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MINIREVIEWS

Small bowel neuroendocrine tumors: From pathophysiology to clinical approach

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Abstract

Neuroendocrine tumors (NETs), defined as epithelial tumors with predominant neuroendocrine differentiation, are among the most frequent types of small bowel neoplasm. They represent a rare, slow-growing neoplasm with some characteristics common to all forms and others attributable to the organ of origin. The diagnosis of this subgroup of neoplasia is not usually straight-forward for several reasons. Being a rare form of neoplasm they are frequently not readily considered in the differential diagnosis. Also, clinical manifestations are nonspecific lending the clinician no clue that points directly to this entity. However, the annual incidence of NETs has risen in the last years to 40 to 50 cases per million probably not due to a real increase in incidence but rather due to better diagnostic tools that have become progressively available. Being a rare malignancy, investigation regarding its pathophysiology and efforts toward better understanding and classification of these tumors has been limited until recently. Clinical societies dedicated to this matter are emerging (NANETS, ENETS and UKINETS) and several guidelines were published in an effort to standardize the nomenclature, grading and staging systems as well as diagnosis and management of NETs. Also, some investigation on the genetic behavior of small bowel NETs has been recently released, shedding some light on the pathophysiology of these tumors, and pointing some new directions on the possible treating options. In this review we focus on the current status of the overall knowledge about small bowel NETs, focusing on recent breakthroughs and its potential application on clinical practice.

Key words: Neuroendocrine tumors; Gastrointestinal tumors; Small bowel neoplasms; Carcinoid; Diagnostic markers

Core tip: Annual incidence of neuroendocrine tumors (NETs) has risen in the last years to 40 to 50 cases per million probably due to better diagnostic tools. Recurrent loss of chromosomes 11 and 18 and gains of chromosomes 4, 5, 19 and 20 have been shown in NETs. Several cancer-related pathways were implied in NETs associated mutations, including PI3K/Akt/mTOR and TGF-β pathways. Genes involved in secretory activity were conserved in NETs, however alterations in transcription factors associated with neurodevelopmental process were reported. Studies suggest that miRNA may have a role in ileal NETs development and progression.

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INTRODUCTION

Neuroendocrine tumors (NETs), defined as epithelial tumors with predominant neuroendocrine differentiation, are among the most frequent types of small bowel neoplasm. They represent a rare, slow-growing neoplasm with some characteristics common to all forms and others attributable to the organ of origin. The diagnosis of this subgroup of neoplasia is not usually straight-forward for several reasons. Being a rare form of neoplasm they are frequently not readily considered in the differential diagnosis. Also, clinical manifestations are nonspecific lending the clinician no clue that points directly to this entity. However, the annual incidence of NETs has risen in the last years to 40 to 50 cases per million probably not due to a real increase in incidence but rather due to better diagnostic tools that have become progressively available.

Being a rare malignancy, investigation regarding its pathophysiology and efforts toward better understanding and classification of these tumors has been limited until recently. Clinical societies dedicated to this matter are emerging (NANETS, ENETS and UKINETS) and several guidelines were published in an effort to standardize the nomenclature, grading and staging systems as well as diagnosis and management of NETs. Also, some investigation on the genetic behavior of small bowel NETs has been recently released, shedding some light on the pathophysiology of these tumors, and pointing some new directions on the possible treating options.

In this review we focus on the current status of the overall knowledge about small bowel NETs, focusing on recent breakthroughs and its potential application on clinical practice.

EPIDEMIOLOGY

Duodenal NETs comprise 1%-3% of all primary duodenal tumors and 2.8% of all carcinoid tumors according to the PAN-SEER Registry (1973-1999)[1]. According to SEER Program, the age-adjusted annual incidence of NETs arising from jejunum and ileum is 0.67 per 100000 and for appendix NETs it is 0.16 per 100000[2]. However, data extracted from large autopsies series indicates that the incidence of small bowel NETs may be up to 0.7%[3]. Also, time-trend analyses have shown a rise in the incidence of all these forms of NETs. This is probably not due to a real increase in the number of cases, but rather due to an increased diagnosis efficacy.

CLASSIFICATION, GRADING AND STAGING

NETs are rare neoplasms and can arise in most organs of the body. Some of their features are shared by all NETs, while others are attributable to their organ of origin[4]. Most of the studies regarding NETs have focused on the most frequent locations, such as pancreatic and gastrointestinal, limiting extensive knowledge of other less common forms of the disease.

All these features have contributed to the emergence of several nomenclatures, grading and classification systems. Although most of these systems proved themselves useful, the lack of a standard classification system has hindered the normalization of NETs classification and consequently, scientific community wide consensus. Since some of these systems are now firmly established and no clinical data favors one system over the others, it may be unpractical to adopt a single system, rejecting the remaining. Thus, while ENETS[5,6] favor the use of World Health Organization classification system, NANETS[7] propose that some basic data elements (proliferative rate, extent of local spread, immunohistochemical markers) should be specified and documented on pathological reports and that a specified system of nomenclature, grading and staging should be used. This can assure that the basic data are recorded, allowing retrospective comparison of NETs regardless of the specific classification system used.

CLINICAL FEATURES

Regarding clinical features there are several differences between duodenal and most distal NETs of jejunum and ileum.

Duodenal NETs are usually diagnosed in the sixth decade with a slight male predominance[8,9]. There are five main forms: Duodenal gastrinoma, the most common type; duodenal somatostatinoma; non-functioning duodenal NETs; duodenal gangliocytic paraganglioma and poorly differentiated neuroendocrine duodenal carcinomas[4,8]. Some authors also consider periampullary NETs as a different category given their different clinical, histological and growth behavior[8]. Most duodenal NETs

are small, single lesions, usually limited to the mucosa and submucosa. Regional lymph node metastases may be found in up to 60% of cases, while liver metastasis usually occur in less than 10%[8]. Since about 90% of duodenal NETs are not associated with clinical syndrome, most diagnoses are made accidentally during a routine workup or the patient develops symptoms attributable to the mass itself[8]. Most frequently reported presenting symptoms include pain, jaundice (more frequent in peri-ampullary NETS), nausea, vomits, diarrhea, obstruction, active bleeding or anemia[8,9]. In the minority of duodenal NETs that cause a functional syndrome the two main presentations are Zollinger-Ellison syndrome (ZES) and carcinoid syndrome[6].

ZES in duodenal gastrinomas usually presents with abdominal pain, diarrhea and reflux esophagitis[10]. Its diagnosis requires the demonstration of inappropriate hypergastrinemia and there are several conditions that can cause hypergastrinemia and complicate the diagnosis of a ZES. If the fasting serum gastrin is 1000 ng/L or greater and gastric pH is less than 2.5 the diagnosis is established if the patient is normocalcemic, has a normal renal function and doesn't have pyloric obstruction[11]. Duodenal NETs presenting with ZES can be sporadic or associated to MEN1 syndrome. While sporadic forms usually result from single lesions, MEN1 display multiple lesions[8,10].

Carcinoid syndrome is usually present in patients with liver metastasis[5,12] and is caused by excessive secretion of endogenous substances, more frequently serotonin. Patients can present with flushing, diarrhea, cough, whezzing and carcinoid heart disease[12]. Carcinoid heart disease is a right sided cardiac insufficiency, and in about 35% of patients that develop this condition death arises not due to tumor progression but rather to heart failure[12]. Regarding prognosis, patients with well-differentiated duodenal NETs have a global 5-year survival rate of nearly 85%[13]. The stage of disease at diagnosis highly influence prognosis, with 10-year survival of 95% for patients with local disease and 10% for those with distant metastases[9].

NETs of jejunum and ileum are usually diagnosed in the sixth/seventh decade[14] but, in opposition to duodenal NETs, have no gender preference. Most of them are nonfunctioning tumors but about 20% of patients show liver metastases and may present with carcinoid syndrome. At diagnosis, lesions are commonly > 2 cm, with invasion of muscularis propria and metastasis to regional lymph nodes[4]. Multiple lesions may be found in up to 40% of cases[4]. Clinical manifestations include abdominal pain, bowel obstruction, diarrhea, weight loss and bleeding[15]. The prognosis of these NETs is generally unfavorable when compared with other location tumors of comparable size since they have a higher tendency to grow and spread before the diagnosis is firmed[14,15]. The 5-year survival correlates with the stage of disease at diagnosis, being of 65% for patients with localized disease and only 36% for those with distant metastases[5].

PATHOPHYSIOLOGY

Small bowel tumors correspond to 1%-2% of all gastrointestinal malignancies, and NETs are only one of the subtypes of these rare neoplasms. Being an unusual form of oncologic disease, research towards better understanding these tumors has been scarce.

Phenotypically these neoplasms are composed by neuroendocrine cells which, in the gastrointestinal tract, are scattered through the mucosa. These cells get their name from their ability to express some proteins classically attributable to neural cells, as neuron-specific enolase and synaptophysin, and also to their capacity to produce hormones, such as somatostatin, substance P and vasoactive intestinal peptide. The tumorigenesis of NETs has not yet been elucidated, however recent efforts to clarify the genetic alterations in these tumors have been made.

Recently, two exome/genome-wide tumor DNA sequencing for the small intestine (SI) NET have been reported. The first one, from Banck *et al*[16], matched germline DNA of 48 small bowel NETs, with samples consisting of well differentiated primary tumors. More than 20000 genes were sequenced and the data from tumor was compared to normal tissue to identify genetic alterations. This study found point mutations, termed single nucleotide variants (SNV), at an average rate of 0.1 SNV per 10^6 nucleotides. This classifies small bowel NETs as a genomically stable cancer, with low mutation rates. SNV were found in 197 genes, most of which were known for being cancer genes. Those included *VHL*, *BRAF*, *FGFR2*, *MEN1*, *MLF1*, *SRC*, *SMAD* and *FANCD2* among others. Banck *et al*[16] also looked for somatic copy number alterations, that consist of large deletions or amplifications that can cause the inactivation of tumor suppressor genes or the excessive expression of oncogenes. This analyses revealed a recurrent loss of chromosomes 11 and 18 and gains of chromosomes 4, 5, 19 and 20. Furthermore, with resource to bioinformatic analysis, several cancer-related pathways were implied in these mutations, including PI3K/Akt/mTOR and TGF-β pathways. The involvement of mTOR pathway support the findings of recent clinical trials in which mTOR inhibitors seem active in the treatment of some SI NETs[17]. Also, TGF-β pathway had previously been implied as a regulator in small bowel NETs. A study based on immunohistochemistry staining of 104 NETs showed enhanced expression of TGF-β in all but 1 tumor[18]. Also, cell lines studies suggest that small bowel NET neoplastic cells were induced to proliferate by TGF-β1 but the same effect was not reproducible in normal small bowel cells[19]. This suggests that TGF-β pathway targeting therapies might be of use in NETs management, as previously pointed out in some studies[20].

Francis *et al*[21] published a multicenter study of whole exome sequencing of 29 small bowel NETs and whole genome sequencing of 15 primary small bowel NETs, focusing on analysis of small insertion and deletion termed indels. They found recurrent heterozygous

inactivating indels in the cell cycle inhibitor gene *CDKN1B* in 8% of small bowel NETs. With the release of this information, Banck *et al*[16] reviewed their results targeting *CDKN1B* gene, coming to similar results. This finding suggests that cell cycle inhibitory drugs may be of interest in the treatment of a subset of patients. Curiously, germline mutations in *CDKN1B* are known to cause MEN-4, a cancerous syndrome with known association to endocrine NETs, and *CDKN1B* mutations have been implied in other cancers, like colorectal, breast and prostate.

In an effort to understand the expression profiles and regulatory networks involved in NETs, Kidd *et al*[22] re-analysed two small intestinal tumor transcriptomes. They reported that in small bowel NETs the genes involved in secretory activity were conserved; however alterations in transcription factors associated with neurodevelopmental process were reported, suggesting that abnormalities of this process may be relevant in the neoplastic evolution. The study group was also able to confirm the loss of SDHD expression, a finding usually associated with benign tumors.

Another recent breakthrough in the understanding of NETs pathophysiology is the study of microRNAs (miRNAs). MiRNAs consist of small (19-25 nucleotides), non-coding RNAs with the capability to regulate the expression of at least one-third of protein-coding genes. Their deregulation has been associated with the development of cancer, and some subsets of neoplasm have been extensively studied in the field of miRNAs with results that point to the influence of deregulated miRNAs in the staging, prognosis and response to therapy[23]. They have the capacity to regulate gene expression, to influence neighbor cells and even to be packed and transported extracellularly, entering the bloodstream, and modulating cells at distant site in an hormone-like action[24].

This subtype of RNA can be extracted from several body fluids, is long-living *in vivo* and very stable *in vitro* which enables miRNA profiling techniques to be extremely sensitive, objective and standardized, characteristics that make miRNAs potential biomarkers[25]. Also, they can act as potential therapeutic targets with preclinical models pointing to the efficacy of miRNA based therapies[26].

Regarding SI NETs, two recent miRNA expression profile studies showed that miRNA deregulation played a role in small bowel NETs tumorigenesis. The first one associated miRNA-133a downregulation with progression from primary to metastatic disease. This suggests that this miRNA may have a role in ileal NETs development and progression, being a potential marker of diagnosis and/or prognosis[27]. Interestingly, miRNA-133a is located to chromosome 18, which was shown to be recurrently lost in whole genome studies. In the second study, the expression of miRNAs in well-differentiated small bowel NETs was evaluated, with the goal to provide new disease biomarkers. They reported that five miRNAs were upregulated (miRNA-96,-182,-183,-196 and-200) and four were downregulated (miRNA-31, -129-5p, -133a and-215) during tumor progression[28].

Although these findings might be promising, there is still much to be understood regarding the mechanisms behind NETs development. Nevertheless, this recent knowledge has allowed to guide the scientific community, with the emergence of clinical trials with therapies targeting the genetic alterations described so far.

BIOMARKERS AND OTHER LABORATORY TESTS

Several circulating tumor markers have been evaluated for the diagnosis and follow-up of NETs. Currently, chromogranin A (CgA) is the most important of these markers, and current guidelines recommend measurement of serum CgA at diagnosis[5,6,29]. It consists of a polypeptide widely expressed in secretory granules of neuroendocrine cells. Plasma CgA is elevated in 60%-100% of patients with NET, either functioning or nonfunctioning, with a sensitivity and specificity for detecting NET of 70% to 100%[29]. However, CgA levels are influenced by the assay used[30] and are highly influenced by several common conditions, and false elevation of this marker has been reported in patients using proton pump inhibitors, with renal or liver failure and even in chronic gastritis[31]. Other proposed markers are plasma neuron-specific enolase, urinary 5-HIAA (as a marker of carcinoid syndrome) and a variety of other secreted amines such as chromogranin B and C, substance P, neurotensin, among others[29].

In an effort to find better NETs biomarkers, Modlin *et al*[32] recently published a multi-transcript molecular signature for PCR blood analysis which may facilitate future diagnosis of NETs. They analyzed transcripts of 3 microarray datasets (NETs peripheral blood, NETs tissue and adenocarcinoma) and found 51 significantly elevated transcript markers. Based on that, gene-based classifiers were created and were able to detect NETs with high sensitivity (85%-98%), specificity (93%-97%), positive predictive value (95%-96%) and negative predictive value (87%-98%). The transcript marker was similarly effective in recognizing pancreatic and gastrointestinal NETs, as well as, metastases. Moreover, the gene-based classifier was significantly more accurate than CgA and, in patients with low CgA, the transcript markers were elevated in 91% of cases[32]. This may reflect the future utility of genetic markers as diagnostic tools of NETs, however further investigation needs to be done to validate this hypothesis.

DIAGNOSTIC IMAGING

For duodenal NETs diagnosis, upper gastrointestinal endoscopy with biopsies (or endoscopic removal of the lesion for histopathological assessment whenever feasible) is the most sensitive diagnostic test. This

Table 1 Duodenal neuroendocrine tumors treatment

Duodenal NETs – surgical treatment	
⩽ 1 cm	Local ressection (if possible)
⩾ 2 cm OR lymph nodes metastasis	Surgical ressection
Potentially resectable hepatic metastases without distant metastases and no other significant comorbility	Palliative surgery
Duodenal NETs – farmacological treatment	
Functional duodenal NETs	Hormone suppression treatment
Well-differentiated NETs	Systemic chemotherapy if advanced metastatic disease
Poorly differentiated tumors	Combination chemotherapy – variable duration disease remission mTOR, tyrosine kinase and VEGF inhibitors – phase 3 trials with promising results
Metastatic or inoperable disease	Peptide receptor radionuclide therapy When all other treatment options fail If positive octreoscan

NETs: Neuroendocrine tumors; VEGF: Vascular endothelial growth factor.

can be coupled with endoscopic ultrasound in order to locally stage the disease, by evaluating the depth of involvement and the presence of local lymph nodes metastases[6,33]. Endoscopic ultrasound may be complemented with fine-needle aspiration (FNA) to obtain cells in deeper layers such as the submucosa, for histological diagnosis. Regarding jejunal and ileal NETs, ileocolonoscopy can make the diagnosis in more distal lesions but until recently, most of the small bowel extent was not accessible to direct mucosal visualization. With the evolution of enteroscopic diagnostic tools, physicians have now at their disposal new, promising diagnostic tools like capsule enteroscopy (CE) and balloon-assisted enteroscopy. CE proved itself useful in the study of suspected small bowel neoplasms, due to its high diagnostic yield and non-invasiveness, obtaining high quality endoscopic imaging even in the absence of bowel preparation[34]. Also, CE seems better than CT and enteroclysis in detecting primary NETs and has a similar diagnostic yield as somatostatin receptor scintigraphy (SRS) with the advantage that the first one can differentiate between intestinal and mesenterial localization[35]. In a review of our center epidemiology on small bowel tumors diagnosed by CE, 1510 CE performed between 2006-2014 were reviewed and included those classified as having suspect small bowel tumors with ⩾ 10 mm dimension. Lesions suspect of SI tumor were identified in 19 EC (1.3%), and histological confirmation of primary small bowel neoplasm was obtained for 6 cases, of which 2 patients were diagnosed with NET - one duodenal and another ileal - (unpublished data).

After the diagnosis, thorax X-ray, Helical CT or MRI of the abdomen and pelvis coupled with SRS should be done to assess disease extent and search for distant metastasis[5,6,31]. SRS is an imaging diagnostic test in which a somatostatin analog, octreotide, is radiolabeled and administered to the patient. Since the majority of NETs express one or more subtypes of somatostatin receptors, this technique allows detection of local and distant disease. In patients with advanced disease, especially liver metastases, bone scintigraphy and MRI of the spine should also be done to exclude bone metastasis[5,6].

PET scan using its classic tracer ^{18}F-deoxyglucose is not effective in the diagnosis of well differentiated NETs. However, using this diagnostic technique with specific neuroendocrine tracers has shown good results, with better detection of small primary tumors and lymph node metastases than CT, MRI and even SRS[36,37].

Moreover, for patients with carcinoid syndrome it is mandatory to perform an echocardiography to evaluate the presence and severity of carcinoid heart disease[5].

TREATMENT

Concerning treatment, clinical societies state that curative surgery should be aimed for in patients with duodenal, jejunal and ileal NETs whenever possible[5,6,29,38].

For small (⩽ 1 cm) duodenal NETs local endoscopic resection is an option but larger duodenal NETs (⩾ 2 cm) or the presence of lymph node metastases should be treated surgically[6]. Palliative surgery should be offered for those patients with potentially resectable hepatic metastases without distant metastases and no other medical conditions that can markedly compromise life expectancy. In the minority of duodenal NETs that display functional hormonal syndromes, specific treatment for hormone excess suppression should be given to the patient[6] (Table 1).

Jejunal and ileal NETs have a greater propensity to metastasize and are more frequently multiple lesions therefore, even in small tumors, surgery should involve search for additional tumors by inspection and palpation[29] as well as wide lymphadenectomy[5]. In patients with liver metastases curative surgery should still be attempted, and intraoperative ultrasonography should be performed for detection of all liver metastases[5]. Palliative surgery should still be considered to prevent complications attributable to the tumor mass in patients not suitable for curative resection[5].

In jejunal and ileal NETs with carcinoid syndrome, somatostatin analogs effectively reduce symptoms in 40%-80% of patients. Also, this therapy proved capable

Table 2 Jejunal and ileal neuroendocrine tumors treatment

Jejunal and ileal NETs – surgical treatment	
Without metastasis, all sizes	Surgical resection with wide lymphadenectomy + search for other lesions
With liver metastases	Attempt curative surgery; intraoperative ultrasonography should be performed for detection of all liver metastases If patient not suitable for curative resection, palliative surgery should be considered to prevent complications attributable to the tumor mass
Jejunal and ileal NETs – farmacological treatment	
Functional jejunal-ileal NETs	1st line: Somatostatin analogs (symptomatic treatment and tumor growth stabilization) 2nd line: Interferon-α
Well-differentiated NETs	Systemic chemotherapy not recommended
Poorly differentiated tumors	Combination chemotherapy – variable duration disease remission mTOR, tyrosine kinase and VEGF inhibitors – phase 3 trials with promising results
Metastatic or inoperable disease	Peptide receptor radionuclide therapy When all other treatment options fail If positive Octreoscan

NETs: Neuroendocrine tumors; VEGF: Vascular endothelial growth factor.

to induce stabilization of tumor growth in up to 50% of cases thus, somastatin analogs are clearly indicated in functional jejunal-ileal NETs[5]. Interferon-α can be used with the same purpose but its toxicity profile make this a second-line treatment option[5,29] (Table 2).

Systemic chemotherapy showed poor results in the treatment of small bowel NETs and is not recommended for well-differentiated NETs of midgut and hindgut[5] and, in well-differentiated duodenal NETs it is reserved for those patients with advanced metastatic disease[6]. However, in patients with poorly differentiated tumors, combination chemotherapy has been shown to induce disease remission with variable duration[39,40]. Consequently, for this group of small bowel NETs chemotherapy constitutes a treatment option[41,42]. Clinical trials using mTOR, tyrosine kinase and VEGF inhibitors in the treatment of NETs are currently being developed, showing promising results. One trial used patients with metastatic or unresectable NETs on stable doses of octreoctide and randomized them to association treatment with either VEGF inhibitor bevacizumab or pegylated (PEG) interferon α-2b for 18 wk. Bevacizumab therapy showed greater reduction of blood flow and longer progression free survival compared to PEG-Interferon therapy. However this trial had a limited number of patients and a larger phase 3 confirmatory study is underway[43]. A phase 3 study compared the association of octreotide long acting-repeatable (LAR) with Everolimus, a mTOR inhibitor, versus its association with placebo. Median progression-free survival was 16.4 mo in the everolimus plus octreotide LAR group and 11.3 mo in the placebo plus octreotide LAR group[17]. These findings point to the survival benefit of everolimus in the treatment of NETs and although it cannot be considered as standard treatment, it can be considered for patients without other treatment options[29].

For patients with metastatic or inoperable disease who have exhausted all other treatment options, peptide receptor radionuclide therapy should be considered if Octreoscan is positive. This treatment uses the somatostatin receptor present on the neoplasic lesion to deliver radio-labeled peptides directly to it. The majority of clinical centers use either ^{90}yttrium or ^{177}lutetium but a recent study tested the combination of both radioisotopes with an improved overall survival compared to single radioisotope treatment[44]. Still, further studies on this new treatment field need to be done.

CONCLUSION

NETs are an unusual neoplastic disease with several unanswered questions regarding its pathophysiology, diagnosis and treatment. Recent breakthroughs have redirected our approach in therapy clinical trials and may bring better diagnostic tools and even new prognostic markers. Still much work has to be done in order to fully understand this disease.

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