DOI: https://doi.org/10.17816/onco642734 EDN: JONKLF

Current Management Strategies for Patients With Gastrointestinal and Pulmonary Neuroendocrine Tumors

Yuliya V. Mikheeva[1], Pavel O. Rumyantsev[2], Konstantin K. Puzakov[1], Konstantin Yu. Slashuk[3], Daniil D. Omelchuk[4], Anastasiya V. Potapenko[2], Sergey P. Medvedev[1]

[1] National Medical Research Centre "Treatment and Rehabilitation Centre", Moscow, Russia;
[2] BELOOSTROV Clinic of High Technologies, Saint Petersburg, Russia;
[3] Endocrinology Research Centre, Moscow, Russia;
[4] Doctor 03, Moscow, Russia

ABSTRACT

Neuroendocrine tumors (NETs) of the gastrointestinal tract and lungs are rare yet clinically significant neoplasms characterized by heterogeneous progression and diverse manifestations. This article systematizes current management strategies based on the latest recommendations and scientific advances. Epidemiological trends are a key focus, including an increase in NET incidence rates over the past few decades (6.4 times in the USA from 1973 to 2012) and the predominance of gastroenteropancreatic NETs (62–70%) and bronchopulmonary NETs (25%). The following key clinical aspects are highlighted, including hormonally active conditions (carcinoid syndrome, gastrinomas, insulinomas) and their complications (carcinoid heart disease and crises). Current approaches to diagnose, treatment, and monitoring of NETs are discussed using recent guidelines and scientific data. Molecular genetic testing is emphasized because of its ability to improve risk stratification and personalize treatment. The following treatment options are discussed: surgery (resection, liver transplantation); pharmacotherapy (somatostatin analogues, telotristat, and targeted therapies such as sunitinib and everolimus); chemotherapy; peptide receptor radionuclide therapy. The key study outcomes are presented. The article also addresses challenges in early diagnosis and the need for a multidisciplinary approach and personalized treatment. Promising areas of using novel biomarkers and imaging techniques are mentioned, and the importance of follow-up is emphasized, including follow-up intervals and watch and wait strategies for small tumors. The article discusses the challenges of early diagnosis and the importance of thorough tumor evaluations and explores prospects for further research to optimize treatment strategies.

Keywords: neuroendocrine tumors; epidemiology; diagnosis; treatment; theragnostics; follow-up.

To cite this article:
Mikheeva YuV, Rumyantsev PO, Puzakov KK, Slaschuk KYu, Omelchuk DD, Potapenko AV, Medvedev SP. Current Management Strategies for Patients With Gastrointestinal and Pulmonary Neuroendocrine Tumors. *Russian Journal of Oncology.* 2025;30(1):41–60. DOI: 10.17816/onco642734 EDN: JONKLF

Submitted: 10.12.2024 **Accepted:** 23.05.2025 **Published online:** 26.05.2025

DOI: https://doi.org/10.17816/onco642734 EDN: JONKLF

Современные алгоритмы ведения пациентов с нейроэндокринными опухолями желудочно-кишечного тракта и лёгких

Ю.В. Михеева[1], П.О. Румянцев[2], К.К. Пузаков[1], К.Ю. Слащук[3], Д.Д. Омельчук[4], А.В. Потапенко[2], С.П. Медведев[1]

[1] Национальный медицинский исследовательский центр «Лечебно-реабилитационный центр», Москва, Россия;
[2] Клиника высоких технологий «Белоостров» ММЦ-ВТ, Санкт-Петербург, Россия;
[3] Национальный медицинский исследовательский центр эндокринологии, Москва, Россия;
[4] ООО «Доктор 03», Москва, Россия

АННОТАЦИЯ

Нейроэндокринные опухоли желудочно-кишечного тракта и лёгких представляют собой редкую, но клинически значимую группу новообразований, характеризующихся гетерогенным течением и разнообразием клинических проявлений. В статье систематизированы современные алгоритмы ведения пациентов с учётом последних рекомендаций и научных достижений. Значительное внимание уделено эпидемиологическим тенденциям: рост заболеваемости нейроэндокринными опухолями за последние десятилетия (в 6,4 раза в США с 1973 по 2012 гг.), преобладание гастроэнтеропанкреатических (62–70%) и бронхолёгочных (25%) локализаций. Особый акцент сделан на ключевых клинических аспектах, включая гормонально-активные формы (карциноидный синдром, гастриномы, инсулиномы) и их осложнения (карциноидная болезнь сердца, кризы). В настоящей статье рассмотрены современные подходы к диагностике, лечению и мониторингу таких пациентов с учётом последних рекомендаций и научных данных. Особое внимание уделено молекулярно-генетическим исследованиям, позволяющим улучшить стратификацию рисков и персонализацию терапии. В разделе лечения детально проанализированы хирургические методы (резекция, трансплантация печени), лекарственная терапия (аналоги соматостатина, телотристат, таргетные препараты — сунитиниб, эверолимус), химиотерапия и пептидная рецепторная радионуклидная терапия. Приведены результаты ключевых исследований. Отдельно освещены сложности ранней диагностики, необходимость мультидисциплинарного подхода и персонализации лечения. Подчёркнуты перспективы применения новых биомаркеров и методов визуализации, а также важность диспансерного наблюдения (интервалы обследования, стратегия «watch and wait» для малых опухолей). Обсуждаются сложности ранней диагностики, необходимость комплексной оценки опухолевого процесса и перспективы дальнейших исследований для оптимизации стратегий лечения.

Ключевые слова: нейроэндокринные опухоли; эпидемиология; диагностика; лечение; тераностика; послеоперационное наблюдение.

Как цитировать:
Михеева Ю.В., Румянцев П.О., Пузаков К.К., Слащук К.Ю., Омельчук Д.Д., Потапенко А.В., Медведев С.П. Современные алгоритмы ведения пациентов с нейроэндокринными опухолями желудочно-кишечного тракта и лёгких // Российский онкологический журнал. 2025. Т. 30, № 1. С. 41–60. DOI: 10.17816/onco642734 EDN: JONKLF

Рукопись получена: 10.12.2024 **Рукопись одобрена:** 23.05.2025 **Опубликована online:** 26.05.2025

BACKGROUND

Neuroendocrine tumors (NETs) are heterogeneous tumors that differ in grade, molecular genetic characteristics, and clinical course: from low-grade NETs to high-grade neuroendocrine carcinomas (NECs) [1]. NETs develop from diffuse neuroendocrine system cells. Therefore, these neoplasms can be found in any organ, but gastrointestinal and bronchopulmonary NETs are the most prevalent [2]. NETs are defined by potential overproduction of biologically active amines and peptide hormones, resulting in a distinct clinical presentation characterized by carcinoid syndrome and hormonal disorders caused by insulinoma, gastrinoma, glucagonoma, and other hormone-active NETs [1, 3]. Despite their indolent behavior, NETs can cause significant morbidity, because their clinical presentation may mimic other diseases, leading to delayed diagnosis and untimely or inappropriate treatment [4].

The growing number of diagnostic tests, including molecular genetic tests, and treatment options necessitates a multidisciplinary approach to managing patients with NETs. The prognosis in these patients varies significantly depending on the primary tumor site, grade, stage, and molecular genetic characteristics; therefore, patients with NETs must be treated in specialized centers. This review focuses on existing management algorithms for patients with the most prevalent NETs (gastrointestinal and pulmonary).

The work aimed to summarize modern approaches to the diagnosis and treatment of gastrointestinal and pulmonary NETs.

SEARCH METHODOLOGY

Methods

The work was based on review and research articles available in the online research libraries *PubMed* and *NCBI*. The search period was 1992 to 2024. The following search terms were used: neuroendocrine tumors (161 thousand sources), neuroendocrine cancer (45 thousand sources), treatment of neuroendocrine tumors (100 thousand sources), diagnosis of neuroendocrine tumors (100 thousand sources), drug care of neuroendocrine tumors (2 thousand sources), and local care of neuroendocrine tumors (1.6 thousand sources). We assessed review articles on the diagnosis and treatment of low-grade NETs (G1, G2, and G3) and NECs. Moreover, the review included the findings of phase 2 and 3 clinical studies, meta analyses, and systematic reviews that were relevant for routine clinical practice. Overall, the review included 87 publications.

DISCUSSION

Epidemiology of Neuroendocrine Tumors

NETs account for approximately 0.5% of all newly diagnosed malignancies [5]. Despite their low prevalence, the incidence of NETs is increasing across all sites, stages, and grades. According to the largest population-based study in patients with NETs, which used the data from the SEER database, the incidence rate of NETs in the United States increased 6.4-fold from 1973 (1.09 per 100,000 population) to 2012 (6.98 per 100,000 population) [5]. The highest and lowest age-adjusted incidence rates were reported in patients aged over 65 (2.53 per 100,000 population in 2012) and under 50 (1.75 per 100,000 population), respectively. However, a significant increase in the incidence since 1973 was reported in all age groups [5]. The general population shows comparable incidence of NETs in males and females; however, according to some studies, gastroenteropancreatic and pulmonary NETs are slightly more prevalent in females (52%–58% of cases) [6, 7].

The most prevalent primary NET sites are the gastroenteropancreatic system (62%–70% of cases) and the bronchopulmonary system (approximately 25% of cases) [1, 2]. Moreover, these sites are associated with the most significant increase in incidence: 15-fold for gastric NETs, 9-fold for rectal NETs, and 4-fold for pulmonary NETs [5]. According to researchers, an increase in the incidence of NETs is primarily associated with a wider use of endoscopy and improved imaging quality. Improved diagnosis has resulted in a significant increase in the incidence of G1 NETs, which accounted for 51% of all confirmed NETs in 2012, whereas G2 and G3 NETs accounted for 16.4% and 32.6%, respectively [5]. Detection rates of locoregional NETs have increased in recent decades, accounting for approximately 72% of all cases. However, the proportion of patients with metastatic disease has remained constant over time, likely owing to earlier diagnosis of asymptomatic NETs and the effect of modern treatment algorithms on overall survival (OS) [5]. A large SEER-based cohort study, which assessed gastroenteropancreatic NETs (GEP-NETs) as the most prevalent, also showed a significant increase in incidence rates between 1975 and 2015 across all stages, sites, and grades [9]. The most significant

increase was observed for localized stages (G1 GEP-NETs). In terms of the primary site, the largest increase in incidence rates was reported for gastric and rectal NETs [9]. These data are consistent with the findings of earlier population-based studies in the United States and other countries [5, 7]. The most prevalent GEP-NET sites were NETs of the rectum and small intestine (28.6% and 28.1%, respectively), whereas NETs of the stomach, large intestine, and appendix were the least prevalent (9.2%, 9.2%, and 8.5%, respectively) [6].

The median OS in the general population of patients with NETs was 112 months (9.3 years) [5]. G1 NETs had better median OS (16.2 years) compared with G2 and G3 NETs (8.3 years and 10 months, respectively). Localized NETs had better median OS (>30 years) compared with regional NETs (10.2 years) and distant NETs (12 months). NETs in the rectum (24.6 years) and appendix (>30.0 years) had the best median OS among primary site groups, whereas NETs in the pancreas (3.6 years) and lung (5.5 years) had the worst median OS [5]. Another study showed better survival rates in patients with NETs, with median OS of 63 months; however, these results were inferior to other GEP-NETs [6]. The survival rate in gastric NETs ranges from 9 to 100 months depending on the stage [6, 7]. The prognosis in patients with NETs also varies significantly. For example, the 5-year OS for typical carcinoids (G1 and G2 NETs) was 75%–100% for localized tumors and 30%–60% for locally advanced tumors and distant metastases [10]. Large-cell and small-cell lung cancers are extremely aggressive diseases. The 5-year OS for small-cell lung cancer (SCLC) and large-cell lung carcinoma (LCLC) is ⩽5% and 15%–57%, respectively; other studies show comparable values for SCLC and LCLC [5, 7].

Clinical Aspects of Hormone-Active Neuroendocrine Tumors

When selecting a treatment strategy for patients with NETs, it is essential not only to control tumor growth, but also to reduce symptoms. NETs develop from diffuse neuroendocrine system cells that are found in all organs and secrete biologically active substances. Therefore, NETs produce biological amines, peptide hormones, and neuropeptides, resulting in characteristic ectopic hormone syndromes [8]. Regarding the most prevalent primary NET sites, hormone-active or functioning NETs (F-NETs) are more frequently found in the pancreas (30%), whereas gastrointestinal and bronchopulmonary F-NETs are reported in 3%–13% of cases and less than 5% of cases, respectively [8].

Carcinoid syndrome (CS) is the most common hormonal disorder in NETs, with an incidence of 1.7% to 18.7% and a 72% increase between 2000 and 2011 [5]. CS is significantly more prevalent in pancreatic and small intestine NETs (40%, especially in NETs with liver metastases), followed by bronchopulmonary NETs and large intestine and rectal NETs (13% and 10%, respectively) [9]. CS is typically present in pulmonary NETs with liver metastases [10]. CS is caused by overproduction of biologically active substances, primarily serotonin, by NETs. However, there is evidence that other vasoactive substances, such as prostaglandins, substance P, neurokinin A, bradykinin, and histamine, have a significant impact on CS symptoms [5]. Typical symptoms of CS include diarrhea (78%), hot flashes and skin flushing (78%), asthma-like symptoms (12%), and hyperkeratosis or hyperpigmentation (1%) [10]. In recent years, there has been evidence of cognitive impairments such as slowed thinking, aggressive behavior, and speech impairment [11]. Carcinoid heart disease (CHD) is reported in approximately 20%–40% of cases, primarily in patients with long-term CS without adequate symptom control [5]. CHD is the leading cause of death in these patients [12]. Overproduction of serotonin in CS activates fibroblasts, causing fibrosis of heart valves (primarily tricuspid and pulmonic) [12]. This results in chronic right heart failure (HF). As CHD progresses, patients may develop restrictive cardiomyopathy and arrythmias, including atrial fibrillation. CHD secondary to poorly controlled CS is associated with an unfavorable prognosis. In an observational cohort study, the median OS in untreated patients with CHD was 11 months [12]. Carcinoid crisis is another potential complication of CS. It is caused by interventions during biopsy, tumor resection, embolization, and anesthesia, resulting in a sudden, significant release of vasoactive substances and a characteristic clinical presentation with severe skin flushing, hemodynamic instability, bronchospasm, and arrythmias [13]. The risk of intraoperative carcinoid crisis is significantly higher in gastrointestinal NETs, particularly NETs in the small intestine and with liver metastases [13]. Preoperative use of somatostatin analogs is a common strategy for carcinoid crisis prevention; however, a pooled analysis of three large studies did not confirm the efficacy of this approach, necessitating research of other prevention strategies [13].

Some hormonal disorders secondary to F-NETs are more common in pancreatic tumors and much

less frequently reported for other tumor sites. There are eight most well-studied hormonal disorders secondary to F-NETs (aside from pancreatic NETs with carcinoid syndrome) [14]. The most prevalent of these are gastrinomas, insulinomas, glucagonomas, VIPomas (Verner–Morrison syndrome), ACTH-producing tumors (ectopic ACTH syndrome), and somatostatinomas [14]. These hormonal disorders have a distinct clinical presentation, differ in terms of diagnosis and treatment strategy, and, like NETs with carcinoid syndrome, require continuous symptom control (Supplement 1).

In Zollinger–Ellison syndrome (gastrinoma), symptoms are caused by overproduction of hydrochloric acid due to ectopic gastrin secretion by NETs (peptic ulcers and gastroesophageal reflux disease accompanied by severe diarrhea; symptoms associated with tumor growth, such as bleeding, pain, and jaundice, are only observed at later stages) [14]. Insulinoma is primarily characterized by signs of neuroglycopenia (90% of all cases), such as confusion, coma, and visual impairment, as well as signs of sympathetic hyperactivity, such as tremor, hyperhidrosis, tachycardia, weakness, and polyphagia. These symptoms become more severe when hungry or on exertion [14]. This requires differential diagnosis between postprandial hypoglycemia, which is caused by previous surgical treatment of obesity, and fasting hypoglycemia, which is observed in insulinoma [14]. VIPomas are characterized by watery diarrhea resulting in dehydration and hypokalemia; excessive secretion of vasoactive intestinal peptide (VIP) is associated with hyperglycemia, hypochlorhydria, and hot flashes, with an incidence of 20% to 50% [14]. Glucagonoma is characterized by necrolytic migratory erythema (55%–90%), weight loss (60%–90%), and diabetes mellitus or impaired glucose tolerance (30%–90%) [14]. Glucagonomas frequently present as large tumors (>5 cm), with liver metastases in 50%–80% of patients [14]. Somatostatinoma is one of the least studied NETs, with typical symptoms including diabetes mellitus, gall bladder disorders, steatorrhea, and weight loss. The majority of reported cases of somatostatinoma lack a typical clinical presentation. Typical symptoms of somatostatinoma are virtually always present in primary pancreatic NETs, but are infrequent in NETs of other organs, such as the small intestine [14]. NETs with ACTH overproduction cause Cushing syndrome, primarily in the thymus and lungs (40%–60%); this syndrome has been reported in both typical and atypical carcinoids [15]. The clinical signs of ectopic ACTH syndrome are typical of Cushing syndrome, including moon face, abdominal obesity, striate atrophy of the skin, muscle atrophy, asthenia, hypokalemia, and hyperglycemia [15].

There are several hereditary syndromes associated with NETs, primarily with pancreatic tumors; these include multiple endocrine neoplasia (MEN1), von Hippel–Lindau disease (VHL), von Recklinghausen syndrome (VRH), neurofibromatosis type I, and tuberous sclerosis [14]. Hereditary NETs have a more aggressive course and a higher incidence of liver metastases than other low-grade NETs [14]. Pancreatic F-NETs with typical hormonal disorders are relatively common in MEN1, accounting for 54% of all cases of hormone-active F-NETs [14]. Zollinger–Ellison syndrome is associated with hereditary MEN1 in 20%–25% of cases, necessitating special care in the management of these patients, including a mandatory geneticist consultation [14]. In this case, gastrinoma symptoms appear on average 10 years earlier and can be relatively mild, frequently going unnoticed [14]. Recent studies have reported NETs in extrapancreatic MEN1 (pulmonary, thymic, or gastric) [14, 16]. According to some studies, up to 31% of pulmonary NETs are associated with hereditary MEN1; previously, it was believed that their incidence did not exceed 5%, with a less favorable prognosis [14]. It was thought that 98% of all pancreatic NETs in von Hippel–Lindau disease are non-functioning. It was later found that the proportion of patients with these symptoms can reach 36% [14].

Immunohistochemistry and Molecular Genetic Testing of Neuroendocrine Tumors

Immunohistochemical markers of NETs

Immunohistochemistry (IHC) staining is used in routine clinical practice to confirm neuroendocrine differentiation and determine NET grade. Conventional neuroendocrine markers include neurosecretory granule proteins, chromogranin A (CgA) and synaptophysin (Syn) [17]. Chromogranin A is considered a more specific marker, whereas synaptophysin is more sensitive [17]. During differential diagnosis between NETs and NECs, low-grade tumors show more intense immunoexpression and staining for CgA and Syn, whereas NECs show diffuse expression of Syn and focal staining for CgA [10]. Neural cell adhesion molecule (NCAM, CD56) is used as the third key IHC marker, in addition to CgA and Syn, for

primary thoracic NETs; however, this marker lacks specificity in gastrointestinal NETs [10, 17]. CD56 expression is significantly higher in lung tumors, especially atypical carcinoids and thymic tumors; however, there is evidence of increased expression in both small-cell and large-cell NECs in other sites [17]. CD56 can be a valuable diagnostic marker for primary foci in metastasis of unknown origin in morphologically confirmed NETs [17].

Insulinoma-associated protein 1 (INSM1) is a well-validated transcription factor of neuroendocrine differentiation that has only recently been evaluated for diagnostic use. The diagnostic value of INSM1 was first demonstrated in 2015, when it was found to be detectable by IHC staining in 88.3% of neuroendocrine tumor samples [18]. Further studies showed that INSM1 expression is significantly more frequently detected in atypical lung carcinoid tumors and small-cell lung cancer compared to conventional markers (CgA, Syn, and CD56) [18]. In pancreatic NETs, INSM1 can have higher sensitivity and specificity than CgA and Syn [18]. Research findings have facilitated a wider use of INSM1 as an immunohistochemical marker of NETs [18]. Somatostatin receptors (SSTRs) can be expressed in almost all NETs, particularly in gastroenteropancreatic tumors. There are five types of SSTRs, the most significant of which are SSTR 2A and 5 [19]. IHC staining is the standard technique for detecting SSTR expression. Somatostatin analogs are the basis of NET treatment; therefore, the identification of SSTRs is mandatory. SSTR expression in NETs is heterogeneous and depends on tumor grade. For example, it amounts to 54%–100% in G1 and G2 NETs versus 4.8%–63% in G3 NETs, depending on the SSTR type [19]. It is advisable to use additional IHC markers in NETs with metastasis of unknown origin. Positive staining for CDX2, TTF1, and islet-1 (ISL-1) indicates a primary focus in the midgut, lung, and pancreas, respectively [20].

Ki-67 is a valuable tool for assessing the proportion of proliferating cells in a tumor. It is determined based on IHC staining using the MIB-1 antibody. Ki-67 can be calculated both manually and automatically [21]. Ki-67 is a prognostic factor for determining the tumor grade. In NETs, Ki-67, along with mitotic index, is the key parameter of tumor classification. A discordance between grade as determined by Ki-67 and mitotic index is observed in up to one-third of NETs, more frequently in biopsy samples than surgical samples (62% vs 38%) [21]. In the majority of these cases (87%), higher Ki-67 values are reported, which correlates with lower survival rates [21]. Several studies suggest that in case of a discordance between grade as determined by Ki-67 and mitotic index, the NET grade should be determined using a larger value, which is typically Ki-67 [21]. The World Health Organization (WHO) included a subgroup of low-grade G3 NETs in the classification of NETs for pancreatic tumors in 2017 and for all NETs in 2022, based on the accumulating evidence of differences in prognosis [22]. Ki-67 was one of the first diagnostic tools to distinguish between G3 NETs and NECs. The threshold of 55% for Ki-67 is optimal for distinguishing between G3 NETs (<55%) and NECs (>55%) [22].

Molecular genetic characteristics of NETs

G3 NETs are currently considered a separate subgroup of low-grade NETs. Despite increased proliferative activity relative to G1 and G2 NETs, this group significantly differs from NECs in terms of clinical course and has a more favorable prognosis. The median OS for G3 NETs is 55 months versus 16 months for NECs [23]. According to the WHO classification criteria for NETs, Ki-67 >20% is used for G3 NETs and NECs [22]. The threshold of 55% for Ki-67, which is used to distinguish between G3 NETs and NECs, does not allow for an accurate assessment of tumor grade [23]. Additional molecular markers are actively used to improve the differential diagnosis between G3 NETs and NECs. A large meta-analysis of pancreatic NETs showed that MEN1 (*DAXX/ATRX*) mutations are relatively common [23]. MEN1 inactivation has been reported in 71% of G3 pancreatic NETs, and *DAXX/ATRX* inactivation in 60% [23]. Local loss of heterozygosity in the MEN1 is common in typical carcinoids (up to 35% of cases) and can be a valuable marker for differential diagnosis with atypical carcinoids [24]. These genetic disorders are currently detected by IHC staining and are used in routine clinical practice to diagnose G3 NETs. There is conflicting data on how these mutations affect survival. However, a large meta-analysis of 78 studies conducted in 2021 showed that *DAXX/ATRX* mutations have a negative impact on progression-free survival (PFS). There were no significant differences in OS [25]. All primary NETs are characterized by Rb1 and p53 knockdown [25, 26]. Moreover, Rb1 and p53 determination is advisable in patients with SCLC transformed EGFR mutant non-small cell lung cancer following treatment with tyrosine kinase inhibitors [27]. SCLC transformation is reported in 4%–15% of patients with resistance to first- and second-generation EGFR inhibitors [28]. Given

the evidence of histological transformation on osimertinib therapy, determination of Rb1 and p53 mutations in non-small cell lung cancer can serve as a predictor of resistance to tyrosine kinase inhibitors [29].

Biomarkers in Blood and Urine

Considering the limited diagnostic value of histological samples and difficulties with morphology-based differential diagnosis of NETs, there is a need for reproducible laboratory biomarkers. They can be a useful diagnostic tool for assessing long-term prognosis and predicting response to therapy and the risk of relapse.

Measuring CgA levels in serum and 5-hydroxyindoleacetic acid (5-HIAA; terminal metabolite of serotonin) levels in urine is a conventional laboratory diagnosis method in NETs [30]. CgA is superior to 5-HIAA, because its levels do not depend on serotonin secretion [30]. The sensitivity and specificity of CgA are 73% and 95%, respectively [30]. CgA levels correlate with the objective response to treatment in gastrointestinal and pulmonary NETs. A decrease in CgA level was shown to correlate with improved PFS and OS [30]. However, the production of this marker is associated with the functional activity of tumors. A decrease in CgA level on treatment with somatostatin analogs likely reflects antisecretory rather than antiproliferative effects [31]. Moreover, more recent studies show that CgA levels are not a reliable marker in the majority of patients with NETs of the colon and rectum, considering that CgA is rarely elevated in these patients, does not reflect tumor burden, and does not predict survival [31]. Furthermore, CgA elevation may be caused by some chronic diseases, including atrophic gastritis, chronic kidney disease, and inflammatory bowel disease, as well as therapy with proton pump inhibitors [31].

The 24-hour urinary 5-HIAA has a sensitivity of 70%–90% and a specificity of up to 100% in CS, as well as a high diagnostic value in NETs of the jejunum and ileum [31]. Given its prognostic value, 5-HIAA is frequently used as a factor when assessing therapeutic options in CS [5]. In patients with CHD, 5-HIAA >300 μmol/24 h is an independent predictor of CHD progression [32]. Moreover, 5-HIAA influences OS in NETs of the small intestine. High 5-HIAA levels (>10 × upper limit of normal) are associated with reduced OS, whereas low 5-HIAA levels are associated with improved OS [32]. One disadvantage of the 5-HIAA urine test is that it requires 24-hour urine collection, which is time-consuming and prone to preanalytical errors. This issue can be addressed by measuring plasma 5-HIAA levels; however, this method is costly, limiting its use in routine clinical practice [3, 32]. Moreover, 5-HIAA levels in urine are highly dependent on the diet: foods rich in tryptophan (precursor of serotonin), such as bananas, legumes, coffee, chocolate, avocado, nuts, fish, cheese, and wine, as well as some drugs (glucocorticosteroids and antidepressants), may cause overestimation or false-positive results [3, 32]. Plasma serotonin measurement has long been one of the easiest and most accessible diagnostic tools in CS. Serotonin levels are routinely determined along with 5-HIAA levels in urine; however, this method has the same limitations as the 5-HIAA urine test. However, clinical signs of NETs are absent despite high 5-HIAA and serotonin levels in 12%–26% of cases [32].

Neuron specific enolase (NSE) is a reliable serum tumor marker in patients with gastroenteropancreatic NETs and SCLC [33]. NSE is elevated in 30%–50% of patients with gastrointestinal NETs. Its sensitivity and specificity for gastrointestinal NETs are 38% and 73%, respectively [33]. Elevated NSE levels in patients with gastrointestinal NETs had a significant impact on median OS. Normal NSE levels, NSE 1–3 × upper limit of normal (ULN), and NSE >3 × ULN corresponded to median OS of 161.8 months, 72.5 months, and 27.8 months, respectively [33]. Furthermore, there is a correlation between tumor burden, response to treatment, and NSE levels in SCLC [34].

Pancreatic polypeptide (PP), which is normally secreted by pancreatic islet cells, is a secondary tumor marker in pancreatic NETs due to its limited sensitivity and specificity. Elevated PP levels are reported in approximately 45% of patients [34]. Some studies indicate that PP levels elevated by >50% are associated with the progression of NETs [32].

There are more specific serological markers that can be used to diagnose rare hormonal disorders in F-NETs. These include insulin, glucagon, vasoactive intestinal peptide (VIP), gastrin, and somatostatin, which are 100% specific for pancreatic F-NETs with distinct clinical syndromes [35].

Imaging Diagnostics

Endoscopic examinations

Endoscopic examinations are successfully used to diagnose NETs as a minimally invasive, efficient, and cost-effective diagnostic and therapeutic option. Advancements in endoscopy have resulted

in an increased incidence of NETs, owing to earlier detection of asymptomatic tumors [5]. Modern high-resolution endoscopes for narrow-band imaging (NBI) have significantly improved imaging sensitivity and specificity. Endoscopic ultrasound (EUS) is an advanced technique that enables minimally invasive diagnostic and therapeutic interventions in conditions that usually require a conventional surgical intervention.

Upper and lower gastrointestinal tract endoscopy and colonoscopy are useful for detecting primary tumor sites and obtaining biopsy samples. Moreover, they help to rule out concomitant malignancies that are reported in 20% of patients with NETs, which is more common than in the general population [7]. Bronchoscopy is a valuable diagnostic tool for determining primary tumor sites and performing biopsies, given that approximately 75% of pulmonary NETs are centrally located [10].

Endoscopic ultrasound (EUS) is becoming a valuable diagnostic tool for assessing primary tumor invasiveness and size [36]. EUS was found to be effective in pancreatic tumors. The sensitivity and specificity of EUS are 87.2% and 98%, respectively [36]. A meta-analysis conducted in 2015 showed that EUS improves the overall detection rate of pancreatic NETs by 25% after other modalities are attempted. It is especially valuable in smaller pancreatic F-NETs [37]. A prospective, observational study that assessed lymph node involvement in non-functioning pancreatic NETs found that EUS had a specificity of up to 98%, outperforming 68Ga-DOTA-TOC PET [38]. EUS-guided fine-needle aspiration biopsy is a preferable diagnosis method in pancreatic tumors, enabling cytology tests with a sensitivity and specificity of 80%–90% and up to 96%, respectively, and a high concordance of Ki-67 and mitotic index with histological samples [37]. In other gastrointestinal NETs, EUS is also the preferred approach for assessing locally advanced tumors and obtaining histology and cytology samples. Several studies found that EUS was not inferior to mucosal incision-assisted biopsy for tissue acquisition in upper gastrointestinal NETs [39]. The diagnostic value of EUS is limited in subepithelial lesions in upper gastrointestinal NETs; moreover, EUS is not an optimal technique in gastric and small intestine NETs, requiring a multimodal approach [40]. EUS has a high specificity for assessing submillimeter bronchial wall invasion in NETs and can be used for monitoring both before and after endobronchial resection. Furthermore, EUS can be useful for assessing lymph node involvement [38].

X-ray and ultrasound examinations

Computed tomography (CT) and magnetic resonance imaging (MRI) are frequently used for initial imaging and staging of NETs [41]. Ultrasound (US) examinations are primarily used to make the initial diagnosis of liver metastases and abdominal lymph node involvement, as well as in pancreatic tumors. Contrast-enhanced US can be more effective when CT and MRI findings are uncertain, with a sensitivity and specificity of 86% and 92%, respectively, for pancreatic NETs, liver metastases, and mesenteric lymph node involvement [41].

Spiral CT was routinely used for many years; however, multidetector tomographs have lately become increasingly available, reducing examination time and producing high-quality 3D images [41]. Given that NETs are typically hypervascularized, contrast-enhanced CT produces more accurate images. According to the European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors (2017), the average sensitivity and specificity of contrast-enhanced CT are 73% and 96%, respectively. However, the findings vary significantly across NET sites. In lymph node involvement, the sensitivity and specificity are 60%–70% and 87%–100%, respectively [41]. Disadvantages of CT examinations include the inability to distinguish between liver and lymph node metastasis in NETs and other malignancies, as well as low sensitivity in bone metastases [41]. MRI outperforms CT in abdominal and bone examinations [41]. MRI more effectively detects liver metastases in NETs than CT, owing to the ability to visualize smaller lesions [41]. The precise sensitivity and specificity ranges for MRI have not been defined; published data indicate a sensitivity of 70%–95% for pancreatic NETs, gastrinomas, and liver metastases [41].

Molecular imaging

NETs are frequently small, with low metabolic rates, limiting the use of conventional imaging techniques (CT, MRI, US), which fail to accurately assess the tumor grade, size, and biological activity [41]. The expression of various types of SSTRs on NET cells has provided a molecular basis for radiodiagnosis. The most common SSTR imaging methods include 68Ga-labeled somatostatin analogs (primarily octreotide) and positron emission tomography/computed tomography (PET/CT) with a chelator (DOTA) and various peptide SSTR agonists (TOC, NOC, TATE), or single-photon emission computed tomography

(SPECT) with 99mTc-tektrotyd (previously, with 111In-octreoscan) [42].

SSTR scintigraphy (SPECT with tektrotyd) provides significant advantages compared to conventional cross-sectional imaging (CT, MRI). A retrospective analysis found that SPECT with tektrotyd had an accuracy, sensitivity, and specificity of 83.3%, 82%–94%, and 88%–96%, respectively. Positive scintigraphy findings were associated with a more favorable prognosis; moreover, this method can be useful for identifying patients eligible for somatostatin analog therapy and peptide receptor radionuclide therapy (PRRT) [43]. Octreoscan is now used much less frequently than tektrotyd. Indirect comparisons show that tektrotyd has a higher sensitivity (~80%) in low-grade NETs. Moreover, tektrotyd uses an isotope produced in a generator (in contrast to octreoscan, which uses an isotope produced in a reactor), which increases accessibility and convenience of use [44].

SSTR PET/CT with 68Ga-DOTA-NOC/TATE/TOC is increasingly used as the most sensitive molecular imaging method for NETs [45]. Several studies found that SSTR PET/CT is superior to SPECT with 99mTc-tektrotyd and 111In-octreoscan, which is significant for small tumors when detecting submillimeter bone, liver, and lymph node metastases, as well as for tumors with a low density of SSTRs [46]. Moreover, SSTR PET/CT determines NET sites more accurately. Significant advantages of SSTR PET/CT over SSTR SPECT include higher spatial resolution and the possibility to identify patients eligible for PRRT with lutetium oxodotreotide (68Ga-DOTA-TATE) [46]. The specificity of SSTR PET/CT approaches 100% [46]. One significant advantage of molecular SSTR imaging (SPECT, PET/CT) is the high concordance of results with IHC findings, which is useful in small tumors with insufficient biopsy sample size when assessing eligibility for somatostatin analog therapy and PRRT [46].

Treatment Algorithms

Surgical treatment

Surgical treatment of NETs is planned taking into account several factors, such as the primary tumor site, grade, lymph node involvement, functional activity, and the presence of hereditary syndrome. Given the heterogeneity of tumor biology, it is difficult to establish standardized indications for surgical treatment.

Surgical resection of the affected organ is the preferred approach for local NET treatment in the majority of cases [47, 48]. In most non-functioning gastrointestinal NETs, resection should be considered in G2 and G3 primary tumors measuring >2 cm. However, the size of G1 extrapancreatic NETs that require resection is still debated [47, 48]. The scope of optimal surgical treatment depends on the primary NET site. In bronchopulmonary NETs, anatomic resection (lobectomy or bilobectomy) is recommended. The outcomes of organ-sparing surgeries are comparable to those of pneumonectomy, with a significantly reduced incidence of postoperative complications and severity of respiratory failure [48]. Atypical lung resection, such as segmentectomy and wedge resection, is significantly less commonly used in real-world practice. There are currently no large prospective comparative studies of atypical and anatomic resection. A single-center, retrospective study found that atypical resection is only recommended for typical carcinoids measuring ⩽1 cm [48]. Ipsilateral lymph node involvement is reported in 11.6% of typical carcinoids (TCs) and 64.3% of atypical carcinoids (ACs). This is associated with an unfavorable prognosis. The 5-year OS for TCs and ACs was 90.1% and 22.2%, respectively, whereas in the absence of lymph node involvement, it was 100% for both TCs and ACs [48]. Therefore, preventive mediastinal lymphadenectomy is more advisable in ACs [48].

Surgical resection with regional lymphadenectomy remains the primary local treatment method in pancreatic NETs. It is recommended in both F-NETs (except for insulinomas) and non-functioning NETs (NF-NETs) measuring ⩾2 cm, given the increased risk of regional and distant metastases [41, 47]. Furthermore, resection of smaller tumors is indicated in cases when the major pancreatic duct, gall bladder, or lymph nodes are affected [47]. The goals of surgical treatment depend on several factors, including the functional status. For example, partial tumor resection sufficient for symptom control is considered clinical success in F-NETs, whereas NF-NETs require total resection [49]. Depending on the tumor location in the pancreas, resection may involve enucleation, central pancreatectomy, distal pancreatectomy with or without splenectomy, or pancreaticoduodenectomy (Whipple procedure). Organ-sparing surgeries (enucleation and central pancreatectomy) reduce the risk of chronic pancreatic insufficiency; however, they do not allow for adequate lymphadenectomy [49].

In a SEER-based retrospective study, the median OS in patients with resected NF-NETs measuring >2 cm was 114 months, compared to 35 months in the group that did not receive

surgical treatment [50]. The need for surgical treatment of pancreatic NETs measuring <2 cm remains debatable. In these cases, the European Neuroendocrine Tumor Society (ENETS) and the American Society of Clinical Oncology (ASCO) recommend the "watch and wait" strategy [49, 51]. The efficacy of this strategy has been demonstrated in both sporadic NF-NETs and MEN1; however, the recommendations are frequently based on retrospective studies alone [49, 51]. A systematic review of 9 studies found that the "watch and wait" strategy resulted in continued tumor growth in 22% of patients with NF-NETs and 52% of patients with MEN1. Surgical resection was required in 12% and 25% of patients, respectively. However, survival rates in this subgroup were comparable, indicating that the "watch and wait" strategy is safe for these patients [52]. There are studies where surgical resection of high-grade tumors is justified; however, the authors do not specify the grade of such pancreatic NETs [4]. According to some studies, pancreatic NF-NETs measuring <2 cm have a median Ki-67 of 1%, indicating a more favorable course of the disease [4]. A novel treatment strategy for this patient population is based on morphological and immunohistochemical examination findings. In small G3 pancreatic NF-NETs, surgical resection is required, given the more aggressive tumor biology [21]. Minimally invasive endoscopic treatment of pancreatic NETs, such as radiofrequency ablation (RFA) and EUS-guided ethanol ablation, can outperform the "watch and wait" strategy in tumors measuring >1 cm to <2 cm, with a complete response rate of 60%–100%. However, these methods are currently not commonly used in routine practice [21]. Moreover, RFA can be a viable alternative for older patients who are not eligible for surgical resection. Despite high progression rates in patients who received RFA, survival rates were comparable [49]. Endoscopic mucosal resection and endoscopic submucosal dissection are widely regarded as the best surgical treatments in gastrointestinal NETs measuring <2 cm [49].

Liver metastases in NETs are reported in 50%–75% of cases in the general population [53]. Surgical treatment consists of curative resection, palliative cytoreductive resection, and transplantation. Curative resection of metastases is feasible in only 7%–15% of patients [53]. Resectability of metastases depends on both technical-anatomic considerations and tumor biology, with no clearly defined criteria [53]. Hepatic resection could be offered to patients who fulfil the following criteria: resectable primary tumor (along with any possible lymph node involvement), absence of CHD, and a sufficient amount of unaffected liver tissue (at least 30%–40%) [53].

According to a Cochrane review, the 5-year and 10-year OS in patients with NETs after total resection is 61%–70% and 35%, respectively, making resection preferable to other approaches (RFA or transarterial chemoembolization [TACE]). There is insufficient data to compare these treatment options with surgical resection [54]. A systematic review of 30 studies found that hepatic resection was not superior to other local treatment modalities [53]. Surgical resection of metastases is justified when R0 resection is possible. However, patients frequently receive additional local therapy (RFA or TACE) or systemic biotherapy with somatostatin analogs, chemotherapy, or targeted therapy, which affects survival rates; therefore, such data must be interpreted with caution [53]. RFA or TACE in addition to surgical treatment may increase the 5-year OS to 72%. However, there are no large comparative studies of such combination therapies; moreover, these findings are comparable to survival rates in patients with surgical resection alone [53, 54].

There are limited research on the use of liver transplantation as a treatment option. Transplantation was mostly assessed in small studies in patients with gastrointestinal NETs; therefore, it is not recommended for routine practice, but can be considered in patients over 50 years with isolated liver metastases and Ki-67 <5% who are not eligible for resection [53].

Drug Therapy

Somatostatin analogs

Long-acting somatostatin analogs (SSAs) (octreotide and lanreotide) are used as first-line therapy for the treatment and control of CS symptoms in tumors with SSTR type 2 or 5. SSAs can also improve symptoms of other hormonal disorders associated with NETs, such as Zollinger–Ellison syndrome [55]. A meta-analysis conducted in 2019 showed comparable efficacy of octreotide and lanreotide in improving CS symptoms, with symptom control rates of 65%–69% and 69%–72% for diarrhea and hot flashes, respectively [55]. Moreover, SSAs significantly reduce the risk of CHD [55].

SSAs can ensure long-term control of CS symptoms; however, many patients experience progression of symptoms. In these cases, SSAs treatment switching, dose escalation, and shorter intervals between doses can be effective.

A retrospective analysis found that escalating a standard octreotide dose (30 mg) to 40–60 mg in refractory CS provided control of the main symptoms (diarrhea, hot flashes, bronchial spasm, and abdominal pain) in 66%–70% cases, with a dose of 40 mg sufficient for many patients [56]. In patients who experienced disease progression when receiving octreotide every 28 days, switching to a dosing interval of every 21 days provided complete or partial control of symptoms in 40% and 60% of cases, respectively [57]. Similar findings were reported when escalating octreotide doses to 40–60 mg [56]. In addition to antisecretory action, several randomized studies demonstrated antiproliferative effects of SSAs.

The randomized, placebo controlled clinical study PROMID assessed the antineoplastic activity of octreotide LAR 30 mg every 28 days in patients with metastatic midgut NETs (small intestine and appendix) [58]. The study included patients with Ki-67 ⩽2%; therefore, all study participants had G1 NETs [58]. The median progression-free survival (mPFS) (primary endpoint) was 14.3 months for octreotide and 6 months for placebo [58]. An updated analysis of long-term outcomes conducted in 2017 found no significant benefits of octreotide for OS in the general population; the median OS was 84.7 months for octreotide and 83.7 months for placebo [58]. In the low-tumor-load subgroup (<10%), there was an improvement in OS (median not reached vs 87.2 months) in the octreotide group; however, the difference was not significant. In the high-tumor-load subgroup, no superiority of octreotide was found [58].

CLARINET, a randomized, placebo-controlled clinical study that assessed the antineoplastic effect of lanreotide, included a larger patient cohort than the PROMID study [59]. In addition to patients with midgut NETs, the study included patients with hindgut (large intestine and rectum) and pancreatic NETs. The study included 200 patients with Ki-67 ⩽10%, in contrast to PROMID, where Ki-67 was ⩽2% [59]. The study met its primary endpoint, with median PFS not achieved in the lanreotide group versus 18 months in the placebo group; the PFS at 24 months was 65.1% and 33.0%, respectively [59]. Moreover, lanreotide demonstrated significant superiority in all key subgroups (G1 NETs, G2 NETs, and hepatic tumor load [<25% or >25%]). However, there were no significant differences in the group of patients with hindgut NETs, which is likely due to the imbalance between the groups and the small sample size [59]. Lanreotide was associated with more gastrointestinal adverse events than placebo (50% vs 25%). The most common study drug–related adverse events were hyperglycemia and cholelithiasis; however, they were not considered serious [59]. Octreotide and lanreotide therapy results in stable disease in the majority of cases (50%–60% of cases), with an objective response rate (ORR) of <10% [60]. There are no large comparative studies on the antineoplastic activity of octreotide and lanreotide. A retrospective comparative study in patients with G1 and G2 small intestine and pancreatic NETs with Ki-67 ⩽10% found no significant differences between octreotide and lanreotide in terms of PFS (median PFS: 29.8 months and 36 months, respectively) [61]. Another study also showed no superiority of lanreotide over octreotide in pancreatic NETs [61]. These findings were consistent with previous retrospective studies. The authors concluded that octreotide and lanreotide have comparable efficacy and can be used interchangeably; however, the findings should be interpreted with caution, given the retrospective design of the studies [61]. Based on the findings of retrospective studies, the ENETS and European Society for Medical Oncology (ESMO) guidelines recommend using octreotide and lanreotide as monotherapy in G1 and G2 gastroenteropancreatic NETs with Ki-67 <10% [49]. The phase 2 study CLARINET-FORTE found that high doses of lanreotide (120 mg every 14 days) can be effective in patients with pancreatic and midgut NETs with Ki-67 <10% who experienced disease progression on standard doses of lanreotide [62]. Lanreotide is currently being studied as an antineoplastic drug for patients with Ki-67 ⩽14% [63]. The antineoplastic effect of SSAs in pulmonary NETs has not been assessed individually. However, the ENETS guidelines recommend considering SSAs in indolent TCs [64]. The phase 2 study ATLANT showed that lanreotide and temozolomide combination therapy can be effective in thoracic NETs [65]. This study primarily included patients with pulmonary NETs (90%); of these, 20% had TCs, 52% had ACs, and 10% had thymic NETs [65]. The study met its primary endpoint: the disease control rate at 9 months was 35.0% [65]. Another therapeutic option is pasireotide, a synthetic somatostatin analog with increased affinity for somatostatin receptors (SSTR1, SSTR2, SSTR3, and SSTR5). It is currently being studied as NET therapy, especially in patients with resistance to octreotide or lanreotide. In a phase 3 randomized study (2015), pasireotide was not inferior to octreotide in terms of symptom control and tumor stabilization in metastatic gastrointestinal NETs, with more pronounced CgA inhibition in some

patients [66]. Another study (2016) demonstrated the efficacy of pasireotide in progressive NETs not responding to first-generation somatostatin analogs, with the median time to progression of 11 months [67]. However, the use of pasireotide is limited by the high incidence of hyperglycemia (up to 60% of cases), which requires treatment [68]. Pasireotide has not been officially approved for the treatment of NETs; however, it may be considered as a second-line therapy in tumors with preserved SSTR expression (especially SSTR5). The 2020 guidelines of the North American Neuroendocrine Tumor Society (NANETS) emphasize that further research is required to assess the role of pasireotide in the treatment of NETs [69].

Interferons

The efficacy of interferon alpha-2b in the control of CS symptoms was first demonstrated in 1983 [70]. The standard dose of interferon in NETs is 3–9 MU subcutaneously, three to seven times/week [70]. The majority of efficacy studies of interferon were conducted between 1982 and 2005, highlighting a tendency toward combination use with SSAs or other biologicals and reduced routine use of interferon as monotherapy [70]. Subjective improvements on interferon alpha therapy are reported in approximately 60%–70% of patients with CS. Furthermore, its antineoplastic activity has been demonstrated. The mean ORR is 11%, with tumor stabilization in 39% of patients [70]. When compared with chemotherapy (streptozotocin plus 5-fluorouracil), the median OS was >80 months in the interferon group and 8 months in the chemotherapy group [71]. Notably, the therapy is frequently associated with side effects such as flu-like symptoms, fever, and asthenia, which may result in treatment interruption [71]. In prospective studies, adding interferon to octreotide and lanreotide did not improve the PFS or treatment outcomes [71]. Currently, interferon alfa is not widely used. It can be prescribed in combination with SSAs in patients refractory to SSAs for symptom control, or alone in tumors without SSTRs, where the use of SSAs is impossible [71].

Telotristat

Telotristat is a small molecule inhibitor of tryptophan hydroxylase that limits serotonin biosynthesis. It is a relatively new biotherapy option in CS refractory to SSAs*. In 2017, the FDA approved telotristat at a dose of 250 mg three times daily in combination with SSAs for the treatment of CS-associated diarrhea refractory to octreotide and lanreotide, based on the findings of the phase 3 study TELESTAR. The study included patients with low-grade NETs and CS, experiencing ⩾4 bowel movements per day while on SSAs, with urinary 5-HIAA levels above the upper limit of normal. The patients were randomized to receive telotristat 250 mg or 500 mg three times daily or placebo while continuing their baseline SSA therapy. The primary endpoint was a reduction in bowel movement frequency from baseline on week 12; moreover, changes in 5-HIAA levels were assessed. Telotristat significantly reduced bowel movement frequency (by ⩾30%) in 44% and 42% of patients in 250 mg and 500 mg groups, respectively, compared to placebo. Urinary 5-HIAA levels decreased by ⩾30% in 78% of patients who received telotristat at any dose, indicating effective tryptophan hydroxylase inhibition. The most common adverse events were nausea and elevated gamma-glutamyltransferase levels; however, they were manageable and did not result in treatment discontinuation. Patients from the TELESTAR study are currently included in the OLE period, where they receive telotristat 500 mg three times daily. The TELESTAR study previously raised concerns that telotristat may cause depression by inhibiting serotonin synthesis. In the 500 mg group, the incidence of depression was higher than in the 250 mg group. However, the randomized phase 3 study TELECAST, which assessed the safety of telotristat, did not confirm these findings [72]. The incidence of depression was higher in the placebo group. However, the interim OLE analysis at week 12 showed that telotristat 500 mg caused depression in 11.9% of cases compared to 4% during the 12-week double-blind treatment period, indicating that the duration of telotristat therapy influences the risk of depression [72].

Given the impact of telotristat on serotonin biosynthesis, its efficacy in other symptoms of refractory CS was assessed. Telotristat is hypothesized to have a protective effect in CHD; moreover, studies on its potential use for postoperative prevention of carcinoid crisis are ongoing [3, 13, 73]. TELEHEART, a randomized phase 3 study assessing the effect of telotristat in combination with SSA in CHD in patients with metastatic NETs, has been conducted since 2021. The primary endpoint is a decrease in NT-proBNP after 6 months of therapy; the primary analysis is planned for 2025 (ClinicalTrials.gov, study ID: NCT04810091). Another study assessing the

* medscape.com [Internet]. FDA Approves Xermelo for Carcinoid Syndrome Diarrhea, Feb 28, 2017. Available at: https://www.medscape.com/viewarticle/876454. Accessed on: May 26, 2025.

efficacy of telotristat in perioperative prevention of carcinoid crisis was terminated due to a lack of funding (ClinicalTrials.gov, study ID: NCT04672876).

Furthermore, antiproliferative effects of telotristat are assessed. TELEACE was a retrospective, single-center chart review study in patients who received telotristat for at least 6 months [71]. The study found that telotristat had an effect on tumor size in patients with G1 and G2 NETs and Ki-67 ⩽20%, regardless of SSA therapy. The mean reduction in tumor size was 8.5%; tumor stabilization after 6–9 months of treatment was reported in 81%–97% of patients [74]. Given that the study was retrospective and had numerous limitations, further prospective randomized studies are required to assess the antineoplastic effect of telotristat.

Targeted therapy

Several targeted therapy drugs approved for antitumor therapy in NETs are currently available. Everolimus and sunitinib, the first targeted therapy drugs with confirmed efficacy, were approved as a second-line therapy in combination with SSAs in G1 and G2 NETs and alone as a first-line therapy in NETs with Ki-67 >10% to <20% or in tumors without SSTRs, where the use of an SSA alone is impossible [35].

Sunitinib, a multikinase inhibitor, is the first targeted therapy drug that has been approved for the treatment of advanced low-grade pancreatic NETs based on phase 3 study findings [75]. The study included 171 patients who previously received at least one line of antitumor therapy (primarily chemotherapy) [75]. In 2009, the study was terminated early due to high mortality rates and serious side effects in the placebo group [75]. Sunitinib demonstrated significant advantages, with median PFS of 11.4 months compared to 5.5 months in the placebo group [75]. The ORR was 9.3%. A subgroup analysis showed no superiority of sunitinib in terms of PFS in several key subgroups (Ki-67 >5% and extrahepatic metastases), making the use of sunitinib debatable in these patient populations [75]. The median OS in the updated analysis in 2017 was 38.6 months in the sunitinib group and 29.1 months in the placebo group, despite the apparent superiority of sunitinib. The difference was not significant, which could be explained by a crossover from placebo to sunitinib in 69% of patients due to disease progression or after study termination [75].

The efficacy of everolimus, an m-TOR inhibitor, in progressive NETs, was assessed in a series of phase 2 and 3 studies (RADIANT). The antineoplastic effect of everolimus 5 mg/day and 10 mg/day for 28 days was first demonstrated in the phase 2 study RADIANT-1 [75]. In contrast to the efficacy study, RADIANT-1 included patients with pancreatic and small intestine NETs. The mean Ki-67 was also higher (3%–20%) [76]. The ORR for everolimus was 20%; tumor stabilization was reported in 70% of patients. The PFS after 6 and 12 months was 80% and 59%, respectively, in all patients [76]. The promising results of the phase 2 study prompted the phase 3 study RADIANT-2, which assessed a combination of everolimus 10 mg and octreotide in progressive gastrointestinal NETs [77]. The study did not meet its primary PFS endpoint, despite the numerically higher median PFS for everolimus and octreotide compared to octreotide alone (16.4 months vs 11.3 months). Poor study outcomes could be explained by switching from placebo to everolimus in case of disease progression [77]. The phase 3 study RADIANT-3 assessed the efficacy of everolimus in progressive pancreatic NETs. The study met its primary PFS endpoint; the median PFS was 11 months in the everolimus group and 4.6 months in the placebo group [78]. A pooled analysis of the phase 3 sunitinib study and RADIANT-3 (everolimus) showed comparable efficacy of these drugs in low-grade metastatic pancreatic NETs. Sunitinib and everolimus reduced the risk of disease progression by 58% and 65%, respectively. However, the differences were not significant, with comparable PFS and OS [79]. The phase 3 study RADIANT-4 assessed everolimus 10 mg as monotherapy. The study included treatment-experienced patients, primarily with low-grade small intestine and pulmonary NETs. The proportion of patients with G2 NETs was up to 40%; switching from placebo to everolimus in case of disease progression was not allowed [80]. Everolimus significantly improved PFS (median: 11 months for everolimus vs 3.9 months for placebo). Everolimus reduced the risk of disease progression or fatal outcome by 52% [80]. A pooled analysis of RADIANT-3 and RADIANT-4 data showed that everolimus can be used as targeted therapy in a wide range of G1 and G2 gastrointestinal and pulmonary NETs.

Pazopanib, both alone and in combination with SSAs, demonstrated promising antineoplastic effects in progressive gastrointestinal NETs in phase 2 studies [81]. In a phase 2 study that assessed the efficacy of pazopanib in gastrointestinal NETs, the ORR was 18.9%, with tumor stabilization in 56.8% of patients. The median PFS was 9.1 months, whereas the median OS was not reached [81]. Notably, this study included patients with more aggressive

NETs than in sunitinib and everolimus studies. The proportion of patients with G2 and G3 NETs was 43% and 35%, respectively [82]. A pooled analysis of phase 2 pazopanib studies in NETs showed a disease control rate of 91.3%; median PFS and OS were 11.6 months and 24.4 months, respectively [82]. Previous therapy, including targeted therapy, did not reduce the efficacy of pazopanib. Moreover, adding an SSA resulted in a synergistic effect, improving the disease control rate [82]. Therefore, pazopanib is a promising treatment option for patients with disease progression on previous chemotherapy or targeted therapy, as well as patients with G2 and G3 NETs. However, phase 3 studies are required to test these hypotheses.

Belzutifan is a first-in-class oral hypoxia-inducible factor 2-alpha (HIF-2α) inhibitor. In 2021, the FDA approved belzutifan for patients with von Hippel–Lindau disease who require therapy for associated renal cell carcinoma, central nervous system hemangioblastomas, or pancreatic NETs [83]. The drug was approved for this indication based on the phase 2 study MK-6482-004. According to a subgroup analysis, the ORR in patients with pancreatic NETs was 83%, whereas the median duration of response was not reached [83]. Belzutifan is the only effective therapeutic option for these patients, apart from surgical treatment, with a significantly lower risk of complications [83].

Chemotherapy

Recent studies confirm the efficacy of cytostatic chemotherapy (CT) agents in NETs. One of the reasons is the recently established subgroup of G3 gastrointestinal NETs, which are less aggressive than NECs, but require more intensive therapy than G1 and G2 NETs. The clinical study NORDIC NEC investigated the differences in the biology of G3 NETs and NECs [85]. According to a retrospective analysis, the G3 NET group included tumors with Ki-67 20%–55%, which were less aggressive, but had a lower ORR with platinum-based CT (15% vs 42% in the NEC group with Ki-67 >55%). However, this group had a better OS (14 months vs 10 months) [84]. A combination of streptozotocin (STZ) and 5-fluorouracil (5-FU) was the first CT regimen approved for low-grade NETs. This combination has proven to be effective, especially in progressive pancreatic NETs [85]. The ORR was 69%, with complete response in 39% of patients and median OS of 26 months. This CT regimen is associated with significant gastrointestinal toxicity; however, it is used as a standard of care [85]. Capecitabine and temozolomide (CAPTEM) is recommended by all recent guidelines as a preferred option in low-grade NETs. However, most of the data on its efficacy come from retrospective studies, whereas only four phase 1–2 studies, which primarily assessed its use in gastrointestinal NETs, have been published [86]. The largest systematic review, which assessed CAPTEM in both gastrointestinal and pulmonary NETs, reported an ORR of 34.8%. Complete response was reported in 2.3% of cases, with tumor stabilization in 40% of patients; the median PFS was 9.4–12 months [86]. This systematic review showed significant advantages of CAPTEM over FOLFOX, platinum/etoposide, cisplatin, and carboplatin in G3 NETs with Ki-67 20%–55%. Therefore, CAPTEM is the best first-line therapy option [86]. CAPTEM can be used as a neoadjuvant therapy in resectable metastatic NETs. A retrospective analysis found that this approach results in ORR 43%, median PFS 28.2 months, and 5-year OS 63%. The mean Ki-67 for included NETs was 3.5%, indicating a favorable tumor biology, which must be confirmed in prospective studies [86]. Oxaliplatin was significantly superior to cisplatin and carboplatin in low-grade NETs. Combinations with 5-FU (FOLFOX) and capecitabine (XELOX and CAPOX) are currently approved for progressive G2 and G3 gastrointestinal NETs and typical carcinoids. However, their use is recommended after progression on CAPTEM [85].

Etoposide plus cisplatin (EP) or etoposide plus carboplatin (EC), as well as irinotecan plus cisplatin (IP), are the standard first-line therapy in metastatic NETs, with ORR 31%–60%, median PFS 5–7 months, and median OS 12–14 months [85]. Alternatively, the triplet FOLFIRINOX regimen (5-FU, oxaliplatin, and irinotecan) can be used. Several retrospective analyses showed objective response in 46%–70% of patients with NETs, with median OS of 18–20 months, which was superior to historical control data. As a result, a phase 3 study comparing FOLFIRINOX and EP/EC as a first-line therapy in NETs was initiated [87].

Peptide Receptor Radionuclide Therapy

Visualization of SSTR expression using 68Ga-DOTA-TATE/TOC/NOC PET/CT in NETs served as a foundation for radiotheranostics, where a targeted ligand labeled with a diagnostic and therapeutic radionuclide is used as an antineoplastic agent. The potential therapeutic effect of this approach was first reported in 1994 [88]. In 2017, the FDA approved 177Lu-DOTA-TATE as a second-line therapy for patients with progressive/metastatic G1 and G2 gastrointestinal NETs expressing SSTRs, based on the findings of the randomized phase 3 study

NETTER-1 [88]. The study included patients with G1 and G2 metastatic small and large intestine NETs, with SSTR expression and Ki-67 ⩽20%, progressing on SSA therapy [88]. The patients received four 177Lu-DOTA-TATE courses with an 8-week interval plus octreotide 30 mg or SSA 60 mg. PFS was the primary endpoint [88]. Among included patients, 83% had bone metastases, 66% had lymph node involvement, and 11% had bone and lung metastases. G1 NETs were observed in 66% and 72% of patients in the PRRT and SSA groups, respectively [88]. The study met its primary endpoint. During the primary analysis, median PFS was not reached for PRRT plus octreotide and was 8.4 months for octreotide alone. Significant superiority of ^{177}Lu-DOTA-TATE was demonstrated in all key clinical subgroups. The risk of disease progression or fatal outcome was 79% lower in the PRRT group than in the control group [88]. Objective response and disease control for >20 months were reported in 18% and 65% of patients in the 177Lu-DOTA-TATE group, compared to 3% and 10.8% in the control group [88]. During the final analysis, the median OS for PRRT plus SAA and SAA alone was 48 months and 36.3 months, respectively. The differences were not significant, likely because patients from the control group were allowed to switch to PRRT. Overall, 36% of patients received 177Lu-DOTA-TATE.

In 2024, the results of the randomized phase 3 study NETTER-2 were published. The study compared the efficacy of a high-dose long-acting SSA alone and 177Lu-DOTA-TATE plus long-acting SSA at standard doses as a first-line therapy in metastatic G2 and G3 gastrointestinal NETs with Ki-67 >10% to ⩽55% [89]. In contrast to NETTER-1, this study included patients with small and large intestine NETs, as well as pancreatic NETs (54%); G2 and G3 NETs were observed in 66% and 33% of participants, respectively [89]. The study met its primary endpoint (PFS); the median PFS was 22.8 months in the PRRT group and 8.5 months in the SSA group. Improvements in PFS did not depend on the primary tumor site and grade [89]. The ORR was 43% and 9.3%, respectively; disease control was achieved in 90.3% of patients in the 177Lu-DOTA-TATE group and 66.7% of patients in the SAA group [89]. This study was the first to demonstrate the efficacy of PRRT in G3 gastrointestinal NETs. Notably, combinations of SSAs and targeted therapy or chemotherapy are used as a first-line therapy in G2 and G3 NETs, respectively, in real-world practice. Therefore, it may be inappropriate to compare PRRT with SAA monotherapy. However, the PFS observed in NETTER-2 was superior to historical control data [89].

Follow-Up Care in Patients with NETs

Clinical outcomes in patients with localized and locally advanced low-grade gastrointestinal NETs after radical resection indicate the long-term risk of relapse or distant metastases of 50% [21]. There are currently no prospective studies that assess treatment strategies. According to the NANETS Consensus Guidelines (2018), patients must be followed up for at least 5 years after surgical treatment [90]. There is currently no consensus over whether follow-up should continue beyond 10 years. However, it may be recommended in younger patients or those considered to be at particularly high risk of disease progression (e.g., numerous involved lymph nodes or radical resection of liver metastases) [90]. The majority of experts agreed that radiographic examinations should be performed every 6 months during the first year, and then once a year in the absence of recurrence or progression [90]. Furthermore, follow-up is recommended in patients with asymptomatic pancreatic NETs measuring <2 cm, including in hereditary MEN1 [49, 51]. If the “watch and wait” strategy is used, a more thorough follow-up is recommended, with radiographic examinations every 3–4 months. In case of remission, examinations after the first year of follow-up can be performed every 6 months [90].

CONCLUSION

NETs are a heterogeneous group of tumors with varying biology (ranging from indolent to aggressive course). The current management of patients with gastrointestinal and pulmonary NETs involves multi-stage algorithms and requires a personalized approach, given the wide variety of available treatment options. The introduction of SSAs and telotristat has significantly improved treatment outcomes in CS, delaying its progression to CHD. Distinguishing between G3 NETs and NECs, which have different prognoses, has significantly influenced drug treatment strategies, with a shift from platinum-based CT to platinum-free regimens and targeted therapy. PRRT has become another valuable antitumor therapy option in NETs.

An interdisciplinary approach is essential when selecting a treatment strategy in this patient population. Patients with NETs are examined and treated in reference centers, and the disease is frequently detected at advanced stages or with severe manifestations of CS. Raising awareness of NETs among oncologists and primary care physicians will facilitate earlier disease detection and improve treatment outcomes.

ADDITIONAL INFORMATION

Supplement 1. Diagnosis algorithm for gastrointestinal and pulmonary neuroendocrine tumors. doi: 10.17816/onco642734-4330053

Author contributions: Yu.V. Mikheeva: conceptualization, data curation, writing—original draft, writing—review & editing; P.O. Rumyantsev: supervision, project administration; K.K. Puzakov, K.Yu. Slashchuk, D.D. Omelchuk, A.V. Potapenko, S.P. Medvedev: writing—original draft. All the authors approved the version of the manuscript to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding sources: No funding.

Disclosure of interests: The authors have no relationships, activities, or interests for the last three years related to for-profit or not-for-profit third parties whose interests may be affected by the content of the article.

REFERENCES | СПИСОК ЛИТЕРАТУРЫ

1. Klöppel G. Neuroendocrine Neoplasms: Dichotomy, Origin and Classifications. *Visc Med*. 2017;33(5):324–330. doi: 10.1159/000481390

2. Fraenkel M, Faggiano A, Valk GD. Epidemiology of Neuroendocrine Tumors. *Frontiers of Hormone Research*. 2015;44:1–23. doi: 10.1159/000381970

3. Ito T, Lee L, Jensen RT. Carcinoid-syndrome: recent advances, current status and controversies. *Current Opinion in Endocrinology & Diabetes and Obesity*. 2018;25(1):22–35. doi: 10.1097/MED.0000000000000376

4. Fang JM, Li J, Shi J. An update on the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. *World J Gastroenterol*. 2022;28(10):1009–1023. doi: 10.3748/wjg.v28.i10.1009

5. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol*. 2017;3(10):1335–1342. doi: 10.1001/jamaoncol.2017.0589

6. Xu Z, Wang L, Dai S, et al. Epidemiologic Trends of and Factors Associated With Overall Survival for Patients With Gastroenteropancreatic Neuroendocrine Tumors in the United States. *JAMA Netw Open*. 2021;4(9):e2124750. doi: 10.1001/jamanetworkopen.2021.24750

7. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*. 2003;97(4):934–59. doi: 10.1002/cncr.11105

8. Clift AK, Kidd M, Bodei L, et al. Neuroendocrine Neoplasms of the Small Bowel and Pancreas. *Neuroendocrinology*. 2020;110(6):444–476. doi: 10.1159/000503721

9. Halperin DM, Shen C, Dasari A, et al. Frequency of carcinoid syndrome at neuroendocrine tumour diagnosis: a population-based study. *Lancet Oncol*. 2017;18:525–534. doi: 10.1016/S1470-2045(17)30110-9

10. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing But NET: A Review of Neuroendocrine Tumors and Carcinomas. *Neoplasia*. 2017;19(12):991–1002. doi: 10.1016/j.neo.2017.09.002

11. Russo S, Nielen MM, Boon JC, et al. Neuropsychological investigation into the carcinoid syndrome. *Psychopharmacology (Berl)*. 2003;168:324–328. doi: 10.1007/s00213-003-1455-5

12. Jin C, Sharma AN, Thevakumar B, et al. Pathophysiology, Pathology, Clinical Manifestations, and Management. *Cardiology*. 2021;146(1):65–73. doi: 10.1159/000507847

13. Xu A, Suz P, Reljic T, et al. Perioperative Carcinoid Crisis: A Systematic Review and Meta-Analysis. *Cancers (Basel)*. 2022;14(12):2966. doi: 10.3390/cancers14122966

14. Ito T, Lee L, Jensen RT. Treatment of symptomatic neuroendocrine tumor syndromes: recent advances and controversies. *Expert Opin Pharmacother*. 2016;17(16):2191–2205. doi: 10.1080/14656566.2016.1236916

15. Landry JP, Clemente-Gutierrez U, Pieterman CRC, et al. Management of adrenocorticotropic hormone-secreting neuroendocrine tumors and the role of bilateral adrenalectomy in ectopic Cushing syndrome. *Surgery*. 2022;172(2):559–566. doi: 10.1016/j.surg.2022.03.014

16. Gibril F, Chen YJ, Schrump DS, et al. Prospective study of thymic carcinoids in patients with multiple endocrine neoplasia type 1. *J Clin Endocrinol Metab*. 2003;88(3):1066–1081. doi: 10.1210/jc.2002-021314

17. Fang JM, Li J, Shi J. An update on the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. *World J Gastroenterol*. 2022;28(10):1009–1023. doi: 10.3748/wjg.v28.i10.1009

18. Rooper LM, Sharma R, Li QK, et al. INSM1 Demonstrates Superior Performance to the Individual and Combined Use of Synaptophysin, Chromogranin and CD56 for Diagnosing Neuroendocrine Tumors of the Thoracic Cavity. *Am J Surg Pathol*. 2017;41(11):1561–1569. doi: 10.1097/PAS.0000000000000916

19. Hankus J, Tomaszewska R. Neuroendocrine neoplasms and somatostatin receptor subtypes expression. *Nucl Med Rev Cent East Eur*. 2016;19(2):111–117. doi: 10.5603/NMR.2016.0022

20. Strosberg JR, Halfdanarson TR, Bellizzi AM, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors. *Pancreas*. 2017;46(6):707–714. doi: 10.1097/MPA.0000000000000850

21. McCall CM, Shi C, Cornish TC, et al. Grading of well-differentiated pancreatic neuroendocrine tumors is improved by the inclusion of both Ki67 proliferative index and mitotic rate. *Am J Surg Pathol*. 2013;37(11):1671–1677. doi: 10.1097/PAS.0000000000000089

22. Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol*. 2018;31(12):1770–1786. doi: 10.1038/s41379-018-0110-y

23. Tang LH, Untch BR, Reidy DL, et al. Well-Differentiated Neuroendocrine Tumors with a Morphologically Apparent High-Grade Component: A Pathway Distinct from Poorly Differentiated Neuroendocrine Carcinomas. *Clin Cancer Res*. 2016;22(4):1011–1017. doi: 10.1158/1078-0432.CCR-15-0548

24. Simbolo M, Mafficini A, Sikora KO, et al. Lung neuroendocrine tumours: deep sequencing of the four World Health Organization histotypes reveals chromatin-remodelling genes as major players and a prognostic role for

TERT, RB1, MEN1 and KMT2D. *J Pathol*. 2017;241(4):488–500. doi: 10.1002/path.4853
25. Wang F, Xu X, Ye Z, et al. Prognostic Significance of Altered ATRX/DAXX Gene in Pancreatic Neuroendocrine Tumors: A Meta-Analysis. *Front. Endocrinol*. 2021;12:691557. doi: 10.3389/fendo.2021.691557
26. Bellizzi AM. Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: what can brown do for you? *Hum Pathol*. 2020;96:8–33. doi: 10.1016/j.humpath.2019.12.002
27. Niederst MJ, Sequist LV, Poirier JT, et al. RB loss in resistant EGFR mutant lung adenocarcinomas that transform to small-cell lung cancer. *Nat Commun*. 2015;6:6377. doi: 10.1038/ncomms7377
28. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*. 2011;3(75):75ra26. doi: 10.1126/scitranslmed.3002003
29. Leonetti A, Sharma S, Minari R, et al. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer*. 2019;121(9):725–737. doi: 10.1038/s41416-019-0573-8
30. Kulke MH. Clinical presentation and management of carcinoid tumors. *Hematol Oncol Clin North Am*. 2007;21(3):433–455. doi: 10.1016/j.hoc.2007.04.004
31. Di Giacinto P, Rota F, Rizza L, et al. Chromogranin A: From Laboratory to Clinical Aspects of Patients with Neuroendocrine Tumors. *Int J Endocrinol*. 2018;8126087. doi: 10.1155/2018/8126087
32. Bhattacharyya S, Toumpanakis C, Chilkunda D, et al. Risk Factors for the Development and Progression of Carcinoid Heart Disease. *Am. J. Cardiol*. 2011;107:1221–1226. doi: 10.1016/j.amjcard.2010.12.025
33. Kalligeros M, Diamantopoulos L, Toumpanakis C. Biomarkers in Small Intestine NETs and Carcinoid Heart Disease: A Comprehensive Review. *Biology (Basel)*. 2021;10(10):950. doi: 10.3390/biology10100950
34. Isgrò MA, Bottoni P, Scatena R. Neuron-Specific Enolase as a Biomarker: Biochemical and Clinical Aspects. *Adv Exp Med Biol*. 2015;867:125–143. doi: 10.1007/978-94-017-7215-0_9
35. Ma ZY, Gong YF, Zhuang HK, et al. Pancreatic neuroendocrine tumors: A review of serum biomarkers, staging, and management. *World J Gastroenterol*. 2020;26(19):2305–2322. doi: 10.3748/wjg.v26.i19.2305
36. Puli SR, Kalva N, Bechtold ML, et al. Diagnostic accuracy of endoscopic ultrasound in pancreatic neuroendocrine tumors: a systematic review and meta analysis. *World J Gastroenterol*. 2013;19(23):3678–3684. doi: 10.3748/wjg.v19.i23.3678
37. James PD, Tsolakis AV, Zhang M, et al. Incremental benefit of preoperative EUS for the detection of pancreatic neuroendocrine tumors: a meta-analysis. *Gastrointest Endosc*. 2015;81:848–856.e1. doi: 10.1016/j.gie.2014.12.031
38. Partelli S, Muffatti F, Andreasi V, et al. A Single-center Prospective Observational Study Investigating the Accuracy of Preoperative Diagnostic Procedures in the Assessment of Lymph Node Metastases in Nonfunctioning Pancreatic Neuroendocrine Tumors. *Ann Surg*. 2022;276(5):921–928. doi: 10.1097/SLA.0000000000005615
39. Giri S, Afzalpurkar S, Angadi S, et al. Mucosal incision-assisted biopsy versus endoscopic ultrasound-assisted tissue acquisition for subepithelial lesions: a systematic review and meta-analysis. *Clin Endosc*. 2022;55(5):615–625. doi: 10.5946/ce.2022.133
40. Iabichino G, Di Leo M, Arena M, et al. Diagnosis, treatment, and current concepts in the endoscopic management of gastroenteropancreatic neuroendocrine neoplasms. *World J Gastroenterol*. 2022;28(34):4943–4958. doi: 10.3748/wjg.v28.i34.4943
41. Sundin A, Arnold R, Baudin E, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Radiological, Nuclear Medicine and Hybrid Imaging. *Neuroendocrinology*. 2017;105(3):212–245. doi: 10.1159/000471879
42. Lee ST, Kulkarni HR, Singh A, Baum RP. Theranostics of Neuroendocrine Tumors. *Visc Med.* 2017;33(5):358–366. doi: 10.1159/000480383
43. Saponjski J, Macut D, Petrovic N, et al. Diagnostic and prognostic value of 99mTc-Tektrotyd scintigraphy and 18F-FDG PET/CT in a single-center cohort of neuroendocrine tumors. *Arch Med Sci*. 2021;19(6):1753–1759. doi: 10.5114/aoms/130996
44. Artiko V, Afgan A, Petrović J, et al. Evaluation of neuroendocrine tumors with 99mTc-EDDA/HYNIC TOC. *Nucl Med Rev Cent East Eur*. 2016;19(2):99–103. doi: 10.5603/NMR.2016.0020
45. Sharma P, Singh H, Bal C, Kumar R. PET/CT imaging of neuroendocrine tumors with (68)Gallium-labeled somatostatin analogues: An overview and single institutional experience from India. *Indian J Nucl Med*. 2014;29(1):2–12. doi: 10.4103/0972-3919.125760
46. Kunikowska J, Lewington V, Krolicki L. Optimizing Somatostatin Receptor Imaging in Patients With Neuroendocrine Tumors: The Impact of 99mTc-HYNICTOC SPECT/SPECT/CT Versus 68Ga-DOTATATE PET/CT Upon Clinical Management. *Clin Nucl Med*. 2017;42(12):905–911. doi: 10.1097/RLU.0000000000001877
47. Wang R, Zheng-Pywell R, Chen HA, et al. Management of Gastrointestinal Neuroendocrine Tumors. *Clin Med Insights Endocrinol Diabetes*. 2019;12. doi: 10.1177/1179551419884058
48. Hendifar AE, Marchevsky AM, Tuli R. Neuroendocrine Tumors of the Lung: Current Challenges and Advances in the Diagnosis and Management of Well-Differentiated Disease. *J Thorac Oncol*. 2017;12(3):425–436. doi: 10.1016/j.jtho.2016.11.2222
49. Hofland J, Falconi M, Christ E, et al. European Neuroendocrine Tumor Society 2023 guidance paper for functioning pancreatic neuroendocrine tumour syndromes. *J Neuroendocrinol*. 2023;35(8):e13318. doi: 10.1111/jne.13318
50. Dumlu EG, Karakoc D, Ozdemir A. Nonfunctional Pancreatic Neuroendocrine Tumors: Advances in Diagnosis, Management, and Controversies. *Int Surg*. 2015;100(6):1089–1097. doi: 10.9738/INTSURG-D-14-00204.1
51. Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol*. 2009;27(1):127–145. doi: 10.1200/JCO.2008.17.2627
52. Sallinen V, Le Large TY, Galeev S, et al. Surveillance strategy for small asymptomatic non-functional pancreatic neuroendocrine tumors — a systematic review and meta-analysis. *HPB (Oxford)*. 2017;19(4):310–320. doi: 10.1016/j.hpb.2016.12.010
53. Lesurtel M, Nagorney DM, Mazzaferro V, et al. When should a liver resection be performed in patients with liver metastases from neuroendocrine tumours? A systematic review with practice recommendations. *HPB (Oxford)*. 2015;17(1):17–22. doi: 10.1111/hpb.12225

54. Gurusamy KS, Ramamoorthy R, Sharma D, et al. Liver resection versus other treatments for neuroendocrine tumours in patients with resectable liver metastases. *Cochrane Database Syst Rev*. 2009;2009(2):CD007060. doi: 10.1002/14651858
55. Phan AT. Metastatic pancreatic neuroendocrine tumors (pNET): placing current findings into perspective. *Cancer Treat Rev*. 2013;39(1):3–9. doi: 10.1016/j.ctrv.2012.02.010
56. Al-Efraij K, Aljarma MA, Kennecke HF. Association of dose escalation of octreotide long-acting release on clinical symptoms and tumor markers and response among patients with neuroendocrine tumors. *Cancer Med*. 2015;4(6):864–870. doi: 10.1002/cam4.435
57. Ferolla P, Faggiano A, Grimaldi F, et al. Shortened interval of long-acting octreotide administration is effective in patients with well-differentiated neuroendocrine carcinomas in progression on standard doses. *J Endocrinol Invest*. 2012;35(3):326–331. doi: 10.3275/7869
58. Rinke A, Wittenberg M, Schade-Brittinger C, et al. PROMID Study Group. 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 (PROMID): Results of Long-Term Survival. *Neuroendocrinology*. 2017;104(1):26–32. doi: 10.1159/000443612
59. Caplin ME, Pavel M, Cwikla JB, et al. CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224–233. doi: 10.1056/NEJMoa1316158
60. Stueven AK, Kayser A, Wetz C, et al. Somatostatin Analogues in the Treatment of Neuroendocrine Tumors: Past, Present and Future. *Int J Mol Sci*. 2019;20(12):3049. doi: 10.3390/ijms20123049
61. Kiesewetter B, Pflugerr FF, Melhorn P, et al. Long-term experience with octreotide and lanreotide for the treatment of gastroenteropancreatic neuroendocrine tumors. *Clin Transl Oncol*. 2024. doi: 10.1007/s12094-024-03732-w
62. Pavel M, Cwikla JB, Lombard-Bohas C, et al. Efficacy and safety of high-dose lanreotide autogel in patients with progressive pancreatic or midgut neuroendocrine tumours: CLARINET FORTE phase 2 study results. *Eur J Cancer*. 2021;157:403–414. doi: 10.1016/j.ejca.2021.06.056
63. Diamantopoulos LN, Laskaratos FM, Kalligeros M, et al. Antiproliferative Effect of Above-Label Doses of Somatostatin Analogs for the Management of Gastroenteropancreatic Neuroendocrine Tumors. *Neuroendocrinology*. 2021;111(7):650–659. doi: 10.1159/000509420
64. Caplin ME, Baudin E, Ferolla P, et al. ENETS consensus conference participants. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. *Ann Oncol*. 2015;26(8):1604–1620. doi: 10.1093/annonc/mdv041
65. Ferolla P, Berruti A, Spada F, et al. Efficacy and Safety of Lanreotide Autogel and Temozolomide Combination Therapy in Progressive Thoracic Neuroendocrine Tumors (Carcinoid): Results from the Phase 2 ATLANT Study. *Neuroendocrinology*. 2023;113(3):332–342. doi: 10.1159/000526811
66. Wolin EM, Jarzab B, Eriksson B, et al. Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues. *Drug Des Devel Ther*. 2015;9:5075–5086. doi: 10.2147/DDDT.S84177
67. Cives M, Kunz PL, Morse B, et al. Phase II clinical trial of pasireotide long-acting repeatable in patients with metastatic neuroendocrine tumors. *Endocr Relat Cancer*. 2015;22(1):1–9. doi: 10.1530/ERC-14-0360
68. Gadelha MR, Umpierrez GE. Management of hyperglycemia in hospitalized patients. *Ann N Y Acad Sci*. 2010;1212:1–11. doi: 10.1111/j.1749-6632.2010.05805.x
69. Fishbein L, Del Rivero J, Else T, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Management of Metastatic and/or Unresectable Pheochromocytoma and Paraganglioma. Pancreas. 2021;50(4):469–493. doi: 10.1097/MPA.0000000000001792
70. Oberg K. Interferons in the management of neuroendocrine tumors and their possible mechanism of action. *Yale J Biol Med*. 1992;65(5):519–529
71. Oberg K, Eriksson B, Janson ET. Interferons alone or in combination with chemotherapy or other biologicals in the treatment of neuroendocrine gut and pancreatic tumors. *Digestion*. 1994;55(3):64–69. doi: 10.1159/000201204
72. Pavel M, Gross DJ, Benavent M, et al. Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial. *Endocr Relat Cancer*. 2018;25(3):309–322. doi: 10.1530/ERC-17-0455
73. Herrera-Martínez AD, Fuentes-Fayos AC, Sanchez-Sanchez R, et al. Does Telotristat Have a Role in Preventing Carcinoid Heart Disease? *Int J Mol Sci*. 2024;25(4):2036. doi: 10.3390/ijms25042036
74. Morse MA, Liu E, Joish VN, et al. Antiproliferative Effects of Telotristat Ethyl in Patients with Neuroendocrine Tumors: The TELEACE Real-World Chart Review Study. *Cancer Manag Res*. 2020;12:6607–6614. doi: 10.2147/CMAR.S261257
75. Faivre S, Niccoli P, Castellano D, et al. Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. *Ann Oncol*. 2017;28(2):339–343. doi: 10.1093/annonc/mdw561
76. Yao JC, Phan AT, Chang DZ, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. *J Clin Oncol*. 2008;26(26):4311–8. doi: 10.1200/JCO.2008.16.7858
77. Pavel ME, Hainsworth JD, Baudin E, et al. RADIANT-2 Study Group. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2011;378(9808):2005–2012. doi: 10.1016/S0140-6736(11)61742-X
78. Yao JC, Shah MH, Ito T, et al. RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):514–523. doi: 10.1056/NEJMoa1009290
79. Ishak KJ, Rael M, Hicks M, et al. Relative effectiveness of sunitinib versus everolimus in advanced pancreatic neuroendocrine tumors: an updated matching-adjusted indirect comparison. *J Comp Eff Res*. 2018;7(10):947–958. doi: 10.2217/cer-2018-0020
80. Yao JC, Fazio N, Singh S, et al. RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4)

Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387(10022):968–977. doi: 10.1016/S0140-6736(15)00817-X

81. Ahn HK, Choi SH, Park SH, et al. Phase II study of pazopanib monotherapy in metastatic gastroenteropancreatic neuroendocrine tumours. *Br J Cancer*. 2013;109(6):1414–1419. doi: 10.1038/bjc.2013.470

82. Bongiovanni A, Liverani C, Recine F, et al. Phase-II Trials of Pazopanib in Metastatic Neuroendocrine Neoplasia (mNEN): A Systematic Review and Meta-Analysis. *Front Oncol*. 2020;10:414. doi: 10.3389/fonc.2020.00414

83. Fallah J, Brave MH, Weinstok C, et al. FDA Approval Summary: Belzutifan for von Hippel-Lindau Disease-Associated Tumors. *Clin Cancer Res*. 2022;28(22):4843–4848. doi: 10.1158/1078-0432.CCR-22-1054

84. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol*. 2013;24(1):152–60. doi: 10.1093/annonc/mds276

85. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1980;303(21):1189–1194. doi: 10.1056/NEJM198011203032101

86. Arrivi G, Verrico M, Roberto M, et al. Capecitabine and Temozolomide (CAPTEM) in Advanced Neuroendocrine Neoplasms (NENs): A Systematic Review and Pooled Analysis. *Cancer Manag Res*. 2022;14:3507–3523. doi: 10.2147/CMAR.S372776

87. Borghesani M, Reni A, Lauricella E, et al. Efficacy and Toxicity Analysis of mFOLFIRINOX in High-Grade Gastroenteropancreatic Neuroendocrine Neoplasms. *J Natl Compr Canc Netw*. 2024;22(5):e247005. doi: 10.6004/jnccn.2024.7005

88. Strosberg JR, Caplin ME, Kunz PL, et al. NETTER-1 investigators. 177Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2021;22(12):1752–1763. doi: 10.1016/S1470-2045(21)00572-6

89. Singh S, Halperin D, Myrehaug S, et al. All the NETTER-2 Trial Investigators. [177Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2-3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study. *Lancet*. 2024;403(10446):2807–2817. doi: 10.1016/S0140-6736(24)00701-3

90. Strosberg JR, Halfdanarson TR, Bellizzi AM, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors. *Pancreas*. 2017;46(6):707–714. doi: 10.1097/MPA.0000000000000850

ОБ АВТОРАХ

*** Михеева Юлия Вадимовна,** канд. мед. наук;
адрес: Россия, 125367, Москва, Иваньковское ш., д. 3;
ORCID: 0009-0009-2644-3102;
eLibrary SPIN: 2298-1810;
e-mail: Yuliya.mikheeva@gmail.com

Румянцев Павел Олегович, д-р. мед. наук;
ORCID: 0000-0002-7721-634X;
eLibrary SPIN: 7085-7976;
e-mail: pavelrum@gmail.com

Пузаков Константин Константинович;
ORCID: 0000-0001-8784-895X;
eLibrary SPIN: 5800-6834;
e-mail: k_kovalchik@mail.ru

Слащук Константин Юрьевич, канд. мед. наук;
ORCID: 0000-0002-3220-2438;
eLibrary SPIN: 3079-8033;
e-mail: slashuk911@gmail.com

Омельчук Даниил Давидович;
ORCID: 0000-0002-2788-2352;
eLibrary SPIN: 6398-0656;
e-mail: lebedevldd@gmail.com

Потапенко Анастасия Витальевна;
ORCID: 0000-0001-8903-7325;
eLibrary SPIN: 6774-4710;
e-mail: osipchukanastasiia@gmail.com

Медведев Сергей Петрович;
ORCID: 0009-0008-2395-3169;
eLibrary SPIN: 6815-3714;
e-mail: feelyou2017@mail.ru

AUTHORS' INFO

*** Yuliya V. Mikheeva,** MD, Cand. Sci. (Medicine);
address: 3 Ivankovskoe highway, Moscow, Russia, 125367;
ORCID: 0009-0009-2644-3102;
eLibrary SPIN: 2298-1810;
e-mail: Yuliya.mikheeva@gmail.com

Pavel O. Rumyantsev, MD, Dr. Sci. (Medicine);
ORCID: 0000-0002-7721-634X;
eLibrary SPIN: 7085-7976;
e-mail: pavelrum@gmail.com

Konstantin K. Puzakov;
ORCID: 0000-0001-8784-895X;
eLibrary SPIN: 5800-6834;
e-mail: k_kovalchik@mail.ru

Konstantin Yu. Slashuk, MD, Cand. Sci. (Medicine);
ORCID: 0000-0002-3220-2438;
eLibrary SPIN: 3079-8033;
e-mail: slashuk911@gmail.com

Daniil D. Omelchuk;
ORCID: 0000-0002-2788-2352;
eLibrary SPIN: 6398-0656;
e-mail: lebedevldd@gmail.com

Anastasiya V. Potapenko;
ORCID: 0000-0001-8903-7325;
eLibrary SPIN: 6774-4710;
e-mail: osipchukanastasiia@gmail.com

Sergey P. Medvedev;
ORCID: 0009-0008-2395-3169;
eLibrary SPIN: 6815-3714;
e-mail: feelyou2017@mail.ru

* Corresponding author / Автор, ответственный за переписку