Gastroduodenal neuroendocrine neoplasms, including gastrinoma — management guidelines (recommended by the Polish Network of Neuroendocrine Tumours)

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Abstract

This paper presents the updated Polish Neuroendocrine Tumour Network expert panel recommendations on the management of neuroendocrine neoplasms (NENs) of the stomach and duodenum, including gastrinoma. The recommendations discuss the epidemiology, pathogenesis, and clinical presentation of these tumours as well as their diagnosis, including biochemical, histopathological, and localisation diagnoses. The principles of treatment are discussed, including endoscopic, surgical, pharmacological, and radionuclide treatments. Finally, there are also recommendations on patient monitoring.

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Key words: *neuroendocrine neoplasms; stomach; duodenum; gastrinoma; diagnostics; therapy; guidelines*

1. Epidemiology and pathogenesis

1.1. Neuroendocrine neoplasms of the stomach

Neuroendocrine neoplasms (NEN) constitute approximately 1% of all neoplasms of the stomach [1]. Between 5.6 and 8.7% of gastrointestinal NENs are gastric neuroendocrine neoplasms (g-NENs). However, the rate of g-NENs in the overall group of NENs varies, depending on the site where the studies are conducted. Recently published data from Argentina indicate that g-NENs comprise 6.9% of all gastrointestinal NENs [2], whereas the rate reported in an earlier Austrian study was 5.6% [1]. The percentage of g-NENs in relation to all NENs significantly differs between reports. An Austrian study gave 23%, a Canadian study gave 5%, and Taiwan study gave 7.4%, whereas the SEER programme gave 6% [3, 4]. The differences indicate the need for multicentre, prospective studies with long-term analysis in order to better describe the epidemiology of these neoplasms in Europe. The prevalence is estimated at 1-2 cases per 1,000,000 people per year, (1.2/1,000,000 males, 1.8/1,000,000 females). In the years 1981–2000, an 8–9-fold increase in the diagnosis of g-NENs was observed, due to the continuously extending indications for endoscopic examinations [5,6].

In the stomach three clinical and pathogenetic types of g-NENs are found, with differences in their clinical and histopathological pictures, as well as in the diagnostics and therapeutic management (Table I).

Pathogenesis

Type 1 and 2 tumours arise from the enterochromaffin-like (ECL) cells of the gastric mucosa in response to chronic, excessive secretion of gastrin. Secondary hypergastrinaemia, caused by achlorhydria accompanying chronic atrophic gastritis (CAG), is responsible for the development of g-NENs of type 1. Primary hypergastrinaemia in Zollinger-Ellison Syndrome (ZES), sporadic or associated with multiple endocrine neoplasia 1 (MEN-1), is responsible for g-NENs of type 2. Gastrin and its derivatives stimulate the proliferation, migration, and differentiation of ECL cells, which lead to their hyperplasia and dysplasia. Hypergastrinaemia without the transforming factor(s) does not result in the development of g-NENs [5]. In patients with MEN-1, the transforming factor may be a menin defect. The following are also mentioned in the literature: protein inhibiting apoptosis BCL2, protein p53, fibroblast growth factor (FGF), transforming growth factor-α (TGF-α), and incorrect function of the REGL protein (inhibiting proliferation of ECL cells) [7].

Type 1

Gastric neuroendocrine neoplasms of type 1 (70–80% of g-NENs) are found in patients with atrophic gastritis. They occur in less than 1% of patients, more often in women, and are diagnosed mostly between the ages of 40 and 60 years. The increased availability of endoscopic examinations is expected to lower the age of patients diagnosed with g-NETs of type 1 [8, 9].

They rarely present clinical signs, and are diagnosed during an endoscopic examination performed due to dyspeptic symptoms or anaemia, more frequently due to macrocytic than iron-deficiency anaemia [10].

They are usually small lesions (< 1–2 cm), 65% of them are multiple, and 78% are polyps [6].

70–85% of the tumours belong to the NET G1 group, according to the World Health Organisation (WHO) 2017 classification [10, 11]. They are rarely invasive. 2–5% of cases are metastatic, and the ability to produce metastases increases along with the tumour size [6]. They are almost always slowly growing tumours with good prognosis — mortality rates have not been described, despite the disease advancement (up to 100% of patients with 10-year survival rate). They are non-functional: less than 1% of patients with g-NETs of type 1 present the symptoms of atypical carcinoid syndrome. Blood serum gastrin is significantly elevated, as well as gastric pH.

Type 2

This is the rarest (5–6%) form of g-NET. It occurs exclusively in the course of gastrinoma: in 23–29% of patients with ZES/MEN-1, and in 1–3% of sporadic lesions [5, 9, 12]. Zollinger-Ellison Syndrome is clinically present. Neoplasms are usually small (< 1–2 cm) and frequently multiple, often in the form of polyps. They are mostly located in the fundus and body of the stomach, only occasionally in the gastric cardia. They are classified as well-differentiated NETs (G1/G2 according to WHO 2017), with a good prognosis, regardless of the presence of metastases in as many as 30% of patients at the time of diagnosis [11, 12]. The mortality rate as-

sociated with the disease is less than 10% [6]. Blood serum gastrin is significantly elevated, whereas gastric pH is very low.

Type 3
This type occurs in 14–25% of the cases of g-NENs. It is found more frequently in males over 50 years of age. No predisposing factors have been identified. Tumours are single, usually large (> 2 cm in diameter) polyps, with ulceration on the surface, located in the fundus and body of the stomach. They are usually G3 tumours, classified as gastric neuroendocrine carcinomas (g-NECs according to WHO 2017) [11]. 50–100% of the lesions are associated with metastases to the lymph nodes and liver. Deaths due to g-NEC occur in 25–30% of cases, depending on the level of differentiation and the presence of metastases [6]. Blood serum gastrin concentrations and gastric pH are normal.

Recent publications indicate that, based on the morphological differentiation and Ki-67 values, G3 neoplasms can be divided into prognostic groups: well-differentiated NETs G3 and poorly differentiated NECs G3 [1, 2, 4, 11]. The division according to the proliferation index (Ki-67 > 55%) has clinical consequences for the response to chemotherapy (ChTx) and prognosis: NECs with Ki-67 > 55% demonstrated better response to platin-based ChTx, although the median survival was four months shorter than NETs G3 with lower proliferation index values (20–55%) [13].

The introduction of a new division is considered, as there have been reports of well-differentiated g-NETs of different degrees of malignancy (G1-G3), not associated with chronic atrophic gastritis. Moreover, gastric neoplasms with mixed endocrine and exocrine characteristics have also been described [11]. Presently, the literature presents 68 such cases, but there are no data available on survival [6].

1.2. Neuroendocrine neoplasms of the duodenum
According to American statistics, neuroendocrine neoplasms of the duodenum constitute 2–3% of all gastrointestinal tumours [2, 5, 14]. 50–70% of them are well-differentiated NETs G1 (according to WHO 2017) [11]. Five types of duodenal neuroendocrine tumours (d-NENs) can be distinguished [14]: 1) gastrinoma (27–58%), 2) non-functional neoplasms with positive results of immunohistochemical tests for serotonin and calcitonin, 3) somatostatin (SST)-secreting tumours (23–75%), 4) poorly differentiated duodenal carcinomas, and 5) neoplasms of the gangliocytic paraganglioma type (rare). Some authors exclude from this group tumours located in the ampulla of Vater and its area (approximately 20% of NENs), whose clinical course rather resembles pan-

creatic neoplasms, and are often associated with von Recklinghausen disease (neurofibromatosis type 1, NF-1) [14].

Some authors classify neuroendocrine tumours located in the ampulla of Vater as neuroendocrine neoplasms of the biliary ducts (next to the neuroendocrine neoplasms of the gallbladder and extrahepatic biliary ducts), and they constitute approximately 60% of these tumours. 50–70% of neuroendocrine neoplasms of the ampulla of Vater are well-differentiated NENs (G1 and G2), unlike neuroendocrine neoplasms of the gallbladder, 90–100% of which are neuroendocrine cancers (G3) [15, 16].

Less than 10% of patients with NF-1 develop NEN, which is almost always a duodenal somatostatinoma, mostly without any clinical symptoms. The classification of somatostatinoma as a separate clinical syndrome has been questioned recently because none of 46 patients with a histopathologically diagnosed somatostatinoma tumour described by Garbrecht et al. presented a full set of the symptoms proposed for this syndrome [17].

Over 90% of d-NENs are located in the duodenal bulb (58%) and descending duodenum (33%). Tumours belonging to d-NENs are usually small (> 75% are < 2 cm in diameter), limited to the mucosa and submucosa, but at the moment of diagnosis in 40–60% of cases regional lymph node metastases are present. Hepatic metastases occur in less than 10% of patients. Multiple d-NENs suggest MEN-1 [12].

2. Clinical characteristics

2.1. Neuroendocrine neoplasms of the stomach
Type 1 g-NENs are not characterised by a specific clinical picture. They are usually diagnosed during a gastroscopy performed due to dyspeptic symptoms. The course of the disease is usually mild, and after endoscopic or surgical treatment it only requires periodic endoscopic surveillance. Recurrence is a characteristic feature of these tumours — with an average time to recurrence of 24 months [10].

In g-NENs of type 2 the symptoms of ZES dominate (described for gastrinoma). Examinations described in the first section: "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms" (*see* p. 79–110) are necessary.

G-NECs clinically manifest as abdominal pains, anaemia, and weight loss. Their course is malignant, and they are usually disseminated at the diagnosis [7].

Gastric neuroendocrine neoplasms very rarely (< 1%) cause the symptoms of atypical carcinoid syndrome (concomitant hepatic metastases). Flushing usually lasts longer and is accompanied by lacrimation,

often with lowered arterial pressure. Unlike typical carcinoid syndrome, excess histamine can cause overgrowth of the facial skin ("leonine facies") and its bruising. Endocardial damage may also occur [18].

2.2. Neuroendocrine neoplasms of the duodenum

2.2.1. Gastrinoma

Gastrinomas are neuroendocrine neoplasms located in the duodenum (70%), pancreas (25%), and rarely in other sites (5%: stomach, liver, ovary, and lung), secreting gastrin and causing clinical ZES. Hypergastrinaemia results in hypersecretion of gastric acid, and consequently in peptic ulcer disease and gastroesophageal reflux disease with a severe course [19,20].

Gastrinomas are well-differentiated neoplasms NEN G1/G2. They are malignant in 60-90% of cases.

Recently it has been noted that 81% of patients with ZES due to duodenal tumour (i.e. 60–95% of all patients with ZES) demonstrate a history of long-term alcohol abuse (> 50 g/day). Therefore, this may be a significant risk factor for ZES [21].

Depending on its location and the presence of MEN-1, a gastrinoma demonstrates the following characteristics [12, 20, 22, 23]:

Duodenal gastrinomas:
— 50–88% of gastrinomas in the sporadic form are located in the duodenum;
— 90–100% of gastrinomas in ZES/MEN-1 are located in the duodenum;
— are small (77% < 1 cm); may be multiple;
— demonstrate local invasiveness;
— are usually located in the duodenal bulb and descending duodenum;
— are associated with metastases to the nearest lymph nodes; the primary tumour may also occur in a peripancreatic lymph node [24];
— hepatic metastases are rare (5–10%).

Pancreatic gastrinomas:
— are large (on average 3.8 cm, 6% < 1 cm);
— can be located in any part of the pancreas;
— are associated with frequent hepatic metastases (25–35%).

Gastrinomas in the course of MEN-1/ZES:
— 20–30% of patients with ZES are diagnosed with MEN1;
— 70–100% of MEN-1/ZES are situated in the duodenum, the tumours are almost always multiple;
— 15% demonstrate an aggressive clinical course;
— the average age at diagnosis is 32–35 years (for the sporadic form: 48–55 years);

— in 45% of patients, ZES symptoms precede symptomatic hypercalcaemia by a few years;
— in 25% of MEN1/ZES patients, the family history of MEN-1 is negative.
— in sporadic ZES gastrinomas may occur occasionally in the liver (< 1%) and liver/biliary ducts [20, 25, 26, 27], which has recently been demonstrated also for patients with MEN-1/ZES [28].

Zollinger-Ellison Syndrome should be suspected in patients with ulcer disease with [20]:
— multiple ulcers of the upper part of the gastrointestinal tract, with unusual location,
— relapses after treatment,
— concomitant severe oesophagitis,
— negative *H. pylori* test results,
— complications of the disease (gastrointestinal tract perforation, bleeding),
— diarrhoea,
— thickening of the gastric folds (present in 92% of ZES patients).

The most common symptoms include persistent abdominal pain (79–100% of patients), nausea (38%), vomiting (24%), diarrhoea (30–75%), which disappears after the use of protein pump inhibitors (PPI), a very characteristic feature, body weight loss (12%), and gastrointestinal bleeding. There are no differences between the clinical symptoms of pancreatic and duodenal gastrinoma [20].

Helicobacter pylori infection is less frequent in ZES patients (24–48% of patients) compared to peptic ulcer disease not caused by excessive gastrin secretion (90% of patients). Therefore, negative results of *H. pylori* tests in patients with recurrent peptic ulcer disease, who do not receive NSAIDs or acetylsalicylic acid, should be suggestive of gastrinoma [29].

The clinical course is aggressive in approximately 25% of patients with sporadic gastrinoma, and in 15% of patients with the ZES/MEN-1 form of the disease. The following constitute poor prognostic factors [30]:
— inadequate control of gastric acid hypersecretion,
— hepatic metastases,
— female sex,
— sporadic form,
— short time interval between initial symptoms and diagnosis,
— high fasting serum gastrin (FSG),
— large size (1–3 cm) of the primary tumour,
— pancreatic location of the primary tumour,
— ectopic ACTH secretion in the course of gastrinoma,
— bone metastases,
— angioinvasion and perineum infiltration in the histological examination.

2.2.2. Other neuroendocrine neoplasms of the duodenum

The clinical symptoms of other duodenal NENs vary: abdominal pain (9–64% of patients), bleeding from the upper gastrointestinal tract (11–28%), jaundice (7–32%), anaemia (11–28%), vomiting (4–8%), and duodenal stenosis (1% of patients). Jaundice, bile duct dilatation, vomiting, and diarrhoea often accompany NENs located in the proximity of the ampulla of Vater [30]. Duodenal neuroendocrine neoplasms very rarely cause carcinoid syndrome. In almost all cases the syndrome is atypical (described earlier with gastric carcinoids) [19].

Neuroendocrine neoplasms secreting ectopic hormones

In the literature there are reports describing d-NENs with Cushing's syndrome (5–15% of patients), with acromegaly (ectopic GRH secretion), and symptoms of insulinoma, glucagonoma, and polycythaemia vera [31].

2.2.3. Non-functional duodenal neuroendocrine neoplasms

Non-functional duodenal neuroendocrine neoplasms do not produce any hormone-dependent clinical symptoms. However, an immunohistochemical examination demonstrates the presence of gastrin, serotonin, calcitonin, and somatostatin in the tumour. These neoplasms constitute 70–98% of duodenal tumours. They include gangliocytic paragangliomas, which are most frequently located in the duodenal bulb area. They are usually large and benign tumours, invading the muscular layer [32].

3. Diagnostics

3.1. Biochemical diagnostics

3.1.1. Neuroendocrine neoplasms of the stomach

Biochemical diagnostics of type 1 g-NENs includes determination of the following parameters:
— serum chromogranin A (CgA) concentration [33] (*evidence level 5*),
— fasting gastrin [18] (*evidence level 5*),
— daily urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) (*evidence level 5*),
— serum serotonin concentration. Determination should be performed only in patients with atypical (rarely with typical) carcinoid syndrome (*evidence level 5*),
— vitamin B12 concentration in patients with hypergastrinaemia (*evidence level 3*).

Determination of β-hCG, human chorionic gonadotropin (presence in the granules of tumour cells, possible ectopic secretion), may be useful for the diagnosis [33].

In biochemical diagnostics of type 2 g-NENs

To confirm ZES, the following tests should be performed:
— determination of fasting serum gastrin (*evidence level 3);
— assessment of serum gastrin concentration after stimulation, i.e. the test with secretin (2 units/kg bw IV) or calcium gluconate in uncertain cases (*evidence level 3);
— assessment of serum gastrin concentration in patients after surgery due to gastrinoma, 3–12 months after the surgery, then follow-up tests every 6–12 months for 3–4 years (*evidence level 5);
— determination of serum CgA concentration (*evidence level 5);
— in uncertain cases concerning differentiation of the causes of secondary hypergastrinaemia — determination of gastric pH (pH < 2) [34] (*evidence level 4);
— in the case of suspected MEN-1 syndrome, screening tests described in section 1: "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms" should be performed (*see* p. 79–110). Concomitant MEN-1 syndrome requires confirmation in genetic tests [12] (*evidence level 4).

Diagnostics of ZES

ZES diagnosis requires the evidence of hypergastrinaemia under fasting conditions, with hypersecretion of hydrochloric acid, or low gastric pH (pH < 2). In practice, the diagnostics starts with determination of serum gastrin concentration under fasting conditions (FSG), which is increased to 98% for ZES patients. The evidence of hypergastrinaemia is not sufficient to diagnose ZES because there are other reasons for increased gastrin concentration than gastrinoma [5, 8]:
— with hypo/achlorhydria — atrophic gastritis, using PPI,
— with hyperchlorhydria: *H. pylori* infection, pyloric stenosis, renal failure, antral G-cell syndromes, short bowel syndrome.

In 40–60% of patients with ZES, the FSG value is lower than 10 times the normal gastrin concentration under fasting conditions, and it is comparable to gastrin concentrations in the course of *H. pylori* infection.

Therefore, the effective eradication of *H. pylori* is necessary before a gastrinoma diagnosis can be established [8].

Proton pump inhibitors and histamine H2-receptor antagonists increase gastrin and CgA concentrations in the blood, so previous discontinuation of PPI 10–14 days before the planned determination of blood gastrin concentration is recommended. In patients with suspected gastrinoma, PPI can be substituted in this period with oral H2-receptor antagonists, but it is recommended

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*evidence level according to OCEMB [87]

that they are also discontinued at least 48 hours before the examination [8]. Because sudden discontinuation of PPI in a ZES patient may result in complications due to a sudden increase in hydrochloric acid secretion, some experts currently recommend conducting diagnostics without the withdrawal of PPI, or with a dose reduction. Unfortunately, diagnosis is then very difficult, and using the secretin test is impossible due to the risk of a false-positive result. In ambiguous cases, the patients should be referred to a specialist centre, and if this is not possible a careful attempt to discontinue PPI should be made (in patients without symptoms or active ulcer disease), and an H2 blocker should be introduced.

Gastrinoma can be diagnosed if the fasting gastrin levels are over 10 times the upper limit of normal, and gastric pH < 2. In most cases, increased gastrin level is accompanied by an increased serum CgA concentration. The blood for gastrin determination should be drawn under fasting conditions. If gastrin concentration under fasting conditions is increased by less than a factor of 10 times, and the gastric pH is ≤ 2, the secretin stimulation test should be performed. The test is performed under fasting conditions, and secretin is administered intravenously, at a dose of 2.0 units/kg bw. Gastrin is determined at proper intervals, expressed in minutes relative to the moment of secretin administration: –15, –1, +2, +5, +10, +15 , +20, and +30 minutes. Gastrinoma diagnosis is confirmed by an increase in gastrin concentration by more than 120 pg/ml, at any point during the test, in relation to the baseline value. For this value of increase in gastrin concentration, the sensitivity of the secretin stimulation test is 94% and the specificity is 100%. Increasing the value of the diagnostic gastrin increment to 200 pg/ml reduces the test sensitivity to 82% [8].

The gastrin stimulation test with intravenous calcium gluconate is less sensitive, less specific, and associated with more adverse reactions. It is rarely performed, only if conducting the secretin stimulation test is impossible or if its result is negative, while the clinical suspicion of gastrinoma is strong [18].

Determination of gastrin concentration on consecutive days demonstrates the referential values in less than 0.5% of patients with ZES. Gastric pH above 3, on the other hand, is a strong indicator excluding the presence of gastrinoma. Because in 20–25% of cases gastrinoma is an element in MEN-1 syndrome, every patient with ZES should undergo the screening tests for MEN1 described in section 1: "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms" (see p. 79–110).

In a small proportion of patients with clinical symptoms of ZES resulting from excessive secretion of gastric acid, fasting gastrin concentration is normal, and the secreting test is negative. In such cases, plasma chol-

ecystokinin (CCK) concentration should be determined because the cause could be a CCK-secreting P-NEN [35]. This may be associated with diagnostic difficulties because few laboratories can provide a reliable assessment of CCK concentration.

Biochemical diagnostics of type 3 g-NENs:
— determination of serum CgA concentration is recommended (*evidence level 5);
— level of neuron-specific enolase (NSE) is higher in poorly differentiated neoplasms than in NETs, and it significantly correlates with the length of survival (*evidence level 5);
— determination of CgA (and daily urinary excretion of 5-HIAA in the case of atypical carcinoid syndrome, or serum ACTH and cortisol if ACTH-secreting tumour is suspected) (*evidence level 5).

3.1.2. Neuroendocrine neoplasms of the duodenum
— determination of CgA (*evidence level 5),
— gastrin in patients with ZES, in justified cases the test with secretin [33], (*evidence level 3),
— if clinical symptoms suggestive of ectopic hormone production by duodenal NEN occur, the following hormones should be determined (regardless of clinical symptom characteristics): adrenocorticotropic hormone (ACTH) and cortisol, insulin, and peptide C, as well as glucagon, insulin-like growth factor 1 (IGF 1) and growth hormone (GH), also in functional tests [33], (*evidence level 5);
— in patients with: duodenal NEN and clinical characteristics of MEN-1 syndrome, positive family history of MEN-1, and multi-focal duodenal NEN genetic tests for the presence of germinal menin gene mutation should be performed. Examination of somatic mutation in the tumour is not recommended [12] (*evidence level 4).

Minimal consensus statement on biochemical examinations:

*CgA — regardless of clinical symptoms (*evidence level 5);*

*Gastrin — in ZES (*evidence level 3);*

*5-HIAA — in typical and atypical carcinoid syndrome (*evidence level 3).*

*ACTH and cortisol (in a test with 1 mg of dexamethasone) if ACTH secretion by the tumour is suspected (*evidence level 3).*

3.2. Pathomorphological diagnostics
3.2.1. Pathogenesis
Gastric NENs are usually non-functional tumours arising from enterochromaffin-like (ECL) cells producing histamine, and are most frequently found in the

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Table I. *Types of gastric neuroendocrine neoplasms [6, 36, 37]*

	Type 1	Type 2	Type 3
Frequency	70–80%	Rare	10–15%
Tumour	0.5–1.0 cm	Usually up to 1.5 cm	Varied, mostly > 2 cm
Number of tumours	Multiple, small nodules, polyps	Multiple	Single
Site	Body	Body	Entire stomach
Associated conditions	Hypergastrinaemia Chronic atrophic gastritis ECL hyperplasia	MEN type 1, hypergastrinaemia Zollinger-Ellison Syndrome	Sporadic
Clinical course	Usually mild, limited to mucosa, submucosa	30% metastases	71% of tumours > 2 cm Invasion of *muscularis propria*, vessels, lymph nodes
Demographic characteristics	70–80% females 50–60 years of age	Females = Males, mean age 50 years	Males more frequently, mean age 55 years

fundus and body of the stomach. Less common are gastrin-producing G cells, present in large quantities in the pylorus, somatostatin-producing D cells, diffused in small quantities throughout the stomach, and serotonin-producing ECL cells, very rarely found in the stomach [8,9]. Gastric NENs are divided into three types, according to their clinical and morphological characteristics, following the AJCC Cancer Staging (Eighth Edition 2017) [36] and UICC (Eighth Edition 2017) [37]. Table I presents the characteristics of each group of neoplasms.

Type 1 gastric NENs occur most frequently. They develop in the gastric mucosa in the course of atrophic gastritis with concomitant hypergastrinaemia in the form of multiple polyps and nodules in the body of the stomach. The precursor is a linear or nodular hyperplasia of the ECL cells, associated with an increased risk of ECLoma [6]. Type 1 tumours are usually benign and can disappear after resection of the prepyloric part, although currently this approach is not recommended [38].

In the case of multiple gastric polyps, pathomorphological diagnosis requires differentiation of ECLoma from other lesions, such as hyperplastic or inflammatory polyps, adenomas, or early carcinoma type 0-I. A biopsy of different lesions is recommended, particularly of those that differ in macroscopic appearance, and from the fundus and body of the stomach, in order to verify atrophic inflammation [6].

Type 2 gastric NENs are rare. The tumours are usually more than 2 cm in diameter, invading the muscularis propria and demonstrating angioinvasive properties.

Germinal mutation tests are recommended in patients with suspected MEN-1 in cases with ECLoma and Zollinger-Ellison Syndrome, or with a family history suggestive of MEN-1 or multiple tumours without evidence of atrophic gastritis. Examination of somatic mutations in gastric NETs is not recommended [12].

Gastric NETs of type 1 and 2 are usually well-differentiated neuroendocrine neoplasms (NET G1 or NET G2).

Type 3 is the second most common gastric neuroendocrine neoplasm. It is a sporadic tumour, not associated with atrophic inflammation or hyperplasia of the neuroendocrine cells. Neoplasms of more than 2 cm in diameter, angioinvasion, and infiltration of the muscularis propria are the risk factors for metastases. This neoplasm is characterised by unfavourable prognosis, fast progression, and an aggressive course [6, 7].

3.2.2. Diagnostic algorithm
Diagnosis of gastric NENs is based on the histopathological examination of the polyps after their endoscopic resection in the case of NENs of type 1 and 2 (NET G1 and NET G2), or the surgical material obtained after resection of the stomach and lymph nodes in gastric NENs of type 3 (NETs G3 and NECs) [11, 36, 37].

A. Microscopic assessment of type 1 gastric NETs:
A type 1 gastric NET is a well-differentiated neuroendocrine neoplasm with the macroscopic appearance of a polyp[s]. In such cases, NETs G1 are usually diagnosed, and only sporadically NETs G2 [6].

In the microscopic assessment, the following parameters need to be determined:
— type of neoplasm according to the WHO 2017 classification [11];
— differentiation grade G on the basis of the Ki-67/MIB1 proliferation index and the number of mitotic figures;
— polyp resection margin;
— and angioinvasion properties.

B. Macroscopic assessment of the surgical material includes the following parameters [39]:
The dimensions of the gastric fragment obtained for examination, with the description of the tumour location relative to the resection margins.

Tumour size (if possible, in three dimensions). Condition of the mucosa at the tumour site (ulcerated/non-ulcerated). Tumour position relative to the stomach wall layers; tumour cross-sectional image, taking into consideration the areas of necrosis and extravasations.

Number and size of the lymph nodes.

Image of the mucosa in the remaining part of the slide (all changes need to be examined histopathologically).

Presence of other lesions in the gastric wall.

Width of surgical margins.

C. Microscopic assessment of the surgical material is based on assessment of the following parameters:

Histological type of the NEN according to the WHO 2017 classification [11], including division into NET G1 and NET G2, completed in rare cases with well-differentiated tumours of NET G3, according to the Eighth Edition AJCC Cancer Staging 2017 [36] and UICC 8 2017 [37]. Highly malignant NECs and mixed neoplasms are classified according to the criteria for classical adenocarcinomas.

The histological grade G according to ENETS 2016/ /WHO 2017, including the assessment of the number of mitotic figures in 1-HPF and proliferation index Ki-67, expressed as the percentage of tumour cells with immunohistochemical expression of MIB1 per 500 to 2000 tumour cells in a hot spot.

Pathomorphological pTNM staging according to AJCC/UICC (Table II).

Assessment of surgical margins.

Lesions in the gastric mucosa other than a tumour:
— presence/absence of atrophic inflammation,
— hyperplasia of ECL cells,
— other lesions.

Assessment of immunohistochemical expression of neuroendocrine markers: CgA and synaptophysin, as well the Ki-67/MIB1 proliferative activity (obligatory).

Immunohistochemical assessment of the markers: NSE, CD56, CDX2, and serotonin (conditional).

Histopathological types of the NENs according to the WHO 2017 classification and the histological grade (G) according to the ENETS 2016/WHO 2017 criteria are presented in "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms" (*see* p. 79–110).

3.2.3. Neuroendocrine neoplasms of the duodenum
According to the WHO 2017 classification [11], duodenal neuroendocrine neoplasms are usually well-differentiated NETs G1 (50–75% of cases), less often NETs G2 (25–50% of cases), and are only sporadically poorly differentiated neuroendocrine carcinomas (up to 3% of cases).

Grading of neuroendocrine neoplasms is conducted on the basis of mitotic activity (per ten high-power fields) and proliferation activity measured using the Ki-67 index.

Diagnostic algorithm
A histopathological report from the assessment of the surgical material — duodenal neuroendocrine neoplasms:

A. Macroscopic description [39]:
Dimensions of the duodenum fragment obtained for examination, with the description of the tumour

Table II. *Classification pTNM of gastric and duodenal neuroendocrine tumours according to UICC/AJCC, 2017 [36, 37]*

Primary tumour feature pT	Comments
TX	Primary tumour was not assessed
T0	No tumour structure
T1	Invasion of the lamina propria of the mucosa or submucosa by the tumour, neoplasm, tumour size ≤ 1 cm
T2	Invasion of muscularis propria or tumour size > 1 cm
T3	Invasion of muscularis propria and subserosa, without invasion of serosa
T4	Invasion of serosa or other organs or adjacent structures

location relative to the resection margins and adjacent tissues.

Tumour size (if possible, in three dimensions). Condition of the mucosa at the tumour site (ulcerated/non-ulcerated). Tumour position relative to the duodenum wall layers and adjacent tissues; tumour cross-sectional image, taking into consideration the areas of necrosis and extravasations.

Number and size of the lymph nodes.

Image of the mucosa in the remaining part of the slide (all changes need to be examined histopathologically).

Presence of other lesions in the duodenal wall.

B. Microscopic description:
Histopathological diagnosis (considering all the properties mentioned in the classification):
— histological type according to the WHO 2017 classification [11] and criteria presented in the Eighth Edition AJCC Cancer Staging 2017 [36] and Eighth Edition UICC [37];
— histological grading (G) according to ENETS 2016/ /WHO 2017 and criteria of the Eighth Edition AJCC Cancer Staging 2017 and Eighth Edition UICC; (*see* "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumours)" (p. 79).
— pTNM pathomorphological staging according to the Eighth Edition AJCC Cancer Staging 2017 [36] and Eighth Edition UICC [37].
presence/absence of angioinvasion characteristics.

Tumour position relative to the anatomical layers of the duodenal wall and adjacent tissue (depth of the invasion).

Width of surgical margins.

Lesions in the duodenal mucosa other than the tumour.

Obligatory immunohistochemical examinations: CgA, synaptophysin, and Ki-67/MIB1.

Conditionally — assessment of the neuroendocrine properties of the neoplasm in the immunohistochemical examination (intensity and steadiness of reaction should be reported, and possibly the manufacturer of the reagents used should be mentioned; in patients with MEN-1 syndrome and gastrinoma located in the duodenum, immunohistochemical assessment of gastrin and other hormone expression, both in the primary tumour and in the metastatic foci, should be performed):

— gastrin, serotonin, and SSA (additionally PP, calcitonin, insulin, glucagon);

— S-100, NSE (in the case of gangliocytic paraganglioma).

Fine-needle aspiration biopsy may be useful in the assessment of the stage of clinical advancement of the disease (diagnosis of neoplastic metastases in the lymph nodes and liver). Cytological smears can also be used for immunocytochemical examinations.

TNM classification of duodenal neuroendocrine tumours (Tables II and III) [36, 37].

T — primary tumour;

TX — primary tumour cannot be evaluated;

T1 — tumour invades lamina propria or submucosa and is ≤ 1 cm in diameter (duodenal neoplasm);

T2 — tumour invades muscularis propria or is > 1 cm (duodenal neoplasms);

Neoplasm invades through the sphincter submucosal membrane or muscularis propria, or is > 1 cm in diameter (neoplasms of the ampulla).

T3 — tumour invades the pancreas or peripancreatic fat tissue;

T4 — neoplasm invades the peritoneum or other organs

(for each T add "m" in multiple lesions).

N — regional lymph nodes

NX — regional lymph nodes cannot be assessed;

N0 — no metastases in the regional lymph nodes;

N1 — presence of lymph node metastases.

M — distant metastases

MX — distant metastases cannot be assessed;

M0 — no distant metastases;

M1 — distant metastases;

M1a — only hepatic metastases;

M1b — metastases to at least one extrahepatic location (e.g. lungs, ovaries, extra-regional lymph nodes, peritoneum, bones);

M1c — hepatic and extrahepatic metastases;

Clinical advancement staging is presented in Table III.

Table III. *Disease staging for gastric and duodenal neuroendocrine tumours [36,37]*

Stage	T feature	N feature	M feature
I	T1	N0	M0
IIa	T2	N0	M0
IIb	T3	N0	M0
IIIa	T4	N0	M0
III	Any T	N1	M0
IV	Any T	Any N	M1

Minimal consensus statement on pathomorphological examination:

Minimal histopathological report for gastroduodenal NEN should include:

— *histological type of the neoplasm according to the WHO classification, considering the division into well-differentiated neuroendocrine neoplasms (NET G1, NET G2, and NET G3) and neuroendocrine carcinomas (NECs) or mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN); (see "Diagnostic and therapeutic guidelines for gastro-enteropancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumours)" (p. 79–110);*

— *histological G grading referring to well-differentiated neoplasms (NET G1, NET G2, NET G3);*

— *assessment of polyp resection or surgical margins in the surgical material;*

— *pTNM histopathological staging according to ENETS and AJCC or UICC classifications (it is important to provide the affiliation of the classification in each case).*

— *The histopathological diagnosis of the NEN must be confirmed by immunohistochemical tests assessing expression of the neuroendocrine markers: synaptophysin and chromogranin A, as well as Ki-67 proliferative activity using the MIB1 antigen (*evidence level 3).*

3.3. Location diagnostics of gastroduodenal neuroendocrine neoplasms

3.3.1. Neuroendocrine neoplasms of the stomach

Gastric neuroendocrine tumour type 1:

Gastric neuroendocrine neoplasms of type 1 usually occur as multiple, small polyps of < 1–2 cm in patients with atrophic gastritis. The basic examination in imaging diagnostics is endoscopy of the upper gastrointestinal tract with a biopsy and/or complete removal of the largest tumour for histopathological examination. Also, two samples from the antrum need to be obtained for histopathological examination, as well as four samples from the fundus/body of the stomach [6, 40, 41]. It is also recommended to obtain a biopsy from the antrum and from the body of the stomach for a quick urease test if *Helicobacter pylori* infection was not assessed with the use of other methods.

*evidence level according to OCEMB [87]

In the case of tumours > 1–2 cm and/or multiple tumours, endoscopic ultrasonography should be performed before deciding on endoscopic treatment, to assess the depth of the intramural invasion [10, 42].

In selected cases, to assess the disease staging, three-phase CT (computed tomography) examination with water-filling of the stomach and after IV contrast administration should be performed as an initial (baseline) examination, and usually every six months, or depending on the clinical symptoms, as a surveillance examination during the clinical follow-up [43].

Gastric neuroendocrine tumours type 2:
Similarly to type 1 lesions, type 2 gastric neuroendocrine tumours are usually small (< 1–2 cm), often multiple polyps, typically located in the fundus and body of the stomach. As they develop in the course of gastrinoma, they may be associated with other changes, such as severe reflux oesophagitis or thickening of the gastric folds. The basic diagnostic tests include endoscopy of the upper gastrointestinal tract with a biopsy and/or complete removal of a small tumour for histopathological examination; also, in the case of larger and/or multiple tumours, two samples from the antrum need to be obtained for histopathological examination, as well as four samples from the fundus/body of the stomach, and tests should be performed to determine the *H. pylori* infection [6].

In the case of tumours > 1–2 cm and/or multiple tumours, EUS should be performed in order to assess the depth of the intramural invasion [10, 42].

As in the case of type 1 lesions, to exclude the presence of metastases, a three-phase computed tomography examination should be further considered as an initial (baseline) examination, and then every six months, or depending on the clinical symptoms, as a surveillance examination during clinical follow--up [43].

A radioisotope somatostatin receptor imaging (SRI) test should be performed in well-differentiated lesions to determine the disease staging during clinical follow--up, usually every 9–12 months, or depending on the clinical symptoms, and if discrepancies between the clinical, biochemical and structural examination results occur. This test is necessary before introducing therapy with somatostatin analogues (PRRT) [6].

Gastric neuroendocrine tumours type 3 (sporadic):
These are single, ulcerated, large lesions > 2 cm in diameter, usually located in the fundus and body of the stomach. Endoscopy of the upper gastrointestinal tract should be performed, and tumour samples obtained for diagnosis.

EUS can be used to assess the depth of intramural invasion, and the presence of metastases to the regional lymph nodes [6].

Abdominal ultrasonography (USG) enables identification of hepatic and lymph node metastases, providing the optimal conditions for the examination of the abdominal cavity or superficial lymph nodes, as well as other tissues involved in the neoplastic process.

Three-phase CT examination with water-filling of the stomach and after IV contrast administration according to the protocol, as in the case of gastric neuroendocrine neoplasms of type 1, should be performed each time, to assess the staging as an initial (baseline) examination, and during the clinical follow-up, as a surveillance test, usually every 3–6 months, or depending on the histopathological diagnosis, baseline staging, and the conducted active antineoplastic treatment in the case of advanced disease, non-resectable neoplasms, with or without progression, as well as according to the concurrent symptoms of local advancement or clinical and biochemical symptoms, such as carcinoid syndrome [43, 44].

If a CT scan cannot be performed (allergy to iodine agents is not an absolute contraindication for the test, which may be performed after proper antiallergenic premedication), magnetic resonance imaging (MRI) of the abdominal cavity before and after IV contrast administration should be performed. Particularly useful for the assessment of hepatic metastases are sequences DWI and 3D, T1 before and after contrast administration — a dynamic examination, e.g. LAVA/VIBE [44, 45].

Magnetic resonance of the spine or bone scintigraphy should be performed if any osseous metastases are clinically suspected or visible on the CT scan.

If bone metastases are present, accompanied by clinical symptoms (pain), palliative radioisotope therapy of bone pain should be considered (^{89}Sr, ^{153}Sm), following a positive verification in a ^{99m}TcMDP scintigraphic examination [46] (*evidence level 3).

3.3.2. Neuroendocrine neoplasms of the duodenum:
A sensitive method for detecting duodenal neuroendocrine tumours is endoscopy of the upper gastrointestinal tract, conducted with the use of straight/curved probes with biopsy and/or complete removal of the tumour for histopathological examination. In the case of hormonally functional tumours with characteristics of gastrinoma, upper gastrointestinal endoscopy may demonstrate specific lesions associated with gastric hypersecretion, such as multiple gastric and duodenal ulcers, and even small intestinal ulcers, or severe reflux oesophagitis (Zollinger-Ellison syndrome) [6,47].

EUS with an optional fine-needle aspiration biopsy should be performed in the case of larger tumours, to

*evidence level according to OCEMB [87]

assess the extent of the intramural invasion, and in any non-diagnostic endoscopy [48,49,50,51].

To assess the disease staging, the following examinations need to be further performed:

— three-phase computed tomography after oral administration of water in two stages — 500 mL half an hour before the test, and, optimally, 500 mL immediately before the test, if possible, depending on the patient's clinical condition, for optimal expansion of the gastroduodenal lumen, and after IV contrast administration [44].

The test should be performed in order to determine the disease staging, as an initial (baseline) examination, and, depending on the disease stage, as a surveillance examination during active combined treatment, to assess the effectiveness in the case of advanced lesions.

— an SRI test should be performed in advanced lesions, to determine the disease staging during follow-up, usually every 9–12 months, or depending on the clinical symptoms, and if discrepancies between clinical, biochemical, and structural examination results occur. This test is necessary before introducing therapy with somatostatin analogues/PRRT [6] — if duodenal neuroendocrine tumours are not visible in the structural and functional examinations, and in the case of a functional tumour, intraoperative USG is the examination of choice;

— magnetic resonance of the spine or bone scintigraphy should be performed if any osseous metastases are clinically suspected or visible on the CT scan, in order to assess the staging. If bone metastases are present, accompanied by clinical symptoms (pain), palliative radioisotope therapy of bone pain should be considered, following a positive verification in a ^{99m}Tc-MDP scintigraphic examination [46] (*evidence level 3).

Minimal consensus statement on location examinations:

— *Upper gastrointestinal endoscopy with a histopathological examination of the obtained material and endoscopic ultrasonography are the methods of choice in the diagnostics of most gastroduodenal neuroendocrine tumours.*

— *Computed tomography of the abdominal cavity following contrast IV, magnetic resonance, and receptor scintigraphy imaging should be used to assess the disease staging and detect potential distant metastases.*

— *In patients with advanced disease (e.g. with hepatic metastases), structural examinations (endoscopy, EUS, CT, and MRI) should be performed, and in NET, radioisotope somatostatin receptor imaging (SRI) should be conducted, to establish the optimal future treatment (*evidence level 3).*

4. Treatment

4. 1. Endoscopic and surgical treatment of gastroduodenal neuroendocrine tumours

4.1.1. Gastric neuroendocrine tumours (type 1–3)
In well-differentiated neoplasms less than 1 cm, only observation and control endoscopy every 12 months is possible [52], or endoscopic excision [10].

In well-differentiated neoplasms larger than 1 cm, in EUS test not invading the muscularis propria, endoscopic mucosal dissection (ESD) is the preferred method [53].

After endoscopic treatment it is recommended that a surveillance examination is conducted every 12 months [54, 55, 56]

In type 3 neoplasms, with the exception of small lesions that can be removed with ESD [57], the preferred method, as in other types deeply invading the organ wall, is surgical procedure.

4.1.2. Neuroendocrine neoplasms of the duodenum
In tumours of ≤ 1 cm, not invading the muscularis propria in the EUS examination, after exclusion of metastases, if it is possible from the technical point of view, and there is access to a centre with suitable experience, they may be removed via endoscopic submucosal dissection [6, 58, 59].

If ESD cannot be performed, consideration of local surgical removal is recommended.

Tumours larger than 2 cm and any tumour with lymph node metastases, regardless of its size, should be managed radically by surgical treatment.

Tumours of 1–2 cm:
— without lymph node invasion: local excision;
— with invasion of lymph nodes: radical surgical procedure.
— neoplasms with hepatic metastases: if surgical excision or local ablation of metastases is
— possible, a radical surgical procedure within the duodenum should be performed [60, 61].

4.1.3. Gastrinoma
Sporadic gastrinoma:
— if the disease is not generalised, distal pancreatectomy should be performed, if the tumour is located in the peripheral part of the pancreas;
— with the tumour located in the pancreatic head — if it is possible from the technical point of view, an attempt should be made to enucleate the tumour; if this is not possible, a pancreatoduodenectomy should be performed;
— with the tumour located in the duodenal wall it is necessary to perform duodenectomy with tumour excision or pancreatoduodenectomy.

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*evidence level according to OCEMB [87]

Gastrinoma in MEN-1 (most frequently multiple) — radical treatment is rarely possible. If the disease seems to be limited, an attempt to perform a radical resection can be made [39].

Minimal consensus statement on endoscopic/surgical treatment:

In gastric NENs of type 1, larger than 1 cm, without invasion of muscularis propria, endoscopic submucosal dissection is the treatment of choice. Smaller tumours may be observed.

In gastric NENs of type 3, as in other types of neoplasm deeply invading the organ wall, surgical procedure is the treatment of choice.

In duodenal NENs of ≤ 1 cm, without invasion of muscularis propria, after exclusion of metastases, endoscopic submucosal dissection is the treatment of choice. Tumours larger than 2 cm, and any tumour invading the muscularis propria or/ /and with lymph node metastases, should be surgically treated.

In the case of gastrinoma, surgical removal of the primary tumour(s) should be the target (*evidence level 3).

4.2. Pharmacological treatment
4.2.2. Neuroendocrine neoplasms of the stomach

Gastric neuroendocrine tumours of type 1
Typically, patients with gastric NENs of type 1 do not require pharmacological treatment [32]. Sometimes individual attempts are made to introduce treatment with somatostatin analogues (SSA) because they inhibit hypergastrinaemia, prevent hyperplasia of the ECL cells, and result in tumour regression [6]. It should be emphasised that the effect of SSA has not been compared to the surveillance strategies; therefore, SSA treatment cannot be recommended in early disease stages. SSA may be useful in the treatment of patients with multiple, small lesions, which are difficult to remove endoscopically [62]. This therapy may be the right option for patients with metastatic disease and proven SSTR2 expression, as well as low Ki-67 value. Studies without control groups revealed that netazepid, an antagonist of the gastrin/cholecystokinin receptor, demonstrates antiproliferative properties in g-NEN [63, 64]. However, it cannot be universally recommended, and further assessment of this therapy in controlled randomised studies is necessary *(*evidence level 5).*

Gastric neuroendocrine tumours of type 2
Zollinger-Ellison Syndrome (ZES)
The aims of ZES therapy are: 1) to normalise secretion of hydrochloric acid, 2) to manage gastrinoma, and 3) to treat gastric type 2 NET (which develops in 13–30% of patients with ZES/MEN-1) [12].

Excessive secretion of gastric acid in gastrinoma must be inhibited pharmacologically in all patients with gastrinoma, in order to prevent complications.

The treatment of choice involves PPI (**evidence level 3*). All marketed PPI (omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole) reveal similar effectiveness. Administration of PPI once or twice a day is effective in most patients. According to the available guidelines [23, 30], PPI used in high doses (3–4 times the standard dose) are the medications of choice. The recommended initial dose for omeprazole in sporadic forms of ZES is 60 mg once a day, for pantoprazole — 80 mg once a day, for rabeprazole — 60 mg once a day, and for esomeprazole — 2×40 mg. In patients with ZES complications (MEN-1 with hypercalcaemia, severe GERD symptoms, preceding Billroth II resection), higher doses of anti-secretive medications are used (daily dose for omeprazole is up to 120 mg, for pantoprazole — 160 mg, and for rabeprazole — up to 120 mg, for esomeprazole — up to 160 mg — each of them in two divided doses) [7]. In individual cases, PPI therapy may begin with intravenous administration (e.g. pantoprazole 80 mg every eight hours [65]). Intravenous administration is also recommended if medications cannot be taken orally. Good control of symptoms caused by excessive production of hydrochloric acid achieved with PPI therapy enables surgical intervention [66]. If surgical treatment is not possible, PPI therapy should be continued for an indeterminate period of time. It should be emphasised that in patients after a successful gastrinoma resection, use of PPI may still be necessary because in most of these patients, despite the surgery, hypersecretion is observed [67]. Discontinuation of PPI and resulting rebound hypersecretion may result in severe complications, such as perforation or gastrointestinal stenosis [68]. However, in some patients PPI doses may be reduced during the follow-up [64].

The effectiveness and favourable safety profile of long-term therapy with high doses of PPI has been confirmed by studies [69].

The most recent studies [70–72] do not confirm previous reports regarding the effect of long-term PPI therapy on vitamins B12 and D3 concentrations. However, there have been reports suggesting an increased risk of *Clostridium difficile* infection and community-acquired pneumonia in patients using PPI.

Histamine H2-receptor antagonists may also be used in patients with ZES. It should be noted that the time of action of H2-receptor inhibitors is shorter compared to PPI, and tachyphylaxis is observed, which makes them second-line medications. Patients with gastrinoma

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*evidence level according to OCEMB [87]

require higher and more frequent doses of H2 blockers than patients with idiopathic peptic ulcer disease. High doses of histamine H2-receptor antagonists can also be administered by constant intravenous infusion.

Long-acting somatostatin analogues are not first-line medications, and they should be used only in the case of a PPI treatment-resistant, malignant gastrinoma (*evidence level 3). Presently, studies on the effectiveness of treatment of g-NET type patients with gastrin//cholecystokinin receptor antagonist (netazepid) are being conducted.

In MEN1 syndrome, surgical resection of the parathyroids in primary hyperparathyroidism reduces excessive secretion of hydrochloric acid [30].

In the view of the RADIANT-4 study results, in patients with advanced non-functional NET G1/G2, after progression is observed, within six months the recommended treatment is everolimus (presently non--refundable in Poland) [73].

Gastric neuroendocrine tumours of type 3

Systemic treatment may be used in patients with inoperable lesions or in generalised stage (CS IV) [6].

Neuroendocrine carcinoma (NEC)

In patients diagnosed with NEC, the principles of local and systemic treatment are the same as in patients with adenocarcinoma. The systemic treatment of choice is chemotherapy (recommendations presented in the section on general guidelines). Cytostatics such as: 5-fluorouracil, capecitabine, dacarbazine, oxaliplatin, streptozocin, or temozolomide may be considered in patients with progressing disease in metastatic NENs and NECs, if there are no other therapeutic options [74] (*evidence level 3*).

There are no studies on the role of perioperative chemotherapy in patients with locally advanced gastric NEC. After radical surgical treatment of NEC with high proliferation index (Ki 67 > 55%), adjuvant chemotherapy using platin derivatives combined with etoposide is recommended [75].

In patients with non-resectable, locally advanced, or generalised disease, chemotherapy is the treatment of choice, provided the patient is in good condition and liver, kidney, and bone function is satisfactory (a detailed description of this form of treatment is presented in general guidelines on the management of GEP NEN, *see* p. 79–110).

4.2.3. Neuroendocrine neoplasms of the duodenum

Treatment of gastrinoma should be analogous to that of gastric NETs of type 2, whereas other tumours, especially disseminated ones associated with carcinoid syndrome, should be treated like gastric tumours at the same stage of advancement.

Chemotherapy in the treatment of poorly differentiated duodenal neuroendocrine neoplasms is similar to that used for the therapy of small-cell carcinoma.

Minimal consensus on pharmacotherapy:

1. Stomach:

*Type 1 — eradication of H. pylori (*evidence level 3).*

*Type 2 — eradication of H. pylori, PPI (*evidence level 3).*

*With somatostatin analogues to be considered in the case of: malignant gastrinoma, multiple, small g-NETs of type 1 (difficult to remove endoscopically), metastatic disease with confirmed SSTR2 expression, and low Ki-67 value (*evidence level 5).*

Type 3

*Chemotherapy in patients with a locally advanced non-resectable disease and/or generalised disease (*evidence level 3).*

2. Duodenum:

*ZES — PPI, H2 blockers (*evidence level 3).*

*ZES/MEN1 — PPI, treatment of hypercalcaemia (*evidence level 3).*

*Hormonally non-functional neoplasms — symptomatic treatment (*evidence level 4).*

*Functional neoplasms — treatment specific for the type of hormonal activity, somatostatin analogues (*evidence level 3).*

4.3. Radioisotope therapy

4.3.1. Gastroduodenal neuroendocrine tumours

Isotope therapy with labelled somatostatin analogues (Peptide Receptor Radionuclide Therapy — PRRT) is a form of palliative treatment rarely used in gastric NENs [46, 76, 77]. Eligibility for the treatment is in accordance with the principles presented in the general section.

In NETs of type 1 or type 2 there are no data regarding radioisotope treatment. Apart from surgical treatment, chemotherapy is the basic treatment for gastric neuroendocrine tumours of type 3, in the case of disseminated disease [78]. Information on the possible use of PRRT treatment in gastric NETs of type 3 is very limited, the literature data present only individual cases. Both in gastric NETs of type 3 and duodenal NETs, PRRT may be used in advanced, non-resectable, progressive processed cases, after the failure of previous treatment [79–81]. This treatment may be conducted in the case of the confirmed high expression of somatostatin receptors (SSTR) on the tumour cells in an SRI examination, and when there are no contraindications for this type of therapy [79-84]. Early radioisotope diagnostics allow the determination of the advancement of the neoplastic process, and eligibility for the treatment with radio-isotope-labelled somatostatin analogues. After PRRT, somatostatin receptor imaging enables assessment of treatment effectiveness [85].

In NETs associated with the clinical symptoms of functional tumour, such as carcinoid syndrome (stom-

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*evidence level according OCEMB [87]

ach) and Zollinger-Ellison Syndrome (ZES, stomach, and duodenum), where exacerbation of the symptoms or lack of symptom control with other forms of treatment is observed, PRRT should be considered earlier, often in combination with symptomatic treatment using "cold" somatostatin analogues [86]. In advanced gastroduodenal NET G3, PRRT may be considered when other treatment methods have been exhausted, and a high somatostatin receptor expression is maintained in the SRI examination. The literature data on this subject are limited to individual cases [46, 77, 79, 80–81].

Summary

PRRT in gastric NETs is rarely used. Information on this subject is very limited. It may be considered in type 3 gastric NETs G1 and G2, temporarily in NETs G3, in advanced, non-resectable, and progressive process, if previous therapy is ineffective and/or not tolerated, provided a high expression of receptors is confirmed in the SRI examination (*evidence level 4*).

In duodenal NETs, PRRT may be considered in an advanced, non-resectable, and progressive process, if the previous therapy is ineffective and/or not tolerated, provided a high expression of receptors is confirmed in the SRI examination. Similarly, in duodenal NETs G3, PRRT may be considered if the conditions presented above are met (*evidence level 4*).

Minimal consensus statement on radioisotope treatment:

The basic form of therapy in gastroduodenal NETs is endoscopic or surgical treatment, in the case of large lesions and an inability to provide endoscopic treatment.

In gastroduodenal NETs G1 and G2, PRRT may be considered in advanced, non-resectable, and progressive processes, if the previous therapy proves ineffective, and a high SSTR expression is confirmed in the SRI examination.

*In NETs G3 of the stomach and duodenum, PRRT is considered individually, in the case of advanced, progressive disease, if other therapeutic options have been ineffective, and a high SSTR expression has been confirmed in the SRI examination (*evidence level 4*).*

5. Follow-up

Minimal consensus statement on follow-up [39]:
Biochemical tests:
Stomach:
type 1 and type 2:
— *1–3 years — anamnesis and physical examination every 6–12 months;*
— *4–10 years — anamnesis and physical examination every 12 months (*evidence level 3);*
  type 3:

— *first year: anamnesis and physical examination every 3–12 months (*evidence level 3), CgA every 3-12 months (*evidence level 5);*
— *2-10 years: anamnesis and physical examination every 12 months (*evidence level 3), CgA every 12 months (*evidence level 5).*
Duodenum:
— *first year: every 3–12 months anamnesis and physical examination, CgA (*evidence level 5);*
— *2-10 years: every 6–12 months anamnesis and physical examination (*evidence level 3), CgA (*evidence level 5).*
Gastrinoma:
— *first year: every 3–12 months anamnesis and physical examination (evidence level 3), gastrin (*evidence level 3), CgA (*evidence level 5);*
— *2–10 years: every 6–12 months anamnesis and physical examination (*evidence level 3), gastrin (*evidence level 3), CgA (*evidence level 5);*
Imaging examinations
Stomach:
— *type 1 and type 2: upper gastrointestinal endoscopy every 6–12 months, other imaging examinations (CT, MRI) depending on the stage of the disease;*
— *type 3: upper gastrointestinal endoscopy every 3–6 months, other imaging examinations (CT, MRI) every 3–6 months.*
Duodenum:

NET — upper gastrointestinal endoscopy every 6–12 months, other imaging examinations (CT, MRI), depending on the stage of the disease, every 6–12 months;

NEC — upper gastrointestinal endoscopy every 3–6 months, other imaging examinations (CT, MRI) every 3–6 months.

In individual cases for patients with previously confirmed somatostatin receptor expression, an SRI examination should be included in the monitoring of NET.

References:
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