NON APPENDICEAL GASTROENTEROPANCREATIC NEUROENDOCRINE NEOPLASMS IN CHILDREN AND ADOLESCENTS

-

EUROPEAN STANDARD CLINICAL PRACTICE RECOMMENDATIONS

DISCLAIMER

These ESCP guidance documents were produced by the relevant tumour group or specialist committee as recommendations on current best practice. The ESCP guidance documents are not clinical trial protocols.

The interpretation and responsibility of the use of ESCP guidance documents lies fully with the user who retains full responsibility for the use of these guidance documents and his actions and (treatment) decisions based thereon, such as, but without limitation thereto: checking and prescribing certain doses, checking prescriptions, etc. A user should never base its decision solely on the content of these guidance documents and should always check any other relevant medical information that is available and make appropriate use of all relevant medical information.

These guidance documents have been made publicly available by SIOP Europe – the European Society of Paediatric Oncology and the European Reference Network for Paediatric Oncology (ERN PaedCan). It is the responsibility of the user who downloads these documents to make sure that:

- their use within the Paediatric Clinical Unit / Hospital is approved according to the local clinical governance procedures.
- appropriate document control measures are in place to ensure that the most up-to-date locally approved versions are considered.
- any anomalies or discrepancies within the documents are immediately brought to the attention of the relevant special interest group chair and the European Clinical Study Group who has developed the ESCP guidance document.

Every care has been taken whilst preparing these documents to ensure that they are free of errors. Nonetheless, SIOP Europe and ERN PaedCan and coauthors cannot be held liable for possible errors or mistakes in these guidance documents, nor can SIOP Europe and ERN PaedCan and coauthors held liable for any kind of damage resulting out of the use of these guidance documents.

NON-APPENDICEAL GASTROENTEROPANCREATIC NEUROENDOCRINE NEOPLASMS IN CHILDREN AND ADOLESCENTS

Document version: 1 (November 2025)

This document has been developed by EXPeRT members and collaborators.

Working Group of this recommendation (including non-EXPeRT specialists):

- Pediatric oncologists: Michaela Kuhlen (Germany), Antje Redlich (Germany), Bilgehan Yalcin (Turkey), Charlotte Rigaud (France), Daniel Orbach (France)
- Surgeons: Calogero Virgone (Italy), Joerg Fuchs (Germany)
- Pathologist: Christian Vokuhl (Germany)
- Nuclear medicine physician: Constantin Lapa (Germany), Segolene Hescot (France)

External advisors:

- Medical oncologist: Rainer Claus (Germany), Julien Hadoux (France), Thomas Walter (France)

EXPeRT members (03/2025):

President: Daniel Orbach

Vice-president: Ines B. Brecht

Board Members (in alphabetical order):

Michael Abele
Tal Ben-Ami
Ewa Bien
Gianni Bisogno
Maja Mazic Cesen
Andrea Ferrari
Michaela Kuhlen
Ricardo Lopez Almaraz
Yves Reguerre
Malgorzata A. Krawczyk
Dominik T. Schneider
Calogero Virgone

Table of contents

1. Background and Rationale

1.1 Summary

Paediatric very rare tumours (VRT) constitute an extremely heterogeneous group of neoplasms. Some of them are typical for paediatric age, while others more commonly arise during adulthood and only rarely develop in children and adolescents. Using the definition *any solid malignancy or tumour of uncertain clinical behaviour characterized by an annual incidence < 2/million individuals <18 years of age*, the European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT) has initially identified a number of paediatric VRT (1). Due to the low number of patients, it is very difficult – or even impossible – to conduct prospective clinical trials, and this makes it demanding to develop evidence-based treatment guidelines. Consequently, the treatment of patients with VRT is often individualized.

Paediatric gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) represent an exceptionally rare and heterogeneous group of tumours. [1-7] They arise from neuroendocrine cells dispersed throughout the gastrointestinal tract, pancreas, and only exceptionally, the hepatobiliary system. [8-10] Their annual incidence is estimated at <0.1 per million individuals under 18 years of age, placing them among the rarest solid tumours of childhood. [11] The median age at diagnosis lies in mid-adolescence (approximately 14–16 years), with only sporadic cases reported in younger children, the youngest published case being six years old. [7,12-16] Up to 20–30% of paediatric GEP-NENs occur in the context of hereditary cancer predisposition syndromes, including multiple endocrine neoplasia type 1 (MEN1), von Hippel–Lindau (VHL) disease, neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC). [14,15,17-19]

In accordance with the 2019 WHO classification, these neoplasms are stratified into well-differentiated neuroendocrine tumours (NETs, grades [G] 1–3) and poorly differentiated neuroendocrine carcinomas (NECs). [20-23] In paediatric series including the Surveillance, Epidemiology, and End Results Program, NET G1 and G2 predominate, though cases of NET G3 and, very rarely, NEC have also been documented. [3-5,12-16,24,25]

The most common entity in childhood is appendiceal NEN, typically diagnosed incidentally during appendectomy. [26,27] Among non-appendiceal / non-pulmonary primaries, pancreatic NENs predominate, with functional subtypes (e.g., insulinoma, gastrinoma) occurring but non-functional tumours being more frequent. Gastric, small intestinal, and colorectal NENs are rare and have been described mostly in registry analyses and isolated case reports. Appendiceal

NENs and pulmonary NENs are not covered here since they are subject of dedicated ESCP recommendations. [27,28]

The prognosis of paediatric GEP-NETs is generally favourable in localized disease when complete surgical resection is feasible, with 5-year overall survival exceeding 90%. [12-16] In contrast, outcomes in metastatic disease are substantially worse, with reported survival rates of 40%–60% in metastatic pancreatic NETs, depending on grade, tumour burden, and access to multimodal therapy. [12,13,15] Surgical resection is the only curative approach. Advanced or unresectable disease is managed with locoregional and/or systemic treatments largely adapted from adult practice, including somatostatin analogues, radiopharmaceutical therapy [RPT], targeted agents such as everolimus, sunitinib, cabozantinib and belzutifan, and chemotherapy. Paediatric GEP-NECs are very rare and generally associated with a poor prognosis, although prolonged survival has been described in isolated cases following intensive multimodal therapy. [12,13,15,16] The present ESCP recommendations were developed by the European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT) and affiliated experts in paediatric oncology, endocrinology, surgery, nuclear medicine, pathology, and radiotherapy, and are published as a briefer version of the full document in Pediatric Blood & Cancer. [29]

1.2 Background

GEP-NENs in children and adolescents represent an exceptionally rare and heterogeneous group of tumours, accounting for <0.5 % of all paediatric malignancies. Within this category, appendiceal followed by pulmonary NETs constitute the most frequent subtypes, but are the subject of a separate dedicated European Standard Clinical Practice (ESCP) document and are not addressed here. [26,27] The present guideline therefore focuses on paediatric NENs arising in the pancreas, gastrointestinal tract, and on neoplasms of unknown primary site.

The reported incidence of these paediatric GEP-NENs is below 0.1 cases per million children and adolescents per year.[11] Pancreatic NENs are the most common non-appendiceal / non-pulmonary subtype, followed by gastric, duodenal, and colorectal NENs, whereas small-intestinal primaries are distinctly uncommon. [2,3,6,30-32] Within NET, a considerable proportion of paediatric cases occur in the context of hereditary cancer predisposition syndromes, particularly MEN1, VHL, NF1, and TSC. [14,15,17-19]

Clinical presentation is variable. Both functional and non-functional pancreatic NETs occur in children and adolescents, with insulinomas being the most common functional subtype, typically presenting with recurrent hypoglycaemia, seizures, or other neuroglycopenic

symptoms. [12,13,15,33] Gastrinomas are also observed, mainly in the setting of MEN1, whereas VIPomas and glucagonomas are exceptional. Registry data suggest that non-functional tumours are at least equally frequent, although differences in ascertainment and reporting may influence observed distributions. [12,13,15,33] Such tumours often present with non-specific abdominal symptoms, a palpable mass, or are detected incidentally. Gastrointestinal NETs may manifest with abdominal pain, anaemia, gastrointestinal bleeding, or bowel obstruction. [13] Carcinoid syndrome is exceedingly rare in the paediatric population. [34] NECs are more aggressive, usually non-functional neoplasms that tend to present with rapidly progressive mass-related symptoms and/or disseminated disease. [12-15]

Histopathological classification follows the current World Health Organization (WHO) framework. (Appendix 1) NETs are graded G1–G3 by mitotic activity and Ki-67 proliferation index, while NECs represent a distinct high-grade entity. [20-22] In children and adolescents, the majority of GEP-NENs are NET G1 or G2. NET G3 and NEC are rare but clinically relevant subgroups requiring specific therapeutic considerations. [4,5,12-15,33,35]

Prognosis is generally favourable in localised, completely resected NETs, with long-term survival exceeding 90% in most series. [12-14] In contrast, advanced and metastatic NETs are associated with limited survival and significant morbidity despite multimodal therapy, and paediatric NECs typically follow an even more aggressive course and may constitute an oncological emergency at presentation. [12,13,15,16] For children and adolescents with NETs, treatment decisions must balance oncological efficacy with preservation of organ function, prevention of late sequelae, and careful integration of genetic counselling and life-long surveillance, whereas in NECs, rapid disease control and stabilisation are often the primary priorities.

Although paediatric GEP-NENs are managed in part by extrapolating from adult guidelines, [36-47] important differences in epidemiology, tumour biology and distribution, hereditary predisposition, and long-term survivorship require dedicated recommendations. [7] Adult frameworks, while comprehensive, cannot be adopted wholesale given the unique biology and rarity of paediatric disease. This ESCP document therefore aims to provide structured, paediatric-specific guidance to harmonise diagnostics, treatment, and follow-up across Europe.

2. Methodology

According to the Consensus Conference Standard Operating Procedure methodology, the levels of evidence can be classified from Level I to V and the grades of recommendation A to E (*Table 1) (54)*.

Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Disease Society of America-United States Public Health Service Grading System)

Levels of Evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of Recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

EXPeRT members recognized that due to the rarity of this tumour, no evidence of Level I to II exists for this age group. Therefore, recommendations for VRTs are developed based on the evidence collected from some published prospective studies (Level III), but more frequently retrospective series (Level IV), case reports (Level V) and personal expertise (Level V). In addition, the "strength" of recommendations will be categorized by additional grading (Grade A to E).

To identify tumours that need shared recommendations, EXPeRT members designed the following procedure:

1. Identification of the tumour of interest on the basis of its relevance, and previous EXPeRT experience, (i.e., data analysis and publication). Tumours should be classified as VRT (i.e. < 2/100.000/inhabitants/year), not already analysed in previous Expo-r-Net project, as pulmonary pneumoblastoma, pancreatoblastoma, thymic tumours, rare sarcomas, not included in specific international protocols and frequent enough to be of interest[1].
2. Designation of two main coordinators for each VRT based on their experience (data analysis, publications, personal experience).

Coordinators must:

1. Analyse the medical literature and select the relevant papers.
2. Propose a series of recommendations in the form of a first draft of recommendations.
3. Identify the main diagnostic and therapeutic problems for the designated VRT. The first drafts will be shared and discussed, along with the relevant publications, with a selected expert group of EXpERT members and annotated.
4. A mature version of recommendations will be produced, considering proposals from the group of selected EXPeRT members.
5. The annotated draft will then be proposed to external experts identified by the coordinators based on a recognized experience on the tumour (paediatrician, medical oncologist, radiation oncologist, surgeon…).
6. The final version will be validated by the whole group. In case of remaining disagreements, a vote will be done, during a physical consensus meeting, to agree on in a final consensus.
7. Validated version will be submitted for publication in an open-source peer review journal.

The final document including recommendations will be available on EXPeRT and SIOPe websites.

NB: These guidelines may change over time according to new data available. Local clinicians remain responsible for the care of their patients. The EXPeRT members and co-authors are not responsible for results or complications related to their use. If necessary, medical discussions are possible with EXPeRT members via the ERN CPMS website: CPMS 2.0

3. Diagnostic Assessment

Accurate diagnosis of paediatric GEP-NENs requires a structured, multimodal approach that integrates clinical evaluation, biochemical testing, multimodality imaging, and histopathological confirmation. Because these neoplasms are exceedingly rare in children and adolescents and may mimic other paediatric tumour entities, centralised review in specialised centres with access to expert pathology and multidisciplinary tumour boards is strongly recommended. [18] Only through such comprehensive evaluation can the diagnosis be established with sufficient certainty to guide treatment decisions. *[Level IV; Grade A]*

3.1 Clinical Presentation

The clinical presentation of paediatric GEP-NENs is heterogeneous and depends on tumour location, functional status, differentiation, and extent of disease. [6,7,12-16] *Functional pancreatic NETs* may present with classical endocrine syndromes: insulinomas with recurrent hypoglycaemia and neuroglycopenic or adrenergic symptoms; gastrinomas with peptic ulcer disease and refractory gastro-oesophageal reflux (Zollinger-Ellison Syndrome); and, more rarely, VIPomas or glucagonomas with chronic diarrhoea, electrolyte disturbances, or necrolytic migratory erythema. [12,15,33] *Non-functional tumours* may remain asymptomatic for long periods and are often detected because of mass effect, abdominal pain, or incidental imaging. *Gastrointestinal NENs* in children and adolescents typically present with non-specific abdominal symptoms or bleeding. Carcinoid syndrome is distinctly uncommon. [13,14] *NEN of unknown primary* (NEN-CUP) may present with disseminated disease. [16]

A careful clinical examination is essential in the diagnostic assessment. Beyond documenting localised or systemic symptoms, clinicians should actively search for stigmata suggestive of hereditary tumour predisposition syndromes, which are comparatively frequent in this population. [17,35] Examples include café-au-lait macules, cutaneous neurofibromas, or axillary freckling (NF1), angiofibromas or hypopigmented macules (TSC), retinal angiomas, haemangioblastomas, or features suggestive of adrenal paraganglial tumours (VHL), and parathyroid or pituitary abnormalities (MEN1). Documenting a detailed family history of endocrine tumours and related manifestations is equally important. *[Level IV; Grade A]*

These findings may provide critical early diagnostic cues, influence treatment decisions and tumour surveillance strategies, and guide genetic testing. [48-50] At the same time, clinicians must remain aware that, in many children and adolescents, more common entities such as solid pseudopapillary neoplasms of the pancreas, neuroblastoma, gastric GIST, or inflammatory myofibroblastic tumours of the intestine, are more likely than a GEP-NEN and should be carefully excluded during the diagnostic work-up.

3.2 Laboratory and Biochemical Evaluation

Laboratory assessment serves two purposes in paediatric GEP-NENs: (i) to confirm or refute functional hormone secretion when clinically suspected, and (ii) to establish a baseline of systemic health and comorbidity that may influence imaging, surgery, and systemic therapy. [51] Initial testing should include a complete blood count, serum electrolytes, renal and liver function tests, inflammatory markers if indicated, and a pregnancy test in adolescents where appropriate. *[Level IV; Grade B]*

Interpretation must use age-appropriate reference intervals and consider comedications (notably proton-pump inhibitors [PPIs], H2 blockers, selective serotonin-reuptake inhibitors [SSRIs], and depot octreotide/lanreotide), which can materially affect endocrine markers. *[Level III; Grade A]*

In addition, hormone levels or general NEN markers that are clearly abnormal at baseline may be followed over time as supportive indicators of treatment response or relapse, although they should not be used as standalone tumour markers for decision-making.

3.2.1 General NEN markers

Chromogranin A (CgA) has historically been used in adults for prognostication and follow-up, but its diagnostic performance is modest and its value in paediatric GEP-NENs is particularly limited. It is not recommended for screening and should only be considered in selected cases where a clear baseline elevation is documented and follow-up trends might provide supportive information. CgA levels are frequently confounded by proton pump inhibitors (PPIs), renal impairment, inflammatory states, and atrophic gastritis. Values should therefore be interpreted with great caution and, where possible, measured after PPI withdrawal (typically ≥2 weeks). Given these limitations and the growing move away from CgA in adult practice, its routine use in children and adolescents is discouraged. *[Level V; Grade C]*

Neuron-specific enolase (NSE) may be performed in NEC management but is non-specific. Emerging multianalyte assays are investigational and are not recommended for routine paediatric use. *[Level V; Grade C]*

3.2.2 Functional NETs

3.2.2.1 Pancreatic and duodenal

Biochemical work-up is symptom-directed. [52] In suspected insulinoma, a supervised fast should be performed in a controlled setting with paediatric endocrine support. Diagnostic criteria rely on Whipple's triad (symptoms of neuroglycopenia, low plasma glucose, relief with glucose) plus inappropriately high insulin secretion at the time of hypoglycaemia: concomitant insulin, C-peptide, and proinsulin that are not suppressed, suppressed β-hydroxybutyrate/free fatty acids, and a rise in glucose after glucagon support endogenous hyperinsulinism (absolute numeric thresholds vary by assay and age; centre-specific standards should be applied). *[Level III; Grade B]*

In suspected gastrinoma, fasting serum gastrin should be measured alongside gastric pH (ideally off PPIs. If withdrawal is unsafe, results should be interpreted with caution or bridging with H2 blockers considered). Marked hypergastrinaemia with gastric achlorhydria suggests type-1 gastric NEN pathophysiology, whereas hypergastrinaemia with acid hypersecretion suggests Zollinger–Ellison syndrome. *[Level III; Grade B]* Most gastrinomas/Zollinger-Ellison syndromes arise from duodenal NETs and are frequently associated with MEN1, underscoring the need for genetic evaluation. A secretin stimulation test may be helpful in equivocal cases when expertise is available. For rarer functional entities, VIP (profuse watery diarrhoea, hypokalaemia; but also possible in neuroblastoma), glucagon (diabetes/weight loss/dermatitis), and somatostatin (diabetes, steatorrhoea, cholelithiasis) may be assessed. *[Level III; Grade C]* In practice, these are very uncommon in children and adolescents. Testing should be driven by clinical presentation.

3.2.2.2 Gastric

True type-1 or type-2 gastric NETs are rare in paediatrics. When suspected, fasting gastrin, gastric pH (or basal acid output where expertise exists), vitamin B12, and anti-parietal cell/intrinsic-factor antibodies should be evaluated to delineate autoimmune atrophic gastritis.

3.2.2.3 Small-intestinal

Carcinoid syndrome is exceptional in children and adolescents, it only occurs at metastatic stage. Nevertheless, in the presence of suggestive features (episodic flushing, secretory diarrhoea, right-sided valvular disease), serotonin metabolism with 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) or plasma 5-HIAA should be quantified. Pre-analytic control is essential: dietary restrictions (avoid banana, pineapple, kiwi, walnuts, pecans, eggplant, tomatoes, chocolate) for 48–72 hours, and review of medications that interfere (e.g., SSRIs, acetaminophen, phenothiazines). [39,53] Adequate urine collection and creatinine indexing in younger children need to be ensured. *[Level III; Grade B]*

3.2.3 Non-functional NENs

3.2.3.1 Pancreatic and duodenal

Non-functional pancreatic NENs lack a defining hormonal / biochemistry signature. [38] Laboratory evaluation therefore focuses on systemic status (e.g., anaemia, nutritional parameters, pancreatic exocrine function if clinically indicated) and on hereditary context (see below). *[Level V; Grade B]*

3.2.3.2 Colorectal

There are no specific circulating markers for colorectal NENs. Laboratory abnormalities usually reflect site-related morbidity (e.g., iron-deficiency anaemia due to rectal bleeding or cholestatic/hepatocellular enzyme elevations in the presence of liver involvement).

In children and adolescent with a liver lesion in whom NEN is suspected, routine biochemistry cannot distinguish primary hepatic NEN from metastasis. Given that true primary hepatic NEN are at best extraordinarily rare and may not exist as a distinct entity, liver involvement should be considered metastatic —or secondary to another primary tumour —until proven otherwise. Diagnosis and classification rely on dedicated liver MRI and histopathological evaluation of tissue obtained by biopsy or resection. relies on imaging (liver MRI) and pathological analysis. *[Level V; Grade C]*

3.2.3.3 NEN of unknown primary (CUP)

Biochemical testing in paediatric NEN-CUP is hypothesis-generating rather than diagnostic. [54-56] A focused and rational panel may be applied based on symptomatology (e.g., insulin/C-

peptide if hypoglycaemia, gastrin if ulcer disease), while avoiding indiscriminate testing. In addition, measurement of calcitonin and plasma or urinary metanephrines should be considered to exclude medullary thyroid carcinoma and intra-/extraadrenal paraganglioma, respectively, particularly in the absence of a clear gastrointestinal or pancreatic primary. *[Level IV; Grade B]*

Results should guide imaging and biopsy strategy rather than be used in isolation to infer the site of origin. *[Level IV; Grade B]*

3.2.4 Hereditary context and syndrome-directed labs

Because hereditary predisposition is relatively common in paediatric GEP-NETs, baseline evaluation should incorporate other syndrome-specific screens: serum calcium and PTH (MEN1), pituitary axis (prolactin, IGF-1) as indicated, and plasma/urine metanephrines when VHL or other pheochromocytoma-prone syndromes are suspected. These tests inform both index tumour management (e.g., multifocality in MEN1) and long-term surveillance. *[Level III; Grade B]*

The clinical impact to find a hereditary syndrome is important for both, the family and the patient because it will guide the follow-up and may guide the systemic treatment (such the use of belzutifan in VHL patients).

3.2.5 Practical pitfalls and pre-analytics

Drug effects: PPIs elevate gastrin and CgA; where safe, PPIs should be withhold ≥2 weeks or measures interpreted with caution. SSA therapy may blunt hormonal secretion and alter marker kinetics. *[Level IV; Grade B]*

Renal function: Reduced GFR elevates serum CgA and 5-HIAA; interpretation may need adjustment. *[Level III; Grade C]*

Sampling conditions: For hypoglycaemia evaluation, glucose, insulin, C-peptide, proinsulin, ketones, and free fatty acids during symptoms or a supervised fast must be obtained simultaneously. *[Level III; Grade A]*

Reference standards: Assay- and age-specific thresholds must be used; uncritical import of adult cut-offs should be avoided. *[Level III; Grade A]*

Follow-up use: For functioning tumours, the culprit hormone that was clearly elevated at baseline may be followed longitudinally as a supportive indicator of response or relapse. Routine use of non-specific markers (such as CgA) for follow-up is not recommended, and they should not drive management decisions. Measurement of 5-HIAA is generally reserved for selected patients with metastatic small-intestinal NET and documented serotonin excess, in whom it may inform screening for carcinoid heart disease. Such situations are exceptional in paediatrics. *[Level IV; Grade B]*

3.3 Imaging

Imaging plays a central role in the diagnostic work-up, staging, and treatment planning of paediatric GEP-NENs. The optimal initial modality depends strongly on the mode of presentation: in some children the tumour is first suspected because of an abdominal mass on physical examination or ultrasound, while in others it is identified incidentally during imaging or endoscopy performed for unrelated indications. A structured, stepwise approach is essential, balancing sensitivity with the need to minimise radiation exposure and sedation, and integrating anatomical and functional information.

3.3.1 General principles

Ultrasound is the first-line modality in children with abdominal pain or mass suspicion and may detect larger intra-abdominal tumours or hepatic lesions. For cross-sectional imaging, magnetic resonance imaging (MRI) is preferred over computed tomography (CT) to avoid cumulative radiation, particularly in long-term surveillance. *[Level III; Grade A]*

When CT is required—for example, in acute situations or when MRI is not feasible—dose-optimised paediatric protocols should be used. *[Level III; Grade B]*

All imaging should ideally be performed in centres with paediatric radiology expertise and reviewed centrally. *[Level IV; Grade A]*

3.3.2 Pancreatic NENs

High-resolution MRI with dedicated pancreatic sequences is the modality of choice for staging and localisation. Insulinomas may be small and difficult to detect; in such cases, ultrasound can

occasionally be helpful, but endoscopic ultrasound (EUS) is often most sensitive for small lesions. EUS also provides the option for biopsy when needed. Non-functional tumours are often larger at presentation and more readily visualised with MRI. CT may still be required in selected cases to assess vascular involvement prior to surgery. *[Level IV; Grade A]*

3.3.3 Gastric and duodenal NENs

These are most often identified during upper endoscopy with biopsy, which remains the gold standard for diagnosis. Endoscopic ultrasound is valuable for assessing local invasion and lymph node involvement, particularly in duodenal primaries, and for evaluating submucosal extension that may not be evident on superficial biopsy. *[Level IV; Grade A]*

3.3.4 Small intestinal NETs

These are rare in children but can present as occult bleeding or nonspecific abdominal symptoms. MRI enterography is the modality of choice to assess the small bowel and mesentery. *[Level V; Grade B]* While mesenteric fibrosis is a hallmark finding in adults, it is extremely rare in children but should still be assessed if suspected.

3.3.5 Colorectal NENs

Colonoscopy with biopsy is the standard diagnostic modality. In rectal lesions, pelvic MRI can provide detailed local staging, especially for larger or higher-grade tumours. Cross-sectional imaging of the abdomen and pelvis is indicated to assess for nodal or hepatic involvement in higher-stage disease. *[Level IV; Grade A]*

3.3.6 Hepatic lesions

The liver is commonly a site of metastasis from other GEP-NENs. Dedicated liver MRI is recommended to characterise focal lesions. *[Level IV; Grade A]* Differentiation from hepatoblastoma, hepatocellular carcinoma, or metastatic disease of other origin requires histological confirmation with immunohistochemistry. [16,34,57]

3.3.7 Functional imaging

Somatostatin receptor (SSTR) imaging is essential in staging and treatment planning. [58-60] SSTR-directed PET/CT or PET/MRI is the modality of choice for well-differentiated NETs (G1–G2 and selected G3), offering high sensitivity and specificity. In children, PET/MRI is

particularly advantageous to reduce radiation exposure. SSTR imaging is not recommended in NEC. *[Level III; Grade A].*

[^{18}F]FDG PET/CT should be considered in NET G3 when the result is expected to influence management (e.g., in suspected localized disease or discordant behaviour) or to detect SSTR-negative, biologically aggressive components. *[Level III; Grade A]* The combination of functional and cross-sectional imaging guides eligibility for PRRT and has prognostic value, as higher FDG uptake and absent SSTR expression are associated with more aggressive disease. at baseline.

In NET-CUP, [^{18}F]DOPA PET/CT should be added if no primary is found on SSTR imaging. *[Level III; Grade A]* However, it should be recognised that even advanced cross-sectional and functional imaging may identify multiple sites of tracer uptake or metastatic disease without reliably localising the primary tumour. [61]

In NEC, [^{18}F]FDG PET/CT is the only functional imaging modality routinely recommended. *[Level III; Grade A]* SSTR imaging is not recommended in NEC. *[Level III; Grade E]*

3.3.8 Paediatric considerations

Sedation may be required for MRI and PET/MRI in younger children, underscoring the importance of careful preparation and child-friendly protocols. To avoid repeated anaesthesia, staging studies should be coordinated across modalities whenever possible. Given the rarity of paediatric GEP-NENs, images should be reviewed by radiologists experienced in neuroendocrine tumours, ideally within a reference centre or expert network. *[Level IV; Grade A]*

3.4 Pathology

Histopathological confirmation is generally required for the diagnosis of paediatric GEP-NENs and should be obtained whenever safely feasible. *[Level III; Grade A]* All tumour specimens should be assessed according to the WHO 2019 classification, which distinguishes NET G1–G3 from NEC, using morphology and both mitotic count and Ki-67 proliferation index as grading criteria. (see Appendix 1) [20,21,62] *[Level III; Grade A]* In very selected situations—such as multiple small pancreatic nodules in TSC/MEN1 without clear clinical progression—a

multidisciplinary tumour board may decide on initial clinical and radiological surveillance without immediate tissue confirmation. *[Level V; Grade C]*

Because of the rarity of these tumours in the paediatric population and the frequent overlap with other small round cell tumours or paediatric-specific neoplasms, centralised pathology review by a panel expert in these diseases is strongly recommended. *[Level IV; Grade A]*

Immunohistochemistry (IHC) forms the cornerstone of diagnosis. Synaptophysin and CgA are the standard neuroendocrine markers and should be applied in all cases. If one is negative, other markers should be used (such as INSM1, CgB, CD56). Ki-67 immunostaining is mandatory for grading and must be quantified rigorously, ideally using digital image analysis to improve reproducibility. Additional markers such as CD56 and broad-spectrum cytokeratins (e.g. AE1/AE3) can support the diagnosis and exclude paraganglioma as a differential diagnosis, although they lack specificity. *[Level IV; Grade A]*

The use of site-specific IHC panels is crucial for differential diagnosis in paediatric practice. A carefully selected antibody panel interpreted in the context of morphology and clinical findings is therefore critical to avoid misclassification. For pancreatic tumours, β-catenin nuclear staining may suggest solid pseudopapillary neoplasm, which is a common mimic. In gastrointestinal stromal tumour (GIST), expression of DOG1 and KIT (CD117) is characteristic. For soft tissue mimics such as rhabdomyosarcoma, desmin and myogenin are essential discriminators. In poorly differentiated neoplasms, INI1/SMARCB1 may be considered to exclude *SMARCB1* deficient tumours. *[Level V; Grade B]*

Given the prognostic and therapeutic implications, grading must be based on both morphology and Ki-67 index, with attention to tumour heterogeneity. In those cases, the highest Ki-67/mitotic index should be reported. [63]

3.5 Molecular Pathology and Analysis of Potential Therapeutic Targets

The role of molecular pathology in paediatric GEP-NENs remains evolving. In adults, recurrent somatic alterations in *MEN1*, *DAXX*, and *ATRX* are frequently observed in pancreatic NETs (but not in NEC), while mutations affecting the mTOR signalling pathway (*TSC2*, *PTEN*, *PIK3CA*) are recurrently described and have been implicated in disease progression. However, with the notable exception of VHL-associated tumours, these alterations currently lack high-level clinical actionability according to the ESMO Scale for Clinical Actionability of molecular

Targets (ESCAT). [64] By contrast, paediatric data are sparse. *[Level V; Grade C]* Registry reports and small series suggest that germline alterations associated with MEN1, VHL, NF1, and TSC syndromes account for a substantial fraction of paediatric cases, whereas the prevalence and clinical impact of the adult-typical somatic alterations are not well established.

Extended molecular profiling using next-generation sequencing (NGS) may occasionally reveal targetable alterations or help to refine diagnosis. However, given the rarity of paediatric GEP-NENs, such testing should be considered in advanced disease, refractory cases, or within clinical trials and research protocols, rather than as routine practice. *[Level V; Grade B]* Importantly, any molecular findings should be interpreted within the context of a multidisciplinary molecular tumour board, ensuring alignment with clinical relevance and treatment feasibility. *[Level V; Grade B]*

3.6 Biopsy

Whenever feasible, primary resection specimen provides the most reliable basis for diagnosis, grading, and comprehensive immunohistochemical analysis. In cases of locally advanced or metastatic disease, image-guided core needle biopsy is recommended. *[Level IV; Grade B]* Fine-needle aspiration (FNA) alone is insufficient to establish a definitive diagnosis, as it often fails to provide adequate material for grading and immunohistochemical profiling. However, it may assist in excluding alternative diagnoses.

For luminal gastrointestinal lesions, endoscopic biopsy is appropriate. *[Level IV; Grade A]* For pancreatic/duodeno-pancreatic lesions, endoscopic ultrasound-guided tissue sampling may be considered. *[Level V; Grade C]*

The approach of the biopsy should consider the risk of peritoneal spread during the technics. Retroperitoneal lesions should be biopsied by a posterior approach. Transperitoneal biopsy by anterior approach should be avoided. *[Level IV, Grade E]*

A key limitation in small biopsy specimens is the potential to underestimate tumour grade, since mitotic activity and Ki-67 proliferation index may not be representative of the whole tumour. Repeat sampling should therefore be considered if the clinical course or imaging findings are discordant with the initial histopathological classification. *[Level V; Grade B]*

3.7 Genetic Counselling and Testing

Given the high prevalence of hereditary cancer predisposition syndromes in paediatric GEP-NETs, [17,18] genetic counselling is strongly recommended for all patients. Testing should be offered for key genes associated with these tumours, including *MEN1*, *VHL*, *NF1*, and *TSC*, with additional genes considered based on tumour type and family history. *[Level IV; Grade A]*

Germline testing is ultimately the decision of the individual and their family and is subject to national legal and ethical frameworks. It should therefore only be performed after thorough genetic counselling, informed consent, and in compliance with relevant regulations. *[Level IV; Grade B]*

A germline pathogenic variant finding has important consequences. It confirms a heritable cancer predisposition, informs surveillance strategies for the patient, and necessitates tailored long-term follow-up to detect additional tumours at an early stage. It also has implications for at-risk relatives, who may benefit from cascade testing, counselling, and preventive measures. Conversely, a negative result in the context of a strong clinical suspicion does not exclude hereditary predisposition, and clinical surveillance may still be appropriate. Lastly, genetic results may also influence therapeutic management in certain syndromic contexts. For example, the hypoxia-inducible factor-2α inhibitor belzutifan has demonstrated substantial efficacy in VHL-associated tumours, [49] underscoring the relevance of precise molecular diagnosis for targeted treatment decisions in case of progressive disease.

Taken together, genetic counselling and testing form a cornerstone of the multidisciplinary management of paediatric GEP-NENs, guiding not only treatment and follow-up for the affected child but also risk assessment and preventive care within the family.

3.8 Additional Assessments

Cardiac evaluation should be considered in children with carcinoid syndrome (serotonin-producing tumours), given the risk of carcinoid heart disease. *[Level V; Grade B]* Although this complication is exceedingly rare in paediatrics compared to adults, echocardiography is indicated in cases with persistently elevated urinary or plasma 5-HIAA levels or clinical suspicion of valvular involvement. Measurement of NT-proBNP (or proBNP) may be used as

an additional screening tool in analogy to adult practice. [51] *[Level V; Grade C]* Early detection of cardiac dysfunction is essential to guide timely cardiology referral and management.

Psychosocial assessment is a central component of care, as paediatric patients and their families face significant challenges related to the rarity and chronic nature of GEP-NENs, the implications of hereditary syndromes, and the need for life-long surveillance. Structured psychosocial support, including access to psycho-oncology and genetic counselling services, should be offered at diagnosis and revisited throughout the disease course. *[Level IV; Grade A]*

All paediatric GEP-NEN cases should undergo review in a **multidisciplinary tumour board**, preferably within or in close collaboration with an expert centre for paediatric rare tumours and/or adults neuroendocrine neoplasms. *[Level IV; Grade A]* This ensures that diagnostic findings, treatment planning, and surveillance strategies benefit from the combined expertise of paediatric oncology, endocrinology, gastroenterology, surgery, nuclear medicine, pathology, and genetics. Centralised discussion is strongly recommended to mitigate the risks associated with very low case numbers in individual institutions and to harmonise care according to best available evidence.

4. Treatment Details

4.1 General considerations

Given the extreme rarity of these tumours, all cases should be discussed in a multidisciplinary tumour board with expertise in paediatric oncology, surgery, endocrinology, nuclear medicine, gastroenterology, pathology, and genetics. *[Level IV; Grade A]* Multidisciplinary tumour board review is crucial to balance oncological radicality with organ preservation, endocrine and exocrine function, and long-term survivorship in children and adolescents with NETs.

Surgical resection remains the cornerstone of curative treatment for most localised paediatric GEP-NENs. [6,12-16,65] Whenever technically feasible and clinically indicated, complete macroscopic and microscopic resection (R0) should be pursued, as this is the strongest prognostic factor for long-term survival. *[Level IV; Grade A]* Surgery is not mandatory in all cases: in very selected situations—such as small, asymptomatic, well differentiated lesions in the context of hereditary syndromes (e.g. MEN1, TSC) without radiological progression—an initial active surveillance strategy with close imaging may be appropriate after multidisciplinary discussion. [66] *[Level V; Grade C]* For advanced or metastatic disease, systemic therapies

adapted from adult protocols are increasingly used, although prospective paediatric data remain sparse.

NECs, however, represent a biologically distinct, highly aggressive entity and require rapid diagnostic work-up and prompt initiation of systemic therapy, rather than upfront surgical resection in most cases, with early involvement of centres experienced in high-grade NEN management. *[Level V; Grade A]*

Children and adolescents with advanced or metastatic disease should also be referred to expert reference centres with established experience in NENs, ensuring access to advanced diagnostics such as SSTR-directed PET/CT, molecular pathology, and multimodal therapeutic options including PRRT and clinical trials as applicable. [67] *[Level V; Grade A]*

4.2 Surgery

Surgical management follows general oncological principles. R0 resection is the treatment goal, but in children there is a particular emphasis on organ- and function-preserving techniques whenever this can be achieved without compromising oncological safety. Lymphadenectomy is generally recommended as part of standard oncological resection for GEP-NENs, even when nodal disease is not overtly suspected, with the extent of nodal clearance tailored to tumour site, size, and grade. [68] *[Level IV; Grade A]* Extensive, prophylactic lymph-node dissection beyond the regional basin—particularly in small NETs without radiological or intraoperative suspicion of nodal involvement—is not recommended in NETs. *[Level V; Grade D]*

4.2.1 Pancreatic NETs

Insulinomas are typically small and solitary. Enucleation with free margins is often sufficient, provided the lesion is well localised and at a safe distance from the main pancreatic duct. *[Level IV; Grade B]* Intraoperative ultrasound, with or without contrast enhancement, is a helpful tool to localise the lesion, assess its relation to the ductal system, and guide the extent of resection. *[Level IV; Grade B]* In adults, endoscopic ultrasound-guided radiofrequency ablation has emerged as a minimally invasive option for selected insulinomas. In children, experience is very limited, and such procedures should be considered only on an individual basis in expert centres. *[Level V; Grade C]*

Non-functional tumours require an approach guided by size, location, growth behaviour, and ductal involvement. Options include enucleation for small, peripherally located lesions, distal

pancreatic tail resection (with or without splenic preservation) for body/tail tumors, and and Whipple procedure for large or duct-involving head tumors. [69] *[Level IV; Grade B]*

During formal pancreatic resections, regional lymph-node assessment is recommended, whereas in atypical or parenchyma-sparing resections, sampling of peripancreatic nodes with or without frozen-section analysis is advisable to document nodal status. *[Level IV; Grade B]* Fresh frozen sections from the resection margins should be obtained when possible to confirm complete tumour removal and reduce the need for re-operation. *[Level V; Grade B]*

MEN1- and TSC-associated disease frequently present with multifocal, often non-functioning pancreatic NETs. In these contexts, management should balance the risk of progression against surgical morbidity and the long-term burden of endocrine and exocrine insufficiency. In line with adult consensus guidance, small, asymptomatic NETs (<2 cm), without radiological suspicion of regional nodal disease and stable in size, may be managed with active surveillance. *[Level IV; Grade B]* Resection should be considered in larger, growing, or symptomatic tumours, and in younger patients with good performance status, after multidisciplinary discussion. *[Level IV; Grade B]* When surgery is undertaken, parenchyma-sparing procedures (limited resection, enucleations) are preferred, combined with vigilant long-term surveillance recognising the high risk of recurrence and metachronous lesions. *[Level IV; Grade B]*

Appendix 2 presents the flowchart for the initial diagnostic and treatment pathway in pancreatic NEN.

4.2.2 Gastrointestinal NETs

Gastric and duodenal NETs usually present as small, localised lesions. Local excision or limited segmental resection is often sufficient. [39,70] In MEN1-associated gastrinomas, surgical strategy must carefully balance oncological control with morbidity, and extensive resections are rarely indicated in children. *[Level V; Grade B]*

Small intestinal NETs should be treated with segmental bowel resection and mesenteric lymphadenectomy, analogous to adult management. [46,53] *[Level V; Grade A]*

Colorectal NETs generally require segmental colectomy with regional lymph-node dissection for lesions not meeting the criteria for purely endoscopic treatment, following oncological principles applied in colorectal carcinoma surgery and in accordance with adult colorectal NET guidelines. [41] *[Level V; Grade A]* Lymph-node dissection should follow standard surgical principles as used in colon carcinoma, aiming to remove nodes along the relevant vascular

pedicle. The extent should be tailored to tumour size, grade, depth of invasion, and regional anatomy, avoiding extensive systematic lymphadenectomy beyond tumour-specific drainage basin in the absence of radiological or intraoperative suspicion of further nodal involvement. *[Level V; Grade C]*

In contrast, small rectal NETs (< 1 cm) without adverse prognostic features (low grade, absence of lymphovascular invasion and muscularis propria involvement) may be appropriately managed with local endoscopic excision. *[Level V; Grade B]*

The flowchart in Appendix 2 outlines the initial diagnostic and treatment pathway for gastrointestinal NEN.

4.2.3 Hepatic lesions

In most cases, liver lesions represent metastatic disease from an extrahepatic primary. Partial hepatic resection may be considered in selected patients with resectable liver-dominant metastases, provided sufficient hepatic reserve can be maintained. *[Level V; Grade B]*

Liver transplantation is not established for neuroendocrine metastases in children and adolescents and should therefore be considered investigational. In adults, transplantation has been explored in highly selected cases (e.g. low-grade NET, liver-only disease, durable disease control, and absence of extrahepatic spread), but evidence remains limited and long-term outcomes are variable. In paediatric GEP-NEN, data are anecdotal, and the potential benefits must be weighed against the risks of immunosuppression, including tumour recurrence. If considered at all, evaluation should occur only in specialised centres within a rigorous multidisciplinary and ethical review framework. *[Level V; Grade C]*

4.2.4 NEN of unknown primary (CUP)

Paediatric NEN-CUP typically presents at an advanced, metastatic stage. Curative surgery is rarely feasible, and the role of resection is usually limited to obtaining adequate tissue for diagnosis or for palliative interventions such as relieving obstruction. *[Level V; Grade B]*

4.3 Systemic Therapies

Systemic therapy is largely guided by extrapolation from adult evidence from randomized/phase III trials and consensus guidelines, complemented by growing but still limited paediatric experience.

Systemic therapy is indicated in children and adolescents for unresectable, metastatic, or clearly progressive disease, and for persistent symptoms in functioning tumours despite optimal local management. [42,43,51]

The choice of systemic treatment depends on tumour grade and differentiation, somatostatin receptor expression, the extent and tempo of disease, and the presence of hormonal symptoms. The rarity of these tumours in children and adolescents mandates case discussion in a multidisciplinary setting, preferably in or in close consultation with expert centres. *[Level IV; Grade A]*

4.3.1 Somatostatin Analogues (SSA)

Somatostatin analogues (octreotide LAR, lanreotide autogel) represent the cornerstone of systemic therapy in NETs. [42,71-73] In adults, the PROMID and CLARINET trials demonstrated an anti-proliferative effect and prolonged progression-free survival in midgut and enteropancreatic NETs, respectively. [72,73]

In paediatric patients, experience remains limited to registry reports and small series, but SSAs are widely used due to their favourable safety profile and their ability to control hormone-related symptoms in functioning tumours. Typical adverse effects are mild, including gastrointestinal discomfort and gallstone formation. Growth and pubertal development do not appear to be adversely affected by standard dosing, although prospective data are lacking.

In this context, SSAs are regarded as first-line systemic therapy for children and adolescents with progressive and/or unresectable SSTR-positive NETs, or for those with persistent hormonal symptoms despite surgery. *[Level V; Grade B]*

In clinically stable, asymptomatic patients with low-burden, well-differentiated disease, a watch-and-wait strategy with close surveillance may be appropriate. *[Level V; Grade B]*

4.3.2 Radiopharmaceutical Therapy (RPT)

RPT with [^{177}Lu]Lu-DOTATATE has transformed the treatment of adult SSTR-positive NETs. The NETTER-1 study established a clear PFS benefit in midgut NETs, while NETTER-2 and COMPETE confirmed its role in higher-grade and broader GEP-NET populations.

Paediatric experience is more recent: retrospective case series indicate feasibility, and the prospective NETTER-P study demonstrated safety and promising efficacy in children and adolescents, with manageable toxicity when renal protection protocols are applied. [74-78] Long-

term follow-up is crucial, particularly for haematologic and gonadal late effects, which may be more relevant in the paediatric setting. RPT is recommended for progressive, SSTR-positive NETs after SSA failure or in selected cases earlier in the treatment sequence if the tumour burden is high or the growth dynamics are rapid. [79-81] *[Level IV; Grade B]* It should only be delivered in specialised centres with paediatric nuclear medicine expertise. *[Level V; Grade A]*

4.3.3 Targeted Therapies

Targeted agents approved in adults—everolimus (a mTOR inhibitor, approved for progressive pancreatic NETs G1-G2 in RADIANT-3 study and for non-functional gastrointestinal NETs in RADIANT-4), [82-84] cabozantinib (for progressive extra- pancreatic and pancreatic NETs based on the CABINET trial), [85] and sunitinib (for progressive pancreatic NET G1-2)—have all demonstrated prolonged PFS compared with placebo. Belzutifan is additionally approved for VHL-associated tumours, including pancreatic NETs, for adolescents aged ≥ 12 years. [83-86]

The use of targeted agents in children and adolescents with NETs is off-label and remains rare, but registry data and case reports suggest potential benefit in progressive pancreatic NETs, especially when PRRT is not feasible or after PRRT failure. *[Level V; Grade B]* Toxicity profiles must be carefully managed: everolimus can cause stomatitis, hyperglycaemia, and immunosuppression, while sunitinib may induce hypertension, cytopenias, and cardiac toxicity. Dose adjustments are required, and careful monitoring must be ensured.

Given their oral administration, prior experience in paediatric populations from other disease contexts, and generally manageable toxicity profiles, targeted agents may be considered a reasonable option in selected cases, ideally within registry documentation.

4.3.4 Chemotherapy

Cytotoxic chemotherapy has a limited role in paediatric NETs but remains essential for NET G3 and NEC. [43,87-91] *[Level V; Grade B]* Platinum–etoposide is the standard first-line regimen in NEC, yielding response rates but short-lived remissions in adult settings. *[Level V; Grade B]*

For well-differentiated NET G3 and selected progressive NET G2, temozolomide-based regimens (CAPTEM) have shown efficacy in adults and are occasionally used in older children and adolescents, though paediatric-specific evidence is sparse. [92-94] It can be considered in selected progressive NET G2-G3. *[Level V; Grade B]* Cytotoxic chemotherapy should be restricted to aggressive disease, with central documentation and long-term follow-up. *[Level V; Grade A]*

4.3.5 Other and Emerging Therapies

Beyond established systemic treatments, several additional approaches have been explored in adult and paediatric GEP-NENs, but none can currently be regarded as standard of care in children. *[Level V; Grade C]*

Liver-directed therapies such as transarterial embolisation (TAE), chemoembolisation (TACE), or radioembolization/selective internal radiation therapy (SIRT) are used in adults with unresectable, liver-dominant disease. [95,96] In paediatrics, experience is limited to anecdotal reports, and such interventions should be restricted to specialised centres and considered only in highly selected cases. *[Level V; Grade C]* However, this technique may be helpful to decrease hormonal secretion in case of uncontrolled functional NET.

Immunotherapy with checkpoint inhibitors has shown limited activity in well-differentiated NETs but occasional benefit in NEC with high tumour mutational burden or mismatch-repair deficiency. [97-102] In children, reports are extremely scarce. Testing for microsatellite instability (MSI) or high mutational load may help identify candidates (particularly in the context of Lynch syndrome/Hereditary Non-Polyposis Colorectal Cancer, where associated tumours are often MSI), but use should generally be confined to clinical trials. *[Level V; Grade C]*

Novel radioligand therapies—including alpha-emitting RPT and other next-generation radionuclides—are under investigation in adults and, to a very limited extent, in paediatric populations, but remain experimental.

Overall, these emerging approaches underline the importance of referring paediatric patients with advanced or refractory disease to clinical trials or highly specialised centres, where innovative therapies can be explored safely with structured documentation and long-term follow-up. *[Level V; Grade A]*

In summary, in paediatric GEP-NETs, systemic therapy is indicated primarily for unresectable, progressive, or metastatic disease. SSAs are the first-line choice in SSTR-positive NET, RPT is increasingly validated by paediatric data and should be considered in progressive disease, targeted therapies or chemotherapy are reserved for later lines or high-grade NET, while platinum-etoposide is the standard for NEC. Long-term toxicity, developmental stage, and hereditary background must guide treatment selection, and inclusion in registries and collaborative trials is strongly encouraged.

4.4 Radiotherapy

External beam radiotherapy has no established curative role in GEP-NENs. Its use is largely limited to palliation of symptomatic metastases, such as painful bone lesions or unresectable local recurrences causing obstruction or pain. In adults, stereotactic body radiotherapy (SBRT) has occasionally been applied to oligometastatic sites, but experience in children is anecdotal. *[Level V; Grade B]*

4.5 Supportive Therapy

Supportive care is an integral component of management. Hormone-related symptoms should be controlled with targeted therapy: hypoglycaemia in insulinoma with dietary measures and diazoxide until resection; gastric acid hypersecretion with high dosages of PPIs in gastrinoma; diarrhoea in VIPoma with fluid/electrolyte replacement and SSAs. Nutritional support is essential in children with chronic diarrhoea, pancreatic insufficiency after resection, or extensive disease. *[Level IV; Grade B]*

5. Follow-up and Surveillance

Long-term follow-up is an essential component in the care of children and adolescents with GEP-NENs. [37,45,47] *[Level IV; Grade A]* Even after complete surgical resection, the risk of recurrence—although lower in well-differentiated tumours than in adults—necessitates structured surveillance. Moreover, hereditary syndromes are common, and survivors face unique risks of late effects related to treatment and the long natural history of the disease. Accordingly, follow-up must be risk-adapted, life-long, and ideally coordinated in expert centres with transition to adult services when appropriate. *[Level IV; Grade A]*

5.1 General principles

Surveillance strategies should be stratified according to tumour grade, stage at diagnosis, completeness of resection, and hereditary background. Clinical assessment, biochemical monitoring, and imaging represent the main pillars of follow-up. The schedule and intensity of

surveillance must balance the risk of relapse with the need to limit cumulative radiation exposure and to minimise the psychosocial burden of repeated investigations.

5.2 Clinical follow-up

Clinical review should be performed every 3–6 months for the first two years after resection and subsequently every 6–12 months, depending on risk profile. *[Level V; Grade B]*

Visits should include thorough history-taking for recurrent symptoms (hypoglycaemia, peptic symptoms, flushing, diarrhoea), physical examination, and specific assessment for signs of hereditary syndromes. Nutritional status, growth and pubertal development, and treatment-related sequelae (e.g. pancreatic insufficiency, diabetes, postsurgical complications) require regular evaluation. *[Level IV; Grade B]*

Psychosocial and educational aspects should also be assessed, reflecting the chronic nature of NEN care. *[Level V; Grade B]*

5.3 Biochemical monitoring

Laboratory surveillance should be tailored to tumour biology and initial presentation. *[Level V; Grade B]* CgA has limited sensitivity and specificity in both adults and children. Its use in follow-up should be restricted to patients with a clearly elevated baseline value, where serial measurements may provide complementary information only. *[Level V; Grade C]* For functional tumours, the relevant hormone that was abnormal at diagnosis (e.g. insulin, gastrin, VIP, glucagon, serotonin/5-HIAA) may be re-measured if symptoms recur or if there is clinical or radiological suspicion of progression, but routine repeated testing in asymptomatic patients is not recommended. . *[Level V; Grade B]* In hereditary cases, syndrome-specific biochemical screening should be integrated into long-term surveillance protocols according to dedicated guidelines. *[Level IV; Grade B]*

5.4 Imaging

Cross-sectional imaging remains the cornerstone of surveillance. MRI is the preferred modality in children and adolescents to avoid radiation, particularly for abdominal and pelvic assessment. CT should be reserved for cases where MRI is inconclusive or unavailable. Functional imaging

with SSTR-directed PET/CT should be considered in high-risk patients or when recurrence is suspected but not localised on conventional imaging. [^{18}F]FDG-PET/CT may be warranted in NET G3 or NEC. For local disease, endoscopy and endoscopic ultrasound play an important role in the surveillance of gastric and duodeno-pancreatic primaries, particularly in hereditary contexts such as MEN1, and colonoscopy (with endoscopic ultrasound for selected rectal lesions) is similarly relevant for colorectal primaries.

Suggested intervals:

Low-risk disease (completely resected NET G1, localised, no hereditary syndrome): MRI approximately every 12 months for 5–10 years, then adapted to individual context. *[Level IV; Grade B]*

Intermediate risk (NET G2, nodal involvement, hereditary syndromes): MRI every 6–12 months for the first 5 years, then annually and adapted thereafter to individual context. Functional imaging only as clinically indicated (e.g., suspicion of recurrence not clarified by MRI). *[Level IV; Grade B]*

High risk (NET G3, NEC, metastatic disease): MRI every 3–6 months. SSTR-directed and/or [^{18}F]FDG PET/CT repeated only when the result is expected to change management (e.g., suspected progression not adequately assessed by conventional imaging). *[Level IV; Grade B]*

5.5 Hereditary considerations

For patients with germline predisposition (MEN1, VHL, NF1, TSC), surveillance must include syndrome-specific screening independent of the index tumour. *[Level III; Grade A]* Rather than relying on broad, unspecific biochemical panels, follow-up should be guided by the most up-to-date international or national guidelines for each syndrome, typically combining targeted biochemical tests and imaging of relevant organs at defined intervals. Close coordination between paediatric oncology, endocrinology, and clinical genetics is essential to ensure that surveillance remains evidence based as recommendations evolve.

5.6 Transition of care

Given the life-long course of GEP-NENs, structured transition to adult services is mandatory. This should begin in adolescence and involve preparation of a comprehensive survivorship plan, detailing initial diagnosis, treatments received (including dosimetry for PRRT where applicable), hereditary findings, and long-term risks. *[Level IV; Grade A]*

6. Treatment of Relapsed or Progressive Disease

Relapse or progression in paediatric GEP-NENs is uncommon after complete resection of localised, well-differentiated tumours but may occur in patients with advanced stage disease at diagnosis, incomplete resections, or higher-grade tumours. [103,104]

Management requires careful reassessment of tumour biology and extent, ideally within a specialised multidisciplinary tumour board with paediatric oncology, endocrine surgery, nuclear medicine, radiology, and pathology expertise. *[Level V; Grade A]*

At relapse, a new diagnostic work-up is mandatory. This includes high-resolution cross-sectional imaging (MRI preferred, CT when clinically indicated), SSTR-directed PET/CT in NET, and [^{18}F]FDG-PET/CT in higher-grade NET and NEC. Repeat biopsy should be considered if there is a significant change in tumour behaviour, as grade progression may occur. *[Level IV; Grade A]* Comprehensive somatic molecular characterisation may help to identify potential targeted agents. *[Level V; Grade C]*

In cases of localised relapse or oligometastatic disease, surgical resection and/or focal therapy of metastatic sites (e.g. thermal ablation, liver embolization, stereotactic radiotherapy) remains the treatment of choice if complete local control is feasible without undue morbidity. Parenchyma-sparing approaches should be balanced against the need for oncological clearance, especially in the pancreas. *[Level V; Grade A]* In selected patients with diffuse, liver-dominant metastases, prior complete control of the primary tumour and slowly progressive disease, liver transplantation has been reported in adults. In children, it should be regarded as experimental and considered only in expert centres after thorough multidisciplinary discussion. *[Level V; Grade C]*

For disseminated or unresectable relapse, systemic therapy follows the same principles as primary advanced disease. *[Level IV; Grade A]* Enrolment in national or European precision oncology programmes should be considered to enable access to investigational approaches.

[Level IV; Grade A] These may include agents targeting mTOR signalling, angiogenesis, or other oncogenic pathways, as well as innovative radionuclide therapies such as dual-isotope PRRT and novel radionuclides including auger electron and alpha particle emitters. At present, paediatric-specific efficacy data are lacking, and such approaches should therefore be pursued within the framework of clinical trials or structured registries. *[Level IV; Grade A]*

Relapse generally portends a less favourable prognosis than primary localised disease, but long-term survival is still possible with multimodal therapy. Treatment decisions must balance disease control with the late effects of repeated interventions, radiation exposure, and systemic therapies, underscoring the need for life-long follow-up. *[Level IV; Grade B]*

The most important recommendations from this ESCP document are summarized in Appendix 3.

7. Reference list

1. Haddad T, Fard-Esfahani A, Vali R. A review of pediatric neuroendocrine tumors, their detection, and treatment by radioisotopes. *Nucl Med Commun*. Jan 2021;42(1):21-31. doi:10.1097/MNM.0000000000001305
2. Farooqui ZA, Chauhan A. Neuroendocrine Tumors in Pediatrics. *Glob Pediatr Health*. 2019;6:2333794X19862712. doi:10.1177/2333794X19862712
3. Stawarski A, Maleika P. Neuroendocrine tumors of the gastrointestinal tract and pancreas: Is it also a challenge for pediatricians? *Adv Clin Exp Med*. Feb 2020;29(2):265-270. doi:10.17219/acem/111806
4. Navalkele P, O'Dorisio MS, O'Dorisio TM, Zamba GK, Lynch CF. Incidence, survival, and prevalence of neuroendocrine tumors versus neuroblastoma in children and young adults: nine standard SEER registries, 1975-2006. *Pediatr Blood Cancer*. Jan 2011;56(1):50-7. doi:10.1002/pbc.22559
5. Allan B, Davis J, Perez E, Lew J, Sola J. Malignant neuroendocrine tumors: incidence and outcomes in pediatric patients. *Eur J Pediatr Surg*. Oct 2013;23(5):394-9. doi:10.1055/s-0033-1333643
6. Castle JT, Levy BE, Chauhan A. Pediatric Neuroendocrine Neoplasms: Rare Malignancies with Incredible Variability. *Cancers (Basel)*. Oct 15 2022;14(20)doi:10.3390/cancers14205049
7. Kuhlen M, Claus R, Pavel ME, et al. Gastroenteropancreatic neuroendocrine neoplasms in children and adults: a comparative review. Review. *Front Endocrinol (Lausanne)*. 2026;doi:10.3389/fendo.2025.1736543
8. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol*. Jan 2008;9(1):61-72. doi:10.1016/S1470-2045(07)70410-2
9. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing But NET: A Review of Neuroendocrine Tumors and Carcinomas. *Neoplasia*. Dec 2017;19(12):991-1002. doi:10.1016/j.neo.2017.09.002
10. Rosai J. The origin of neuroendocrine tumors and the neural crest saga. *Mod Pathol*. Apr 2011;24 Suppl 2:S53-7. doi:10.1038/modpathol.2010.166
11. Ankerstjerne MP, Giovannoni S, Christensen LG, et al. Pediatric Neuroendocrine Tumors in Denmark: Incidence, Management, and Outcome From 1995 to 2020. *Pediatr Blood Cancer*. Feb 2025;72(2):e31420. doi:10.1002/pbc.31420

12. Courtel T, Orbach D, Lacour B, et al. Childhood pancreatic neuroendocrine neoplasms: A national experience. *Pediatr Blood Cancer*. Feb 2025;72(2):e31258. doi:10.1002/pbc.31258
13. Virgone C, Ferrari A, Chiaravalli S, et al. Extra-appendicular neuroendocrine tumors: A report from the TREP project (2000-2020). *Pediatr Blood Cancer*. Apr 2021;68(4):e28880. doi:10.1002/pbc.28880
14. Karges K, Kunstreich M, Abele M, et al. Gastrointestinal neuroendocrine neoplasms in children and adolescents - data from the German MET studies (1997-2024). *Neuroendocrinology*. Sep 25 2025:1-21. doi:10.1159/000548618
15. Karges K, Kunstreich M, Pape UF, et al. Pancreatic neuroendocrine tumors in children and adolescents-Data from the German MET studies (1997-2023). *J Neuroendocrinol*. May 11 2025;n/a(n/a):e70039. doi:10.1111/jne.70039
16. Kuhlen M, Karges K, Kunstreich M, et al. Invisible Origins: Paediatric Neuroendocrine Neoplasms of Unknown Primary Site in the MET Registry and SEER Database. *ESMO Rare Cancers*. 2025/08/05/ 2025:100026. doi:https://doi.org/10.1016/j.esmorc.2025.100026
17. Diets IJ, Nagtegaal ID, Loeffen J, et al. Childhood neuroendocrine tumours: a descriptive study revealing clues for genetic predisposition. *Br J Cancer*. Jan 17 2017;116(2):163-168. doi:10.1038/bjc.2016.408
18. Gaal J, de Krijger RR. Neuroendocrine tumors and tumor syndromes in childhood. *Pediatr Dev Pathol*. Nov-Dec 2010;13(6):427-41. doi:10.2350/09-04-0635-CP.1
19. Lodish MB, Stratakis CA. Endocrine tumours in neurofibromatosis type 1, tuberous sclerosis and related syndromes. *Best Pract Res Clin Endocrinol Metab*. Jun 2010;24(3):439-49. doi:10.1016/j.beem.2010.02.002
20. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. Jan 2020;76(2):182-188. doi:10.1111/his.13975
21. Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol*. Dec 2018;31(12):1770-1786. doi:10.1038/s41379-018-0110-y
22. Tang LH, Untch BR, Reidy DL, et al. Well-Differentiated Neuroendocrine Tumors with a Morphologically Apparent High-Grade Component: A Pathway Distinct from Poorly Differentiated Neuroendocrine Carcinomas. *Clin Cancer Res*. Feb 15 2016;22(4):1011-7. doi:10.1158/1078-0432.CCR-15-0548
23. La Rosa S, Uccella S. Classification of neuroendocrine neoplasms: lights and shadows. *Rev Endocr Metab Disord*. Sep 2021;22(3):527-538. doi:10.1007/s11154-020-09612-2
24. Virgone C, Cecchetto G, Alaggio R, et al. Appendiceal neuroendocrine tumours in childhood: Italian TREP project. *J Pediatr Gastroenterol Nutr*. Mar 2014;58(3):333-8. doi:10.1097/MPG.0000000000000217
25. Lin W, Zhu Z, Shang Y. Gastroenteropancreatic neuroendocrine carcinoma in children and adolescents: a population-based study. *J Cancer Res Clin Oncol*. Jan 2 2024;150(1):4. doi:10.1007/s00432-023-05568-3
26. Kuhlen M, Kunstreich M, Pape UF, et al. Lymph node metastases are more frequent in paediatric appendiceal NET >/=1.5 cm but without impact on outcome - Data from the German MET studies. *Eur J Surg Oncol*. Apr 2024;50(4):108051. doi:10.1016/j.ejso.2024.108051
27. Virgone C, Roganovic J, Rindi G, et al. Appendiceal neuroendocrine tumors in children and adolescents: The European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) diagnostic and therapeutic recommendations. *Surgery*. May 31 2025;184:109451. doi:10.1016/j.surg.2025.109451
28. Abele M, Virgone C, Kuhlen M, et al. Carcinomas and Carcinoid Tumors of the Lungs and Bronchi in Children and Adolescents: The EXPeRT Recommendations. *Pediatr Blood Cancer*. Mar 15 2026:e70190. doi:10.1002/1545-5017.70190
29. Kuhlen M, Virgone C, Redlich A, et al. European Standard Clinical Practice Guideline and EXPeRT Recommendations for the Diagnosis and Management of Gastroenteropancreatic Neuroendocrine Neoplasms in Children and Adolescents. *Pediatr Blood Cancer*. Mar 15 2026:e70194. doi:10.1002/1545-5017.70194

30. Johnson PR. Gastroenteropancreatic neuroendocrine (carcinoid) tumors in children. *Semin Pediatr Surg*. Apr 2014;23(2):91-5. doi:10.1053/j.sempedsurg.2014.03.007
31. Khanna G, O'Dorisio SM, Menda Y, Kirby P, Kao S, Sato Y. Gastroenteropancreatic neuroendocrine tumors in children and young adults. *Pediatr Radiol*. Mar 2008;38(3):251-9, quiz 358-9. doi:10.1007/s00247-007-0564-4
32. Yildirim UM, Koca D, Kebudi R. Gastroenteropancreatic neuroendocrine tumors in children and adolescents. *Turk J Pediatr*. Jul 11 2024;66(3):332-339. doi:10.24953/turkjpediatr.2024.4526
33. Dall'igna P, Cecchetto G, Bisogno G, et al. Pancreatic tumors in children and adolescents: the Italian TREP project experience. *Pediatr Blood Cancer*. May 2010;54(5):675-80. doi:10.1002/pbc.22385
34. Samady Khanghah A, Madadi-Sanjani O, Abdolzadeh A, Atqiaee K. Primary hepatic neuroendocrine neoplasms of children, a systematic review. *J Neuroendocrinol*. Apr 2025;37(4):e13495. doi:10.1111/jne.13495
35. Kuhlen M, Karges K, Kunstreich M, et al. Invisible origins: paediatric neuroendocrine neoplasms of unknown primary site in the MET registry and SEER database. *ESMO Rare Cancers*. doi:10.1016/j.esmorc.2025.100026
36. Pavel M, Oberg K, Falconi M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. Jul 2020;31(7):844-860. doi:10.1016/j.annonc.2020.03.304
37. Knigge U, Capdevila J, Bartsch DK, et al. ENETS Consensus Recommendations for the Standards of Care in Neuroendocrine Neoplasms: Follow-Up and Documentation. *Neuroendocrinology*. 2017;105(3):310-319. doi:10.1159/000458155
38. Kos-Kudla B, Castano JP, Denecke T, et al. European Neuroendocrine Tumour Society (ENETS) 2023 guidance paper for nonfunctioning pancreatic neuroendocrine tumours. *J Neuroendocrinol*. Dec 2023;35(12):e13343. doi:10.1111/jne.13343
39. Panzuto F, Ramage J, Pritchard DM, et al. European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for gastroduodenal neuroendocrine tumours (NETs) G1-G3. *J Neuroendocrinol*. Aug 2023;35(8):e13306. doi:10.1111/jne.13306
40. Panzuto F, O'Toole D, Kloppel G, et al. Controversies in NEN: An ENETS position statement on the endoscopic management of localised gastric, duodenal and rectal neuroendocrine neoplasms. *J Neuroendocrinol*. Jun 16 2025:e70060. doi:10.1111/jne.70060
41. Rinke A, Ambrosini V, Dromain C, et al. European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for colorectal neuroendocrine tumours. *J Neuroendocrinol*. Jun 2023;35(6):e13309. doi:10.1111/jne.13309
42. Del Rivero J, Perez K, Kennedy EB, et al. Systemic Therapy for Tumor Control in Metastatic Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors: ASCO Guideline. *J Clin Oncol*. Nov 10 2023;41(32):5049-5067. doi:10.1200/JCO.23.01529
43. Eads JR, Halfdanarson TR, Asmis T, et al. Expert Consensus Practice Recommendations of the North American Neuroendocrine Tumor Society for the management of high grade gastroenteropancreatic and gynecologic neuroendocrine neoplasms. *Endocr Relat Cancer*. Aug 1 2023;30(8)doi:10.1530/ERC-22-0206
44. Fishbein L, Del Rivero J, Else T, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Management of Metastatic and/or Unresectable Pheochromocytoma and Paraganglioma. *Pancreas*. Apr 1 2021;50(4):469-493. doi:10.1097/MPA.0000000000001792
45. Halfdanarson TR, Strosberg JR, Tang L, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Pancreatic Neuroendocrine Tumors. *Pancreas*. Aug 2020;49(7):863-881. doi:10.1097/MPA.0000000000001597
46. Howe JR, Cardona K, Fraker DL, et al. The Surgical Management of Small Bowel Neuroendocrine Tumors: Consensus Guidelines of the North American Neuroendocrine Tumor Society. *Pancreas*. Jul 2017;46(6):715-731. doi:10.1097/MPA.0000000000000846
47. Singh S, Moody L, Chan DL, et al. Follow-up Recommendations for Completely Resected Gastroenteropancreatic Neuroendocrine Tumors. *JAMA Oncol*. Nov 1 2018;4(11):1597-1604. doi:10.1001/jamaoncol.2018.2428

48. Jongmans MC, Loeffen JL, Waanders E, et al. Recognition of genetic predisposition in pediatric cancer patients: An easy-to-use selection tool. *Eur J Med Genet*. Mar 2016;59(3):116-25. doi:10.1016/j.ejmg.2016.01.008
49. Toledo RA, Jimenez C, Armaiz-Pena G, Arenillas C, Capdevila J, Dahia PLM. Hypoxia-Inducible Factor 2 Alpha (HIF2alpha) Inhibitors: Targeting Genetically Driven Tumor Hypoxia. *Endocr Rev*. Mar 4 2023;44(2):312-322. doi:10.1210/endrev/bnac025
50. Ruggeri RM, Benevento E, De Cicco F, et al. Neuroendocrine neoplasms in the context of inherited tumor syndromes: a reappraisal focused on targeted therapies. *J Endocrinol Invest*. Feb 2023;46(2):213-234. doi:10.1007/s40618-022-01905-4
51. Loree JM, Chan D, Lim J, et al. Biomarkers to Inform Prognosis and Treatment for Unresectable or Metastatic GEP-NENs. *JAMA Oncol*. Dec 1 2024;10(12):1707-1720. doi:10.1001/jamaoncol.2024.4330
52. Hofland J, Falconi M, Christ E, et al. European Neuroendocrine Tumor Society 2023 guidance paper for functioning pancreatic neuroendocrine tumour syndromes. *J Neuroendocrinol*. Aug 2023;35(8):e13318. doi:10.1111/jne.13318
53. Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum. *Pancreas*. Aug 2010;39(6):753-66. doi:10.1097/MPA.0b013e3181ebb2a5
54. Hadoux J, Lamarca A, Grande E, et al. Neuroendocrine neoplasms of head and neck, genitourinary and gynaecological systems, unknown primaries, parathyroid carcinomas and intrathyroid thymic neoplasms: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *ESMO Open*. Oct 2024;9(10):103664. doi:10.1016/j.esmoop.2024.103664
55. Fizazi K, Greco FA, Pavlidis N, et al. Cancers of unknown primary site: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. Sep 2015;26 Suppl 5:v133-8. doi:10.1093/annonc/mdv305
56. Massard C, Loriot Y, Fizazi K. Carcinomas of an unknown primary origin--diagnosis and treatment. *Nat Rev Clin Oncol*. Nov 1 2011;8(12):701-10. doi:10.1038/nrclinonc.2011.158
57. de Mestier L, Nicolle R, Pote N, et al. Molecular deciphering of primary liver neuroendocrine neoplasms confirms their distinct existence with foregut-like profile. *J Pathol*. Sep 2022;258(1):58-68. doi:10.1002/path.5977
58. Ambrosini V, Kunikowska J, Baudin E, et al. Consensus on molecular imaging and theranostics in neuroendocrine neoplasms. *Eur J Cancer*. Mar 2021;146:56-73. doi:10.1016/j.ejca.2021.01.008
59. Diakatou E, Alexandraki KI, Tsolakis AV, et al. Somatostatin and dopamine receptor expression in neuroendocrine neoplasms: correlation of immunohistochemical findings with somatostatin receptor scintigraphy visual scores. *Clin Endocrinol (Oxf)*. Sep 2015;83(3):420-8. doi:10.1111/cen.12775
60. Helderman NC, Suerink M, Kilinc G, van den Berg JG, Nielsen M, Tesselaar MET. Relation between WHO Classification and Location- and Functionality-Based Classifications of Neuroendocrine Neoplasms of the Digestive Tract. *Neuroendocrinology*. 2024;114(2):120-133. doi:10.1159/000534035
61. Berner AM, Pipinikas C, Ryan A, et al. Diagnostic Approaches to Neuroendocrine Neoplasms of Unknown Primary Site. *Neuroendocrinology*. 2020;110(7-8):563-573. doi:10.1159/000504370
62. Gheorghisan-Galateanu AA, Iliesiu A, Lambrescu IM, Tapoi DA. The Complex Histopathological and Immunohistochemical Spectrum of Neuroendocrine Tumors-An Overview of the Latest Classifications. *Int J Mol Sci*. Jan 11 2023;24(2)doi:10.3390/ijms24021418
63. Rindi G, Inzani F. Differentiation Versus Grade for Pancreatic Neuroendocrine Neoplasms. *Arch Pathol Lab Med*. Mar 4 2025;doi:10.5858/arpa.2024-0410-RA
64. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol*. Sep 1 2018;29(9):1895-1902. doi:10.1093/annonc/mdy263
65. Tasto O, Raitio A, Losty PD. Management and outcomes of pediatric neuroendocrine tumors - A systematic review of published studies. *Eur J Surg Oncol*. Oct 2025;51(10):110388. doi:10.1016/j.ejso.2025.110388

66. Koc G, Sugimoto S, Kuperman R, Kammen BF, Karakas SP. Pancreatic tumors in children and young adults with tuberous sclerosis complex. *Pediatr Radiol*. Jan 2017;47(1):39-45. doi:10.1007/s00247-016-3701-0
67. Corti F, Rossi RE, Cafaro P, et al. Emerging Treatment Options for Neuroendocrine Neoplasms of Unknown Primary Origin: Current Evidence and Future Perspectives. *Cancers (Basel)*. May 27 2024;16(11)doi:10.3390/cancers16112025
68. Grillo F, Albertelli M, Malandrino P, et al. Prognostic Effect of Lymph Node Metastases and Mesenteric Deposits in Neuroendocrine Tumors of the Small Bowel. *J Clin Endocrinol Metab*. Nov 25 2022;107(12):3209-3221. doi:10.1210/clinem/dgac326
69. Fuchs J, Loos M, Kinny-Koster B, et al. Pancreatic Surgery in Children: Complex, Safe, and Effective. *Ann Surg*. Aug 1 2024;280(2):332-339. doi:10.1097/SLA.0000000000006125
70. Exarchou K, Kamieniarz L, Tsoli M, et al. Is local excision sufficient in selected grade 1 or 2 type III gastric neuroendocrine neoplasms? *Endocrine*. Nov 2021;74(2):421-429. doi:10.1007/s12020-021-02775-1
71. Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. Jul 17 2014;371(3):224-33. doi:10.1056/NEJMoa1316158
72. Pavel M, Cwikla JB, Lombard-Bohas C, et al. Efficacy and safety of high-dose lanreotide autogel in patients with progressive pancreatic or midgut neuroendocrine tumours: CLARINET FORTE phase 2 study results. *Eur J Cancer*. Nov 2021;157:403-414. doi:10.1016/j.ejca.2021.06.056
73. Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. Oct 1 2009;27(28):4656-63. doi:10.1200/JCO.2009.22.8510
74. Gaze MN, Handkiewicz-Junak D, Hladun R, et al. Safety and dosimetry of [(177)Lu]Lu-DOTA-TATE in adolescent patients with somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours, or pheochromocytomas and paragangliomas: Primary analysis of the Phase II NETTER-P study. *Eur J Nucl Med Mol Imaging*. Apr 8 2025;doi:10.1007/s00259-025-07246-7
75. Ballal S, Yadav MP, Damle NA, Sahoo RK, Bal C. Concomitant 177Lu-DOTATATE and Capecitabine Therapy in Patients With Advanced Neuroendocrine Tumors: A Long-term-Outcome, Toxicity, Survival, and Quality-of-Life Study. *Clin Nucl Med*. Nov 2017;42(11):e457-e466. doi:10.1097/RLU.0000000000001816
76. Menda Y, O'Dorisio MS, Kao S, et al. Phase I trial of 90Y-DOTATOC therapy in children and young adults with refractory solid tumors that express somatostatin receptors. *J Nucl Med*. Oct 2010;51(10):1524-31. doi:10.2967/jnumed.110.075226
77. Aggarwal P, Satapathy S, Sood A, et al. Safety and Efficacy of 177 Lu-DOTATATE in Children and Young Adult Population : A Single-Center Experience. *Clin Nucl Med*. Jul 1 2024;49(7):e312-e318. doi:10.1097/RLU.0000000000005233
78. Foster JH, Sher A, Seghers V, et al. Peptide receptor radionuclide therapy for treatment of metastatic neuroendocrine tumors in children. *Pediatr Blood Cancer*. Jul 2021;68(7):e29056. doi:10.1002/pbc.29056
79. Singh S, Halperin D, Myrehaug S, et al. [(177)Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2-3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study. *Lancet*. Jun 29 2024;403(10446):2807-2817. doi:10.1016/S0140-6736(24)00701-3
80. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of (177)Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med*. Jan 12 2017;376(2):125-135. doi:10.1056/NEJMoa1607427
81. Pavel ME, Rinke A, Baum RP. COMPETE trial: Peptide receptor radionuclide therapy (PRRT) with 177Lu-edotreotide vs. everolimus in progressive GEP-NET. *Annals of Oncology*. 2018;29:viii478. doi:10.1093/annonc/mdy293.028
82. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. Feb 10 2011;364(6):514-23. doi:10.1056/NEJMoa1009290
83. Yao JC, Pavel M, Lombard-Bohas C, et al. Everolimus for the Treatment of Advanced Pancreatic Neuroendocrine Tumors: Overall Survival and Circulating Biomarkers From the

Randomized, Phase III RADIANT-3 Study. *J Clin Oncol*. Nov 10 2016;34(32):3906-3913. doi:10.1200/JCO.2016.68.0702
84. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. Mar 5 2016;387(10022):968-977. doi:10.1016/S0140-6736(15)00817-X
85. Chan JA, Geyer S, Zemla T, et al. Phase 3 Trial of Cabozantinib to Treat Advanced Neuroendocrine Tumors. *N Engl J Med*. Feb 13 2025;392(7):653-665. doi:10.1056/NEJMoa2403991
86. Blumenthal GM, Cortazar P, Zhang JJ, et al. FDA approval summary: sunitinib for the treatment of progressive well-differentiated locally advanced or metastatic pancreatic neuroendocrine tumors. *Oncologist*. 2012;17(8):1108-13. doi:10.1634/theoncologist.2012-0044
87. Arrivi G, Fazio N, Tafuto S, et al. The efficacy of streptozotocin in managing pancreatic neuroendocrine neoplasms - A systematic review. *Cancer Treat Rev*. Mar 2025;134:102899. doi:10.1016/j.ctrv.2025.102899
88. Chantrill LA, Ransom D, Chan D, et al. NABNEC: A randomised phase II study of nab -paclitaxel in combination with carboplatin as first line treatment of gastrointestinal neuroendocrine carcinomas (GI-NECs). *Journal of Clinical Oncology*. 2024;42(3_suppl):589-589. doi:10.1200/JCO.2024.42.3_suppl.589
89. Morizane C, Machida N, Honma Y, et al. Effectiveness of Etoposide and Cisplatin vs Irinotecan and Cisplatin Therapy for Patients With Advanced Neuroendocrine Carcinoma of the Digestive System: The TOPIC-NEC Phase 3 Randomized Clinical Trial. *JAMA Oncol*. Oct 1 2022;8(10):1447-1455. doi:10.1001/jamaoncol.2022.3395
90. Ohmoto A, Fujiwara Y, Horita N, Nakano K, Takahashi S. Platinum-doublet chemotherapy for advanced gastroenteropancreatic neuroendocrine carcinoma: a systematic review and meta-analysis. *Discov Oncol*. May 30 2022;13(1):40. doi:10.1007/s12672-022-00499-w
91. Riesco-Martinez MC, Capdevila J, Alonso V, et al. Nivolumab plus platinum-doublet chemotherapy in treatment-naive patients with advanced grade 3 Neuroendocrine Neoplasms of gastroenteropancreatic or unknown origin: The multicenter phase 2 NICE-NEC trial (GETNE-T1913). *Nat Commun*. Aug 8 2024;15(1):6753. doi:10.1038/s41467-024-50969-8
92. Fine RL, Gulati AP, Krantz BA, et al. Capecitabine and temozolomide (CAPTEM) for metastatic, well-differentiated neuroendocrine cancers: The Pancreas Center at Columbia University experience. *Cancer Chemother Pharmacol*. Mar 2013;71(3):663-70. doi:10.1007/s00280-012-2055-z
93. Al-Toubah T, Pelle E, Valone T, Haider M, Strosberg JR. Efficacy and Toxicity Analysis of Capecitabine and Temozolomide in Neuroendocrine Neoplasms. *J Natl Compr Canc Netw*. Aug 24 2021;20(1):29-36. doi:10.6004/jnccn.2021.7017
94. Morken S, Langer SW, Sundlov A, et al. Phase II study of everolimus and temozolomide as first-line treatment in metastatic high-grade gastroenteropancreatic neuroendocrine neoplasms. *Br J Cancer*. Dec 2023;129(12):1930-1939. doi:10.1038/s41416-023-02462-0
95. de Mestier L, Zappa M, Hentic O, Vilgrain V, Ruszniewski P. Liver transarterial embolizations in metastatic neuroendocrine tumors. *Rev Endocr Metab Disord*. Dec 2017;18(4):459-471. doi:10.1007/s11154-017-9431-2
96. Do Minh D, Chapiro J, Gorodetski B, et al. Intra-arterial therapy of neuroendocrine tumour liver metastases: comparing conventional TACE, drug-eluting beads TACE and yttrium-90 radioembolisation as treatment options using a propensity score analysis model. *Eur Radiol*. Dec 2017;27(12):4995-5005. doi:10.1007/s00330-017-4856-2
97. Garcia-Alvarez A, Cubero JH, Capdevila J. What Is the Status of Immunotherapy in Neuroendocrine Neoplasms? *Curr Oncol Rep*. Apr 2022;24(4):451-461. doi:10.1007/s11912-022-01235-x
98. Girard N, Mazieres J, Otto J, et al. LBA41 Nivolumab (nivo)±ipilimumab (ipi) in pre-treated patients with advanced, refractory pulmonary or gastroenteropancreatic poorly differentiated neuroendocrine tumors (NECs)(GCO-001 NIPINEC). *Annals of Oncology*. 2021;32:S1318.
99. Jeong SY, Park YS, Lee J, et al. Tumor mutation burden in gastro-entero-pancreatic-neuroendocrine neoplasms. *J Gastrointest Oncol*. Aug 31 2023;14(4):1707-1714. doi:10.21037/jgo-22-1190

100. Mehnert JM, Bergsland E, O'Neil BH, et al. Pembrolizumab for the treatment of programmed death-ligand 1-positive advanced carcinoid or pancreatic neuroendocrine tumors: Results from the KEYNOTE-028 study. *Cancer*. Jul 1 2020;126(13):3021-3030. doi:10.1002/cncr.32883
101. Morse MA, Crosby EJ, Halperin DM, et al. Phase Ib/II study of Pembrolizumab with Lanreotide depot for advanced, progressive Gastroenteropancreatic neuroendocrine tumors (PLANET). *J Neuroendocrinol*. Apr 2025;37(4):e13496. doi:10.1111/jne.13496
102. Park EJ, Park HJ, Kim KW, et al. Efficacy of Immune Checkpoint Inhibitors against Advanced or Metastatic Neuroendocrine Neoplasms: A Systematic Review and Meta-Analysis. *Cancers (Basel)*. Feb 4 2022;14(3)doi:10.3390/cancers14030794
103. Andreasi V, Ricci C, Partelli S, et al. Predictors of disease recurrence after curative surgery for nonfunctioning pancreatic neuroendocrine neoplasms (NF-PanNENs): a systematic review and meta-analysis. *J Endocrinol Invest*. Apr 2022;45(4):705-718. doi:10.1007/s40618-021-01705-2
104. Chan H, Zhang L, Choti MA, et al. Recurrence Patterns After Surgical Resection of Gastroenteropancreatic Neuroendocrine Tumors: Analysis From the National Comprehensive Cancer Network Oncology Outcomes Database. *Pancreas*. Apr 1 2021;50(4):506-512. doi:10.1097/MPA.0000000000001791

APPENDIX 1

World Health Organization (WHO) 2019 Classification and grading criteria for neuroendocrine neoplasms (NENs) of the GI tract and hepatopancreatobiliary organs

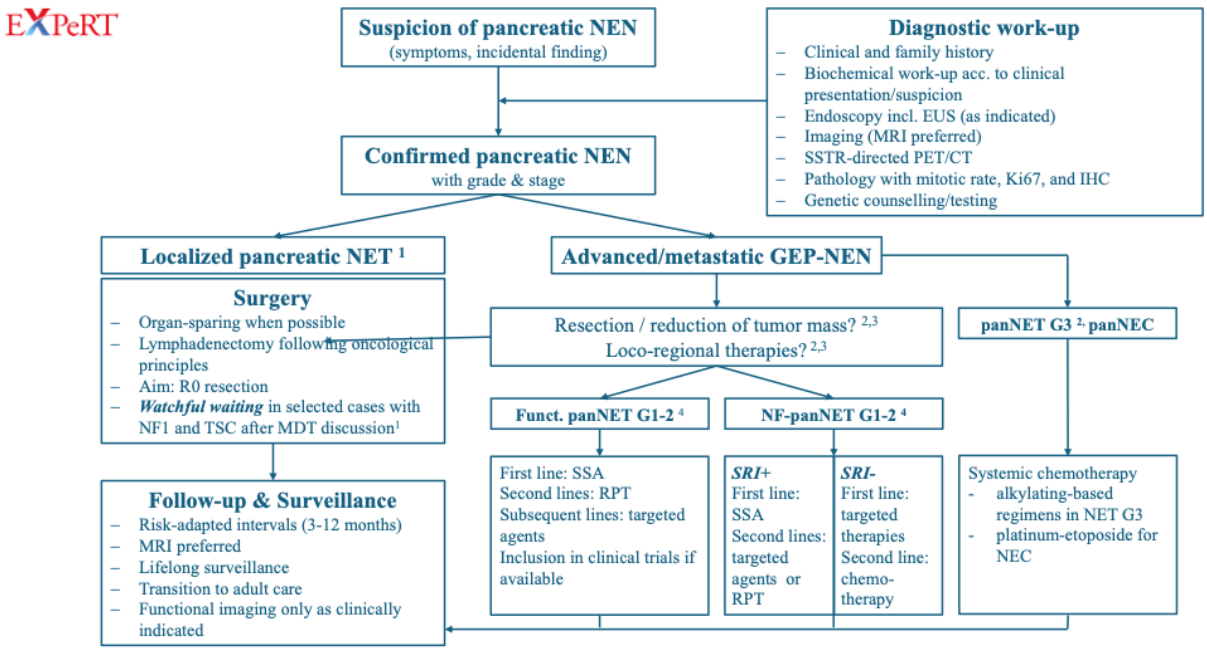
Terminology	Differentiation	Mitotic rate (mitoses/2 mm^2)	Ki-67 index
NET, G1	Well differentiated	<2	<3%
NET, G2		2–20	3–20%
NET, G3		>20	>20%
NEC, small-cell type (SCNEC)	Poorly differentiated	>20	>20%
NEC, large-cell type (LCNEC)		>20	>20%
MiNEN	Well or poorly differentiated	Variable	Variable

[#] Poorly differentiated NECs are not formally graded, but are considered high-grade by definition.

LCNEC, Large-cell neuroendocrine carcinoma; MiNEN, Mixed neuroendocrine–non-neuroendocrine neoplasm; NEC, Neuroendocrine carcinoma; NET, Neuroendocrine tumour; SCNEC, Small-cell neuroendocrine carcinoma.

APPENDIX 2

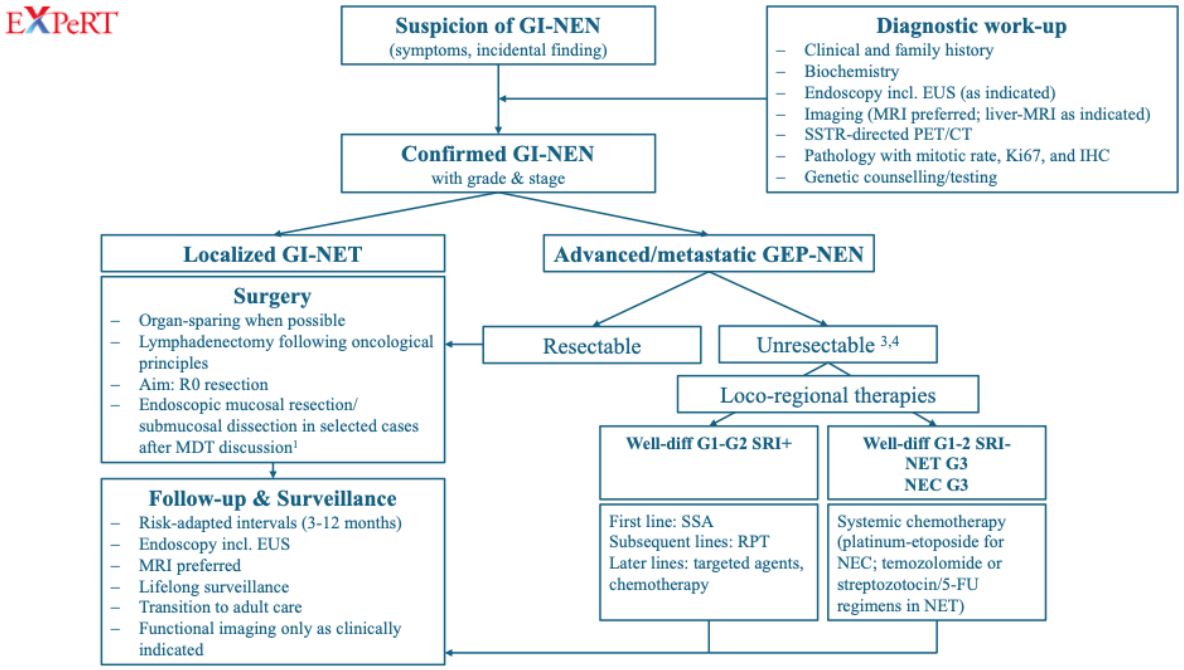
Flowchart 1: Initial Diagnostic and Treatment Pathway for Pancreatic NEN



acc., according; EUS, endoscopic ultrasound; funct, functioning; MDT, multidisciplinary tumor board; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; NF, non-functioning; NF1, neurofibromatosis type 1; pan, pancreatic; SRI, somatostatin receptor imaging; RPT, radiopharmaceutical therapy; SSA, somatostatin analogue; TSC, tuberous sclerosis syndrome

[1] Exceptions for MEN1- and TSC-associated multifocal pancreatic NET
[2] Consider sites, grade, and slope of progression
[3] Consider liver-directed therapies in liver-dominant metastatic disease
[4] asymptomatic and/or stable/slowly growing; in symptomatic and/or fast-growing: first line: alkylating-based chemotherapy, subsequently lines: targeted therapy, or RPT in SRI positive

Flowchart 2: Initial Diagnostic and Treatment Pathway for Gastrointestinal NEN



EUS, endoscopic ultrasound; GI, gastrointestinal; MDT, multidisciplinary tumor board; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; SRI, somatostatin receptor imaging; RPT, radiopharmaceutical therapy; SSA, somatostatin analogue

[1] in (very) small lesions not invading muscle layer and no lymph node metastases
[2] Consider sites, grade, and slope of progression
[3] Consider liver-directed therapies in liver-dominant metastatic disease
[4] inclusion in clinical trials if available

APPENDIX 3

Table 1. Recommendations for Diagnostic Assessment in Pediatric GEP-NENs

Domain	*Recommendation*	*Level*	*Grade*
Overall diagnostic approach	Diagnostic evaluation of suspected pediatric GEP-NENs should be performed at, or in collaboration with, a specialized reference center with expertise in (pediatric) NENs, including expert pathology review and multidisciplinary tumor board discussion.	IV	A
Clinical evaluation	A detailed clinical history and examination should assess symptoms suggestive of hormone hypersecretion, tumor mass effect, and signs of hereditary tumor predisposition syndromes (MEN1, VHL, NF1, TSC).	IV	A
Baseline laboratory tests	Initial laboratory assessment should include full blood count, electrolytes, renal and liver function tests, and pregnancy testing in adolescents where appropriate.	IV	B
Use of age-specific references	Interpretation of biochemical results must use assay- and age-specific reference ranges; adult cut-offs should not be applied uncritically.	III	A
Chromogranin A	Routine use of chromogranin A for diagnosis or surveillance is not recommended. It may be considered only in selected cases with a clearly elevated baseline value and interpreted with caution.	V	C
Insulinoma work-up	Suspected insulinoma should be evaluated with a supervised fast documenting Whipple's triad and simultaneous measurement of glucose, insulin, C-peptide, proinsulin, ketones, and free fatty acids.	III	B
Gastrinoma work-up	Fasting gastrin with gastric pH measurement should be performed, ideally after PPI withdrawal; MEN1 evaluation is recommended.	III	B
Small-intestinal NETs	In suspected carcinoid syndrome, 24-hour urinary or plasma 5-HIAA should be measured with strict dietary and medication control.	III	B
NEN of unknown primary (CUP)	Biochemical testing in pediatric NEN-CUP is hypothesis-generating only and should guide imaging and biopsy rather than infer tumor origin. Calcitonin and metanephrines should be measured to exclude medullary thyroid carcinoma and intra-/extraadrenal paraganglioma.	IV	B
Hereditary syndromes	Genetic counseling should be offered to all patients, with germline testing for MEN1, VHL, NF1, and TSC based on clinical context.	IV	A

Table 2. Imaging Recommendations

Scenario	Recommendation	Level	Grade
Initial evaluation (abdominal pain / mass suspicion)	Ultrasound is an appropriate first-line modality in children presenting with abdominal pain or suspected abdominal mass.	V	B
First-line cross-sectional imaging	MRI is the preferred modality for staging and follow-up to minimize radiation exposure.	III	A
Pancreatic lesions	High-resolution MRI with dedicated pancreatic sequences is recommended for localization and staging.	IV	A
Suspected insulinoma	In negative or equivocal cross-sectional imaging, EUS is recommended to improve lesion detection, assess proximity to the pancreatic ductal system, and enable tissue acquisition when histological confirmation is required.	IV	A
Gastric and duodenal NETs	Upper gastrointestinal endoscopy with biopsy is recommended as the diagnostic gold standard. EUS is recommended when local staging (depth of invasion, submucosal spread, regional lymph nodes) will influence treatment decisions, particularly in duodenal primaries.	IV	A
Suspected small-intestinal NET	MRI enterography is recommended to evaluate the small bowel and mesentery without radiation exposure. Mesenteric fibrosis should be assessed when clinically suspected, while recognizing it is extremely rare in pediatric patients.	V	B
Colorectal / rectal NETs	Colonoscopy with biopsy is recommended to establish diagnosis. Pelvic MRI is recommended for rectal lesions to stage locally and assess mesorectal involvement, and cross-sectional imaging of the abdomen/pelvis is recommended in higher-stage disease to evaluate nodal and hepatic involvement.	IV	A
Liver lesions	Dedicated liver MRI is recommended for characterization of focal lesions in NET G2-3 and NEC; histological confirmation is required when diagnosis is uncertain.	IV	A
CT imaging	CT should be reserved for acute situations or when MRI is not feasible, using pediatric dose-optimized protocols.	III	B
SSTR imaging	SSTR-directed PET/CT or PET/MRI is recommended for staging and treatment planning in well-differentiated NETs (G1–G2 and selected G3).	III	A
FDG-PET/CT	FDG-PET/CT should be considered in NET G3 when results may influence management and is the only functional imaging routinely recommended in NEC.	III	A
Pediatric considerations	Imaging should be coordinated to minimize sedation and reviewed by radiologists experienced in pediatric NENs.	IV	A

Table 3. Recommendations for Pathology Review and Biopsy

Aspect	Recommendation	Level	Grade
Histopathology	Histopathological confirmation should be obtained whenever safely feasible and classified according to WHO 2019 criteria (NET G1–G3 vs NEC).	III	A
Immunohistochemistry	Diagnosis requires positivity for at least one neuroendocrine marker (e.g. synaptophysin, chromogranin A).	IV	A
Grading	Ki-67 index and mitotic count must be reported; the highest value should define grade in heterogeneous tumors.	III	A
Site-specific IHC panels	Site-specific immunohistochemical panels are recommended to avoid misclassification and to exclude key mimics	V	B
Molecular profiling	Extended molecular profiling (e.g., NGS) should be considered only in advanced or refractory disease or within clinical trials/research protocols, and results should be reviewed in a multidisciplinary molecular tumor board to confirm clinical relevance and feasibility of targeted therapy.	V	B
Central pathology review	All specimens should undergo review by a pathologist experienced in pediatric and neuroendocrine tumors.	IV	A
Biopsy technique	Image-guided core needle biopsy is recommended when resection is not feasible; FNA alone is insufficient for definitive diagnosis and grading.	IV	B
Biopsy approach	Retroperitoneal lesions should be biopsied via a posterior approach; transperitoneal anterior biopsy should be avoided where possible.	IV	E
	For luminal gastrointestinal lesions, endoscopic biopsy is recommended.	IV	A
	For pancreatic or duodeno-pancreatic lesions, EUS-guided tissue sampling may be considered when surgical resection is not immediately planned.	V	C
Sampling limitations	Small biopsies may underestimate tumor grade; repeat sampling should be considered when clinical or imaging findings are discordant with pathology.	V	B
Exceptions to biopsy	In very selected cases (e.g. multiple small pancreatic lesions in TSC/MEN1 without progression), surveillance without immediate biopsy may be considered after MDT discussion.	V	C

Table 4. Recommendations for Surgical Management

Tumor Type	Recommendation	Level	Grade
General	All cases should be discussed in a multidisciplinary tumor board; pursue complete R0 resection whenever feasible, prioritizing organ- and function-preserving approaches where oncological safety can be maintained.	IV	A
Lymphadenectomy	Regional lymph-node dissection should accompany oncological resections; extensive prophylactic dissection beyond the regional basin is not recommended in small NETs without nodal suspicion.	IV / V	A / D
Insulinoma	Enucleation with clear margins is recommended for small, solitary insulinomas when safely distant from the main pancreatic duct; intraoperative ultrasound (with or without contrast) should be used to localize lesions, assess ductal relationships, and guide the extent of resection.	IV	B
Non-functional pancreatic NET	Surgical approach should be guided by size, location, ductal involvement, and growth behavior and frozen-section margin analysis should be performed when feasible.	IV	B
MEN1/TSC pancreatic NETs	Active surveillance may be appropriate for small (<2 cm), asymptomatic, stable tumors; surgery should favor parenchyma-sparing approaches.	IV	B
Small-intestinal NET	Segmental bowel resection with mesenteric lymphadenectomy is recommended.	V	A
Colorectal NET	Segmental colectomy with regional lymph-node dissection is recommended unless endoscopic criteria are met.	V	A
Rectal NET (<1 cm)	Local endoscopic excision is appropriate in the absence of adverse features.	V	B
NEN-CUP	Surgery should generally be limited to diagnostic and/or palliative indications, as curative resection is rarely feasible.	V	B
Liver metastases	Wedge resection, enucleation, or anatomical liver resection may be considered in selected liver-dominant disease; liver transplantation is investigational only.	V	B / C
EUS-guided RFA (selected cases)	Endoscopic ultrasound-guided radiofrequency ablation should be considered only exceptionally and on an individual basis in children, within expert centers.	V	C

Table 5. Recommendations for Systemic Therapies

Therapy	Recommendation	Level	Grade
Somatostatin analogues (SSA)	SSA are recommended as first-line therapy for progressive or unresectable SSTR-positive NETs and for symptom control in functioning tumors.	V	B
PRRT (^177Lu-DOTATATE)	PRRT is recommended for progressive SSTR-positive NET after SSA failure or earlier in selected high-burden disease; use in expert centers only.	IV	B/A
Targeted agents	Targeted agents should be considered in selected progressive NETs (especially pancreatic) as off-label use with careful monitoring and registry documentation.	V	B
Chemotherapy (CAPTEM)	Temozolomide-based regimens (e.g. CAPTEM) can be considered in selected progressive NET G2–G3.	V	B
Chemotherapy (platinum–etoposide)	Platinum-etoposide is recommended as standard first-line therapy for NEC.	V	B
Immunotherapy	Immunotherapy may be consider only for NEC with MSI-high or high TMB, preferably in clinical trials.	V	C
Liver-directed therapies	Liver-directed therapies (TAE, TACE, SIRT) should be restricted to highly selected pediatric cases and performed in expert centers.	V	C
Advanced/ metastatic disease	Children and adolescents with advanced or metastatic disease should be referred to expert reference centers to ensure access to multimodal therapies.	V	A
Decision-making	Systemic treatment decisions should be made within a multidisciplinary setting, preferably in specialist centers.	IV	A

Table 6. Recommendations for Follow-up and Surveillance

Risk Group	Recommendation	Notes	Level	Grade
General Principles	Long-term, risk-adapted follow-up is recommended, coordinated in expert centers with structured transition to adult care.	Stratify surveillance by tumor grade, stage, completeness of resection (R status), and hereditary background.	IV	A
Clinical follow-up	Clinical follow-up is recommended every 3–6 months for the first 2 years and every 6–12 months thereafter, tailored to risk profile.		V	B
Biochemical monitoring	Non-specific markers should only be monitored if significantly elevated at baseline.		V	C
	Hormone levels relevant to functional tumors should be re-assessed only if symptoms recur or progression is suspected.		V	B
Surveillance imaging	MRI is recommended as the preferred surveillance modality to limit radiation exposure.	Typical intervals: ~12 months (low risk), 6–12 months (mid risk), 3–6 months (high risk); adapt if clinical situation changes.	IV	B
Functional imaging in surveillance	Functional imaging should be reserved for situations where results are expected to lead to a change in management.		IV	B

Table 7. Recommendations for Relapsed or Progressive Disease

Scenario	Recommendation	Level	Grade
MDT reassessment	Relapse or progression should be managed with reassessment of tumor biology and disease extent within a specialized multidisciplinary tumor board.	V	A
Restaging	Restaging is recommended using cross-sectional imaging, appropriate functional imaging, and consideration of repeat biopsy to detect grade progression.	IV	A
Oligometastatic relapse	Surgical resection or focal therapy is recommended where feasible.	V	A
Disseminated relapse	Disseminated relapse should be treated according to principles used for primary advanced disease, with strong consideration for enrollment in precision oncology programs and/or clinical trials.	IV	A
Liver-dominant relapse	Liver transplantation is experimental and should be considered only in exceptional cases at expert centers.	V	C