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Neuroendocrine Neoplasms: Pancreatic NEN, gastrointestinal NEN and neuroendocrine tumors of the lung

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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Neuroendocrine Neoplasms: Pancreatic NEN, gastrointestinal NEN and neuroendocrine tumors of the lung

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Compliance rules:

- Guideline
- Conflict of interests

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1 Summary

Neuroendocrine neoplasms (NENs) are a heterogeneous group of rare tumor diseases that occur predominantly in the gastrointestinal tract and pancreas (GEP-NENs) as well as in the lungs. They are classified based on their morphological differentiation and proliferative activity into well-differentiated neuroendocrine tumors (NETs G1-G3) and poorly differentiated neuroendocrine carcinomas (NECs). The majority of NETs are initially asymptomatic; some of the tumors are functionally active and can cause specific hormonal syndromes through the secretion of bioactive substances.

Prognosis and treatment are largely determined by the primary tumor site, differentiation, grading, tumor stage, growth rate, hormonal activity, and somatostatin receptor (SSTR) expression. Well-differentiated NETs often have a relatively slow disease course. Even in cases of metastatic disease, patients can live with their condition for many years, sometimes even decades. In contrast, NECs are characterized by high proliferative activity, rapid progression, and a significantly poorer prognosis. In addition to morphological imaging using CT and MRI, SSTR-PET/CT plays a central role in staging and treatment planning for well-differentiated NETs.

For localized NETs, complete surgical resection - or, in selected gastrointestinal NETs, endoscopic resection - is the treatment of choice. For small, asymptomatic pancreatic NETs, active surveillance may be preferred in specific situations. Treatment of advanced NETs is individualized and multimodal. Systemic treatment options include somatostatin analogs, peptide receptor radionuclide therapy (PRRT), molecularly targeted therapies, and chemotherapy; in addition, surgical and local ablative procedures may be employed. The selection and sequence of treatment modalities depend on tumor biology, SSTR expression, tumor dynamics, tumor burden, clinical symptoms, and treatment goals. For metastatic NEC, platinum-based chemotherapy remains the cornerstone of first-line therapy; increasing molecular characterization may open up additional targeted or immunotherapeutic options for selected patients.

Due to the biological heterogeneity and the often long-term course of the disease, the treatment of NETs should be multidisciplinary and, whenever possible, conducted at an experienced center. In addition to tumor control, the treatment of hormonal syndromes, nutrition and supportive care, rehabilitation, and long-term, risk-adapted follow-up are of high importance.

2 Basics

2.1 Definition and Basic Information

Neuroendocrine neoplasms (NENs) are rare epithelial tumors with neuroendocrine differentiation that can arise from cells of the diffuse neuroendocrine system and, in principle, develop in nearly all organs. This guideline addresses neuroendocrine neoplasms of the pancreas (pNEN), gastrointestinal neuroendocrine neoplasms (GI-NEN, with a focus on the small intestine), and neuroendocrine tumors of the lung (typical and atypical carcinoids), as these entities share commonalities in terms of biology, diagnosis, prognosis and treatment, but also exhibit significant differences.

Classification is based on the current WHO classification of tumors of the endocrine, thoracic, and gastrointestinal organs [1, 2]. For staging, the UICC TNM classifications (8th edition) [3] as well as - depending on the specific primary tumor location - the established ENETS-TNM classifications are used. Grading and histopathological classification are based on morphology, including immunohistochemistry, the Ki-67 proliferation index, mitotic count and, where applicable, areas of necrosis.

2.2 Epidemiology

NETs represent a rare and biologically heterogeneous group of tumors. The median age at diagnosis ranges from 65 to 68 years (with the exception of appendiceal NETs, where the median is 48 years). The age-standardized incidence of all NENs in Western countries is currently approximately 6-8 new cases per 100,000 inhabitants per year, with a steadily rising incidence over the past few decades, particularly for well-differentiated NETs [4, 5]. For Germany, this currently corresponds to an estimated 6,000-7,000 new cases per year, with gastroenteropancreatic NENs accounting for the largest proportion (2023: 816 pNENs, 3,937 GI-NENs, 1,205 lung NETs). Current German registry data confirm the ongoing rise in incidence as well as differences between the individual primary tumor sites and between NETs and NECs [6, 7]. Slightly more than 20% of all gastrointestinal NENs are G3 NENs (2% G3 NETs, 15% NECs, 5% high-grade Mixed Neuroendocrine-Non-Neuroendocrine Neoplasms [MiNEN]). G3 NENs are particularly common in the stomach, colon and pancreas (24%, 60% and 26%, respectively).

2.2.1 Pancreatic Neuroendocrine Neoplasms

Pancreatic NENs account for approximately 5-10% of all neuroendocrine neoplasms. The incidence of pancreatic NETs is currently about 0.8-1.2 per 100,000 inhabitants per year, while pancreatic NECs occur much less frequently, at about 0.05-0.1 per 100,000 inhabitants per year [4, 5].

2.2.2 Gastrointestinal Neuroendocrine Neoplasms (focus on the small intestine)

Gastrointestinal NENs constitute the largest group of neuroendocrine neoplasms, with approximately 4,000 cases per year in Germany. Small bowel NETs have an incidence of approximately 1.0-1.3 per 100,000 inhabitants per year and are among the most common gastroenteropancreatic NETs. Gastrointestinal NECs are significantly rarer, with an incidence of approximately 0.2-0.3 per 100,000 inhabitants per year [4, 7].

2.2.3 Neuroendocrine Neoplasms of the Lung

Pulmonary NETs (typical and atypical carcinoids) have an incidence of approximately 0.7–1.0 per 100,000 inhabitants per year. In Germany, just under 1,200 pulmonary NETs were diagnosed in 2023. In contrast, pulmonary NECs (small-cell and large-cell neuroendocrine carcinomas) represent the most common neuroendocrine neoplasms of the lung; these are not discussed in detail in this Onkopedia guideline [7]. Due to lung cancer screening, which has been established as a reimbursed service in Germany since April 2026, a significant increase in the incidence of bronchopulmonary carcinoids is expected for the coming years.

2.2.4 Mortality and Prognosis

The prognosis for NENs is largely determined by the degree of differentiation, tumor stage, and primary tumor location. Overall, GEP-NETs have a 5-year and 10-year survival rate of 83% and 76%, respectively [5].

Well-differentiated NETs generally have a favorable long-term prognosis. In population-based analyses, median overall survival (OS) is often >10 years. The 10-year OS rate for NETs is approximately 80% for non-metastatic cases and 40% for NETs with distant metastases, depending on the primary tumor and tumor stage [4, 5]. Some entities, such as localized type I appendix, rectal and gastric NETs, have an excellent long-term prognosis with virtually no restrictions.

NEC, on the other hand, are associated with a significantly poorer prognosis. The median OS for metastatic disease is usually 6-12 months, while the 5-year OS rate is less than 10-20% [7]. Accordingly, disease-specific mortality is significantly higher for NEC than for NETs.

The prognosis for pulmonary NETs is largely determined by the histological subtype and the tumor stage. Typical carcinoids have an excellent prognosis; the 5-year OS rate is >95% for localized disease and remains around 50-60% even for metastatic disease. Atypical carcinoids, on the other hand, exhibit more aggressive biological behavior, with a 5-year OS rate of 80-90% in the localized stage and 20-35% in cases of distant metastasis [4, 8]. Long-term data also confirm a 10-year OS rate of 82-95% for typical carcinoids and 31-67% for atypical carcinoids [4, 8].

2.3 Pathogenesis

The pathogenesis of NENs is still only partially understood and differs significantly between pancreatic, gastrointestinal, and pulmonary tumors. Common to all NENs is their origin from neuroendocrine-differentiated cells of the diffuse neuroendocrine system. While well-differentiated NETs are predominantly characterized by organ-specific molecular alterations with slow tumor progression, poorly differentiated NECs arise via distinct molecular mechanisms and exhibit pronounced genomic instability.

2.3.1 Pancreatic Neuroendocrine Neoplasms

Pancreatic NETs are predominantly sporadic; approximately 10-20% occur in the context of hereditary tumor syndromes, particularly *MEN1* syndrome. Characteristic features include alterations in chromatin remodeling and telomere stability due to mutations in *MEN1*, *DAXX,* and *ATRX*, as well as changes in the mTOR signaling pathway, which contribute significantly to tumor initiation and progression. In contrast, pancreatic NECs typically exhibit inactivations of *TP53* and *RB1*, as well as high genomic instability, suggesting a tumorigenesis independent of NETs [9, 10, 11].

2.3.2 Gastrointestinal Neuroendocrine Neoplasms

The pathogenesis of gastrointestinal NETs varies depending on the primary tumor site. Small intestine NETs are characterized by a low mutation burden; recurrent chromosomal aberrations and epigenetic alterations appear to play a greater role than classic driver mutations. In contrast, gastrointestinal NECs frequently exhibit alterations in *TP53*, *RB1*, *KRAS*, and *BRAF* and often share a mutation profile similar to that of classic adenocarcinomas of the same location [12, 13, 14, 15].

2.3.3 Neuroendocrine Tumors of the Lung

The pathogenesis of pulmonary NETs differs fundamentally from that of poorly differentiated, high-grade pulmonary NECs. Recurrent genetic alterations primarily involve *MEN1* as well as genes involved in chromatin remodeling (e.g., *ARID1A*, *EIF1AX* and members of the SWI/SNF complex), while mutations in classic oncogenic drivers such as *KRAS*, *EGFR* or *ALK* alterations are rarely detected [16, 17].

Compared to typical carcinoids (Ki-67 < 5%), atypical carcinoids exhibit a higher proliferation rate, greater chromosomal instability, and more frequent mutations in cell cycle regulation genes. However, molecular evidence does not support a transition to high-grade NECs. Rather, small-cell and large-cell NECs are considered biologically distinct entities characterized by near-universal inactivation of *TP53* and *RB1*, a high tumor mutation burden (TMB), and pronounced genomic instability. These fundamental molecular differences are also reflected in the significantly more aggressive clinical course of pulmonary NECs compared to well-differentiated carcinoids [16, 17, 18].

2.4 Risk Factors

The majority of NENs arise sporadically. Only a small proportion is attributable to hereditary tumor predisposition syndromes. The known risk factors differ between pancreatic, gastrointestinal, and pulmonary NENs.

2.4.1 Pancreatic Neuroendocrine Neoplasms

2.4.1.1 Genetic/Hereditary Risk Factors

Approximately 10-20% of pancreatic NETs arise in the context of hereditary tumor syndromes. The highest risk is associated with multiple endocrine neoplasia type 1 (*MEN1*) syndrome. Other predisposing syndromes include von Hippel-Lindau (*VHL*) syndrome, neurofibromatosis type 1 (*NF1*), tuberous sclerosis (*TSC1/TSC2*), and, rarely, MEN4 syndrome (CDKN1B) [19].

2.4.1.2 Acquired Risk Factors

For sporadic pNETs, advanced age as well as diabetes mellitus, obesity, and a positive family history have been described as potential risk factors. However, the evidence for these factors is weaker than for hereditary syndromes, and a causal relationship has not yet been conclusively demonstrated [19].

2.4.2 Gastrointestinal Neuroendocrine Neoplasms

2.4.2.1 Genetic/Hereditary Risk Factors

Hereditary syndromes play a lesser role overall in gastrointestinal NETs than in pNETs. Duodenal NETs can occur as part of *MEN1* syndrome; associations with *NF1* have also been described, particularly in periampullary or duodenal NETs [19, 20]. Furthermore, familial clusters of small bowel NETs have been described, although no specific syndrome has yet been defined [21].

2.4.2.2 Acquired Risk Factors

To date, only a few established acquired risk factors have been identified for small intestinal NETs. There is currently no consistent evidence regarding smoking, alcohol consumption, or dietary factors [22].

2.4.3 Neuroendocrine Tumors of the Lung

2.4.3.1 Genetic/Hereditary Risk Factors

Bronchopulmonary NETs are predominantly sporadic. However, a small proportion of pulmonary carcinoids occur in the context of *MEN1* syndrome; associations with other hereditary tumor syndromes have been described much less frequently [19].

2.4.3.2 Acquired Risk Factors

To date, no consistent association with cigarette smoking has been demonstrated for typical and atypical bronchopulmonary carcinoids. In contrast, smoking is the most important risk factor for neuroendocrine lung carcinomas, particularly small-cell lung cancer. No other established acquired risk factors for pulmonary NETs have been identified to date.

3 Prevention and Early Detection

3.1 Prevention

There are currently no specific evidence-based measures for the primary prevention of NETs. Since the majority of tumors arise sporadically and the underlying pathogenic mechanisms are only partially understood, no targeted strategies for preventing tumor development can be recommended.

General measures for cancer prevention - including avoiding tobacco use, maintaining a normal body weight, engaging in regular physical activity, and following a balanced diet - are generally recommended, although a specific protective effect for well-differentiated NENs has not yet been demonstrated. For pulmonary neuroendocrine carcinomas, cigarette smoking in particular represents the most important preventable risk factor.

For patients with hereditary tumor predisposition syndromes - particularly multiple endocrine neoplasia type 1 (*MEN1*) syndrome and, less commonly, VHL syndrome, *NF1*, or tuberous sclerosis - genetic counseling and organ-specific surveillance programs are of central importance. Through structured screening, NENs in these high-risk populations can often be diagnosed at early stages when curative treatment is still possible.

3.2 Early Detection

There are currently no established population-based early detection programs for NENs. However, some gastroenteropancreatic NENs are discovered incidentally during endoscopic screening examinations of the gastrointestinal tract, particularly during screening colonoscopy or diagnostic gastroscopy. For example, the prevalence of rectal NETs detected during screening colonoscopy is 0.05-0.07% [23].

There is also no specific screening for NETs of the lung. However, as part of structured lung cancer screening programs using low-dose computed tomography (low-dose CT) in individuals with high tobacco consumption, pulmonary carcinoids are occasionally diagnosed incidentally (as of April 2026, this will be part of the statutory screening program for former and current heavy smokers in Germany). For patients with hereditary tumor predisposition syndromes (e.g., *MEN1*), organ-specific surveillance programs are recommended.

4 Clinical characteristics

The clinical presentation of NENs is heterogeneous and is determined by the primary tumor site, tumor size, metastasis, and potential hormonal activity. A significant proportion of patients with well-differentiated NETs remain asymptomatic even in the metastatic stage of the disease, so the diagnosis is often made incidentally during ultrasound, imaging, or endoscopic examinations. In contrast, due to their rapid tumor growth, NECs usually manifest early with clinical complaints and systemic symptoms.

4.1 Pancreatic Neuroendocrine Tumors

Pancreatic NETs can be hormonally active or inactive. Non-functional pNETs, accounting for approximately 60-90%, represent the most common subgroup and often remain asymptomatic for a long time. As the tumor grows, upper abdominal pain, nausea, bloating, weight loss, or symptoms resulting from local tumor compression may occur.

Functional pNETs produce biologically active hormones/peptides and often lead to characteristic clinical syndromes even when the tumors are small. The most common functional tumors are insulinomas, which manifest as recurrent hypoglycemia accompanied by sweating, tremors, confusion or impaired consciousness (Whipple’s triad). Gastrinomas cause Zollinger-Ellison syndrome, characterized by multiple treatment-resistant peptic ulcers and chronic diarrhea. Less commonly, glucagonomas (diabetes mellitus, weight loss, necrolytic migratory erythema), VIPomas (profuse secretory diarrhea, hypokalemia, and achlorhydria; WDHA/Verner-Morrison syndrome) and somatostatinomas (diabetes mellitus, cholelithiasis, steatorrhea, and weight loss) are diagnosed. Other rare functional pNETs produce, for example, ACTH, GHRH or calcitonin and lead to corresponding endocrine syndromes.

4.2 Gastrointestinal Neuroendocrine Tumors

Gastrointestinal NETs, particularly those in the small intestine, often remain clinically asymptomatic for years. Symptoms usually arise only as a result of local tumor growth or mesenteric desmoplasia (retractile mesenteritis caused by local serotonin release) in the context of small intestine NETs and include intermittent abdominal pain, subileus, ileus, gastrointestinal bleeding, or iron-deficiency anemia.

4.3 Neuroendocrine Tumors of the Lung

Bronchopulmonary NETs are increasingly diagnosed as incidental findings during thoracic imaging. Centrally located tumors may present with symptoms such as chronic cough, hemoptysis, recurrent post-stenotic pneumonia, wheezing, or dyspnea - among other manifestations - and may be misdiagnosed as asthma or COPD. Peripherally located carcinoids, on the other hand, often remain asymptomatic even in advanced stages. Less commonly, hormone-related syndromes such as carcinoid syndrome, ectopic ACTH production leading to Cushing's syndrome, or GHRH secretion resulting in acromegaly may occur.

4.4 Carcinoid Syndrome

Carcinoid syndrome develops in approximately 20-30% of patients with metastatic small-intestinal NETs (typically in the presence of liver metastases), due to the bypassing of hepatic serotonin inactivation. The underlying cause is the release of vasoactive substances, particularly serotonin, into the systemic circulation. Clinically, the main symptoms are flushing, secretory diarrhea, abdominal cramps, and bronchospasm. Over the long term, carcinoid-related heart valve disease may develop, primarily affecting the tricuspid and pulmonary valves (endocardial fibrosis, Hedinger syndrome), which represents a significant prognostic factor.

5 Diagnosis

Table 1 shows the most relevant diagnostic methods for GEP-NETs and pulmonary NETs. These methods are used for the diagnosis of locally advanced or metastatic NETs. Individual entities such as type I gastric NETs, localized NETs of the appendix or rectum without risk factors do not require systemic staging examinations. In cases of uncertainty, this should be determined by a NET tumor board.

Table 1: Diagnosis and Staging of Neuroendocrine Tumors: Overview of Recommended Diagnostic Tests for pNET, Gastrointestinal NETs, and Pulmonary NETs

Procedures	pNET	GI-NET (primarily small intestine)	Pulmonary NET
Medical history and physical examination	Functional symptoms, family history (MEN1)	Abdominal symptoms, flushing, diarrhea, ileus	Cough, hemoptysis, dyspnea, pneumonia, endocrine symptoms
Clinical chemistry NET	Basic laboratory tests + HbA1c; hormone testing if suspected; chromogranin A*	Basic laboratory tests + chromogranin A*, 5-HIAA (always at initial diagnosis)	Complete blood count, liver/kidney function tests, chromogranin A*; ACTH/cortisol if suspected, 5-HIAA if suspected
Clinical chemistry NEC	Basic lab tests + Neuron-specific enolase (NSE)	Basic lab + neuron-specific enolase (NSE)	Basic lab + neuron-specific enolase (NSE)
Diagnosis of carcinoid syndrome	5-HIAA, serotonin, TTE	5-HIAA, serotonin, TTE	5-HIAA, serotonin, TTE
Abdominal ultrasound	Complementary to cross-sectional imaging	Complementary to cross-sectional imaging	Complementary to cross-sectional imaging
Contrast-enhanced CT	thorax/abdomen/pelvis	Thorax/abdomen/pelvis	Chest with upper abdomen
MRI	Liver MRI, pancreas MRI as needed	Liver MRI for liver lesions	Liver MRI for liver lesions Cerebral MRI recommended only if symptoms are present
Endoscopy	Endosonography ± biopsy	Gastroscopy, colonoscopy, capsule/balloon enteroscopy if necessary	Depending on the location, bronchoscopy with biopsy (Note: risk of bleeding)
Functional imaging	SSTR-PET/CT (^{68}Ga)#	SSTR-PET/CT (^{68}Ga)	SSTR-PET/CT (^{68}Ga) - note: heterogeneous expression FDG-PET/CT, if indicated, for atypical carcinoids, high proliferation, or lack of SSTR expression
Functional imaging for NET G3 or NEC	SSTR-PET/CT (^{68}Ga) and/or FDG-PET/CT**	SSTR-PET/CT (^{68}Ga) and/or FDG-PET/CT**	
Histology	WHO, Ki-67, IHC	WHO, Ki-67, IHC	WHO, Ki-67, mitoses, necrosis, IHC

Legend:
** Chromogranin A should be interpreted only as a supplementary finding due to its limited specificity.*
*** FDG-PET/CT for NEC in localized stages to rule out occult distant metastases*
 # For insulinomas, a ^{68}Ga-DOTA-exendin-4 PET/CT may also be offered to improve localization (alternatively, ^{18}F-F-DOPA)

5.1 Classification and Grading

The histopathological classification of NENs is performed according to the current WHO Classification of Tumors (5th edition), with organ-specific classifications for gastroenteropancreatic, thoracic, and endocrine tumors. A fundamental distinction is made between well-differentiated NETs and poorly differentiated NECs (Table 2). These entities differ fundamentally in terms of morphology, molecular biology, clinical course, and therapeutic approach and should therefore not be regarded as different grades of the same disease.

Table 2: WHO Classification of Neuroendocrine Neoplasms (5th edition, 2022) [24]

Differentiation	Non-thoracic organs, such as GEP-NETs			Thoracic organs		
	Terminology	Mitoses / 2 mm²	Ki-67 index	Terminology	Mitosis/Necrosis	Ki-67 index
Well-differentiated	NET G1	<2	<3%	Typical carcinoid (TC)	0–1; no necrosis	up to 5%**
	NET G2*	2–20	3–20%	Atypical carcinoid (AC)	2–10; focal necrosis	up to 20%**
	NET G3	>20	>20%	–	–	–
Poorly differentiated	Large-cell NEC	>20	>20%	LCNEC	>10; necrosis present	40–80%**
	Small-cell NEC	>20	>20%	SCLC	>10; necrosis present	50–100%**
Mixed neoplasms	MiNEN***	–	–	Combined SCLC/ LCNEC****	–	–

Legend:
** For pancreatic NETs, a subdivision of G2 into G2a and G2b has been proposed.*
*** The Ki-67 index is not currently a formal grading criterion in the WHO classification of thoracic tumors.*
**** Each tumor component comprises at least 30% of the tumor cell population.*
***** No minimum proportion is defined for the non-neuroendocrine component.*
Abbreviations: TC = typical carcinoid; AC = atypical carcinoid; LCNEC = large cell neuroendocrine carcinoma; SCLC = small cell lung carcinoma; NET = neuroendocrine tumor; NEC = neuroendocrine carcinoma; MiNEN = mixed neuroendocrine/non-neuroendocrine neoplasm.

The grading of gastroenteropancreatic NETs is based on the Ki-67 proliferation index and the mitotic count per 2 mm² and is classified according to the WHO into NET G1, G2 and G3. Poorly differentiated NECs are classified as high-grade neoplasms regardless of the Ki-67 index and are subdivided into small-cell and large-cell NECs. The current WHO classification thus explicitly recognizes that G3 NETs represent a distinct tumor entity biologically and clinically and differ significantly from NECs [25].

For pulmonary NENs, the WHO classification continues to be based on morphological criteria, distinguishing between typical carcinoid (TC), atypical carcinoid (AC), large-cell NEC (LCNEC), and small-cell lung cancer (SCLC). The distinction between TC and AC is based on the mitotic count and the presence of necrosis. The Ki-67 proliferation index can aid in diagnostic classification but is not yet a formal WHO grading criterion for thoracic PNETs.

In clinical practice, in addition to the histological subtype, the tumor stage (TNM), Ki-67 proliferation index, mitotic count, degree of differentiation, somatostatin receptor expression, and the functional activity of the tumor are particularly crucial, as these parameters significantly influence both prognosis and treatment planning. The recent statement from the International Association for the Study of Lung Cancer (IASLC) proposed a further refinement of the classification of pulmonary NENs. In addition to retaining the established histological classification into typical and atypical carcinoids, the statement recommends, for the first time, a closer alignment with the classification of gastroenteropancreatic NETs. This includes the incorporation of the Ki-67 proliferation index as a supplementary diagnostic criterion, as well as the formal recognition of a rare pulmonary NET G3 (NET G1: Ki-67 ≤ 5%; NET G2: Ki-67 5–20%; NET G3: Ki-67 > 20%). These tumors exhibit increased proliferative activity but continue to display the morphological and molecular characteristics of well-differentiated NETs, thereby differing fundamentally from small-cell and large-cell NECs. The proposed classification is intended to improve diagnostic accuracy and enable more biologically oriented treatment decisions in the future [18].

The current WHO classification also takes into account that the proliferation index may change over the course of the disease. In particular, in cases of disease progression during therapy, an increase in the Ki-67 index with a transition to a higher grade has been described for both gas-

troenteropancreatic and pulmonary NETs. In cases of clinically unexpected progression or a discrepancy between imaging findings and previous tumor behavior, a repeat biopsy should therefore be considered to reevaluate morphology and Ki-67 index.

5.2 Immunohistochemistry

Immunohistochemical testing is used to confirm neuroendocrine differentiation, identify the primary tumor, and distinguish the tumor from other neoplasms. Synaptophysin, chromogranin A, and INSM1 (insulinoma-associated protein 1) are used as standard markers for gastroenteropancreatic and pulmonary NETs. The Ki-67 proliferation index is an essential component of histopathological evaluation and forms the basis for WHO grading in gastroenteropancreatic NETs [26].

For gastroenteropancreatic NENs (GEP-NENs), organ-specific markers such as CDX2, PITX2 (small intestine), ISL1, PAX8, PDX1 (pancreas), as well as hormonal markers (e.g., insulin, gastrin, glucagon, somatostatin, serotonin) may help to identify the primary tumor and characterize functional NETs.

For pulmonary NETs, TTF-1, OTP (Orthopedia Homeobox), and ASCL1 are additionally recommended. OTP, in particular, has high specificity for well-differentiated pulmonary carcinoids and is associated with a more favorable prognosis. The IASLC further recommends routine determination of the Ki-67 proliferation index as a supplementary diagnostic parameter, particularly to distinguish highly proliferative carcinoids from small-cell and large-cell NEC, even though Ki-67 is not yet a formal WHO grading criterion for thoracic PNETs [18].

5.3 Molecular Pathology

Molecular diagnostics are not currently a mandatory component of routine diagnostics for NENs, but they can help distinguish well-differentiated NETs from poorly differentiated NECs in diagnostically challenging cases. The diagnosis continues to be based primarily on morphology, immunohistochemistry and proliferative activity. Molecular analyses represent a complementary diagnostic method and should be considered in specialized centers, particularly for highly proliferative or morphologically ambiguous tumors [18, 27].

Well-differentiated GEP-NETs - particularly pancreatic NETs - are molecularly characterized predominantly by alterations in *MEN1*, *DAXX,* and *ATRX,* as well as changes in the mTOR signaling pathway. In contrast, GEP-NEC typically exhibit inactivations of *TP53* and *RB1*, as well as significantly higher genomic instability and tumor mutation burden. These distinct molecular profiles support the view that NETs and NECs represent biologically distinct tumor entities.

NETs and NECs also differ fundamentally in pulmonary NENs. Pulmonary carcinoids generally have a low mutation burden and predominantly exhibit alterations in chromatin regulation genes (e.g., *MEN1*), while TP53 and RB1 alterations are rarely detected. In contrast, small-cell and large-cell NEC are almost invariably characterized by biallelic inactivations of *TP53* and *RB1*. In principle, molecular findings should be considered as supplementary diagnostic information, particularly in highly proliferative G3 NETs and morphologically borderline cases. However, molecular diagnostics do not replace histopathological evaluation [18].

5.4 Differentiation Between NET G3, NEC, and MiNEN

Distinguishing between G3 NETs, poorly differentiated NECs, and high-grade mixed neuroendocrine/non-neuroendocrine neoplasms (MiNEN) is essential due to their differing prognoses and therapeutic implications. The diagnosis should always be based on an integrated evalua-

tion of histomorphology, immunohistochemistry and - in selected cases - molecular pathological findings; no single parameter allows for reliable differentiation [18, 28].

Morphology is the primary factor in distinguishing between these two entities. Despite a Ki-67 index >20%, G3 NETs continue to exhibit the typical organoid architecture of well-differentiated NETs. In contrast, NECs exhibit a poorly differentiated morphology with marked cellular atypia, high mitotic activity, diffuse growth, and, in most cases, extensive necrosis. MiNENs are defined by the simultaneous presence of a neuroendocrine and a non-neuroendocrine epithelial tumor component (each component must account for at least 30%, which, by definition, cannot be determined from biopsies), both of which must be morphologically distinct [28].

Immunohistochemistry aids in diagnosis and is particularly useful for confirming neuroendocrine differentiation as well as characterizing both tumor components in MiNEN. In diagnostically challenging cases, molecular pathology can further assist in classification. However, the current WHO and IASLC recommendations emphasize that molecular alterations complement morphological assessment but do not replace it [18].

5.5 Laboratory Diagnostics

Laboratory diagnostics play a supplementary role in NEN and do not replace either histopathological confirmation or morphological and functional imaging. Routine tumor markers are not suitable for screening for or ruling out a NEN due to their limited sensitivity and specificity. The selection of laboratory tests should therefore be guided by the clinical question as well as the tumor's potential hormonal function (see Table 3).

Table 3: Laboratory Markers for Neuroendocrine Neoplasms

Marker	Main Indication	Important Limitations / Confounders
Chromogranin A (CgA)	Supplementary follow-up monitoring of selected well-differentiated NETs	Not suitable for screening; PPI therapy, renal insufficiency, atrophic gastritis, hypergastrinemia, liver disease, inflammation, heart failure
Neuron-specific enolase (NSE)	Supplementary for highly proliferative NECs	Low sensitivity in NETs; hemolysis, neurological disorders, and other neuroendocrine tumors may affect the results
5-HIAA (24-hour urine or plasma)	Diagnosis and course of carcinoid syndrome	Serotonin-rich diet (e.g., bananas, pineapple, kiwi, avocado, tomatoes, walnuts), medications, renal function, collection errors

Note: None of the markers listed are suitable for screening for or ruling out a NET. All laboratory parameters should be interpreted in a clinical context and with consideration of potential confounding factors.

5.5.1 Chromogranin A (CgA)

Chromogranin A (CgA) is the most commonly measured circulating biomarker in well-differentiated NETs. It may correlate with the tumor mass, particularly in cases of metastasis or high tumor burden, and can be used in the individual patient's course to supplement the assessment of treatment response [29, 30].

Interpreting increased CgA levels is complicated by numerous confounding factors. The most common causes of false-positive results include:

- Treatment with proton pump inhibitors (PPIs) (most common cause; discontinue treatment at least ≥2 weeks before testing)
- Chronic renal insufficiency
- Atrophic gastritis or pernicious anemia

- Hypergastrinemia
- Chronic liver disease
- Chronic inflammatory diseases
- Heart failure
- Other malignant diseases

An isolated increase in CgA levels should therefore never lead to a diagnosis of a NEN, but should always be interpreted within the clinical context.

5.5.2 Neuron-Specific Enolase (NSE)

Neuron-specific enolase (NSE) has only low sensitivity and specificity in well-differentiated NETs and is therefore not routinely recommended. Increased levels are more commonly found in highly proliferative NECs, particularly in SCLC and extrapulmonary NECs, but can also be influenced by numerous non-neoplastic causes. These include, in particular, hemolysis, neurological disorders, and other neuroendocrine or neuroectodermal tumors. The value of NSE therefore lies primarily in the supplementary assessment of disease progression in selected NECs and not in primary diagnosis [31].

5.5.3 5-Hydroxyindoleacetic Acid (5-HIAA)

Measurement of 5-hydroxyindoleacetic acid (5-HIAA) in a 24-hour urine collection is the established laboratory marker for suspected carcinoid syndrome and should be performed, in particular, in patients with flushing, secretory diarrhea, or suspected serotonin-producing small intestinal NETs. A one-time 5-HIAA test should also be performed in all patients with metastatic small intestinal NETs. Increased 5-HIAA levels correlate with serotonin production and are associated with the risk of carcinoid-related heart disease [32].

Potential confounding factors should be taken into account prior to the test. Serotonin-rich foods should be avoided for at least 48-72 hours before and during the collection period, including in particular:

- Bananas
- Pineapples
- Kiwis
- Avocados
- Plums
- Tomatoes
- Eggplants
- Walnuts

Various medications can also influence test results and should be taken into account - provided it is clinically justifiable. These include, among others, acetaminophen, levodopa, methyldopa, amphetamines, and serotonin-modulating medications. In addition, malabsorption syndromes, chronic diarrhea, or impaired kidney function can complicate the interpretation of results.

Alternatively, the measurement of 5-HIAA in plasma is becoming increasingly important, as it offers comparable diagnostic value and eliminates the need for a 24-hour urine collection. However, its availability is currently still limited, and the method has not yet been widely established [33].

5.6 TNM/UICC and ENETS Classification

Staging is performed according to UICC 8 [3]. For PNETs of the pancreas and appendix, a different ENETS classification applies [34, 35]; therefore, the classification used for these two organs should be specified, or ideally, both classification systems should be used.

5.7 Functional Imaging Using SSTR PET/CT and FDG PET/CT

For well-differentiated GEP-NETs and pulmonary NETs, SSTR PET/CT, usually with ^{68}Ga-labeled somatostatin analogs, is part of the initial staging. It complements contrast-enhanced CT or MRI and, in particular, improves the detection of small primary tumors (especially in small intestinal NETs), locoregional lymph node metastases, as well as bone and other distant metastases. Furthermore, it assesses SSTR expression in all tumor sites and can thereby influence tumor staging as well as the planning of surgical or systemic therapy [36, 37]. In pulmonary NETs, it is particularly relevant for typical and atypical carcinoids; an additional ^{18}F-FDG PET/CT should be considered in cases of atypical histology, high proliferation, rapid progression, or discordant findings [38].

In NEC, ^{18}F-FDG-PET/CT is primarily relevant due to the typically low or heterogeneous SSTR expression. It is used to assess the locoregional extent of the tumor and, in particular, to detect or rule out clinically occult distant metastases. In cases of suspected localized or locoregionally confined disease where curative/local therapy is planned, an FDG-PET/CT scan is mandatory, as the detection of additional metastases fundamentally alters the treatment plan. However, for generally metastatic NEC, PET/CT does not replace contrast-enhanced CT or MRI and offers no additional benefit in most cases. A supplementary SSTR-PET/CT is indicated in NEC only in selected cases, e.g., in cases of low proliferation (Ki-67 < 55%) or if there is immunohistochemical evidence of SSTR expression [37].

The intensity of tumor uptake on SSTR-PET/CT can be described semiquantitatively using the modified Krenning score:

0: no pathological uptake

1: Uptake lower than that of the liver

2: Uptake approximately equivalent to that of the liver

3: Uptake greater than that of the liver

4: Uptake higher than that of the spleen

Uptake at least equal to that of the liver, corresponding to a Krenning score ≥2, is generally considered a prerequisite for considering PRRT. However, receptor positivity of all relevant tumor manifestations, possible SSTR-negative or FDG-positive lesions, and the overall clinical situation must also be taken into account. Since SSTR-PET/CT can yield higher Krenning scores than historical ^{111}in-pentetreotide scintigraphy, particularly for small lesions, the score must always be interpreted in the context of the method used [36, 39].

6 Treatment

6.1 Treatment Structure

The treatment of NENs should always be conducted on a multidisciplinary basis, involving medical oncology, visceral surgery, radiation oncology, gastroenterology, radiology, endocrinology, pathology, and nuclear medicine. Due to the rarity of the disease, diagnosis and treatment are

recommended to be performed, whenever possible, at an experienced center or within the framework of a specialized neuroendocrine tumor board. Multidisciplinary planning is required for every initial treatment recommendation and when changing therapy. In addition to determining the best possible standard therapy, the potential inclusion in clinical trials should be part of the discussion in the tumor board.

6.1.1 Localized Stages in NETs

6.1.1.1 Pancreatic NETs

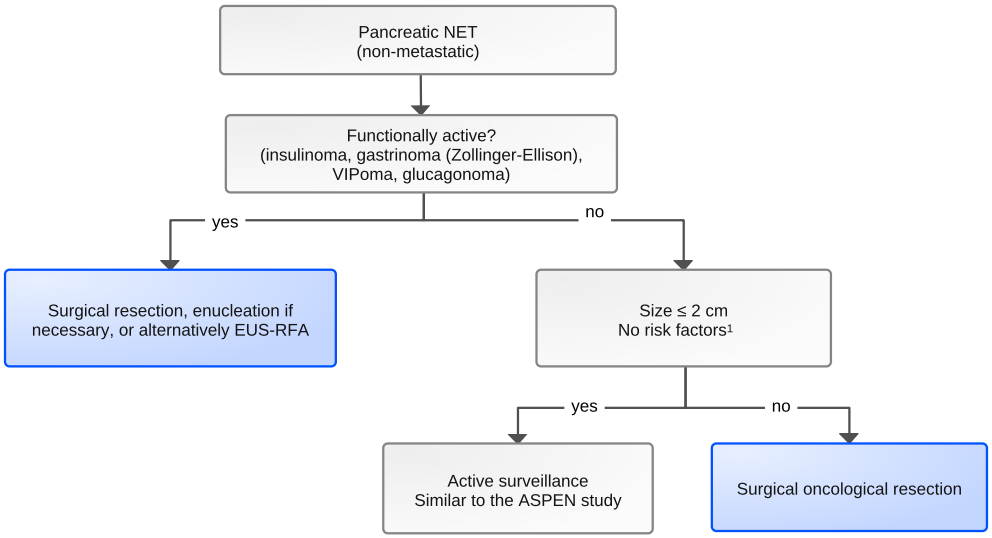
Complete surgical resection, following standardized comprehensive staging and preoperative review by the tumor board, is the only established potentially curative therapy for localized functional pNETs as well as for non-functional pNETs with an increased risk of progression or metastasis. The approach depends on tumor size and location, functionality, growth, Ki-67 index, relationship to the main duct, possible lymph node involvement, age, comorbidities, and hereditary background. Depending on the findings, oncological resections with regional lymphadenectomy or, for selected small tumors, parenchyma-sparing procedures such as enucleation or central pancreatic resections may be considered [40, 41]. In recent years, endoscopic, endosonography-guided radiofrequency ablation has proven to be a safe method for treating insulinomas and non-functioning pNETs up to 2 cm in size, comparable to surgery. The latter applies particularly to patients with comorbidities and an increased surgical risk [42, 43].

For asymptomatic, sporadic, non-functioning pNETs up to 2 cm, structured active surveillance should be considered as an alternative to surgery. The interim analysis of the prospective, multicenter ASPEN study showed that this approach appears safe in the short term for carefully selected patients [44]. However, a size limit of 2 cm alone is not sufficient for making this decision. Factors strongly supporting surgery include, in particular, clinical symptoms or hormonal activity, significant tumor growth, a dilated main pancreatic duct, imaging-suspicious lymph nodes, infiltrative growth, higher tumor grade or a Ki-67 index in the G2 range, a tumor size > 2 cm, and young age. The ASPEN analysis found histological risk features in a significant proportion of the tumors that underwent surgery; therefore, lesions larger than 1 cm in particular should be evaluated on a case-by-case basis. The follow-up program should include high-quality contrast-enhanced CT or MRI and, if necessary, endosonography, initially after approximately 6 months and subsequently at individually tailored intervals if the course remains stable.

Neoadjuvant therapy is not indicated for primarily resectable pNETs. For borderline-resectable or locally advanced tumors where an R0 resection appears achievable following significant remission, PRRT or remission-inducing chemotherapy, particularly capecitabine/temozolomide or streptozotocin/5-FU, may be used on a case-by-case basis. This strategy is not well-established and should be performed at an experienced center, preferably within the context of clinical trials. Current guidelines cite small retrospective series and case reports in this regard; reliable patient selection criteria have not yet been defined.

Following R0 or R1 resection of a well-differentiated pNET, there is no indication for adjuvant therapy outside of clinical trials. To date, no benefit regarding recurrence-free or OS has been demonstrated for somatostatin analogs, chemotherapy, targeted therapies, or PRRT. Prospective studies are currently investigating adjuvant approaches in patients at increased risk of recurrence.

Figure 1: First-line therapy for non-metastatic pancreatic NET



Legend:
curative intent
[1] Risk factors: Size ≥2 cm, growth rate (>0.5 cm/year), main duct dilation, suspicious lymph nodes, G2 (Ki-67 >5%)
EUS-RFA – endosonography-guided radiofrequency ablation

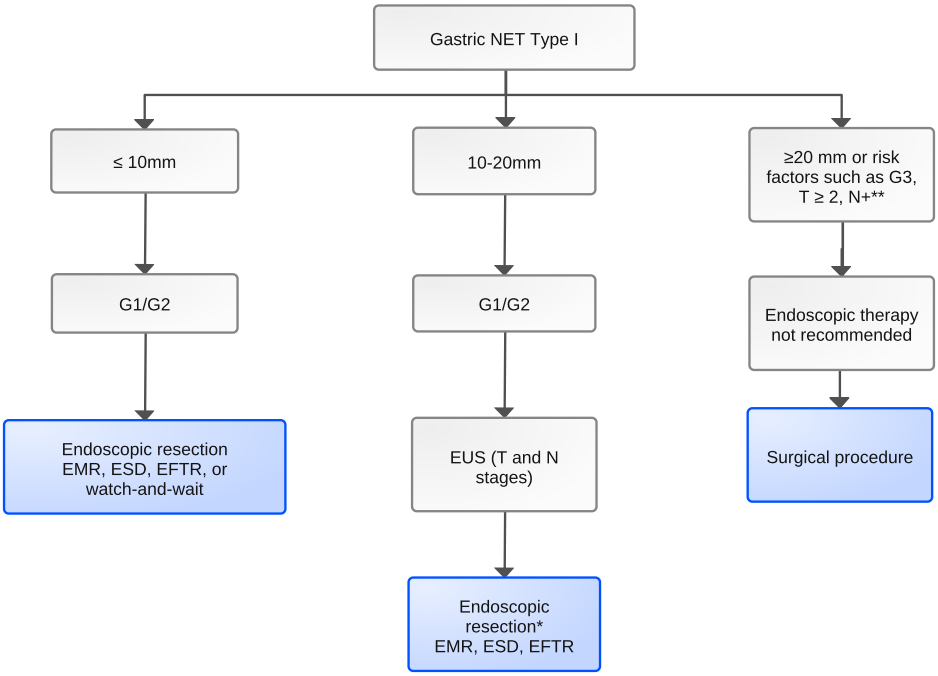
6.1.1.2 Gastrointestinal NETs

For gastrointestinal NETs as well, complete surgical resection, including adequate lymphadenectomy, is the standard of care for localized disease. The surgical approach depends on the primary tumor location, tumor size and, if applicable, the pattern of local metastatic spread. In addition to surgical procedures, endoscopic resection techniques play an important role in selected gastric, duodenal and rectal NETs. The endoscopic therapy is primarily determined by the primary tumor location, size, depth of invasion, grade and lymphovascular invasion. Depending on the size and depth of invasion, conventional or modified endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), or full-thickness resection (EFTR) may be considered.

Endoscopic local therapy is not suitable for small intestinal NETs of the jejunum or ileum. The standard of care is oncological resection with systematic regional lymphadenectomy of 8-12 lymph nodes and exploration of the entire small intestine, as the tumors are often multifocal and mesenteric lymph node metastases may be present even in small primary tumors.

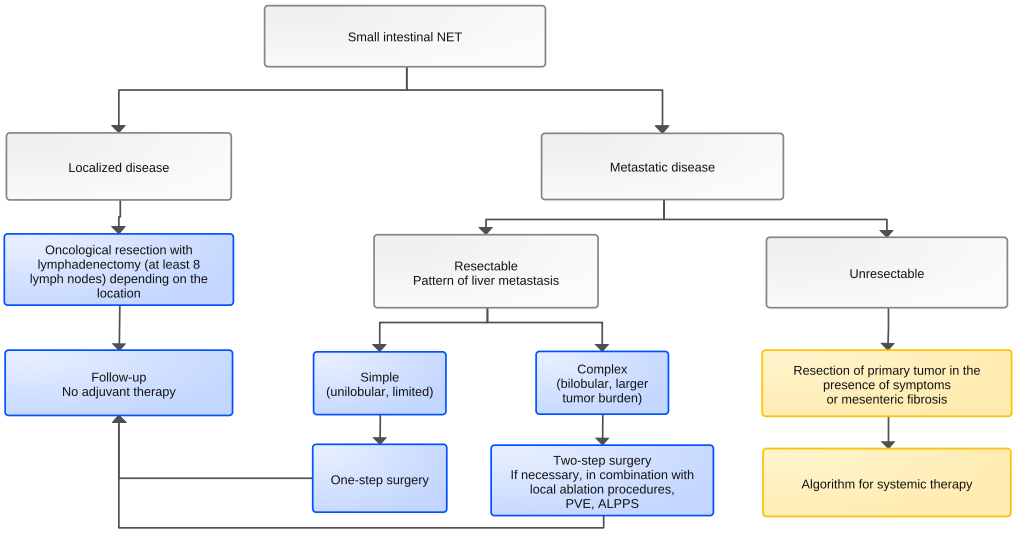
Neoadjuvant therapy is not established for localized GI-NETs. Likewise, there is no indication for adjuvant systemic therapy following R0 resection. Retrospective analyses have failed to demonstrate a benefit for either chemotherapy or somatostatin analogs in terms of recurrence-free survival (RFS) or OS. The role of adjuvant PRRT in resected small bowel NETs with lymph node involvement is currently being investigated in prospective studies (APSIN; EudraCT 2024-518236-36-00). For localized gastric NETs (Types 1 through 3), duodenal NETs and rectal NETs, separate organ-specific algorithms should be used due to differences in biology and local treatment strategies. For more information, please refer to the available ENETS guidelines [45, 46].

Figure 2: Management of Type I Gastric NETs



Legend:
curative intent
EMR – endoscopic mucosal resection; ESD – endoscopic submucosal dissection; EFTR – endoscopic full-thickness resection
** for uT1 and uN0*
*** Additional preoperative staging with CT/MRI and Ga-68 PET/CT is required*

Figure 3: First-Line Therapy for Small Intestinal NETs



Legend:
curative intent; non-curative intent
PVE – portal vein embolization; ALPPS – Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy: ligation of the right portal vein, combined with parenchymal dissection along the planned resection line

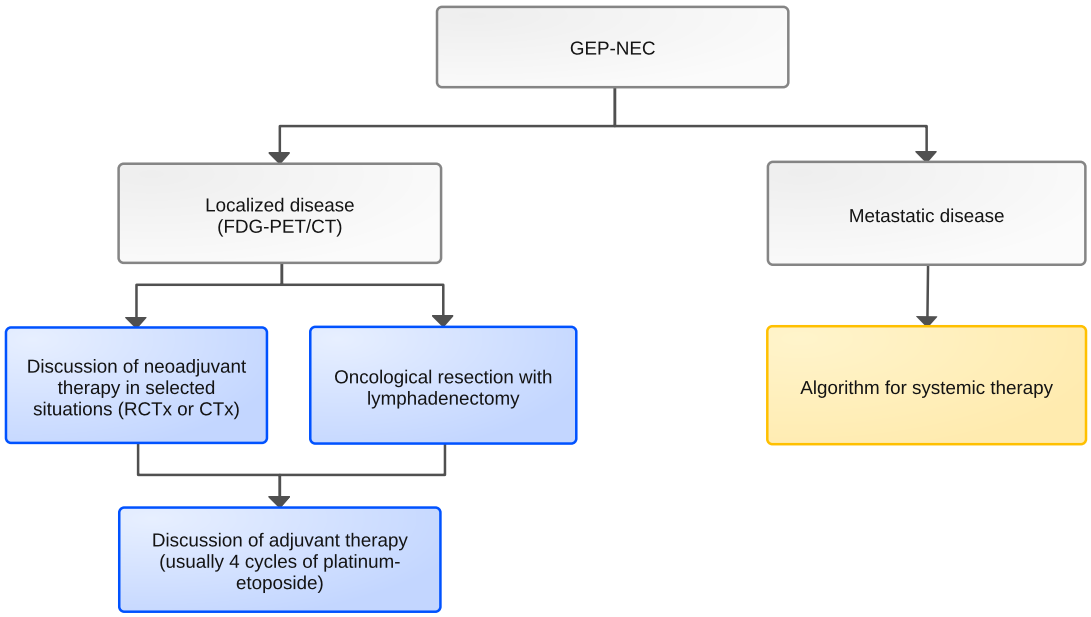
6.1.1.3 Localized Stages in GEP-NEC

In cases of localized GEP-NEC, a complete staging evaluation, including FDG-PET/CT, should be performed first to identify or rule out occult distant metastases. Only patients without distant metastases are eligible for a curative treatment approach due to the overall very poor prognosis.

Due to the high rate of systemic micrometastasis, a multimodal treatment approach is frequently recommended for resectable localized NEC. Depending on the primary tumor site, neoadjuvant or perioperative platinum-based chemotherapy may be considered, although prospective randomized data are lacking. This applies in particular to NEC of the esophagus and rectum, where neoadjuvant chemoradiotherapy may also be used. The treatment decision should be made by an experienced multidisciplinary tumor board [35].

Following curative resection, adjuvant platinum-based chemotherapy may be considered in selected patients. A proven benefit in terms of OS has not been demonstrated; the recommendation is based primarily on retrospective data and expert consensus [35, 47]. Adjuvant therapy appears particularly appropriate in cases of high recurrence risk, e.g., lymph node-positive disease, R1 resection, high tumor burden, high proliferative activity or other unfavorable histopathological risk factors. A regimen of carboplatin/cisplatin plus etoposide for 4 cycles may be used. This should be followed by close radiological monitoring.

Figure 4: Therapeutic Approach for GEP-NEC



Legend:
curative intent; non-curative intent
RCTx – Radiochemotherapy; CTx – Chemotherapy; Platinum – Cisplatin or Carboplatin

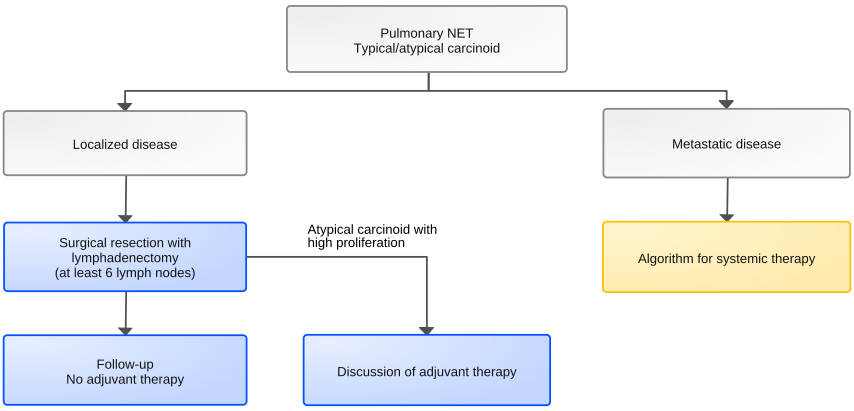
6.1.1.4 Localized Stages of Lung NETs

For typical and atypical pulmonary carcinoids, complete surgical resection with systematic mediastinal lymph node evaluation or dissection is the treatment of choice, following complete staging and preoperative review by a multidisciplinary tumor board. The goal is a parenchyma-sparing, oncologically complete resection while preserving as much lung function as possible. The surgical approach depends on tumor location, tumor size, and pulmonary reserve. Pathological lymph node staging is mandatory. A TNM classification should be performed. All patients who undergo surgery should be presented to a certified tumor board postoperatively.

Neoadjuvant therapy is not currently recommended for typical or atypical carcinoids.

There is also no evidence to date supporting adjuvant systemic therapy. Therefore, structured follow-up is recommended after complete resection. Only in cases of atypical carcinoids with a high risk of recurrence may a multidisciplinary discussion take place on a case-by-case basis; however, prospective studies are lacking [48].

Figure 5: Therapeutic Approach for Pulmonary NETs



Legend:
curative intent; non-curative intent

6.2 Treatment Options for Symptom Control

Treatment of hormonally active NETs aims to control hormone-related symptoms and improve quality of life. Somatostatin analogs (SSAs; octreotide LAR or lanreotide autogel) are the standard first-line therapy, regardless of the primary tumor location. Control of flushing and diarrhea is achieved in approximately 60-80% of patients. Consequently, a biochemical response, documented by a decrease in 5-HIAA levels, is also observed in approximately 50% of cases. SSA are generally well tolerated; common, mostly transient side effects include gastrointestinal symptoms such as diarrhea, abdominal pain, flatulence and nausea [49, 50, 51].

If adequate symptom control is not achieved with SSA, additional therapeutic options and approaches may be initiated. These include telotristat ethyl (for diarrhea), intensification of SSA therapy, addition of IFN-alpha, ablative or locoregional procedures, surgical procedures to reduce tumor mass and PRRT.

Patients with persistent carcinoid diarrhea despite SSA therapy should additionally receive telotristat ethyl (250 mg every 8 hours per day). As a tryptophan hydroxylase inhibitor, telotristatethyl reduces serotonin synthesis and leads to a significant reduction in stool frequency of approximately 45%, as well as an improvement in quality of life (TELESTAR, TELECAST, TELEPRO studies). The drug is approved for use in combination with somatostatin analogs to treat inadequately controlled carcinoid diarrhea [52, 53, 54].

In cases of persistent hormonal symptoms despite radiologically stable disease or slow tumor growth, a dose escalation by shortening the administration interval of long-acting somatostatin analogs (e.g., to every 3 or 2 weeks) may be considered. Although prospective data are limited, this approach is consistent with clinical practice. Alternatively, short-acting subcutaneous octreotide injections can be used for symptom-oriented treatment as needed.

Locoregional and local ablative procedures, as well as surgical debulking, are effective therapies for improving carcinoid syndrome. A meta-analysis by Hofland, based on 25 studies involving over 500 patients, showed an improvement in symptom control in approximately 80% of cases, with a biochemical response in 5-HIAA in 60% of cases [50].

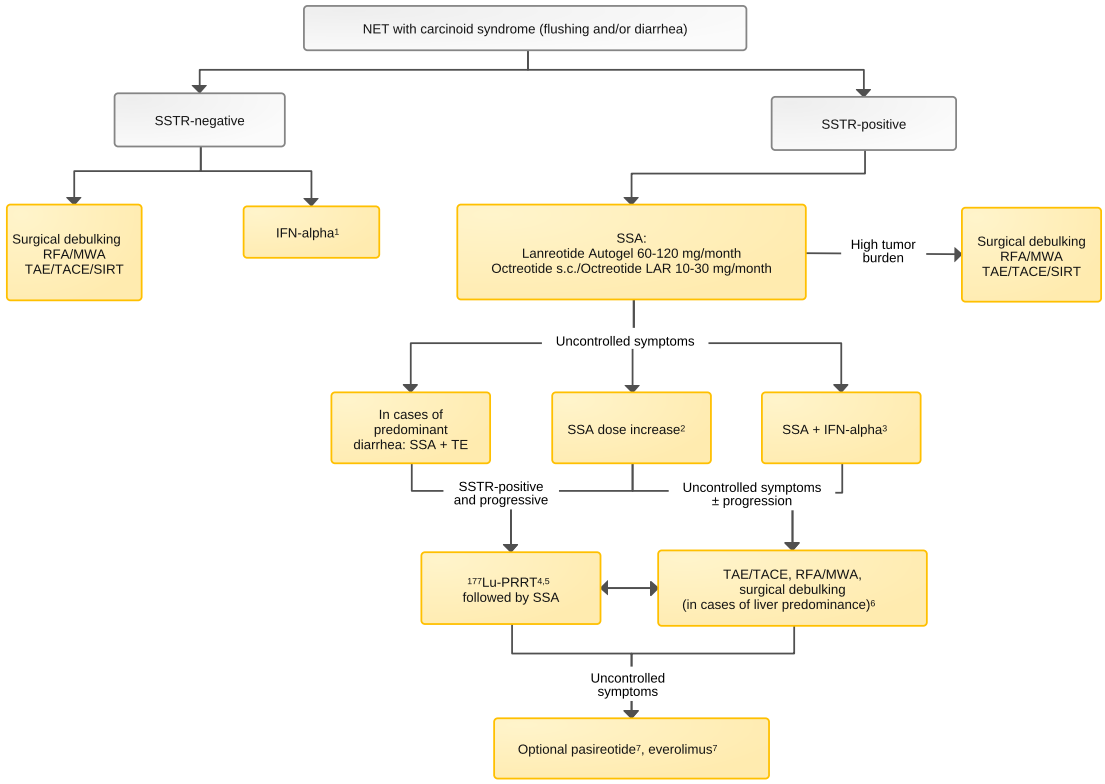
If symptom control is inadequate with somatostatin analogs, interferon-α (IFN-α, 3-5 million IU subcutaneously 3 times per week) may be considered as an add-on second-line therapy. However, due to its less favorable side effect profile (fatigue, weight loss, depressive mood swings), it is now used only in select cases. Furthermore, IFN-α is now rarely available.

Pasireotide LAR may be considered as an off-label therapy for treatment-refractory carcinoid syndrome [55]. Furthermore, ondansetron has been reported to be effective in diarrhea-predominant carcinoid syndrome [56].

In cases of progressive disease, peptide receptor radionuclide therapy (PRRT) can help control hormonal symptoms in addition to its antitumor effect. The NETTER-1 study in particular demonstrated a delayed decline in quality of life related to diarrhea. During or immediately after PRRT, there may be a temporary exacerbation of hormonal symptoms, such as an increase in hypoglycemia in insulinoma or diarrhea in carcinoid syndrome. Close clinical monitoring is therefore required [57, 58, 59].

For certain functionally active pancreatic NETs, additional syndrome-specific measures are indicated. In metastatic insulinoma, diazoxide can be used to control hypoglycemia, and somatostatin analogs should be administered under careful monitoring due to the potential for increased hypoglycemia. For gastrinomas, high-dose proton pump inhibitors are the standard of care for controlling acid hypersecretion; SSA may be added if symptoms persist. SSA are also part of the standard treatment for VIPomas, glucagonomas and other hormonally active pancreatic NETs. If symptoms remain inadequately controlled despite SSA therapy, PRRT is an effective treatment option [37].

Figure 6: Treatment of Carcinoid Syndrome (adapted from [37])



Legend:
non-curative intent
SSTR – somatostatin receptor; RFA – radiofrequency ablation; MWA – microwave ablation; TAE – transarterial embolization; TACE – transarterial chemoembolization; SIRT – selective internal radiation therapy; IFN – interferon; SSA – somatostatin analogs; TE – telotristat; Lu – Lutetium; PRRT – Peptide receptor-targeted radioligand therapy; We. – Week; Mon. – Month; s.c. – Subcutaneous
[1] SSA may also be considered here, particularly in cases of low tumor burden (very small lesion, possibly false-negative SSTR diagnosis)
[2] Shorten the dosing interval to 2 or 3 weeks (off-label) or add short-acting octreotide s.c.
[3] IFN-alpha should be discontinued if PRRT is planned
[4] Long-acting SSAs should be paused at least 4 weeks before PRRT and resumed not earlier than 1 hour after a PRRT cycle
[5] PRRT may be considered in patients without prior tumor progression who have a high tumor burden and uncontrolled diarrhea (off-label)
6 Telotristat may also be administered if the patient benefits; it is not indicated in cases of predominant flushing symptoms
[7] off-label

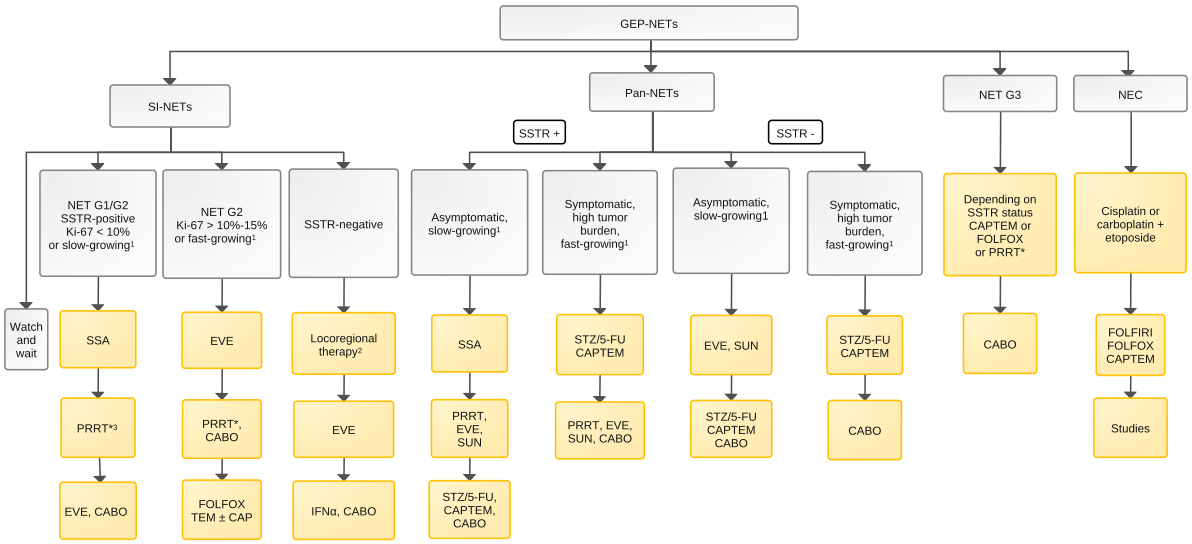
6.3 Treatment Options for Advanced GEP-NET

Predictive biomarkers for selecting the optimal systemic therapy are not yet available. The treatment decision should therefore be made on an individual basis, taking into account tumor biology (WHO grade, differentiation), tumor extent, tumor dynamics, somatostatin receptor (SSTR) expression, the need for a therapeutic response, functionality, comorbidities and patient preference. Due to the limited evidence supporting a fixed treatment sequence, the selection of initial and subsequent therapies should be made on a multidisciplinary basis by an experienced NET tumor board.

The available antiproliferative treatment options include SSA, PRRT, targeted therapies, and chemotherapy. In addition to SSA, targeted drug therapies include the mTOR inhibitor everolimus and tyrosine kinase inhibitors such as sunitinib and cabozantinib. Treatment choice is based on the criteria mentioned above and the current approval status (PRRT is not approved as first-line therapy; cabozantinib is approved only after disease progression on standard therapy other than SSA).

None of the currently available systemic therapies are curative. The goal of treatment is to achieve the longest possible tumor control, delay disease progression, manage hormonal symptoms, and maintain quality of life. The duration of the therapeutic response is largely determined by tumor biology, the WHO grade, the extent of the tumor and tumor dynamics.

Figure 7: Treatment Algorithm for Advanced NETs and NEC



Legend:
Non-curative intent
[1] Slow-growing: stable disease according to RECIST for > 1 year; fast-growing: disease progression within one year
[2] For liver-dominant or exclusively hepatic disease
[3] If PRRT is not possible, everolimus may be used as second-line therapy*
** off-label*
GEP-NET: gastroenteropancreatic neuroendocrine neoplasm; IFN-α: interferon alpha; NEC: neuroendocrine carcinoma; NET: neuroendocrine tumor; Pan-NET: pancreatic neuroendocrine tumor; PRRT: peptide receptor-targeted radionuclide therapy; RECIST: Response Evaluation Criteria in Solid Tumors; SI-NET: small intestinal NET; SSA: somatostatin analog; SSTR: somatostatin receptor;

6.3.1 SSA Therapy

Somatostatin analogs are an established antiproliferative therapy for metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Due to their good tolerability and favorable safety profile, they are the preferred first-line therapy for SSTR-positive G1 NETs as well as low-proliferative G2 NETs (up to 10% Ki-67) with low to moderate tumor burden and slow tumor growth. The objective tumor response rate is low at <5%; the therapeutic goal is primarily long-term disease control and delaying disease progression.

The antiproliferative efficacy of octreotide LAR was demonstrated in the PROMID study in treatment-naive patients with metastatic midgut NETs. This resulted in an extension of the median time to tumor progression from 6.0 to 14.3 months [60]. For lanreotide autogel, the CLARINET study demonstrated a significant prolongation of progression-free survival (PFS) compared with placebo in patients with SSTR-positive, non-functional enteropancreatic NETs with Ki-67 ≤10% [61]. In both studies, documented tumor progression at the time of treatment initiation was not a formal inclusion criterion, meaning that antiproliferative therapy can be initiated regardless of the progression status.

For patients with slow tumor progression on a standard dose of an SSA, dose escalation by shortening the administration interval may be considered. The CLARINET-FORTE study showed that intensifying treatment to lanreotide autogel 120 mg every 14 days following progression on the standard dose can lead to further disease control. The median PFS was 8.3 months for small intestinal NETs and 5.6 months for pancreatic NETs; the benefit was particularly pro-

nounced in tumors with Ki-67 ≤10% [62]. Similar data on high-dose therapy were observed in the NETTER-1 study with octreotide LAR 60 mg every 4 weeks following disease progression while on the standard SSA dose, with a median PFS of 8.4 months in this group [59]. The NETTER-1 study primarily enrolled patients with small intestinal NETs. High-dose SSA therapy may therefore be considered as a bridging or sequential therapy for patients with low tumor activity or who are not suitable for PRRT or other systemic therapies.

6.3.2 PRRT

Peptide receptor radionuclide therapy is an established systemic therapy for patients with progressive, well-differentiated, SSTR-positive NETs. A prerequisite is sufficient and, as far as possible, homogeneous SSTR expression across all tumor manifestations as demonstrated by functional imaging. Today, ^{177}Lu-DOTATATE or ^{177}Lu-edotreotide are used almost exclusively, as ^{177}Lu has a more favorable safety profile than ^{90}Y-labeled radiopharmaceuticals, particularly with regard to nephrotoxicity.

The phase III NETTER-1 trial established PRRT as the standard of care for progressive midgut NETs following pretreatment with SSA. Compared with high-dose octreotide LAR, ^{177}Lu-DOTATATE resulted in a significant prolongation of PFS (28.4 vs. 8.5 months; HR 0.21), a higher objective response rate (18% vs. 3%), and an improvement in health-related quality of life and hormone-related symptoms [57, 59].

The NETTER-2 study investigated the role of PRRT in first-line therapy. In patients with SSTR-positive GEP-NETs G2 and G3 (Ki-67 10–55%), ^{177} Lu-DOTATATE plus octreotide LAR, compared with high-dose octreotide LAR, resulted in a significant prolongation of PFS and a higher objective response rate (mPFS 22.8 months; ORR 43%). In the updated analysis, 35% of the enrolled patients had a G3 NET; the median Ki-67 was 30%. The ORR was 51.2% for pan-NETs and 33.3% for gastrointestinal NETs. These data support the early use of PRRT in more proliferative, SSTR-positive GEP-NETs. In the EU, there is still no specific approval for first-line use; therefore, treatment should be administered following a multidisciplinary benefit-risk assessment. In contrast, the U.S. approval of ^{177}Lu-DOTATATE for SSTR-positive GEP-NET is not tied to a specific line of therapy [63].

The evidence for PRRT has also expanded significantly in pancreatic NETs. In the randomized phase II OCLURANDOM trial, $^{(177)}$Lu-DOTATATE achieved a 12-month PFS rate of approximately 80% in patients with progressive, SSTR-positive pancreatic NETs, thereby meeting the primary endpoint of the study. The median PFS was 20.7 months with PRRT and 11.0 months with sunitinib; however, due to the limited number of cases and the study design, the trial was not powered to demonstrate formal superiority of PRRT over sunitinib. Nearly 60% of patients had received prior chemotherapy, and approximately 50% had already received at least two lines of therapy [64].

The phase III COMPETE trial was the first to prospectively compare PRRT directly with targeted therapy. In patients with progressive G1/G2 GEP-NET, 177Lu-edotreotide resulted in a significant prolongation of progression-free survival compared with everolimus (23.9 vs. 14.1 months; HR 0.67) while exhibiting a more favorable safety profile. The study confirms the high efficacy of PRRT beyond midgut NETs (40% small bowel NETs, 60% pancreatic NETs) and supports its early use prior to targeted therapies, including in pancreatic NETs [65].

Treatment with ^{177}Lu-DOTATATE is generally well tolerated. Transient hematologic side effects and mild impairments in renal function frequently occur. Severe long-term complications, such as myelodysplastic syndrome or treatment-associated leukemia, are rare and have been observed in approximately 1-4% of patients in larger series; the risk may be higher following intensive alkylating pretreatment [66].

Several ongoing randomized trials will further define the role of PRRT in the coming years. The phase III COMPOSE trial (NCT04919226) is evaluating ^{177}lu-edotreotide in aggressive SSTR-positive G2 and G3 GEP-NETs (Ki-67 15-55%) compared with investigator-selected systemic therapy (CAPTEM, FOLFOX [see below], or everolimus). Since no uniform therapy has been established for this setting, one should not speak of a “best possible standard of care.” The results will contribute in particular to determining the treatment sequence for more proliferative GEP-NETs.

6.3.3 Everolimus

Everolimus is an oral inhibitor of the mammalian target of rapamycin (mTOR) and represents an established treatment option for progressive, well-differentiated G1/G2 GEP-NETs. Its antiproliferative effect is primarily based on disease stabilization; objective tumor remissions are rare and are observed in fewer than 10% of patients.

The efficacy of everolimus in pan-NETs has been demonstrated in several prospective studies. In the randomized phase III RADIANT-3 trial, everolimus resulted in a significant prolongation of PFS compared with placebo in patients with progressive, metastatic pan-NETs (11.0 vs. 4.6 months; HR 0.35 [67]). A large proportion of study participants had already received prior systemic therapy, particularly with SSA and/or chemotherapy. Everolimus is therefore an established treatment option for progressive pan-NET; the choice of treatment line depends on tumor dynamics, the need for remission, and prior treatments.

In the phase III RADIANT-4 trial, a significant PFS prolongation was also demonstrated in patients with non-functional gastrointestinal NETs (11.0 vs. 3.9 months; HR 0.48 [68]). Efficacy was consistent across gastrointestinal, pulmonary and other NETs.

In the COOPERATE-2 study, the combination of everolimus and pasireotide in pan-NET resulted in a higher objective response rate but did not lead to a significant prolongation of PFS (the primary endpoint); in addition, significant additional adverse effects occurred [69]. Routine use of this combination is therefore not recommended. However, more recent data, including those from the Japanese STARTER-NET study with everolimus plus lanreotide, suggest that the role of combination therapy with SSA has not yet been definitively established.

The optimal place of everolimus within the treatment sequence has changed based on recent randomized trials. The phase III COMPETE trial demonstrated significantly longer PFS in patients with progressive SSTR-positive GEP-NETs treated with ^{177}Lu-edotreotide compared to everolimus (23.9 vs. 14.1 months; HR 0.67 [65]).

The randomized SEQTOR trial compared, in patients with progressive pan-NET, the sequence of everolimus followed by STZ/5-FU (see below) with the reverse sequence of STZ/5-FU followed by everolimus. Chemotherapy was not shown to be superior to everolimus in terms of PFS; nor did either sequence demonstrate an advantage in terms of OS. The median PFS in the first-line setting was 19.4 months with everolimus and 22.7 months with STZ/5-FU. However, STZ/5-FU achieved a higher objective response rate (30.3% vs. 11.6%). Interpretation is limited by the fact that a significant proportion of the included patients, despite the requirement for disease progression, did not show progression and had previously received systemic antitumor therapy (40% received SSA). Therefore, chemotherapy is often preferred in cases of high tumor burden or when tumor remission is necessary, while everolimus can be used to stabilize the disease, particularly in cases of slowly progressive disease [70].

For functionally active NETs, everolimus is not approved for the treatment of hormonal syndromes. A clinical benefit may be observed in individual cases, particularly in metastatic insulinoma or in treatment-refractory hormonal syndromes.

The most common side effects include stomatitis, diarrhea, fatigue, infections, hyperglycemia, and non-infectious pneumonitis. Most side effects can be managed by reducing the dose or interrupting therapy. Due to the risk of severe infections, metabolic complications, and rare but serious pulmonary side effects, careful patient education and regular clinical and laboratory monitoring are required.

For selected G3 NETs, everolimus may be considered on a case-by-case basis; however, robust prospective data are not yet available.

6.3.4 Tyrosine Kinase Inhibitors

Sunitinib is an oral multi-tyrosine kinase inhibitor (TKI) that inhibits, among others, *VEGFR, PDGFR, KIT, FLT3,* and RET signaling pathways and represents an established treatment option for progressive, well-differentiated pancreatic NETs (G1/G2). The antiproliferative effect is primarily due to inhibition of tumor angiogenesis and stabilization of tumor growth; objective tumor remissions are rarely observed. Approval is based on a randomized, placebo-controlled phase III trial in patients with advanced, unresectable or metastatic pancreatic NETs. With sunitinib (37.5 mg once daily as a continuous infusion), median PFS was significantly prolonged compared with placebo (11.4 vs. 5.5 months; HR 0.42). In addition, a higher objective response rate (9.3% vs. 0%) was observed, as well as a trend toward improved OS [71, 72, 73]. Sunitinib is therefore a standard treatment for progressive G1/G2 pancreatic NETs and can be used both before and after chemotherapy or everolimus. Outside the setting of pancreatic NETs, there are insufficient data to justify treatment with sunitinib. The most common side effects include diarrhea, nausea, fatigue, hypertension, hand-foot syndrome, mucositis, hypothyroidism, cytopenias and hair discoloration. Blood pressure, thyroid function, and laboratory parameters should be monitored regularly. Dose reductions or treatment interruptions are necessary in some patients but usually allow treatment to continue.

Cabozantinib is an oral multi-TKI with activity against *MET, VEGFR2, AXL, RET, KIT, ROS1*, and other signaling pathways. By simultaneously inhibiting multiple proangiogenic and tumor-specific signaling pathways, cabozantinib exhibits pronounced antiproliferative and antiangiogenic effects and represents an important treatment option for previously treated NETs. The approval is based on the randomized phase III CABINET trial, which enrolled patients with progressive, previously treated pancreatic and extrapancreatic NETs (50% GI-NET, 20% lung-NET, 16% CUP-NET). Both groups had received prior treatment, with a median of 2 prior therapies in the extrapancreatic NET cohort and 3 prior therapies in the pancreatic NET cohort.

In both independent study cohorts, cabozantinib resulted in a significant prolongation of PFS compared with placebo. For pancreatic NETs, the median PFS was 13.8 vs. 4.4 months (HR 0.23); for extrapancreatic NETs, it was 8.4 vs. 3.9 months (HR 0.40). In addition, higher objective response rates and sustained disease control were achieved [74]. A recent predefined subgroup analysis of the CABINET study examined for the first time the role of cabozantinib in well-differentiated G3 NETs (Ki-67 >20%). A total of 24 patients with pancreatic and extrapancreatic G3 NETs were evaluated. Cabozantinib prolonged median PFS compared with placebo from 3.0 to 7.9 months (HR 0.15; 95% CI 0.04–0.57). The objective response rate was 25% with cabozantinib compared with 0% with placebo [70]; the safety profile was consistent with the results of the overall study. Although the number of patients was limited, this analysis provides the first randomized evidence of the efficacy of a TKI in well-differentiated G3 NETs and supports the use of cabozantinib in this patient group as well [75]. Cabozantinib thus represents an important treatment option for progressive pancreatic and extrapancreatic NETs following at least one prior systemic therapy (excluding SSA). The most common side effects include diarrhea, fatigue, hypertension, mucositis, palmar-plantar erythrodysesthesia (hand-foot syndrome), weight loss, loss of appetite, proteinuria and laboratory abnormalities in liver function tests. Rare but potentially serious side effects include gastrointestinal perforations, fistula formation,

bleeding and thromboembolic events. Close clinical and laboratory monitoring, as well as consistent management of side effects, are therefore required.

6.3.5 Chemotherapy for GEP-NET

Systemic chemotherapy plays an important role, particularly in advanced pancreatic NETs and in GEP-NET G3. In contrast, response rates are low for well-differentiated non-pancreatic gastrointestinal NETs (G1/G2); routine chemotherapy is therefore not recommended. It may be considered on a case-by-case basis for cases with high tumor activity, high tumor burden, a Ki-67 score in the upper G2 range, or when rapid tumor reduction is required.

6.3.5.1 Pancreatic NETs G1/G2

For unresectable or metastatic pancreatic NETs G1/G2, streptozotocin (STZ)-based and temozolomide-based regimens are established treatment options. Chemotherapy is particularly appropriate in cases of rapid progression, high tumor burden, tumor-related symptoms or the need for objective tumor remission, and may be initiated in these situations even without prior documented progression.

For the combination of STZ and 5-fluorouracil (5-FU), older randomized trials as well as more recent retrospective series show objective response rates of approximately 30-40%. The randomized phase III SEQTOR trial, published in 2025, compared the sequence of everolimus followed by STZ/5-FU with the reverse sequence in patients with advanced, well-differentiated pancreatic NETs. No significant advantage of one sequence over the other was observed in terms of the 12-month PFS rate, median PFS or OS. The median PFS in the first-line setting was 19.4 months with everolimus and 22.7 months with STZ/5-FU. However, STZ/5-FU resulted in a significantly higher objective response rate than everolimus (30.3% vs. 11.6%). The data therefore confirm the importance of STZ-based chemotherapy, particularly when tumor reduction is required [70].

The combination of capecitabine and temozolomide (CAPTEM) was compared with temozolomide monotherapy in the randomized phase II ECOG-ACRIN E2211 trial [76]. The study included 144 patients with advanced pancreatic NETs that had progressed within the preceding 12 months. CAPTEM significantly prolonged the median PFS from 14.4 to 22.7 months (HR 0.58). Median OS was 58.7 months with CAPTEM and 53.8 months with temozolomide alone; this difference was not statistically significant. Objective response rates were approximately 40% with CAPTEM and approximately 34% with temozolomide (n.s.). CAPTEM may therefore, similar to STZ/5-FU, represent a preferred chemotherapy option for pancreatic NETs in patients with high tumor burden, rapid progression or a need for tumor reduction [76].

The optimal duration of treatment with STZ/5-FU and CAPTEM has not been definitively established. In clinical practice, chemotherapy is often administered for approximately 6-12 months and then paused or switched to maintenance therapy with if disease control persists. The duration should be determined on an individual basis based on response, tolerability, and cumulative hematologic or renal toxicity.

The significance of MGMT (O6-methylguanine DNA methyltransferase) as a predictive biomarker for temozolomide-based therapies remains unclear. MGMT deficiency may be associated with a higher likelihood of response; however, due to a lack of standardization and limited prospective evidence, routine MGMT testing for treatment selection is not currently recommended.

FOLFOX or CAPOX may be used in rapidly progressive pancreatic NETs, following failure of temozolomide- or STZ-based regimens, and in highly proliferative tumors (especially G3 NETs). The evidence is based primarily on retrospective analyses [77, 78].

6.3.5.2 Non-Pancreatic Gastrointestinal G1/G2 NETs

For well-differentiated gastrointestinal NETs outside the pancreas, the efficacy of conventional chemotherapy is limited. Objective response rates average only about 10%. Routine chemotherapy is therefore not recommended [79].

In selected patients with rapid progression, high tumor burden, a Ki-67 score in the upper G2 range or a lack of suitable treatment alternatives, temozolomide- or oxaliplatin-based regimens may be considered. The decision should be made by a multidisciplinary NET tumor board [78].

6.3.5.3 GEP-NET G3

Well-differentiated GEP-NET G3 should be considered separately from poorly differentiated NECs with respect to treatment. Platinum/etoposide has only limited efficacy, particularly when Ki-67 is below 55%, and is not recommended for well-differentiated G3 NETs [80].

For pancreatic G3 NETs, CAPTEM, STZ/5-FU, and FOLFOX are particularly suitable chemotherapy options. For gastrointestinal G3 NETs originating from other primary sites, FOLFOX or CAPTEM are the primary treatment options. The choice depends on the primary tumor site, Ki-67, growth rate, tumor burden, SSTR expression and FDG avidity, as well as the need for rapid remission.

In cases of high and homogeneous SSTR expression, PRRT should be considered early on as an adjunctive treatment. A fixed sequence between chemotherapy, PRRT, and targeted therapies has not been established and is the subject of ongoing studies.

6.3.5.4 Maintenance Therapy Following Chemotherapy

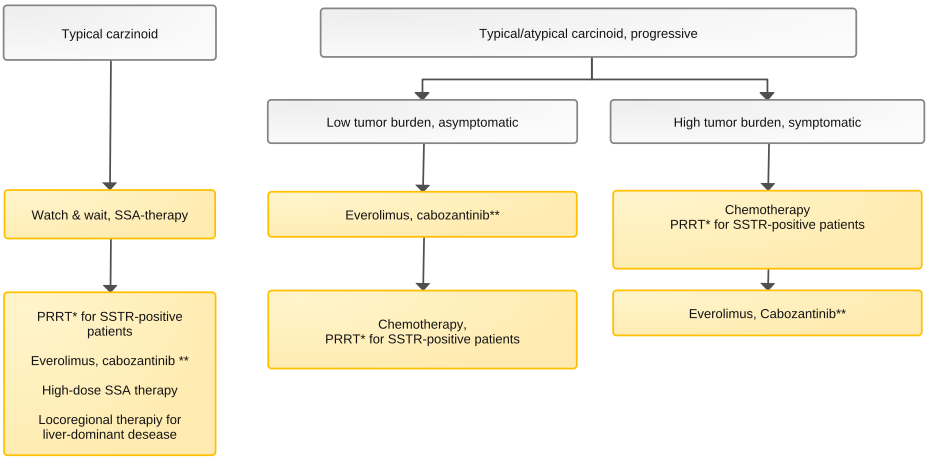
Following successful induction therapy with CAPTEM or streptozotocin-based chemotherapy, maintenance therapy with SSA may be considered for SSTR-positive G1/G2 pancreatic NETs. In the randomized, placebo-controlled phase II REMINET (PRODIGE 31) trial, systemic chemotherapy was limited to 6 months; maintenance therapy with lanreotide after achieving disease control with first-line chemotherapy resulted in a significant prolongation of median PFS from 7.6 to 19.4 months. The 6-month PFS rate was 73.1% with lanreotide compared with 54.2% with placebo. The treatment was generally well tolerated and did not significantly impair quality of life. The results suggest that maintenance therapy with an SSA should be considered for patients with sustained disease control after discontinuation of chemotherapy due to cumulative toxicity or a planned treatment break [81].

6.4 Treatment Options for Advanced-Stage Pulmonary NETs

For unresectable, locally advanced, or metastatic pulmonary NETs (typical or atypical carcinoids), the indication for systemic therapy depends on tumor dynamics, tumor burden, clinical symptoms, SSTR expression, proliferative activity, prior treatments and comorbidities. For asymptomatic patients with a low tumor burden and disease that has remained stable over an extended period, active surveillance may be initiated initially. In cases of clinically relevant or radiologically confirmed progression, SSA, everolimus, PRRT, temozolomide-based chemotherapy (temozolomide or CAPTEM), oxaliplatin-based chemotherapy (e.g., FOLFOX) and cabozantinib are available. Prospective data on temozolomide for thoracic NETs are available, among

other sources, from the ATLANT study [82]. A standard treatment sequence has not been established; treatment decisions should be made by a multidisciplinary NET tumor board.

Figure 8: Treatment Algorithm for Advanced-Stage Pulmonary NETs



Legend:
non-curative intent
SSA – somatostatin analog; PRRT – peptide receptor-targeted radioligand therapy; SSTR – somatostatin receptor;
**off-label;*
***Approval only after 1 systemic therapy other than SSA*

6.4.1 Somatostatin Analogs

SSAs are the first-line therapy for controlling hormone-related symptoms in functionally active pulmonary NETs. Antiproliferative therapy with octreotide LAR or lanreotide may also be used in SSTR-positive, slowly progressive pulmonary NETs with low to moderate tumor burden. The evidence is based primarily on retrospective series, small prospective studies, and extrapolated data from GEP-NET studies [83]. In the SPINET study of pulmonary NETs, a median PFS of 16.6 months was observed with SSA therapy (21.9 months in typical carcinoids and 13.8 months in atypical carcinoids). In cases of significant tumor progression, high tumor burden, or when tumor reduction is required, SSA therapy alone is generally insufficient. Formally, there is no approval for SSA therapy in patients with pulmonary NETs for antiproliferative purposes. If hormonal symptoms such as carcinoid syndrome worsen, shortening the administration interval or administering additional short-acting octreotide may be considered, even if the disease is radiologically stable. Radiological progression while on standard-dose SSA, however, should prompt consideration of a more effective antiproliferative therapy.

6.4.2 Everolimus

Everolimus is an established therapy approved in the European Union for progressive, non-functioning, well-differentiated pulmonary NETs. This approval is based in particular on the phase III RADIANT-4 trial, in which everolimus significantly prolonged PFS compared with placebo in patients with non-functioning gastrointestinal and pulmonary NETs [68]. In the prespecified pulmonary NET subgroup, a significant reduction in the risk of progression was also observed. Everolimus is particularly suitable for radiologically progressive disease, cases without high remission pressure, and cases with insufficient or heterogeneous SSTR expression. The objective response rate is low (less than 5%); the primary treatment goal is disease stabilization. The randomized phase II LUNA trial demonstrated antiproliferative activity of everolimus in advanced pulmonary and thymic carcinoids. However, the combination with pasireotide did not result in a sufficiently demonstrated added benefit; therefore, routine combination of targeted agents with SSA outside of clinical trials is not recommended [84].

6.4.3 Peptide Receptor Radionuclide Therapy

PRRT with ^{177}Lu-DOTATATE may be considered for progressive pulmonary NETs with high and homogeneous SSTR expression. Before starting therapy, an SSTR-PET/CT should be performed to ensure that all clinically relevant tumor manifestations exhibit sufficient receptor expression. In cases of higher tumor dynamics or discordant imaging, a supplementary FDG-PET/CT scan may be useful for detecting SSTR-negative, biologically aggressive tumor components. However, atypical carcinoids exhibit sufficient SSTR expression in only about 50% of cases. To date, no completed randomized phase III data are available for pulmonary NETs. Retrospective studies and prospective cohorts, however, demonstrate significant disease control and response rates, as well as frequently prolonged progression-free intervals [85, 86]. PRRT is therefore an important treatment option, particularly for progressive, SSTR-positive disease following SSA, everolimus, or chemotherapy. The ongoing randomized phase III LEVEL study ^{177}compares Lu-edotreotide directly with everolimus in advanced pulmonary and thymic NETs and aims to further define the role and optimal sequence of PRRT [87]. Until these data become available, the indication should be determined on a case-by-case basis by the NEN tumor board.

6.4.4 Chemotherapy

Temozolomide-based chemotherapy can be used for progressive pulmonary NETs, either as temozolomide monotherapy or in combination with capecitabine (CAPTEM). It is particularly indicated for atypical carcinoids, higher proliferation activity, rapid tumor progression, high tumor burden, or when objective tumor reduction is required. Prospective data are available, among other sources, from the phase II ATLANT study on the combination of lanreotide and temozolomide; in addition, there are smaller prospective and retrospective series. CAPTEM demonstrates relevant disease control and response rates [48, 82, 88].

Oxaliplatin-based combinations, primarily FOLFOX and, less commonly, GemOX, are also used for pulmonary NETs, with an ORR of 20% and a median PFS of 15 months [89]. Therapy with platinum plus etoposide is generally not used for pulmonary NETs. For patients with atypical carcinoid tumors, very rapid progression, high proliferative activity, or particularly aggressive morphological behavior, this therapy may be considered on a case-by-case basis; however, a repeat pathological differentiation from NEC should be performed beforehand.

6.4.5 Tyrosine Kinase Inhibitors and Other Targeted Therapies

Antiangiogenic TKIs have been shown to have antiproliferative effects in extrapancreatic NETs. However, the evidence specifically for pulmonary NETs is limited. Their use should be guided by approval status, prior therapies, and an individual benefit-risk assessment. In the CABINET study, cabozantinib prolonged PFS in previously treated patients with extrapancreatic NETs. Since this cohort also included patients with pulmonary NETs (median PFS 8.2 months), cabozantinib is an approved treatment option following prior systemic therapy [74].

6.4.6 Treatment Selection and Sequence

For SSTR-positive, slowly progressive disease, treatment with SSA is an initial option. In the event of significant progression, everolimus, PRRT, chemotherapy, and, in later lines, cabozantinib may be considered. Everolimus and cabozantinib are approved therapies; PRRT is off-label for pulmonary NETs. Whether PRRT is preferable to everolimus remains unclear and is being investigated in the LEVEL study. Therefore, a rigid treatment sequence has not been validated: PRRT can be initiated early in cases of high, homogeneous SSTR expression, whereas everolimus is particularly suitable for cases with low or heterogeneous receptor expression. In

cases of high tumor burden, rapid progression, or when tumor reduction is required, temozolomide- or oxaliplatin-based chemotherapy should be considered at an early stage. The choice should be based on tumor growth, SSTR and, if applicable, FDG-PET findings, histology, proliferation activity, the need for remission, organ function, comorbidities and patient preference.

6.5 Treatment Options for Advanced GEP-NEC

Gastroenteropancreatic NECs are poorly differentiated, highly proliferative neoplasms and must be distinguished therapeutically from well-differentiated G3 NETs. In cases of unresectable locally advanced or metastatic disease, rapid initiation of systemic therapy is generally indicated due to the high tumor dynamics. Treatment should be determined by an experienced multidisciplinary tumor board. In parallel with first-line therapy, expanded molecular pathological diagnostics should be initiated early to enable the evaluation of precision medicine options without delay in the event of disease progression [35].

6.5.1 First-Line Therapy

The standard first-line therapy is a combination of carboplatin and etoposide or, alternatively, cisplatin and etoposide, regardless of the primary gastroenteropancreatic tumor location or whether the morphology is small-cell or large-cell. A clear efficacy advantage of cisplatin over carboplatin has not been demonstrated; however, carboplatin is often preferred due to its generally better tolerability. Objective response rates are approximately 30-50%, and median OS is predominantly between 7 and 12 months [37].

In a randomized phase III trial, cisplatin plus irinotecan was not superior to cisplatin plus etoposide and is not the preferred standard of care in Europe. There is also currently insufficient evidence to support the use of CAPTEM or FOLFIRINOX as standard first-line therapy for GEP-NEC. Unlike in SCLC, the initial combination of platinum-based chemotherapy with an immune checkpoint inhibitor (ICI) cannot currently be recommended for GEP-NEC outside of clinical trials.

If there is a response and adequate tolerability, four to six cycles (often six cycles) are typically administered. Due to the significant proportion of primarily refractory cases, an initial follow-up imaging examination should be performed as early as 8-12 weeks.

6.5.2 Second- and Subsequent-Line Therapy

Following progression on platinum-based first-line therapy, there is no established standard of care based on phase III trials. In the absence of a molecularly stratified treatment option, FOLFIRI represents the most extensively studied second-line chemotherapy. In the randomized phase II PRODIGE 41-BEVANEC trial, the addition of bevacizumab did not result in an improvement in OS. With FOLFIRI alone, an objective response rate of 18%, a median PFS of 3.5 months, and a median OS of 8.9 months were achieved. FOLFIRI can therefore be used as the preferred second-line option in patients with adequate general condition [90].

Alternatives include FOLFOX or CAPOX. The evidence is more limited and is based primarily on retrospective analyses. Temozolomide-based therapy, particularly CAPTEM, may be considered in selected cases; however, for morphologically confirmed NEC, the evidence base is significantly less robust than for well-differentiated G3 NETs.

In the randomized phase II NET-02 trial, the combination of nanoliposomal irinotecan, 5-FU, and folinic acid met the prespecified endpoint of the 6-month PFS rate and represents another possible subsequent-line option. Docetaxel did not meet this endpoint. A clear efficacy advantage over conventional FOLFIRI has not been demonstrated [91].

For patients who respond well to first-line therapy and have had a sufficiently long platinum-free interval of 6 months, a re-challenge with carboplatin or cisplatin plus etoposide may be considered. In retrospective series, objective remissions and disease stabilization were again observed; the decision should be based on the duration and depth of the initial response, general condition and cumulative toxicity.

6.5.3 Immunotherapy

Non-biomarker-selected monotherapy with PD-1 or PD-L1 inhibitors shows only low overall response rates in GEP-NEC and does not represent a general standard of care. The routine combination of immunotherapy with platinum/etoposide is also currently not sufficiently supported by evidence.

However, if dMMR/MSI-H or a high tumor mutation burden is detected, tumor-agnostic immunotherapy may be used. dMMR/MSI-H is found in approximately 5% of GEP-NEC cases, and a TMB ≥10 mutations/megabase in about 7%. For such molecularly defined tumors, PD-1 inhibitors such as pembrolizumab or, in the case of dMMR, dostarlimab are particularly suitable, depending on approval status, prior therapy, and primary tumor location. Use is guided by the respective tumor-agnostic approval or may require individual cost coverage. The decision should be made by the molecular tumor board.

6.5.4 Molecularly Targeted Therapy

Due to the limited efficacy of conventional follow-up therapies, broad DNA-based, and, if applicable, RNA-based, molecular profiling should be performed as early as possible in cases of advanced GEP-NEC. The results should be evaluated by the molecular tumor board.

6.5.5 BRAF

BRAF mutations are observed in approximately 7-20% of GEP-NEC cases; in colorectal NEC, they are significantly more common in some series. *BRAF* V600E is of particular clinical relevance. For non-colorectal *BRAF* V600E-mutated NEC, combined *BRAF/MEK* inhibition, for example, with dabrafenib and trametinib, may be considered. In cases with a primary colorectal location, due to EGFR-mediated resistance, a combination of encorafenib and cetuximab is preferred, in accordance with the treatment strategies for *BRAF* V600E-mutated colorectal carcinoma. To date, the evidence specifically for NEC is based primarily on case series and molecularly stratified cohorts.

6.5.6 KRAS and Other Genomic Alterations

Depending on the primary tumor site, *KRAS* mutations are found in approximately 8-30% of GEP-NEC cases. *KRAS* status should therefore be determined as part of a comprehensive molecular profiling panel. For the majority of *KRAS* variants, there is currently no established NEC-specific therapy. For the very rare, theoretically treatable alterations seen in NEC, such as *KRAS* G12C, treatment should be considered based on recommendations from the molecular tumor board and, preferably, within clinical trials. Regarding the newer pan-*RAS* or specific selective *KRAS* inhibitors, there are currently no reliable data outside of pancreatic cancer and, in particular, for NEC.

The panel should also include rare but potentially relevant alterations such as *NTRK, RET* or *ALK* fusions; *HER2* amplification; *BRCA1/2* or other homologous recombination defects; and other tumor-specific alterations that can be targeted. The clinical relevance of broad genomic and transcriptomic profiling in advanced NENs is supported by the current analysis from the NCT/

DKTK-MASTER program [92]. Treatment is guided by evidence, approval status and expected clinical benefit.

6.5.7 DLL3-Targeted Therapy

DLL3 is expressed in a high proportion of NECs and represents a promising therapeutic target. Detection is performed immunohistochemically; a uniform, generally validated definition of the required expression level for GEP-NEC does not yet exist. *DLL3* immunohistochemistry should be considered, particularly in cases of advanced, previously treated GEP-NEC, if enrollment in a DLL3-targeted clinical trial is possible.

The DLL3/CD3 bispecific T-cell engager obrixtamig (BI 764532) demonstrated clinical activity in previous studies in DLL3-expressing NEC. In a preselected cohort of extrapulmonary NEC cases with high DLL3 expression, preliminary results reported an objective response rate of approximately 40%, a disease control rate of 67%, and a median duration of response of 7.9 months [93]. The published phase I data thus confirm the clinical activity of obrixtamig in DLL3-expressing NEC; there is currently no regular approval for GEP-NEC.

Tarlatamab is also a DLL3/CD3 bispecific T-cell engager and is approved in Germany for previously treated SCLC [94]. There is currently no approval or sufficiently robust evidence for GEP-NEC. Its use in DLL3-positive GEP-NEC should therefore be limited to clinical trials [95]. Adverse effects such as cytokine release syndrome and neurological toxicity require treatment at centers with appropriate expertise.

6.6 Supportive Care and Nutrition

Supportive measures are an integral part of the treatment of patients with NETs. In addition to managing treatment-related side effects, the focus is particularly on the prevention and treatment of malnutrition, gastrointestinal dysfunction, and hormone-related symptoms. Patients with GEP-NETs often present with complex nutritional problems due to hormonal activity, frequently extensive surgical resections, and systemic therapies. An early, structured nutritional assessment and the involvement of a qualified dietitian are therefore recommended.

6.6.1 Nutrition

Malnutrition is common in patients with advanced NETs and can be caused by reduced food intake, chronic diarrhea, maldigestion, malabsorption, or tumor-induced hypermetabolism. Regular weight monitoring and standardized screening for malnutrition should be part of every follow-up visit. The goal of nutritional therapy is to maintain body weight, muscle mass, and quality of life. Restrictive diets without established evidence, including ketogenic or so-called “cancer diets”, are not recommended.

In general, a personalized, balanced mixed diet is recommended. Several smaller meals spread throughout the day are often better tolerated than a few large meals. If symptoms persist, a food diary can be helpful in identifying foods that an individual cannot tolerate. A general elimination diet, on the other hand, is not advisable.

6.6.2 Nutrition While Taking Somatostatin Analogs

In addition to inhibiting hormonal secretion, SSA also suppress exocrine pancreatic function and gallbladder motility. This can lead to steatorrhea, bloating, abdominal discomfort and deficiencies in fat-soluble vitamins. Therefore, when diarrhea develops for the first time while on SSA,

the diagnosis should not be limited to tumor progression but should also consider exocrine pancreatic insufficiency.

If maldigestion is clinically suspected, fecal elastase levels should be measured, and, if appropriate, a trial of pancreatic enzyme replacement therapy should be initiated. The enzymes should be taken with all main meals and snacks and dosed according to the fat content of the meal. If steatorrhea persists despite adequate enzyme therapy, the dosage, timing of administration, and, if necessary, additional acid suppression should be reviewed. In addition, lipid-soluble vitamins (A, D, E, and K) should be monitored regularly and supplemented as needed.

6.6.3 Nutrition Following Pancreatic Resection

Following partial or total pancreatectomy, many patients develop exocrine pancreatic insufficiency, and following total pancreatectomy, they additionally develop insulin-dependent diabetes mellitus. Lifelong enzyme replacement therapy is indicated in cases of clinical or laboratory-confirmed exocrine insufficiency.

The diet should be rich in energy and protein. Fat restriction is generally not necessary with sufficient enzyme replacement. Rather, the enzyme dose should be adjusted to the fat content of the meal. In addition, vitamin B12 (following duodenopancreatectomy), iron, folic acid, calcium, vitamin D and other micronutrients should be monitored regularly.

6.6.4 Nutrition Following Small Intestine Resection

Patients who have undergone ileal or extensive small bowel resections often develop bile acid malabsorption, accelerated intestinal transit, and malabsorption of vitamin B12 and lipid-soluble vitamins. In cases of major ileal resections, short bowel syndrome may also develop.

The diet should be tailored to the individual. Smaller, more frequent meals are usually better tolerated. In cases of bile acid loss syndrome, treatment with bile acid binders (such as colestyramine) may be beneficial. Vitamin B12 levels should be monitored regularly, and in cases of terminal ileal resection, parenteral supplementation is usually required. Foods rich in oxalate should be consumed only in moderate amounts, particularly following extensive ileal resections, due to the increased risk of enteric hyperoxaluria and nephrolithiasis.

6.6.5 Nutrition in Carcinoid Syndrome

In carcinoid syndrome, diarrhea, accelerated intestinal transit, and hormone-mediated metabolic changes can contribute to weight loss and malnutrition. Adequate control of carcinoid syndrome through SSA is the most important supportive measure.

Some patients report an increase in symptoms after consuming foods rich in histamine or biogenic amines. These include, among others, aged cheeses, smoked or fermented meats and sausages, alcohol (especially red wine), sauerkraut and certain fish products. Since individual differences exist, a general list of prohibited foods should be avoided. Instead, it is recommended to identify personal triggers using a food diary and to avoid them specifically.

In cases of pronounced serotonin excess, increased tryptophan consumption can lead to a niacin (vitamin B3) deficiency, potentially progressing to pellagra. If a deficiency is clinically suspected or confirmed, appropriate supplementation should be provided. Regular monitoring of nutritional status and micronutrient levels is particularly advisable for patients with chronic diarrhea or weight loss. Those affected can also find further important information on nutrition in the patient brochure from the patient advocate network (https://www.netzwerk-net.de/wp-content/uploads/2024/06/net_ernaehrungsbroschuere-2024).

6.6.6 Vitamin and Micronutrient Replacement

In patients with chronic diarrhea, exocrine pancreatic insufficiency, or following gastrointestinal resections, levels of vitamin B12, vitamin D, lipid-soluble vitamins (A, E, K), iron, folic acid, zinc, selenium, and, if necessary, magnesium should be measured regularly. Supplementation should be administered only in cases of proven or clinically probable deficiency. Routine administration of high-dose vitamins or trace elements in the absence of a confirmed deficiency is not recommended.

6.6.7 Diagnosis and Treatment of Bone Metastases

Bone metastases are not uncommon in advanced neuroendocrine neoplasms and are being diagnosed more frequently due to the increasing use of sensitive functional imaging, particularly SSTR-PET/CT. In a meta-analysis, their prevalence was approximately 18%; in a recent large SSTR-PET/CT series of patients with small intestinal and pancreatic NETs, bone metastases were detected in 18.4% of cases and were significantly more common in small intestinal NETs than in pancreatic NETs. In a German single-center series, bone metastases were found in 12.6% of all PNET patients; approximately 42% of the affected patients had bone pain and 12% had pathological fractures. Bone metastases predominantly affect the axial skeleton and are often multifocal [96, 97].

Treatment should be guided by symptoms, the number and location of the metastases, the risk of fracture or compression and the systemic tumor status. In the case of an asymptomatic, isolated bone metastasis without a risk of fracture or impending neurological complications, particularly in slowly proliferating NETs, active surveillance (“watch and wait”) with follow-up imaging is justifiable. This is also in line with the recommendation of the German AWMF NET guidelines.

In cases of multiple bone metastases, particularly osteolytic ones, bisphosphonates, especially zoledronic acid, or denosumab may be used to prevent skeletal-related events. However, there are no NET-specific randomized trials on the benefits of these agents; therefore, the indication and duration of therapy should be determined on an individual basis. Before and during antiresorptive therapy, particular attention should be paid to renal function, calcium and vitamin D status, and the risk of osteonecrosis of the jaw. Even in the absence of bone metastases, attention should be paid to bone health in NET patients. A recent study revealed frequent vitamin D deficiency, osteopenia, and impaired trabecular bone structure [98].

In cases of painful bone metastases, impending fracture, or local compression, local radiotherapy is an effective treatment option and should be initiated early. In cases of SSTR-positive multifocal bone metastases, PRRT may also be part of the systemic treatment plan; however, for isolated painful lesions that are amenable to radiation, local radiotherapy should be preferred [99].

Surgical management should be considered in cases of impending or manifest pathological fractures, instability of weight-bearing skeletal segments, vertebral metastases with instability or neurological compromise, as well as in selected solitary or oligometastatic lesions. Unlike many aggressive metastatic tumors, patients with well-differentiated NETs can live for many years despite distant metastases. Therefore, in cases of mechanically significant bone metastases, the approach should not be exclusively palliative; in suitable patients, long-term stable surgical reconstruction or stabilization may be appropriate. The decision should be made on a multidisciplinary basis, involving orthopedics/trauma surgery or spinal surgery and radiotherapy. The current references underscore the clinical relevance of bone manifestations even in lung NETs [100].

7 Rehabilitation

Patients with GEP-NETs and pulmonary NETs may develop significant physical, functional and psychosocial limitations due to the tumor disease, hormonal syndromes, extensive surgical procedures and systemic therapies. At the same time, modern multimodal treatment approaches often result in a long-term, chronic disease course, particularly in the case of well-differentiated NETs. Even in cases of metastatic disease, many patients can achieve good disease control and life expectancy over a period of years to decades. Accordingly, rehabilitation not only aims to facilitate recovery following cancer treatment but is also an integral part of a long-term treatment plan designed to maintain functional capacity, independence, quality of life and participation in professional and social activities.

Rehabilitation measures should be individually tailored to the tumor type, disease stage and functional limitations. Key components include structured physical training, nutritional counseling, including treatment for exocrine pancreatic insufficiency or short bowel syndrome, pain management, psycho-oncological care, social-medical counseling and treatment for fatigue. For patients with carcinoid syndrome, control of hormone-related symptoms and optimization of drug therapy should also be considered.

Inpatient oncological rehabilitation may be appropriate following major pancreatic, small bowel, liver, or thoracic surgery, as well as after multimodal treatment regimens. Furthermore, patients with advanced or metastatic disease often benefit from rehabilitative measures, provided their general condition is sufficient. Due to the often long-term course of the disease, rehabilitative measures may be required repeatedly over time, for example, after subsequent surgeries, following PRRT or chemotherapy, or in cases of progressive functional limitations. The indication should therefore be based on individual rehabilitation needs and not solely on the presence of metastatic disease.

Regular physical activity appropriate to the individual capacity is recommended for all patients. It improves physical performance, reduces fatigue, and contributes to the long-term maintenance of quality of life and activities of daily living.

8 Monitoring and Follow-up Procedures

Table 4: Risk-adapted Monitoring and Follow-up for Patients with Neuroendocrine Neoplasms (aligned with current ENETS, ESMO, and NCCN recommendations as well as organ-specific guidelines).

Disease Status	Clinical and Laboratory Monitoring	Morphological Imaging	Functional Imaging	Duration
GEP-NET G1 following R0 resection	Every 6 months	CT or MRI every 6 months; annually thereafter for low-risk patients	SSTR-PET/CT at baseline, in cases of unclear findings, or if recurrence is suspected	At least 10 years; longer depending on risk
GEP-NET G2 after R0 resection	Every 6 months	CT or MRI every 6 months for 2-3 years, then annually	SSTR-PET/CT for higher risk, unclear findings, or treatment decision	At least 10 years, often long-term
GEP-NET G3 following R0 resection	Every 3 months	CT or MRI every 3 months; later, if stable, every 6 months	SSTR-PET/CT and, if necessary, FDG-PET/CT based on risk assessment	At least 5-10 years
Metastatic G1 NET	Every 6 months	Initial follow-up after 6 months; every 6-12 months if stable	SSTR-PET/CT not routinely, but as clinically indicated	Lifelong
Metastatic NET G2	Every 3 months	CT or MRI every 3-6 months	SSTR-PET/CT in cases of unclear progression or prior to PRRT; FDG-PET/CT in cases of elevated Ki-67 or suspected dedifferentiation in selected situations	Lifelong
Metastatic NET G3	Every 2-3 months	CT or MRI every 2-3 months	SSTR- and FDG-PET/CT for biological characterization when clinically indicated	Lifelong
GEP-NEC following curative therapy	Every 3 months for 2 years, then every 3-6 months	CT of the chest, abdomen, and pelvis every 3 months for 2 years, then every 3-6 months	FDG-PET/CT for unclear findings; SSTR-PET/CT not routinely performed	At least 5 years
Metastatic GEP-NEC	Clinically before each treatment cycle or every 2-3 weeks	Initial follow-up after 2-3 cycles, followed by every 6-9 weeks or every 2-3 months	FDG-PET/CT only when there is a specific clinical indication	Throughout the entire course of therapy
Typical pulmonary NET after R0 resection, low risk	Annually	Baseline CT after 3-6 months, then annually	SSTR-PET/CT in cases of unclear findings or suspected recurrence	At least 10 years, often longer
Atypical or lymph node-positive pulmonary NET after R0 resection	Every 6 months for 2-3 years, then annually	Chest and abdominal CT or abdominal MRI every 6 months, then annually	SSTR-PET/CT approximately 12 months postoperatively and risk-adapted; FDG-PET/CT for aggressive biology	Long-term, often lifelong
Metastatic pulmonary NET	Every 3 months	Initial follow-up after 8-12 weeks, then every 3-6 months	SSTR-PET/CT when deciding on treatment or prior to PRRT; FDG-PET/CT in cases of rapid progression	For life

The goals of monitoring and follow-up for NENs are the early detection of relapse or progression, the assessment of treatment response, the identification of hormonal syndromes and long-term treatment-related effects and the timely initiation of further treatment measures. Prospective data on the optimal examination method and follow-up intervals are largely lacking. Recommendations from the NCCN, ESMO, ENETS, and the German AWMF guideline [26] therefore differ in detail and are based primarily on retrospective data and expert consensus. Monitoring intervals should be individualized based on differentiation, grading, primary tumor location, tumor stage, growth kinetics, SSTR expression, hormonal activity and current therapy.

8.1 Imaging Techniques

Imaging disease monitoring is typically performed using contrast-enhanced CT or MRI. Whenever possible, the same imaging modality with a comparable contrast agent protocol should be used throughout the course of follow-up to reliably assess changes in tumor size.

Multiphase CT of the thorax, abdomen, and pelvis is widely available and allows for the assessment of pulmonary, nodal, and abdominal manifestations. Due to the often long-term course of well-differentiated NETs and the cumulative radiation exposure, MRI should be preferred for repeat follow-up examinations, or combined with a low-dose chest CT, whenever clinically appropriate. In some cases, it may also be sufficient to perform chest imaging only once a year, provided that no thoracic tumor manifestations have been observed to date.

Contrast-enhanced MRI of the liver has high sensitivity, particularly for small or numerous liver metastases, and is especially suitable for liver-dominant disease, unclear CT findings, and for preparing liver-targeted therapies. In addition, a liver MRI should be performed before any liver surgery to identify all possible malignant lesions and determine the extent of a potential resection. For patients with a long-lasting disease course, an abdominal MRI combined with a low-dose chest CT can reduce radiation exposure. For monitoring disease progression, switching between CT and MRI should not be done without a clinical indication.

SSTR-PET/CT, preferably using ^{68}Ga-labeled SSA, is the gold standard functional imaging modality for well-differentiated SSTR-positive NETs. It is particularly relevant for initial staging, when conventional imaging results are inconclusive, prior to PRRT, in cases of suspected progression with a possible change in treatment strategy, and for assessing potential tumor heterogeneity. SSTR-PET/CT offers the highest sensitivity, particularly in the diagnosis of lymph node or bone metastases. However, routine SSTR-PET/CT at every follow-up visit is not necessary and should only be performed if it has clinical implications or if pulmonary or bone metastases are suspected. During systemic therapy, an SSTR-PET/CT can be performed every 2-3 years.

For NETs with higher proliferative activity, discordant clinical and morphological course, loss of SSTR expression, or suspected dedifferentiation, a supplemental ^{18}F-FDG-PET/CT may be useful. This applies in particular to G3 NETs and selected G2 NETs with Ki-67 levels above approximately 10%. For NEC, FDG-PET/CT is the preferred functional imaging modality; however, it is not a substitute for contrast-enhanced CT or MRI.

8.2 Clinical and Laboratory Monitoring

At each follow-up visit, the patient’s general condition, weight changes, pain, gastrointestinal and pulmonary symptoms, fatigue, functional limitations, and signs of a hormonal syndrome should be assessed. During ongoing therapy, substance-specific laboratory tests are also required.

Tumor markers should only be used if they were initially pathologically increased and were meaningful in the individual’s clinical course. Chromogranin A can be influenced by proton pump inhibitors, renal insufficiency, and other factors and should not be used in isolation to diagnose disease progression. In cases of carcinoid syndrome, 5-HIAA levels should be monitored in 24-hour urine or plasma. If 5-HIAA levels are increased or clinical signs of carcinoid syndrome are present, regular monitoring for carcinoid heart disease using NT-proBNP and echocardiography is required.

8.3 GEP-NET

8.3.1 Follow-up after Complete Resection

Even after R0 resection, there remains a long-term risk of recurrence in GEP-NET. Late recurrences can occur even more than 10 years later, particularly in pancreatic and small intestinal NETs as well as in typical bronchial carcinoids. Follow-up should therefore be long-term and frequently extend beyond 10 years if there is a significant risk of recurrence. In young patients, those with lymph node-positive disease, higher tumor grading, or other risk factors, lifelong clinical follow-up may be warranted.

Following R0 resection, follow-up should be tailored to the primary tumor and risk profile. For G1 pan-NETs without additional risk factors, the first imaging follow-up can be performed after approximately 6 months. For G2 pan-NETs, particularly higher-grade G2 tumors, lymph node-positive disease, or initial liver metastases following complete resection, postoperative staging should be performed as early as approximately 3 months. For G3 NETs, initial follow-up every 3 months is appropriate. If no evidence of tumor is found over time, the intervals can be extended as the patient progresses.

For pan-NETs, due to the higher and biologically more heterogeneous risk of recurrence compared to small intestinal NETs, more frequent risk-adapted follow-up is recommended: for G2 or the presence of additional risk factors, initial imaging after approximately 3 months; for low risk/G1, after approximately 6 months; followed by imaging every 6 months for the first 2-3 years and annually thereafter. Small-intestinal NETs often exhibit a different, generally more indolent biology; following a postoperative baseline examination after approximately 6 months, intervals of 6-12 months may be selected for low-risk patients. Follow-up should be long-term.

Following local or endoscopic resection of small gastric, duodenal, or rectal NETs, organ-specific follow-up protocols apply. For very small, completely resected tumors without risk factors, follow-up can be reduced. For example, no tumor-specific follow-up is required for an R0-resected appendix NET smaller than 1 cm without risk factors.

8.4 Follow-up for Metastatic Disease

For metastatic GEP-NETs, the follow-up interval depends on the grade, tumor burden, growth rate, and treatment. When systemic therapy is newly initiated, the first radiological evaluation should generally take place after approximately 3 months (6 months is possible for G1 NETs). For slow-growing G1 NETs under stable therapy, follow-up intervals of 6 months may subsequently be chosen; in selected cases where the disease has been stable for many years, intervals of 6-12 months may be selected. For G2 NETs, intervals of 3-6 months are generally recommended. For G3 NETs or cases of rapid progression, follow-up should occur approximately every 3 months. The German AWMF guideline [26] recommends intervals of 6-12 months for metastatic G1 NETs, 6 months for G2 NETs, and initially at least 3 months for G3 NETs or NECs; rapidly growing or clinically symptomatic tumors require shorter intervals.

Under a watch-and-wait strategy, the first morphological follow-up should take place after 3-6 months. If stability is documented, the intervals can be extended to approximately 6 months.

As part of PRRT, a morphological follow-up should be performed after 2 treatment cycles and approximately 3 months after completion of treatment (typically 4 cycles of PRRT). In cases of ambiguous findings or discordant disease progression, an SSTR-PET/CT may also be used. A temporary increase in the size of individual lesions following PRRT should not automatically be interpreted as progression; course of the disease, enhancement, diffusion, and functional imaging should be evaluated collectively. Furthermore, differences often emerge in the intermodal

comparison between PET/CT and contrast-enhanced CT or MRI, which should be carefully interpreted by a specialized tumor board.

8.5 Gastroenteropancreatic NEC

8.5.1 Follow-up After Curative Therapy

GEP-NEC carries a high risk of early relapses and distant metastases. After completion of curative therapy, clinical and imaging follow-up should be performed approximately every 3 months for the first two years. In the third year, intervals of 3-6 months may be chosen; thereafter, if the patient remains tumor-free, follow-up should be conducted every 6-12 months. Follow-up should continue for at least five years; it may be extended based on individual risk.

The standard procedure is a contrast-enhanced CT scan of the thorax, abdomen, and pelvis. A liver MRI is indicated in cases of unclear or liver-dominant findings. An SSTR-PET/CT does not have routine diagnostic value in poorly differentiated NEC due to frequently low or heterogeneous receptor expression. An FDG-PET/CT may be used as a supplementary tool in cases of curative treatment, unclear CT findings, or suspicion of an undetected relapse. However, FDG-PET/CT should not be performed for routine follow-up. For highly proliferative PNETs, the German AWMF guideline [26] recommends initial imaging follow-up at least every three months.

8.5.2 Follow-up Monitoring for Metastatic Disease

During systemic therapy, the first radiological follow-up should take place after two to three treatment cycles, typically after 6-9 weeks. Subsequent follow-ups should be performed approximately every 2-3 months. Previous imaging is required in cases of clinical deterioration or suspected primary refractoriness.

Follow-up monitoring is primarily performed using CT scans of the thorax, abdomen, and pelvis. MRI may be used as a supplement in cases of liver, CNS, or bone manifestations. FDG-PET/CT may be helpful in cases of discrepant findings or prior to a potentially local- ablative or curative intervention; however, it is not required for every routine follow-up.

8.6 Pulmonary NET

8.6.1 Follow-up After Complete Resection

Typical and atypical pulmonary carcinoids can recur even after long disease-free intervals. Follow-up should therefore be long-term and, particularly in cases of atypical carcinoid, lymph node-positive disease, high mitotic activity, or necrosis, should be continued for at least ten years, and often for life.

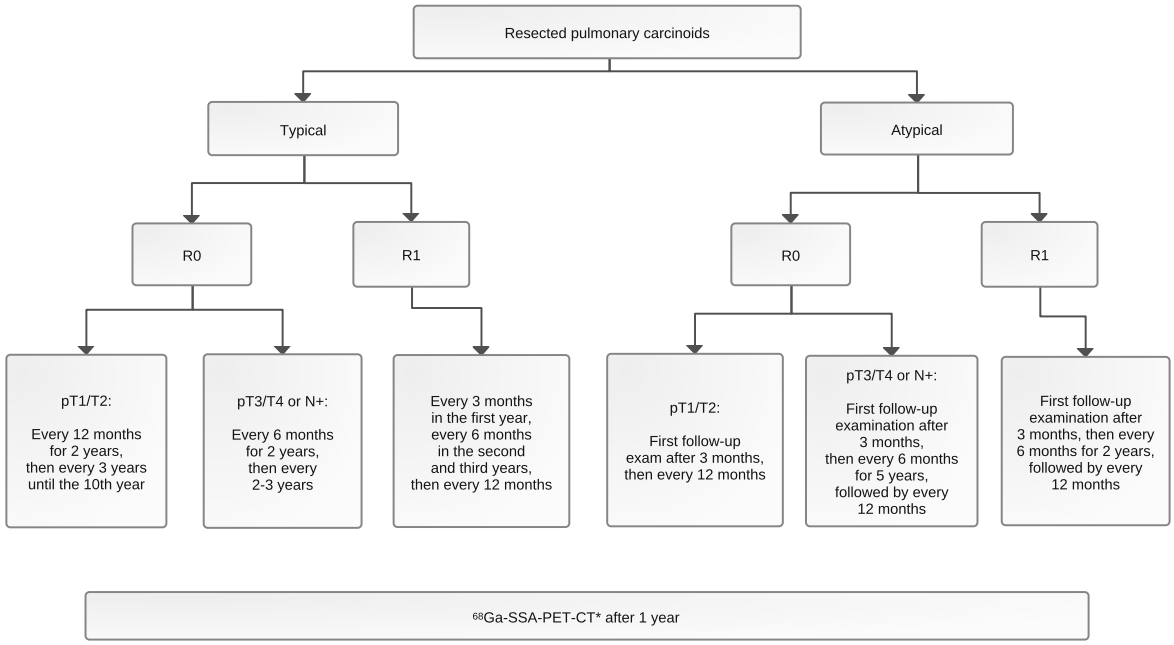
Following curative resection, baseline imaging should be performed postoperatively depending on histology, TNM classification, and R-status (see Figure 6).

For typical carcinoids without risk factors, longer intervals - often annual - may be sufficient following the initial postoperative follow-up. For atypical carcinoids, particularly in cases of lymph node-positive disease or other risk factors, follow-up should be more frequent; in the first few years, check-ups approximately every 3-6 months are generally appropriate. The intervals should subsequently be extended depending on histology, TNM stage and the course of the disease to date.

Due to the need for long-term follow-up, radiation-sparing approaches should be considered for pulmonary NETs, such as MRI of the mediastinum and abdomen in combination with a low-dose chest CT. An SSTR-PET/CT is not routinely required for all patients after one year. It should be used in particular if the tumor was already SSTR-positive preoperatively, in cases of unclear conventional findings, suspected clinical recurrence, or if the result influences a treatment decision. For atypical carcinoids that were SSTR-negative preoperatively, routine SSTR-PET/CT during follow-up is not recommended.

Routine bronchoscopy is not required after peripheral R0 resection. It may be appropriate on a case-by-case basis following bronchoplastic procedures (e.g., after endobronchial ablation of an endobronchial lesion in typical carcinoid tumors), in cases of a central tumor location, or when endobronchial relapse is suspected.

Figure 9: Follow-up after Surgery for Pulmonary Carcinoids (adapted from: [48])



Legend:
R0 – microscopically tumor-free resection margins; R1 – microscopic evidence of tumor at the resection margin; CT – computed tomography; MRI – magnetic resonance imaging; PET-CT – positron emission tomography-computed tomography; Mo. – months
**For PET-CT, the same tracer that was positive in the initial PET-CT should be used, typically ^{68}Ga-SSTR-PET-CT; an ^{111}In-DTPA scintigraphy should only be considered if a ^{68}Ga-SSTR-PET-CT is not available. An ^{18}F-FDG-PET may be considered in specific cases, e.g., if it was initially superior to somatostatin receptor imaging, if the growth pattern was inconsistent with the Ki67 index, in cases of discrepancies between CT/MRI and somatostatin receptor imaging, or if a secondary neoplasm is suspected.*

8.6.2 Follow-up Monitoring for Metastatic Disease

For metastatic pulmonary NETs, the first radiological follow-up should generally be performed approximately 8-12 weeks after initiation of a new active systemic therapy. This applies not only to chemotherapy but also to everolimus, cabozantinib, and other antiproliferative therapies. In cases of stable, slow-growing disease, the intervals can subsequently be extended to 3-6 months; intervals of 6-12 months are only considered for disease that has been stable for many years under minimally active therapy or observation. For atypical carcinoids with a higher growth rate, more frequent follow-up is required.

The baseline examination consists of a CT scan of the thorax including the upper abdomen or a CT scan of the thorax, abdomen, and pelvis. In cases of liver-dominant disease, a liver MRI should be used as a supplement or alternative. SSTR-PET/CT is relevant for SSTR-positive pulmonary NETs, particularly in cases of suspected progression, unclear findings, and prior to

PRRT. In cases of high proliferation, rapid progression, or discordant SSTR imaging, an additional FDG-PET/CT may be useful for detecting aggressive tumor components.

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16 Disclosures of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.