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Original Article

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ABSTRACT

Background: Neuroendocrine neoplasms of unknown primary (NEN-CUP) are rare in adults but remain virtually uncharacterized in children. The distinction between true CUP and undetected primaries is diagnostically and clinically significant yet poorly defined in children.

Methods: We retrospectively analysed patients aged <18 years with histologically confirmed NEN-CUP enrolled in the German Malignant Endocrine Tumour (MET) Registry between 1997 and 2024. All patients had metastatic disease with no identifiable primary despite comprehensive diagnostic work-up. Complementary population-level data were obtained from the SEER database using neuroendocrine histology and unknown primary topography codes.

Results: Eight paediatric NEN-CUP patients were identified in the MET Registry. The median age at diagnosis was 14.6 years (range, 12.2–18.6), and six were male. Presenting symptoms were non-specific and all tumours were non-functional. Somatostatin receptor imaging was positive in 5/7 cases. Tumour grading revealed five poorly differentiated NECs, two well-differentiated grade 2 NETs, and one grade 1 NET. Complete resection was not achieved in any patient. The 1-year and 2-year overall survival rates were 83.3% and 33.3%, respectively. The SEER analysis identified an additional 12 paediatric NEN-CUP cases over several decades, underscoring the extreme rarity of this disease entity.

Conclusions: Paediatric NEN-CUP is an exceptionally rare and clinically heterogenous group of tumours. Diagnostic ambiguity persists despite modern imaging and pathology. Our findings suggest both truly occult primaries and rare, under-recognized sites may contribute to this phenotype. Paediatric-specific diagnostic criteria and collaborative frameworks are urgently needed to better define and manage children and adolescents with NEN-CUP.

INTRODUCTION

Cancer of unknown primary (CUP) is defined as a metastatic malignancy in which the site of origin remains unidentified despite comprehensive clinical, imaging, and pathological evaluation. [1-3] In adults, CUP accounts for approximately 3–5% of all cancers and is generally associated with a poor prognosis. [2] Adult CUP is categorized into favourable (15−20%) and unfavourable (80−85%) prognostic subsets, primarily based on performance status and LDH level. Notably, favourable subsets include neuroendocrine carcinoma (NEC) of unknown primary. Recently, new site-specific subsets−colorectal, lung, and renal CUP−have been recognized, which may allow more targeted management approaches. [4] In contrast, CUP is exceedingly rare in children and adolescents, and data on incidence, clinicopathological features, and outcomes remain sparse. [5,6]Among the histologic subtypes of CUP, neuroendocrine neoplasms (NENs) of unknown primary (NEN-CUP) represent a distinct

clinical entity characterized by neuroendocrine differentiation and variable biological aggressiveness. In adult series, NEN-CUPs account for 9–22% of NEN and less than 5% of all CUP cases. [2,7,8] These tumours range from well-differentiated neuroendocrine tumours (G1-3 NETs) to poorly differentiated neuroendocrine carcinomas (G3 NECs), with tumour grade playing a key role in prognosis and therapeutic decision-making. [9,10]

Well-differentiated NEN-CUPs, especially those with somatostatin receptor (SSTR) expression and low proliferative indices, often demonstrate an indolent course with median overall survival extending beyond 5 years. [10,11] In contrast, poorly differentiated NECs are highly aggressive, typically associated with median survival below one year despite intensive chemotherapy. [10,12] Diagnostic advances such as ^{68}Gallium-labeled SSTR-directed positron emission tomography/computed tomography (^{68}Ga-PET/CT), have improved detection of occult primaries, though a significant subset of patients remains classified as NEN-CUP despite extensive work-up. [3,9]

In paediatric populations, NENs are themselves rare, accounting for less than 2% of all malignancies in children and adolescents. [13,14] The most frequent primary sites include the appendix and respiratory tract, with most paediatric NENs being well-differentiated and associated with favourable outcomes when diagnosed at localized stages. [15] However, systematic data on metastatic NENs – particularly those without an identifiable primary site – are exceptionally limited, and no paediatric-specific definition for NEN-CUP currently exists.

Moreover, the extent to which adult-based definitions of NEN-CUP apply to paediatric cases remains unclear. In adults, NEN-CUPs are thought to most commonly originate from small, clinically occult primaries in the gastrointestinal tract, especially the small intestine or pancreas. [10,16] Whether a similar pattern holds true in children is unknown due to the extreme rarity of cases and the absence of standardized diagnostic frameworks.

An additional diagnostic challenge arises in cases with hepatic involvement. While the liver is a common site of metastasis for NENs, primary hepatic NENs are extraordinarily rare in children, accounting for fewer than 0.5% of all paediatric liver tumours. [17] Imaging and histopathology are typically insufficient to definitively distinguish between primary and metastatic liver lesions, complicating the classification of such cases. This uncertainty is particularly relevant in paediatric patients presenting with isolated or predominant hepatic disease and no detectable extrahepatic primary.

Finally, the biological behaviour, genetic landscape, and treatment responsiveness of paediatric NENs may differ significantly from their adult counterparts, limiting the applicability of adult-derived data and treatment strategies.

In the present study, we aim to systematically characterize the clinical presentation, pathological features, treatment modalities, and outcomes of children and adolescents diagnosed with NEN-CUP over a 27-year period. We additionally use data from a large population-based registry to contextualize the metastatic patterns observed in our cohort and

explore the diagnostic relevance of rare anatomical sites that may mimic or represent occult primary NENs outside the pancreas and gastrointestinal tract in paediatric patients.

METHODS

We retrospectively analysed data from two independent sources: the German Malignant Endocrine Tumour (MET) Registry and the Surveillance, Epidemiology, and End Results (SEER) database of the U.S. National Cancer Institute.

MET Registry Cohort

The German MET Registry is a prospective national database established to systematically document the clinical, pathological, and therapeutic characteristics of paediatric patients diagnosed with endocrine and neuroendocrine tumours. For this study, we included all patients aged 0 to 18 years at the time of diagnosis who were registered between January 1, 1997, and June 30, 2024, with a histologically confirmed diagnosis of a NEN and no clearly identifiable primary tumour site. Cases were classified as CUP when the primary tumour remained undetectable following comprehensive diagnostic evaluation, including clinical examination, imaging, and pathological assessment, as per standards applicable at the time of diagnosis. Patients with metastatic NENs in whom a primary tumour site was identified – either at initial presentation or during follow-up – were excluded from the analysis. Tumour grading was performed according to the World Health Organization classification system in use at the time of diagnosis.

Variables extracted from the MET Registry included patient demographics, presenting symptoms, imaging modalities employed during staging, histopathologic features, treatment strategies, disease extent at presentation, and clinical outcomes. Follow-up data were up to date as of August 31, 2024. The MET Registry and this study were conducted in accordance with the Declaration of Helsinki and received approval from the ethics committees of the University of Lübeck (IRB 97125), the Otto-von-Guericke University Magdeburg (IRB 174/12 and 52/22), and respective institutional review boards of all participating centres. Written informed consent for data collection and analysis was obtained from all patients or their legal guardians.

SEER Database Cohort

To complement the MET cohort and provide additional epidemiological context, we queried the SEER database for paediatric cases meeting analogous criteria. The SEER Program collects population-based cancer incidence and survival data from registries covering approximately 50% of the U.S. population. [18]

We identified all patients under the age of 20 years at the time of diagnosis who had histologically confirmed NENs and no reported primary tumour site, restricting the search to topography code C80.9 (unknown primary site) and to relevant ICD-O-3 histology codes

8240/3 (carcinoid tumour, not otherwise specified (NOS)), 8241/3 (enterochromaffin cell carcinoid), 8242/3 (enterochromaffin-like cell tumour), and 8246/3 (neuroendocrine carcinoma, NOS).

Of note, in SEER, age is captured in predefined age groups rather than exact age, with the upper adolescent category including patients aged 15–19 years, explaining the minor discrepancy in age limits compared to the MET cohort.

In a second step, we reviewed patterns of metastatic spread to assess the frequency of involvement of anatomical sites that are rare but possible primary origins in paediatric NEN, including the liver (C22.0), gonads (ovary or testis; C56.9 or C62.9), kidneys (C64.9), and adrenals (C74.9). This exploratory analysis was intended to support interpretation of tumour dissemination rather than to infer definitive primary sites. For the exploratory analysis, we included only patients with distant-stage disease, excluding those with tumours confined to the primary site or regional lymph nodes, to maintain comparability with the disseminated nature of CUP presentations.

The SEER dataset was current until December 31, 2022.

Data Analysis

Descriptive statistics were used to summarize patient demographics, clinical characteristics, diagnostic findings, treatment modalities, and outcomes. Categorical variables are reported as absolute counts and percentages, while continuous variables are presented as medians with ranges, where appropriate.

Given the limited cohort size, formal statistical comparisons were not planned. For illustrative purposes, overall survival (OS) and event-free survival (EFS) was estimated using the Kaplan–Meier method. OS was defined as the time from diagnosis to death from any cause or last follow-up. EFS was defined as the time from diagnosis to the first occurrence of disease progression, relapse, or death. Due to the small sample size, hypothesis testing was not applied.

For the SEER cohort, only OS data were available; information on disease progression, relapse, or event-free survival was not captured in the dataset.

All statistical analyses were conducted using R statistical software.

RESULTS

MET Cohort

A total of eight paediatric and adolescent patients (6 males, 2 females) with histologically confirmed NENs of unknown primary origin were identified. The median age at diagnosis was 14.6 years (range, 12.2–18.6 years). An overview of tumour site involvement by patient is shown in Figure 1.

At the time of diagnosis, clinical performance status was markedly reduced in three patients. Presenting symptoms included tumour-related pain (n = 3), weight loss (n = 2), fatigue (n = 2), a palpable mass (n = 2), and nausea with vomiting (n = 1). Additional or unspecified symptoms

were documented in six patients. In one patient, the tumour was detected incidentally during hepatic surgery for traumatic liver rupture and subsequently identified through histopathological examination. No cases exhibited clinical or biochemical evidence of functional hormone secretion.

Initial suspicion of a malignancy was raised through ultrasound (n = 3), magnetic resonance imaging (MRI; n = 3), and plain radiography (n = 1).

Functional somatostatin receptor imaging was performed in seven patients and yielded positive results in five. In both patients with negative SSTR imaging, ^{18}F-FDG PET scans were subsequently performed and demonstrated metabolic activity; both patients were subsequently classified as having G3 NEC based on histopathological findings.

Tumour grading revealed five patients with poorly differentiated grade 3 NECs, two with well-differentiated grade 2 NETs, and one with a grade 1 NET. Immunohistochemical staining for somatostatin receptor subtype 2 was performed in three cases and was positive in all three, including one patient who had negative findings on SSTR imaging.

One patient underwent ovariectomy with pulmonary and cerebral metastasectomy; another underwent hepatic segmentectomy for traumatic rupture with incidental discovery of NEN, followed by revision segmentectomy for incomplete resection. No other patients received definitive surgical therapy, as all remaining tumours were deemed not resectable at presentation due to widespread metastatic diseaseSeven patients were treated with cytotoxic chemotherapy, using a variety of regimens including FOLFIRI, GEMOX, PEI, MI/MII, VIDE, and high-dose chemotherapy with autologous stem cell support. Two patients received somatostatin analogues (octreotide), and one patient with a grade 2 NET was treated with the mTOR inhibitor everolimus, temozolomide, and three cycles of peptide receptor radionuclide therapy.

Additional treatments included external beam radiotherapy for brain or bone metastases in four patients.

Outcomes were poor across the cohort: six patients experienced progressive disease and ultimately died of disease, with a median time to death of 1.6 years (range, 0.8–3.1 years). One patient with a low-grade NET was lost to follow-up shortly after diagnosis. Another patient with a grade 1 NET was alive with stable disease at last contact (0.1 years from diagnosis). Treatment details are summarized in Table 1.

The 1- and 2-year EFS rates were 50.0% and 33.3%, respectively, and the corresponding OS rates were 83.3% and 33.3% (Figure 2).

Given the rarity of paediatric NEN-CUP and the diverse metastatic patterns observed in our MET cohort—including frequent involvement of the liver, gonads, and kidney—we sought to contextualize these findings within a broader population-based dataset. We therefore performed a two-step analysis of the SEER database: first identifying paediatric patients with NEN-CUP (unknown primary site) and then exploring the distribution and outcomes of

paediatric NENs arising from anatomical sites that may represent potential but rarely confirmed primary locations.

SEER Cohort

A total of 12 paediatric and adolescent patients with histologically confirmed NENs and unknown primary site (topography code C80.9) were identified in the SEER database.

The majority were adolescents, with the following age distribution: 10–14 years (n = 1) and 15–19 years (n = 11). Eight patients were male and four were female. The most frequent histologic subtype was neuroendocrine carcinoma, NOS (ICD-O-3 code 8246/3), accounting for 10 of 12 cases, while the remaining two cases were classified as carcinoid tumour, NOS (8240/3).

Surgical intervention was documented in four patients, and chemotherapy was administered in five. Radiation therapy was not reported for any case.

At last follow-up, five of the 12 patients were alive. Among the seven patients who had died, six had died of cancer-related causes, while one was attributed to other causes. The median survival time from diagnosis was 2.5 years.

In a refined exploratory analysis restricted to paediatric patients with distant-stage disease, three cases of NENs were identified in the SEER database with topography codes corresponding to potential but rare primary sites. These included two patients with adrenal gland tumours (C74.9) and one with a kidney tumour (C64.9). All three were male and had histologically confirmed neuroendocrine carcinoma, NOS (ICD-O-3 code 8246/3). Two were adolescents (15–19 years), while one was diagnosed in the neonatal period. At the time of last follow-up, two patients had died of cancer-related causes, and one with a kidney NEC was alive 10 years after diagnosis. No patients with distant-stage disease were identified in the liver (C22.0), ovary (C56.9), or testis (C62.9).

DISCUSSION

In this multisite, registry-based retrospective study, we identified and characterized a cohort of children and adolescents with NEN-CUP, a diagnostic entity that remains virtually undescribed in the paediatric population. Over a 27-year period, only eight such patients were identified in the German MET Registry. This group is clearly distinct from previously reported MET cohorts with confirmed primary sites, including those with bronchial carcinoid tumours, [19] pancreatic NENs, [20] and gastrointestinal NENs. Here, all patients presented with disseminated neuroendocrine disease for which no primary site could be determined, despite comprehensive clinical, imaging, and pathological evaluation. CUP accounts for 3–5% of all malignancies in adults. From a biomarker perspective, approximately 28 % of adult CUP patients exhibit at least one predictive biomarker for immune checkpoint inhibitor (ICI) therapy. PD-L1 expression is seen in ≥5 % of tumour cells in ~22 % of cases and in ≥1 % in ~34 %, while tumour-infiltrating lymphocytes show ≥5 % PD-L1 positivity in ~59 %. Microsatellite instability-high (MSI-H) is

present in ~1.5 % of cases, and a tumour mutational burden (TMB) ≥17 mutations/Mb in ~12 %. Patients with TMB >10 mutations/Mb may have a benefit from ICI therapy, although these biomarkers are not yet validated for routine clinical decision-making in CUP. [21]

In contrast, CUP is exceedingly rare in paediatric oncology, with published estimates suggesting an annual incidence of approximately 0.4 cases per million adolescents and young adults. [5,6] Within this already rare group, NEN-CUPs appear to be vanishingly uncommon. To our knowledge, no paediatric-specific classification system on CUP, let alone NEN-CUP, exists. [9] NENs themselves constitute fewer than 2% of all childhood cancers and disseminated NENs without a detectable primary are so rare that they are often reported only anecdotally. [6,13,15,22] Thus, our study provides a foundational dataset for this uncharacterized and under-recognized clinical entity.

The MET cohort demonstrated notable clinical heterogeneity. Presenting symptoms ranged from nonspecific systemic complaints such as fatigue and weight loss to incidental findings. All tumours were non-functional, and no primary tumour site could be identified despite advanced diagnostic approaches including SSTR imaging, FDG-PET, and extensive histopathological work-up. Tumour grading ranged from well-differentiated NETs to poorly differentiated NECs, reflecting biological diversity. Notably, SSTR expression was not universally concordant between imaging and immunohistochemistry. In one patient, SSTR immunohistochemistry was positive despite negative SSTR-directed imaging; the reason remains unclear, as lesion size (4-4.5 cm) suggests volume alone does not explain the discordance. [23,24]To contextualize our findings, we analysed data from the SEER database. Using strict inclusion criteria, only 12 paediatric patients were identified with NEN-CUP, reinforcing the extreme rarity of this diagnosis at the population level. Age and outcome distributions in the SEER cohort mirrored our findings, with some patients surviving beyond one year, suggesting that, unlike adult NEN-CUPs—where poorly differentiated disease predominates—some paediatric cases may follow a more indolent course. Nevertheless, the possibility remains that some cases classified as NEN-CUP may harbour a small, clinically occult primary tumour. In adult NEN-CUPs, primaries are most often presumed to originate from the gastrointestinal or pancreaticobiliary tract—sites that may elude detection even with advanced imaging. [10,16] Whether this applies to children is unknown. To explore this, we conducted a secondary SEER analysis focused on paediatric NENs with distant-stage disease arising from anatomical sites that may rarely serve as primary origins, including the liver, kidney, adrenal gland, and gonads. Only three cases met these criteria, involving the adrenal gland (n = 2) and kidney (n = 1), all with NEC histology. Notably, no cases with distant-stage NENs of hepatic, ovarian, or testicular origin were found. These findings align with prior registry-based analyses, where liver and gonadal NENs accounted for only a handful of paediatric cases over multiple decades. [14,25,26] This observation is consistent with recent literature. The Italian TREP project reported only 13 cases of paediatric extra-appendiceal NENs across 12 centres over 20 years, with just two involving the liver. [26] Similarly, a combined analysis of the French National Registry of Childhood Cancers (RNCE)

and the paediatric very rare tumours PRAETURE database identified only isolated cases of pancreatic NENs with atypical metastatic patterns. [25] While primary hepatic NENs have been described in children, they represent fewer than 0.5% of paediatric liver tumours and remain diagnostically indistinguishable from hepatic metastases based on imaging or histology alone. [17] These findings suggest that in most paediatric cases, hepatic or pelvic involvement likely reflects metastatic spread rather than a primary origin. [27]

Taken together, these data suggest that the paediatric NEN-CUP population may comprise both cases with truly occult primary tumours and others involving atypical primary sites not detected by imaging. This ambiguity highlights the need to broaden differential diagnostic considerations in paediatric NENs presenting with disseminated disease, particularly when conventional work-up fails to reveal a primary origin. The most recent ESMO Clinical Practice Guideline provides key recommendations for managing CUP in adults, and a recent review further summarizes contemporary approaches. [28,29] In addition, to support clinicians, we propose a diagnostic and management algorithm for paediatric NEN-CUP, summarizing key steps from initial presentation to therapeutic considerations. (Figure 3) Notably, all stages of work-up should not be mandated before initiating therapy, as this could delay timely treatment initiation, particularly in cases of poorly differentiated tumours. One challenge in CUPs is determining when to stop searching for a primary tumour and proceed with therapy. This critical balance—between thorough diagnostic work-up and avoiding undue delay in treatment—requires careful multidisciplinary discussion and individualised clinical judgement.

Despite the insights gained, our findings must be interpreted with caution. The total number of cases remains extremely small, even when combining MET and SEER cohorts, which limits the generalizability of our conclusions and precludes meaningful statistical analysis. Moreover, the absence of molecular profiling or next-generation imaging in many patients restricts our ability to explore biologic drivers, molecular signatures, or specific patterns of metastatic spread that might inform origin or therapeutic susceptibility. [3,9,16] Although a substantial proportion of patients in the MET cohort had poorly differentiated tumours suggestive of aggressive behaviour, well-differentiated NETs with low proliferation indices were also observed, reinforcing the biological heterogeneity of paediatric NEN-CUP.

This raises a fundamental and unresolved question: do these patients truly harbour cancers of unknown primary, or are their primaries simply undetectable by current diagnostic modalities? In the era of targeted therapies, accurate histopathological and molecular classification is crucial to enable tailored treatment strategies. Epigenetic classifications have contributed to this effort, as CUP tumours frequently exhibit substantial global DNA hypomethylation (20–60% reduction in 5-methylcytosine) alongside promoter CpG island hypermethylation, both of which can alter gene expression and drive cancer progression. [30] While this distinction may seem a semantic distinction, it has important implications for classification, treatment strategy, and long-term outcomes. With future advances in molecular diagnostics, functional imaging,

and tumour profiling, it is conceivable that a subset of these cases could eventually be reclassified, allowing for more targeted interventions. [31]

However, current CUP trials comparing site-specific therapies and empiric chemotherapy face significant limitations, including patient accrual challenges, long recruitment periods, and study design shortcomings. The heterogeneity of molecular classifiers (e.g., epigenetic versus transcriptomic profiling) and the variability of therapies further complicate interpretation. Recent analyses have proposed visionary and pragmatic trial frameworks to address these gaps and improve outcomes. [32]

CONCLUSION

Paediatric NEN-CUP is an exceptionally rare and poorly understood entity. This study provides the first systematic characterization of these patients, drawing on both registry-based and population-level data. Our findings underscore the diagnostic and biological heterogeneity of this group and highlight the urgent need for international collaboration to develop paediatric-specific definitions, diagnostic algorithms, and therapeutic frameworks for managing NEN-CUP in children and adolescents.

DECLARATION OF INTERESTS:

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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Legends

Figure 1. Tumour site involvement per patient with neuroendocrine cancer of unknown primary (n = 8). The matrix displays the presence (grey cell) or absence (white cell) of tumour involvement at specific anatomical sites for each patient. Each row represents an individual patient (Patient 1–8), and each column corresponds to an anatomical site.

Figure 2. Kaplan–Meier estimates of and overall survival (OS) and event-free survival (EFS) in paediatric patients with NEN-CUPs registered in the German MET Registry.

Figure 3. Proposed diagnostic and management algorithm for pediatric neuroendocrine neoplasms of unknown primary (NEN-CUP). The flowchart outlines key steps in the diagnostic work-up and treatment planning, including imaging, histopathological assessment, functional imaging, and multidisciplinary discussion.

* *Note:* All stages of work-up outlined in the algorithm should not be mandated before initiating therapy, particularly in poorly differentiated tumours, where prompt treatment is critical. The decision to conclude the diagnostic search and commence therapy should be guided by multidisciplinary discussion and individual clinical judgement to avoid unnecessary delays.

Table 1. Details on systemic therapies in paediatric patients with NEN-CUPs registered in the German MET Registry

Table 1. Details on systemic therapies in pediatric patients with NEN-CUPs registered in the German MET Registry

Patient	Age at diagnosis	Sex	Grading	SSTR-based imaging/ SSTR IHC	Surgical therapies	Systemic therapy	Other therapy	Outcome
1	18.6	F	G3 NEC	- / not done ^{18}F-FDG +	Ovarectomy, Pulmonary and cerebral metastasectomy	1x PEI 7x MI/ MII High-dose chemotherapy with autologous stem cell support	EBRT for bone metastases	CR achieved following initial treatment Event occurred with DOD 3.1 years from initial diagnosis
2	17.9	F	G3 NEC	+ / +	-	12x FOLFIRI Octreotide GEMOX Gemcitabine	EBRT for brain metastases	PR initially, followed by PD; DOD at 1.6 years from diagnosis
3	12.2	M	G2 NET	+ / not done	Hepatic segmentectomy; Re-segmentectomy*	-	-	FU duration: 0.3 years without CR; patient lost to follow-up
4	13.7	M	G3 NEC	Not done	-	6x Gemcitabine/ oxaliplatin/ irinotecan 2x cycles soft tissue sarcoma chemotherapy High-dose chemotherapy with autologous stem cell support	EBRT for brain metastases	DOD at 1.5 years from diagnosis
5	16.4	M	G3 NEC	+ / not done	-	6x MI/ MII	-	PR initially, followed by PD; DOD at 1 year from diagnosis
6	17.4	M	G3 NEC	- / + ^{18}F-FDG +	-	6x VIDE	EBRT for bone metastases	PR initially, followed by PD; DOD at 0.8 years from diagnosis
7	13.6	M	G1 NET	+ / not done	-	Octreotide	-	SD at 0.1 years from diagnosis

Table 1. Details on systemic therapies in pediatric patients with NEN-CUPs registered in the German MET Registry

8	14.6	M	G2 NET	+ / +	-	2x Cisplatin/ etoposide Everolimus/ temozolomide	3x PRRT (21.6 GBq)	PD with DOD at 2.8 years from diagnosis

Legend: CR, complete remission; DOD, death of disease; f, female; EBRT, external beam radiation therapy; FOLFIRI, irinotecan/ leucovorin/ 5-fluorouracil; FU, follow up; GBq, Gigabecquerel; GEMOX, gemcitabine/ oxaliplatin; m, male; IHC, immunohistochemistry; MI, vincristine 1.5 mg/m2 day 1+8, etoposide 100 mg/m2 day 1-4, cisplatin 40 mg/m2 day 1-4; MII, vindesine 3 mg/m2 day 1+8, dacarbazine 200 mg/m2 day 1-4, ifosfamide 1,500 mg/m2 day 1-4, doxorubicin 35 mg/m2 day 4+5; PD, progressive disease; PEI, cisplatin/ etoposide/ ifosfamide; PR, partial remission; PRRT, peptide receptor radionuclide therapy; SD, stable disease; VIDE, vincristine/ ifosfamide/ doxorubicin/ etoposide; *segmentectomy for traumatic hepatic rupture with incidental discovery of NET, followed by revision segmentectomy for incomplete excision

Initial Presentation

- Symptoms: pain, weight loss, fatigue, palpable mass, or incidental finding
- Detailed history and physical examination
- Performance status assessment

↓

Initial Laboratory Workup

- Full blood count, biochemistry, LDH
- Tumour markers: chromogranin A, NSE optional site-directed markers (e.g., AFP, β-HCG)

↓

First-line Imaging *

- Ultrasound (if applicable, e.g. abdominal mass)
- Cross-sectional imaging (CT or MRI of chest/abdomen/pelvis)
- SSTR imaging (68Ga-DOTATATE PET/CT or octreoscan)
- FDG-PET (especially if SSTR imaging negative or NEC suspected)

↓

Histopathological Confirmation *

- Biopsy of accessible lesion
- IHC panel: synaptophysin, chromogranin, INSM1
- Grading: Ki-67 index, mitotic count
- SSTR2 immunohistochemistry

↓

Molecular Profiling *

- Consider NGS panel, DNA methylation classifier, or transcriptomic profiling in challenging cases

↓

Multidisciplinary Tumour Board Discussion

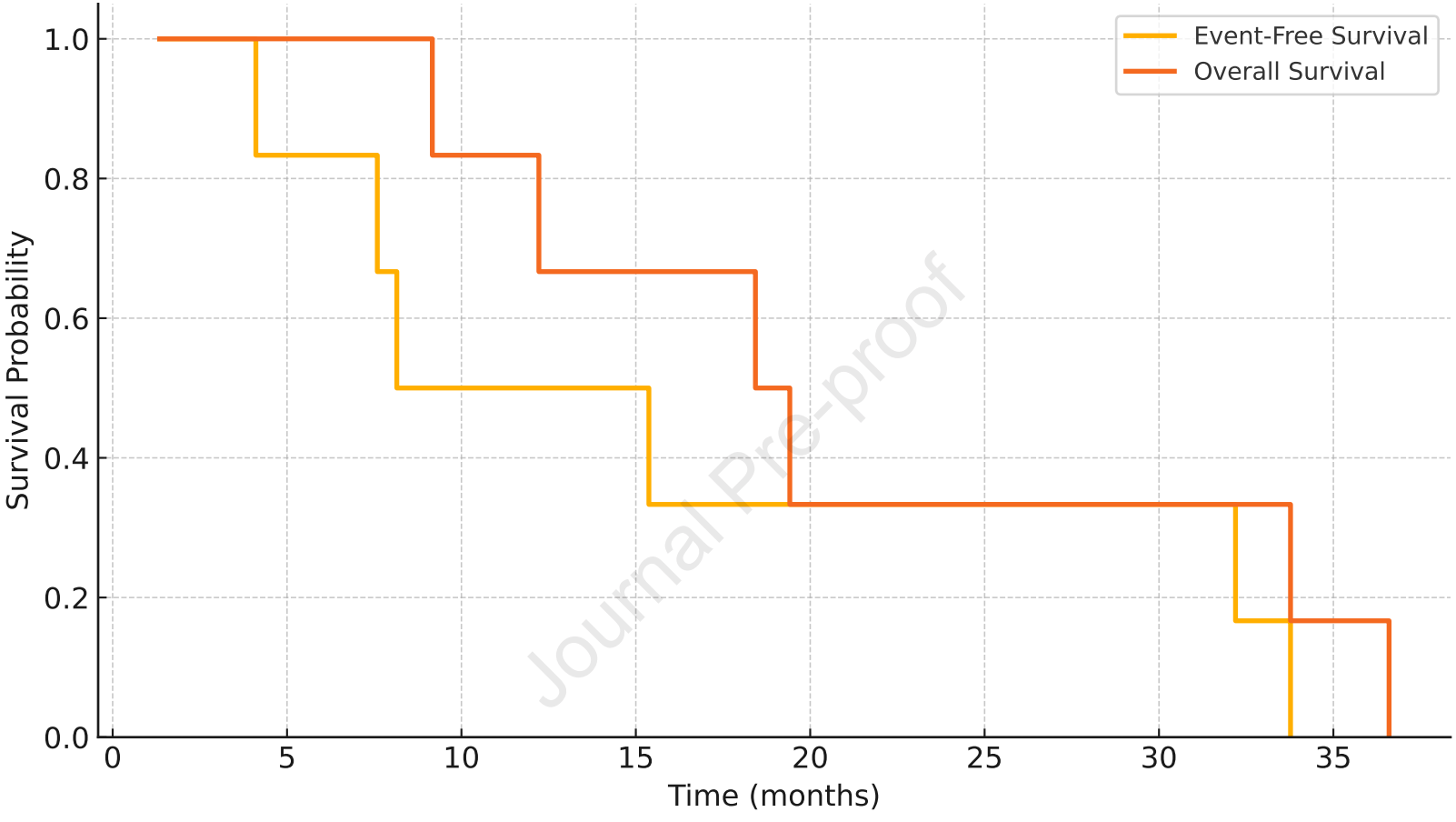
- Integration of all findings
- Evaluate surgical options (if resectable)
- Systemic therapy decision: somatostatin analogues, chemotherapy (grade-dependent)

↓

Follow-up / Reassessment

- Periodic imaging (SSTR PET/CT or CT/MRI)
- Clinical and lab monitoring

Patient	Liver	Lung	Kidney	Bone	Lymph Nodes	Soft Tissue	Ab-dominal	Ovary	Testis	Adrenal
1										
2										
3										
4										
5										
6										
7										
8										



Time (months)	0	12	24
EFS:	8	3	2
OS:	8	5	2

Highlights

- Eight paediatric NEN-CUP cases were identified in the German MET Registry
- Clinical presentation was heterogeneous; all tumours were non-functional
- Tumour grades ranged from well-differentiated NET to poorly differentiated NEC
- SEER data confirm the exceptional rarity of paediatric NEN-CUP (12 cases)
- True CUP and undetected rare primary sites both remain possible in children