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Diagnostic and therapeutic guidelines for gastro-entero--pancreatic neuroendocrine neoplasms (recommended by the Polish Network of Neuroendocrine Tumours)

Zalecenia ogólne dotyczące postępowania w nowotworach neuroendokrynnych układu pokarmowego (rekomendowane przez Polską Sieć Guzów Neuroendokrynnych)

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Abstract

An increased interest in gastro-entero-pancreatic neuroendocrine neoplasms (GEP NENs) has recently been observed. These are rare neoplasms and their detection in recent years has improved. Over 50% of GEP NENs are carcinoids, and they are usually found incidentally during surgery in the small intestine and appendix and at diagnosis in distant metastases, mainly to the liver.

There is a need for co-operation between specialists in various disciplines of medicine in order to work out the diagnostic and therapeutic guidelines. In this publication, we present general recommendations of the Polish Network of Neuroendocrine Tumours for the management of patients with GEP NENs, developed at the Consensus Conference which took place in Kamień Śląski in April 2013. Members of the guidelines working groups were assigned sections of the 2008 guidance to update.

In the subsequent parts of this publication, we present the rules of diagnostic and therapeutic management of:
— neuroendocrine neoplasms of the stomach and duodenum (including gastrinoma);
— pancreatic neuroendocrine neoplasms;
— neuroendocrine neoplasms of the small intestine and the appendix;
— colorectal neuroendocrine neoplasms.

The proposed recommendations by Polish and foreign experts representing different fields of medicine (endocrinology, gastroenterology, surgery, oncology, nuclear medicine and pathology) will be helpful in the diagnosis and treatment of GEP NENs patients. **(Endokrynol Pol 2013; 64 (6): 418–443)**

Key words: *gastro-entero-pancreatic neuroendocrine neoplasm; diagnosis; therapy*

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Streszczenie
W ostatnim czasie obserwuje się większe zainteresowanie rzadkimi nowotworami neuroendokrynnymi żołądkowo-jelitowo-trzustkowymi (GEP NEN). Wykrywalność nowotworów neuroendokrynnych w ostatnich latach wzrosła. Ponad 50% GEP NEN stanowią rakowiaki, które najczęściej są znajdowane przypadkowo podczas zabiegu operacyjnego w jelicie cienkim i w wyrostku robaczkowym oraz w momencie rozpoznania przerzutów odległych, głównie do wątroby. Istnieje konieczność współdziałania specjalistów różnych dziedzin medycyny w celu opracowania właściwych zasad postępowania diagnostyczno-leczniczego w tej grupie chorych.
W niniejszej publikacji przedstawiono ogólne zalecenia Polskiej Sieci Guzów Neuroendokrynnych dotyczące postępowania u chorych z GEP NEN, opracowane podczas Konferencji, która odbyła się w Kamieniu Śląskim w kwietniu w 2013 roku. Członkowie grup roboczych zaktualizowali rekomendacje z 2008 roku.
W kolejnych częściach tego opracowania przedstawiono zasady postępowania w:
— nowotworach neuroendokrynnych żołądka i dwunastnicy (z uwzględnieniem *gastrinoma*);
— nowotworach neuroendokrynnych trzustki;
— nowotworach neuroendokrynnych jelita cienkiego i wyrostka robaczkowego;
— nowotworach neuroendokrynnych jelita grubego.
Zaproponowane rekomendacje przez ekspertów polskich i zagranicznych reprezentujących różne dziedziny medycyny (endokrynologię, gastroenterologię, chirurgię, onkologię, medycynę nuklearną i patomorfologię) powinny być pomocne w diagnostyce i leczeniu tych chorych. **(Endokrynol Pol 2013; 64 (6): 418–443)**

Słowa kluczowe: *nowotwory neuroendokrynne żołądkowo-jelitowo-trzustkowe; diagnostyka; leczenie*

1. Epidemiology

Gastro-entero-pancreatic neuroendocrine neoplasms (GEP NENs) arise from the diffuse endocrine system (DES) cells disseminated in the gastrointestinal tract and in the pancreas [1]. The detection rate for neuroendocrine neoplasms (NENs) has risen in recent years. Between 1973 and 2004, NEN incidence increased from 2.1 to 5.25 new cases/100,000 persons/year, with the most commonly described primary site being the small intestine (37.4%). According to epidemiological studies conducted in the USA (SEER, *the Surveillance Epidemiology End Results*) and Norway (NRC, *the Norwegian Registry of Cancer*), an increase in the incidence of gastric and rectal NENs has been observed, as well as a lower incidence of NENs of the appendix [1, 2]. According to the SEER data, these tumours are most frequently diagnosed in African-Americans, the incidence rate being 6.5/100,000/year [2], and the most common primary tumour site is in the rectum (27%). Among those of Caucasian race, the lung is the most common primary tumour site (30% of new cases of NENs) [3]. Presently, the mean general prevalence rate for these neoplasms is 35 cases in 100,000. A slight predominance of male patients (5.35/100,000/year) has been observed, compared to females (4.76/100,000/year) [2, 4]. No predisposing factors for NENs have been described, although increases in the diagnoses of NEN have been observed in patients with atrophic gastritis, and in Afro-Caribbean patients [5]. Approximately 70% of neuroendocrine neoplasms are GEP NENs, which account for ca. 2% of all gastrointestinal neoplasms [6, 7]. They constitute a rare, heterogeneous group of neoplasms [8, 9]. The molecular basis for the development of NENs is still unclear, but new reports indicate that identification of common genetic factors might be useful in creating a new classification system, and they could become new elements affecting tumour progression [9–11]. These neoplasms may demonstrate hormonal activity, and then they are referred to as functional tumours. Some of them do not produce hormones and/or biogenic amines in quantities sufficient to present clinical symptoms, so they are called non-functional tumours. Over 50% of GEP NENs are carcinoids, and they are most frequently found accidentally, during a surgical procedure, in the small intestine and in the appendix, as well as at the diagnosis of distant metastases, mostly to the liver [12].

The incidence rate of NENs, both functional and non-functional, derived from different parts of the gastrointestinal tract and the pancreas, is discussed in other sections of this document.

2. Diagnostics

2.1. Biochemical diagnostics

In biochemical diagnostics of NENs, the following should be considered:

A. Non-specific markers

Determination of serum chromogranin A (CgA) concentration is the most commonly used test [13–15]. CgA is a secretory acidic protein produced in the granules of diffuse endocrine system cells. Therefore, immunohistochemical assessment of CgA and synaptophysin expression in the histopathological material is essential for the diagnosis of NEN. In blood, CgA is a relatively stable protein. However, there are different methods of determination of CgA concentration: radioimmunological (RIA) or enzymatic (ELISA) methods using blood serum or plasma [16]. Unfortunately, there are no international CgA standards, and the differences between available tests are significant. To monitor the course of the disease, it is recommended to determine CgA concentration using the same method [11, 12].

Chromogranin A assay is useful in:

1. Diagnosing NEN. CgA values are often increased in most GEP NENs, particularly in advanced disease, but results within the reference range do not exclude the diagnosis of NEN. CgA concentration depends on a few factors (Fig. 1).

The sensitivity of the CgA concentration test varies in different neoplasms, ranging from 10% to 100%, and its specificity is 68–100%. The highest sensitivity has been observed in *gastrinoma, glucagonoma* and small intestinal NENs. Particularly high CgA concentrations are found in NENs of the small intestine, with hepatic metastases and carcinoid syndrome, where the CgA concentration may be increased by as much as a few dozen times. On the other hand, in benign *insulinoma,* CgA concentrations are often within the reference range. In neuroendocrine carcinomas (NEC), CgA concentrations are often lower than in well-differentiated tumours (G1, G2 NEN). A concentration exceeding the reference values is not always caused by NEN, and it is not tantamount to a diagnosis [17–20]. Therefore, while interpreting the CgA results, it is necessary to know the test that has been used and possible causes for false positives or false negatives (Table I) [11,12].

2. As a prognostic factor for survival and a marker for monitoring the course of the disease and GEP NEN treatment. CgA concentrations are independent prognostic factors for survival in patients with small intestinal and pancreatic NENs [21]. Using somatostatin analogues (SSA) considerably lowers CgA concentrations; in cases of progressing disease, increased CgA concentration during treatment with SSA may reflect a lack of control of tumour secretory function and/or its growth. An early decrease of CgA concentration in patients with pancreatic NEN during treatment with everolimus is also a favourable prognostic factor for progression-free survival [21].

Another non-specific NEN marker is neuron-specific enolase (NSE). Generally, NSE is characterised by lower sensitivity and specificity (30-50%) in diagnosing GEP NEN, compared to CgA [13]. Increased NSE concentration may be associated with poorly differentiated NEC. Therefore, simultaneous CgA and NSE determination is more sensitive and specific in the diagnosis of NEN. NSE is also a prognostic factor for survival and a marker for monitoring the treatment of pancreatic NENs [21].

Pancreatic polypeptide (PP) may be a useful marker of non-functional pancreatic NENs, especially those associated with MEN1 (sensitivity 50–80% in pancreatic NENs and > 30% in all NENs).

In the differential diagnostics of increased PP concentration, one should consider not only diarrhoea, laxatives, intestinal inflammation and chronic renal diseases, but also ingested meal, physical effort and advanced age [13]. The availability of the test in Poland is limited.

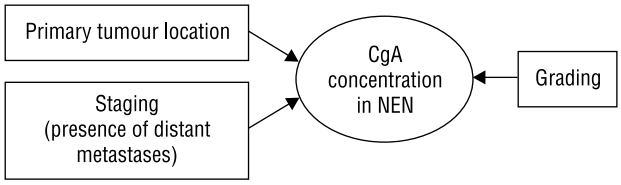

Figure 1. *Neoplastic factors affecting CgA concentration*

Rycina 1. *Czynniki nowotworowe wpływające na stężenie CgA*

Table I. ***Reasons for increased serum CgA concentration other than GEP NEN [11, 12]***

Tabela I. ***Inne niż GEP NEN przyczyny podwyższonego stężenia CgA w surowicy [11, 12]***

Reasons for increased serum CgA concentration other than GEP NEN:
receiving proton pump inhibitors and histamine H_2-receptor blockers (**if possible, they should be discontinued at least 7–14 days before the test**)
atrophic gastritis
renal failure
meal or physical effort 2-4 hours before the blood draw
other neoplasms: prostate cancer, small cell lung carcinoma, medullary thyroid cancer, pheochromocytoma, hepatic cancer, pancreatic adenocarcinoma
Other non-neoplastic causes of increased CgA concentration (usually with a lesser effect on CgA levels):
chronic inflammations, including rheumatoid arthritis (presence of IgM rheumatoid factor), COPD
gastrointestinal diseases, including inflammatory bowel disease, hepatitis, cirrhosis, and pancreatitis
cardio-vascular diseases, including cardiac failure, cardiac infarction
endocrine diseases, including hyperthyroidism or hyperparathyroidism, treatment with glucocorticoids
other, e.g. Parkinson's disease

Due to high availability, β-subunit of human chorionic gonadotropin (HCG) is often determined in patients with NENs, but the test value is limited and not clearly established, compared to CgA.

Chromogranin B (CgB) is also mentioned as a non-specific marker, as its concentration may be increased in *insulinoma*, rectal NENs and NENs of the ovaries. Pancreostatin is part of CgA, and studies have suggested that PPI does not affect pancreostatin concentration. The availability of these tests in Poland is also limited [13].

B. Specific markers

The choice of specific GEP NEN markers depends on the clinical manifestation and type of neoplasm suspected (Table II) [8, 18, 22, 23]. Direct measurement

Table II. *Selected biochemical markers in the diagnostics of GEP NENs [8, 18, 24, 25]*
Tabela II. *Wybrane markery biochemiczne w diagnostyce GEP NEN [8, 18, 24, 25]*

Primary NEN	Clinical picture	Biochemical markers
Stomach, type I, II	Atrophic gastritis	Gastrin
Duodenum, stomach type II	Zollinger-Ellison syndrome	Gastrin
Duodenum, pancreas	Somatostatinoma	SST (somatostatin)
Small intestine, ileum, proximal large intestine	Classical carcinoid syndrome	5HIAA
Pancreas	Insulinoma	glucose, insulin, peptide C
	Zollinger-Ellison syndrome	Gastrin
	Glucagonoma	Glucagon
	Verner-Morrison syndrome	VIP

of concentrations of specific peptides, biogenic amines and hormones produced by NEN cells is useful not only in diagnosing, but also in monitoring the treatment of, GEP NENs [18].

This article will discuss laboratory diagnostics in carcinoid syndrome. Details of biochemical diagnostics in other clinical syndromes are discussed in other sections of our recommendations.

The most frequently observed set of clinical symptoms associated with hormonal activity of NEN is carcinoid syndrome. The clinical picture is discussed in the section on NEN of the small intestine and the appendix. The classical form mainly depends on excessive serotonin secretion. The atypical form is observed in pulmonary carcinoid tumours and gastric NENs; it depends on excessive secretion of serotonin, 5-hydroxytryptophan (5-HT; serotonin precursor) and/or histamine.

Serotonin is produced by 70% of NENs, mostly arising in the small intestine, including the ileum, the proximal large intestine, the appendix and in 10–35% of gastric and pulmonary NENs. The screening test for carcinoid syndrome includes two assays of daily urinary excretion of a serotonin metabolite: 5-hydroxyindoleacetic acid (5-HIAA), provided a proper diet has been followed. It is also important to acidify the urine during the sample collection (Table III). The reference range is 2-8 mg/day (10–42 mmol/d). Possible false-positives and false-negatives are presented in Table III [13, 17, 18].

In unclear cases, serum serotonin concentration may be determined. During the measurement of blood serotonin concentration, it is important to remember frequent pre-laboratory errors due to the considerable serotonin storage in blood platelets. Determination of blood 5-HT or histamine is limited [13, 17, 18].

C. Ectopic hormone production and single-gene inherited multi-gland syndromes

It is also noteworthy that gastrointestinal NENs (mostly of the pancreas) may cause ectopic production of ACTH (causing ACTH-dependent Cushing's syndrome), GHRH (causing acromegaly), vasopressin (causing SIADH), and PTH-RP (causing hypercalcemia).

Diagnostics of these syndromes depends on the clinical symptoms [12].

In all patients with *foregut* NENs, particularly patients with NENs of the thymus, duodenum (gastrinoma) and pancreas, examinations for multiple endocrine neoplasia type 1 (MEN1) should be performed [20, 21]. Basic screening tests in MEN1 include concentrations of ionised or total calcium, parathyroid hormone (intact PTH), gastrin, prolactin and growth hormone (GH) or IGF-1. In patients with suspected MEN1, molecular tests should be considered to detect mutation in the *MEN1* menin-coding gene.

Moreover, pancreatic NEN may occur in von Hippel-Lindau syndrome, and very rare duodenal NENs, somatostatinomas, may occur in patients with type 1 neurofibromatosis [12, 20].

Minimal consensus statement on biochemical diagnostics:

— *in patients with suspected NEN, CgA concentration should be determined (*evidence level 3);*
— *in patients diagnosed with NEN, CgA concentration should be determined (*evidence level 3) — also concentration of hormones and substances specific for a given syndrome, depending on the clinical symptoms presented by the patient;*
— *if MEN1 is suspected, it is recommended to determine the concentration of ionised calcium, parathyroid hormone (PTH), pituitary hormones (prolactin, GH), and to consider conducting genetic tests (*evidence level 3).*

** evidence level according to CEBM [145]*

Table III. *False-positive and false-negative results of daily urinary 5-HIAA excretion [13, 17, 18]*
Tabela III. *Fałszywie dodatnie i ujemne wyniki oznaczania dobowego wydalania 5-HIAA w moczu [13, 17, 18]*

False-positives	False-negatives
Food products rich in tryptophan: avocado, bananas, kiwi, pineapples, walnuts, plums, aubergine, cheese.	Food products: ethanol
Discontinue 3 days before the collection	
Medicines: paracetamol, phenobarbital, ephedrine, certain cytostatics (cisplatin, 5-fluorouracil)	Medicines: neuroleptics, MAO inhibitors, methyldopa, isoniazid, acetylsalicylic acid, heparin, tricyclic antidepressants
Discontinue 3 days before the collection	Discontinue 3 days before the collection
	Renal failure
	Abnormal urine acidification
	During the sample collection, add 10 mL of 25% HCl to urine, to reduce the pH to 1.5–4.0.
	Incorrectly collected daily urine sample
	(determination of daily creatinine excretion, plastic containers, stored in a fridge)

2.2. Pathomorphological diagnostics

2.2.1. The WHO 2010 classification of GEP NENs

Further changes in the pathomorphological diagnostics of GEP NENs were introduced in 2010, when NENs were divided into two basic groups: either well-differentiated or poorly-differentiated neoplasms.

This was proposed by the WHO and adopted. It was primarily based on an assessment of tumour morphology compared to the structures created by non-neoplastic cells. Another parameter was tumour grading (G), which reflected the potential clinical behaviour of the neoplasm. Compared to the classification system of 2000, the major difference was in referring to well-differentiated tumours and well-differentiated carcinomas by the same term — neuroendocrine tumours/ /neoplasms (NEN), while the G feature determined their grade (G1 or G2). Secondly, poorly-differentiated neuroendocrine small cell or large cell type (G3) cancers were referred to as neuroendocrine carcinomas (NEC), and treated as classical cancers with regard to their diagnostic criteria and treatment methods [26–28]. Tables IV and V present the WHO NENs classification systems introduced in 1980, 2000 and 2010.

The histopathological grade (G) appears to be the key microscopic feature with a prognostic and a predictive value in the treatment of patients with gastrointestinal NENs. As mentioned before, it is an independent parameter dividing NENs into three groups, according to the predicted clinical behaviour of the disease: lesions of low (G1), intermediate (G2) and high (G3) malignancy. The criteria for the assessment of G feature defined by ENETS in 2006 were subsequently adopted by the WHO, which resulted in the ENETS/WHO 2010 integrated system for the assessment of histological grading of NENs.

Table VI presents two methods for assessing the histological malignancy grading of NENs, based on the number of mitotic figures counted in ten high-power fields with magnification of 400 x (1 HPF = 2 mm^2), and the Ki-67 proliferation index determined by immunohistochemical analysis of the MIB1 antigen expression, calculated as the number of cells per 2,000 cells studied in the field containing cells with the highest staining intensity *(hot-spot)*, according to ENETS guidelines. Where the assessment by these two methods provides different grades for the tumour, the higher grade should be accepted. This division of NENs into two groups forms the basis for classification systems and therapeutic choices for this group of neoplasms [23, 29, 30].

The WHO 2010 classification system introduced the division of NENs into two basic categories, significantly different with regard to diagnostics, clinical behaviour and treatment. This division is presented in Table IV. The first group comprises well-differentiated neoplasms (formerly carcinoids) NEN G1 and NEN G2, made up of cells resembling normal neuroendocrine cells, expressing neuroendocrine markers, usually demonstrating extensive synaptophysin and CgA expression, with hormonal expression dependent on the tumour location, and a small and medium nuclear atypia, below 20 mitotic figures/10 HPF. Tumours in this category are classified and treated according to the criteria applicable to NEN [31, 32].

Another group, poorly differentiated and highly malignant neoplasms, NECs, are composed of small or large cells, only sometimes creating structures similar to neuroendocrine ones; they demonstrate an intense and extensive expression of synaptophysin, with a weaker expression of chromogranin A, marked nuclear atypia, necrosis and over 20 mitotic figures/ 10 HPF. The synonymous terms are small cell or large cell neuroendocrine carcinoma, or poorly differentiated carcinoma.

Table IV. *WHO classification systems for neuroendocrine neoplasms introduced in 1980, 2000 and 2010*
Tabela IV. *Klasyfikacje WHO nowotworów neuroendokrynnych w roku 1980, 2000 i 2010*

WHO 1980	WHO 2000	WHO 2010
I. Carcinoid	1. Well-differentiated neuroendocrine tumour — WDET	1. G1 neuroendocrine neoplasm/tumour (carcinoid) (NEN/NET G1)
	2. Well-differentiated neuroendocrine carcinoma — WDEC	2. G2 neuroendocrine neoplasm/tumour (NEN/NET G2)
	3. Poorly differentiated neuroendocrine carcinoma — PDEC	3. Neuroendocrine carcinoma (NEC), large cell or small cell type
II. Mucocarcinoid	4. Mixed exocrine-endocrine carcinoma — MEEC	4. Mixed adenoneuroendocrine carcinoma — MANEC
III. Mixed forms carcinoid-adenocarcinoma		
IV. Pseudotumour lesions	5. Tumour-like lesions — TLL	5. Hyperplastic and preneoplastic lesions

Table V. *NENs classification system according to 2010 WHO*
Tabela V. *Klasyfikacja nowotworów neuroendokrynnych według WHO z 2010 roku*

Morphological differentiation grade	Malignancy (grade)
Well-differentiated	Low grade, ENETS G1, NEN G1
	Intermediate grade, ENETS G2, NEN G2
Poorly-differentiated	High grade, ENETS G3, NEC

Table VI. *Criteria for the assessment of grading of neuroendocrine tumours (G)*
Tabela VI. *Kryteria oceny stopnia histologicznej dojrzałości nowotworów neuroendokrynnych (cecha G)*

Histological malignancy grade of NEN (G)	Mitotic activity/ number of mitotic figures/10 HPF	Ki-67 proliferation index/% of cells (per 2,000 cells)
G1 — well-differentiated, of low malignancy	< 2	≤ 2
G2 — intermediate differentiation, of medium malignancy	2–20	3–20
G3 — poorly differentiated, of high malignancy	> 20	> 20

They are classified according to the criteria for classical cancers occurring in the specific organ. They are treated following the general oncological guidelines.

The next group consists of neoplasms referred to as MANEC. They are characterised by a complex structure, containing two components: glandular and neuroendocrine, and at least 30% content of a given component determines its diagnosis. The diagnosis of this type of neoplasm is confirmed by immunohistochemical examinations with the use of particular antibodies [33–36].

2.2.2. Obligatory and conditional methods of pathomorphological examination in NENs

The ENETS guidelines present the rules for examinations of the sample, depending on its type. Fine-needle aspiration biopsy is not recommended as a diagnostic method in the case of a non-diagnosed primary tumour. It may be used to confirm the presence of metastasis from the established point of origin [37–39].

The principles of preparation of the biopsy sample from the primary tumour or from metastases, and of the surgical tissue specimen, are presented below in Tables VII and VIII.

Minimal consensus statement on pathomorphological examination:

1. In the pathomorphological diagnostics of a small biopsy (excision from the lesion), it is recommended to diagnose the type of neoplasm, well-differentiated — NEN, or poorly differentiated — NEC, MANEC — neuroendocrine tumour/ /neoplasm, and the grade (G1, G2 in NENs). TNM staging of the neoplasm is also recommended in the diagnostics of polyps with the morphology of NENs or a biopsy from liver, with established original tumour site, or to complete the data from imaging examinations. Pathomorphological diagnosis of NENs should always be confirmed by immunohistochemical examination, including the assessment of expression of chromogranin A, synaptophysin and the Ki-67 proliferation activity with MIB1 antibody.

2. Minimal histopathological report for the NEN surgical tissue sample should include:

— clinical data: tumour anatomical location and size, and clinical symptoms in the case of functional neoplasms;

— macroscopic features: tumour description including its location, cross-section appearance, relation to the surrounding tissue and surgical margins, according to the guidelines for the organ;

— microscopic features: description of the histoformative tumour structures and determination of the cell type, deter-

Table VII. ***Principles for examination of cytological and histopathological tissue specimens in neuroendocrine neoplasms***

Tabela VII. ***Zasady badania materiału cytologicznego i histopatologicznego w nowotworach neuroendokrynnych***

Type of material tested	Recommendations, assessment methods
FNA — fine-needle aspiration	In metastases with an established primary tumour site
Biopsy from the primary tumour or from metastases (liver, lymph nodes), surgical material	Biopsy sample preserved in formalin; the preparation directly undergoes the process of technical preparation (without macroscopic assessment) **Conditional:** Recommended freezing of a tumour fragment before preservation in formalin **Obligatory:** Tissue specimen preserved in formalin, examined macroscopically, undergoes the process of technical preparation for microscopic preparations

Table VIII. ***Principles of macroscopic examination of surgical NENs material***

Tabela VIII. ***Zasady badania makroskopowego materiału operacyjnego NEN***

Macroscopic examination of surgical NENs material
Obligatory:
— determination of: location, number of tumours, size (three dimensions)
— assessment of tumour cross-section appearance: solid/cystic, necrosis present
— assessment of tissues surrounding the tumour/invasion of adjacent organs
— marking surgical margins with ink
— excision of lymph nodes
Conditional:
— obtaining and preservation of a fresh fragment of the tumour for scientific research,
Immunohistochemical examination
Obligatory:
— Immunohistochemical assessment of neuroendocrine markers: synaptophysin, CgA
— Immunohistochemical assessment of Ki-67/MIB1 proliferative activity
Conditional:
Immunohistochemical examination of hormonal expression (insulin, gastrin, serotonin and other) if the symptoms of tumour hormonal activity occur:
— assessment of metastases of functional tumours to the liver or lymph nodes if the original tumour site is unknown
— confirmation of the clinical symptoms of functional tumours
— immunohistochemical assessment of somatostatin receptors (e.g. SSTR2) for therapeutic purposes
— immunohistochemical assessment of vascular markers expression in order to examine angioinvasion

mination of feature G based on the Ki-67/MIB1 proliferation index, and of mitotic index according to the ENETS/WHO system (G1-G3), studied in the regions of the highest activity (hot-spot);

— description of histopathological parameters of tumour invasion: angiolymphatic invasion, nerve infiltration, presence of necrosis, invasion of the tumour capsule (pseudocapsule) and determination of the depth of infiltration into the intestinal wall or adjacent tissue and organs;

— determination of imunohistochemical expression: obligatory chromogranin A, synaptophysin and Ki-67/MIB1, and conditionally, as ordered by clinicians, other hormonal markers;

— description of the tumour metastases, if present;

— description of surgical margins;

— description of other parameters, if present, such as inflammation, another neoplastic component.

3. Diagnosis (pathomorphological diagnosis)

Histopathological report should end with a diagnosis containing the following parameters:

— obligatory type of the neoplasm according to the World Health Organisation's 2010 classification system;

— obligatory histological grade (G) according to the ENETS/WHO 2010 guidelines;

— obligatory pTNM pathological staging according to the ENETS and/or TNM AJCC/UICC criteria, with the year of edition;

— margins polypectomy or surgical margins;

— assessment of the dominant cell type (for example, B if insulin is secreted, G for gastrin, EC for serotonin);

*— suggested original tumour sites in cases of hepatic tumours or metastases to the lymph nodes with unknown original NENs location (*evidence level 3).*

2.3. Location diagnostics

Diagnostic imaging of NENs is associated with a range of difficulties due to their small size, often atypical location, and non-specific clinical symptoms. Therefore, it is necessary to use different imaging methods, both anatomical and functional.

The anatomical imaging methods include:

— ultrasonography (USG), especially endoscopic ultrasonography (EUS),

** evidence level according to CEBM [145]*

— computed tomography (CT),
— magnetic resonance imaging (MR),
— endoscopy,
— capsule endoscopy.

Classical imaging methods (i.e. CT, USG, MR) are useful primarily in the assessment of the stage of the disease, and monitoring of the response to treatment. They also play an important role in planning the surgical management of the primary tumour. Moreover, they enable performing a fine-needle or large-needle biopsy.

Over the last few years, endoscopic techniques have been developed significantly. Their accessibility has also increased. Today, these methods enable conducting both diagnostic and therapeutic procedures.

An important achievement in the diagnostics of NENs was the introduction of scintigraphic examinations demonstrating the expression of somatostatin receptors (SRS, somatostatin receptor scintigraphy). These are functional tests, which enable the characterisation of lesions on the molecular level.

Another important achievement has been the recent introduction of somatostatin analogues labelled with a positron radiation emitter — ^{68}Ga: ^{68}Ga-DOTA-D-Phe1,Tyr3-Octreotide (^{68}Ga-DOTATOC), ^{68}Ga-DOTA-D-Phe^{1},Tyr^{3}-octreotate (^{68}Ga-DOTATATE) and ^{68}Ga-DOTA-1-NaI3-Octreotide (^{68}Ga-DOTANOC) to the PET/CT examinations. Tests using these radiopharmaceuticals demonstrate a higher sensitivity in the diagnosis of primary tumours, as well as osseous and pulmonary metastases.

The combined use of morphological and functional imaging techniques has allowed increases in the sensitivity and specificity of diagnostic methods in NEN [40–43].

Both morphological and functional examinations are used in:
— assessment of the extension of the disease,
— localisation of the primary tumour,
— planning the surgical treatment,
— assessment of the response to treatment,
— qualification for radioisotope therapy.

2.3.1. Ultrasonography

Transabdominal ultrasonography

USG examination, due to its high availability and low cost, is usually the first imaging test performed. The sensitivity of the test depends on the tumour location, the experience of the doctor conducting the examination, and anatomical and technical conditions [34].

In clinical practice, a USG examination is used mostly in preliminary diagnostics of pancreatic endocrine tumours and hepatic metastases.

Due to technical limitations, USG is not useful in the assessment of other parts of the gastrointestinal tract.

The image of NEN in a USG examination is non-specific. The tumour is often well-circumscribed, hypoechogenic, sometimes with a hyperechogenic capsule, foci of necrosis, and calcifications. However, the tumour may also be hyperechogenic or isoechogenic. Most tumour foci in a Doppler examination demonstrate rich vascularisation.

The sensitivity of transabdominal USG in the diagnostics of metastatic foci in the liver ranges from 82% to 88%, and specificity is between 92% and 95% [44]. The method's sensitivity in the diagnosis of pancreatic tumours is much lower — 39% (17–79%) [38, 45–50].

Using contrast medium in ultrasonographic diagnostics (contrast enhanced ultrasonography, CEUS) is very useful; 78–86% of tumour foci demonstrate contrast enhancement in the arterial phase. The sensitivity of CEUS in the diagnostics of hepatic metastases increases to 99% [51].

Endoscopic ultrasonography

Presently, the basic examination in the diagnostics of NENs of the pancreas (PNENs) and rectum is endoscopic ultrasonography (EUS). The small distance between the source of ultrasounds and the object studied enables the use of ultrasonic waves of higher frequency than in a conventional USG device. This results in much better image resolution.

The accepted indications for EUS include the assessment of local advancement of neoplastic lesions located within the gastrointestinal tract, including the diagnostics of submucosal lesions and diseases of the pancreas and bile ducts, together with the assessment of the lymph nodes. The examination enables the demonstration of a small-volume lesion, a few tumour foci, the tumour within the duodenal wall, and the assessment of the regional lymph nodes. This method allows the precise determination of anatomical relations (i.e. tumour location relative to the bile ducts and main vessels), and primarily, an assessment of the depth of the gastrointestinal wall infiltration.

EUS examination is particularly useful for the diagnosis of pancreatic NENs (due to their typically small size). The method's sensitivity depends on the location of the tumour: for tumours located in the head and body of the pancreas, it is approximately 90% (77–100%) [39–46]; for tumours located peripherally it is 75–80% [45, 46]. The specificity of the method is estimated at 95% [46]. In the diagnostics of the neoplastic foci located in the pancreas in high-risk patients, EUS is more sensitive than CT [52].

** evidence level according to CEBM [145]*

Transrectal EUS is the most sensitive method of pre-operative assessment of the stage of rectal tumour advancement; its sensitivity in the assessment of the tumour and invasion of the rectum wall is 76–93%, and of the regional lymph nodes metastases it is 61–88% [53].

Intra-operative ultrasound

Intra-operative ultrasonography (IOUS) is used primarily to diagnose focal lesions in the pancreas. The sensitivity of this technique is 90% (74–96%), especially in combination with intra-operative palpation assessment [42, 54, 55].

Intraductal ultrasonography

Mini-probes may be introduced through the endoscope biopsy channel into the pancreatic duct or bile duct. This technique enables the assessment of the inside of the duct and its wall (intraductal sonography, IDUS). It allows better, compared to EUS, visualisation of pancreatic NEN in the immediate vicinity of the pancreatic duct, and of the endo-luminal lesions. Sensitivity of this examination is approximately 94% [56], and it increases to almost 100% for the lesions larger than 3 mm, located in the pancreatic duct [57].

2.3.2. Endoscopic examinations

Upper gastrointestional endoscopy (oesophago-gastroduodenoscopy) or colonoscopy with ileoscopy are frequently the first examinations to be performed in patients with suspected or diagnosed NENs. Endosocpy is the best method for evaluation gastric and duodenal NENs. It is worth emphasising that they are usually found accidentally. These tumours are usually in the form of polypoid mucosal elevation, and only histopathological examination enables a proper diagnosis [58].

Video Capsule Endoscopy (VCE), Wireless Endoscopy — is a non-invasive examination of the small intestine performed with a single-use, wireless capsule swallowed by the patient. The capsule passively moves through the gastrointestinal tract, allowing assessment of the small intestinal mucosa along its entire length. This examination does not substitute gastroscopy or colonoscopy. Unlike a traditional endoscope, the capsules used presently are not steerable, so another more precise assessment of a chosen part of the intestine is impossible.

The limitation of this technique is the run-time of the battery inside the capsule (eight hours). Therefore, in some patients with disturbed peristalsis, the distal part of the ileum may remain unexamined.

The most common complication (0.75% of all patients, 1.25% of patients with Crohn's disease) is capsule incarceration in the small intestine, most frequently in the narrowing of the intestine resulting from the use of anti-inflammatory medicines or due to other diseases.

Present reports indicate a relatively low sensitivity of the test with the use of an endoscopic capsule in the detection of *midgut* lesions, especially in the detection of submucosal and eccentric lesions; the sensitivity is approximately 45%. Small intestinal tumours are diagnosed mostly by accident, during diagnostics of e.g. gastrointestinal haemorrhage [59].

Another diagnostic method which enables the assessment of the small intestine and obtaining the material for histopathological examination with the possibility of endoscopic treatment is *balloon enteroscopy (single-balloon, double-balloon) or spiral enteroscopy*.

While conducting the examination, it is possible to use simultaneously endoscopic ultrasonography (EUS) with miniature heads whose external diameter is 2 or 2.6 mm, introduced through the enteroscope biopsy channel [60].

Enteroscopy enables visualisation of 177–270 cm of the small intestine in transoral examination and ca. 150 cm in transrectal examination [61, 62]. The examination takes 20-240 minutes [63]. Capsule endoscopy and balloon enteroscopy are complementary methods. Non-invasive capsule endoscopy enables initial localisation of the tumour focus, whereas enteroscopy helps to obtain material for histopathological examination and conducting therapeutic procedures [64, 65].

A complete assessment of the small intestine is achieved in approximately 80% of patients, and diagnostic efficacy of the examination is ca. 55% [61].

2.3.3. Computed tomography

Computed tomography examination is presently the standard method in assessment of the location of tumour foci and determination of the NEN stage [34]. CT is also used to monitor the effects of treatment. However, this examination demonstrates relatively low sensitivity in locating the primary tumour site [34].

Currently, spiral MDCT — *multidetector computed tomography* — devices are in common use. Depending on the manner of filling the gastrointestinal lumen, the examination is referred to as CT enterography if the patient receives low-absorption contrast material, or CT enteroclysis if it is administered using a probe introduced into the small intestine. After proper filling of the gastrointestinal tract, a CT examination is performed before and after the administration of contrast material. Scanning after intravenous administration of the contrast material should be conducted in two phases — arterial and portal venous, comprising all the intestines and the liver — to detect possible metastases).

Symptoms indicating malignancy of the tumour include: large volume, necrosis, characteristics of infiltration of adjacent tissues (lesions occur in approximately 20% of patients). In the arterial phase, hyperdense lesions are most frequently found, but more rarely they are hypovascularised or cystic. In the portal

venous phase, NENs are mostly hypodense lesions, as the contrast material is quickly washed out from them.

The sensitivity of the CT examination in the diagnostics of pancreatic tumours is 73% (63–82%), and specificity is 96% (83–100%) [66–69]. The test's sensitivity in the assessment of hepatic metastases is 82% (78–100%), and specificity is 92% (83–100%) [38, 70, 71]. In the diagnostics of extrahepatic metastases, the sensitivity of CT examination is 75% (63–90%), and specificity is 99% (98–100%) [38, 66, 67].

CT colonography

Computed tomography also enables virtual colonoscopy (VC) to be conducted. This method allows the production of three-dimensional images of the walls and content of the large intestine. To obtain perfect 3D reconstructions, it is necessary to perform the examination using a submillimetre layer.

The patient requires proper preparation, similarly to traditional colonoscopy. The preparation consists in complete emptying of the large intestine from faecal masses and liquid (residual faecal masses may result in false-positives) [72–74].

Full assessment of the examination includes the analysis of topical scan and the axial cross-section images (treated as reference images), and the analysis of multiplanar and three-dimensional reconstructions (including 3D algorithms of navigator type). A novelty that improves the effectiveness of results interpretation is computer aided diagnosis (CAD).

CT colonography is a safe and well-tolerated diagnostic method. The sensitivity and specificity of the method are comparable with classical colonoscopy.

The sensitivity of CT and endoscopic colonography is similar; according to different authors, it is 90% for lesions > 10 mm, and 85 % for lesions > 6 mm; the sensitivity and specificity in the diagnostics of malignant neoplasms is 88–100%, and in benign neoplasms it is 86% [75, 76].

The quality of the obtained images depends on patient co-operation and preparation [77].

2.3.4. Magnetic resonance imaging

The sensitivity and specificity of magnetic resonance imaging (MR) are similar to CT in the diagnosis of the primary focus and metastases of NENs [78]. The examination protocol includes performance of the following images/sequences:

— T1-weighted (*spin-echo*, SE),
— T1-weighted with fat saturation,
— T1-weighted (*gradient echo*, GRE) after administration of the contrast material (dynamic and static examination),
— T2-weighted (*fast spin-echo*, FSE),
— T2-weighted with fat saturation [79],
— DWI with ADC mapping.

Tumours demonstrate a hypointense signal in T1-weighted images, and a hyperintense signal in T2-weighted images (rarely hypointense — if they contain a large fibrous tissue component), and they are visibly enhanced after administration of the contrast material. Cystic tumours with necrotic foci are ring-enhanced. 75% of metastatic foci in the MR scan demonstrate a hypointense signal in T1-weighted images, most of them are strongly enhanced after administration of contrast material. The MR technique also enables conducting of a CT colonography-type examination. The advantages and disadvantages of this method are similar to CT colonography.

MR imaging — following the optimal protocol — allows the diagnosis of 80–95% of metastatic foci in the liver [34, 67, 76, 80], and 73–93% of pancreatic NENs [25, 34, 36]. In the diagnostics of extra-pancreatic and extra-hepatic foci, the test's sensitivity is much lower, i.e. 68–89% [34, 67].

Whole-body MR imaging is considered to be a second-line test in the assessment of hepatic metastases smaller than 10 mm, and in the assessment of foci with non-specific enhancement on the CT scan. It is also recommended in patients allergic to iodine contrast material used in CT scanning.

2.3.5. CT/MR enteroclysis/enterography

Presently, to assess the small intestine, CT/MR enterography/enteroclysis are used (see above). These methods increase the CT sensitivity to 86–97% [3, 81].

The techniques enable identification of even small, segmental thickening of the intestinal wall, small nodules in the intestinal wall, and segmental narrowing of the lumen. MRI examination provides better tissue resolution than CT; it enables assessment of intestinal wall layers and of the level of its infiltration by the tumour. The scope of the examination should include the field from the level of the liver to the pubic symphysis.

In CT/MR enteroclysis, contrast medium is administered through a probe introduced under fluoroscopic control beyond the duodenojejunal angle. An anti-reflux balloon prevents reflux of the contrast material into the duodenum. After the contrast material has been administered, MR examination of the abdominal cavity is performed, using a surface coil. Fast T1-weighted and T2-weighted sequences should be performed (HASTE, FIESTA), as well as T2-weighted sequences with fat saturation, and examination after intravenous administration of contrast material (T1-weighted images). The layers should be 3–5 mm thick. As a standard procedure, the patient should be in the supine position (the prone position is uncomfortable, and the patient cannot stay in it for long; therefore, it is rarely used, e.g. if artefacts are present). In CT enteroclysis, intravenous contrast material is administered, 1.5–2 mL/kg,

Table IX. *Sensitivity and specificity of imaging examinations in the diagnostics of GEP NENs [38]*
Tabela IX. *Czułość i swoistość badań obrazowych w diagnostyce GEP NEN [38]*

Type of examination	CT (sensitivity/specificity)	MRI (sensitivity/specificity)	USG (sensitivity/specificity)
Pancreatic endocrine tumours	73%/96%	93%/88%	93%/95% (EUS)
Hepatic metastases	82%/92%	80–95%	88%/95%
Metastases outside the liver to soft tissues	75%/99%	89%/100%	–
Small intestinal lesions	50%/25%	–	–
	85%/97% (enteroclysis)		

at 3–4 mL/s, the test is performed with 30–60 s delay (from 45 seconds — intestinal phase), and the layers should be 1.25–2.5 mm thick [82].

In MR/CT enterography, the contrast medium is administered orally an hour before the examination. Intravenous administration of medicines slowing intestinal peristalsis is recommended.

Enteroclysis provides a better level of extension of the intestinal loops, and the ability to assess peristalsis; however, patient tolerance of the test is lower compared to enterography. Sensitivity of CT enterography and enteroclysis is similar. Due to a long time of data acquisition in the MR imaging, enteroclysis is recommended in this test [79].

The examination time in CT enteroclysis is shorter than in MR enteroclysis. Therefore, the quality of the test is less dependent on co-operation with the patient. However, it is associated with patient exposure to ionising radiation.

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 negative MR/CT enterography results and with clinical symptoms of small intestine diseases (Table IX).

Minimal consensus statement on imaging tests:

*The choice of imaging examination depends on the primary focus location and the stage of the disease: USG, CT, MRI, endoscopy (*evidence level 3–4).*

Individual GEP NENs are discussed in detail in other sections of our recommendations.

2.4. Radioisotope diagnostics

2.4.1. Isotope diagnostics using isotope-labelled somatostatin analogues

Isotope diagnostics using isotope-labelled somatostatin analogues is the most sensitive method of the diagnostic imaging of NENs. The sensitivity of somatostatin receptor scintigraphy (SRS) is approximately 80–90% [83] for most types and locations of GEP NENs. Insulinoma is an exception, probably due to a lower somatostatin receptor expression. Clinical indications for SRS include: localisation of the primary focus, determination of the stage of the disease, monitoring of the patient following a radical surgical treatment, and qualification of patients for treatment with 'cold' and 'hot' SSA.

2.4.2. Isotope diagnostics with the use of ^{111}In-OctreoScan

In 1994, the USA Federal Drug Administration (FDA) authorised indium-labelled ^{111}DTPA0-D-Phe1-octreotide (^{111}In-OctreoScan®, pentreotide) for marketing. This compound demonstrates a high affinity to SST2 (IC50 2 nM), a much lower affinity to SST5 (22 nM) and SST3 (IC 50 187 nM), and no affinity to SST1 and SST4 [81]. In a multicentre study, the sensitivity of receptor scintigraphy with the use of pentreotide was approximately 80% [84], including 100% for glucagonoma, 89% for VIP, 87% for carcinoid and 82% for non-functional pancreatic tumours. Presently, due to the higher sensitivity of tests with other tracers, in most centres the use of 111-In-OctreOscan has been renounced (**evidence level 3*).

2.4.3. Diagnostics with the use of technetium-labelled SSA (^{99}Tc)

Technet-labelled SSA are increasingly often used in the isotope diagnostics of NENs [85–88]. The physical properties of technetium increase the number of counts detected and the quality of scintigraphy. Similarly to pentreotide, the highest sensitivity is achieved with the SPECT technique. Due to the positive Polish experience with (^{99}Tc-EDDA/HYNIC) octreotate–tectreotide — indicating a high sensitivity of scintigraphy [85], scintigraphy with the use of pentreotide has been completely substituted by this method, especially in centres which do not offer positron emission tomography (**evidence level 3*).

** evidence level according to CEBM [145]*

2.4.4. Diagnostics with the use of positron emitting tracer-labelled SSA

Scintigraphy using positron emitting tracers is an imaging method characterised by the highest resolution among all the isotope examinations. Literature data suggests higher sensitivity of scintigraphy with somatostatin analogues labelled with positron emitting tracers (^{68}Ga) compared to the SPECT test with 111In-pentreotide [89]. The sensitivity, specificity and diagnostic accuracy in PET examinations using ^{68}Ga-labelled SSA are 97%, 92% and 96%, respectively [40, 90]. In over 50% of patients with neuroendocrine neoplasms, the PET examination affects a change of the disease stage, and determines further treatment [99].

There is no comparative data on ^{99}Tc radiopeptides. In centres with a PET scanner, examination with ^{68}Ga should be the test of choice (**evidence level 3*).

2.4.4. Isotope diagnostics with the use of ^{18}F-FDG

The ^{18}FDG — PET/CT examination (fluorodeoxyglucose) is usually negative in well-differentiated NENs, mainly G1 NENs [92, 93]. However, it has been demonstrated that collection of ^{18}FGD in neoplastic foci is a negative prognostic factor [90]. The PET/CT scan with ^{18}FDG, and the assessment of somatostatin receptor expression in a ^{68}Ga- PET/CT is useful in qualification for radioisotope treatment, particularly in NENs G2 [94].

2.4.5. Isotope diagnostics with ^{18}F-DOPA

PET diagnostics with the use of ^{18}F-DOPA tracer (^{18}F-DOPA-PET) is a new, promising method of NEN imaging. In the diagnosis of NEN, ^{18}F-DOPA-PET has demonstrated a sensitivity of 89%, compared to 56% for CT and 47% for SRS [95].

2.4.6. Diagnostics with the use of m-IBG

Another tracer used in the diagnostics and therapy of NEN is m-IBG (metaiodobenzylguanidine). Imaging with the use of $^{123/131}$m-IBG is performed primarily in pheochromocytoma and neuroblastoma, rarely in the case of other neoplasms of neuroendocrine differentiation. The sensitivity of m-IBG scintigraphy in NEN is approximately 70% (40–85%), and it is lower than that of the test with 111In-pentreotide [96]. The best results are achieved using ^{123}m-IBG in visualisation of hepatic metastases. However, also in this case receptor scintigraphy is more sensitive [97]. Therefore, presently m-IBG scintigraphy is justified in patient qualification for isotope treatment if receptor scintigraphy is negative.

In addition to these radiomarkers, research is currently being conducted into other tags receptors: GLP1 analogues, gastrin, and bombesin.

Minimal consensus statement on radioisotope tests:

— *receptor scintigraphy (SPECT/CT) with labelled somatostatin analogue (in Poland: labelled with technetium) or ^{68}Ga-PET/CT in G1 and G2 NENs (*evidence level 3);*

— *^{18}FDG-PET/CT in NECs (in individual cases for G2, G1 NENs) (*evidence level 4).*

3. Treatment

3.1. Surgical treatment

In GEP NENs, the treatment of choice is surgical management. Its scope depends on the patient's general condition and on the location, stage and specificity (biology) of the neoplasm (**evidence level 4*) [8, 98]:

1. Therapy with the intention to cure (radical) — resection.

2. Cytoreductive therapy (reduction of the tumour mass by ca. 90%).

3. Palliative therapy (improvement of the quality of life):

— management of metastases:
- resection,
- ablation,
- embolisation,
- transplantation;

— management of mechanical jaundice:
- by-pass,
- prosthesis;

— management of obstruction of the gastrointestinal tract:
- palliative resection,
- by-pass;

— management of gastrointestinal bleeding;

— pain management (e.g. solar plexus neurolysis).

The varied biology and clinical picture of GEP NENs, compared to the most frequent gastrointestinal adenocarcinomas, affects the methods of treatment and indications for surgical management, discussed in detail for different parts of the gastrointestinal tract in further sections of this document. The same principles of oncological management apply to NENs, especially to malignant forms (high level of cell proliferation, possible metastases to other organs), as to other malignant neoplasms.

They include:

1. Diagnostics and staging.

2. Treatment, including combined therapy (neoadjuvant, inductive, adjuvant, palliative).

* *evidence level according to CEBM [145]*

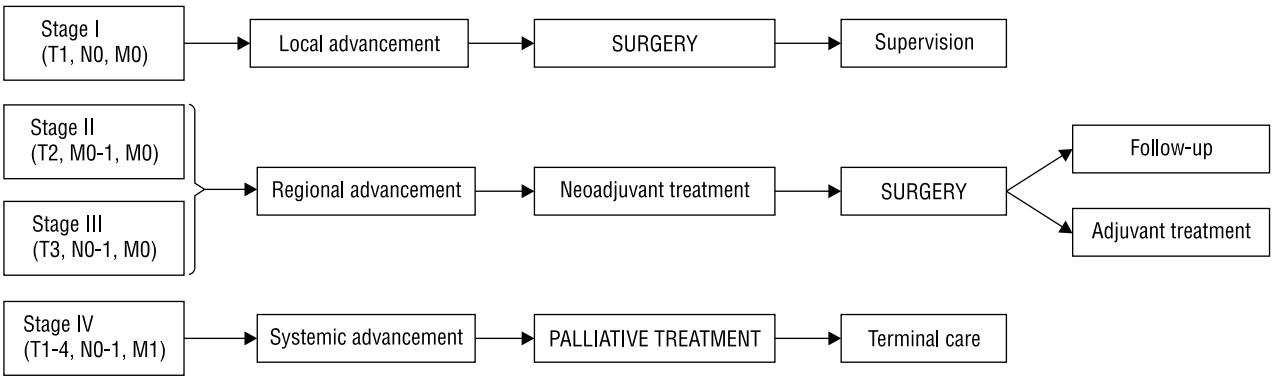

Figure 2. *Treatment principles for gastrointestinal malignant tumours according to disease UICC (Union Internationale contre le Cancer) staging [101]*

Rycina 2. *Zasady leczenia złośliwych nowotworów układu pokarmowego w zależności od stopnia klinicznego zaawansowania według klasyfikacji Międzynarodowej Unii Przeciwrakowej (UICC, Union Internationale contre le Cancer) [101]*

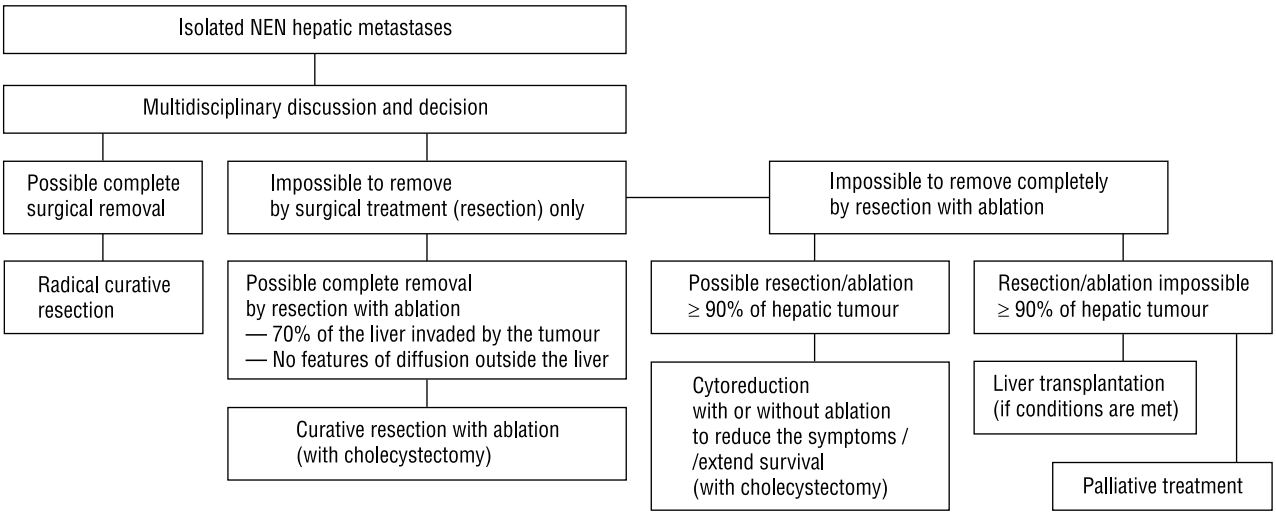

Figure 3. *Treatment principles for NEN metastases to the liver [99]*

Rycina 3. *Zasady leczenia przerzutów NEN do wątroby [99]*

3. Monitoring of the effects of treatment (oncological supervision).

The principles of GEP NEN treatment are presented in Figure 2 [101]. This scheme applies primarily to poorly-differentiated neuroendocrine carcinomas. In clinical stages I, II and III, treatment with the intention to cure, i.e. radical treatment, may be considered. In stage IV clinical advancement, when the neoplasm reaches the systemic scope (presence of distant metastases, e.g. in the liver, lungs), palliative therapy may be introduced in order to improve the quality of life (e.g. somatostatin analogues, pain management) and/ /or extend the survival (e.g. surgery, chemotherapy, radioisotope therapy — individual or combined). In the case of well-differentiated NENs, radical resection may also be considered, if there are liver metastases [99, 100]. Similarly, as in colonic cancer, radical resection of the primary tumour and hepatic metastasis may result in a complete curative effect. In the case of resectable primary and metastatic tumours, aggressive radical surgery is the best therapeutic option. In stage IV G1-G2 GEP NENs which feature M1 in the liver, the surgical procedure does not have to be tantamount to palliative treatment [97]. Resection of the metastases should be accompanied by removal of the regional lymph nodes [97]. The principles of the treatment of NEN metastases to the liver are presented in Figure 3 [97].

Palliative surgical treatment of NENs may consist of treating the obstruction of the gastrointestinal tract (*by-pass,* palliative resection), management of gastrointestinal bleeding (*argon plasma coagulation* — APC, laser therapy, palliative resection), management of metastases, including: resection, ablation (e.g. *radiofrequency thermoablation* [RFA]), embolisation, and liver

transplant. A specific form of palliative treatment of NEN is cytoreductive therapy, which consists in reduction of the neoplasm mass by ca. 90%, and further systemic management (chemotherapy), or biotherapy (SSA, interferon alpha [INF]).

Aspects related to the treatment of NEN include [12]:

1. Epidemiological conditions — rare neoplasms (approximately 2% of gastrointestinal neoplasms).

2. Diagnostic conditions:

— early cases are rare;

— single tumours occur sporadically;

— multiple tumours are multi-focal, or occur in multiple endocrine neoplasia (MEN) syndromes.

3. Biological conditions:

— functional tumours (approx. 20%);

— non-functional tumours;

— low proliferation index.

4. Oncological conditions:

— benign neoplasms are less common;

— malignant neoplasms are more common;

— prognosis, regardless of the character of the neoplasm (benign/malignant), is usually good.

Indications for liver transplantation in GEP — NENs

Treatment by liver transplant in patients with GEP NENs should be considered when non-resectable neoplastic lesions are found in the liver parenchyma, both primary and metastatic. This method of treatment is also indicated in patients with hepatic recurrence of the neoplastic disease, after liver resection, ablation therapy or systemic treatment due to GEP NEN. Liver transplant may be performed in the case of symptomatic or non-symptomatic tumours [4 , 100, 102, 103].

Qualification for liver transplantation depends on confirmation of exclusively hepatic location of the metastases or the primary GEP NEN by imaging examinations (no extra-hepatic metastases), and on its histopathological grade G1 or G2 according to the WHO classification system [101, 104, 105] (**evidence level 3*).

The risk factors for worse outcomes of the transplantation (i.e. complications and recurrence), and thus for patient survival, include [101, 106, 107]:

A — primary tumour located in the pancreas or duodenum,

B — hepatomegaly,

C — gastrin-secreting tumour,

D — high proliferation activity (Ki-67 > 5%),

E — high metastatic activity (lowered E-cadherin),

F — recipient's age > 55 years,

G — resection of extra-hepatic lesions during OLTx,

H — type III hepatic metastases of GEP NENs (multiple, diffused lesions in both lobes of the liver),

I — extensive multi-organ resection preceding OLTx.

The outcomes of the treatment by liver transplantation in this group of patients are considerably worse than in the group of patients with a better prognosis. One-year survival is achieved by 43–76% of patients, and five-year survival by 12% of patients. Re-surgery in the period immediately after the operation is necessary in up to 35% of patients [101–103, 106–108] (**evidence level 3*).

Factors improving the prognosis after OLTx include [101, 106–108]:

A — primary tumour location other than the pancreas or duodenum,

B — carcinoma,

C — possible oncologically radical resection (R0) prior to OLTx,

D — low proliferation activity (Ki-67 > 5%),

E — low metastatic activity (normal E-cadherin),

F — serotonin-secreting tumour,

G — recipient's age < 50 years,

H —— no progression of the neoplastic disease within six months,

I — neoplasm infiltration of < 50% of hepatic parenchyma,

J — absence of hepatomegaly.

In such a group of recipients, one-year survival may be achieved by 88–90% of patients, five-year survival by 47–80% of patients, and ten-year survival by 28–50% of patients. Complications are found in 18–35% of patients, and the death rate is 4.5–17% of patients after the surgery. An unresolved and still pressing problem is the recurrence of the underlying disease: within a year after liver transplantation, it affects 44% of patients, within three years 63%, and within five years 80% [101–103, 106–108] (**evidence level 3*).

Minimal consensus statement on surgical treatment:

*In GEP NENs, the treatment of choice is surgical management. Its scope depends on the patient's general condition and on the location, stage and specificity (biology) of the neoplasm (*evidence level 4). Treatment options include resection with the intention to cure (radical), cytoreductive therapy (reduction of the tumour mass by approximately 90%), and palliative treatment.*

— *In patients with the disease limited to a resectable primary lesion and regional lymph nodes, radical surgical treatment is introduced with the intention to cure (*evidence level 4). In individual cases, particularly of G1-G2 NENs, in potentially resectable lesions with hepatic metastases, surgical resection should also be considered (resection of the primary and metastatic tumour) (*evidence level 4). In*

** evidence level according to CEBM [145]*

*non-resectable primary tumours, cytoreductive or palliative procedures are performed. A selected group of patients with non-resectable hepatic lesions and uncontrolled symptoms which do not disappear after implementation of available treatment methods may be qualified for liver transplantation (*evidence level 3).*

— *Liver transplant should be considered in patients with non-resectable G1 or G2 GEP NENs in the liver parenchyma, if PET-CT examination or diagnostic laparoscopy/ /laparotomy does not reveal metastases outside the liver. Another essential condition is the removal of the primary tumour before liver transplantation, and Ki-67 < 10% (*evidence level 3).*

3.2. Endoscopic treatment

The main purpose of the treatment of GEP NENs is radical removal of the tumour, and in the case of functional tumours — control of the clinical symptoms associated with the production of specific hormones.

Although the basic method of radical treatment is surgical resection, technological progress in endoscopic equipment plus the development of new therapeutic endoscopic techniques justify using this treatment in certain cases [108, 109].

This is possible mainly due to the introduction of methods such as endoscopic ultrasonography (EUS), which enables a precise assessment of the gastrointestinal tract wall and its individual layers with surrounding structures, and adequate qualification of patients for endoscopic or surgical procedures, as well as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) [110].

The therapeutic approach in GEP NENs located in the upper gastrointestinal tract and in the large intestine, often detected during a diagnostic endoscopic examination, depends on the tumour size, depth of invasion and the presence of metastases at the diagnosis. Endoscopic resection of GEP-NET may be used as a treatment method only in well-differentiated G1 and T1 tumours, according to the TNM classification system. Before deciding on endoscopic treatment, an endosonographic examination is necessary to determine the size of the lesion and the depth of infiltration into the gastrointestinal tract wall, as well as to assess the regional lymph nodes. The test may be completed with fine-needle biopsy of the primary lesion and lymph nodes.

Only lesions limited to the mucosa and submucosa qualify for endoscopic removal, while in all other cases local or radical surgical excision is recommended, possibly with supporting therapy or chemotherapy.

It is estimated that approximately 20% of gastric NENs, 10% of duodenal NENs, and as many as 70% of rectal tumours qualify for endoscopic removal.

The following histopathological criteria confirm completeness of the endoscopic procedure results: complete removal of the lesion (negative margin), absence of angioinvasion, low mitotic activity, and low proliferative index.

In most cases, after the endoscopic treatment, further supervision is recommended although its principles have not been clearly defined for all cases [111].

Classical polypectomy performed with the use of an electrocoagulation loop is not recommended as a therapeutic method in GEP NENs, as it often leaves a positive margin after the procedure, so the optimal method is endoscopic mucosal resection. Endoscopic resection conducted by the injection and cut technique consists in lifting the lesion from the muscular layer of the wall by submucosal administration of a substance (saline with adrenalin) which creates a 'bubble' under the lesion, and in subsequent removal of the lesion with a diathermic loop. Lifting of the lesion is a condition for qualifying for this procedure; absence of this phenomenon (non-lifting sign) indicates infiltration of deeper layers of the gastrointestinal tract wall, and is a contraindication for endoscopic resection. Other EMR techniques include injection, lifting and section (strip biopsy), endoscopic mucosal resection with ligation (EMR-L) or cap assisted endoscopic mucosal resection (EMR-C). Lesions limited to the mucosa, well-differentiated, convex, smaller than 2 cm and without ulceration qualify for endoscopic resection [112].

Endoscopic submucosal dissection is a technique which enables removing lesions even greater than 3 cm in diameter in one piece (en-bloc) within the normal tissue. It involves marking by means of electrocoagulation of the mucosa surrounding the lesion, injecting solution into the submucosal membrane and lifting the lesion above the muscularis propria, performing circular dissection of lamina propria mucosa around the lesion, and removing the lesion together with the submucosal membrane [113].

The most common complication following mucosal resection and endoscopic submucosal dissection is haemorrhage (10–20%) and perforation (1%). They are more frequent in cases of duodenal or gastric lesions removal than in rectal lesions. ESD, compared to EMR, is characterised by a higher size-independent ratio of lesions removed en-bloc (OR 13.87), and a lower local recurrence ratio (OR 0.09), but this technique

** evidence level according to CEBM [145]*

takes longer to perform and demonstrates a higher rate of complications (haemorrhage OR 2.2; perforation OR 4.09).

Endoscopic methods can also be used in palliative treatment of NEN in the case of:

— mechanical jaundice due to obstruction of the biliary tree (stenting of the biliary tree);
— obstruction of the gastrointestinal tract (stenting of the gastrointestinal tract);
— gastrointestinal bleeding (endoscopic hemostasis);
— pain (EUS-controlled celiac plexus neurolysis);
— functional tumours with clinical symptoms (EUS-controlled ablation).

Minimal consensus statement on endoscopic treatment:

— *In certain clinical situations (well-differentiated gastric, duodenal and rectal G1 and T1 tumours, according to TNM classification), endoscopic methods such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) may provide a beneficial alternative to surgical treatment. Endoscopic ultrasonography (EUS) enables precise assessment of the gastrointestinal tract wall and its individual layers with surrounding structures, as well as adequate qualification of patients for endoscopic or surgical procedures.*
— *Endoscopy also enables palliative treatment of mechanical jaundice due to obstruction on the biliary ducts, obstruction of the gastrointestinal tract, gastrointestinal bleeding, pain (EUS-controlled celiac plexus neurolysis) and — in special cases — ablation of functional tumours causing clinical symptoms (*evidence level 3).*

3.3. Pharmacological treatment

3.3.1. Biotherapy: somatostatin analogues (SSA) and interferon

In most cases, radical surgical treatment of a neoplasm is impossible due to a late stage of the disease at the diagnosis [8, 114]. SSA play a major role in the pharmacological treatment of GEP NENs [8].

A. Reduction of clinical symptoms and improvement of the quality of life in patients with functional tumours

SSA are the 'gold standard' in the treatment of functional tumours; these medications reduce secretion of hormones and biologically active substances, control the symptoms of the disease, and significantly improve the quality of life. The beneficial effects of SSA in GEP NEN result from their multidirectional impact on the gastrointestinal system through inhibition of the secretion of pancreatic and intestinal hormones, including insulin, glucagon, gastrin, secretin and VIP, as well as by inhibition of its motility and intestinal transportation, blood flow in the peritoneal vessels, and the growth and tissue differentiation [8, 18, 115].

Presently two SSA are available — octreotide and lanreotide, of which the most frequently used are preparations of prolonged action: octreotide-LAR im, and lanreotide Autogel sc. (every 4–8 weeks) [12, 116]. Therapy with long-acting SSA is the treatment of choice in cases of the following symptoms:

— Carcinoid syndrome. Before the introduction of SSA, a large number of patients died as a result of complications due to carcinoid syndrome, including carcinoid crisis. Presently, during long-term treatment with SSA, an improvement of clinical symptoms is observed, including diarrhoea and *flushing*, in 60–70% and 70–80% of patients with GEP NEN, respectively. Detailed dosing of SSA in the treatment of carcinoid syndrome and carcinoid crisis is presented in the section on small intestinal NEN;
— Glucagonoma. Improvement or disappearance of necrolytic migratory erythema was found in 80–90% of patients; lower efficiency is observed with respect to body weight loss control, diabetes and thromboembolic disease;
— VIPoma. Diarrhoea disappears and water-electrolyte disturbances improve in 80-90% of patients.

SSA are not the first-line therapy in insulinoma and gastrinoma [8]. In 50% of cases, insulin-producing tumours do not demonstrate SSTR2 or SSTR5 expression. Moreover, special care should be taken with *insulinoma* patients, as SSA may increase hypoglycaemia (reduced glucagon secretion, reduced secretion of the growth hormone). However, in malignant forms of *insulinoma*, during SSA therapy clinical symptoms may be reduced, and the disease stabilised [117]. In the case of malignant forms of gastrinoma, using SSA as second-line therapy can also be effective in alleviating disease symptoms [99].

Short-acting SSA are still used if a prompt control of GEP NEN symptoms is required (including carcinoid crisis), in the peri-operative period or before introducing the treatment with long-acting analogues, in order to assess drug tolerance (e.g. in patients with *insulinoma*) [97, 99].

B. Stabilisation of the disease

SSA demonstrate an antiproliferative effect, which has been confirmed in *in vitro* and *in vivo* studies. The

** evidence level according to CEBM [145]*

antineoplastic activity of SSA (cytotoxic and cytostatic) has been proven; it may consist in direct effect on the receptors on the tumour membrane cells, as well as in indirect impact by inhibiting the secretion of tumour growth factors, cytokines and hormones, which are responsible for uncontrollable growth and metastatic potential. Indirect effects also include inhibition of angiogenesis, induction of apoptosis and the impact on the immune system, particularly on the proliferation of lymphocytes and immunoglobulin synthesis [23]. A randomised, placebo-controlled, double-blind phase III study published in 2009 provided evidence on the antiproliferative effect of octreotide in patients with well-differentiated *midgut* NETs with metastases. Using octreotide LAR 30 mg extended the mean progression-free survival, and after six months of therapy the disease was stabilised in approximately 67% of patients, regardless of NET's hormonal activity. The progression-free survival was assessed as 14.3 months, compared to six months in the control group [118]. The best result was achieved in patients with hepatic invasion of less than 10%, and resected primary tumour [119]. Some clinical trials have also demonstrated the antiproliferative effects of lanreotide: in the phase II study in patients with NEN (40% migut NEN, 27% pancreatic NEN) treated with lanreotide Autogel (120 mg every 28 days), the mean progression-free survival was 12.9 months.

Recently, the results of the randomised, double-blind, placebo-controlled phase IIICLARINET study on the use of Lanreotide Autogel 120 mg in GEP NEN have been announced; they confirmed antiproliferative effect of this analogue [120]. The study involved 204 patients with G1 and G2 nonfunctional NETs (Ki-67 < 10%) with the primary location being in the pancreas (45%), midgut (36%), hindgut (7%) and unknown (13%), and with hepatic invasion > 25% in 33% of patients. Two-year treatment with Lanreotide Autogel 120 mg every four weeks demonstrated the absence of disease progression or death in 62% of treated patients, compared to 22% of the placebo patients. Lanreotide Autogel statistically significantly extended the PFS vs. placebo (mean PFS was not achieved in the treatment group, compared to 18 months in the placebo group) (**evidence level 1*).

A decision to introduce SSA to therapy should be taken individually for each patient. Previous study results have indicated that SSA therapy is beneficial in patients with functional and non-functional NENs (with a good somatostatin receptor expression) and/or slow progression of the disease, preferably in patients with low Ki-67 up to 10%.

SSA are usually well-tolerated, and associated adverse reactions are rare. Initial side effects such as discomfort in the abdominal cavity, flatulence or steatorrhea usually disappear spontaneously within a few weeks, or during the symptomatic treatment (e.g. pancreatic enzymes preparations). Other side effects include impaired glucose tolerance and cholelithiasis, and occur in 20–50% of patients (rarely symptomatic) [18]. Therefore, if surgical treatment and long-term pharmacotherapy with long-acting SSA are planned, cholecystectomy should be considered. During a long-term treatment with SSA, the response to treatment may be reduced or lost. This is explained by tachyphylaxis and resistance to treatment. It may be caused by reduced somatostatin receptor expression on the tumour cells due to *down-regulation*, loss of receptor sensitivity, heterogeneous receptor expression or growth of the clones of SSTR-negative cells [119].

Detailed information on treatment with SSA is provided in the section on small intestinal NENs.

Currently, studies are being conducted on the use of new SSA, e.g. pasireotide (SOM-230), in the treatment of functional NENs, also those resistant to octreotide or lanreotide.

The pre-operative pharmacological preparation of patients with the use of SSA has been discussed in the section on small intestinal NENs.

C. Interferon alpha

Interferon alpha (INF-α) is used for similar indications as SSA. As its effect in controlling clinical symptoms is delayed, it is not used in the treatment of carcinoid crisis. Due to a larger number of adverse reactions, it is the second-line treatment to control clinical symptoms of functional tumours. INF-α therapy may be indicated for GEP NENs with the proliferative index lower than 2–3% [1, 121]. In Poland, there is no previous experience of using INF-α for GEP NEN management.

There are single reports concerning the use of interferon-alpha indicating that the patient may benefit from this therapy only if the mitotic index of the tumour is low [122].

Minimal consensus statement on biotherapy:

*Therapy with SSA is the treatment of choice in patients with functional and non-functional GEP NENs and/or slowly progressing disease, preferably in patients with low Ki-67 proliferative index (*evidence level 1).*

** evidence level according to CEBM [145]*

3.3.2. Chemotherapy and molecularly targeted therapy

Well-differentiated and moderately-differentiated neoplasms (G1 and G2)

The place of chemotherapy (using medicines with cytotoxic effect) in patients with GEP NENs depends primarily on the histological characteristics (differentiation grade of the neoplasm), and on its primary location. In patients with well-differentiated and moderately-differentiated neoplasms (G1 and G2), chemotherapy may be considered only in the advanced stage of the disease (incomplete primary surgical treatment results, or recurrence of the disease after initial radical treatment). The most important criterion in qualification for chemotherapy is symptomatic character of the disease or its progression dynamics. Patients with the disease so advanced that it entails the risk of organ failure (e.g. liver, lungs), or causes clinical symptoms which cannot be controlled by other methods (e.g. pain), are qualified for the treatment. If these features are absent, the qualification criterion may be confirmation of tumour progression according to RECIST criteria within the period of up to one year. RECIST progression in the period of more than a year is not treated as an independent indication for chemotherapy.

In each case of advanced GEP NEN, before deciding on chemotherapy, palliative local treatment (excision, thermoablation or cryoablation of the metastases and embolisation), or less toxic methods of systemic management should be considered (biotherapy with cold SSA, isotope therapy with hot SSA — PRRT). The above suggestions are based on the opinions of experts, compliant with most of the world's management guidelines (**evidence level 5*).

The present state of knowledge does not justify using chemotherapy as an adjuvant therapy after complete surgical management of G1-2 neoplasms (adjuvant chemotherapy, with the intention to eradicate the foci of micro-diffusion). There is no conclusive evidence that it has a positive effect on extending the disease free survival (DFS) or overall survival (OS) of patients [123].

The effectiveness of chemotherapy on well-differentiated or moderately-differentiated GEP NENs should be considered separately in cases of neoplasms of pancreatic origin, and those with different locations (stomach, duodenum, small intestine, appendix and large intestine). An indirect comparison of the results of clinical studies involving patients with GEP NENs demonstrates a higher probability of response in patients treated due to pancreatic NENs (15–35% compared to 5–15%) [124]. Interpretation of the results of previous studies is difficult due to the heterogeneity of the groups of patients regarding prognostic factors, and the criteria used to assess the response (a considerable part of the studies involved patients who were not stratified according to the level of tumour differentiation; moreover, in earlier analyses, the radiological assessment of the response to chemotherapy was suboptimal from today's perspective).

In well-differentiated pancreatic NENs, the highest activity in monotherapy (response rate — 20–40%) is demonstrated by streptozocin, doxorubicin, fluorouracil, dacarbazine and temozolomide. Using multi-drug regimens is more effective than monotherapy regarding the effect on response and survival rates (mean survival — 15–30 months).

The use of streptozocin (STZ) in monotherapy resulted in a response rate (RR) of approximately 36%, and OS of ca. 17 months. Combining streptozocin with 5-fluorouracil (5-FU) increased the response rate to 63%, and extended the mean overall survival to 26 months [125]. A breakthrough in chemotherapy of pancreatic NENs was the phase III study by Moertel et al. in 1992 [126], in which 69 patients were randomised to two chemotherapy arms: streptozocin-based, i.e. with doxorubicin (DOX) and chemotherapy with 5-FU, demonstrating RR of 69% *v.* 45%, respectively, with mean clinical response time of 18 months vs. 14 months, and mean overall survival of 26 months *v.* 17 months (**evidence level 3*). Although such positive outcomes could not be repeated in any subsequent clinical study, further publications confirmed the clinical response rate after the use of STZ + DOX or STZ + 5-FU of 35–55%, with the response time of 11–22 months, and the mean overall survival of a little over 20 months [124, 127] (**evidence level 4*).

More recent studies, conducted in the 21st century, have documented the effectiveness of chemotherapy with streptozocin combined with doxorubicin. Delaunoit et al. [128] demonstrated RR = 36% and a two-year and three-year OS in 50% and 24% of 45 patients with pancreatic G1/G2 NENs, respectively.

Kouvaraki [129], adding 5-FU to streptozotocin and doxorubicin (FAS regimen), in a group of 63 patients achieved RR = 39%, with a response time of 9.3 months, as well as a two-year PFS in 41% and a two-year OS in 71% of patients. The study by Kouvaraki et al. suggests that there is no statistically significant correlation between OS and the tumour type, histological differentiation or surgical resection; however, progression-free survival was characteristically shorter in poorly dif-

* *evidence level according to CEBM [145]*

ferentiated NENs (p = 0.003), and when FAS chemotherapy was used as the second-line treatment (p = 0.05). In statistical multifactorial analysis, only the size of metastases in the liver (> 75% invasion of the organ) was associated with shorter PFS [130]. Substituting STZ with dacarbazine (e.g. the FDE regimen — 5-fluorouracil + dacarbazine + epirubicin) was associated with lower RR (11%) and shorter response time (mean ten months) [124,128] (**evidence level 4*).

It is worth noting that comparison of the results of the studies has not provided conclusive evidence that an increased number of medications in the regimen improves the treatment outcome, although it may be associated with a greater risk of adverse reactions. However, studies conducted over a long period of time (i.e. more than 20 years) do not allow a direct comparison of the response rates and progression-free survival, as the groups of patients and methods of monitoring the therapy are significantly different.

Considering the above, in palliative chemotherapy of pancreatic NENs, the expert panel recommends combining streptozocin (the medicine is not registered in Poland, but is available as a direct import) with doxorubicin and fluorouracil, and in patients with a greater risk of complications or not qualifying for the treatment including anthracyclines, using a two-drug chemotherapy.

It is difficult to assess the actual value of chemotherapy in patients with well-differentiated and moderately-differentiated GEP NENs located outside the pancreas, due to a limited number of studies and their contradictory results. Chemotherapy regimens are analogous to those used for pancreatic neoplasms, although there is no evidence of effectiveness of the streptozocin-based therapy. In clinical practice, a regimen with doxorubicin and 5-fluorouracil is usually chosen (**evidence level 5*).

The value of proliferation index is unquestionably a prognostic factor (Ki-67 > 10% — worse prognosis). The predictive value of increased proliferation index — considered as an additional factor while deciding on the chemotherapy treatment — requires confirmation in prospective studies (retrospective analyses of previous studies suggest a higher probability of response in patients with increased Ki-67 value) [130].

In patients with pancreatic NEN (PNEN), it is now possible to use new, molecularly targeted medicines, including primarily two available medicines, everolimus and sunitinib, which are treatment options in advanced disease. They are discussed in the section on recommendations for PNENs (*pp. 459–479*).

Poorly-differentiated neoplasms (G3) — neuroendocrine carcinomas

Chemotherapy is the basic method of palliative treatment in advanced, poorly-differentiated NENs (G3). A standard procedure in the case of disease progression following the surgical treatment of poorly-differentiated GEP NENs, incomplete surgical procedure or metastases, is chemotherapy with cisplatin and etoposide-based regimens, which results in an objective response in 40–70% of patients (including complete response in approximately 20–25% of patients), with mean survival of 12–15 months [131] (**evidence level 3*).

This regimen, modified by introduction of a third medicine (paclitaxel) and the substitution of cisplatin with carboplatin, results in response and survival extension in a large group of patients, but at the same time significantly increases the risk of myelotoxicity [126]. In clinical practice, it is not recommended to use other regimens (e.g. cisplatin and irinotecan, or oxaliplatin and fluorouracil with calcium folinate) as the first-line treatment. Implementation of the second-line chemotherapy (after progression following therapy with cisplatin and etoposide) may be individually considered only in patients with good function; in the case of a long-term response to the first-line therapy, it may be considered to repeat this therapy; in resistant patients another chemotherapy regimen can be introduced (**evidence level 4*) for the use of irinotecan, 5-fluorouracil and sodium folinate [132].

In neuroendocrine carcinoma (NEC), introduction of adjuvant therapy may be considered in patients undergoing radical surgical treatment. In patients with small cell G3 neoplasms, adjuvant chemotherapy based on platinum analogues should be standard procedure — it seems, although there are no randomised studies, that in this group of patients, by analogy to small cell lung carcinoma, chemotherapy including cisplatin (or carboplatin) with etoposide may prolong disease-free survival (**evidence level 4*). In some cases, certain groups of experts recommend also using adjuvant radiotherapy, although here there is no conclusive evidence either for the benefits of such treatment — this therapy may be considered in patients after radical resections of locally advanced NECs, e.g. of the stomach or rectum, but the decision must be highly individualised.

Similarly, a highly individualised therapeutic decision must be made in the case of indications for adjuvant chemotherapy in patients with large cell neuroendocrine carcinoma — this applies to a large proportion of all neuroendocrine tumours.

** evidence level according to CEBM [145]*

Minimal consensus statement on chemotherapy and targeted therapy:

— *Advanced G1/G2 NENs — systemic chemotherapy including streptozocin with doxorubicin (± 5-FU) (*evidence level 3).*
— *If the disease progresses after chemotherapy, everolimus or sunitinib (± SSA) in pancreatic NENs (*evidence level 1).*
— *The basic treatment of NEC is chemotherapy based on the cisplatin plus etoposide regimen (*evidence level 3).*

3.4. Radioisotope treatment

3.4.1. Peptide Receptor Radionuclide Therapy (PRRT)

Patients with advanced, non-surgical GEP NENs are qualified for isotope treatment. There are no indications for isotope treatment as an adjuvant therapy following radical surgical management.

Isotope-labelled SSA and metaiodobenzylguanidine are used in the isotope therapy of NENs.

A. Treatment with isotope-labelled SSA

Previous experience in isotope therapy of GEP NENs comprises mostly the use of DOTA-Tyr3-octreotide and DOTA-Tyr3-octreotate labelled with the isotopes ^{177}Lu, ^{90}Y, or a combination of the two. Data from non-randomised clinical studies indicates that a response to treatment (complete or partial remission) can be achieved in approximately 8–46% of patients, and the mean progression-free survival after the treatment is 25 to 36 months [133–141]. These studies apply mostly to patients with well-differentiated neoplasms (G1 and G2), and these recommendations are for this group of patients. Presently, no results of prospective, randomised clinical studies are available to assess the effectiveness of the therapy with isotope-labelled SSA (a study comparing the effectiveness of ^{177}Lu + octreotide *v.* octreotide is in progress).

Patients with intensive collection of tracer in all the neoplastic foci, in the case of small lesions with homogenous tracer collection, are good candidates for the treatment. If not all of the neoplastic foci collect radiopeptide and/or large foci of necrosis are found, the aim of the treatment is a palliative effect in the form of extended progression-free survival, and reduction of the neoplastic disease symptoms (e.g. pain, carcinoid syndrome symptoms). In individual cases, isotope therapy as a neoadjuvant treatment may be considered in order to reduce the tumour mass before the surgical treatment [142].

Qualification for the treatment with isotope-labelled SSA

Qualified for the treatment with isotope-labelled SSA are patients with well-differentiated NENs, which demonstrate high somatostatin receptor expression confirmed by receptor scintigraphy SPECT or PET/CT examination — collection should be at least comparable with a collection of radiotracer in the healthy liver, or higher [137].

Exclusion criteria for PRRT treatment

1. Patients younger than 18 years.
2. Pregnant patients (a negative pregnancy test is required).
3. Assessment of the patient's performance status (PS) according to the WHO classification PS status 3 or 4, or according to Karnofsky classification (< 60).
4. Abnormal blood test results:
   — Hb < 8g/dL,
   — platelets < 80x10^3/μL,
   — WBC < 2x10^3/μL*,
   — Lymphocytes < 0.5x10^3/μL,
   — Neutrocytes below 1x10^3/μL,
   — Renal failure (GFR < 30 mL/min)*, BUN > 45 mg/dL; creatinine > 150 μmol/L
   — Liver failure (bilirubin > 30 μL/min.)*.

Due to increased risk of adverse reactions, patients with leukocytosis < 3,000, neutropoenia < 1,500, thrombocytopoenia < 100,000 and creatinine clearance < 60 mg/mL, should be qualified for the treatment individually [137, 139].

Qualification tests before starting the PRRT:

Neuroendocrine tumour confirmed by histopathological examination or biopsy:

— Positive result of receptor scintigraphy with labelled somatostatin receptors within 12 weeks from starting the therapy, in order to assess the radioisotope collection in the lesions;
— Before the therapy, or within three weeks of it starting, the patient should undergo a multiphase CT examination, or, alternatively, a dynamic MR examination to assess the extent of the disease;
— GFR assessment (in non-conclusive cases, assessment based on a scintigraphic examination is recommended);
— Before the treatment, the patient should have the following laboratory tests:
  • Complete blood count with a smear,
  • Urea and creatinine, uric acid, with biochemical assessment of GFR,
  • ALAT, ASPAT,
  • CgA,
  • Other laboratory tests according to the clinical stage,

** evidence level according to CEBM [145]*

- Patient's informed consent for the treatment is required.

Depending on the dosimetric data, the therapy may be conducted in out-patient settings; in special cases, determined by the clinical condition, it may take place in hospital [139].

Isotope treatment regimens

Treatment is usually conducted in 4-5 cycles, with intervals of 6–12 weeks, with the use of SSA labelled with ^{90}Y ^{177}Lu, or ^{90}Y/^{177}Lu. During isotope treatment, it is necessary to administer intravenously a solution of amino acids for radioprotection of the kidneys [137, 139].

There is no conclusive evidence that treatment with octreotide/lanreotide reduces the effectiveness of isotope-labelled SSA therapy. This therapy should not be discontinued during isotope treatment; however, it would be best if the interval between administrations of a long-acting analogue was 4–7 weeks. If the treatment with a SSA needs to be continued, short-acting analogues are recommended [140].

Side-effects of the treatment with isotope-labelled SSA

The side effects of the treatment mostly affect the haematopoietic system and kidneys. Possible adverse reactions should be monitored. The risk of post-radiation damage to the kidneys is reduced by intravenous administration of positively charged amino acids — L-lysine + + arginine — prior to the treatment. Patients with carcinoid syndrome, who may experience carcinoid crisis during therapy, require special attention. Short-acting SSA should be used with these patients [141,142].

Retreatment with isotope-labelled SSA

In the case of progression after achieving a long-lasting, good effect of isotope therapy, retreatment may be considered [141].

Depending on dosimetric data, the therapy may be conducted in out-patient settings; in special cases determined by the patient's clinical condition, it may take place in hospital conditions.

3.4.2. Treatment with ^{131}I-mIBG

Treatment with ^{131}I-mIBG may be considered in patients with negative receptor scintigraphy results, and m-IBG collection in the tumour and/or in the metastases. This treatment is primarily palliative, and enables reduction of pain and carcinoid syndrome symptoms. A treatment with radical intention is rarely possible [143, 144]. Contraindications for the therapy include bone marrow suppression (according to the above criteria). In patients with a functional thyroid gland, it is necessary to block the uptake of free iodine 131 not bound with mIBG carrier (Lugol's solution or sodium perchlorate may be used).

Qualification for isotope treatment

Basic tests performed to qualify a patient for isotope treatment include diagnostic ^{131}I-mIBG scintigraphy, and comparing the location of tracer collection with locations of metastatic foci in a CT or MR examination, complete blood count with a smear, and liver and kidney function tests, including creatinine clearance [141, 142].

3.4.3. Evaluation of therapy effects

Evaluation of therapy effects should include morphological examinations (e.g. CT, MR) and functional tests (scintigraphy/receptor PET) three months after the treatment, then every six months for two years. Further supervision depends on the clinical course of the disease. The optimal criteria for evaluation of the therapy effects are still under discussion [140].

3.4.4. Place of isotope treatment in the therapy of advanced neuroendocrine neoplasms

The literature does not offer conclusive data on the GEP NEN treatment stage at which isotope treatment should be considered. Progression of the neoplastic disease is an indication for the implementation of cytotoxic therapy (chemotherapy/radiotherapy/targeted therapy), but there are no studies evaluating which of these is the most effective as the first-line treatment.

It seems that location of the primary focus and high expression of somatostatin receptors should be taken into account. In patients with a high somatostatin receptor expression, depending on the stage of the disease, PPRT may be considered as the first-line treatment [138, 140].

3.5. Summary

Treatment of patients with non-surgical GEP NENs should be conducted using isotope-labelled (^{177}Lu and ^{90}Y) SSA (**evidence level 3*).

Treatment of patients with non-surgical GEP NENs with negative receptor scintigraphy results should be conducted using ^{131}I-mIBG (**evidence level 3*).

Minimal consensus statement on radioisotope treatment:

*PPRT may be considered as the first-line treatment in patients with high somatostatin receptor expression, depending on the stage of the disease (*evidence level 4).*

** evidence level according to CEBM [145]*

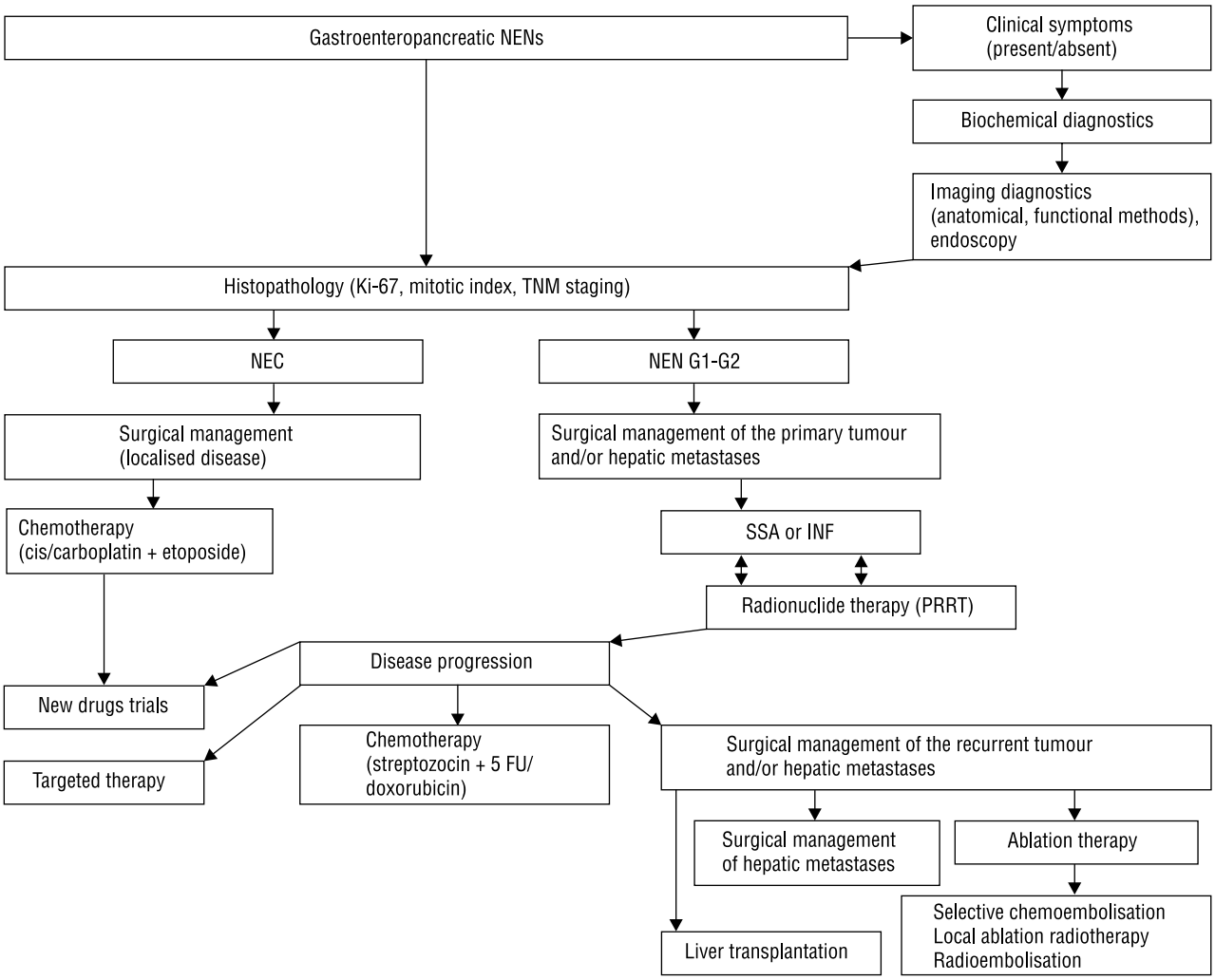

Figure 4. *Proposed algorithm of management in GEP NEN*
Rycina 4. *Proponowany algorytm postępowania w GEP NEN*

4. Follow-up

Monitoring of the treatment should include clinical examinations, laboratory tests (CgA) and imaging methods.

It is recommended to monitor the disease by means of imaging examinations, such as USG, MR and CT, endoscopic examinations, and determination of biochemical markers (CgA) every 6–12 months in G1-G2 NETs. Functional imaging (SRS or ^{68}Ga PET/TC) should be performed 4–6 months after the surgical treatment. In NETs demonstrating somatostatin receptor expression, it should be repeated every 12–24 months and in further follow-up depends on the tumour clinical advancement and location.

In patients with NEC, imaging examinations should be performed every 3–6 months, depending on the course of the disease.

References

1. Plöckinger U, Rindi G, Arnold R et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. Neuroendocrinology 2004; 80: 394–424.
2. 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.
3. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003; 97: 934–959.
4. Öberg K, Knigge U, Kwekkebom D et al. On behalf of the ESMO guidelines working group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23: 124–130.
5. Haselkorn T, Whittemore AS, Lilienfeld DE. Incidence of small bowel cancer in the United States and worldwide: geographic, temporal, and racial differences. Cancer Causes Control 2005; 16: 781–787.
6. Bordi C, D'Adda T, Azzoni C et al. Biological and molecular aspects of gastroenteropancreatic neuroendocrine tumors. W: Baldelli R, Casanueva FF, Tamburrano G, red. Udine Centro UD 2004: 65–96.
7. Kajdaniuk D, Marek B, Foltyn W et al. Vascular endothelial growth factor (VEGF) - part 2: in endocrinology and oncology. Endokrynol Pol 2011; 62: 456–464.
8. Ramage JK, Ahmed A, Ardill J et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012; 61: 6–32.

9. Blicharz-Dorniak J, Kos-Kudła B, Foltyn W et al. Is determination of matrix metalloproteinases and their tissue inhibitors serum concentrations useful in patients with gastroenteropancreatic and bronchopulmonary neuroendocrine neoplasms? Endokrynol Pol 2012; 63: 470–476.
10. Duerr EM, Mizukami Y, Ng A et al. Defining molecular classifications and targets in gastroenteropancreatic neuroendocrine tumors through DNA microarray analysis. Endocr Relat Cancer 2008; 15: 243–256.
11. Kidd M, Modlin IM, Mane SM et al. Utility of molecular genetic signatures in the delineation of gastric neoplasia. Cancer 2006; 106: 1480–1488.
12. Kos-Kudła B, Bolanowski M, Handkiewicz-Junak D et al. Diagnostic and therapeutic guidelines for gastrointestinal neuroendocrine tumors (recommended by the polish network of neuroendocrine tumors). Endokrynol Pol 2008; 59: 41–56.
13. Glinicki P, Jeske W. Chromogranin A (CgA)-the influence of various factors in vivo and in vitro, and existing disorders on it's concentration in blood. Endokrynol Pol 2010; 61: 384–387.
14. Lawrence B, Gustafsson BI, Kidd M et al. The clinical relevance of chromogranin A as a biomarker for gastroenteropancreatic neuroendocrine tumors. Endocrinol Metab Clin North Am 2001; 40: 111–134.
15. Kanakis G, Kaltsas G. Biochemical markers for gastroenteropancreatic neuroendocrine tumours (GEP-NETs). Best Pract Res Clin Gastroenterol 2012; 26: 791–802.
16. Glinicki P, Kapuścińska R, Jeske W. The differences in chromogranin A (CgA) concentrations measured in serum and in plasma by IRMA and ELISA methods. Endokrynol Pol 2010; 61: 346–350.
17. Witkowska A, Jańczyk A, Nyckowski P et al. Elevated serum chromogranin A patient with incidentally detected tumors in the caudate lobe of the liver plan. Endokrynol Pol 2012; 63 (Suppl 3): 7–8.
18. Telega A, Kos-Kudła B, Foltyn W et al. Selected neuroendocrine tumour markers, growth factors and their receptors in typical and atypical bronchopulmonary carcinoids. Endokrynol Pol 2012; 63: 477–482.
19. Bednarczuk T, Dębski M., Chojnowski K. et al. Przełom rakowiaka. Medycyna Praktyczna 2009; 216: 164–169.
20. Kos-Kudła B, Zemczak A. Contemporary methods of diagnosis and treatment of neuroendocrine gastrointestinal tumors. Endokrynol Pol 2006; 57: 174–186.
21. Yao JC, Pavel M, Phan AT et al. Chromogranin A and neuron-specific enolase as prognostic markers in patients with advanced pNET treated with everolimus. J Clin Endocrinol Metab 2011; 96: 3741–3749.
22. Thakker RV, Newey PJ, Walls GV et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012; 97: 2990–3011.
23. Rosiek V, Kunikowska J, Kos-Kudła B. A non-functioning pancreatic neuroendocrine tumour: a case report. Endokrynol Pol 2012; 63: 59–64.
24. Gaztambide S, Vazquez F, Castaño L. Diagnosis and treatment of multiple endocrine neoplasia type 1 (MEN1). Minerva Endocrinol 2013; 38: 17–28.
25. Kajdaniuk D, Marek B, Borgiel-Marek H et al. Transforming growth factor β1 (TGFβ1) in physiology and pathology. Endokrynol Pol 2013; 64(5): 384–396.
26. Bosman FT, Carneiro F, Hruban RH et al. WHO Classification of Tumours of the Digestive System. IARC: Lyon 2010: 13–14.
27. Klimstra DES, Modlin IR, Adsay NV et al. Pathology Reporting of Neuroendocrine Tumors: Application of the Delphic Consensus Process to the Development of a Minimum Pathology Data Set. Am J Surg Pathol 2010; 34: 300–313.
28. 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.
29. Klimstra DS, Modlin IR, Coppolla D et al. The Pathologic Classification of Neuroendocrine Tumors. A Review of Nomenclature, Grading, and Staging System. Pancreas 2010; 39: 707–712.
30. Kloppel G, Rindi G, Perren A et al. The ENETS and AJCC/UICC TNM classifications of the neuroendocrine tumors of the gastrointestinal tract and the pancreas: a statement. Virchows Arch 2010; 456: 595–597.
31. Kvols L.K., Brendtro K.L. The North American Neuroendocrine Tumor Society (NANETS) Guidelines. Pancreas 2010; 39: 705–706.
32. Maroun J, Kocha W, Kvols L et al. Guidelines for the diagnosis and management of carcinoid tumours. Part 1: The gastrointestinal tract. A statement from a Canadian National Carcinoid Expert Group. Current Oncology 2010; 13: 67–76.
33. Nasierowska-Guttmejer A. Patomorfologia guzów neuroendokrynnych układu pokarmowego. Onk po Dyplomie 2005: 25–30.
34. Nasierowska-Guttmejer A, Malinowska M. Guzy neuroendokrynne układu pokarmowego (GEP/NET) — dyskusja wokół nazewnictwa i klasyfikacji. Przegl Gastroenterol 2006; 1: 1–4.
35. Nasierowska-Guttmejer A. Nowa klasyfikacja NET. Onco Review 2011: 1: 46–50.
36. Oberg K, Akerstrom G, Rindi G et al. Neuroendocrine gastroenteropancreatic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 (Suppl. 5): 223–227.
37. Rindi G, Arnold R, Bosman FT et al. TNM staging of foregut (neuro) endocrine tumors; a consensus proposal including a grading system. Virchows Arch 2006; 449: 393–401.
38. Rindi G, de Herder WW, O'Toole D et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumors: why such guidelines and how we went about it. Neuroendocrinology 2006: 84: 155–157.
39. Rindi G, de Herder WW, O'Toole D et al. Consensus guidelines for the management of patients with digestive neuroendocrine tumors: the second event and some final consideration. Neuroendocrinology 2008: 87: 5–7.
40. Sundin A, Vullierme MP, Kaltsas G et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: radiological examinations Neuroendocrinology 2009; 90: 167–183.
41. Kwekkeboom D, Krenning E, Scheidhauer K et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Somatostatin Receptor Imaging with 111 In-Pentetreotide Neuroendocrinology 2009; 90: 184–189.
42. Gabriel M, Decristoforo C, Kendler D et al. 68Ga-DOTA-Tyr3-Octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med 2007; 48: 508–518.
43. Fanti S, Ambrosini V, Tomassetti P et al. Evaluation of unusual neuroendocrine tumours by means of 68Ga-DOTA-NOC PET. Biomedicine & Pharmacotherapy 2008; 62: 667–671.
44. Chiti A, Fanti S, Savelli G et al. Comparison of somatostatin receptor imaging, computed tomography and ultrasound in the clinical management of neuroendocrine gastro-entero- pancreatic tumours. Eur J Nucl Med 1998; 25: 1396–1403.
45. Zimmer T, Ziegler K, Bader M, Fett U, Hamm B, Riecken EO, Wiedenmann B: Localisation of neuroendocrine tumours of the upper gastrointestinal tract. Gut 1994; 35: 471–475.
46. Zimmer T, Stolzel U, Bader M et al. Endoscopic ultrasonography and somatostatin receptor scintigraphy in the preoperative localisation of insulinomas and gastrinomas. Gut 1996; 39: 562–568.
47. Angeli E, Vanzulli A, Castrucci M et al. Value of abdominal sonography and MR imaging at 0.5 T in preoperative detection of pancreatic insulinoma: a comparisonwith dynamic CT and angiography. Abdom Imaging 1997; 22: 295–303.
48. De Angelis C, Carucci P, Repici A et al. Endosonography in decision-making and management of gastrointestinal endocrine tumors. Eur J Ultrasound 1999; 10: 139–150.
49. Gouya H, Vignaux O, Augui J et al. CT, endoscopic sonography, and a combined protocol for preoperative evaluation of pancreatic insulinomas. Am J Roentgenol 2003; 181: 987–992.
50. Anderson MA, Carpenter S, Thompson N et al. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. Am J Gastroenterol 2000; 95: 2271–2277.
51. Hoeffel C, Job L, Ladam-Marcus V et al. Detection of hepatic metastases from carcinoid tumor: prospective evaluation of contrast-enhanced ultrasonography. Dig Dis Sci 2009; 54: 2040–2046.
52. Canto MI, Goggins M Hoeffel C et al. Detection of hepatic metastases from carcinoid tumor: prospective evaluation of contrast-enhanced ultrasonography. Dig Dis Sci 2009; 54: 2040–2046.
53. Nelson H, Petrelli N, Carlin A. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst 2001; 93: 583–596.
54. Hiramoto JS, Feldstein VA, LaBerge JM et al. Intraoperative ultrasound and preoperative localization detects all occult insulinomas. Arch Surg 2001; 136: 1020–1026.
55. Mork H, Ignee A, Schuessler G et al. Analysis of neuroendocrine tumour metastases in the liver using contrast-enhanced ultrasonography. Scand J Gastroenterol 2007; 42: 652–662.
56. Yamao K, Nakamura T, Suzuki T et al. Endoscopic diagnosis and staging of mucinous cystic neoplasms and intraductal papillary-mucinous tumors. J Hepatobiliary Pancreat Surg 2003; 10: 142–146.
57. Yasuda K, Sakata M, Ueda M et al. The use of pancreatoscopy in the diagnosis of intraductal papillary mucinous tumor lesions of the pancreas. Clin Gastroenterol Hepatol 2005; 3: 53–57.
58. Attili F, Capurso G, Vanella G et al. Diagnostic and therapeutic role of endoscopy in gastroenteropancreatic neuroendocrine neoplasms. Dig Liver Dis 2013; 1590–8658.
59. Neumann H, Fry LC, Neurath F. Review article on current applications and future concepts of capsule endoscopy. Digestion 2013; 87: 91–97.
60. Fukumoto A, Manabe N, Tanaka S et al. Usefulness of EUS with double-balloon enteroscopy for diagnosis of small-bowel disease. Gastrointest Endosc 2007; 65: 412–420.
61. Domagk D, Bretthauer M, Lenz P et al. Carbon dioxide insufflation improves intubation depth in double-balloon enteroscopy: a randomized, controlled, double-blind study. Endoscopy 2007; 39: 1064–1067.

62. May A, Nachbar L, Pohl J et al. Endoscopic interventions in the small bowel using double balloon enteroscopy: feasibility and limitations. Am J Gastroenterol 2007; 102: 527–535.
63. Kopacova M, Rejchrt S, Tacheci I et al. Hyperamylasaemia of uncertain significance associated with oral double-balloon enteroscopy. Gastrointest Endosc 2007; 66: 1133–1138.
64. Milewski J, Rydzewska G. Enteroskopia dwubalonowa — nowa technika diagnostyki i terapii endoskopowej chorób jelita cienkiego. Przegl Gastroenterol 2006; 1: 54–59.
65. Kosmala W, Milewski J, Rydzewska G. Cztery lata doświadczeń w enteroskopii dwubalonowej na świecie. Przegl Gastroenterol 2007; 2: 305–310.
66. Rossi P, Baert A, Passariello R et al. CT of functioning tumors of the pancreas. AJR Am J Roentgenol 1985; 144: 57–60.
67. Van Hoe L, Gryspeerdt S, Marchal G et al. Helical CT for the preoperative localization of islet cell tumors of the pancreas: value of arterial and parenchymal phase images. AJR Am J Roentgenol 1995; 165: 1437–1439.
68. Procacci C, Carbognin G, Accordini S et al. Nonfunctioning endocrine tumors of the pancreas: possibilities of spiral CT characterization. Eur Radiol 2001; 11: 1175–1183.
69. Fidler JL, Fletcher JG, Reading CC et al. Preoperative detection of pancreatic insulinomas on multiphasic helical CT. AJR Am J Roentgenol 2003; 181: 775–780.
70. Kumbasar B, Kamel IR, Tekes A, Eng J, Fishman EK, Wahl RL. Imaging of neuroendocrine tumors: accuracy of helical CT versus SRS. Abdom Imaging 2004; 29: 696–670.
71. Cwikła JB, Buscombe JR, Caplin ME et al. Diagnostic imaging of carcinoid metastases to the abdomen and pelvis. Med Sci Monit 2004; 10: 9–16.
72. Vinning DJ, Gelfand DW, Bechtold RE et al. Technical feasibility of colon imaging with helical CT and virtual reality. Am J Roentgenol 1994; 162: 104.
73. Fletcher JG, Lumboldt W. CT colonography current status, research directions and comparision. Eur Radiol 2000; 10: 786–801.
74. Gluecker TM, Johnson CD, Harmsen WS et al. Colorectal cancer screening with CT colonography, colonoscopy, and double-contrast barium enema examination: prospective assessment of patient perceptions and preferences. Radiology 2003; 227: 378–384.
75. Johnson CD, Chen MH, Toledano AY et al. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med 2008; 359: 1207–1217.
76. Regge D, Laudi C, Galatola G et al. Diagnostic accuracy of computed tomographic colonography for the detection of advanced neoplasia in individuals at increased risk of colorectal cancer. JAMA 2009; 301: 2453–2461.
77. Ginnerup Pedersen B, Rosenkilde M, Christiansen TE et al. Extracolonic findings at computed tomography colonography are a challenge. Gut 2003; 52: 1744–1747.
78. Kaltsas G, Rockall A, Papadogias D et al. Recent advances in radiological and radionuclide imaging and therapy of neuroendocrine tumours. Eur J Endocrinol 2004; 151: 15–27.
79. Thoeni RF, Mueller-Lisse UG, Chan R et al. Detection of small, functional islet cell tumors in the pancreas: selection of MR imaging sequences for optimal sensitivity. Radiology 2000; 214: 483–490.
80. Dromain C, de Baere T, Lumbroso J et al. Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. J Clin Oncol 2005; 23: 70–78.
81. Reguła J, Rupiński M, Kraszewska E et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med 2006; 355: 1863–1872.
82. Leszczyński S, Pilch-Kowalczyk J. Diagnostyka obrazowa układ trawienny PZWL 2012.
83. Reubi JC, Schar JC, Waser B et al. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med 2000; 27: 273–282.
84. Krenning EP, Kwekkeboom DJ, Oei HY et al. Somatostatin-receptor scintigraphy in gastroenteropancreatic tumors. An overview of European results. Ann N Y Acad Sci 1994; 733: 416–424.
85. Decristoforo C, Mather SJ, Cholewinski W et al. 99mTc-EDDA/HYNIC-TOC: a new 99mTc-labelled radiopharmaceutical for imaging somatostatin receptor-positive tumours; first clinical results and intra-patient comparison with 111In-labelled octreotide derivatives. Eur J Nucl Med 2000; 27: 1318–1325.
86. Hubalewska A, Fröss K, Mikołajczak R et al. 99mTc-EDDA/HYNIC TATAE scintigraphy: A method for diagnosis and staging of NET? Medimond 2004: 1483–1487.
87. Hubalewska-Dydejczyk A, Frass-Baron K, Mikolajczak R et al. 99mTc-EDDA/HYNIC-octreotate scintigraphy, an efficient method for the detection and staging of carcinoid tumours: results of 3 years' experience. Eur J Nucl Med Mol Imaging 2006; 33: 1123–1133.
88. Hubalewska-Dydejczyk A, Sowa-Staszczak A, Tomaszuk M. Comment on: Somatostatin receptor SPECT. Eur J Nucl Med Mol Imaging 2012; 39: 1656–1657.
89. Krausz Y, Freedman N, Rubinstein R et al. 68Ga-DOTA-NOC PET/CT imaging of neuroendocrine tumors: comparison with ^{111}In-DTPA-octreotide (OctreoScan®). Mol Imaging Biol 2011; 13: 583–593.
90. Virgolini I, Ambrosini V, Bomanji JB et al. Procedure guidelines for PET/CT tumour imaging with 68Ga-DOTA-conjugated peptides: 68Ga-DOTA-TOC, 68Ga-DOTA-NOC, 68Ga-DOTA-TATE. Eur J Nucl Med Mol Imaging 2010; 37: 2004–2010.
91. 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.
92. Balogova S, Talbot JN, Nataf V et al. 18F-fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type. Eur J Nucl Med Mol Imaging 2013; 40: 943–966.
93. Scanga DR, Martin WH, Delbeke D. Value of FDG PET imaging in the management of patients with thyroid, neuroendocrine, and neural crest tumors. Clin Nucl Med 2004; 29: 86–90.
94. Severi S, Nanni O, Bodei L et al. Role of 18FDG PET/CT in patients treated with 177Lu-DOTATATE for advanced differentiated neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2013; 40: 881.
95. Koopmans KP, Neels ON, Kema IP et al. Molecular imaging in neuroendocrine tumors: Molecular uptake mechanisms and clinical results. Crit Rev in Oncol Hematol 2009; 71: 199–213.
96. Cwikla JB, Nasierowska-Guttmejer A, Jeziorski KG et al. Diagnostic imaging approach to gastro-entero-pancreatic carcinomas of neuroendocrine origin — single NET center experience in Poland. Neuro Endocrinol Lett 2007; 28: 789–800.
97. Rufini V, Calcagni ML, Baum RP. Imaging of neuroendocrine tumors. Semin Nucl Med 2006; 36: 228–247.
98. Kos-Kudła B, Ćwikła J, Jarząb et al. Polish diagnostic and therapeutic guidelines in gastroenteropancreatic neuroendocrine tumors (GEP NET). Endokrynol Pol 2006; 57: 267–272.
99. Lee SY, Cheow PC, Teo JY et al. Surgical treatment of neuroendocrine liver metastases. Int J Hepatol 2012; 2012: 146590.
100. Öberg K, Knigge U, Kwekkeboom et al. Neuroendocrine gastro-enteropancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23 (Suppl. 7): 124–130.
101. Szawłowski AW. Zasady rozpoznawania i leczenia nowotworów złośliwych.W: Noszczyk W (red.). Chirurgia. Tom I. Wyd. PZWL, Warszawa 2005: 123–134.
102. Le Treut Y.P, Gregoire E, Klempnauer J et al. Liver transplantation for neuroendocrine tumors in Europe — results and trends in patient selection. Ann Surg 2013; 257: 807–815.
103. Gu P, Wu J, Newman E et al. Treatment of liver metastases in patients with neuroendocrine tumors of gastroesophageal and pancreatic origin. Int J Hepatolog 2012; 10: 1155–1163.
104. Kudo A, Ban D, Akashi T et al. Prognoses of GEP-Nets with undetermined malignant potentials of their primary Sites. Hepato-Gastroenterol 2012; 59: 1682–1686.
105. Pavel M, Baudin E, Couvelard A et al. ENETS Consensus guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgu, and unknown primary. Neuroendocrinology 2012; 95: 157–176.
106. Gedaly R, Daily MF, Davenport D et al. Liver transplantation for the treatment of liver metastases from neuroendocrine tumors: an analysis of the UNOS database. Arch Surg 2011; 146: 953–958.
107. Máthé Z, Tagkalos E, Paul A et al. Liver transplantation for hepatic metastases of neuroendocrine pancreatic tumors: a survival-based analysis. Transplantation 2011; 91: 575–582.
108. Fendrich V, Bartsch DK. Surgical treatment of gastrointestinal neuroendocrine tumors. Langenbecks Arch Surg 2011; 396: 299–311.
109. Kiran K. Turaga KK, Kvols LK. Recent progress in the understanding, diagnosis, and treatment of gastroenteropancreatic neuroendocrine tumors. CA: A Cancer Journal for Clinicians 2011; 61: 113–132.
110. De Angelis C, Pellicano R, Rizzetto M et al. Role of endoscopy in the management of gastroenteropancreatic neuroendocrine tumours. Minerva Gastroenterol Dietol 2011; 57: 129–137.
111. Arnold R, Chen YJ, Costa F et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: follow-up and documentation. Neuroendocrinology 2009; 90: 227–233.
112. Antillon MR, Chen Y. Leczenie endoskopowe nowotworów żołądka. W: Ginsber G, Kochman ML, Norton J, Gostout ChJ (eds.) Kliniczna endoskopia przewodu pokarmowego. Medipage, Warszawa 2009: 533–560.
113. Gotoda T, Kondo H, Ono H et al. A new endoscopic mucosal resection (EMR) procedure using an insulation-tipped diathermic (IT) knife for rectal flat lesions. Gastrointest Endosc 1999; 50: 560–563.
114. Öberg 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.

115. Melen-Mucha G, Lawnicka H, Kierszniewska-Stepien D et al. The place of somatostatin analogs in the diagnosis and treatment of the neuoroendocrine glands tumors. Recent Pat Anticancer Drug Discov 2006; 1: 237–254.
116. Öberg K. Chemotherapy and biotherapy in the treatment of neuroendocrine tumors. Ann Oncol 2001; (Suppl. 2): 111–114.
117. Jawiarczyk A, Bolanowski M, Syrycka J et al. Effective therapy of insulinoma by using long-acting somatostatin analogue. A case report and literature review. Exp Clin Endocrinol Diabetes 2012; 120: 68–72.
118. Rinke A, Muller HH, Schade-Brittinger C et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009; 27: 4656–4663.
119. Eriksson B, Oberg K, Stridsberg M. Tumor markers in neuroendocrine-tumours. Digestion 2000; 62 (Supl. 1): 33–38.
120. Caplin A, Ruszniewski P, Pavel M et al. A randomized double-blind palcebo controlled study with lanreotide antyproliferative response in patinets with gastroneteropancreatic neuroendocrine tumors (CLARINET) Eur J Cancer 2013; 49 (Suppl. 3): S3.
121. Falconi M, Plockinger U, Kwekkeboom DJ et al. Well-differentiated pancreatic nonfunctioning tumors/carcinoma. Neuroendocrinology 2006; 84: 196–211.
122. Nehar D, Lombard-Bohas C, Olivieri S et al. Interest of Chromogranin A for diagnosis and follow-up of endocrine tumours. Clin Endocrinol (Oxf) 2004; 60: 644–652.
123. Deptała A, Asendrych A, Omyla-Staszewska J et al. Rola terapii systemowej w leczeniu guzów neuroendokrynnych układu pokarmowego. Przegląd Gastroenterol 2006; 1: 10–15.
124. Sun W, Lipsitz S, Catalano P et al. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group study E1281. J Clin Oncol 2005; 23: 4897–4904.
125. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. N Eng J Med 1980; 303: 1189–1194.
126. Moertel CG, Lefkopoulo M, Lipsitz S et al. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Eng J Med 1992; 326: 519–523.
127. O'Toole D et al. Handbook of GEP and Thoracic NET 2011: 131–134.
128. Delaunoit T, Ducreux M, Boige V et al. The doxorubicin-streptozotocin combination for the treatment of advanced well-differentiated pancreatic endocrine carcinoma: a judicious opinion? Eur J Cancer 2004; 40: 515–520.
129. Kouvaraki MA, Ajani JA, Hoff P et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 2004; 22: 4710–4719.
130. Vilar E, Salazar R, Perez-Garcia J et al. Chemotherapy and role of the proliferation marker Ki-67 in digestive neuroendocrine tumors. Endocr Relat Cancer 2007; 14: 221–232.
131. Hainsworth JD, Spigel DR, Litchy S et al. Phase II trial of paclitaxel, carboplatin, and etoposide in advanced poorly differentiated neuroendocrine carcinoma: a Minnie Pearl Cancer Research Network study. J Clin Oncol 2006; 24: 3548–3554.
132. Hentic O, Couvelard A, Rebours V et al. Ki-67 index, tumor differentiation, and extent of liver involvement are independent prognostic factors in patients with liver metastases of digestive endocrine carcinomas. Endocr Relat Cancer 2010; 18: 51–59.
133. Paganelli G, Bodei L, Handkiewicz Junak D et al. 90Y-DOTA-D-Phe1-Try3-octreotide in therapy of neuroendocrine malignancies. Biopolymers 2002; 66: 393–398.
134. Kwekkeboom DJ, Teunissen JJ, Bakker WH et al. Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. J Clin Oncol 2005; 23: 2754–2762.
135. Sowa-Staszczak A, Pach D, Kunikowska J et al. Efficacy and safety of 90Y-DOTATATE therapy in neuroendocrine tumours. Endokrynol Pol 2011; 62: 392–400.
136. Bodei L, Cremonesi M, Grana CM et al. Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging 2011; 38: 2125–2135.
137. Imhof A, Brunner P, Marincek N et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol 2011; 29: 2416–2422.
138. Filice A, Fraternali A, Frasoldati A et al. Radiolabeled somatostatin analogues therapy in advanced neuroendocrine tumors: a single centre experience. J Oncol 2012; 2012: 320198.
139. Pach D, Sowa-Staszczak A, Kunikowska J et al. Repeated cycles of peptide receptor radionuclide therapy (PRRT)-results and side-effects of the radioisotope 90Y-DOTA TATE, 177Lu-DOTA TATE or 90Y/177Lu-DOTA TATE therapy in patients with disseminated NET. Radiother Oncol 2012; 102: 45–50.
140. Kunikowska J, Królicki L, Sowa-Staszczak A et al. Polish experience in Peptide receptor radionuclide therapy. Recent Results Cancer Res 2013; 194: 467–478.
141. Vinjamuri S, Gilbert TM, Banks M et al. Peptide receptor radionuclide therapy with (90)Y-DOTATATE/(90)Y-DOTATOC in patients with progressive metastatic neuroendocrine tumours: assessment of response, survival and toxicity. Br J Cancer 2013; 108: 1440–1448.
142. Sowa-Staszczak A, Pach D, Stefańska A et al. Case report of a patient with initially inoperable well-differentiated midgut neuroendocrine tumor (WDNT)-PRRT and long-acting somatostatin analogs as the neoadjuvant therapy. Nucl Med Rev Cent East Eur 2012; 26; 15: 137–139.
143. 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.
144. Bomanji JB, Papathanasiou ND. ^{111}In-DTPA^{0}-octreotide (Octreoscan), ^{131}I-MIBG and other agents for radionuclide therapy of NETs. Eur J Nucl Med Mol Imaging 2012; 39 (Suppl. 1): S113–125.
145. 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.

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