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Review

Current insights and future directions in systemic therapies for gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) in children and adolescents: a critical review of advancements and challenges

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ABSTRACT

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) in children and adolescents are rare and biologically heterogeneous. Due to their low incidence, therapeutic strategies are largely adapted from adult protocols, underscoring a critical need for paediatric-specific evidence.

Surgical resection remains the mainstay of curative treatment for localized disease and should be prioritized before the initiation of systemic therapy whenever feasible. This review synthesizes current knowledge on systemic therapies in paediatric GEP-NENs,

including somatostatin analogues (SSAs), peptide receptor radionuclide therapy (PRRT), chemotherapy, small molecules (e.g., everolimus, sunitinib), and immune checkpoint inhibitors (ICIs). While SSAs remain the mainstay for well-differentiated, somatostatin receptor (SSTR)-positive tumours, emerging data support the safety and potential efficacy of PRRT in paediatric populations, despite limited prospective evidence. Chemotherapy continues to play a role in high-grade or progressive disease, although responses are variable.

Supportive therapies, including high-dose proton pump inhibitors (PPIs), are also important in managing functional tumours and can significantly alleviate clinical symptoms in advanced disease.

Novel approaches, including SSTR antagonists, α- and β-emitting radiopharmaceuticals, and oncolytic virotherapy (e.g., SVV-001), are under active investigation in adults and may inform future paediatric protocols. Resistance mechanisms—particularly to SSAs—highlight the dynamic nature of tumour evolution and the need for individualized strategies.

These insights underscore the importance of molecular profiling and imaging-based SSTR assessment to guide therapeutic selection, particularly in refractory or complex paediatric cases. Future efforts should prioritize international collaboration, the design of rational combination regimens, and the integration of radiomics, genomics, and biomarker-driven approaches to advance precision medicine in paediatric GEP-NENs.

1. Introduction

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) constitute a rare and biologically heterogeneous group of neoplasms arising from the diffuse neuroendocrine system within the gastrointestinal tract and pancreas. [1] According to the 2019 World Health Organization (WHO) classification system, GEP-NENs are stratified into well-differentiated neuroendocrine tumours (NETs; G1–3) and poorly-differentiated neuroendocrine carcinomas (NECs; G3), [2] with the recently recognized category of G3 NETs demonstrating distinct

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histological and molecular characteristics from G3 NECs. [3–5]

The overall incidence of NENs in the general population has increased over recent decades from 4.9 cases per 100,000 individuals in 2000 to 8.2 per 100,000 individuals in 2018. [6] In contrast, paediatric incidence remains markedly lower and stable, with Danish registry data reporting 6.8 cases per 1 million annually from 1995 to 2020. [7] In children and adolescents, GEP-NENs are extremely rare and are estimated to account for less than 0.1 % of all malignancies. Appendiceal NETs are by far the most frequently reported subtype in this age group, typically discovered incidentally during appendectomy. [8–10] Pancreatic NETs represent the second most common entity, based on available case series and registry reports. [11,12] Gastric, small intestinal, and colonic NENs are significantly less common and have primarily been described in isolated case reports. Functional tumours such as gastrinomas and insulinomas can occur but are rare. [11] Well-differentiated NETs predominate in paediatric populations, while poorly differentiated NECs are exceedingly rare. While robust epidemiological data are scarce, [7,13,14] emerging data from multi-institutional efforts, including the French FRACTURE group, the Italian TREP project, and the German MET Registry, have begun to characterize paediatric pancreatic NENs. [11,15,16] We have recently reported 28 paediatric cases of pancreatic NETs and eight paediatric cases of NENs of unknown primary site enrolled in the MET Registry. [11] In contrast, literature on gastric, small intestinal, or colonic NENs remains largely limited to single cases included in extra-appendiceal NET reports. [12] Overall, appendiceal NETs constitute the majority of paediatric GEP-NENs, [9,10] with other subtypes representing a small but clinically important minority.

This persistent data gap poses a major challenge to developing standardized, evidence-based therapeutic guidelines for paediatric patients.

In adults, GEP-NENs most commonly occur in the small intestine (33.3 %), pancreas (21.7 %), and rectum (19.0 %), with only 12.0 % of GEP-NENs located in the cecum and appendix. [17] Clinical manifestations vary depending on tumour location, functional status, and extent of metastatic disease. [18] Many patients, particularly those with early-stage disease, are asymptomatic, with diagnoses often made incidentally during imaging or endoscopic procedures performed for unrelated conditions. In symptomatic cases, presentations may include abdominal pain, weight loss, diarrhoea, and gastrointestinal bleeding. Functionally active tumours that secrete bioactive peptides can result in hormone-related syndromes, most notably carcinoid syndrome - characterized by cutaneous flushing, secretory diarrhoea, bronchospasm, and right-sided cardiac valvulopathy due to excess serotonin production. [19] These manifestations, however, occur infrequently in paediatric patients. [11,15]

Prognosis for paediatric patients with localized disease is generally favourable (80–100 %), particularly when complete surgical resection is achieved. [11,14,20] In this context, surgery remains the gold standard and should be pursued whenever feasible for localized or resectable disease. In contrast, outcomes for unresectable or metastatic disease remain poor, with reported survival rates as low as 20–30 %, reflecting the limited availability of effective systemic therapies. [20] While adults with metastatic well-differentiated GEP-NENs have historically demonstrated five-year survival rates ranging between 35 % and 60 %, often benefiting from recent advances in diagnosis and treatment, [17] paediatric-specific survival data are sparse. [11,14,20] Management is further complicated by the fact, that some paediatric patients present with metastatic disease where the primary tumour origin cannot be identified. [13]

Given their rarity, paediatric GEP-NENs are typically managed using treatment algorithms developed for adults. Major guidelines, including those from the European Neuroendocrine Tumour Society (ENETS), the European Society for Medical Oncology (ESMO) the North American Neuroendocrine Tumor Society (NANETS), and the American Society of Clinical Oncology (ASCO), guide therapeutic decisions in adult patients based on tumour grade, primary site, disease stage, and somatostatin receptor (SSTR) expression status. [21–28] Surgical resection remains the cornerstone of curative treatment for localized disease and is the preferred approach in paediatric patients in whom complete excision can be achieved. However, the broader therapeutic framework used in adults—including systemic treatment algorithms and risk stratification tools— may not always translate directly to children due to developmental, biological, and pharmacologic differences. [29] Moreover, long-term toxicity profiles and age-specific treatment tolerability necessitate cautious evaluation of systemic therapies in children and adolescents. In select cases of indolent, well-differentiated metastatic NETs—particularly those with low tumour burden and stable disease—an initial observational approach may be reasonable. However, patients with symptomatic, progressive, or high-grade disease typically require the initiation of systemic therapy promptly after diagnosis. Despite increasing recognition of paediatric GEP-NENs, the rarity of these tumours has severely limited the development of dedicated clinical trials, leaving major gaps in evidence regarding optimal systemic treatment strategies. In this context, we undertook a comprehensive review of the current literature on systemic therapies used in paediatric GEP-NENs, aiming to synthesize available data, evaluate their applicability, and highlight critical areas for future research and guideline development.

2. Methods

We conducted a comprehensive literature search using PubMed to identify relevant publications on systemic therapies for GEP-NENs in paediatric populations. The search strategy employed the following terms: "paediatrics", "neuroendocrine tumours/cancers", "gastroenteropancreatic", and "treatment", or “somatostatin analogue”, “mTOR”, “everolimus”, “sunitinib”, “chemotherapy”, and “peptide receptor radionuclide therapy”. Additionally, we performed a manual review of reference lists from identified publications to capture relevant studies that may not have appeared in the initial database search. Articles were included if they reported on systemic therapeutic approaches for pancreatic or gastrointestinal NENs in patients under 18 years of age. Only publications in English or German language were considered for inclusion. No publication date restrictions were applied.

3. Systemic therapies

3.1. Somatostatin analogues-based regimens

Somatostatin is a 14-amino acid peptide that exerts inhibitory effects on hormone secretion and cell proliferation by binding to five somatostatin receptor subtypes (SSTR1–5), which are variably expressed in neuroendocrine cells. At the molecular level, SSTR1–5 are G protein-coupled receptors (GPCRs) that initiate distinct intracellular signalling cascades upon ligand binding. All five SSTRs primarily couple to inhibitory G proteins (Gi/Go), leading to decreased adenylate cyclase activity and reduced cyclic AMP (cAMP) levels. Additional downstream effects include activation of phosphotyrosine phosphatases (e.g., SHP-1/2), inhibition of mitogen-activated protein kinase (MAPK) and PI3K/Akt pathways, and modulation of ion channels and calcium flux. (Fig. 1) Each SSTR subtype exhibits unique signalling properties and tissue distribution, with SSTR2 and SSTR5 particularly implicated in the therapeutic actions of somatostatin analogues in NETs.

Synthetic somatostatin analogues (SSAs), including octreotide and lanreotide, are engineered to selectively target SSTR2 and SSTR5, the subtypes most frequently overexpressed in well-differentiated NETs.

SSAs are standard therapies for functional NETs and are widely recommended for adult patients with SSTR-positive and/or non-functional, well-differentiated (G1-G2) GEP-NETs. Two pivotal randomized phase III trials, PROMID and CLARINET, demonstrated a significant prolongation of time to progression and progression-free

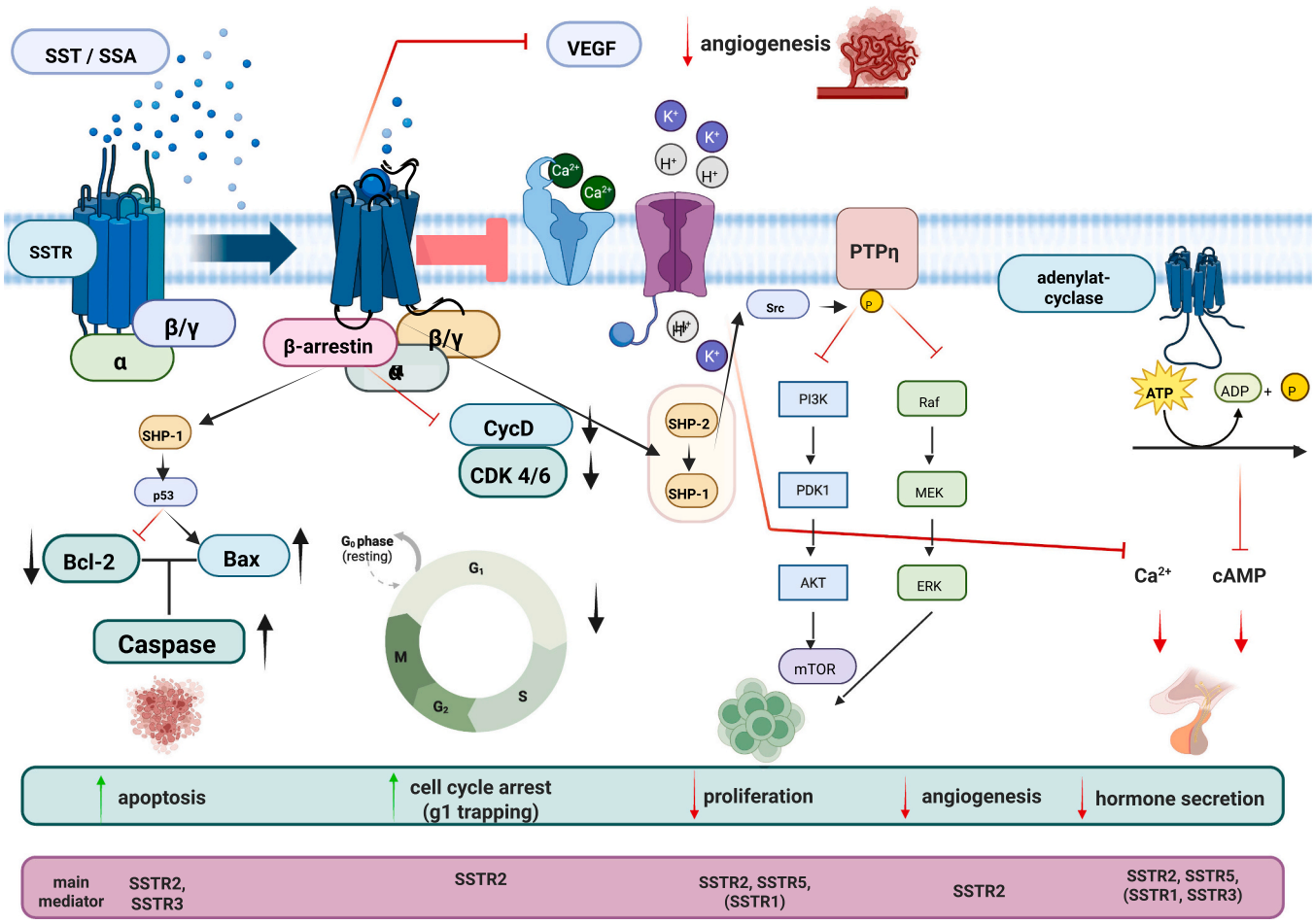

Fig. 1. Mechanistic overview of antitumor signalling cascades activated by somatostatin receptor ligand binding. Schematic representation of the signalling pathways activated by somatostatin receptor subtypes SSTR1–5. Upon ligand binding, SSTRs inhibit adenylate cyclase via Gi proteins, reducing cAMP and PKA activity. They also modulate MAPK, PI3K/Akt, and calcium signalling, leading to suppression of hormone secretion, cell proliferation, and tumour growth. Differential coupling to downstream effectors underlies the functional diversity among SSTR subtypes. *Created in BioRender. Claus, R. (2025)* https://BioRender.com/3zv6p1q.

survival with SSA therapy compared to placebo in adult patients with midgut and non-functioning GEP-NETs, respectively. [30,31]

Current ENETS, ESMO, NANETS, and ASCO guidelines recommend SSAs as first-line therapy for adults with metastatic G1–G2 midgut NETs, and also endorse their use in functioning pancreatic NETs and other SSTR-positive tumours exhibiting low tumour burden and indolent clinical behaviour. [21–28]

SSAs serve a dual therapeutic purpose: they effectively control hormone-related symptoms, such as those seen in carcinoid syndrome, and exert antiproliferative effects, thereby stabilizing disease in a substantial proportion of patients. Owing to their favourable safety profile, SSAs are also increasingly employed in combination regimens, particularly with peptide receptor radionuclide therapy (PRRT), to enhance disease control in progressive or high-risk cases. [32]

3.1.1. Paediatric evidence on SSA

Evidence for the use of SSA in paediatric GEP-NENs remains limited and largely retrospective. (Tables 1–3) The French FRACTURE registry reported on four paediatric patients receiving SSA as first-line therapy for functional disease: one with localized G2 pancreatic NET and three with metastatic tumours (two G2 and one NEC). Five additional patients received SSA in subsequent treatment lines. All but one patient, who had NEC, were alive at last follow-up, suggesting potential disease stabilization in well-differentiated cases. [15] The Italian TREP project described one case of metastatic gastrinoma with liver metastases in a patient presenting with Zollinger-Ellison syndrome. The patient was treated with octreotide, achieving stable disease for at least 16 months following diagnosis. [16] Our own MET cohort encompasses three paediatric patients with metastatic pancreatic NETs treated with SSAs: one G2 patient received octreotide combined with chemotherapy and ultimately died of progression; a second G2 patient received octreotide with [^{131}I]I-Metaiodobenzylguanidine therapy after partial chemotherapy response but also succumbed to disease; the third patient (G3 NET) was treated with lanreotide at relapse but experienced progressive disease. [11]

A retrospective Turkish study reported two cases (G2 NET): one patient with pancreatic NET received one year of adjuvant SSA therapy after extensive resection; the other, with gastric NET, received SSA for six months post-operatively. Both remained in remission 75 and 82 months after initial diagnosis, respectively. [33] A well-documented case involved a 7-year-old girl with metastatic duodenal gastrinoma treated with octreotide and interferon-alpha, alongside proton pump inhibitors and surgical debulking. The disease remained stable for several years under SSA therapy but eventually progressed with liver metastases three years later, prompting the addition of chemotherapy. [34]

Notably, no paediatric cases were identified in the literature involving SSA combination therapies with VEGF inhibitors, mammalian Target of Rapamycin (mTOR) inhibitors, or immune checkpoint inhibitors, despite increasing evidence supporting such combinations in

Table 1
Summary of systemic therapies and paediatric evidence.

Therapy Class	Adult Indication	Paediatric Use Reported	Reported Outcomes
SSAs	G1–G2 NETs, functional tumours, SSTR-positive disease	Yes (limited series and case reports)	Variable symptom control, disease stabilization in some cases
PRRT	SSTR-positive, progressive well-differentiated NETs	Yes (case series, registry data, prospective NETTER-P trial)	Some disease control in SSTR-positive patients; NETTER-P showed favourable safety profile and dosimetry comparable to adults
Targeted Therapies (Everolimus, Sunitinib)	Progressive, unresectable/ metastatic G1–G2 pancreatic NETs	Yes (retrospective and registry data)	Mixed outcomes; stable disease in few, progression in others
Cytotoxic Chemotherapy	High-grade NECs, refractory or bulky NETs	Yes (varied regimens across small series)	Short-term control in selected high-grade or bulky cases
ICIs	High-grade NECs, high TMB/MSI-H tumours	No (only extrapolated adult data)	Limited or no activity in well-differentiated NETs

Abbreviations: ICI = immune checkpoint inhibitor; NET = neuroendocrine tumour; MSI-H = microsatellite instability-high; NEC = neuroendocrine carcinoma; PRRT = peptide receptor radionuclide therapy; SSA = somatostatin analogue; SSTR = somatostatin receptor; TMB = tumour mutational burden.

adult patients. [27,35]

3.1.2. Dosing and resistance considerations

Paediatric dosing of SSAs is typically extrapolated from adult protocols. Long-acting formulations, such as octreotide long-acting release (LAR) and lanreotide depot, are preferred for their sustained release profiles and practicality in long-term management. However, resistance to SSAs can develop over time, particularly in patients with high tumour burden, poorly differentiated histology, or progressive disease. Several mechanisms have been proposed to underlie resistance, including downregulation or loss of SSTR2 expression, receptor desensitization through internalization or phosphorylation, and alterations in downstream signalling pathways such as MAPK and PI3K/Akt that bypass somatostatin-mediated inhibition. Tumour heterogeneity in SSTR subtype expression may also limit therapeutic efficacy, as some lesions may lack sufficient SSTR2/SSTR5 expression for SSA responsiveness. (reviewed in [36,37])

In adult patients, dose escalation and switching between SSA agents have been explored as potential strategies to delay progression. [38,39] Phase II and III studies such as CLARINET FORTE and NETTER-1 have reported modest prolongation of progression-free survival (PFS) with high-dose SSA regimens. [31,40] However, the relevance of these strategies in paediatric patients remains uncertain.

New-generation SSAs, like pasireotide and paltusotine, are under development and may offer improved efficacy or reduced side effects; their roles in paediatric patients remain to be explored. [41]

3.2. Interferon-α-Based regimens

Interferon-alpha (IFN-α) has historically been used in the treatment of well-differentiated NETs for its antiproliferative and immunomodulatory effects. It can suppress hormone secretion and slow tumour growth, particularly in functional NETs resistant to SSAs. However, its clinical use has declined due to limited efficacy data, significant toxicity (e.g., fatigue, cytopenias), and the availability of better-tolerated alternatives. In paediatric settings, evidence is anecdotal and largely restricted to extrapolation from adult data.

Table 2
Detailed paediatric case series and registry data.

Study / Source	Patient Cohort	Therapies Used	Reported Outcomes
MET Registry (Karges et al., 2025)	28 paediatric patients with pancreatic NETs	SSAs, PRRT, chemotherapy (CAPTEM, platinum-based), targeted agents	Variable; some stable disease, high mortality in progressive cases
MET Registry (Kuhlen et al., 2025)	8 paediatric patients with NEN of unknown primary	Chemotherapy (FOLFIRI, GEMOX, PEI, MI/MII, VIDE), high-dose chemotherapy with autologous stem cell support. SSAs, PRRT, targeted agents	Predominantly poor outcomes; high mortality in progressive cases, limited follow-up in indolent NETs
FRACTURE Registry (Courtel et al.)	13 paediatric patients with well-differentiated pancreatic NETs, 2 patients with NECs	SSAs, chemotherapy (platinum, temozolomide, streptozotocin), targeted agents	Heterogeneous; G3 and metastatic cases with poor prognosis
TREP Project (Virgone et al.)	12 paediatric patients with pancreatic NET, 1 patient with Meckel's diverticulum NET, 1 patient with liver NET, 1 patient with gastrointestinal tract	SSAs, PRRT, chemotherapy (streptozotocin, temozolomide, platinum-based)	Selected stable disease; limited long-term follow-up
Hartmann et al., 2011	12 paediatric patients with relapsed/refractory tumours including 3 patients with NEC	Oxaliplatin, irinotecan, gemcitabine	Disease control in majority; manageable toxicity
Additional Literature Reports	Individual paediatric NET case reports	Multimodal (e.g., SSA + interferon; PRRT + chemotherapy)	Mixed outcomes; some long-term survival, others with progression

Abbreviations: CAPTEM = capecitabine, temozolomide; FOLFIRI = folinic acid, fluorouracil, irinotecan; FRACTURE = French Very Rare Tumors Committee; GEMOX = gemcitabine, oxaliplatin; MI = vincristine, etoposide, cisplatin / MII = vindesine, dacarbazine, ifosfamide, doxorubicin; (GEP-) NEN = (gastroenteropancreatic) neuroendocrine neoplasm; NET = neuroendocrine tumour; MET = malignant endocrine tumour; NEC = neuroendocrine carcinoma; PEI = cisplatin, etoposide, ifosfamide; PRRT = peptide receptor radionuclide therapy; SSA = somatostatin analogue; TREP = Tumori Rari in Età Pediatrica = Italian Rare Tumours in Paediatric Age project; VIDE = vincristine, ifosfamide, doxorubicin, etoposide.

3.3. Peptide receptor radionuclide / radiopharmaceutical therapy-based regimens

PRRT, recently termed radiopharmaceutical therapy (RPT), is a molecularly targeted treatment that delivers radionuclides such as [^{177}Lu]Lu-DOTATATE (SSTR2) or [^{177}Lu]Lu-DOTA-TOC (SSTR2 > SSTR5) to tumour cells expressing SSTRs. These agents are somatostatin receptor agonists that bind to the receptor, triggering internalization of the receptor-ligand complex via endocytosis. Once internalized, the conjugated radionuclide emits localized ß-radiation, inducing DNA damage and subsequent tumour cell death.

In adults, PRRT is recommended for patients with progressive, well-differentiated (G1–G2), metastatic, SSTR-positive GEP-NETs following failure of SSA therapy. [21–27] The phase III NETTER-1 trial established [^{177}Lu]Lu-DOTATATE as the standard second-line therapy in midgut NETs, demonstrating a 79 % reduction in the risk of disease progression

Table 3
Summary of key adult clinical trials relevant to paediatric GEP-NENs, including one paediatric study.

Trial Name	Therapy Studied	Patient Population	Main Findings
PROMID (NCT00171873)	Octreotide vs. placebo	Metastatic midgut NETs; ages 38–82 years	Delayed tumour progression
CLARINET (NCT00353496)	Lanreotide vs. placebo	Non-functional GEP-NETs; ages 51–73 years	Prolonged PFS in non-functional tumours
NETTER−1 (NCT01578239)	[177Lu]Lu-DOTATATE vs. high-dose octreotide	Progressive midgut NETs; ages 54–74 years	Improved PFS over high-dose SSA
NETTER-P (NCT04711135)	[177Lu]Lu-DOTATATE (standard protocol)	Paediatric and adolescent patients with GEP-NETs, pheochromocytoma/paraganglioma, ages 13–17 years	First prospective paediatric PRRT trial; No new safety signals, acceptable dosimetry (≤29 Gy kidneys, ≤2 Gy marrow); supports use of adult protocol in adolescents
COMPETE (NCT03049189)	[177Lu]Lu-edotreotide vs. everolimus	Advanced well-differentiated GEP-NETs; ages eligible for study: 18 years and older,	Superior PFS for PRRT vs. everolimus
OCLURANDOM (NCT02230176)	PRRT vs. sunitinib	Advanced pancreatic NETs; ages eligible for study: 18 years and older, mean 63 years	PRRT delayed progression vs. sunitinib
CABINET (NCT03375320)	Cabozantinib in previously treated NETs	Advanced pancreatic and extrapancreatic NETs; ages 28–86 years	Efficacy in pretreated NETs, including pNETs
DART SWOG 1609 (NCT02834013)	Nivolumab + ipilimumab	High-grade NECs; ages 36–81 years	High ORR in NECs; limited in well-differentiated NETs
KEYNOTE−158 (NCT02628067)	Pembrolizumab monotherapy	Previously treated GEP-NETs; ages 20–87 years	Low ORR; modest benefit in G1–G2 tumours
NICE-NEC (NCT03980925)	Nivolumab + EP chemotherapy	Untreated advanced NECs; ages 28–84 years	Short PFS despite response in NECs

Abbreviations: EP = etoposide, carboplatin; (GEP-) NET = (gastroenteropancreatic) neuroendocrine tumour; NEC = neuroendocrine carcinoma; ORR = objective response rate; PFS = progression-free survival; PRRT = peptide receptor radionuclide therapy; SSA = somatostatin analogue.

or death compared to high-dose octreotide LAR (hazard ratio [HR]= 0.21; 95 % CI: 0.13–0.33; $p < 0.0001$). [40]

Similarly, the phase III COMPETE (NCT03049189) trial evaluated [^{177}Lu]Lu-DOTA-TOC ([^{177}Lu]Lu-edotreotide) versus everolimus in patients with progressive well-differentiated (G1–2) GEP-NETs, showing a significant longer median PFS with PRRT (23.9 months vs 11.0 months; $p = 0.002$). [42,43]

More recently, the prospective phase III NETTER-2 trial investigated [^{177}Lu]Lu-DOTA-TATE combined with long-acting octreotide in treatment-naive patients with advanced, well-differentiated G2–3 SSTR-positive GEP-NETs. The addition of PRRT resulted in a 14-months improvement in median PFS extended median PFS compared to standard therapy, supporting its potential role as a new first-line standard in this higher-grade population. [44]

3.3.1. *Paediatric evidence on PRRT*

Clinical experience with PRRT in paediatric GEP-NENs remains limited and is primarily derived from small retrospective studies, registry data, and individual case reports. (Tables 1–3) In the MET registry, five patients with metastatic panNETs received 1–7 cycles of [^{90}Y]Y-DOTATOC, with treatment responses ranging from partial response to stable disease. Four patients ultimately experienced disease progression and died, while one remained alive with progressive disease at last follow-up. [11] [^{90}Y]Y-DOTATOC differs from [^{177}Lu]Lu-based compounds by emitting higher-energy ß-particles with longer tissue penetration, potentially improving efficacy in larger tumours but also increasing the risk of off-target toxicity, particularly nephrotoxicity. [45] The FRACTURE study and TREP did not explicitly describe any PRRT-treated cases. [12,15,16]

A phase I trial further evaluated [^{90}Y]Y-DOTATOC in paediatric and young adult patients with refractory, SSTR-positive solid tumours, including five with GEP-NENs (four gastrinomas, one pancreatic NET). Partial responses were observed in 12 % of the overall cohort, with minor responses in 29 %. Notably, the highest response rates were reported among patients with NETs. [46]

A retrospective analysis by Aggarwal et al. assessed the use of [^{177}Lu]Lu-DOTATATE in 19 paediatric and young adult patients (aged ≤29 years) with metastatic or inoperable NETs. Patients received up to six body-weight–adjusted (50–200 mCi per cycle) cycles, administered in combination with oral capecitabine. The objective response rate was 41 %, and disease control was achieved in 94 % of cases, with most adverse events being low grade. At five years, the reported PFS was 54 %. Two patients with FDG-avid disease were treated using a "sandwich" protocol of alternating cycles of CAPTEM and PRRT ([47]), both deriving clinical benefit. [48]

Individual case reports have further documented the application of PRRT in children. Foster et al. described symptomatic improvement and radiographic stability in two patients aged 8 and 13 years following four cycles of [^{177}Lu]Lu-DOTATATE. [49] Similarly, Hlogawa et al. reported stable disease and good tolerability in a 9-year-old treated with four cycles, with no toxicity observed at 37 months post-treatment. [50]

Additional safety data from paediatric neuroblastoma studies support the feasibility and tolerability of PRRT in children. The use of [^{68}Ga]Ga-DOTATATE PET imaging for patient selection has proven effective, and [^{177}Lu]Lu-DOTATATE therapy has demonstrated favourable tolerability in children with relapsed or refractory high-risk disease. These findings contributed to the design of the LuDO-N trial, under which [^{177}Lu]Lu-DOTATATE received EMA approval for paediatric use in molecular radiotherapy. [51]

Finally, the phase II NETTER-P trial was the first prospective study to assess the safety and dosimetry of [^{177}Lu]Lu-DOTATATE in adolescents with GEP-NETs and pheochromocytoma/paraganglioma. Patients received four cycles of PRRT (7.4 GBq every 8 ± 1 weeks). While long-term follow-up is ongoing, no new safety signals were observed relative to adult cohorts. Dosimetry results indicated that mean cumulative absorbed doses to organs at risk remained below predefined safety threshold (≤ 29 Gy for kidneys and ≤ 2 Gy for bone marrow), suggesting that standard PRRT dosing schedules may be suitable for adolescents with NETs. [52]

3.3.2. *Emerging directions in PRRT*

3.3.2.1. Ongoing trials. Several ongoing and recently completed clinical trials in adults continue to shape the radiotheranostic landscape and may inform future treatment strategies in paediatric GEP-NENs. The OCLURANDOM trial (NCT02230176) demonstrated greater efficacy of PRRT compared to sunitinib in patients with progressive pancreatic

NETs. [53] The STARTER-NET study is evaluating the efficacy of everolimus with or without lanreotide in aggressive GEP-NETs, [54] while the LEVEL trial (GETNE T-2217) is comparing [^{177}Lu]Lu-DOTATOC to everolimus in lung and thymic NETs, with quality of life and overall survival as key endpoints. [55]

In the paediatric population, the KinLET trial is an open-label, multicentre phase I study designed to determine the optimal administered activity of [^{177}Lu]Lu-edotreotide based on safety and pharmacokinetic parameters in children and adolescents with SSTR-positive tumours, including NETs. [56]

3.3.2.2. Dual isotope PRRT. In adult patients, combination radionuclide therapies with both [^{90}Y]Y-DOTATOC and [^{177}Lu]Lu-DOTATATE, referred to as "dual PRRT," have been explored to enhance efficacy by capitalizing on the distinct physical properties of each isotope. [57,58] [^{90}Y]Y has a longer tissue penetration range, potentially improving outcomes in bulky tumours, while [^{177}Lu]Lu delivers more localized radiation, favouring small-volume or diffuse disease. [59] Preliminary clinical data suggest that this approach may improve tumour control in selected adult patients with heterogeneous disease. [58] To date, no studies have evaluated dual PRRT in paediatric patients with GEP-NENs.

3.3.2.3. Combination strategies with targeted or chemotherapeutic agents. Combining PRRT with targeted therapies, particularly mTOR inhibitors such as everolimus, has demonstrated synergistic potential in preclinical models and early-phase clinical trials involving adult patients. [60] mTOR pathway inhibition may enhance radiosensitivity and inhibit tumour cell proliferation, thereby increasing the therapeutic efficacy of PRRT. However, these combination strategies have not yet been explored in paediatric GEP-NENs.

Poly(ADP-ribose) polymerase (PARP) inhibitors have emerged as potential therapeutic agents in tumours with homologous recombination deficiency or high genomic instability. In NENs, preclinical data suggest that PARP inhibition may enhance DNA damage in combination with PRRT or chemotherapy. Early-phase studies are ongoing, particularly in high-grade or poorly differentiated NENs, but clinical data remain sparse, and no paediatric-specific evidence is currently available. [61]

Multiple additional combinatorial approaches aim to amplify therapeutic impact by interfering with various cellular processes. These include enhancing DNA damage through conventional chemotherapy, sensitizing tumours to radiation by inhibiting DNA repair mechanisms, disrupting cell cycle regulation, targeting nicotinamide adenine dinucleotide (NAD^+) metabolism, and modulating immune evasion via immune checkpoint inhibition. (NCT02736500, NCT04086485, NCT04086485, NCT04086485, NCT04086485 NCT04375267, NCT03629847) [60,62–80]

3.3.2.4. Use of new radionuclides, including auger electron and alpha emitters. Among emerging radionuclides, ^{161}Terbium is of particular interest. It shares similar physical characteristics with ^{177}Lu but also emits short-range conversion and Auger electrons with high linear energy transfer (4–26 keV/μm), which may enhance the cytotoxic efficacy against micrometastatic disease and single tumour cells. [81] PRRT using ^{161}Terbium-labeled SSTR ligands is currently being investigated in adult patients with NETs (NCT05359146).

Another promising radiopharmaceutical is [^{67}Cu]Cu-SARTATE, currently being evaluated in paediatric neuroblastoma, along with its PET imaging counterpart, [^{64}Cu]Cu-SARTATE (NCT04023331).

In parallel, alpha-emitting agents (with a linear energy transfer of 50–230 keV/μm) such as [^{213}Bi]Bi-DOTATOC, [^{225}Ac]Ac-DOTATATE and [^{212}Pb]Pb-DOTAMTATE are under investigation for their potential to deliver more potent cytotoxic effects with limited penetration into surrounding tissues, thereby reducing off-target toxicity. [82,83] Both pre-clinical as well as clinical reports have recently demonstrated encouraging results, [84–88] , and various agents are currently being investigated in clinical trials (NCT05477576, NCT06732505, NCT05153772). The most recent developments in the field of alpha-emitting radionuclides is reviewed in [89].

3.3.2.5. SSTR-Antagonists. Furthermore, novel somatostatin receptor antagonists are emerging as potential alternative to traditional agonists in PRRT. Unlike agonists, which require receptor internalization, antagonists bind to a broader range of receptor conformations without triggering endocytosis. This expanded binding profile enables higher tumour uptake and superior tumour-to-background ratios, as demonstrated in both preclinical and early-phase clinical studies. [90,91] Radiolabeled SSTR antagonists such as [^{177}Lu]Lu-satoreotide tetraxetan have shown improved tumour retention compared to agonists like [^{177}Lu]Lu-DOTATATE in mice, suggesting a potentially enhanced therapeutic index. [92]

3.3.2.6. Technological innovations and future perspectives. Additional developments—including radiomics, individualized dosimetry, and next-generation radioligands (e.g., somatostatin antagonists or alpha-emitting constructs)—offer potential for refining patient selection and optimizing therapeutic response. (reviewed in [93]) These innovations are currently restricted to adult research settings. Systematic inclusion of paediatric cohorts in future PRRT trials will be essential for ensuring evidence-based translation of these technologies into younger populations.

3.4. Small molecule therapy-based regimens

Targeted molecular therapies have become integral to the management of progressive, well-differentiated GEP-NETs in adults. Two key classes of agents are currently used: mTOR inhibitors, such as everolimus, which suppress cell metabolism, growth, proliferation, and angiogenesis; and tyrosine kinase inhibitors (TKIs), such as sunitinib and surufatinib, which primarily target the vascular endothelial growth factor (VEGF) pathway, thereby inhibiting tumour-associated angiogenesis.

In adult patients with unresectable or metastatic G1–G2 pancreatic NETs (panNETs), both everolimus and sunitinib have demonstrated significant clinical efficacy and are approved for use in this setting. [94–97] These agents are recommended in major guidelines, including those from ENETS, NANETS, and ASCO. [22,23,27]

Everolimus may also serve as an alternative for patients with SSTR-negative tumours or those unsuitable for PRRT due to hematologic risk. [95] In randomized trials, everolimus has been shown to prolong progression-free survival in non-functional, metastatic GEP-NETs and is often integrated into combination strategies aimed at enhancing antitumour response. [27]

A precision oncology approach was explored in a phase II study by Neychev et al., in which adult patients with advanced low- or intermediate-grade GEP-NENs were assigned to either everolimus or sunitinib based on tumour molecular profiles. [98] Although paediatric patients were not included, this study reflects the growing role of genomics in guiding individualized treatment selection.

3.4.1. Paediatric evidence on targeted therapies

Clinical experience with targeted therapies in paediatric GEP-NENs also remains limited and is based primarily on small retrospective series and case-level data. (Tables 1–3) In the MET cohort, three children with metastatic pancreatic NETs were treated with everolimus. One patient achieved prolonged stable disease for over four years, while two others experienced progression and ultimately died from their disease. One additional patient with macroscopic residual disease following surgical resection received sunitinib, achieving transient disease stabilization before relapse. [11] The FRACTURE registry included paediatric

patients with metastatic pancreatic NETs treated with targeted therapies, including everolimus and sunitinib, as part of multimodal treatment approaches. Outcomes were variable, with progression reported in several cases. [15] Similarly, in the TREP project, targeted agents were used in select patients with extra-appendiceal NETs; everolimus and sunitinib were each administered in at least one case, typically following surgery or PRRT. [12,16]

3.4.2. Combination of everolimus and temozolomide

Combination strategies incorporating targeted therapies and cytotoxic agents have been evaluated in adult patients. A phase II trial by Morken et al. investigated everolimus plus temozolomide as first-line therapy in adults with metastatic high-grade GEP-NENs. The regimen yielded an objective response rate of 32 % and a median progression-free survival of 9.1 months. [99] To date, no paediatric-specific data are available on this combination.

3.4.3. Brief overview of emerging adult trials

Several adult clinical trials continue to expand the therapeutic scope of targeted agents in NENs, offering potential insights for future paediatric strategies. The CABINET trial evaluated cabozantinib, a multikinase inhibitor targeting VEGFR, MET, and AXL, in patients with previously treated advanced NETs. The study demonstrated a significant PFS benefit in both pancreatic and extra-pancreatic NET subtypes, positioning cabozantinib as a promising option in the second-line setting. [100]

Other multitargeted tyrosine kinase inhibitors (TKIs) have also been explored. Pazopanib, which targets VEGFR, PDGFR, and c-KIT, showed modest antitumour activity in phase II studies, particularly in pancreatic NETs, although with limited durability. Lenvatinib, a VEGFR1–3, FGFR, PDGFRα, RET, and KIT inhibitor, has demonstrated higher disease control rates and is under active investigation in combination with everolimus or immune checkpoint inhibitors. Axitinib, a selective VEGFR1–3 inhibitor, has also shown preliminary efficacy in well-differentiated NETs. Sorafenib, targeting RAF, VEGFR, and PDGFR, was investigated primarily in poorly differentiated NECs, but yielded modest responses and is not widely adopted. (reviewed in [101,102])

In parallel, adult clinical trials such as COMPETE (evaluating [^{177}Lu]Lu-edotreotide vs. everolimus), [43] STARTER-NET (everolimus ± lanreotide), [54] and LEVEL (PRRT vs. everolimus in lung/thymic NETs) [55], continue to shape future treatment paradigms. Although these studies are adult-specific, their trial designs and outcomes may serve as a blueprint for paediatric protocol development.

Beyond TKIs, several novel molecular targets are under investigation. These include 4–1BB (CD137), a T-cell costimulatory receptor, and DLL3 (delta-like ligand 3), a Notch pathway component overexpressed in high grade NECs. [103] While these targets have not yet been evaluated in paediatric GEP-NENs, their emergence reflects an increasingly molecularly tailored therapeutic landscape that could inform future approaches as molecular profiling of paediatric tumours becomes more widespread.

3.5. Chemotherapy-based regimens

Chemotherapy remains an essential component of systemic treatment for NENs, particularly in patients with high tumour burden, aggressive clinical behaviour, or Ki-67 indices exceeding 15 %. Its effectiveness is strongly influenced by tumour grade and degree of differentiation.

In adults with poorly differentiated NECs, platinum-based doublet regimens, typically cisplatin or carboplatin combined with etoposide, are widely accepted as first-line treatment. This approach is supported by response rates of approximately 30 % and modest PFS. [104] Alternative combinations, including cisplatin plus irinotecan and nab-paclitaxel with carboplatin, have also been explored. [105–107]

Second-line chemotherapy options for NECs are notably sparse and supported by low-level evidence. For example, the PRODIGE 41-BEVANEC trial investigated bevacizumab in combination with FOLFIRI but demonstrated only limited clinical benefit. [108] Overall, outcomes in the relapsed setting remain poor.

For well-differentiated G1–G2 NETs, chemotherapy is reserved for cases with progressive, high-volume disease or resistance to other systemic treatments. Alkylating-agent regimens such as capecitabine–temozolomide (CAPTEM) and streptozotocin (STZ)-based combinations are used most frequently, with varying response rates. [109,110] Retrospective data suggest modest benefit of the FOLFOX regimen in pancreatic and extra-pancreatic NETs, especially in patients with low MGMT expression. [111]

While numerous chemotherapy protocols have been assessed in adults, evidence supporting their use in paediatric patients remains scarce and largely extrapolated.

3.5.1. Paediatric evidence on chemotherapy

Chemotherapy has been employed in paediatric patients with advanced or metastatic GEP-NENs, primarily in cases of poorly differentiated tumours or progressive disease unresponsive to other modalities. However, the available data remain limited to retrospective reports and small case series.

The FRACTURE study reported chemotherapy use in several patients, predominantly in the context of G3 tumours or metastatic disease. Agents included platinum plus etoposide, temozolomide, and STZ-based combinations. Survival outcomes were poor in high-grade disease, with five-year overall survival reported at 28 % for G3 tumours and 35 % for metastatic presentations. [15]

In the TREP project, chemotherapy was also utilized in selected cases. One patient with a malignant islet cell tumour achieved stable disease upon six cycles of adriamycine, 5-FU, and streptozotocin. [12] In the MET cohort, several patients with metastatic pancreatic NETs received chemotherapy, including oxaliplatin plus irinotecan plus gemcitabine, cisplatin plus etoposide, and CAPTEM. One patient achieved stable disease for 12 months before progression, while others experienced limited responses and ultimately died from disease progression. [11]

Findings from the broader literature provide further insight into real-world chemotherapy use. A retrospective series evaluated a combination of oxaliplatin, irinotecan, and gemcitabine in 12 children with relapsed or refractory solid tumours, including three with unresectable NEC. Administered in an outpatient setting, the regimen demonstrated manageable toxicity and disease control in the majority of patients. [112]

Other case reports describe highly variable outcomes. A 7-year-old girl with metastatic duodenal gastrinoma received multimodal therapy including octreotide, interferon-alpha, SZT, and 5-FU, achieving initial disease control before ultimately progressing and requiring hepatic embolization. [34] Another report documented a 12-year-old with primary hepatic NEC who achieved complete remission after neoadjuvant ifosfamide, carboplatin, and etoposide, followed by adjuvant irinotecan, gemcitabine, and oxaliplatin. [113]

While regimens such as CAPTEM and platinum-based combinations are among the most frequently employed, their use in paediatric GEP-NENs is limited by a lack of standardized dosing strategies and prospective validation. Most paediatric tumours are well-differentiated and slow-growing, raising questions about the ideal timing and selection criteria for chemotherapy initiation.

Taken together, these findings suggest that chemotherapy may offer clinical benefit in selected paediatric patients, particularly those with NEC, symptomatic progression, or unresectable tumours. However, outcomes remain inconsistent, and potential toxicities must be weighed carefully on a case-by-case basis.

3.6. Immunotherapeutic approaches

3.6.1. Immune-checkpoint inhibitors (ICIs)

Immune checkpoint inhibitors (ICIs), including agents targeting PD-1, PD-L1, and CTLA-4, are under investigation for their role in NENs. In adults, ICIs have demonstrated limited clinical activity when used as monotherapy in well-differentiated G1–G2 GEP-NETs. [114,115] Responses appear to be infrequent in high-grade or poorly differentiated NECs, but, when present, can be profound. However, durable benefit remains rare overall.

Dual checkpoint blockade with anti-PD-1 and anti-CTLA-4 antibodies has shown increased response rates in adult patients with NECs. However, these benefits are typically modest, and activity in well-differentiated tumours remains limited. [116]

3.6.2. Combination therapies

Combinatorial strategies incorporating ICIs with chemotherapy, anti-angiogenic agents or tyrosine kinase inhibitors are being explored in adult studies. [117,118] While early results are encouraging in selected subgroups, such as patients with NECs, microsatellite instability, mismatch repair deficiency, or high tumour mutational burden, no paediatric-specific data are currently available on ICI monotherapy or combination regimens in GEP-NENs. [119,120]

3.6.3. Oncolytic virotherapy

Oncolytic virotherapy is an emerging immunotherapeutic approach in NENs. Seneca Valley virus (SVV-001), a replication-competent picornavirus with selective tropism for neuroendocrine tumour cells, has demonstrated safety and preliminary antitumour activity in a phase I trial involving patients with advanced solid tumours exhibiting neuroendocrine features. [121] Building on these findings, a phase I trial (NCT06889493) is currently evaluating SVV-001 in combination with nivolumab and ipilimumab in patients with NECs or well-differentiated high-grade NETs. While paediatric-specific data are not yet available, the tumour selectivity and immunogenic potential of SVV-001 highlight its promise as a future adjunct to immunotherapy in aggressive or treatment-refractory GEP-NENs.

4. Conclusions and futures perspectives

Systemic treatment options for paediatric GEP-NENs remain limited and largely extrapolated from adult practice. (Tables 1–3) Our review

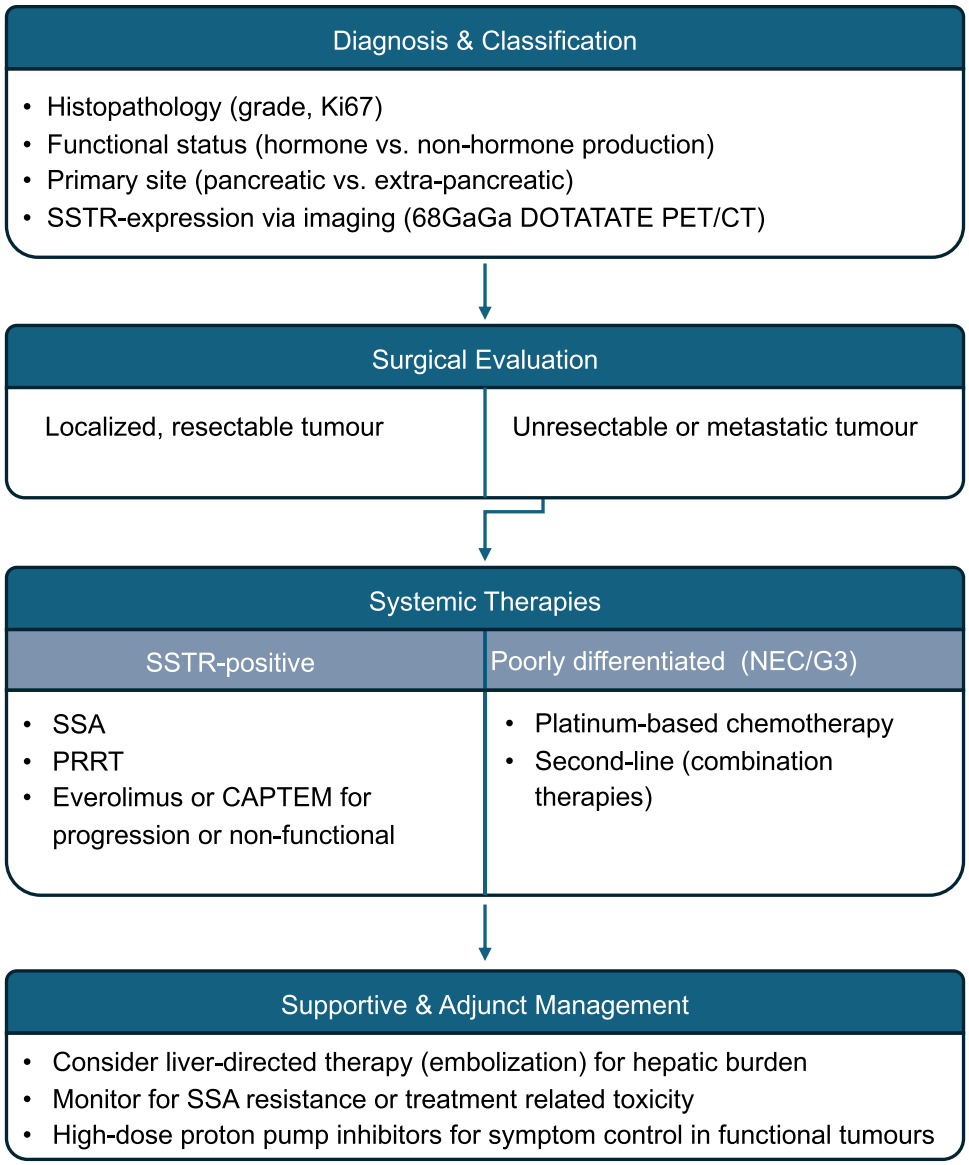

Fig. 2. Schematic Treatment Algorithm for Paediatric GEP-NENs.

underscores the considerable heterogeneity of these tumours, coupled with the scarcity of paediatric-specific data across all therapeutic classes. Treatment decisions in children and adolescents must carefully account for tumour grade, primary site, SSTR expression, functional status, disease burden, and individual patient factors. (Fig. 2) Whenever feasible, care should be guided by a multidisciplinary team—including a paediatric oncologist and a medical oncologist with specific expertise in NENs—and involve shared decision-making with patients and families. While SSAs, PRRT, targeted agents (e.g., everolimus, sunitinib), and chemotherapy form the cornerstone of systemic therapy in adults, their application in paediatric populations remains inadequately studied. Evidence for ICIs is even more limited, with response largely confined to high-grade or poorly differentiated tumours.

Resistance to SSAs remains an important clinical challenge. While the mechanisms are not fully elucidated, they may involve down-regulation of somatostatin receptor expression or clonal evolution leading to receptor-negative tumour subpopulations. [122] In adults, strategies to prolong SSA efficacy include dose escalation or switching to alternative analogues; however, these approaches remain untested in children. Additionally, reducing hepatic tumour burden through locoregional treatments, such as embolization, may help extend the functional benefit of SSA therapy by lowering overall neuroendocrine activity and delaying resistance onset. [123]

The concept of sequential therapy, long applied in adult NETs, warrants further exploration in paediatric care. Decisions surrounding treatment sequencing, maintenance strategies, and the timing of monotherapy versus combination therapy must be personalized, particularly in the absence of clear evidence-based algorithms. Tumour origin also appears to influence drug efficacy; while many systemic therapies are used across organ types, the clinical response may vary significantly between pancreatic and extra-pancreatic primaries. In selected cases, rechallenge with previously effective agents may also be considered following a treatment break, although this approach remains untested in paediatric populations.

These insights underscore the need for molecular profiling and imaging-based SSTR assessment to guide therapeutic strategies, especially in unresectable or refractory paediatric cases where evidence is limited. Such approaches may enable better risk stratification, improve treatment personalization, and facilitate the identification of patients most likely to benefit from advanced or experimental therapies.

Future research efforts should prioritize:

1. Establishing standardized treatment protocols tailored to paediatric patients;
2. Investigating rational combination regimens, including PRRT- and mTOR-based approaches;
3. Exploring novel immunotherapeutic and molecularly targeted strategies;
4. Evaluating long-term toxicities, survivorship, and quality of life;
5. Enhancing patient selection through SSTR imaging, radiomics, and genomic profiling.

The rarity of paediatric GEP-NENs poses significant challenges to conducting prospective trials. Nevertheless, international collaboration, innovative study designs, and registry-based research will be essential to generate meaningful clinical evidence. A coordinated effort to collect clinical data both retrospectively and prospectively through national and international registries is crucial to overcoming limitations in sample size and heterogeneity. Such registries not only support observational research but also lay the groundwork for interventional studies and facilitate long-term follow-up. Molecular profiling, including MGMT status, SSTR subtyping, and emerging biomarkers such as DLL3 or 4–1BB, may help stratify risk and guide future precision medicine approaches.

To this end, the establishment of expert networks and data-sharing infrastructures must be prioritized. These networks can accelerate insights by integrating clinical data, imaging, biological samples, and genomic data across institutions and countries, enhancing both scientific understanding and clinical care. Multidisciplinary engagement and international harmonization of data collection standards will further enable the translation of research into practice.

In conclusion, while paediatric GEP-NEN management is currently informed by adult-derived paradigms, advancing care will require dedicated paediatric studies, collaborative infrastructure, and a deeper understanding of the biological and clinical nuances unique to younger patients.

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CRediT authorship contribution statement

Conzeptualization: MiKu. Formal analysis: MiKu, CL. Investigation: MiKu, CL. Methodology: MiKu. Visualization: MiKu, MS, RC. Writing – original draft: MiKu. Writing – review & editing: MaKu, AR, MS, RC, CL.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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