Fosmark R, Sordal O, Jianu CS, Qvigstad G, Nordrum IS, Boyce M, Waldum HL. Treatment of gastric carcinoids type 1 with the gastrin receptor antagonist netazepide (YF476) results in regression of tumours and normalisation of serum chromogranin A. Aliment Pharmacol Ther 2012; 36: 1067-1075 [PMID: 23072686 DOI: 10.1111/apt.12090]

88 Boyce M, Moore AR, Sagatun L, Parsons BN, Varro A, Campbell F, Fosmark R, Waldum HL, Pritchard DM. Netazepide, a gastrin/cholecystokinin-2 receptor antagonist, can eradicate gastric neuroendocrine tumours in patients with autoimmune chronic atrophic gastritis. Br J Clin Pharmacol 2017; 83: 466-475 [PMID: 27704617 DOI: 10.1111/bcp.13146]

89 Lloyd KA, Parsons BN, Burkitt MD, Moore AR, Papoutspoulos S, Boyce M, Duckworth CA, Exarchou K, Howes N, Rainbow L, Fang Y, Oxvig C, Dodd S, Varro A, Hall N, Pritchard DM. Netazepide Inhibits Expression of Pappalyisin 2 in Type I Gastric Neuroendocrine Tumours. Cell Mol Gastroenterol Hepatol 2020; 10: 113-132 [PMID: 32004755 DOI: 10.1016/j.gastrohep.2020.01.010]

90 Kwon YH, Jeon SW, Kim GH, Kim JI, Chung IK, Jee SR, Kim HU, Sng GA, Baik GH, Choi KD, Moon JS. Long-term follow up of endoscopic resection for type 3 gastric NET. World J Gastroenterol 2013; 19: 8703-8708 [PMID: 24379580 DOI: 10.3748/wjg.v19.i46.8703]

91 Pavel M, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, Anlauf M, Wiedenmann B, Salazar R; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology 2012; 95: 157-176 [PMID: 22262022 DOI: 10.1159/000335597]

92 Tierney JF, Chivukula SV, Wang X, Pappas SG, Schadde E, Hertl M, Poirier J, Keutgen XM. Resection of primary tumor may prolong survival in metastatic gastroenteropancreatic neuroendocrine tumors. Surgery 2019; 165: 644-651 [PMID: 30366604 DOI: 10.1016/j.surg.2018.09.006]
92 Tsilimigras DI, Hyer JM, Paredes AZ, Ejaz A, Cloyd JM, Beane JD, Dillhoff M, Tsung A, Pawlik TM. Resection of Primary Gastrointestinal Neuroendocrine Tumor Among Patients with Non-Resected Metastases Is Associated with Improved Survival: A SEER-Medicare Analysis. J Gastrointest Surg 2021 [PMID: 33403563 DOI: 10.1007/s11605-020-04898-8]

93 Lewis A, Raof M, Iuarte PHG, Williams J, Melstrom L, Di D, Lee B, Singh G. Resection of the Primary Gastrointestinal Neuroendocrine Tumor Improves Survival With or Without Liver Treatment. Ann Surg 2019; 270: 1131-1137 [PMID: 29746336 DOI: 10.1097/SLA.0000000000002809]

94 Ahlman H, Friman S, Cahlin C, Nilsson O, Jansson S, Wängberg B, Olausson M. Liver transplantation for treatment of metastatic neuroendocrine tumors. Ann N Y Acad Sci 2004; 1014: 265-269 [PMID: 15153443 DOI: 10.1196/annals.1294.029]

95 Fan ST, Le Treut YP, Mazzaferro V, Burroughs AK, Olausson M, Breitenstein S, Frilling A. Liver transplantation for neuroendocrine tumour liver metastases. HPB (Oxford) 2015; 17: 23-28 [PMID: 24992918 DOI: 10.1111/hpb.12308]

96 Egger ME, Armstrong E, Martin RC 2nd, Scoggins CR, Philips P, Shah M, Konda B, Dillhoff M, Pawlik TM, Cloyd JM. Transarterial Chemoembolization vs Radioembolization for Neuroendocrine Liver Metastases: A Multi-Institutional Analysis. J Am Coll Surg 2020; 230: 363-370 [PMID: 32032719 DOI: 10.1016/j.jamcollsurg.2019.12.026]

97 Okita NT, Kato K, Takahari D, Hirashima Y, Nakajima TE, Matsubara J, Hamaguchi T, Yamada Y, Shimada Y, Taniguchi H, Shirao K. Neuroendocrine tumors of the stomach: chemotherapy with cisplatin plus irinotecan is effective for gastric poorly-differentiated neuroendocrine carcinoma. Gastric Cancer 2011; 14: 161-165 [PMID: 21327441 DOI: 10.1007/s10120-011-0025-5]

98 Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chesen B, Mitra E, Kunz PL, Kulke MH, Jacene H, Bushnell D, O’Dorisio TM, Baum RP, Kulkarni HR, Lebthi R, Hobday T, Delpassand E, Van Cutsen E, Benson A, Strizajaskanthan R, Pavel M, Mora J, Berlin J, Grande E, Reed N, Seregny E, Öberg K, Lopera Sierra M, Santoro P, Thevenet T, Erion JL, Ruszniewski P, Kwkkeboom D, Rentzen H; NETTER-1 Trial Investigators. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med 2017; 376: 125-135 [PMID: 28076709 DOI: 10.1056/NEJMoa1607427]

99 Carlsen EA, Fazio N, Granberg D, Grozinsky-Glasberg S, Ahmadzadehfar H, Grana CM, Zandee WT, Cwikla J, Walter MA, Oturai PS, Rinke A, Weaver A, Frilling A, Gritti S, Arvescough AK, Meirovitz A, Knigge U, Sorbye H. Peptide receptor radionuclide therapy in gastroenteropancreatic NEN G3: a multicenter cohort study. Endocr Relat Cancer 2019; 26: 227-239 [PMID: 30540557 DOI: 10.1530/ERC-18-0424]

100 Ravizza D, Fiori G, Trovato C, Fazio N, Bonomo G, Luca F, Bodei L, Pelosi G, Tamayo D, Crosta C. Long-term endoscopic and clinical follow-up of untreated type 1 gastric neuroendocrine tumours. Dig Liver Dis 2007; 39: 537-543 [PMID: 17433795 DOI: 10.1016/j.dld.2007.01.018]

101 Ito T, Igarashi H, Uehara H, Berna MJ, Jensen RT. Causes of death and prognostic factors in multiple endocrine neoplasia type 1: a prospective study: comparison of 106 MEN1/Zollinger-Ellison syndrome patients with 1613 Literature MEN1 patients with or without pancreatic endocrine tumours. Medicine (Baltimore) 2013; 92: 135-181 [PMID: 23645327 DOI: 10.1097/MD.0b013e31829544a1f]

102 La Rosa S, Inzani F, Yanoli A, Klersy C, Dainese L, Rindi G, Capella C, Bordi C, Solcia E. Histologic characterization and improved prognostic evaluation of 209 gastric neuroendocrine neoplasms. Hum Pathol 2011; 42: 1373-1384 [PMID: 21531442 DOI: 10.1016/j.humpath.2011.01.018]
