Neuroendocrine tumors (NETs), originating from neuroendocrine cells, are heterogeneous tumors representing distinct clinical and biological features. Neuroendocrine cells are widely distributed in many organ systems in the body and thus neuroendocrine tumors (NETs) can arise in almost any part of the body.\(^1\) NETs are rare in children. The incidence is approximately 6 cases per 100,000 in adults and 2.8 cases per million in children.\(^2,3\)

Tumors arising from neuroendocrine cells occurring anywhere along the gastrointestinal tract are called gastroenteropancreatic neuroendocrine tumors (GEP-NETs).\(^4\) Pediatric neuroendocrine tumors are most commonly located in the appendix. Although liver is a rare primary tumor localization, it is the most common site for metastatic disease.\(^5-8\)

In this study, we aimed to evaluate the demographic, clinical characteristics, treatment and outcomes of children and adolescents diagnosed with GEP-NET.

**Materials and Methods**

The medical files of children and adolescents under the age of 18 years with a diagnosis of GEP-NET between the years 1993 and 2022 at the Istanbul University Oncology Institute...
were retrospectively evaluated regarding demographic, clinical characteristics, treatment and outcomes.

The histopathological characteristics of the specimens, stained with hematoxylin and eosin, were assessed. These characteristics included the size and location of the tumor, degree of differentiation, extent of appendix wall infiltration, perineural invasion, and lymphovascular invasion. Ki-67 proliferation index was used to determine the proliferative rate. Histologic grading was reported.9

This study was reviewed and approved by Institutional Ethics Committee of Istanbul University Oncology Institute (2023/1627403).

Results

Fourteen patients (11 girls, 3 boys) were diagnosed with GEP-NET. The median age at diagnosis was 13 (9-18) years. Tumor localization was the appendix in 12 patients, stomach and pancreas in one each. Characteristics of the patients are given in Table I.

Patients with appendiceal neuroendocrine tumors (aNETs) were all diagnosed after an appendectomy performed due to the preliminary diagnosis of acute appendicitis. The patients were reported to have at least one of the symptoms of abdominal pain, nausea, and vomiting at hospital admission. The patient with a tumor located in the stomach was diagnosed after endoscopic polypectomy due to prolonged dyspeptic complaints resistant to medical treatment. The patient with pancreatic NET (pNET) had been admitted to the hospital due to prolonged abdominal pain and MRI revealed a mass in the pancreas with metastasis in the liver. A trucut biopsy of the lesions in the pancreas and liver confirmed the diagnosis.

The size of the tumor was less than 2 cm in 13 patients (range 0.1 cm-1.4 cm) with primary tumors arising from appendix and stomach. One patient with pancreas primary had a tumor size of 10 cm. A total of seven patients had grade I and seven had grade II NET. Histopathological examination revealed mesoappendix invasion in four patients two of whom underwent right hemicolecction and lymph node dissection (>20 lymph nodes removed). Of those two patients who underwent right hemicolecction (RHC) and lymph node dissection (LND), one was found to have three lymph nodes positive for NET metastasis and the other was negative. The parents of the other two patients with mesoappendix invasion refused the recommendation for RHC and LND. Both patients are still under regular follow-up with no evidence of disease.

Of the 14 patients, at diagnosis one with aNET and lymph node metastasis had carcinoid syndrome. The patient described episodes of hot flushes with transient non-pruritic, macular erythematous rash, mostly localized on the face. Serum chromogranin A (CgA) level was found to be high at diagnosis in the patient with pNET and liver metastasis. Urine 5-hydroxyindoleacetic acid (5-HIAA) levels investigated after surgery were within normal ranges in all the other patients.

Imaging studies with gallium-68 (Ga-68) dotatate positron emission tomography/computed tomography (PET/CT) were performed in all patients after histopathological diagnosis was established. There was no somatostatin receptor expression in any of the patients, except the patient with pNET whose study with Ga-68 dotatate PET/CT revealed significant increased somatostatin receptor expression in the pancreas and metastatic lesions in liver and spleen.

The patient with pNET was treated with resection of the tumor in pancreas tail and liver, splenectomy and cholecystectomy followed by somatostatin for one year and is under regular follow up without evidence of disease (NED).

The patient with gastric NET was treated with somatostatin for six months after surgery. She is followed with NED. None of the other patients received further treatment after surgery.
<table>
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<th>Tumor diameter (cm)</th>
<th>LN involvement</th>
<th>Ki 67 (%)</th>
<th>Histology / grade</th>
<th>Invasion</th>
<th>Carcinoid syndrome</th>
<th>Treatment</th>
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*This is the only patient with metastasis (liver and spleen)
Patients were followed up by physical examination, laboratory tests for serum CgA and urine 5-HIAA and imaging studies with ultrasound every three months during treatment and for the first two years after treatment, every six months until five years after treatment and yearly thereafter. The median follow-up of the patients was 85 months (7-226 months). All patients are alive with no evidence of disease.

Discussion

Neuroendocrine tumors (NETs) are rare and slow growing tumors with various histological and clinical features constituting 2% of all malignant tumors of the gastrointestinal tract.

The incidence of GEP-NETs is reported to be 3.6/100,000 people annually by the National Cancer Institute Surveillance, Epidemiology, and End Results Program. The epidemiological data of childhood NETs is limited due to their rarity among children. An incidence of 2.8 cases per million among children and adults under age of 30 constituting less than 1% of childhood malignancies has been reported.

The World Health Organization (WHO) categorized NETs as grade I, grade II, or grade III considering mitotic number and Ki-67 proliferation index of tumors in 2010. Through studies reporting the differences in survival statistics of patients with grade III tumors, WHO reported an updated classification of NETs in 2017 based on histologic features in which grade III tumors with well-differentiation were denominated as “neuroendocrine tumors” whereas those with poor differentiation as “neuroendocrine carcinomas”. All tissue samples in our study were re-classified histologically according to WHO classification.

Neuroendocrine tumors originate from diffuse enterochromaffin (Kulchitsky) cells throughout the gastrointestinal (GI) tract and bronchopulmonary system. Though GEP-NETs can form in different parts of the GI tract, the most common site of origin in pediatric patients is the appendix representing almost 80% of cases. In our series, 85.7% of the cases were located in the appendix.

GEP-NETs can cause various clinical signs and symptoms. Patients diagnosed with aNET often are admitted with the complaint of abdominal pain accompanied by nausea and/or vomiting, and they are diagnosed incidentally after being operated with a preliminary diagnosis of acute appendicitis. In a study reviewing related publications including more than 350000 appendectomy cases, the incidence of aNET was reported as 2-5 case per 1000 appendectomies, and the overall incidence in childhood was reported to be between 1:100,000 and 1.14:1 million per year. Most aNETs are diagnosed postoperatively, often are hormonally inactive small tumors (<1.5-2 cm) and have a good prognosis. Tumor diameters of >2 cm were frequently reported in patients with extra-aNET. The size of the tumor in the patient with pNET and liver metastasis was 10 cm in our study.

Pancreatic NETs constitute approximately 30% of pancreatic tumors in children and adolescents and represent about a third of all GEP-NETs. Pancreatic NETs frequently tend to be multifocal. Approximately half of pNETs have metastasis at diagnosis, and the most common site of metastasis is the liver. Symptoms may occur due to the local effects of the pancreatic mass and/or the hepatic metastases.

Unlike adults, carcinoid syndrome leading to symptoms such as diarrhea, flushing, and wheezing due to the release of vasoactive substances secreted by the tumor, has been reported less frequently in children.

Neuroendocrine neoplasms can be sporadic or occur as part of inherited disorders. About 5% of NETs arise in the context of an inherited tumor syndrome. Hereditary syndromes shown to be associated with NETs include familial adenomatous polyposis (FAP),
multiple endocrine neoplasia type 1 (MEN-1), multiple endocrine neoplasia type 2 (MEN-2), multiple endocrine neoplasia type 4 (MEN-4); neurofibromatosis type 1 (NF-1), and von Hippel–Lindau syndrome (VHL). Some NETs may also be associated with ectopic Cushing’s syndrome due to adrenocorticotropic hormone (ACTH) hypersecretion. The most common ectopic ACTH producing NETs have been reported in pediatric cases with bronchial and pancreatic localizations.

Gastrin-secreting neuroendocrine neoplasms may cause Zollinger-Ellison syndrome which can present as severe peptic ulcer disease, gastroesophageal reflux disease (GERD), and chronic diarrhea caused by a recurrent epigastric pain and malabsorption from gastric and duodenal ulcers and diarrhea. In our study, the patient with dyspeptic complaints resistant to medical treatment was diagnosed with gastric NET after endoscopic polypectomy. There was no patient with an inherited disorder in our series.

Various imaging modalities can be used in the detection and follow-up of NETs including ultrasound, computed tomography (CT), and magnetic resonance imaging. Some of these modalities have limitations such as low sensitivity of CT for tumors <2 cm and the low metabolic activity in PET/CT for well-differentiated tumors. Ga-68 dotatate PET/CT is a functional imaging modality used with somatostatin receptor (SSR) analogues. Studies suggest Ga-68 dotatate PET/CT should be considered a first-line diagnostic tool in adult and pediatric patient populations which surpasses conventional diagnostic imaging techniques with its high sensitivity in detecting well-differentiated NETs, identifying NETs in cases of unknown primary sites, and detecting metastases. All of our patients had a postoperative Ga-68 dotatate PET/CT study, there was no uptake in any of our patients, except the one with the pancreatic origin with metastasis in the liver and spleen. After total resection of the tumor, Ga-68 dotatate PET/CT was negative in this patient also.

Tumor size and mesoappendix involvement have been considered the primary determinatives for aggressiveness of aNETs. More controversial prognostic factors include lymphovascular invasion, subserosal invasion, and infiltration of the base of the appendix. For patients with aNET, RHC has been recommended for tumors larger than 1.5-2 cm in diameter, with mesoappendiceal or vascular invasion or with high mitotic activity. The guidelines from the European Neuroendocrine Tumor Society (ENETS) advocate for appendectomy alone in cases of appendiceal NETs ≤2 cm. For tumors <2 cm but with positive or unclear margins, or exhibiting deep mesoappendiceal invasion, ENETS recommends a right hemicolectomy. In cases of tumors >2 cm, ENETS also suggests a right hemicolecotomy. On the other hand, the North American Neuroendocrine Tumour Society (NANETS) guidelines propose a right hemicolectomy for tumors >2 cm, those that are incompletely resected, those showing invasion at the base of the appendix or mesoappendix, as well as those with lymphovascular invasion or positive lymph nodes. These guidelines are intended for adults; therefore, they should be used cautiously in children and adolescents. The interdisciplinary GPOH-MET study group suggests RHC after complete resected tumors larger than 15 mm in children. Dall’Igna et al. recommend partial checectomy or ileocecal resection to perform more extensive surgery in cases where the tumor cannot be completely removed and/or when surgical margins are not tumor free. There are also reports of low percentage of lymphatic spread and distant metastases in aNETs larger than 2 cm in diameter in children who had not undergone secondary surgery.

According to the publication by Njere et al. where more than 900 pediatric cases were evaluated, it was reported that although the risk of positive lymph nodes is increased 28-fold when the tumor size was >2 cm compared to <2 cm, there was no difference in terms of recurrence or mortality between those who
were followed up after appendectomy and those who underwent second surgery. Similarly, Yalçın et al.\textsuperscript{36} in their institutional experience with 33 appendiceal NETs, presented a good outcome with observed cases exhibiting tumors ≤2 cm regardless of local invasion after appendectomy alone which could have been deemed as indications for additional surgery, thus contradicting recommendations drawn from adult experiences.

In our series, two of the four patients with mesoappendix invasion underwent RHC and lymph node dissection; lymph node metastasis was observed in one of these. No recurrence was observed in the two other patients with mesoappendix invasion who did not have RHC and LND. Although, this is a very limited series, our findings are parallel with the recommendation of limiting additional surgery (RHC) in small tumors with mesoappendiceal invasion.\textsuperscript{36,37}

Although surgical total resection is the preferred primary treatment for NETs, other treatment options such as somatostatin analogues, cytotoxic chemotherapy, molecular targeted therapies and peptide receptor radionuclide therapy (PRRT) are used in metastatic and locally advanced cases which are generally considered unresectable.

As increased somatostatin receptors may exist in NETs, targeted treatment with octreotide which is a somatostatin analogue, has been shown to have antitumor activity and a cytostatic effect.\textsuperscript{38}

Traditionally, cytotoxic chemotherapy has been known to have limited effects on NETs, however it has been used in some cases. A combination of capecitabine and temozolomide has been reported to provide favorable survival outcomes in patients with metastatic NETs.\textsuperscript{39} Pediatric and adult patients with NETs have been reported to respond to treatment with cyclophosphamide, vincristine and dacarbazine. Irinotecan and cisplatin may also be an alternative treatment modality.\textsuperscript{40} Everolimus, an mTOR inhibitor, has been found to be effective in metastatic progressive NETs of gastrointestinal tract and bronchial origin and progression-free survival benefit was confirmed in the RADIANT 4 trial.\textsuperscript{41}

In conclusion, NETs are rare in children and most are localized in the appendix. aNETs often cause sign and symptoms of acute appendicitis and have a good prognosis. Primary healthcare physicians, pediatricians and pediatric surgeons should be aware of NET in the differential diagnosis of acute appendicitis. Different from adults, children and adolescents typically have a consistently positive prognosis and additional surgical interventions beyond simple appendectomies generally do not provide benefits. According to recent data, in cases with mesoappendix invasion, RHC may be avoided. Specific pediatric guidelines are needed.

**Acknowledgement**

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**Ethical approval**

This study was reviewed and approved by Istanbul University, Oncology Institute Review Board (2023/1627403).

**Author contribution**

Study conception and design: RK; data collection: UMY, DK; analysis and interpretation of results: UMY; draft manuscript preparation: UMY. All authors reviewed the results and approved the final version of the manuscript.
Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES


