Extra-appendicular neuroendocrine tumors: A report from the TREP project (2000-2020)

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Part of these data have been discussed as an oral presentation at the 48th Annual Congress of the International Society of Pediatric Oncology (SIOP) held in Kyoto, Japan in November 2019: "Extra-Appendicular Neuroendocrine Tumors: A Report from the TREP Project (2000-2018)," in *Pediatric Blood & Cancer* 65, S16-S17.

Abstract

Background: Extra-appendicular neuroendocrine tumors (NETs) are very rare tumors. While diagnostic and therapeutic guidelines are well established for adults, data on children and adolescents are lacking.

Patients and Methods: Patients with a diagnosis of extra-appendicular NET registered on the Tumori Rari in Età Pediatrica - Rare Tumors in Pediatric Age (TREP) from 2000 to 2020 were analyzed. Clinical characteristics including patients' presentation, tumor features, treatment, and outcome were reviewed.

Results: Twenty-seven patients with extra-appendicular NET registered on TREP with a median age of 173 months. The primary site was the pancreas (12) or bronchi (10) in the majority of cases. Other primary sites included the thymus, Meckel's diverticulum, and liver. Thirteen (48%) of tumors extended beyond the organ of origin: four invaded neighboring organs and/or regional nodes and nine involved distant metastases. The 3-year event-free survival (EFS) for those with localized disease was superior to those with metastatic disease (66.6% 95% CI 5-95% vs 33% 95% CI 5-68%, respectively; $P = .005$). A complete resection was feasible in 17 patients. The 3-year EFS in these patients was superior to those with no or incomplete resection (R0 vs R1/R2,

Abbreviations: AWD, alive with disease; CR, complete remission; CT, computed tomography; EFS, event-free survival; GEMOX, gemcitabine and oxaliplatin; MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumors; OLT, orthotopic liver transplantation; OS, overall survival; TACE, transcatheter arterial chemoembolization; TREP, Tumori Rari in Età Pediatrica; TS, tuberosus sclerosis

respectively; $P = .007$). Overall, 16 children had no evidence of disease at follow-up, and one is alive with disease; five died, and five were lost to follow-up.

Conclusions: Data from our experience demonstrated a wide heterogeneity of presentation and outcome of these tumors. Localized disease and complete surgical resection were the main prognostic factors of good outcome. Other therapies may have a role in prolonging survival in metastatic disease.

KEYWORDS

carcinoid tumors, children, extra-appendicular neuroendocrine tumors, neuroendocrine tumors, rare cancer

1 | INTRODUCTION

Extra-appendicular neuroendocrine tumors (NETs) are very rare tumors arising from the chromaffin cells, present in several sites and organs. They are slow-growing malignancies¹ included in the group of the so called “orphan diseases.” The current incidence in adults ranges from 3.24/100 000 in North Europe to 5.25/100 000 in the United States.² In children, the incidence is estimated to be around 0.5 cases per million/year.³

NETs are sporadic in most cases, but may also be part of a hereditary syndrome: pancreatic NETs are associated with tuberous sclerosis (TS), multiple endocrine neoplasia type 1 (MEN1), von Hippel Lindau syndrome, and neurofibromatosis type 1 (NF1); bronchial and thymic NETs with MEN1.^{4–6} Tumors of pancreas and bronchi are the most common, and, even if rare, they represent the majority of malignant tumors of these sites in childhood.^{3,7}

The recent 2010 classification for gastroenteropancreatic NETs introduced a grading system based on mitotic count and Ki67 proliferation index, recognizing three grades of malignancy: NET grade 1: $\leq 2\%$ well differentiated; NET grade 2: 3–20% moderately differentiated; and NET grade 3: $> 20\%$ neuroendocrine carcinoma. The importance of Ki67 labeling index is also crucial in differential diagnosis of lung carcinoids, which are classified into typical carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma, and small-cell neuroendocrine carcinoma.⁸

Diagnostic and therapeutic guidelines in adult patients are well standardized^{9–12}: the mainstay of treatment in localized tumors is the complete surgical resection,¹² but in case of locoregional invasiveness or distant metastasis, the treatment options are challenging^{14,15} because the response to conventional chemotherapy is poor. In metastatic patients, a partial improvement of overall survival (OS) has been observed with the use of somatostatin analogs and a multimodal approach.^{11,12} Data in children are lacking, and precise guidelines for diagnosis and treatment are not established.

In Italy, since 2000, all pediatric patients with extra-appendicular NET have been registered within the TREP project (Tumori Rari in Età Pediatrica - Rare Tumors in Pediatric Age), an Italian multi-institutional network on rare tumors in children and adolescents, launched under the auspices of the Italian Association of Pediatric

Oncology (AIEOP) and the Italian Society of Pediatric Surgery (SICP), with the aim of expanding our knowledge on epidemiology of very rare tumors, as well as identifying possible guidelines for their diagnosis and treatment.

This work describes the data obtained from all patients affected by extra-appendicular NETs, who entered the project, giving information on patients' presentation, tumor features, diagnostic and treatment modalities, and outcome.

2 | MATERIALS AND METHODS

The records of patients with extra-appendicular NET enrolled in the TREP project between January 2000 and June 2020 were reviewed. Inclusion criteria for enrollment were the diagnosis of a very rare solid tumor (incidence of less than two cases per million children/year), not included in other registries or protocols, and age at diagnosis of less than 18 years. Clinical presentation, diagnostic workup, treatment, outcome, and follow-up (FU) were obtained prospectively through special printed forms from the physicians in charge from 11 centers of pediatric oncology and pediatric surgery in Italy, and the records of all the cases were centrally reviewed for this analysis. All of the patients, or their guardians, gave informed consent for their involvement in the TREP study.

All data were analyzed using descriptive statistical methods. Survival time was calculated from the date of diagnosis to the time of the last FU or event. Events were defined as tumor progression, relapse after remission, or death from any cause. Both OS and event-free survival (EFS) were estimated using the Kaplan-Meier method. Survival curves with log-rank test were calculated by the Kaplan-Meier method: a P -value of $< .05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 26.

3 | RESULTS

Twenty-seven patients were enrolled into the TREP project from January 2000 to June 2020. Fourteen were males and 13 females (1:1)

with a mean age of 162 months (range 70-212, median 173). The primary sites were pancreas (12 cases), bronchi - main or lobar bronchus (10 cases), liver, Meckel diverticulum, and thymus (one each). In two patients with mediastinal and gastrointestinal tumors, the exact origin of the primary tumor could not be defined. Thirteen patients presented with a locally advanced and/or metastatic disease at diagnosis (six pancreas, three bronchi, one thymus, one liver, two undetermined primary). Resection was complete (R0) in 17 patients (eight pancreas, eight bronchi, and one Meckel's diverticulum); in one (pancreas) microscopic residuals (R1) were left and in three (two bronchi and one pancreas, all with metastases at diagnosis) a resection with macroscopic residuals (R2) was performed. All the remaining patients were deemed inoperable and received a biopsy only.

3.1 | Pancreatic NETs - 12 patients

The mean age at presentation was 170.5 months with a slight male predominance (7:5). The symptoms were mostly unspecific (pain and weight loss); less frequently they were due to tumor's secretion (diarrhea, hypoglycemia, and Zollinger-Ellison syndrome). Sometimes, the unusual presentation (due, for instance, to gastrin over secretion) determined a delay of diagnosis up to 60 months in one case (mean 2, median 8). Five patients presented a germline mutation: three were affected by TS, and two by MEN1 (Table 1).

At diagnosis, the disease was extending beyond the pancreas in six cases: in three to surrounding structures and/or regional nodes, in two distant metastases were present (liver), in one involvement of the aortocaval axis and a supraclavicular node metastasis were reported.

All patients underwent conventional imaging, and six additional functional imaging: ^{111}In -pentreotide scintigraphy (six), positron emission tomography/computed tomography (PET/CT) with ^{11}C -5-hydroxytryptophan (^{11}C -5-HTP) (one), bone scintiscan with Technetium $^{99\text{m}}$ (one).

Seven patients underwent an upfront surgery (two Traverso-Longmire pancreaticoduodenectomies, three spleno-pancreatectomies, one distal pancreatic resection, and one enucleation). An initial imaging-guided biopsy was performed in five patients: after obtaining the diagnosis, one underwent a Whipple procedure, two a distal pancreatectomy, and two patients could not be operated on due to the extension of the disease. In eight out of 10 cases, a complete resection of the primary was obtained. Three patients needed a further surgical procedure. One, with multiple liver metastases, received hepatic transcatheter arterial chemoembolization (TACE), before being treated with an orthotopic liver transplantation (OLT), and he is alive and well 64 months after diagnosis. Two patients underwent lung surgery to remove a suspicious nodule, which was negative at histology (Table 1).

The two patients, who did not receive surgery of the primary tumor, were treated, respectively, with somatostatin analogs only, and somatostatin analogs associated with conventional chemotherapy (ifosfamide, vincristine, and cisplatin as first-line, and carboplatin,

epidoxorubicin, and vincristine as second-line therapy), but they progressed and died 96 and 3 months after diagnosis. Two patients, after an initial complete resection of a poorly differentiated NET and a malignant islet cell tumor, received adjuvant therapy; the first with somatostatin analog only, and the second with six cycles of adriamycin, 5-fluorouracil, and streptozotocin, and both are in their first complete remission (CR) at 55 and 77 months from diagnosis. One patient with local relapse 15 months after a Whipple pancreaticoduodenectomy (R0) abandoned the study and was lost to FU.

Eight patients are alive without evidence of disease, one is alive with disease (AWD), one was lost to FU with disease, and two are deceased (mean FU 43.2 months; range 3-96).

3.2 | Bronchial NETs - 10 patients

The mean age at presentation was 166.5 months with a slight female predominance (6:4). Main symptoms were recurrent pneumonia, cough, and hemoptysis. The diagnostic delay, mostly seen in patients with recurrent pneumonias, reached a median value of 29.6 months (mean 15, range 0-132).

Two patients had tumors extending to surrounding structures and/or regional nodes, plus distant metastases to contralateral lung, bone marrow, skull base, and brain. One patient had a micrometastasis in a regional node. CT or magnetic resonance imaging scans were performed in all patients, an additional ^{111}In -pentreotide scintiscan in three.

Two patients received an upfront surgery (lobectomy), while eight underwent endoscopic biopsy of the lesion, which was diagnostic in seven: all had resection of the primary tumor (four lobectomies, two endoscopic tumorectomies, one pneumonectomy) without any neoadjuvant or adjuvant treatment. Resection was complete in all, except one with secondary lesion to the contralateral lung. Pathology reports, available in eight cases, showed a typical carcinoid tumor in seven and an undifferentiated carcinoma in one.

In one patient, a diagnosis of neuroblastoma was initially obtained, and a treatment with rapid COJEC (cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide) was started before the central pathology revision could confirm the diagnosis of undifferentiated NET. Later, he received a surgical debulking, followed by adjuvant chemotherapy (four cycles of epidoxorubicin, vincristine, carboplatin, and etoposide), external radiotherapy, four doses of vinorelbine, and autologous bone marrow transplant. Unfortunately, a metastatic liver relapse occurred 4 months later, and after further treatments with cisplatin and 5-fluorouracil, with no response, he was given a second-line therapy with gemcitabine and oxaliplatin (GEMOX) but, despite the good response, the patient died of infectious complications after the fifth cycle.

Eight patients are alive without evidence of disease, one was lost to FU with disease, and one died of toxicity (mean FU 55.2 months; range 6-168). Table 2 describes the clinical characteristics of these patients.

TABLE 1 Clinical features: Pancreatic NET

	Age (months)	Sex	Site	Symptoms	Diagnostic delay ^a (months)	Pathology	Stage	Treatment	Quality of resection	Outcome
1	209	F	Head-body	Incidental (screening for MEN1)	0	Well differentiated (glucagonoma)	L	Traverso-Longmire pancreaticoduodenectomy	R1	CR
2	84	M	Body	Abdominal pain, weightloss	7	Poorly differentiated	LR	Distal pancreatectomy; ChT	R0	CR
3	70	M	Tail	Incidental (screening for TS)	0	Malignant islet cell tumor	L	Distal pancreatectomy; ChT; resection of lung nodule ^b	R0	CR
4	186	M	Head	Unknown	0	Well differentiated	L	Traverso-Longmire pancreaticoduodenectomy	R0	CR
5	165	F	Head	Zollinger-Ellison syndrome	60	Well differentiated (gastrinoma)	M	CT-guided biopsy; ChT	R2	DOD
6	122	M	Body-tail	Incidental (screening for TS)	2	Well differentiated	L	Distal pancreatectomy	R0	CR ^c
7	184	M	Body-tail	Abdominal pain, diarrhea, vomit	10	Well differentiated (gastrinoma)	M	US-guided biopsy; distal pancreatectomy; TACE; OLT	R2	CR
8	174	M	Tail	Abdominal and shoulder pain	4	Well differentiated	M	Distal pancreatectomy; resection of lung nodule ^b	R0	CR
9	120	F	Head	Abdominal pain, vomit	0	Well differentiated	LR	EUS-FNA; Whipple pancreaticoduodenectomy	R0	AWD ^c
10	180	F	Head	Abdominal pain, weightloss	8	Poorly differentiated	LR	CT-guided biopsy; ChT	R2	DOD
11	187	F	Head	Hypoglycemia	0	Well differentiated (insulinoma)	L	Enucleation	R0	CR
12	167	M	Body-tail	Incidental (screening for TS)	0	Well differentiated	L	EUS-FNA; distal pancreatectomy	R0	CR

Abbreviations: AWD, alive with disease; ChT, chemotherapy; CR, complete remission; DOD, died of disease; EUS-FNA, endoscopic ultrasound-guided fine needle aspiration; L, localized; LR, locoregional disease; M, metastatic; MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumor; OLT, orthotopic liver transplantation; RT, radiotherapy; TACE, transcatheter arterial chemoembolization; TS, tuberous sclerosis.

^aTime between the onset of tumor-related symptoms and the first surgery (biopsy or resection).

^bAt histology: nonneoplastic disease.

^cLost to follow-up.

TABLE 2 Clinical features: Bronchial NETs

	Age (months)	Sex	Site	Symptoms	Diagnostic delay ^a (months)	Pathology	Stage	Treatment	Quality of resection	Outcome
1	185	M	Right lower bronchus	Recurrent pneumonia	132	Low grade/typical carcinoid	L	Endoscopic biopsy; lobectomy	R0	CR
2	197	F	Left superior bronchus	Recurrent pneumonia, pain	24	Low grade/typical carcinoid	L	Endoscopic biopsy; lobectomy	R0	CR ^c
3	142	M	Main left bronchus	Recurrent pneumonia, atelectasia	15	Low grade/typical carcinoid	L	Endoscopic biopsy; endoscopic resection	R0	CR
4	160	M	Main left bronchus	Recurrent pneumonia	19	Not available	L	Endoscopic biopsy; pneumonectomy	R0	CR
5	173	F	Right lung	Unknown	-	Low grade/typical carcinoid	M	Lobectomy	R2	AWD ^c
6	192	F	Right lung	Cough, mild dyspnoea	None	Undifferentiated NET	M	Open biopsy; neoadjuvant ChT; debulking; adjuvant ChT; RT; ABMT ^b	R2	DOD (toxicity)
7	212	F	Main left bronchus	Fever, cough, hemoptysis	12	Low grade/typical carcinoid	L	Endoscopic biopsy; unspecified resection	R0	CR
8	147	F	Right lower bronchus	Unknown	-	Not available	L	Lobectomy	R0	CR
9	146	F	Right median bronchus	Recurrent pneumonia, atelectasis	5	Low grade/typical carcinoid	L	Endoscopic biopsy; endoscopic resection	R0	CR
10	146	M	Right lower bronchus	Recurrent pneumonia, hemoptysis	7	Low grade/typical carcinoid	LR	Endoscopic biopsy; lobectomy	R0	CR

Abbreviations: ABMT, autologous bone marrow transplant; AWD, alive with disease; ChT, chemotherapy; CR, complete remission; DOD, died of disease; L, localized; LR, locoregional disease; M, metastatic; NETs, neuroendocrine tumors; RT, radiotherapy.

^aTime between the onset of tumor-related symptoms and the first surgery (biopsy or resection).

^bAfter liver metastatic relapse, received further chemotherapy.

^cLost to follow-up.

FIGURE 1 Event-free survival (A) and overall survival (B) of extra-appendicular neuroendocrine tumors (NETs) according to site of origin ($P = .002$ and $.005$, respectively). Event-free survival (C) and overall survival (D) of extra-appendicular NETs according to stage at diagnosis (R0 vs R2; $P = .002$ and $.008$, respectively)

3.3 | Rarer sites and NETs of unknown origin - five patients

Three patients had tumors in thymus, liver, and Meckel's diverticulum (in this last case the tumor was discovered incidentally during appendectomy); two had tumors localized in the mediastinum and gastrointestinal tract, but the primary was not evident. All, except the patient with a NET of the Meckel's diverticulum, had advanced disease at diagnosis and, after biopsy, received adjuvant treatment with poor outcome. Two of them abandoned the study looking for a second opinion and were lost to FU. Table 3 describes the clinical characteristics of these patients.

3.4 | Overall outcome and statistical analysis

Among patients with disease limited to the organ of origin, all 14 are alive in their first CR (3-year OS 100%; 3-year EFS 100%). Among

those with locoregional disease, three are in CR and one was lost to FU with disease (3-year OS 100%; 3-year EFS 66.6%, 95% CI 5-95%). Metastatic disease led to a dismal outcome (3-year OS 33%, 95% CI 5-68%; 3-year EFS 33%, 95% CI 5-68%): only one patient is in CR, two were AWD when lost to FU, four died of disease, and one because of treatment-related toxicity. A statistically significant difference was found both in OS and EFS with respect to stage at diagnosis ($P = .002$ and $.005$, respectively) (Figure 1).

Bronchial NETs showed a 3-year OS and 3-year EFS of 85.7% (95% CI 33-98%), while pancreatic NETs a 3-year OS of 81.4% (95% CI 44-95%) and a 3-year EFS of 91.6% (95% CI 54-99%) (Figure 1). A statistically significant difference was found both in OS and EFS with respect to primary site ($P = .019$ and $.008$, respectively).

Similar results were found in 3-year OS (R0 91.6%, 95% CI 54-99%; R1-R2 42.8%, 95% CI 10-73%) and 3-year EFS (R0 91.6%, 95% CI 54-99%; R1-R2 42.8%, 95% CI 10-73%) with respect to completeness of surgery (R0 vs R1/R2; $P = .001$ and $.007$, respectively). With regards to histology, well-differentiated NET/typical carcinoid had a better 3-year EFS (90%, 95% CI 47-99%) and 3-year OS (100%) than undifferentiated

TABLE 3 Clinical features: Rarer sites and NETs of unknown origin

	Age (months)	Sex	Site	Symptoms	Diagnostic delay ^a	Pathology	Stage	Treatment	Outcome	Follow-up (months)
1	186	F	Thymus	Pain	4 months	Not available	Locoregional advanced disease and bone metastases	Cisplatin and etoposide	DOD	14
2	95	M	Meckel's diverticulum	Incidental diagnosis (appendicitis)	None	Typical carcinoid/low grade	Localized	None	CR ^b	6
3	167	M	Liver	Fever, fatigue, pain	5 months	Well-differentiated carcinoma	Bone metastases	Metabolic radiotherapy, lanreotide	AWD ^b	1
4	177	M	Unknown(GI tract?)	Jaundice, chronic pancreatitis, pain	5 years	Well-differentiated carcinoma	Retroperitoneal nodes, multiple liver and bone metastases	Lanreotide, etoposide (palliative)	DOD	4
5	198	F	Unknown (mediastinum)	Cough	None	Poorly differentiated carcinoma	Locoregional advanced disease and node metastases	None (opted out)	AWD ^b	-

Abbreviations: AWD, alive with disease; CR, complete remission; DOD, died of disease; NETs, neuroendocrine tumors.
^aTime between the onset of tumor-related symptoms and the first surgery (biopsy or resection).
^bLost to follow-up.

FIGURE 2 Overall survival (A) and event-free survival (B) of extra-appendicular neuroendocrine tumors (NETs)

tumors/carcinomas (50%, 95% CI 11-80% for both OS and EFS) with a *P*-value of .044 and .007, respectively.

Overall, 16 children are in CR and one is AWD, while five children were lost to FU with disease (relapsed, stable, or progressing). Five died (3-year OS 79.7%, 95% CI 54-92%; 3-year EFS 75%, 95% CI 50-89%) (Figure 2). The mean FU was 43 months (range 3-168; median 26).

4 | DISCUSSION

As already described by reports from the analysis of NET Registries,^{3,14,15} our series showed a wide heterogeneity of primary sites, clinical presentation, and outcome. Bronchi and pancreas seem to represent the most frequent sites in extra-appendicular NET,^{3,14} but it is undoubted that the true incidence remains currently unveiled. A report from the Surveillance, Epidemiology, and End Results (SEER) registry demonstrated that in children the bronchial NETs occurred more frequently than the appendicular tumors,³ but the number of appendicular NET might be underestimated due to their benign course.^{1,16-18} Moreover, series from single institution, though covering a long frame of time, seem to alternately over- or underestimate the site of occurrence.^{15,19,20} Some considerations need to be done. Some children and most adolescents are operated on in adult centers: accordingly, despite the establishment of specific pediatric registries (TREP project in Italy,²¹ Groupe Francais Des Tumeurs Rares de l'Enfant in France [FRACTURE] in France,²² Seltene Tumoren in der Pädiatrie [STEP] and German Society for Pediatric Oncology and Hematology Malignant Endocrine Tumors Study [GPOH-MET] in Germany,^{23,24} Polish Rare Pediatric Tumor Study Group [PPRSTG] in Poland²⁵), the enrollment may cover only part of the entire population, and be ineffective to delineate a complete epidemiologic picture.^{14,26} Moreover, the enrollment in population-based registries or cancer-specific registries is probably biased, since those rarely focus on this population.

Another issue is the high proportion of patients lost to FU or who opted out, as it happened in six patients of our series (23% of the total

population). This was often reported in the past,^{14,16,27} and in our experience it seems a consequence of parents' decision to look for a second or third opinion in other centers outside the pediatric network.

The rarity of NETs and their peculiar feature to originate from different sites and causing variable, nonspecific symptoms may lead to an extremely delayed diagnosis that has been estimated by some authors to reach up to 10 years.^{3,14,16,28} This has been confirmed by our findings.

The use of more modern functional imaging techniques (gallium-68 dodecanetetraacetic acid-Tyr (3)-octreotate [68Ga-DOTATATE], gallium-68 dodecanetetraacetic acid-Tyr (3)-octreotide [68Ga-DOTATOC], gallium-68 dodecanetetraacetic acid-1-Nal (3)-octreotide [68Ga-DOTANOC]) is mandatory according to the adult oncology guidelines, because they have been found to have an excellent sensitivity in the staging of NETs.^{12,29} Unfortunately, in line with previous reports,¹⁴ such methods were not used in the majority of our patients.

Because extra-appendicular NETs may be part of a syndrome harbored by a germline mutation, even if less frequently than other neoplasms,³⁰ the diagnostic workup in children should include the genetic counseling, especially considering their rarity and the need of more precise epidemiologic data.^{31,32}

Localized NETs do benefit from a complete surgical resection. Since pediatric NETs seem to develop mostly at the tail of the pancreas,¹⁵ these tumors are usually treated with a caudectomy or an enucleation. Interestingly, in our series, the rate of pancreatic head tumors was higher than expected (41.6% of cases), and required complex surgical procedures to control the disease. Lung-sparing surgery (sleeve resections and bronchoplasty for central NETs)³³ is considered the treatment of choice in bronchial NET. The endoscopic enucleation of selected tumors is also possible, but it has been described mostly in adults series,³³ and only anecdotally in children.^{28,34-36} This approach is still debated^{37,38} because of the risk of intraoperative bleeding and the impossibility to perform lymphadenectomy. Remarkably, 20% of our patients were successfully treated through an endoscopic approach. Recent evidences suggest that a mini-invasive

endobronchial approach could be considered for small selected bronchial NETs, without signs of locoregional spread or distant metastases.³³

A multimodal treatment with chemotherapy or somatostatin analogs has been used for non-operable tumors at diagnosis; however, it is difficult to determine their impact on survival. Locally advanced and metastatic tumors may rarely benefit from regimens including dacarbazine, streptozotocin, oxaliplatin, cisplatin, etoposide, and everolimus, but the use of octreotide and peptide receptor radionuclide therapy, when tumors express somatostatin receptors, has been found to increase the overall survival.^{15,39} In most cases of our series, however, these strategies were ineffective in obtaining a good response, or simply prolonging survival. Only one patient with a metastatic bronchial NET showed some kind of response to conventional chemotherapy and autologous BMT; however, after an early relapse, when a good response to GEMOX was recorded, the child died from toxicity. Another patient with a metastatic pancreatic NET showed a prolonged survival (76 months) with the use of somatostatin analog.

Metastases may also benefit of a complete surgery. In most cases, however, surgery is not feasible and other techniques should be considered, such as radiofrequency ablation and chemoembolization, whose utilization in children is becoming more and more attractive for various histotypes.^{31,40,41} OLT has been previously attempted in patients with multifocal metastases limited to the liver.⁴² The combination of TACE and OLT was beneficial for one patient with a metastatic pancreatic NET, who is alive well at 64 months from diagnosis.

In conclusion, extra-appendicular NETs are very rare tumors in children, and a few data are available on their real epidemiology. A complete surgical resection, when available, is the main prognostic factor for a good outcome. Other therapies may have a role in prolonging survival in metastatic and unresectable locally advanced disease, which, however, normally show a dismal outcome in the majority of cases. The establishment of larger International cooperative networks^{43,44} is necessary to better define epidemiology, prognostic factors, the impact of local and systemic therapies, and the overall survival. The nationwide multidisciplinary TREP experience demonstrated over the years that cooperative studies on such very rare tumors are feasible.^{20,31,45} The keys for success are the capability to meet both the need of data collection and research, as well as to provide a network of experts able to offer practical patient management approaches along with an advisory service. It is also of primary importance to underline how these patients may benefit from referral to institutions with major experience on the treatment of adult NETs,^{14,46} also in consideration that pediatric guidelines are not currently available due to difficulty to run trials or protocols in very rare diseases in children.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING INFORMATION

Fondazione Giovanni Celegghin ONLUS

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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How to cite this article: Virgone C, Ferrari A, Chiaravalli S, et al. Extra-appendicular neuroendocrine tumors: A report from the TREP project (2000-2020). *Pediatr Blood Cancer*. 2021;68:e28880. <https://doi.org/10.1002/pbc.28880>