Neuroendocrine Tumors in Pediatrics

Global Pediatric Health
Volume 6: 1–7

DOI: 10.1177/2333794X19862712
journals.sagepub.com/home/gph
SAGE

Zainab Azam Farooqui[1] and Aman Chauhan, MD[2,3]

Abstract

Neuroendocrine cells are dispersed diffusely throughout many organ systems in the body and hence neuroendocrine tumors (NETs) can arise from almost anywhere in the body. NETs are considered rare tumors, and the current incidence is reported to be about 6 cases in 100 000 in adults and about 2.8 cases per million in the pediatric age group. Despite the indolent nature of these tumors, they have the potential for metastasis and significant morbidity. NETs can be asymptomatic at the time of diagnosis or can present with flushing, diarrhea, wheezing, weight loss, and fatigue among other symptoms. Due to the ambiguity of presenting symptoms, it is not uncommon for NETs to be diagnosed late in the disease course. Despite low incidence, the prevalence of the disease is high since patients live for many years and sometimes decades. Early detection of well-differentiated NETs has excellent outcomes with the majority of early-stage diseases being cured with surgical resection alone. There have been recent advancements in the management of metastatic progressive NETs with approval of peptide receptor radionuclide therapy, telotristat, and everolimus. Awareness of these rare tumors and its management is crucial for optimal management. This article will focus on pediatric NETs and current advances in its management.

Keywords

Pediatric neuroendocrine tumors, Neuroendocrine tumor

Received April 22, 2019. Received revised May 14, 2019. Accepted for publication May 15, 2019.

Introduction

Recent studies have shown that the prevalence and incidence of neuroendocrine tumors (NETs) have been gradually increasing over the last few decades. Dasari et al used the Surveillance Epidemiology, and End Results (SEER) to analyze NET patients from 1973 to 2012.[1] They reported an approximately 6-fold increase in incidence over the past 4 decades. This steady rise can be a result of improved diagnostics and increased detection of the disease.

Neuroendocrine tumors are often considered benign but carry a definite potential for malignant transformation. Due to the indolent nature of the disease, diagnosis is often delayed. It is reported that 10% to 20% of children and young adolescents present with metastatic disease at presentation.[2,3] Early detection is the key since surgical resection can be curative. Most early-stage surgically resected patients show durable relapse-free survival; however, there is a risk of relapse, which is linked to improper excision of the tumor and presence of locoregional or lymphovascular involvement at the time of initial presentation.[3] Lobeck et al reported 10% perineural invasion and about 3% lymphovascular invasion in their series of pediatric appendectomies for NETs.[4] NETs can originate in various organ system but gastrointestinal tract and lung are by far the most common locations. Presenting symptoms can be absent or nonspecific, including weight loss and abdominal pain. These clinical symptoms can be overlooked by physicians or patients for many years.[5]

In 2000, the World Health Organization (WHO) adopted a universal system of diagnosing NETs.[6] Prior to this, there was ambiguity in diagnostic criteria. More appropriate and consistent terminology to report the diverse presentations of NETs into well-differentiated NETs and poorly differentiated neuroendocrine carcinoma were introduced.[7,8] The 2010 WHO classification further stratified the diagnosis of NETs. These tumors

[1]University of Pikeville, Pikeville, KY, USA
[2]Markey Cancer Center, Lexington, KY, USA
[3]University of Kentucky, Lexington, KY, USA

Corresponding Author:
Zainab Azam Farooqui, University of Pikeville, Kentucky College of Osteopathic Medicine, 147 Sycamore Street, Pikeville, KY 41501-9118, USA.
Email: zainabfarooqui@upike.edu

were categorized into grade I, grade II, or grade III based on mitotic count and/or Ki-67 proliferation index. The Ki-67 index of grade I tumor is ≤2%, for grade II it is 3% to 20%, and for grade III it is ≥20%.[9,10] Grade III poorly differentiated carcinomas were recognized to be highly aggressive with unfavorable outcomes. Recent data suggest that not all grade III NETs portend a poor prognosis. Investigators were able to stratify grade III neuroendocrine neoplasms into well-differentiated and poorly differentiated subgroups with stark differences in survival statistics between these 2 groups.[11-13] This led to the reclassification of grade III tumors into 2 distinct subcategories (well-differentiated grade III and poorly differentiated grade III) in the 2017 WHO classification.[14] Well-differentiated neoplasms are termed "neuroendocrine tumors," while poorly differentiated neoplasms are designated as "neuroendocrine carcinomas." Due to the heterogeneous nature of grade III tumors, this new classification system enables treating physician to manage these grade III subentities very differently. Our subsequent discussion will be focused on the pediatric population.

Prevalence and Incidence of NETs in Pediatric Population

There is an overall rise in NET incidence since the last few decades. Dasari et al reported a rise in incidence rate from 1.09 (1973) to 6.98 per 100 000 (2012).[1] A recent analysis of the Kentucky Cancer Registry evaluating 6179 NET patients found a similar linear increase in incidence rate from 3.1 (1995) to 7.1 (2015) per 100 000 population.[15]

Gastroenteropancreatic (GEP) neuroendocrine neoplasms in the United States have increased by 720% in incidence, as well as 213% to 286% in prevalence over the past 40 years.[16,17] Epidemiology data suggest the greatest increase in stomach and rectal GEP-NETs, whereas appendiceal NET was the sole site that showed a decreased in prevalence.

The data specific to pediatric NET epidemiology are limited due to its rare occurrence in this population. Navalkele et al reported the incidence rates of the most common sites of malignant NETs in children and young adults and found lung, breast, and appendix incidence to be 0.6, 0.5, and 0.4 per million population, respectively.[18] The estimated incidence is about 2.8 cases per million and estimated prevalence count is 7724.[18]

According to Sarvida and O'Dorisio, the incidence rates of lung, breast, and appendix NET in children and young adults under the age of 30 years were 0.6, 0.6, and 0.5 per million, respectively.[3] All other sites including colon, small cell carcinoma, and pancreatic NETs had an incidence rate of <0.1 per million. Surprisingly, the majority of their study cohort had bronchial NETs (28%), followed by appendiceal NET (18%).

Presentation of NETs in Pediatric Population

Similar to the adult patient population, NETs have the potential to affect any organ system in the pediatric age group. Midgut NET forms the most common site of origin.[8,19,20] Within midgut NETs, appendix seems to be reported the most common site of origin in the pediatric population. Tumors of the appendix can clinically present as acute appendicitis or abdominal pain. While it is not uncommon for gastrointestinal NETs to present with carcinoid syndrome—a symptom complex of diarrhea, flushing, and wheezing due to the secretion of vasoactive substances secreted by the tumor—carcinoid syndrome is uncommon in pediatric age groups. This could be due to the low incidence of hepatic metastases in pediatric NET patients.[8,19,21] However, it is worth noting that there have been some reports of clinical presentations of carcinoid syndrome in a younger age group, though these findings are not common.[22]

Bronchial NETs are considered the most frequent primary pulmonary tumors in children and adolescents.[22] Diagnosing these neoplasms based on clinical features is difficult due to lack of symptoms at an early stage. Symptoms of cough and wheezing are often attributed to other reactive airway diseases. The patient can also present with recurrent pneumonitis or respiratory distress.[23] Wang et al reported a series of 17 bronchial NETs in the pediatric age group.[22] Median age at presentation was found to be 17 years in their study cohort. Broaddus et al had also concluded that the lung was the most common extra-appendiceal NET primary site with 6 out of 13 patients presenting with BCTs (bronchopulmonary carcinoid tumors) with the mean age range of 12.7 years.[21] A 2017 study that researched 45 cases of reported carcinoid tumors in patients ranging from ages 7 to 21 years found that appendiceal tumors comprised 80% of the diagnoses, followed by bronchial carcinoid tumors at 11%.[24]

It is observed that there is female dominance in pediatric reports of NETs. A short review of 14 appendiceal carcinoid tumors found a female preponderance (64.3%).[25] This was also consistent with recent SEER database analysis of NETs, wherein 34 233 out of total 64 971 NET cases (52.7%) were females.[1] Pawa et al also reported 60.5% female predominance in appendiceal NETs.[26]

Diagnosis and Staging of NETs

Accurate staging of NETs is imperative for optimal clinical management. The 2017 WHO classification of NETs is the adopted framework for many research studies. It grades tumors based on their biological behavior and histology. NETs can also be categorized as functional or nonfunctional. Functional tumors remain hormonally active and exhibit clinical symptoms while nonfunctional tumors do not. This is a key differentiation to make due to important differences in the management of a functional NET versus a non-functional NET.[27]

Ki-67 expression identifies proliferating tumor cells, atypical cytology, and tumor grade. Chromogranin A (CgA) directly correlates to the high number of secretory vessels of NETs, which makes increased serum levels a useful marker for these tumors, especially low-grade NETs. However, poor sensitivity and specificity of CgA pose limitations with routine use for disease monitoring. Twenty-four-hour urine 5-hydroxyindoleacetic acid (5-HIAA) is another useful biomarker that can be measured to confirm serotonin-producing NET and also help in disease monitoring. Gut et al compared the specificity and sensitivity of CgA with 5-HIAA urine test. The 5-HIAA marker had higher specificity (100%) than CgA (86%), but a lower sensitivity (35%) to CgA (68%).[28] The variations in these NET biomarkers makes it difficult to infer a definitive diagnosis, which requires the need for advanced diagnostic modalities.

Radiology Studies of NETs

Proper imaging is key to localize, grade, and confirm diagnoses of NETs. Traditional modalities include contrast-enhanced computed tomography (CT) scans and magnetic resonance imaging (MRI), positron emission tomography (PET) scans, and somatostatin receptor scintigraphy (Octreo scan). Contrast-enhanced CT scan has a broad specificity range of 3% to 100% and a sensitivity range of 63%to 82% when detecting NETs <2 cm.[29] Neoplasms <2 cm were also found to have decreased sensitivity with CT. The specificity (75%) and sensitivity (85%) of MRI in patients with pancreatic NETs were also tested. MRI pancreatic protocol can help in imaging pancreatic NETs and guide surgical candidacy. PET scan with ^{18}F-fluorodeoxyglucose (FDG) has limitations in being unable to detect well-differentiated and low metabolically active NETs. The limitations of these conventional techniques have led to a recent Food and Drug Administration (FDA)-approved imaging modality with impressive diagnostic results: ^{68}Ga-DOTATATE PET/CT.

^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, and ^{68}Ga-DOTANOC are the most common peptides that vary in affinity to different somatostatin receptors when detecting well-differentiated NETs.[30] ^{68}Ga-DOTATATE PET/CT has been very impactful with its high sensitivity in detecting metastases/lesions, identifying NETs of unknown primary sites, and influencing management plans. This diagnostic tool surpasses conventional diagnostic imaging techniques.

Sadowski et al did a prospective study on patients with GEP NETs, comparing ^{68}Ga-DOTATATE PET/CT with ^{111}In-pentetreotide single-photon emission CT (SPECT/CT) and anatomic imaging (CT/MRI).[31] ^{68}Ga-DOTATATE was able to detect a total of 847 lesions, while ^{111}In-pentetreotide SPECT/CT detected 275 and CT/MRI detected 404 in the pancreas, liver, bowel, lung, abdomen, and bone.[31] The DOTATATE scan was also performed on 68 patients with metastatic NETs and unknown primary sites. The scan successfully detected primary sites in 40/68 patients. Prasad et al support these findings by locating primary sites in 59% of patients via the scan.[32,33] Schreiter et al also detected 45.5% primary sites using ^{68}Ga-DOTATOC and only 8% using In-111 DTPA octreotide SPECT/CT.[34] The efficacy of the DOTATATE scan is a breakthrough for NETs. ^{68}Ga-DOTATATE PET/CT is also instrumental in detecting primary sites when conventional imaging fails. NETs of unknown primary make up 10% to 13% of all NETs.[32] Detection of primary sites can influence surgical resections and management options.

Studies suggest ^{68}Ga-DOTATATE PET/CT should be considered a first-line diagnostic tool in adult and pediatric patient populations. Goel et al analyzed 30 NET pediatric patients (median age = 7.6 years) with 13 presenting with bone metastases.[35] ^{68}Ga-DOTATATE PET/CT was able to detect metastasis in all 13 patients, while conventional CT scan could only detect lesions in 9 patients.[35] As far as lesions, a total of 225 bone lesions were found with the DOTATATE scan, while CT only found 84. Jha et al evaluated the lesion detection rates for pediatric patients presenting with pheochromocytomas.[36] ^{68}Ga-DOTATATE PET/CT, F-FDG PET/CT, and conventional CT/MRI detection rates were 93.5%, 79.4%, and 73.8%, respectively.[36] McGowan et al used the DOTATATE scan on a 13-year-old boy to detect residual adrenal tissue that was missed with an MRI or F-FDG-PET scan.[37] This discovery led to changes in the management plan to resect the newfound tumor.

^{68}Ga-DOTATATE shows superiority over most imaging techniques, has low exposure to radiation, low toxicity, fast administration/clearance time, and is cost-effective. The scan is a reliable tool to optimize treatment regimens for pediatric patients. This is especially true because

young patients are less likely to complain of pain or show symptoms, making it difficult to accurately assess them. A new management plan was implemented in a 4-year-old child whose neuroblastoma was revealed with a DOTATATE scan, but not a CT scan.[35] The DOTATATE scan also identified bone metastases in another adolescent patient, which advanced his disease from stage 1 to stage 4.[35] These studies support the clinical significance and evident benefit in using the ^{68}Ga-DOTATATE PET/CT diagnostically for pediatric and adult patients.

Treatment of NETs

Surgical Management of NETs

Clinical management of NETs largely depends on tumor location, tumor grade, tumor growth rate, and the extent of disease and symptoms. Surgical resection is conventionally considered first-line therapy in early-stage disease due to its excellent long-term outcomes.[38-40] Lobeck et al evaluated 30 pediatric appendectomies and found postoperative surveillance (36 months) to be normal with no further treatment required.[4,41,42] Due to the successful outcomes of these procedures, there is an incentive to find ideal strategies for surgery. For example, Bholah and Bunchman reviewed pediatric pheochromocytoma and paragangliomas and found a shift in utilizing laparoscopy over laparotomy in both pediatric and adult populations.[43] Continuous advances in surgical approach are imperative to maintaining curative results with minimal morbidities.

Non-Surgical Management of NETs

Though surgical intervention is favored as first-line treatment for the early-stage disease, metastatic NETs are generally deemed unresectable. Nonsurgical treatment modalities include somatostatin analogs, molecularly targeted therapy, cytotoxic chemotherapy, and peptide receptor radionuclide therapy (PRRT). NETs are unique in their increased expression of somatostatin receptors. Targeted therapy through octreotide, a somatostatin analog, has shown antitumor and cytostatic effects.[44] It is also linked to increased survival in patients with metastatic midgut carcinoid tumors.[41,45,46] Molecular targeted therapy targets growth factors, receptors, and signaling cascades to inhibit tumor growth.[46] Traditionally, cytotoxic chemotherapy has limited benefits in treating unresectable cancers; however, there has been some progress. Temozolomide administration in patients with bronchial and thymic neuroendocrine neoplasms showed a clinical benefit rate of 71% and 90%, respectively.[47] Recently reported randomized phase II clinical trial confirmed both progression-free survival (PFS) as well as overall survival benefit with combination capecitabine and temozolomide in pancreatic NET patients.[48] Combination therapies have also proven to be very effective in the management of NETs. Pediatric and adult patients with NET malignancies have responded well to chemotherapy adjunct with cyclophosphamide, vincristine, and dacarbazine.[43] Out of 11 patients, 5 had a partial response, 5 had stable disease, and 1 showed complete remission.

Molecular targeted therapy with everolimus is now FDA approved for the metastatic progressive NET of gastrointestinal tract and bronchial origin. Everolimus is an oral mTOR (mammalian target of rapamycin) inhibitor. This approval was based on a large international randomized phase III clinical trial (RADIANT 4) and confirmed PFS benefit over control arm.[49]

Last, PRRT has revolutionized the treatment of NETs. PRRT has been widely accepted as a standard treatment for progressive NETs in Europe for about 10 years but PRRT was deemed experimental in the United States due to lack of prospective randomized data. In 2018, the FDA finally approved PRRT as the standard of care treatment for progressive midgut NETs who had progressed on frontline therapy. The FDA approval was based on positive findings from a large randomized phase III clinical trial (NETTER-1).[50] The experimental arm (177 Lutetium DOTATATE) had 65% PFS at 20 months as compared with 10.8% for control (Octreotide) arm. Last but not least, there has been strides in the management of NET supportive care as well. The FDA approved first in its class oral tryptophan hydroxylase inhibitor, which inhibits the production of serotonin. The FDA approval was based on TELESTAR trial, which was a phase III randomized placebo-controlled trial and confirmed improvement in carcinoid diarrhea and reduction of urinary 5-HIAA in treatment arm versus placebo arm.[51]

Conclusion

Neuroendocrine tumors account for a small percentage of pediatric tumors; however, their diagnosis and prevention can be challenging due to their indolent course and vague symptoms. Improvement in diagnostic modalities (Gallium 68 DOTATATE) has markedly improved diagnostic sensitivity and specificity. Awareness of this rare tumor has resulted in accelerated therapeutic development and recent FDA approvals of everolimus, telotristat, and PRRT are a testament to ongoing research efforts. However, most if not all research is focused on adult NETs, and pediatric NETs continue to remain an area of unmet medical need. Understanding the parallel between childhood NETs and genetic variations with

MEN1 hereditary syndromes could be helpful in earlier intervention.[52] It is important to explore therapeutic treatments and validate recently approved NET treatments in the pediatric patient population.

Author Contributions

ZAF: Contributed to conception and design; contributed to analysis; drafted the manuscript; critically revised the manuscript; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
AC: Contributed to conception and design; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical Approval

Ethical approval is not required as this article is a review.

Informed Consent

Informed consent is not required as this article is a review.

ORCID iD

Zainab Azam Farooqui https://orcid.org/0000-0002-7075-9317

References

1. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017;3:1335-1342. doi:10.1001/jamaoncol.2017.0589
2. Parham DM. Neuroectodermal and neuroendocrine tumors principally seen in children. *Am J Clin Pathol*. 2001;115(suppl):S113-S128.
3. Sarvida ME, O'Dorisio MS. Neuroendocrine tumors in children and young adults: rare or not so rare. *Endocrinol Metab Clin North Am*. 2011;40:65-80.
4. Lobeck IN, Jeste N, Geller J, Pressey J, von Allmen D. Surgical management and surveillance of pediatric appendiceal carcinoid tumor. *J Pediatr Surg*. 2017;52:925-927.
5. Vinik AI, Chaya C. Clinical presentation and diagnosis of neuroendocrine tumors. *Hematol Oncol Clin North Am*. 2016;30:21-48. doi:10.1016/j.hoc.2015.08.006
6. Solcia E, Kloppel G, Sobin LH, et al. *Histologic Typing of Endocrine Tumours*. Berlin, Germany: Springer Verlag; 2000.
7. Klöppel G. Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer*. 2011;18(suppl 1):S1-S16. doi:10.1530/ERC-11-0013
8. Khanna G, O'Dorisio SM, Menda Y, Kirby P, Kao S, Sato Y. Gastroenteropancreatic neuroendocrine tumors in children and young adults. *Pediatr Radiol*. 2008;38:251-259. doi:10.1007/s00247-007-0564-4
9. Bu J, Youn S, Kwon W, et al. Prognostic factors of nonfunctioning pancreatic neuroendocrine tumor revisited: the value of WHO 2010 classification. *Ann Hepatobiliary Pancreat Surg*. 2018;22:66-74. doi:10.14701/ahbps.2018.22.1.66
10. Karakuş E, Helvacı A, Ekinci O, Dursun A. Comparison of WHO 2000 and WHO 2010 classifications of gastroenteropancreatic neuroendocrine tumors. *Turk J Gastroenterol*. 2014;25:81-87.
11. Tang LH, Untch BR, Reidy DL, et al. Well differentiated neuroendocrine tumors with a morphologically apparent high grade component: a pathway distinct from poorly differentiated neuroendocrine carcinomas. *Clin Cancer Res*. 2016;22:1011-1017. doi:10.1158/1078-0432.CCR-15-0548
12. Yachida S, Vakiani E, White CM, et al. Small cell and large cell neuroendocrine carcinomas of the pancreas are genetically similar and distinct from well-differentiated pancreatic neuroendocrine tumors. *Am J Surg Pathol*. 2012;36:173-184. doi:10.1097/PAS.0b013e3182417d36
13. Han X, Xu X, Ma H, et al. Clinical relevance of different WHO grade 3 pancreatic neuroendocrine neoplasms based on morphology. *Endocr Connect*. 2018;7:355-363. doi:10.1530/EC-17-0388
14. Lloyd RV, Osamura RY, Klöppel G, Rosai J. *WHO Classification of Tumours of Endocrine Organs*. 4th ed. Lyon, France: International Agency for Research on Cancer; 2017.
15. Chauhan A, Yu Q, Ray N, et al. Global burden of neuroendocrine tumors and changing incidence in Kentucky. *Oncotarget*. 2018;9:19245-19254. doi:10.18632/oncotarget.24983
16. Fitzgerald TL, Dennis SO, Kachare SD, Vohra NA, Zervos EE. Increasing incidence of duodenal neuroendocrine tumors: incidental discovery of indolent disease. *Surgery*. 2015;158:466-471. doi:10.1016/j.surg.2015.03.042
17. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol*. 2008;9:61-72. doi:10.1016/S1470-2045(07)70410-2
18. Navalkele P, O'Dorisio MS, O'Dorisio TM, Zamba GKD, Lynch CF. Incidence, survival and prevalence of neuroendocrine tumors versus neuroblastoma in children and young adults: nine standard SEER registries, 1975-2006. *Pediatr Blood Cancer*. 2011;56:50-57. doi:10.1002/pbc.22559
19. Howell DL, O'Dorisio MS. Management of neuroendocrine tumors in children, adolescents, and young adults. *J Pediatr Hematol Oncol*. 2012;34(suppl 2):S64-S68. doi:10.1097/MPH.0b013e31824e3885

20. Bonekamp D, Raman SP, Horton KM, Fishman EK. Role of computed tomography angiography in detection and staging of small bowel carcinoid tumors. *World J Radiol*. 2015;7:220-235. doi:10.4329/wjr.v7.i9.220
21. Broaddus RR, Herzog CE, Hicks MJ. Neuroendocrine tumors (carcinoid and neuroendocrine carcinoma) presenting at extra-appendiceal sites in childhood and adolescence. *Arch Pathol Lab Med*. 2003;127:1200-1203.
22. Wang LT, Wilkins EW Jr, Bode HH. Bronchial carcinoid tumors in pediatric patients. *Chest*. 1993;103:1426-1428.
23. Guerreiro CV, Ornelas P, Pereira L, Abecasis N, Almodovar MT. Atelectasis in pediatrics: a case of carcinoid tumor. *Rare Tumors*. 2017;9:7049. doi:10.4081/rt.2017.7049
24. Degnan AJ, Tocchio S, Kurtom W, Tadros SS. Pediatric neuroendocrine carcinoid tumors: management, pathology, and imaging findings in a pediatric referral center. *Pediatr Blood Cancer*. 2017;64(9). doi:10.1002/pbc.26477
25. Dall'Igna P, Ferrari A, Luzzatto C, et al. Carcinoid tumor of the appendix in childhood: the experience of two Italian institutions. *J Pediatr Gastroenterol Nutr*. 2005;40:216-219. doi:10.1097/00005176-200502000-00025
26. Pawa N, Clift AK, Osmani H, et al. Surgical management of patients with neuroendocrine neoplasms of the appendix: appendectomy or more? *Neuroendocrinology*. 2018;106:242-251. doi:10.1159/000478742
27. Franko J, Feng W, Yip L, Genovese E, Moser AJ. Nonfunctional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2158 patients. *J Gastrointest Surg*. 2010;14:541-548. doi:10.1007/s11605-009-1115-0
28. Gut P, Czarnywojtek A, Fischbach J, et al. Chromogranin A—unspecific neuroendocrine marker. Clinical utility and potential diagnostic pitfalls. *Arch Med Sci*. 2016;12:1-9. doi:10.5114/aoms.2016.57577
29. Lee DW, Kim MK, Kim HG. Diagnosis of pancreatic neuroendocrine tumors. *Clin Endosc*. 2017;50:537-545. doi:10.5946/ce.2017.131
30. Yang J, Kan Y, Ge BH, Yuan L, Li C, Zhao W. Diagnostic role of gallium-68 DOTATOC and gallium-68 DOTATATE PET in patients with neuroendocrine tumors: a meta-analysis. *Acta Radiol*. 2014;55:389-398.
31. Sadowski SM, Neychev V, Millo C, et al. Prospective study of ^{68}Ga-DOTATATE positron emission tomography/computed tomography for detecting gastro-enteropancreatic neuroendocrine tumors and unknown primary sites. *J Clin Oncol*. 2016;34:588-596. doi:10.1200/JCO.2015.64.0987
32. Pruthi A, Pankaj P, Verma R, Jain A, Belho ES, Mahajan H. Ga-68 DOTANOC PET/CT imaging in detection of primary site in patients with metastatic neuroendocrine tumours of unknown origin and its impact on clinical decision making: experience from a tertiary care centre in India. *J Gastrointest Oncol*. 2016;7:449-461. doi:10.21037/jgo.2016.01.06
33. Prasad V, Ambrosini V, Hommann M, Hoersch D, Fanti S, Baum RP. Detection of unknown primary neuroendocrine tumours (CUP-NET) using (68) Ga-DOTA-NOC receptor PET/CT. *Eur J Nucl Med Mol Imaging*. 2010;37:67-77. doi:10.1007/s00259-009-1205-y
34. Schreiter NF, Ann-Mirja B, Hamm BK, Winfried B, Röttgen R. Comparing the detection of unknown primary neuroendocrine tumors using Ga-68 DOTATOC PET/CT or in-111 DTPA octreotide SPECT/CT. Paper presented at: Radiological Society of North America 2012 Scientific Assembly and Annual Meeting, November 25-30, 2012; Chicago, IL.
35. Goel R, Shukla J, Bansal D, et al. (68)Ga-DOTATATE positron emission tomography/computed tomography scan in the detection of bone metastases in pediatric neuroendocrine tumors. *Indian J Nucl Med*. 2014;29:13-17. doi:10.4103/09723919.125762
36. Jha A, Ling A, Millo C, et al. Superiority of ^{68}Ga-DOTATATE over ^{18}F-FDG and anatomic imaging in the detection of succinate dehydrogenase mutation (SDHx)-related pheochromocytoma and paraganglioma in the pediatric population. *Eur J Nucl Med Mol Imaging*. 2018;45:787-797. doi:10.1007/s00259-017-3896-9
37. McGowan A, An JY, Tanakchi S, et al. Multiple recurrent paraganglioma in a pediatric patient with germline SDH-B mutation. *Urol Case Rep*. 2017;13:107-109. doi:10.1016/j.eucr.2017.03.017
38. Marchegiani G, Crippa S, Malleo G, et al. Surgical treatment of pancreatic tumors in childhood and adolescence: uncommon neoplasms with favorable outcome. *Pancreatology*. 2011;11:383-389. doi:10.1159/000330212
39. Klöppel G, Couvelard A, Perren A, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. *Neuroendocrinology*. 2009;90:162-166.
40. Kulke MH, Benson AB 3rd, Bergsland E, et al; National Comprehensive Cancer Networks. Neuroendocrine tumors. *J Natl Compr Canc Netw*. 2012;10:724-764.
41. Pape UF, Niederle B, Costa F, et al; Vienna Consensus Conference Participants. ENETS consensus guidelines for neuroendocrine neoplasms of the appendix (excluding goblet cell carcinomas). *Neuroendocrinology*. 2016;103:144-152.
42. de Lambert G, Lardy H, Martelli H, Orbach D, Gauthier F, Guérin F. Surgical management of neuroendocrine tumors of the appendix in children and adolescents: a retrospective French multicenter study of 114 cases. *Pediatr Blood Cancer*. 2016;63:598-603.
43. Bholah R, Bunchman TE. Review of pediatric pheochromocytoma and paraganglioma. *Front Pediatr*. 2017;5:155. doi:10.3389/fped.2017.00155
44. Yau H, Kinaan M, Quinn SL, Moraitis AG. Octreotide long-acting repeatable in the treatment of neuroendocrine tumors: patient selection and perspectives. *Biologics*. 2017;11:115-122. doi:10.2147/BTT.S108818
45. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR

in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27:4656-4663. doi:10.1200/JCO.2009.22.8510

46. Kim KW, Krajewski KM, Nishino M, et al. Update on the management of gastroenteropancreatic neuroendocrine tumors with emphasis on the role of imagine. *AJR Am J Roentgenol*. 2013;201:811-824. doi:10.2214/AJR.12.10240
47. Koumarianou A, Kaltsas G, Kulke MH, et al. Temozolomide in advanced neuroendocrine neoplasms: pharmacological and clinical aspects. *Neuroendocrinology*. 2015;101:274-288. doi:10.1159/000430816
48. Kunz PL, Catalano PJ, Nimeiri H, et al. A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: a trial of the ECOG-ACRIN Cancer Research Group (E2211). *J Clin Oncol*. 2018 36(15 suppl):4004.
49. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387:968-977.
50. Strosberg J, El-Haddad G, Wolin E, et al; NETTER-1 Trial Investigators. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376:125-135.
51. Kulke MH, Hörsch D, Caplin ME, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol*. 2017;35:14-23.
52. Diets IJ, Nagtegaal ID, Loeffen J, et al. Childhood neuroendocrine tumours: a descriptive study revealing clues for genetic predisposition. *Br J Cancer*. 2017;116:163-168. doi:10.1038/bjc.2016.408