Endokrynologia Polska
DOI: 10.5603/EP.2013.0029
Tom/Volume 64; Numer/Number 6/2013
ISSN 0423–104X

Neuroendocrine neoplasms of the small intestine and the appendix — management guidelines (recommended by the Polish Network of Neuroendocrine Tumours)

Nowotwory neuroendokrynne jelita cienkiego i wyrostka robaczkowego — zasady postępowania (rekomendowane przez Polską Sieć Guzów Neuroendokrynnych)

Marek Bolanowski[1], Tomasz Bednarczuk[2], Barbara Bobek-Billewicz[3], Daria Handkiewicz-Junak[4], Arkadiusz Jeziorski[5], Ewa Nowakowska-Duława[6], Katarzyna Steinhof-Radwańska[7], Wojciech Zajęcki[8], Anna Zemczak[8], Beata Kos-Kudła[9]

and other participants of the Consensus Conference (affiliations at the end of this section)
Elżbieta Andrysiak-Mamos, Jolanta Blicharz-Dorniak, Andrzej Cichocki, Jarosław B. Ćwikła, Andrzej Deptała, Wanda Foltyn, Marek Hartleb, Alicja Hubalewska-Dydejczyk, Michał Jarząb, Dariusz Kajdaniuk, Grzegorz Kamiński, Aldona Kowalska, Robert Król, Leszek Królicki, Jolanta Kunikowska, Katarzyna Kuśnierz, Paweł Lampe, Dariusz Lange, Anna Lewczuk, Magdalena Londzin-Olesik, Przemysław Majewski, Bogdan Marek, Gabriela Mełeń-Mucha, Anna Nasierowska-Guttmejer, Andrzej Nowak, Waldemar Patkowski, Joanna Pilch-Kowalczyk, Violetta Rosiek, Marek Ruchała, Sławomir Rudzki, Philippe Ruszniewski, Grażyna Rydzewska, Anna Sowa-Staszczak, Teresa Starzyńska, Janusz Strzelczyk, Piotr Zdunowski

[1]*Department of Endocrinology, Diabetology and Isotope Therapy, Medical University of Wroclaw, Wroclaw, Poland*
[2]*Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland*
[3]*Department of Radiodiagnostics, Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch, Poland*
[4]*Department of Nuclear Medicine and Endocrine Oncology, Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch, Poland*
[5]*Department of Surgical Oncology, Medical University of Lodz, Poland*
[6]*Department of Gastroenterology and Hepatology, Medical University of Silesia, Katowice, Poland*
[7]*Department of Radiology, Medical University of Silesia, Katowice, Poland*
[8]*Division of Endocrinology, Medical University of Silesia, Katowice, Poland*
[9]*Division of Endocrinology, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland*

Abstract
We present revised Polish guidelines regarding the management of patients harbouring neuroendocrine neoplasms (NENs) of the small intestine and appendix. The small intestine, especially the ileum, is the most common origin of these neoplasms. Most of them are well differentiated with slow growth. Rarely, they are less differentiated, growing fast with a poor prognosis. Since symptoms can be atypical, the diagnosis is often accidental. Typical symptoms of carcinoid syndrome occur in less than 10% of patients. The most useful laboratory marker is chromogranin A; 5-hydroxyindoleacetic acid is helpful in the monitoring of carcinoid syndrome. Ultrasound, computed tomography, magnetic resonance imaging, colonoscopy, video capsule endoscopy, balloon enteroscopy and somatostatin receptors scintigraphy are used in the visualisation. A histological report is crucial for the proper diagnostics and therapy of NENs, and it has been extensively described. The treatment of choice is surgery, either radical or palliative. Somatostatin analogues are crucial in the pharmacological treatment of the hormonally active and non-active small intestine NENs and NENs of the appendix. Radioisotope therapy is possible in patients with a good expression of somatostatin receptors. Chemotherapy is not effective in general. Everolimus therapy can be applied in patients with generalised NENs of the small intestine in progression and where there has been a failure or an inability to use other treatment options. Finally, we make recommendations regarding the monitoring of patients with NENs of the small intestine and appendix. **(Endokrynol Pol 2013; 64 (6): 480–493)**

Key words: *neuroendocrine neoplasms; small intestine; appendix; carcinoid; diagnostics; therapy; guidelines*

Streszczenie
W pracy przedstawiono uaktualnione polskie zalecenia postępowania z chorymi na nowotwory neuroendokrynne (NEN) jelita cienkiego i wyrostka robaczkowego. Jelito cienkie, a przede wszystkim jelito kręte jest miejscem najczęstszego występowania tych nowotworów. Większość z nich to nowotwory wysokozróżnicowane i wolno rosnące. Rzadko są to nowotwory niskozróżnicowane, szybko rosnące o niekorzystnym rokowaniu. Ich objawy mogą być nietypowe, a rozpoznanie przypadkowe. Typowe objawy zespołu rakowiaka występują

Prof. Beata Kos-Kudła M.D., Ph.D., Division of Endocrinology, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Ceglana St. 35, 40–952 Katowice, Poland, tel./fax: +48 32 358 13 66, e-mail: endoklin@sum.edu.pl

w mniej niż 10% przypadków. W diagnostyce laboratoryjnej najbardziej przydatne jest oznaczenie stężenia chromograniny A, badanie stężenia kwasu 5-hydroksyindolooctowego jest pomocne w monitorowaniu zespołu rakowiaka. W obrazowaniu stosuje się ultrasonografię, tomografię komputerową, rezonans magnetyczny, kolonoskopię, wideoendoskopię kapsułkową, enteroskopię dwubalonową, scyntygrafię receptorów somatostatynowych. Szczegółowe badanie histologiczne jest kluczowym dla właściwego rozpoznania i leczenia chorych z NEN jelita cienkiego i wyrostka robaczkowego. Leczeniem z wyboru jest postępowanie chirurgiczne, radykalne lub paliatywne. W leczeniu farmakologicznym czynnych i nieczynnych hormonalnie NEN jelita cienkiego i wyrostka robaczkowego podstawowe znaczenie mają analogi somatostatyny. Terapia radioizotopowa u chorych z dobrą ekspresją receptorów somatostatynowych stanowi kolejną opcję terapeutyczną. Chemioterapia jest na ogół nieskuteczna. U pacjentów z rozsianym NEN jelita cienkiego i progresją choroby oraz nieskutecznością innych metod terapii można zastosować ewerolimus. Przedstawiono także zalecenia odnośnie monitorowania chorych z NEN jelita cienkiego i wyrostka robaczkowego. **(Endokrynol Pol 2013; 64 (6): 444–493)**

Słowa kluczowe: *nowotwory neuroendokrynne; jelito cienkie; wyrostek robaczkowy; rakowiak; diagnostyka; terapia; zalecenia*

Introduction

Neuroendocrine neoplasms (NENs) of the small intestine originate in the midgut; the small intestine is the second (after the pancreas) most common place of their occurrence. From the clinical point of view, we distinguish between hormonally non-active NENs, and active ones that secrete substances which cause characteristic symptoms known as carcinoid syndrome. Most small intestinal NENs are well differentiated and grow slowly. On rare occasions, they are poorly differentiated, with rapid growth and a poor prognosis. Tumours in this location are very rarely part of MEN syndromes [1–3].

NENs of the terminal part of the small intestine and the appendix are mostly composed of EC (enterochromaffin) cells, responsible for serotonin production. Certain NENs have the ability to secrete enteroglucagon, glucagon and other peptides. It is believed that ileum NENs of that type are more aggressive than neuroendocrine neoplasms of the duodenum, tumours of the stomach built of ECL (*enterochromaffin-like*) cells, or of the rectum. They reveal higher metastatic ability, associated to a lesser degree with the size of the tumour [1–3].

1. Epidemiology

The small intestine, and particularly the ileum, are the most common NENs sites in the human body. Small intestinal NENs occur equally often in male and female patients; they affect all age groups, with the peak in the 6th and 7th decades of life. The estimated prevalence is 0.32–1.12 per 100,000 of the population per year, including malignancy in 0.29 per 100,000; apart from the small intestine, they also affect the appendix and the midgut [4–10]. Post-mortem examinations have reported a possible prevalence of as much as 1.22% [11]. Tumours originating from the lower part of the jejunum and the ileum constitute 23–38% of all gastrointestinal endocrine neoplasms, and they are more common than endocrine neoplasms of the appendix. Hormonally active neuroendocrine neoplasms of the small intestine are often multifocal, and in 15% of cases are associated with other neoplasms such as gastrointestinal adenocarcinoma or breast cancer [3].

The term 'carcinoid' is still associated with a certain ambiguity. In the past, the term referred to a neuroendocrine neoplasm, regardless of the location of the primary tumour site or the level of malignancy. Later, in Europe, carcinoids were limited to neoplasms originating from the midgut, secreting serotonin and associated with carcinoid syndrome symptoms. However, the WHO 2010 classification of the gastrointestinal neuroendocrine neoplasms attributed the term *carcinoid* to G1 neuroendocrine neoplasms. The Polish Network of Neuroendocrine Tumours argues that the term 'carcinoid' should be relinquished, and substituted with the name 'neuroendocrine tumour' or 'neuroendocrine neoplasm' [2–4, 12, 13].

Over the last 30 years, the incidence of neuroendocrine neoplasms of the gastrointestinal tract has increased by 720%, and of the small intestine by 460%. In this period, within the small intestine there has also been an increase in the ileum neuroendocrine neoplasms rate, from 52% to 63.6%. This is very important, as neoplasms in this area in 58% of cases are malignant; this group of tumours constitutes no more than 35% of cases within the whole small intestine. A higher prevalence has been observed in African-Americans and in females compared to Caucasians and males. Although the increase in the incidence of gastric and rectal NENs can be partially explained by the development of endoscopic techniques, such an explanation does not apply to the higher prevalence of small intestinal NENs [2–4].

Most tumours are located in the terminal part of the ileum, in proximity to the ileocaecal valve. The prognosis is these cases is usually poor, as they often involve metastases to the regional lymph nodes, and then to the liver. It depends on the TNM staging assessment and Ki67 grading [13]. The five-year survival rate is 100% for patients with stages I and II small intestinal NENs, 97.1% for patients with stage III, and 84.8% for patients with stage IV. Considering the level of tumour differentiation, the five-year survival rate was 93.8% for G1, 83% for G2, and 50% for G3 [14]. Other studies have reported the five-year survival rate to be 72% in patients

with local tumours, and 55% in patients with distant metastases [15]. Alternative European data shows the five-year survival rate to be 59–74% in patients with NENs of the small intestine and the appendix [8, 16]. Earlier observations revealed a ten-year survival rate of 60% in patients without liver metastases at the diagnosis, and 15–25% in metastatic patients. The prognosis improves if the primary tumour is removed [3].

2. Clinical characteristics

2.1. Symptoms of the hormonally active NENs of the small intestine — carcinoid syndrome

Carcinoid syndrome occurs in approximately 4–10% of NENs patients, mainly with dispersed tumours located in the ileocaecal area. Carcinoid syndrome comprises symptoms resulting from an excessive secretion of serotonin and other biologically active compounds (including kinins, prostaglandins and histamine) by NENs. Serotonin secreted to the portal venous system is metabolised in the liver, and does not cause any clinical symptoms. The symptoms occur if serotonin and other biogenic amines are secreted directly to the systemic circulation; therefore, carcinoid syndrome symptoms occur most often with hepatic metastases from NENs (approximately 95% of cases) [1–4, 17].

Clinical symptoms of carcinoid syndrome include: (i) symptoms affecting the skin (flushing, telangiectasis, pellagra — skin inflammation caused by vitamin PP deficiency, resulting from the use of tryptophan for excessive serotonin production by the neoplasm); (ii) symptoms affecting the gastrointestinal tract (secretory diarrhoea, non-specific or colic abdominal pains); (iii) symptoms affecting the cardiovascular system (tricuspid valve disorders, diseases of the pulmonary trunk, rarely mitral valve and aorta disorders); (iv) symptoms affecting the musculoskeletal system (osteoarticular pains, myopathies) [18, 19].

Flushing is one of the main symptoms of carcinoid syndrome. Flushing that accompanies serotonin secreting NENs of the small intestine (classical carcinoid syndrome) is pale-pink to red, affecting the face and upper chest, and lasting up to 30 minutes. Triggering factors include alcohol, spicy foods, emotional stress, and medications (serotonin reuptake inhibitors). Flushing in the case of foregut NENs (atypical form of carcinoid syndrome) is more intensive, with a crimson shade; it lasts longer (as much as a few days), affects the torso and upper limbs, and is often accompanied by lowered blood pressure and lacrimation [18].

The main causes of death in patients with carcinoid syndrome are heart diseases — referred to as carcinoid heart disease (CHD), which may affect 50% of patients. CHD is mainly characterised by plaques of fibrous tissue on the valves of the right heart, leading to tricuspid valve regurgitation (the most common defect) and/or stenosis/regurgitation of the pulmonary valve. The left side of the heart is affected by the disease in less than 10% of cases, and is associated with the presence of pulmonary NENs, or a right-to-left leak, for instance in the patent foramen ovale. At first, the clinical symptoms of CHD are weakly pronounced; then, the symptoms of right ventricular heart failure progress: weakness, exertional dyspnoea, oedemas and ascites develop. The prognosis for patients with CHD and severe heart failure (NYHA classes III and IV) is unfavourable; the mean survival rate for patients without cardiosurgical treatment is 11 months. The gold standard in CHD diagnosis is echocardiography, which should be performed in all patients with carcinoid syndrome [19–24].

Carcinoid crisis is a rare, life-threatening complication caused by a sudden release of biologically active substances to the systemic circulation. The symptoms include: prolonged skin redness, intense diarrhoea or vomiting, wheezing, blood pressure fluctuations, arrhythmia, disturbed nervous system function, dehydration, shock, acute renal failure or hypercalcaemia. The crisis may occur independently, during infection, or as a result of medical procedures: general anaesthesia, endoscopy, tumour biopsy, surgery, embolisation, radioisotope therapy or chemotherapy. Therefore, it is recommended to use somatostatin analogues in the pre-operative period or during surgery on NENs patients [25–27].

2.2. Symptoms of the hormonally non-active NENs of the small intestine

The clinical picture of the hormonally non-active NENs of the small intestine is related to local symptoms. Small tumours are usually asymptomatic; they are found while identifying the source of metastases, or accidentally during colonoscopy. Larger tumours, of more than 1 cm, are usually malignant and metastatic. Leading local symptoms include transient abdominal pains and discomfort lasting for years, and are often misinterpreted as functional disorders. Over time, the symptoms worsen and may result in transient obstructions of the small intestine caused by the presence of the tumour mass, or by the desmoplastic reaction of the mesentery. Moreover, the desmoplastic reaction can impair the blood supply in the intestines, resulting in intestinal ischaemia, and in severe cases leading to necrosis. A desmoplastic reaction rarely results in retroperitoneal fibrosis or hydronephrosis. Other non-specific symptoms include weight loss, weakness and rarely a fever of unknown aetiology. Severe gastrointestinal bleeding is a rare symptom of the small intestine NENs. In many cases of hormonally

non-active small intestinal NENs, the clinical picture is poorly expressed and highly non-specific; the patient is diagnosed due to discovered (often accidentally) hepatic metastases [2-4].

2.3. Symptoms of NENs of the appendix

Appendicitis is usually the first manifestation of carcinoid in this location. Over 50% of neuroendocrine neoplasms of the appendix are discovered accidentally after appendectomy. Recent data indicates that metastases to the regional lymph nodes occur in 27% of cases, and distant metastases in 8.5% of cases [2–4].

Symptomatology of gastrointestinal neuroendocrine neoplasms, in particular tumours of the small intestine, favours diagnosis of these tumours in more advanced stages. While gastrointestinal neuroendocrine neoplasms are found in 45.4% as local lesions, in the case of the small intestine the rate is 31.3%. These values are much lower than those for NENs of the stomach, appendix and rectum, which have a better prognosis [2–4].

Most NENs of the appendix are diagnosed in earlier stages. This contributes to a high survival rate in patients with tumours in this location, which is particularly visible in children, where over 80% of the diagnosed tumours are smaller than 1 cm. The size of the tumour is of crucial importance for the occurrence of metastases: for tumours smaller than 1 cm in diameter, metastases occur in 2%; for tumours of 1–2 cm in diameter, the figure is 50%; and for tumours bigger than 2 cm, the figure is 80–90% of patients [2–4].

3. Diagnostics

3.1. Biochemical diagnostics

In the biochemical diagnostics of neuroendocrine neoplasms of the small intestine, it is useful to determine the concentration of chromogranin A (CgA) — a sensitive, but not very specific, marker [2–4, 17, 28]. Determination and interpretation of the results have been described in the chapter on general GEP NENs diagnostics. A significantly increased CgA concentration (over 1,000 ng/mL) may be treated as an indicator of poor prognosis.

The assessment of 5-hydroxyindoleacetic acid (5-HIAA) excretion in urine is a sensitive tumour indicator, useful for diagnosis and monitoring of disease progression or treatment in patients with carcinoid syndrome. The sensitivity and specificity of 5-HIAA determination in order to confirm carcinoid syndrome are 70% and 90%, respectively (for details, see the chapter on general GEP NENs diagnostics) [2–4, 29]. The determination of blood serotonin levels can be helpful when 5-HIAA determination is ambiguous.

In diagnostics and assessment of the severity of carcinoid heart disease, the determination of 5-HIAA and NT-proBNP (N-terminal-pro-B-type natriuretic peptide) may be useful [2–4, 17, 30, 31].

Minimal consensus statement on biochemical tests:

— *CgA and 5-HIAA — in patients with suspected carcinoid syndrome (*evidence level 3);*
— *CgA and 5-HIAA in all patients diagnosed with NEN of the small intestine before treatment, and during monitoring (*evidence level 3);*
— *NT-proBNP — in the case of carcinoid heart disease, in order to assess the severity (*evidence level 4).*

3.2. Imaging diagnostics

The aim of diagnostic imaging of NENs in the small intestine is:

— to present the primary focus;
— to determine the local tumour size and presence of metastases;
— to evaluate the response to treatment [32–34].

Computed tomography (CT) scanning is crucial for the location diagnostics of GEP NENs because it is a simple, easily available, and objective imaging method which allows locating the tumour precisely and enables a simultaneous assessment of potential tumour expansion i.e. invasion to the adjacent structures and metastases to the liver or lymph nodes. Preliminary diagnostics of small intestine diseases should involve CT enterography or MR enterography; for the follow-up of small intestine diseases, MR enterography should be applied. MR enteroclysis should be performed in patients with a clinically suspected pathology of the small intestine and with negative MR/CT enterography results [35–37].

Multiphase — mostly three-phase — CT or magnetic resonance (MR) examinations after intravenous administration of the contrast agent are methods evaluating the stage of advancement of the neoplastic disease; they enable monitoring of the disease and assessment of the response to therapy, according to the RECIST criteria [38, 39].

Some NENs are visible only in the arterial phase of the study, that is for a maximum of approximately. 30 seconds after the administration of contrast medium. Therefore the CT and/or MR examination should be multiphase, with delays of 15 s, 30 s, and 80 s, and a layer thickness of 1–2.5 mm. The contrast material

** evidence level according to CEBM [77]*

is administered intravenously, approximately 1.5 mL/ /kg b.w. In the case of MR imaging, the scans include: T1-weighted, T2-weighted, fat-saturated T2-weighted, DWI images with ADC maps, and dynamic imaging following the administration of a contrast agent. Both CT and MR examinations are characterised by a high sensitivity in diagnosing metastatic foci in the liver (88–90%). MR imaging is considered to be a second-line examination in the assessment of hepatic metastases; it is particularly important for the assessment of foci with a non-specific enhancement in the CT scan, and foci smaller than 10 mm. It is also recommended in patients allergic to iodine contrast agents used in CT imaging. CT and MR are also widely used in the diagnostics of metastases to organs other than the liver: lymph nodes, lungs and bones. In the comprehensive assessment of the severity of the neoplastic process, MR of the whole body can be used, including not only the standard T1-weighted, T2-weighted and fat-saturated T2-weighted images, but also DWI scans with ADC maps. Ultrasonography (USG) is of limited use in detecting the primary tumour site. Its sensitivity in the diagnosis of hepatic metastatic foci is estimated to be as much as 80%; however, it is a subjective test, and thus it is not recommended for the evaluation of response to treatment. Using anatomical methods together with functional ones is a standard procedure in diagnostics and assessment of response to the treatment of NENs, because of the insufficient sensitivity and specificity of each examination alone, and due to the evaluation of the expression of somatostatin receptors [40–42].

3.2.1. Endoscopic diagnostics

Endoscopic diagnostics of the small intestine is usually undertaken to identify the primary tumour site in the case of metastases of an unknown origin (often significantly larger than the primary tumour), in the case of non-specific abdominal symptoms, or to find the cause of gastrointestinal bleeding [43].

Classical endoscopy is of little importance in the diagnostics of small intestinal NENs. Although the direct presentation of a NEN located in the small intestine is possible during colonoscopy, when the tumour protrudes through the ileocaecal valve into the caecum lumen, such cases are very rare. Colonoscopy is, however, important to exclude a concomitant neoplastic disease (primarily colorectal cancer). Endoscopic ultrasonography, unlike other locations of GEP NENs lesions, is of no use in the diagnostics of small intestine tumours [35–37].

Video capsule endoscopy (VCE) and balloon or spiral enteroscopy can be used for direct assessment of the jejunum and ileum mucosa, but these methods are not very available [35–37]. A full assessment of the small intestine is achieved in approximately 80% of patients, and the overall diagnostic efficiency of the test is ca. 55% [44]. VCE sensitivity in the diagnosis of neuroendocrine tumours is relatively low, and compared to CT enterography it is 29–37.5% v. 50–92%. Another disadvantage of VCE is inability to locate the tumour precisely [45–47]. Balloon enteroscopy or spiral enteroscopy are free of this shortcoming, but their diagnostic efficiency is not very high [48, 49].

It is worth emphasising that neuroendocrine neoplasms of the small intestine, due to secreted growth factors resulting in desmoplastic reactions of the mesentery, often cause significant narrowing of the intestine, which is an absolute contraindication for video capsule endoscopy, because of the risk of capsule incarceration [50, 51].

3.3. Isotope diagnostics

Compared to radiological examinations, somatostatin receptor scintigraphy (SRS) with the use of radioisotope-labelled SSA is a more sensitive method, especially while identifying the primary tumour site [52]. Indications for SRS include:

— location of the primary site of the tumour;
— determination of the stage of disease advancement;
— monitoring of the patient following a radical surgical treatment (all patients with tumours located in the small intestine and tumours > 1 cm in the appendix);
— qualification of patients for pharmacological treatment and for isotope therapy with SSA.

The sensitivity of the study is over 80% for identification of the primary tumour site [53], whereas in the diagnostics of distant metastases it is over 90% [54]. PET/CT examination with Ga-68 labelled SSA [55] is the preferred approach, particularly when detecting small lesions of less than 1 cm [56].

Minimal consensus statement on imaging:

— *Abdominal ultrasound, three-phase multi-slice CT and/ /or MR and SRS with a labelled somatostatin analogue (SPECT/CT, PET/CT) in all patients with small intestine NENs (*evidence level 3);*
— *For primary tumour detection, CT/MRI enterography, CT/MRI enteroclysis or endoscopic techniques may be required, (*evidence level 3);*
— *Colonoscopy to exclude a concominant neoplastic disease (colon cancer) (*evidence level 4).*

** evidence level according to CEBM [77]*

3.4. Pathomorphological diagnostics

3.4.1. NENs of the small intestine

Pathogenesis

In the small intestine, well differentiated neuroendocrine neoplasms (NEN G1, NEN G2) are more frequently diagnosed than carcinomas (NECs). Most of the small intestinal NENs (95%) are composed of enterochromaffin cells (EC) responsible for serotonin production. Historically, they were referred to as 'carcinoids'. This name referred to well-differentiated neuroendocrine neoplasms with clinical carcinoid syndrome. Carcinoid syndrome is usually (95%) diagnosed in patients with hepatic metastases. Hormonally non-active NENs are usually found by chance during surgery, or due to the symptoms of obstruction (35%) or gastrointestinal bleeding (14%). Acute abdominal symptoms appear suddenly in patients with dyspeptic and pain symptoms in the abdominal cavity (50%) which persist for years, diarrhoea, or weight loss (24–25%).

In patients undergoing surgery due to a NEN of the small intestine, a large mesenteric tumour being a conglomerate of metastatic lymph nodes and a smaller primary tumour in the intestine are usually found in diagnostic imaging or during a surgical procedure. The lesion is rarely located in the Meckel's diverticulum. It may also invade the caecum.

The risk of metastases of the small intestinal NENs increases with a tumour diameter of above 2 cm, muscularis propria infiltration, and proliferative activity. It is noteworthy that tumours of the small intestine have a worse prognosis than neoplasms of the same size but located in different sites [14]. The tendency for metastases to the lymph nodes and the liver significantly worsens the prognosis for patients with NENs of the small intestine.

Diagnosis of NENs of the small intestine, due to a specific clinical course of the disease, is based on a needle biopsy assessment (of a sample obtained for histopathological examination) of a hepatic metastasis, which is often the first clinical symptom, or examination of the removed small intestine material and tumour obtained during a surgical procedure. A fine-needle biopsy is not recommended for the assessment of hepatic lesions, especially as the first test, if the primary tumour has not been diagnosed.

Diagnostic algorithm

In the macroscopic assessment of small intestinal NENs, the following elements are considered:

— The length of the intestinal section obtained for examination, with the description of the tumour location relative to the intestine resection margins, and the width of the removed intestinal mesentery.
— Tumour assessment: number, size in three dimensions, mutual relation of the tumours, cross-section appearance, considering the extravasation and foci of necrosis, relation of the tumour to the layers of the intestinal and mesenteric wall.
— Condition of the mucosa at the tumour site (ulceration present/not present).
— Condition of the serosa at the tumour site.
— Presence and size of the lymph nodes (in the case of a conglomerate of lymph nodes, the lesion looks like a mesenteric tumour).
— Presence of other tumours in the intestinal wall.

Microscopic assessment of NENs:

Histological type of NEN according to the WHO classification of 2010 [13].

Histological grading (G) according to ENETS/WHO 2010 [13, 57–59].

Pathomorphological pTNM staging according to ENETS [58, 59] and AJCC/UICC [61], and clinical staging (S).

Assessment of surgical margins

Assessment of the immunohistochemical expression of neuroendocrine markers: chromogranin A and synaptophysin, as well as Ki67/MIB1 proliferative activity (obligatory).

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

Regarding 1 and 2: Histopathological type of the small intestinal NENs according to the WHO 2010 classification and the histological grade of the NEN according to the integrated ENETS/WHO 2010 system are presented in "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumors)" (*pp. 418–443*).

Regarding 3: pTNM staging classification for the small intestinal NENs is presented in Tables I and II.

The small intestinal NENs staging according to ENETS [58, 59] and AJCC/UICC [60] is presented in Table II.

3.4.3. Neuroendocrine neoplasms of the appendix

Pathogenesis

Most NENs of the appendix are detected during surgery due to acute inflammation of the organ. Table III presents characteristics of the subtypes of NENs of the appendix.

The location of well-differentiated NENs is associated with the anatomical part of the organ. These tumours are mostly found in the end part of the appendix (75%), less frequently in the middle part (15%), and less frequently still in the proximal margin (10%). Macroscopically, they form hard, whitish-yellow, not encapsulated nodules, but their growth margin is usually expanding. Mixed

Table I. *TNM UICC/AJCC and ENETS classification systems [60]*
Tabela I. *Klasyfikacja TNM UICC/AJCC i ENETS [60]*

Feature T — primary tumour x	Comment
TX	The primary tumour cannot be assessed.
T0	No evidence of primary tumour
T1	Tumour invades lamina propria or submucosa and ≤ 1 cm
T2	Tumour invades muscularis propria and/or > 1 cm
T3	Tumour penetrates muscularis propria and invades subserosal tissue
T4	Tumour invades serosa or adjacent structures
N — regional lymph nodes	Comment
NX	Lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M — distant metastasis xx	Comment
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

x — If more than one tumour is present, we add 'm' to the letter T, regardless of the size; xx — If there is evidence of distant metastasis, the anatomical site should be specified in the brackets as follows: PUL for pulmonary; HEP for hepatic; and OSS for osseous.

Table II. *Small intestinal GEP NENs staging*
Tabela II. *Stopień klinicznego zaawansowania (staging) GEP NEN jelita cienkiego*

Stage	T feature	N feature	M feature
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T4	N0	M0
IIIB	Tumour of any diameter	N1	M0
IV	Tumour of any diameter	any	M1

adenoneuroendocrine carcinomas (MANECs) tumours, including goblet cell carcinoid, are white, sometimes mucous, of 1 to 5 cm in diameter (mean diameter 2 cm), and show an infiltrative growth pattern. These neoplasms are malignant; they are classified and treated like classical adenocarcinomas of the appendix.

Diagnostic algorithm

Unlike NENs of the jejunum and ileum, for which a similar consensus was developed regarding the assessment of the T-staging, two classifications are recommended for NENs of the appendix: one by the European Neuroendocrine Tumours Society (ENETS) and the other by the American AJCC/UICC associations. It is recommended to use both classifications. First, because presently there is no evidence in favour of the usefulness of either of them. Second, in cases raising doubts as to the scope of therapeutic management on the basis of one classification, the use of the other one could resolve such doubts.

Macroscopic assessment of NENs of the appendix

A relatively low incidence of NENs of the appendix should always be a reason for very careful macroscopic examination and careful sample collection, following the standard. The samples should be collected from the end of the appendix, its middle part and base (the proximal colonic margin), and the size of the tumour should be stated.

The macroscopic description should include the following:

The length of the appendix obtained for examination, with the description of the tumour location relative to the resection margin.

Table III. *Characteristics of the morphological subtypes of NENs of the appendix*
Tabela III. *Charakterystyka podtypów morfologicznych NEN wyrostka robaczkowego*

Type	Subtype and characteristics
Neuroendocrine neoplasms	Enterochromaffin cell (EC cell NEN)
NEN	Most cases of NENs of the appendix
	They form characteristic solid nests, islets surrounded by a circumferential palisade of cells
	The cells are monomorphic, without any features of polymorphism, without mitotic activity, and with Ki67 index below 2%; they are high-grade G1
	They invade in a dispersed manner the muscularis propria of the appendix wall and nervous trunks; they are angioinvasive
	In 10–40% of cases, they invade the subserosa fat tissue
	Regardless of their aggressive growth, and unlike NENs of the caecum, they rarely cause lymph node metastases or distant metastases
	It produces serotonin, substance P, S100+
	They show positive reactions with chromogranin A, synaptophysin, keratin 8 and 19, CD56, cdx2 and usually negative reactions with keratin 7 and 20, CEA and TTF1
	L cell NENs
	Tumours occur rarely
	They produce glucagon-like peptides, PP/PYYY
	They create a characteristic growth type in the form of trabecular structures
	Mostly 2–3 mm in diameter
	Tubular carcinoid
	Occurs in young patients (around 29 years of age)
	This NEN subtype is sometimes misdiagnosed as adenocarcinoma. It creates small tubes with mucus, short trabecular structures, but no solid nests of neoplastic cells are evident
	It develops at the crypt base
	It produces glucagon, serotonin, s100 minus
Mixed adenoneuroendocrine carcinoma (MANEC)	Goblet cell carcinoid
	It usually affects older patients (mean age 52 years)
	Invasion of the submucosa is predominant
	Positive reaction to mucus is observed
	It produces serotonin, somatostatin and carcinoembryonic antigen (CEA)
	It is reported like adenocarcinoma of the appendix
Neuroendocrine carcinoma (NEC)	Small-cell NEC
	It occurs very rarely
	It is usually a component of the neoplasm beside adenocarcinoma

Tumour assessment: the size in three dimensions, and cross-section appearance.
Condition of the serosa and mesoappendix at the tumour site — it is necessary to collect numerous samples.

Microscopic assessment of NENs of the appendix:
1. Histological type of NEN according to the 2010 WHO classification [57].
2. The histological grade (G) according to ENETS [13, 57–59].
3. Pathomorphological pTNM staging according to ENETS [58, 59] and AJCC/UICC [60].
4. Assessment of immunohistochemical expression of neuroendocrine markers: chromogranin A and synaptophysin, as well as Ki67/MIB1 proliferative activity is obligatory. Immunohistochemical assessment of NSE, CD56, CDX2 markers and serotonin is recommended conditionally, in the case of metastatic differentiation, especially if the original site of the neoplasm is unknown. A positive reaction with cdx-2 and/or serotonin indicates an intestinal, particularly ileocaecal, origin of the neoplasm.

Regarding 1 and 2: Histological types of NENs according to the World Health Organisation (WHO) and the criteria for tumour staging are presented above for NENs of the small intestine.

Regarding 3: The ENETS and AJCC/UICC histopathological grading of NENs, regarding the T-feature

Table IV. *pTNM of NENs of the appendix according to the ENETS and AJCC/UICC classifications*
Tabela IV. *pTNM NEN wyrostka robaczkowego według klasyfikacji ENETS i AJCC/UICC*

T feature	pTNM according to ENETS	pTNM according to AJCC/UICC
T1	≤ 1 cm invading submucosa and muscularis propria	1A — tumour ≤ 1 cm in the biggest dimension
		1B — tumour > 1 cm and ≤ 2 cm
T2	Tumour ≤ 2 cm and/or minimally (up to 3 mm) invading mesoappendix	Tumour > 2 cm and ≤ 4 cm or tumour invading the caecum
T3	Tumour > 2 cm and/or invading subserosa/mesoappendix to a depth greater than 3 mm	Tumour > 4 cm or invading the ileum
T4	Tumour invades serosa or adjacent organs	Tumour invades the peritoneum or other organs or tissues, e.g. abdominal wall or skeletal muscles

Table V. *Staging of NENs of the appendix according to ENETS [58, 59]*
Tabela V. *Stopień klinicznego zaawansowania (staging) NEN wyrostka robaczkowego wg. ENETS [58, 59]*

Stage	T feature	N feature	M feature
I	T1	N0	M0
IIA	T2	N0	M0
IIB	T3	N0	M0
IIIA	T4	N0	M0
IIIB	Tumour of any diameter	N1	M0
IV	Tumour of any diameter	any N	M1

of NENs of the appendix are presented in Table IV, and the clinical staging is demonstrated in Table V.

Prognostic factors for NENs of the appendix

Acording to European and American guidelines, tumour size and infiltration of the mesoappendix are important risk factors of NENs of the appendix; they are the criteria for division into pTNM classification stages. According to a report by the College of American Pathologists, cases in which the diameter of the tumour is above 1 cm and below 2 cm and infiltration of the mesoappendix is present should be treated as ones with uncertain prognosis. Potentially benign tumours are smaller than 1 cm and do not invade the mesoappendix. It is worth emphasising that according to the pTNM 2010 classification, neuroendocrine carcinomas (NECs) of the appendix and MANEC mixed neoplasms composed of classical and neuroendocrine carcinoma components, as well as goblet-cell carcinoids, are diagnosed following the criteria for classical carcinomas, and not those for NENs.

Apart from the above features, the histopathological report should include the assessment of margins: proximal, distal, mesoappendiceal and radial, as well as the angioinvasion of blood vessels. It should be noted that it is necessary to examine the colonic proximal margin, near the base of the appendix. Invasion of the caecum/ /colon determines the treatment method. During the assessment of the slides, particular attention should also be paid to small periserosal vessels, which could be ignored, especially if the samples from the periphery of the tumour were inadequately collected.

Minimal consensus statement on pathomorphological examination:

— *Minimal histopathological report for NENs of the small intestine and the appendix should include:*
  - *histological type of the neoplasm according to WHO classification, considering the division into well-differentiated neuroendocrine neoplasms (NENs) and neuroendocrine carcinomas (NECs) or mixed neoplasms (MANECs);*
  - *histological grading (G) referring to well-differentiated neoplasms (NEN G1, NEN G2);*
  - *pTNM histopathological staging according to ENETS and AJCC/UICC classifications (it is important to provide affiliation of the classification in each case);*
  - *assessment of surgical margins.*
— *The histopathological diagnosis of NEN must be confirmed by immunohistochemical tests assessing expression of*

** evidence level according to CEBM [77]*

*the neuroendocrine markers: synaptophysine and chromogranin A, as well as Ki67 proliferative activity using the MIB1 antigen (*evidence level 3).*

4. Treatment

4.1. Surgical treatment

NENs of the midgut are usually located in the distal part of the small intestine or in the appendix. They frequently present in multi-focal form. The preferred treatment of intestinal NENs is partial or multiple resection (a radical treatment) or palliative, cytoreductive surgery reducing the tumour mass by approximately 90%.

The Polish recommendations concerning the treatment of NENs of the appendix are as follows:

for tumours of 1 cm and less in diameter, located in the distal part of the appendix, without negative prognostic factors, simple appendectomy should be applied [61–63];

indications for right-sided hemicolectomy are the following tumour features:

— diameter of more than 1 cm,
— tumour location at the base of the appendix,
— tumour of any size invading the mesoappendix,
— tumour present in the resection margin,
— mixed exo- and endocrine tumour,
— G2 feature (confirmed by two pathomorphologists),
— goblet cell carcinoid,
— inability to assess the completeness of tumour resection, or doubts as to the completeness of the neoplasm resection.

In NECs the management is the same as in carcinomas. In the case of NENs of the appendix with hepatic metastasis, the recommended management is right-sided hemicolectomy including removal of the metastasis (anatomical and non-anatomical resections). In the case of multiple metastases, a palliative surgery removing the metastases should be considered (resection, thermoablation, chemoembolisation) [64, 65]. In selected patients, liver transplantation may be considered; the decision should follow a careful radioisotope diagnostics, excluding the presence of other, remote neoplastic foci [4].

Minimal consensus statement on surgical treatment:

*Surgical treatment of the midgut tumours involves a complete removal of the tumour within the healthy tissue (*evidence level 3).*

4.2. Pharmacological treatment

Pharmacotherapy of small intestine NENs consists of biotherapy and chemotherapy. The leading biotherapy method is treatment with SSA (lanreotide and octreotide), which are indicated for the symptomatic therapy of hormonally active NENs of the small intestine. SSA are the preferred treatment option for carcinoid crisis [18, 25]. There are ongoing clinical studies on the use of new SSA (pasireotide) in cases of resistance to the standard treatment of carcinoid syndrome [66].

Interferon alpha may be administered for the same indications as SSA, except for carcinoid crisis. The effectiveness of the treatment is similar to that of SSA, and the response to treatment is slightly delayed. Combined therapy with interferon and SSA analogue is not recommended [2, 4, 67]. There is no previous experience of the use of INF-α for GEP NENs management in Poland. Preliminary data suggests the efficacy of combined everolimus plus octreotide LAR regimen in the treatment of advanced neuroendocrine neoplasms with the symptoms of carcinoid syndrome (RADIANT-2) [68]. Everolimus therapy can be considered in patients with generalised NENs of the small intestine in progression after unsuccessful treatment with SSA, and failure or inability to use other treatment options (including PRRT — *see below*).

Due to limited effectiveness, chemotherapy is not recommended as a treatment in patients with well-differentiated, metastatic neuroendocrine neoplasms of the small intestine [2, 4, 17, 69].

Heart failure resulting from expansion of the disease to the cardiac cavities is associated with shortened life expectancy in patients, and it requires proper cardiological and/or cardiosurgical treatment [21, 31].

4.2.1 Treatment with SSA in patients with NENs of the small intestine

Symptomatic treatment in carcinoid syndrome

— In long-term therapy, we use octreotide LAR (10–30 mg i.m. every four weeks, but the lowest dose is rarely used), lanreotide Autogel (60–120 mg s.c. every 4–8 weeks, but the lowest dose is rarely used).
— If carcinoid syndrome symptoms recur before the next SSA analogue injection is due, the interval between injections may be reduced to three weeks.
— During the treatment, a significant reduction in the frequency of carcinoid syndrome symptoms (diarrhoea in 60–70% of patients, flushing in 70–80% of patients) and lower levels of biochemical markers (5-HIAA in 40–60% of patients) are observed.
— Long-term treatment with SSA significantly improves the quality of life in patients with carcinoid syndrome.

** evidence level according to CEBM [77]*

Carcinoid crisis treatment

— There are no clear EBM recommendations for the management of carcinoid crisis.
— The soonest possible introduction of somatostatin analogue therapy is of the greatest importance; a short-acting SSA in high doses is usually administered intravenously (octreotide: 25–500 μg/h i.v.; on average 100–200 μg/h i.v.) [70].
— In carcinoid crisis (particularly in NENs of the foregut), the administration of glucocorticoids and antihistamines can be considered.
— It is necessary to introduce intensive symptomatic treatment of dehydration, acute renal failure, hypercalcaemia, arterial hypertension or hypotonia, cardiac failure and infection [27].

Preparation of patients with NENs of the small intestine and the appendix for surgery

— There are no clear recommendations for preparation of patients with NENs of the small intestine and the appendix for surgery [71].
— In patients with carcinoid syndrome, pre-operative administration of short-acting SSA should be considered, regardless of the long-acting SSA therapy (e.g. octreotide 200–300 μg s.c. before the surgery and/or continuous infusion of 50–100 μg/h intraoperatively and/or 24–48 h after the surgery).
— In patients with hormonally non-active NENs, it is recommended that a short-acting SSA should be available during the operation, and administered in the case of an unstable haemodynamic condition.

Stabilisation of neoplastic disease in patients with well-differentiated NENs of the small intestine in the generalisation period (see "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumors)" [*pp. 418–443*])

— Based on the PROMID study, octreotide LAR (30 mg i.m. every four weeks) was registered for the treatment of patients with advanced NENs originating from the midgut or of unknown primary sites.
— Phase III clinical trials (CLARINET) indicate that lanreotide Autogel (120 mg every four weeks) has antiproliferative effects on midgut NENs.

Other comments on treatment with SSA:

— It is recommended to discontinue SSA before the planned receptor examinations SPECT or PET-CT: at least four weeks in the case of long-acting preparations, and 24–48 hours for short-acting ones.
— Treatment with SSA should be terminated before the planned administration of PRRT; a six-week interval is recommended for long-acting formulations, and a 24-hour interval for short-acting ones [3].

Symptomatic treatment:

In patients with secretory diarrhoea due to NENs of the small intestine, loperamide, ondasetron and cholestyramine are used to bind bile acids, as well as pancreatic enzymes and B vitamins, in cases of deficiency [16].

4.3. Isotope therapy

Chemotherapy is not effective in advanced, inoperable NENs of the small intestine; therefore, in each case radioisotope therapy should be considered. Qualification for the treatment is conducted according to the rules described in the general section. A partial remission of the disease can be achieved in approximately 18–22% of the patients with midgut neoplasms [72, 73]. In patients with small intestine NENs and symptomatic carcinoid syndrome, there is a risk for aggravation of carcinoid syndrome symptoms or even carcinoid crisis. In these cases, a proper preparation of the patient is essential, including intensive paraenteric hydration and administration of short-acting somatostatin analogues [74]. In patients with negative receptor scintigraphy and evidence of mIBG accumulation in the tumour or metastases, therapy with 131I-mIBG can be considered [75] *(*evidence level 3)*.

Minimal consensus statement on the treatment of NENs of the small intestine and the appendix:

— *the preferred treatment of intestinal NENs is partial or multiple resection and removal of potential metastases (radical treatment) or palliative, cytoreductive surgery (*evidence level 3);*
— *SSA are the preferred treatment in the case of hormonally active NENs of the small intestine (carcinoid syndrome and carcinoid crisis), and in patients with hormonally non-active NENs they can be used as antiproliferative therapy (*evidence level 1);*
— *for advanced, inoperable NENs of the small intestine, radioisotope therapy should be considered (*evidence level 2);*
— *everolimus therapy can be considered in patients with generalised NENs of the small intestine in progression after unsuccessful treatment with SSA and failure or inability to use other treatment options (*evidence level 4).*

Proposed treatment sequence:

— **surgical treatment,**
— **SSA in hormonally active and non-active NENs,**
— **radioisotope therapy,**

** evidence level according to CEBM [77]*

— **targeted therapies (everolimus),**
— **symptomatic treatment.**

4.4. Monitoring of the treatment

Determination of CgA and 5-HIAA may be useful for the assessment of treatment efficacy in patients with small intestine NENs. In patients with carcinoid syndrome treated with SSA, lower excretion of 5-HIAA and decreased levels of chromogranin A are associated with reduced intensity and frequency of clinical symptoms (flushing, diarrhoea).

However, it is believed that 5-HIAA excretion does not reflect the progression or the response to treatment as precisely as the monitoring of CgA concentration. A high association (80%) between changes in the tumour size and concentration of chromogranin A has been observed. An even higher association (88%) was found in a group of patients with non-secreting tumours, in whom other markers could not be used [29]. However, in certain patients a very good clinical response to the treatment of carcinoid syndrome with SSA has been observed, without lowered CgA levels [76].

The clinical course, imaging of the size of lesions, and monitoring of chromogranin A levels can be useful to assess the applied treatment of small intestinal NENs. The frequency of follow-up examinations depends on NEN differentiation and staging, as well as on the introduced treatment (see "Diagnostic and therapeutic guidelines for gastro-entero-pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumors)" [*pp. 418–443*]). The anamnesis and physical examination should be performed every three months, and imaging examinations (three-phase CT scanning of the abdominal cavity) and biochemical indicators (CgA and 5-HIAA) should be controlled.

After radical surgery with a curative intent:
— in patients with NEN G1 and G2 every 6-12 months,
— in patients with NEC every three months.
— Not curatively treated:
— in patients with NEN G1 every six months,
— in patients with NEN G2 every three months,
— in patients with NEC every three months.

Minimal examination includes: CgA, 5-HIAA and triphasic CT.

In patients with carcinoid heart disease, echocardiographic examination and NT-proBNP should be repeated every 6–12 months. If the disease progresses, follow-up imaging and biochemical tests need to be conducted more frequently, every three months.

Minimal consensus statement on follow-up:

— *follow-up visits should be planned individually for each patient, considering the clinical picture, grading and staging of the disease, and its treatment. In general, patients should be followed every 6–12 months for NEN G1, every 3–12 months for NEN G2 and every three months for NEC;*
— *minimal examination includes: CgA, 5-HIAA and triphasic CT;*
— *in patients with carcinoid heart disease, echocardiographic examination and NT-proBNP every 6–12 months.*

Reference

1. Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev 2004; 25: 458–511.
2. Plöckinger U, Rindi G, Arnold R et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. Neuroendocrinology 2004; 80: 394–424.
3. Bolanowski M, Jarząb B, Handkiewicz-Junak D et al. Neuroendocrine tumors of the small intestine and the appendix — management guidelines (recommended by The Polish Network of Neuroendocrine Tumors). Endokrynol Pol 2008; 59: 87–96.
4. Pape U-F, Perren A, Niederle B et al. ENETS consensus guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology 2012; 95: 135–156.
5. Ellis L, Shale MJ, Coeman MP. Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. Am J Gastroenterol 2010; 105: 2563–2569.
6. Yao JC, Hassan M, Phan A et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008; 26: 3063–3072.
7. Ito T, Sasano H, Tanaka M et al. Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan. J Gastroenterol 2010; 45: 234–243.
8. Hauso O, Gustafsson BI, Kidd M et al. Neuroendocrine tumor epidemiology: contrasting Norway and North America. Cancer 2008; 113: 2655–2664.
9. Landerholm K, Falkmer S, Jarhult J. Epidemiology of small bowel carcinoids in a defined population. World J Surg 2010; 34: 1500–1505.
10. Niederle MB, Hackl M, Kaserer K et al. 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.
11. Berge T, Linell F. Carcinoid tumours. Frequency in a defined population during a 12-year period. Acta Pathol Microbiol Scand 1976; 84: 322–330.
12. Oberndorfer S. Karzinoide Tumoren des Dunndarms. Frankf Z Pathol 1907; 1: 426–429.
13. Klimstra DS, Arnold R, Capella C et al. In: Bosman FT, Carneiro F, Hruban RH, Theise ND (eds). WHO Classification of the tumors of the Digestive System. Lyon, IARC 2010.
14. Jann H, Roll S, Couvelard A et al. Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. Cancer 2011; 117: 3332–3341.
15. Bordeaux JP, Klimstra DS, Hassan MM et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and caecum. Pancreas 2010; 39: 753–766.
16. Ramage JK, Ahmed A, Ardill J et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012; 61: 6–32.
17. Bolanowski M., Kos-Kudła B. Diagnostic and therapeutic opportunities in neuroendocrine tumors of the gastroenteropancreatic system. Post Hig Med Dosw (online) 2005; 59: 48–55.
18. Vinik AI, Thompson N, Eckhauser F et al. Clinical features of carcinoid syndrome and the use somatostatin analogue in its management. Acta Oncol 1989; 28: 389–402.
19. Walsh JS, Newell-Price JD, Debono M et al. Circulating serotonin and bone density, structure and turnover in carcinoid syndrome. J Clin Endocrinol Metab 2013; 98: 2902–2907.
20. Moller JE, Pellikka PA, Bernheim AM et al. Prognosis of carcinoid heart disease: analysis of 200 cases over two decades. Circulation 2005; 112: 3320–3327.
21. Bernheim AM, Connolly HM, Hobday TJ et al. Carcinoid heart disease. Prog Cardiovasc Dis 2007; 49: 439–451.
22. Plockinger U, Gustafsson B, Ivan D et al. ENETS Consensus Guidelines for the standanrds of care in neuroendocrine tumors: echocardiography. Neuroendocrinology 2009; 90: 190–193.
23. Komoda S, Komoda T, Pavel ME et al. Cardiac surgery for carcinoid heart disease in 12 cases. Gen Thorac Cardiovasc Surg 2011; 59: 780–785.

24. Palaniswamy C, Frishman WH, Aronow WS. Carcinoid heart disease. Cardiol Rev 2012; 20:167–176.
25. Garland J, Buscombe JR, Bouvier C et al. Sandostatin LAR (long-acting octreotide acetate) for malignant carcinoid syndrome: a 3-year experience. Aliment Pharmacol Ther 2003; 17: 437–444.
26. Junik R, Kamińska A, Kamiński M et al. Somatostatin analogs in the treatment of carcinoid syndrome: a case report and review of literature. Pol Arch Med Wewn 2003; 110: 997–1001.
27. Bednarczuk T, Dębski M, Chojnowski K et al. Carcinoid crisis. Med Prakt 2009; 2: 164–169.
28. Bolanowski M, Kos-Kudła B, Rzeszutko M et al. Five year remission of GHRH secreting bronchial neuroendocrine tumor with symptoms of acromegaly. Utility of chromogranin A in the monitoring of the disease. Endokrynol Pol 2006; 57: 32–36.
29. Kanakis G, Kaltsas G. Biochemical markers for gastroenteropancreatic neuroendocrine tumours (GEP-NETs). Best Pract Res Clin Gastroenterol 2012; 26: 791–802.
30. Lim TK, Hayat SA, Gaze D et al. Independent value of echocardiography and N-terminal pro-natriuretic peptide for the prediction of major outcomes in patients with suspected heart failure. Am J Cardiol 2007; 100: 870–875.
31. Dobson R, Burgess MI, Banks M et al. The association of a panel of biomarkers with the presence and severity of carcinoid heart disease: a cross-sectional study. PLoS One 2013; 8: e73679.
32. Masselli G, Polettini E, Casciani E et al. Small-bowel neoplasms: prospective evaluation of MR enteroclysis. Radiology 2009; 251: 743–750.
33. Van Weyenberg SJ, Meijerink MR, Jacobs MA et al. MR enteroclysis in the diagnosis of small-bowel neoplasms. Radiology 2010; 254: 765–773.
34. Masselli G, Gualdi G. MR imaging of the small bowel. Radiology 2012; 264: 333–348.
35. Van Tuyl SAC, van Noorden JT, Timmer J et al. Detection of small-bowel neuroendocrine tumors by video-capsule endoscopy. Gastrointest Endosc 2006; 64: 66–72.
36. Bailey AA, Debinski HS, Appleyard MN et al. Diagnosis and outcome of small bowel tumors found by capsule endoscopy: a three-center Australian experience. Am J Gastroenterol 2006; 101: 2237–2243.
37. Belluti M, Fry LC, Schmitt J et al. Detection of neuroendocrine tumors of the small bowel by double balloon enteroscopy. Dig Dis Sci 2009; 54: 1050–1058.
38. Ricke J, Klose KJ, Mignon M et al. Standarisation of imaging in neuroendocrine tumors: results of a European delphi process. Eur J Radiol 2001; 37: 8–17.
39. Bader TR, Semelka RC, Chiu VC et al. MRI of carcinoid tumors: spectrum of appearances in gastrointestinal tract and liver. J Magn Reson Imaging 2001; 14: 261–269.
40. Negaard A, Paulsen V, Sandvik L et al. A prospective randomized comparison between two MRI studies of the small bowel in Crohn's disease, the oral contrast method and MR enteroclysis. Eur Radiol 2007; 17: 2294–2301.
41. Soyer P, Aout M, Hoeffel C et al. Helical CT-enteroclysis in the detection of small-bowel tumours: a meta-analysis. Eur Radiol 2013; 23: 388–399.
42. Sinha R. Recent advances in intestinal imaging. Indian J Radiol Imaging 2011; 21: 170–175.
43. Wang SC, Parekh JR, Zuraek MB et al. Identification of unknown primary tumors in patients with neuroendocrine liver metastases. Arch Surg 2010; 145: 276–280.
44. Leszczyński S, Pilch-Kowalczyk J (eds). Imaging diagnostics. Digestive system. PZWL 2012.
45. Hakim FA, Alexander JA, Huprich JE et al. CT-enterography may identify small bowel tumors not detected by capsule endoscopy: eight years experience at Mayo Clinic Rochester. Dig Dis Sci 2011; 56: 2914–2919.
46. Johanssen S, Boivin M, Lochs H et al. The yield of wireless capsule endoscopy in the detection of neuroendocrine tumors in comparison with CT enteroclysis. Gastrointest Endosc 2006; 63: 660–665.
47. Rondonotti E, Pennazio M, Toth E et al. Small bowel neoplasms in patients undergoing video capsule endoscopy: a multicenter European study. Endoscopy 2008; 40: 488–495.
48. Yamamoto H, Kita H, Sunada K et al. Clinical outcomes of double-balloon endoscopy for the diagnosis and treatment of small-intestinal disease. Clin Gastroenterol Hepatol 2004; 2: 1010–1016.
49. Pasha SF Leighton JA, Das A et al. Double balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. Clin Gastroenterol Hepatol 2008; 6: 671–676.
50. Chen J, Zhang L, Zhang W et al. A case of neuroendocrine malignant-tumor with capsule retention diagnosed by double-balloon enteroscopy. Case Rep Gastroenterol 2010; 4: 52–56.
51. Strosberg JR, Shibata D, Kvols LK. Intermittent bowel obstruction due to a retained wireless capsule endoscope in a patient with a small bowel carcinoid tumour. Can J Gastroenterol 2007; 21: 113–115.
52. Krenning EP, Kwekkeboom DJ, Oei HY et al. Somatostatin-receptor scintigraphy in gastroenteropancreatic tumors. An overview of European results. Ann NY Acad Sci 1994; 15: 416–424.
53. Krenning EP, Kwekkeboom DJ, Bakker WH et al. Somatostatin receptor scintigraphy with [111 In-DTPA-D-Phe 1]- and [123 I-Tyr 3]-octreotide: the Rotterdam experience with more than 1,000 patients. Eur J Nucl Med 1993; 20: 716–731.
54. Binderup T, Knigge U, Loft A et al. Functional imaging of neuroendocrine tumors: a head-to-head comparison of somatostatin receptor scintigraphy, 123I-MIBG scintigraphy, and 18F-FDG PET. J Nucl Med 2010; 51: 704–712.
55. Ambrosini V, Campana D, Bodei L et al. 68Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors. J Nucl Med 2010; 51: 669–673.
56. Oberg K. Molecular imaging radiotherapy: Theranostics for personalized patient management of neuroendocrine tumors (NETs). Theranostics 2012; 2: 448–458.
57. Kilmstra DS, Modlin IR, Coppola D et al. The pathologic classification of neuroendocrine tumors. A review of nomenclature, grading, and staging system. Pancreas 2010; 39: 707–712.
58. Rindi G, Klöppel G, Cuvelard A et al. TNM staging of midgut et hindgut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch 2007; 451: 757–762.
59. Foltyn W, Zajęcki W, Marek B et al. The value of the Ki-67 proliferation marker as a prognostic factor in gastroenteropancreatic neuroendocrine tumours. Endokrynol Pol 2012; 63: 362–366.
60. Sobin LH, Gospodarowicz MK, Wittekind C (eds). TNM classification of malignant tumors. Chichester, Wiley &Blackwell 2009.
61. Groth SS, Virnig BA, Al-Refaie WB et al. Appendiceal carcinoid tumors: predictors of lymph node metastasis and the impact of right hemicolectomy on survival. J Surg Oncol 2011; 103: 39–45.
62. Alexandraki KI, Griniatsos J, Bramis KI et al. Clinical value of right hemicolectomy for appendiceal carcinoids using pathologic criteria. J Endocrinol Invest 2011; 34: 255–259.
63. Jiang Y, Long H, Wang W et al. Clinicopathological features and immunoexpression profiles of goblet cell carcinoid and typical carcinoid of the appendix. Pathol Oncol Res 2011; 17: 127–132.
64. Chetty R, Klimstra DS, Henson DE et al. Combined classical carcinoid and goblet cell carcinoid umor: a new morphologic variant of carcinoid tumor of the appendix. Am J Surg Pathol 2010; 34: 163–1167.
65. Kwekkeboom DJ, Krenning EP, Lebtahi R et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumours: peptide receptor radionuclide therapy with radiolabeled somatostatin analogs. Neuroendocrinology 2009; 90: 220–226.
66. Kvols LK, Oberg KE, O'Dorisio TM et al. Pasireotide (SOM230) shows efficacy and tolerability in the treatment of patients with advanced neuroendocrine tumors refractory or resistant to octreotide LAR: results from a phase II study. Endocr Relat Cancer 2012; 19: 657–666.
67. Őberg K, Kvols L, Caplin M et al. Consensus report on the use of somatostatin analogs for the management of neuroendocrine tumors of the gastroenteropancreatic system. Ann Oncol 2004; 15: 966–973.
68. Pavel ME, Hainsworth JD, Baudin E et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet 2011; 378: 2005–2012.
69. Kaltsas G, Mukherjee JJ, Plowman PN et al. The role of chemotherapy in the nonsurgical management of malignant neuroendocrine tumours. Clin Endocrinol 2001; 55: 575–587.
70. Seymour N, Sawh SC. Mega-dose intravenous octreotide for the treatment of carcinoid crisis: a systematic review. Can J Anaesth 2013; 60: 492–499.
71. Massimino K, Harrskog O, Pommier S et al. Octreotide LAR and bolus octreotide are insufficient for preventing intraoperative complications in carcinoid patients. J Surg Oncol 2013; 107: 842–846.
72. Cwikla JB, Sankowski A, Seklecka N et al. Efficacy of radionuclide treatment DOTATATE Y-90 in patients with progressive metastatic gastroenteropancreatic neuroendocrine carcinomas (GEP-NETs): a phase II study. Ann Oncol 2010; 21: 787–794.
73. Kwekkeboom DJ, de Herder WW, Kam BL et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008; 26: 2124–2130.
74. de Kaizer B, van Aken MO, Feelders RA et al. Hormonal crises following receptor radionuclide therapy with radiolabeled somatostatin analogue [177Lu-DOTA0,Tyr3]octreotate. Eur J Nucl Med Mol Imaging 2008; 35: 749–755.
75. Buscombe JR, Cwikla JB, Caplin ME et al. Long-term efficacy of low activity meta-[131I]iodobenzylguanidine therapy in patients with disseminated neuroendocrine tumours depends on initial response. Nucl Med Commun 2005; 26: 969–976.
76. Mełeń-Mucha G, Niedziela A, Mucha S et al. Elevated peripheral blood plasma concentrations of Tie-2 and angiopoietin 2 in patients with neuroendocrine tumors. Int J Mol Sci 2012; 13: 1444–1460.
77. OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.

cebm.net/index.aspx?o=5653 * OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson.

List of Participants of the Consensus Conference on the 2013 Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms:

Elżbieta Andrysiak-Mamos (Department of Endocrinology, Metabolic Diseases and Internal Diseases, Pomeranian Medical University, Szczecin, Poland), **Jolanta Blicharz-Dorniak** (Division of Endocrinology, Medical University of Silesia, Katowice, Poland), **Andrzej Cichocki** (Department of Oncological Surgery, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw Branch, Poland), **Jarosław B. Ćwikła** (Department of Radiology, Faculty of Medical Science, University of Varmia and Masuria, Olsztyn, Poland), **Andrzej Deptała** (Department of Oncology and Hematology, Central Clinical Hospital of the Ministry of Interior in Warsaw, Warsaw, Poland; Department of Cancer Prevention Medical University of Warsaw,Warsaw, Poland), **Wanda Foltyn** (Division of Endocrinology, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice), **Marek Hartleb** (Department of Gastroenterology and Hepatology, Medical University of Silesia, Katowice, Poland), **Alicja Hubalewska-Dydejczyk** (Chair and Department of Endocrinology, Jagiellonian University Collegium Medicum, Krakow, Poland), **Michał Jarząb** (Department of Radiotherapy and Chemotherapy, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland), **Dariusz Kajdaniuk** (Division ofPathophysiology, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland), **Grzegorz Kamiński** (Department of Endocrinology and Radioisotopic Therapy, Military Institute of Medicine, Warsaw, Poland), **Aldona Kowalska** (Department of Endocrinology, Holycross Cancer Centre, Kielce, Poland), **Robert Król** (Department of General, Vascular and Transplant Surgery, Medical University of Silesia, Katowice, Poland), **Leszek Królicki** (Nuclear Medicine Department, Medical University of Warsaw, Warsaw, Poland), **Jolanta Kunikowska** (Nuclear Medicine Department, Medical University of Warsaw, Warsaw, Poland), **Katarzyna Kuśnierz** (Department of Gastrointestinal Surgery, Medical University of Silesia, Katowice, Poland), **Paweł Lampe** (Department of Gastrointestinal Surgery, Medical University of Silesia, Katowice, Poland), **Dariusz Lange** (Department of Tumour Pathology, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland), **Anna Lewczuk** (Department of Endocrinology and Internal Medicine, Medical University of Gdansk, Poland), **Magdalena Londzin-Olesik** (Division of Endocrinology, Medical University of Silesia, Katowice, Poland), **Przemysław Majewski** (Department of Clinical Pathomorphology, Poznan University of Medical Sciences, Poznan, Poland), **Bogdan Marek** (Division of Pathophysiology, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland), **Gabriela Mełeń-Mucha** (Department of Immunoendocrinology, Chair of Endocrinology, Medical University of Lodz, Lodz, Poland), **Anna Nasierowska-Guttmejer** (Department of Pathomorphology, Central Clinical Hospital of the Ministry of Internal Affairs in Warsaw, Warsaw; Jan Kochanowski University, Kielce, Poland), **Andrzej Nowak** (Department of Gastroenterology and Hepatology, Medical University of Silesia, Katowice, Poland), **Waldemar Patkowski** (Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland), **Joanna Pilch-Kowalczyk** (Department of Radiology, Medical University of Silesia, Katowice, Poland), **Violetta Rosiek** (Division of Endocrinology, Medical University of Silesia, Katowice, Poland), **Marek Ruchała** (Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland), **Sławomir Rudzki** (Department of General and Transplant Surgery and Nutritional Treatment, Medical University of Lublin, Lublin, Poland), **Philippe Ruszniewski** (Department of Gastroenterology, Hospital Beaujon, AP-HP, University Paris VII, Clichy, France), **Grażyna Rydzewska** (Clinical Department of Internal Medicine and Gastroenterology, Central Clinical Hospital Ministry of Interior, Warsaw, Poland), **Anna Sowa-Staszczak** (Nuclear Medicine Unit, The University Hospital , Krakow, Poland), **Teresa Starzyńska** (Department of Gastroenterology, Pomeranian Medical University, Szczecin, Poland), **Janusz Strzelczyk** (Division of Endocrinology, Department of Pathophysiology and Endocrinology, Medical University of Silesia, Katowice, Poland), **Piotr Zdunowski** (Department of Endocrinology, The Centre of Postgraduate Medical Education, Warsaw, Poland).