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Gastrointestinal Neuroendocrine Neoplasms in Children and Adolescents: Data from the German MET Studies (1997–2024)

Katharina Karges[a] Marina Kunstreich[a, b] Michael Abele[c] Jörg Fuchs[d] Christian Vokuhl[e] Ines B. Brecht[c] Dominik T. Schneider[f] Michael C. Frühwald[a] Peter Vorwerk[b] Constantin Lapa[g] Antje Redlich[b] Michaela Kuhlen[a, b, h]

[a]Pediatrics and Adolescent Medicine, Faculty of Medicine, University of Augsburg, Augsburg, Germany; [b]Department of Pediatrics, Pediatric Hematology/Oncology, Otto-von-Guericke-University, Magdeburg, Germany; [c]Pediatric Hematology and Oncology, University Children's Hospital, Eberhard-Karls University, Tubingen, Germany; [d]Department of Pediatric Surgery and Pediatric Urology, University Children's Hospital, Eberhard-Karls University, Tuebingen, Germany; [e]Section of Pediatric Pathology, Department of Pathology, University Hospital Bonn, Bonn, Germany; [f]Clinic of Pediatrics, Dortmund Municipal Hospital, University Witten/Herdecke, Witten, Germany; [g]Nuclear Medicine, Faculty of Medicine, University of Augsburg, Augsburg, Germany; [h]Bavarian Cancer Research Center (BZKF), Augsburg, Germany

Keywords
Children and adolescents · Neuroendocrine neoplasms · Gastrointestinal tract

Abstract

Introduction: Gastrointestinal neuroendocrine neoplasms (GI-NENs) outside the appendix and pancreas are exceptionally rare in children and adolescents. Limited data on presentation, treatment, and outcomes hinder clinical decision-making. ***Methods:*** We retrospectively analyzed 16 patients under 18 years with histologically confirmed NENs of gastrointestinal origin, enrolled in the German Malignant Endocrine Tumor (MET) Registry from 1997 to 2024. Neuroendocrine carcinomas were eligible for inclusion but were not observed. Findings were compared with a cohort (age 0–20 years) from the SEER database. ***Results:*** Median age at diagnosis was 15.4 years; 62.5% were male. Primary tumor sites included the stomach (43.8%), colorectum (18.8%), duodenum and Meckel's diverticulum (12.5% each), and jejunum and omentum majus (6.3% each). Distant metastases were present in 31.3%, with no isolated lymph node involvement. All tumors were well-differentiated NETs: G1 (43.8%), G2 (37.5%), and G3 (6.3%). Hereditary syndromes were confirmed in 18.8% and suspected in 12.5%. Somatostatin receptor 2 (SSTR2) expression was seen in most tested tumors. At 30.1-month median follow-up, 3-year overall survival (OS) and event-free survival were 93.3% and 73.3%, respectively, both associated with tumor grade, stage, and resection. The SEER cohort ($n = 83$) primarily had rectal primaries, localized disease, and the 3-year OS was 95.2%. ***Conclusion:*** Pediatric GI-NENs may present with advanced disease but have favorable outcomes following

Antje Redlich and Michaela Kuhlen contributed equally to this work.

karger@karger.com
www.karger.com/nen

Correspondence to:
Michaela Kuhlen, michaela.kuhlen@uk-augsburg.de

resection. Given the rarity and complexity, close evaluation by multidisciplinary tumor boards at each treatment step is strongly recommended to support individualized care.

Introduction

Neuroendocrine neoplasms (NENs) of the gastrointestinal tract (GI-NENs) in children and adolescents are rare and poorly understood neoplasms [1]. These tumors include well-differentiated neuroendocrine tumors (NETs, G1–G3) and poorly differentiated neuroendocrine carcinomas (NECs, G3) [2]. Arising from neuroendocrine cells dispersed throughout the gut, these tumors present unique challenges in pediatric oncology due to their rarity and the paucity of comprehensive data [3].

The estimated annual incidence of NENs in the pediatric population is approximately 0.5–1 per 100,000 children [4]. Among these, gastroduodenal NENs and colorectal NENs are particularly rare, together accounting for fewer than 10% of all pediatric NENs. Clarifying the incidence, distribution, and clinical characteristics of these tumors is critical to guiding appropriate diagnostic and therapeutic approaches.

Genetic predispositions are associated with the development of pediatric NENs. Multiple endocrine neoplasia type 1 (MEN1) is the most well-characterized hereditary syndrome associated with GI-NENs, with approximately 15–25% of pediatric patients with MEN1 developing these tumors [5]. Other genetic syndromes, such as von Hippel-Lindau disease and neurofibromatosis type 1, are also associated with an increased risk [5, 6].

The clinical presentation of GI-NENs varies depending on tumor location and hormonal activity. Gastroduodenal NENs often manifest with nonspecific gastrointestinal symptoms, such as abdominal pain, nausea, vomiting, and gastrointestinal bleeding [7]. In rare cases, hormone-related symptoms such as those seen in Zollinger-Ellison syndrome may occur due to excessive gastrin secretion [7]. In contrast, colorectal NENs are often asymptomatic at early stages and are frequently detected incidentally. Symptomatic cases may present with rectal bleeding, altered bowel habits, or abdominal discomfort [8].

Treatment strategies for pediatric GI-NENs are adapted from adult protocols and typically involve surgical resection as the primary modality for localized disease [4]. Procedures range from simple local excision to more extensive interventions such as partial gastrectomy or duodenectomy, depending on tumor size, location, and extent [9]. Medical therapies, including somatostatin analogs (e.g., octreotide, lanreotide), are employed to manage hormone-related symptoms and disease progression [4]. Peptide receptor radionuclide therapy (PRRT) may be considered in advanced cases, while chemotherapy and targeted therapies are reserved for high-grade or metastatic disease, though their role remains limited [10].

Prognosis depends on tumor grade, stage at diagnosis, and underlying genetic factors. Well-differentiated GI-NETs generally have a favorable outcome, with 5-year overall survival (OS) rates of approximately 80–90% in localized disease. However, survival drops significantly in metastatic cases, with reported 5-year survival rates of 40–50% [3]. Patients with hereditary syndromes such as MEN1 often have multiple lesions, which can complicate management and impact prognosis [9].

This study presents a comprehensive analysis of extra-appendiceal and extra-pancreatic pediatric GI-NENs enrolled in the German Malignant Endocrine Tumor (MET) Registry, focusing on incidence, clinical and genetic characteristics, treatment modalities, and outcomes. By delineating the specific features of pediatric GI-NENs, we aimed to enhance understanding and inform clinical decision-making.

Patients and Methods

This retrospective study analyzed data from children and adolescents diagnosed with GI-NENs who were enrolled in the German MET Registry, a prospective clinical registry supported by the German Society of Pediatric Oncology and Hematology. The study period spanned from January 1, 1997, to June 30, 2024, and included individuals under the age of 18 at the time of diagnosis. The data cut-off for follow-up was August 31, 2024.

Eligible patients had histologically confirmed NENs of gastrointestinal origin, specifically including tumors located in the stomach, duodenum, jejunum, Meckel's diverticulum, colorectum, and omentum majus. Tumors arising in the appendix, pancreas, lung, or of unknown primary origin were excluded, as they have been analyzed separately in prior MET Registry publications [11–14]. We included all GI-NENs, encompassing both well-differentiated NETs (G1–G3) and poorly

differentiated NECs, according to the World Health Organization (WHO) classification applicable at the time of diagnosis. However, no NECs were identified in this anatomical subset during the study period.

Data were collected via systematic chart reviews and registry-based queries. Recorded variables included demographic, presenting symptoms and tumor markers, diagnostic modalities, histopathological findings, treatment modalities, and outcomes. Frequencies were calculated to the number of patients with available data per variable.

Diagnosis and classification followed WHO guidelines for tumors of the digestive system. Tumor grading (G1–G3) was based on mitotic count and Ki-67 proliferation index. Imaging modalities included computed tomography (CT), magnetic resonance imaging, and somatostatin receptor imaging using positron emission tomography/CT where available. Biopsy or tumor resection was used to confirm histology. In cases with functioning NENs, diagnosis required the presence of a clinically evident hormonal syndrome with corresponding biochemical confirmation.

Treatment strategy was guided by tumor site, size, grade, and stage. Curative-intent surgery was the primary approach for localized disease. Tumors smaller than 1 cm were generally treated by local excision, while larger or multifocal lesions underwent formal oncologic resection, including segmental bowel resection, partial gastrectomy/duodenectomy, or Whipple resection, depending on anatomical location. Intraoperative lymph node assessment was advised. Systemic therapy was considered in unresectable progressive disease, and treatment decisions were individualized in multidisciplinary tumor boards.

SEER Database Cohort

For international comparison, we extracted a complementary cohort from the SEER Program of the US National Cancer Institute, which covers approximately 50% of the US population [15]. Patients included were those with histologically confirmed GI-NENs (C16.0, C16.2, C16.3, C16.9, C17.0, C17.1, C17.2, C17.3, C17.9, C18.0, C18.7, C18.9, C19.9, C20.9, C26.9, and ICD-0-3 codes 8240/3, 8241/3, 8242/3, 8246/3), aged under 20 years at diagnosis, excluding GI-NENs of mixed histology (e.g., mixed adenoneuroendocrine carcinoma, adenocarcinoid tumor). Data cut-off was December 31, 2022.

In total, we identified 1,407 pediatric NENs across the above-listed anatomical sites in the SEER database from 2000 to 2022. Of these, 83 were GI-NENs, which were used for comparative analysis in this study. A site-specific breakdown of all NENs is provided in online supplementary Table S1 (for all online suppl. material, see https://doi.org/10.1159/000548618).

Statistical Analysis

Statistical analyses were conducted using *R* (version 4.4.1). Continuous variables were described using medians, while categorical variables were summarized using frequencies and percentages. Survival outcomes, including OS and event-free survival (EFS), were estimated using the Kaplan-Meier method, and subgroup comparisons were performed using log-rank tests. A p value <0.05 was considered statistically significant.

Results

Patient Demographics and Clinical Presentation

A total of 16 pediatric patients with histologically confirmed GI-NENs were included in the analysis (Table 1). The median age at diagnosis was 15.4 years (range, 1.3–17.4), with the majority of patients ($n = 11$; 68.8%) between 15 and 18 years of age. Ten patients (62.5%) were male. Three patients (18.8%) had a confirmed genetic predisposition: one each with MEN1, Pacak-Zhuang syndrome, and Wolf-Hirschhorn syndrome. In two additional cases (12.5%), a familial syndrome was suspected but not genetically confirmed.

The most commonly reported symptoms were abdominal or back pain ($n = 10$; 62.5%), vomiting ($n = 5$, 31.3%), melena or hematochezia ($n = 5$; 31.3%), and weight loss ($n = 3$; 18.8%). Four patients (25.0%) were diagnosed incidentally during unrelated evaluations. Most patients ($n = 11$; 68.8%) had an unimpaired or only mildly impaired performance status. Functionally active NENs, all consistent with gastrinomas, were documented in 4 patients (25.0%), while the remaining cases were either nonfunctional ($n = 11$, 68.8%) or of unclear hormonal activity ($n = 1$, 6.3%).

Tumor Characteristics

Tumor size was documented in 7 patients (43.8%), with a median diameter of 2.0 cm (range, 0.3–11.2 cm). Among these, six tumors (85.7%) were ≤5 cm (Table 2).

The most common tumor site was the stomach ($n = 7$, 43.8%), followed by the colorectal region ($n = 3$, 18.8%). Additional sites included the duodenum ($n = 2$), Meckel's diverticulum ($n = 2$), jejunum ($n = 1$), and omentum majus ($n = 1$) (shown in Fig. 1).

Table 1. Demographics and clinical presentation of 16 MET patients with GI-NENs

Characteristics	German MET Registry	
	count	proportion, %
Patients, *N*	16	100
Age at diagnosis		
<10 years	2	12.5
10–14 years	3	18.8
15–18 years	11	68.8
Median age at diagnosis, years	15.4 (range, 1.3–17.4)	
Sex		
Male	10	62.5
Female	6	37.5
Cancer predisposition		
MEN1	1	6.3
Pacak-Zhuang syndrome	1	6.3
Wolf-Hirschhorn syndrome	1	6.3
Unknown	2	12.5
No	11	68.8
Performance status at diagnosis		
Not impaired/mildly impaired	11	68.8
(Severely) impaired	2	12.5
Unknown	3	18.8
Presenting symptoms		
Abdominal/back pain	10	62.5
Weight loss	3	18.8
Palpable abdominal resistance	2	12.5
Vomiting	5	31.3
Diarrhea	2	12.5
Hematemesis	2	12.5
Melena/hematochezia	5	31.3
(Sub-)ileus	3	18.8
Other symptoms	6	37.5
No symptoms/incidental finding	4	25.0
Unknown	1	6.3
Functional/nonfunctional		
Gastrinoma	4	25.0
Nonfunctional	11	68.8
Unknown/unclear	1	6.3
Preoperative diagnostics (positive)		
Chest CT scans	2	12.5
Somatostatin receptor-based imaging	3	18.8
[^{111}In]In octreotide scintigraphy	2	12.5
[^{68}Ga]Ga-DOTATATE PET/CT	5	31.3
[^{18}F]F-FDG PET/CT	2	12.5

PET, positron emission tomography.

At the time of diagnosis, 9 patients (56.3%) had localized disease and five (31.3%) presented with distant metastases. All 5 patients with distant disease also had locoregional lymph node involvement. However, no cases of isolated lymph node metastases without distant spread were observed. Staging information was not available for two cases. The liver was the most frequent site of distant metastases (n = 3), followed by the

omentum majus (n = 2). Histopathological grading was available for 14 patients. Among these, seven tumors (43.8%) were classified as G1, six (37.5%) as G2, and one tumor (6.3%) as G3 NETs; no NECs were observed. The Ki-67 index was ≤10% in 10 patients (62.5%) and >10% in 1 patient, with missing data in five. Somatostatin receptor 2 (SSTR2) expression was detected by immunohistochemistry in 2/3 (67%) patients and confirmed functionally through imaging (e.g., 68Ga-DOTATATE positron emission tomography/CT) in 3/4 (75%) patients.

Treatment Modalities

Six patients (37.5%) underwent endoscopic tumor removal, while nine (56.3%) received surgical resection. Surgical procedures included (partial) gastric resection (n = 2), wedge resection (n = 1), resection of Meckel's diverticulum (n = 3), and small intestine or rectum resection (n = 3). In one of those patients, initial tumor removal was performed endoscopically (polypectomy), but due to residual disease this was followed by a surgical gastrectomy. Four of the 5 patients with distant metastases underwent surgery, all of which were performed with oncologic intent, including resection of the primary tumor and regional lymphadenectomy, where feasible. One patient was deemed inoperable at diagnosis.

Among the 10 patients with available resection outcome data, seven (70.0%) achieved complete (R0) resection, while three (30.0%) had residual microscopic (R1) disease. Two patients underwent subsequent surgical procedures for metastasectomies. In four cases, the resection margin status was not documented.

Medical therapy was administered in 2 patients (12.5%). One patient received a somatostatin analog (octreotide) in combination with [177Lu]Lu-DOTATATE PRRT. The other, who had an unresectable G3 colon NET, was treated with two cycles of FOLFOX chemotherapy.

Survival Outcomes and Subgroup Analysis

At a median follow-up of 30.1 months (range, 0–14.5 years), the estimated 3-year OS was 93.3% (95% CI: 81.5–100%), and the 3-year EFS was 73.3% (95% CI: 54.0–99.5%) (shown in Fig. 2). At last follow-up, 15 patients were alive and 1 patient had died due to progressive disease. Of the surviving patients, ten (66.7%) were in complete remission, two (13.3%) had stable disease, and one (6.7%) had progressive disease. Disease status was unknown for 2 patients (13.3%).

Kaplan-Meier subgroup analyses revealed significantly improved OS and EFS among patients with G1 tumors compared to those with G2 or G3 tumors (OS: p = 0.0025; EFS: p = 0.0023; shown in Fig. 3a,b). Patients who underwent surgical resection had better survival outcomes than those who did not (OS and EFS: p = 0.00018; shown in Fig. 3c,d). In addition, disease stage at diagnosis was significantly associated with EFS (localized vs. distant: p = 0.023) (shown in Fig. 3e,f).

No significant differences in OS were observed based on sex (p = 0.16), tumor location (p = 0.55), distant metastases (p = 0.21), or resection margin status (p = 1). EFS also did not differ significantly by sex (p = 0.41), tumor location (p = 0.67), and resection status (p = 0.59).

Subgroup analysis by tumor grade showed favorable outcomes in G1 NETs (n = 6), most commonly located in the stomach or Meckel's diverticulum. Four were treated endoscopically and two surgically; no patient received additional therapy. At last follow-up, 4 patients were in complete remission, one had a recurrence managed with polypectomy and stable disease, and one had unknown status. Among 6 patients with G2 tumors, four were gastric in origin; five underwent surgical resection (two with multiple surgeries), and one received octreotide plus PRRT. All were alive at last follow-up. The only patient with a G3 tumor was inoperable and died shortly after chemotherapy initiation.

Among patients with localized disease (n = 9), all underwent removal (five endoscopic, four surgical), with no adjuvant therapy. Six were in complete remission and two in stable disease; one had an event (tumor recurrence) but remained alive. In contrast, 5 patients had distant metastases at diagnosis. Four underwent surgery, and one was treated medically only. At last follow-up, four were alive – two in complete remission, one with progressive liver metastases, and one with unknown status.

Clinical Characteristics of the SEER Cohort

A total of 83 patients aged 0 to 20 years with histologically confirmed GI-NENs were identified in the SEER database including 15 patients (18.1%) with NECs. The majority of patients were male (n = 50; 60.2%). Age distribution was skewed toward adolescence, with 67 patients (80.7%) aged 15–19 years, followed by 12 patients (14.5%) aged 10–14 years, 3 patients (3.6%) aged 5–9 years, and 1 patient (1.2%) aged 0–4 years.

The most frequent tumor site was the rectum including the rectosigmoid junction (n = 38; 45.8%), followed by the stomach (n = 10; 12.0%), ileum (n = 9; 10.8%), (sigmoid) colon (n = 7; 8.4%), Meckel's diverticulum (n = 4; 4.8%), duodenum (n = 4; 4.8%), jejunum (n = 2; 2.4.%), and cecum (n = 2; 2.4.%). Additional sites

Table 2. Tumor characteristics in 16 MET patients with GI-NENs

Characteristics GI-NETs	German MET Registry	
	count	proportion, %
Tumor size, histologically		
Median, cm	2.0 (range, 0.3–11.2)	
Size ≤5 cm	6	37.5
Size >5 cm	1	6.3
Unknown	9	56.3
pT stage		
T1	5	31.3
T2	1	6.3
T3	2	12.5
T4	1	6.3
Tx	1	6.3
Unknown	6	37.5
c/pN stage		
N0	9	56.3
N1* (also M+)	5	31.3
Unknown	2	12.5
c/pM stage		
M0	9	56.3
M1	5	31.3
Unknown	2	12.5
R classification		
R0	6	46.2
R1/R2	4	30.8
Rx	1	7.8
Unknown	2	15.4
Grading		
Well-differentiated NET		
G1 (Ki-67 <3%, mitotic index <2)	7	43.8
G2 (Ki-67 3–20%, mitotic index 2–20)	6	37.5
G3 (Ki-67 >20%, mitotic index >20)	1	6.3
Poorly differentiated NEC		
High (Ki-67 >20%, mitotic index >20)	0	0
Unknown	2	12.5
Ki-67 index		
≤10%	10	62.5
>10%	1	6.3
Unknown	5	31.3

not other specified were the small intestine (n = 5; 6.0%) and gastrointestinal tract (n = 2; 2.4%) (shown in Fig. 1).

At the time of diagnosis, 56 patients (67.5%) had localized disease, 2 patients (2.4%) had regional spread, and 8 patients (9.6%) presented with distant metastases. In 17 cases (20.5%), staging information was not available or coded as unknown.

Surgical resection was recorded in 60 patients (72.3%), based on SEER-coded procedures involving partial or total tumor removal, in 2 patients (2.4%) surgical procedure not further specified was coded, and information was not available in 1 additional patient (1.2%). Twenty patients (24.1%) had no surgical intervention documented.

Tumor size was available in 49 patients (59.0%) with a median tumor size of 0.6 cm (range, 0.1–6.0 cm). Among these, only 1 patient was coded with tumor size >5.0 cm.

At last follow-up, 2 patients had died due to their disease. The estimated 3-year OS was 95.2%, calculated among all patients with available follow-up data.

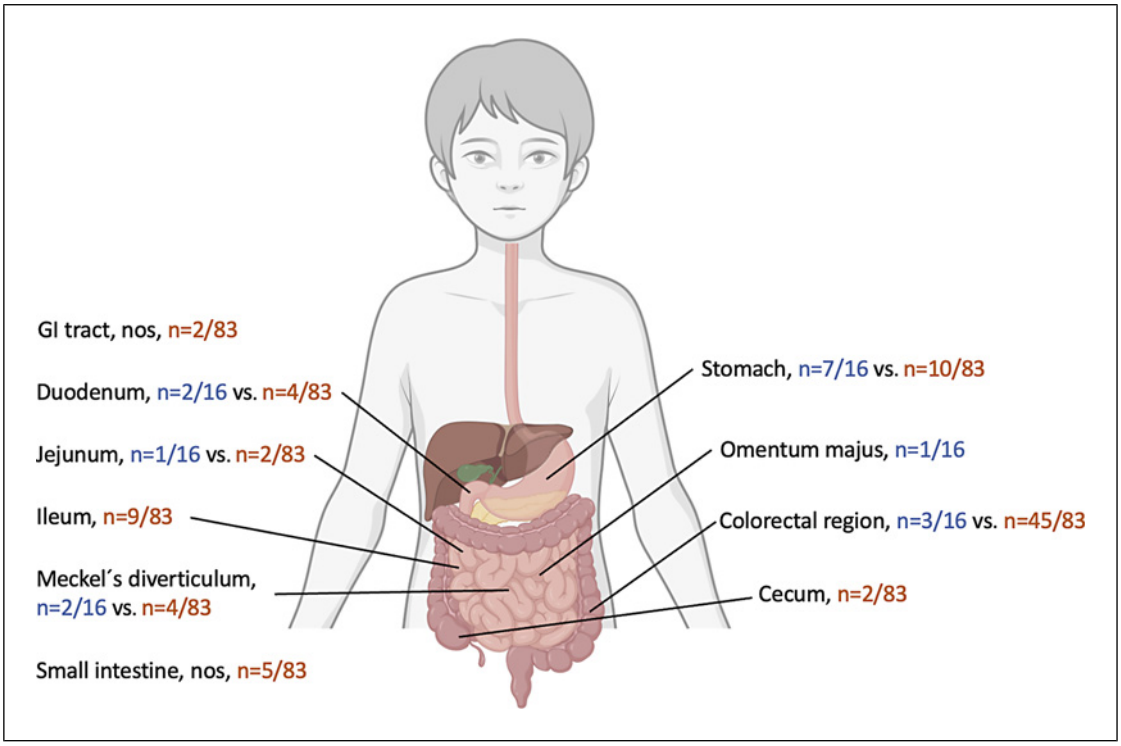


Fig. 1. Anatomical distribution of GI-NENs in 16 children and adolescents from the MET cohort (blue) and 83 children, adolescents, and young adults from the SEER cohort (red). Figure created using BioRender.

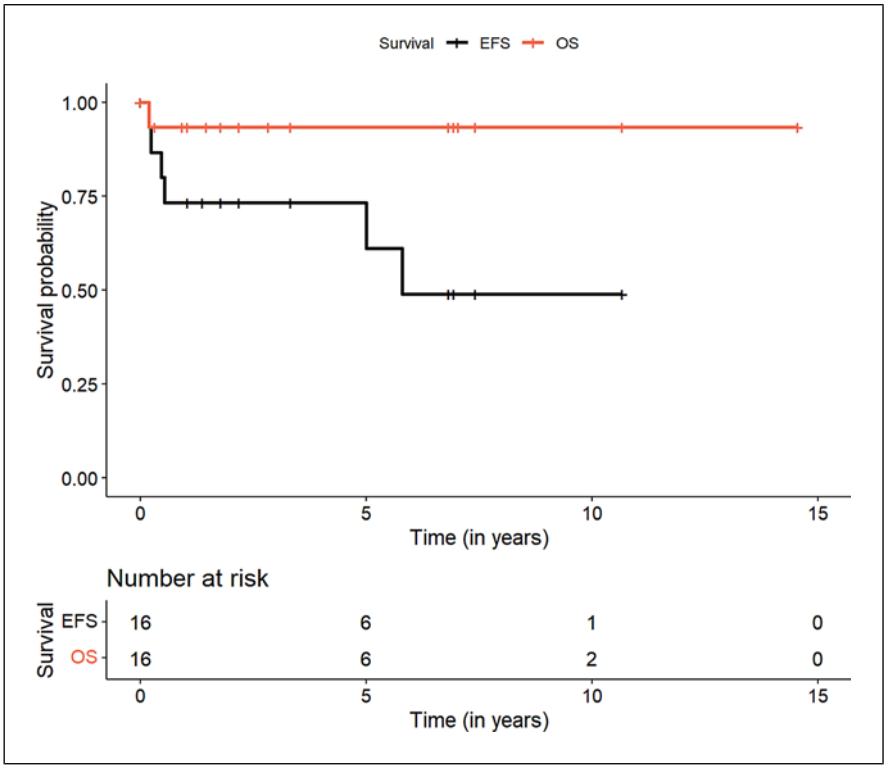
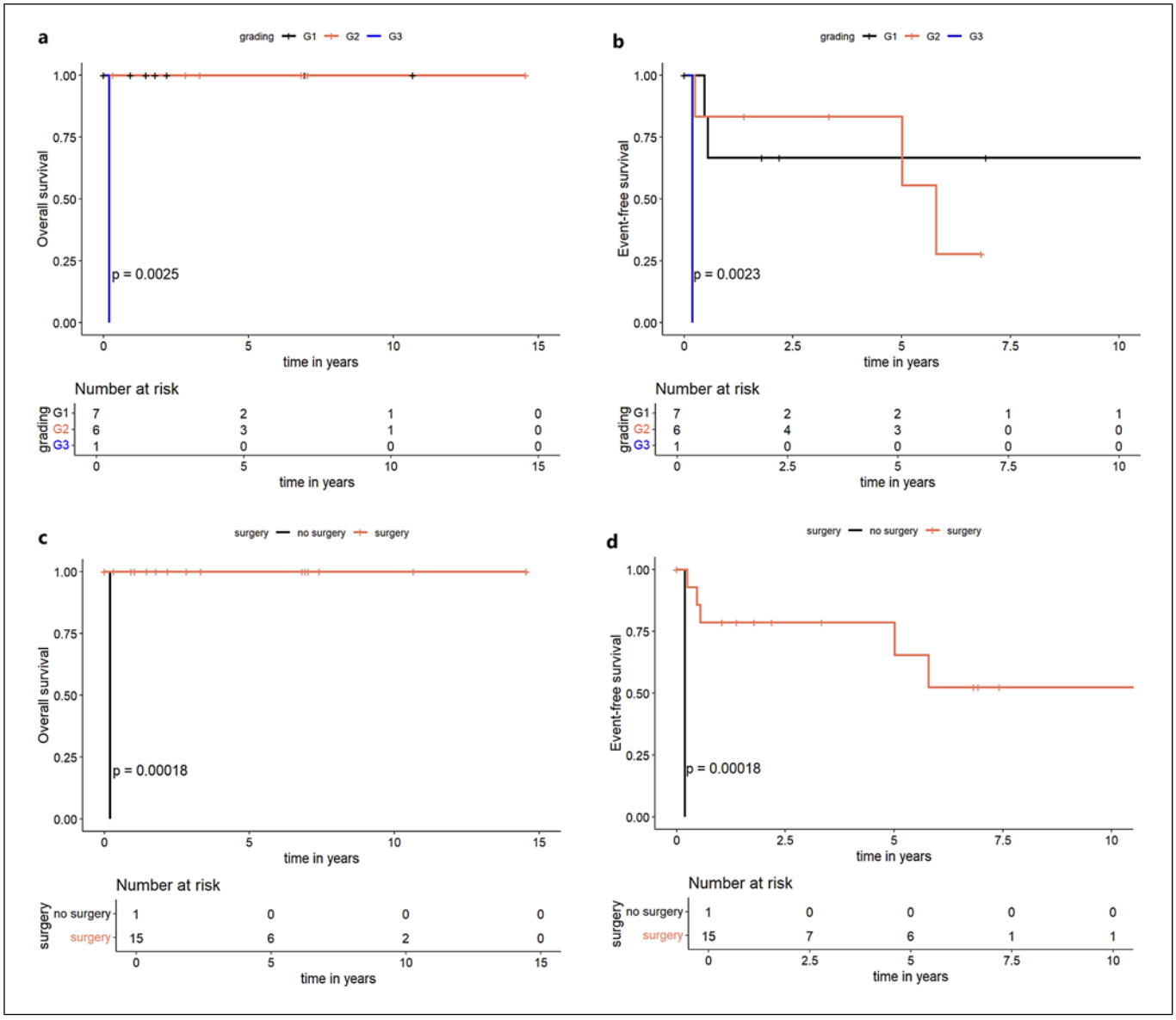


Fig. 2. Kaplan-Meier estimates for OS and EFS in 16 pediatric patients with GI-NENs.



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Comparison with the MET Cohort

A comparison between the MET and SEER cohorts is summarized in Table 3. The sex distribution did not differ significantly between cohorts (male: 62.5% MET vs. 60.2% SEER; $p = 1.0$). The MET cohort ($n = 16$) included a higher proportion of patients presenting with distant metastases (31.2% vs. 9.6%; $p = 0.03$), whereas the SEER cohort ($n = 66$) had a greater percentage of localized cases (67.5% vs. 56.2%; $p = 0.40$). Notably, in both cohorts regional lymph node involvement only was extremely rare (2.4% SEER, 0% MET). Surgical resection rates were comparable (81.2% MET vs. 72.3% SEER; $p = 0.55$). Three-year OS was similar between cohorts (93.3% MET vs. 95.2% SEER).

Discussion

This study presents the largest focused cohort to date of children and adolescents diagnosed with GI-NENs excluding tumors of the appendix and pancreas – two sites that dominate the pediatric NEN literature [4, 5, 16–18]. By focusing specifically on gastric, duodenal,

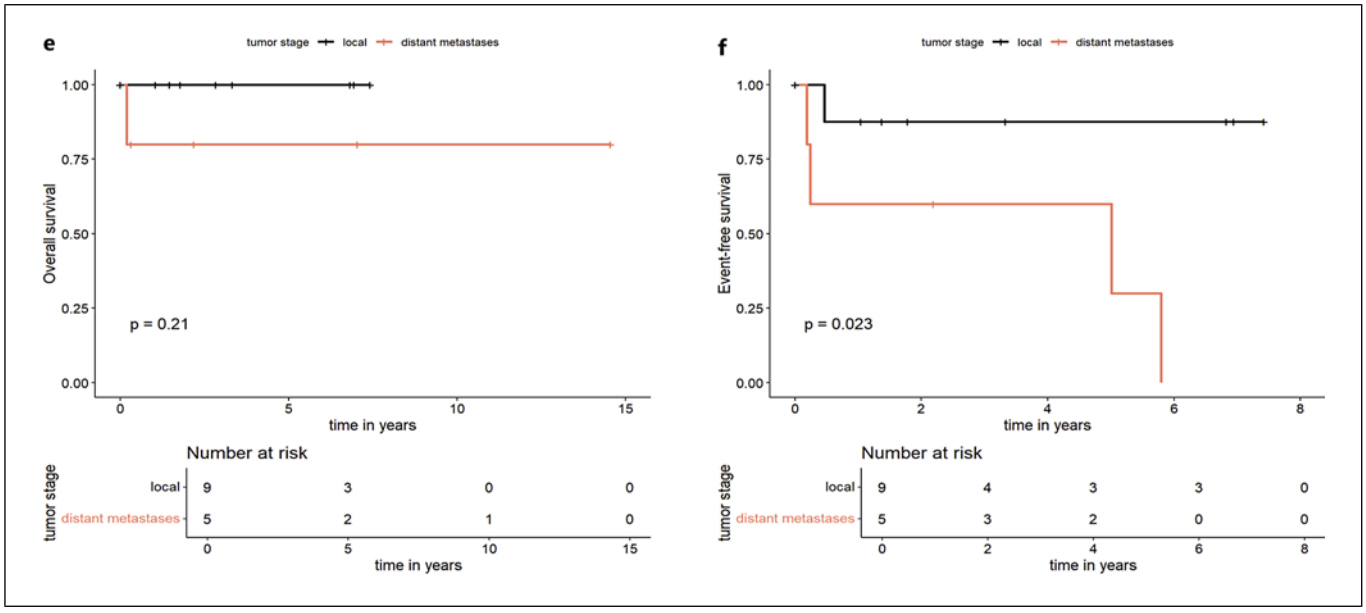

Fig. 3. Kaplan-Meier estimates for overall and EFS in pediatric patients with GI-NENs based on tumor grade (**a**, **b**) and surgical treatment (**c**, **d**) and disease stage (**e**, **f**). In **a**, the survival curves for G1 and G2 overlap at 100% due to the absence of deaths in both groups.

jejunal, colorectal, and Meckel's diverticulum primaries, we aligned our classification strategy with other major pediatric NEN collaborations such as TREP [19] and FRACTURE [20] enabling comparability across studies. While anatomical separation between pancreatic and duodenal NENs may seem artificial in some hereditary contexts (e.g., MEN1), this approach allows for a more precise analysis of clinical behavior in these rarer gastrointestinal subtypes. In our MET cohort, gastric and colorectal primaries predominated, with 31% of patients presenting with distant metastases – a markedly higher rate than seen in appendiceal NENs (<5%) but lower than the ~50% typically reported in adults [12, 21–29]. Importantly, all 5 patients with lymph node involvement also had distant metastases; no patient presented with isolated nodal disease. This could reflect true biological behavior or limitations in nodal sampling during initial surgery.

Tumor grading was heterogeneous, with 37.5% G1, 37.5% G2, and one G3 tumor. Notably, no NECs were observed. Surgical resection – achieved in over 80% of patients – was strongly associated with improved survival, reinforcing its importance as a primary treatment modality. At a median follow-up of 30.1 months, both 3-year OS (93.3%) and EFS (73.3%) were excellent, particularly in well-differentiated tumors. Survival outcomes were significantly associated with tumor grade, stage, and surgical intervention.

To contextualize our findings, we compared them with a population-based SEER cohort of 83 patients aged 0–20 years [15]. While SEER's broader age range introduces a minor discrepancy (as exact ages 18–20 could not be excluded), both cohorts showed a predominance of adolescents aged 15–19 years. SEER patients most commonly presented with rectal primaries (45.8%) and localized disease (67.5%), and only 9.6% had distant metastases. These differences may reflect registry inclusion criteria, healthcare system variations, but are more likely explained by differences in referral patterns, as MET patients were enrolled via tertiary centers.

Crucially, the SEER cohort included 15 patients (18.1%) with NEC histology, although NET G3 cases could not be distinguished due to coding limitations. This highlights the need for more granular, harmonized data collection across pediatric NEN registries. Several noteworthy findings emerged from our cohort.

- First, despite a relatively high rate of metastatic disease, outcomes were favorable following surgery, suggesting a less aggressive course compared to adult GI-NENs.
- Second, nearly one-third of patients had confirmed or suspected hereditary syndromes, underscoring the importance of routine genetic evaluation – though this figure may be underestimated due to variable testing practices and reporting constraints under the German Genetic Diagnostics Act (GenDG).

Table 3. Comparison of key characteristics between the MET and SEER cohorts

Characteristics	MET cohort	SEER cohort
Patients, *N*	16	83
Median age at diagnosis, years	15.4	n/a (age range 0–20)
Sex (male %)	62.5%	60.2%
Most common tumor site	Stomach (43.8%)	Rectum (45.8%)
Localized disease at diagnosis	56.3%	67.5%
Regional disease at diagnosis	0%	2.4%
Distant metastases at diagnosis Missing data	31.3% 12.4%	9.6% 20.5%
Surgery performed	81.3%	72.3%
Estimated 3-year OS	93.3%	95.2%

- Third, most patients were older adolescents (15–18 years), and no NECs were observed in this age group, suggesting possible age-related differences in tumor biology.
- Fourth, SSTR2 expression was seen in most evaluable tumors, consistent with adult patterns, and supports the potential utility of somatostatin analogs and PRRT even in pediatric cases.
- Finally, a slight male predominance (62.5%) was observed and may warrant further study in larger series.

Our study's strengths include a prospective, disease-specific registry with centralized pathology review, detailed clinical data, and long-term follow-up. Its main limitations are small cohort size and the retrospective nature of our registry data that cannot fully account for clinical decision-making or referral biases. The SEER comparison cohort, while large, lacks detailed clinical and treatment data, limiting interpretation of outcomes beyond survival.

Given the rarity and complexity of pediatric GI-NENs, close multidisciplinary tumor board evaluation should occur at each step, from diagnosis to treatment and surveillance. For patients with advanced disease, particularly those requiring systemic therapy or PRRT, structured referral to specialized expert centers is recommended. Furthermore, we actively foster cross-specialty collaboration between pediatric oncologists and adult NEN experts to enhance care quality and access to evolving therapeutic options.

Emerging evidence suggests that pediatric GI-NENs may differ biologically from their adult counterparts, particularly in hormone secretion, grade progression, and metastatic patterns [3, 17, 30]. While adult prognostic models incorporate tumor size, grade, and SSTR2 expression, their relevance in pediatric populations remains uncertain [31–33]. In our cohort, SSTR2 was expressed in most evaluable tumors – by immunohistochemistry or functional imaging – supporting its role in diagnosis and targeted therapy. Although PRRT has shown early promise in pediatric NENs [10, 34, 35], consistent treatment guidelines for its use in children are still lacking and should be prioritized in future research. Continued international collaboration and harmonized prospective registries are essential to advance evidence-based management for pediatric GI-NENs and to better understand the role of genetics, targeted therapies, and long-term outcomes in this understudied population.

Conclusion

Extra-appendiceal and extra-pancreatic pediatric GI-NENs are rare and may present with advanced disease. Optimal management requires a multidisciplinary approach, and given the extreme rarity of pediatric GI-NENs, structured collaboration with adult NEN specialists should be actively pursued. Shared tumor boards and cross-specialty referral networks may help optimize diagnosis, treatment planning, and access to targeted therapies. Prospective registries and collaborative research remain essential to refine risk stratification and develop evidence-based treatment strategies for children and adolescents with GI-NENs.

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Statement of Ethics

The study was performed in accordance with the Declaration of Helsinki and was approved by University of Luebeck (IRB 97125), Otto-von-Guericke-University Magdeburg (IRB 174/12 and 52/22), and institutional review boards of all participating centers. Written informed consent for the minors to participate in this study was obtained from all parents, guardians, or next of kin. This work was performed as part of the medical doctoral thesis of Katharina Karges.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization, funding acquisition, and resources: P.V., A.R., and M. Kuhlen; methodology: M.A. and M. Kuhlen; data curation: K.K., M. Kunstreich, J.F., C.L., A.R., and M. Kuhlen; investigation: M. Kunstreich, M.A., J.F., C.V., M.A., D.T.S., I.B.B., M.C.F., P.W., A.R., and M. Kuhlen; formal analysis, visualization, and writing – original draft: K.K. and M. Kuhlen; supervision: M. Kuhlen; project administration: M. Kunstreich, M.A., D.T.S., I.B.B., P.V., A.R., and M. Kuhlen; writing – review and editing: Ma.Ku., U.F.P., J.F., C.V., M.A., D.T.S., I.B.B., C.L., M.C.F., P.V., A.R., and M. Kuhlen.

Data Availability Statement

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

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