Neuroendocrine neoplasms of the gastroenteropancreatic tract: radiologic semiology and imaging technique

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Learning objectives

- Show the main imaging characteristics of the neuroendocrine neoplasms of the gastroenteropancreatic axis.
- Remember its clinical involvement and association with other neoplasms.
- Describe the requirements of a top-quality study protocol.

Background

INTRODUCTION
The neuroendocrine system is composed of cells derivated from neural crest. These cells may be organized in glands (adrenal medulla, parathyroid, hypophysis and paraganglia) or diffusely (in the pancreas, gastrointestinal tract, biliary tree, liver, lung, urethra, skin, etc.). These cells can give rise to various tumors with very special common characteristics known as neuroendocrine tumors (NET).

The majority of them (67.5%) occur within the gastroenteropancreatic (GEP) axis, because of that they are our study objective. They include the classic "islet cell tumors" originating in the pancreas and peptid-bioactive productors, and the "carcinoid tumors" originating in GEP axis and serotonin producers. Both share the same embryologic origin, biologic behaviour, syndromic clinical setting and radiologic semiology, so it is possible to find gastrinomas in duodeno or pancreatic carcinoids. The next in frequency are bronchial (25.3%).

The NET account for 1-2% of all gastrointestinal neoplasms, with an incidence of 1.6-2 new cases per 100,000 persons per year. In our series the most frequent location was pancreas (n=9), stomach (n=7), jejenum and ileum (n=5), colon (n=2), duodenum (n=1) and appendix (n=1).

Most of the pancreatic islet cell tumors are sporadic but sometimes occur as part of complex familial endocrine cancer syndromes like type 1 multiple endocrine neoplasia (MEN 1), neurofibromatosis 1 (NF-1) or Von Hippel-Lindau (VHL).

CLASSIFICATION
A variety of nomenclature has been used for these tumors, which may be confusing to radiologists.

Actually the gastrointestinal neuroendocrine tumors are classified by the World Health Organization (WHO) 2000 in: "well-differentiated endocrine tumors" (synonymous with the term carcinoid), "well-differentiated endocrine carcinomas" (synonymous with the term malignant carcinoid) and "poorly differentiated endocrine carcinomas". Well-differentiated endocrine tumors demonstrate benign behaviour or uncertain malignant potential, well-differentiated endocrine carcinomas are characterized by a low-grade
malignancy, and poorly differentiated endocrine carcinomas show a high grade malignancy. They can also be classified by the location: stomach, duodenum, jejunum, ileum, appendix, colorectum and pancreas; or biologic behaviour: vascular invasion, mitotic and hormonal activity, presence of metastases, invasion of adjacent organs and association with clinical syndromes (MEN 1, NF-1).

With regard to the pancreatic tumors they are divided on: syndromic ("functioning") and "clinically silent", depending of the hormone production grade. Each one tends to produce different types of hormones, receiving the name according to the predominant type hormone. The most common are gastrinoma and insulinoma.

NEUROENDOCRINE TUMOR MARKERS

The neuroendocrine cells of the diffuse neuroendocrine system contain dense core granules, marker proteins (chromogranin, synaptophysin and neuron-specific enolase) and other peptid and specific hormones. Immunohistochemical techniques are used in the diagnosis of these types of tumors. Cromogranin A has been detected in most neuroendocrine cells and neoplasms and it is considered the most important single marker of neuroendocrine differentiation, although do not exist any specific one.

In pancreatic tumors there have been described markers like CK-19, CD-10, CD-99, Ki-67, pancreatic polypeptid, etc. but they are non-specific and there is not enough evidence that demonstrate its profit on the prognosis of these tumors.

GENERAL PATHOLOGIC FEATURES OF THE GASTROINTESTINAL NEUROENDOCRINE TUMORS

They are usually well-differentiated tumors that originate from cells localized in the intestinal mucosa or submucosa (Kulchitski cells), have low growth, malignant potential and dissemination capacity (direct or lymphatic invasion) along the mesentery. They may associate other gastrointestinal adenocarcinomas.

The clinical presentation is varied: obstruction, abdominal pain, hemorrhage, weight loss, invagination, carcinoid syndrome, etc. This one appears in 10% of the cases, usually in ileal carcinoids with liver or retroperitoneal metastases, and it is originated for the peptids and bioactive amines secreted by the tumor (especially serotonin) with the clinical triad: flushing, diarrhoea and valvulopathy.

Macroscopically they are yellow, polypoids if small or intramural masses. Microscopically contain eosinophilic cytoplasm and round nuclei with no significant mitotic activity and small nucleolus grouped into nests.

GENERAL PATHOLOGIC FEATURES OF THE PANCREATIC NEUROENDOCRINE TUMORS

Pancreatic islet cell tumors (ICTs) represent the 1,3% of the pancreatic tumors, the incidence is about 10 cases per million population per year and affect younger patients than other pancreatic tumors.

They are usually well-differentiated tumors, sporadic and solitary; but when they are associated with syndromes like MEN 1, VHL, NF-1 or tuberous sclerosis they use to be multiple.

About the 68% have malignant potential but they have better prognosis than exocrine adenocarcinoma.
RADIOLOGIC CHARACTERISTICS OF CARCINOIDS

They are typically hyperenhancing (the primary tumor and metastases) and are usually best seen on CT scans obtained during the arterial phase because of their intense vascularization, generally with loss of enhancement at portal venous phase. In many patients the primary tumor is not identifiable in imaging techniques because the small size but in these cases it is possible to detect lymphadenopathy or mesenteric masses. Mesenteric infiltration is common in ileal NET (we discuss them later). The most frequent metastases appear in the liver. In our series 9 patients presented liver metastases, most of them with an hypervascular behaviour (Fig. 1). We found 9 patients with mesenteric metastases (Fig. 2), retroperitoneal and 3 with bone metastases that in our experience can be litic and frequently blastic (Fig. 3 and Fig. 4).

1. Stomach
They account for 8.7% of all gastrointestinal carcinoids. They manifest as epigastralgia, sickness, vomiting, diarrhoea, etc. Loco-regional lymph nodes are frequent (Fig. 5).
There are three types of carcinoids of the stomach:
- Type I: are the most common (70-80% of the cases) and usually manifest as small (< 2 cm) tumors. They occur most frequently in women and grow from the fundus and body (Fig. 6). They are associated with chronic atrophic corpus gastritis (Fig. 7). The 5% are metastatic.
- Type II: are also small (< 2 cm) and often multiple, manifested as mucosal or submucosal nodules that enhanced, and with metastases being reported in 10%-30% of cases. They are frequently associated with Zollinger-Ellison syndrome (ZES) and MEN 1 as result of the hypergastrinemia (Fig. 8 and Fig. 9).
- Type III: They are usually large (> 2 cm) single neoplasms located in the body and fundus and typically show vascular invasion at the time of diagnosis. Often manifest with metastases, which are found in 50%-70% of gastric well-differentiated neuroendocrine carcinomas and in up to 100% of gastric poorly differentiated endocrine carcinomas. They may be ulcerated (Fig. 10). They occur in absence of underlying gastric disease or hypergastrinemia (sporadic tumors).

2. Small intestine
It is the most common location of carcinoids. In 3-50% of the cases are multiple. They are diagnosed later, with metastases or mesenteric fibrosis. At the time of diagnosis they have already metastasized to the regional lymph nodes.
- a) Duodenal:
Abdominal pain is the most common symptom. The most frequent type in this location is gastrinomas, followed by somatostatinomas. Duodenal gastrinomas are either sporadic or associated with MEN 1 and ZES. The first are usually smaller than1 cm and the second are generally multiple, smaller than 5 mm and located predominantly in the upper portion of the duodenum.
At imaging studies duodenal carcinoids manifest as intraluminal polypoid masses or intramural masses, with arterial phase enhancement and loss of enhancement at delayed imaging. Metastases are often found in the regional lymph nodes at the time of diagnosis, despite their small size and their confinement to the duodenal mucosa and submucosa. Metastases to the regional lymph nodes occur at an early stage, whereas liver metastases usually occur late.

b) Jejunum and ileum: represent almost 30% of all gastrointestinal neuroendocrine tumors. The most common clinical signs and symptoms are intermittent intestinal obstruction and vague abdominal pain. The primary tumor usually measure less than 3 cm and may be multiple, although lymph or liver metastases are bigger. Approximately 20% of patients with ileal neuroendocrine tumors have hepatic metastasis. On CT scans they manifest as asymmetric or concentric mural thickening that enhance in arterial phase. Small intestinal carcinoids may produce a kink or curvature of the intestinal wall that has been called a hairpin turn. The kinking is the result of tumor infiltration and fibrosis. Transmural tumor extension is recognized as concentric mural thickening and a focal soft tissue mass of tumor located immediately adjacent to a thickened small intestinal wall. It is characteristic the mass calcification (detected in 70% of the cases), sign that helps to differentiated from other mesenteric tumors (Fig. 11). Desmoplastic reaction may kink the bowel and cause obstruction, or it may obstruct vascular supply, causing ischemia or infarction of the involved segment (Fig. 12).

4. Colon and rectum
Neuroendocrine tumors of the colon are very rare. These tumors occur more commonly in the right colon and tend to produce larger lesions (>5 cm). At histologic analysis, they are poorly differentiated endocrine carcinomas, almost all of them have already metastasized at the time of diagnosis and, therefore, have a poor prognosis. Carcinoid syndrome is common, because of metastatic disease. Rectal neuroendocrine tumors are much more common than colonic neuroendocrine tumors, representing about 11% of all gastrointestinal neuroendocrine tumors. Most of them are still localized at the time of diagnosis. They are usually single lesions, smaller than 1 cm, and manifest as movable submucosal tumors; although may appear as mural enlargement (Fig. 13). Metastases occur in tumors larger than 2 cm and tumors are often positive for serotonin. Transrectal ultrasonography is useful for determining the depth of tumor invasion preoperatively.

5. Appendix
Appendiceal carcinoids are the most common tumors in the appendix and are diagnosed at an earlier patient age than are other carcinoids. They occur primarily in the tip of the appendix and almost always invade the muscularis mucosa and the adjacent fat tissue of the mesoappendix (Fig. 14). Most of them are smaller than 1 cm, and metastases to regional lymph nodes is rare. Appendiceal carcinoids have the most favourable prognosis of all gastrointestinal neuroendocrine tumors. The carcinoid may manifest as a focal soft-tissue mass within the appendix or as diffuse, circumferential mural thickening on cross-sectional images.
We have found many cases of appendiceal carcinoids in the Pathologic reports post-appendectomy but only one of them has been included in our study because it has imaging correlation.

RADIOLOGIC FEATURES OF THE PANCREATIC NEUROENDOCRINE TUMORS
The vast majority are typically hyperenhancing and are usually best seen in the arterial phase but some of them are hypovascular and are best detected in venous phase. Larger masses are heterogeneous, with annular enhancement and central regions of cystic degeneration and necrosis (Fig. 15).
The size is correlated with the calcification and malignant behaviour but the only unequivocal criteria for malignancy are gross invasion of adjacent organs, large vessel invasion and metastases to lymph nodes or distant organs (liver the most common followed by lymph nodes and bone). The histologic differentiation is less important for prognosis. Although they are described as a rare cause of pancreatic duct dilation, in our series we have found four cases with Wirsung dilation, even in small tumors. On ultrasound (US) they manifest as hypoechoic masses when compared with the pancreatic parenchyma, with smooth and well-defined margins. Endoscopic or intraoperative US may be very helpful to detect small tumors and establish their relationships with the pancreatic, biliary ducts and large vessels.

ICTs produce and secrete hormones to a variable degree and are categorized in syndromic (functioning) and nonsyndromic (non-functioning).

a) Syndromic ICTs
They are diagnosed small (less than 3 cm in size) because of the endocrine syndrome related to the hormone production.

Insulinoma: It is the most common syndromic ICT. The 90% are intrapancreatic, single and have a hypervascular behaviour (Fig. 16). Ten percent of insulinomas are associated with MEN 1 and in such cases they are usually multiple, functioning, < 2 cm and have a less malignant potential than the rest of the sporadic tumors (Fig. 17). Ten percent are malignant. Intraoperative ultrasound is useful in small tumors. The classic clinical triad (Whipple triad) includes fasting serum glucose levels less than 50 mg/dL, symptoms of hypoglycemia and relief of symptoms after glucose administration.

Gastrinoma: (Figs. 18, 19, 20 and 21). It is the second most common syndromic ICT. Gastrinomas are usually multiple, manifest as ZES and are often extrapancreatic, in the "gastrinoma triangle" (Fig. 22). They have a less hypervascular behaviour than insulinoma.

Glucagonoma: Most of these lesions are relatively large, with slow growth and metastases at the time of diagnosis. They are usually single and occur in the body or tail of the pancreas. Low-attenuation areas which represent necrosis are frequent. Patients may also experience stomatitis, diarrhoea, anemia, weight loss, depression and deep vein thrombosis (termed the "4D syndrome": dermatosis, diarrhea, depression and deep vein thrombosis).

Vipoma: Most vipomas are usually malignant, over 3 cm in size, unique and are located in the tail of the pancreas. Almost 60% of patients have liver metastases at the time of diagnosis. It is known as Verner-Morrison syndrome. Vipomas produce excessive quantities of vasoactive intestinal polypeptide (VIP) that result in a typical watery diarrhea. They usually contain cystic degeneration areas and necrosis.
Somatostatinoma: it is very rare. It is generally large, unique and presents metastases at the time of diagnosis. Most commonly it is seen in the head of the pancreas and less commonly occurs at the ampulla of Vater. There is association with NF-1.

b) Nonsyndromic ICTs
Nonsyndromic ICTs represent one-half of all ICTs and are larger than syndromic ICTs at initial presentation (>5 cm). Nonsyndromic ICTs show no clinical evidence of hormone production, although these tumors are still hormonally active, and the 90% are malignant. They produce symptoms related to mass effect, local invasion or metastases. They are usually hypervascular, heterogeneous, with necrosis, calcification and cystic areas. The 30% are atypical and indistinguishable from adenocarcinoma (Fig. 23 and Fig. 24).

PROTOCOL OF STUDY
MDCT is considered to be the imaging modality of choice for tumor detection and staging, surgical planning, and follow-up.
In cases with clinical suspicion of pancreatic tumors, because they are often very vascular and small, it is important to establish a two-phase CT protocol without high-density oral contrast agents that allow detect them during the arterial phase. In our hospital we administer 1 liter of water 1 hour prior to the study and 400 mL immediately prior to start it. We inject 120 mL of nonionic contrast material at a rate of 4 mL/sec with dual-phase imaging: delay of 35 seconds for arterial phase (to iliac bone) and of 70 seconds for portal venous phase imaging (including pubis symphysis).

For carcinoid tumors, if a gastric origin is suspect, the prior procedure is valid. If it is not suspect we think it could be useful to execute an Entero-CT, with two ampoules of Duphalac diluted in 1500 mL of water in 1 hour, one ampoule of Primperan at the moment of the ingestion and one ampoule of Buscapina intravenous with the patient on the CT-table. The additional use of a water enema (400 mL) improves the small intestine distension. We execute the dual-phase study with 120 mL of nonionic contrast material at a rate of 5 mL/sec, arterial phase (delay of 35 seconds) and portal venous phase (70 seconds) of complete abdomen. So, the small intestine can become distended and we can visualize with detail the wall and identify very small tumors that with other procedure could go unnoticed.
Routinely we do not use MRI and its diagnostic accuracy to detect NET is lower than MDCT.

111 In pentetreotide scintigraphic studies are used in Medicine Nuclear techniques. Positron emission tomography (PET) has not been shown to depict gastrointestinal carcinoid tumors effectively. The 18 FDG incremented uptake is only seen in the most aggressive and poorly differentiated tumors. Other radionuclides more specific like 18F-DOPA and 68Ga-DOTA-NOC have been described but there are not enough comparative studies.

Images for this section:
Fig. 1: Carcinoid tumor with liver hypervascular metastases, well recognized in the arterial phase and more difficult to identify in the venous phase.
Fig. 2: Fig. 2. Carcinoid tumor in the sigma with metastatic mass in mesentery. These masses usually have spiculated margins and calcifications.
Fig. 3: Litic metastasis in vertebral body with a soft tissue mass associated in the same patient than Fig.2.
Fig. 4: Blastic bone metastases in a patient with carcinoid ileal tumor. Neuroendocrine tumors are a source of blastic bone metastases.
Fig. 5: Type III gastric carcinoid with lymphadenopathy in the gastrohepatic ligament.
Fig. 6: Submucous carcinoid in a 77-year-old female without clinical symptoms, which depends of the minor gastric curvature in the transition fundus-body.
Fig. 7: 54-year-old female with chronic atrophic gastritis, diarrhea and weight loss. Transverse CT scan shows gastric fold enlargement on the minor curvature with pseudopolipoid appearance. Biopsy of a polipoid lesion was made by endoscopy and the result was "well-differentiated carcinoid". Small hypervascular liver lesion in segment VII (arrow).
**Fig. 8:** 70-year-old male with chronic hepatopathy and recurrent peptic ulcer who presented hypervascular submucosal tumor in the major curvature gastric.
**Fig. 9:** Fig. 9. Same patient than in Fig. 8. Contrast-ultrasound demonstrate the high grade vascularization in the submucosal lesion. The first image in B mode shows the nodular hypoechoic lesion (arrow) on the wall of a water-distended estomach (asterisk).
Fig. 10: Fig. 10. Type III gastric carcinoid in a 78-year-old female with weight loss and hematemesis. Oblique reformatted CT. Endoscopy confirmed an ulcerated tumor in the mayor curvature gastric (arrow). The tumor infiltrated the gastrocolic ligament with adenopathy in the gastrohepatic ligament, esplenic hilium and gastrocolic ligament.
**Fig. 11:** Fig. 11. 33-year-old male with diarrhea and weight loss. Concentrical mural ileum enlargement (arrow) with mesenteric mass associated and typical espiculation and calcification (arrowhead). A liver metastases was detected in the course of the study, an example of hipovascular metastases (long arrow), which caused the carcinoid syndrome.
Fig. 12: Fig. 12. 84-year-old female with abdominal pain. Axial CT shows a hypervascular ileal tumor (short arrow) with spiculated mesenteric mass and calcification (arrowhead) that encased the ileocolic artery, producing intestinal ischemia: diffuse and stratified ileal enlargement (thick arrow). Numerous hypervascular peritoneal nodules (circles) that may correspond to tumoral implants in the context of a carcinomatosis or because of the multifocal behaviour of the NET. A hypervascular nodule in the pancreatic head is identified as an additional feature (long arrow). Carcinoid tumors may appear in rare cases as islet cell tumors.
Fig. 13: Fig. 13. 61-year-old male with rectal sessile polyp at endoscopy. Right tumoral enlargement of the 1/3 superior rectum wall with mesorrectal and lymph infiltration that corresponds to a carcinoma with neuroendocrine differentiation, indistinguishable by imaging from an usual adenocarcinoma.
**Fig. 14:** Fig. 14. 21-year-old female who presented two days abdominal pain and peritoneal irritation signs. CT demonstrates a soft-tissue mass int the appendix (arrow). A carcinoid appendiceal tumor without inflammation was observed at pathologic analysis.
Fig. 15: Fig. 15. 56-year-old man with diabetes mellitus who presents a heterogenous mass in the pancreatic body with cystic component and calcifications (arrow). There are multiple hypervascular and cystic liver metastases and many mesenteric lymph metastases (cystic and hypervascular too) which traduce the same appearance than the primary tumor. The pathologic analysis demonstrates a cystic variant of non-functioning islet tumor.
Fig. 16: 43-year-old with suspicion of insulinoma. CT shows a 12 mm hypovascular lesion in the head of the pancreas (arrow). Biopsy confirmed a NET. It is not frequent to find hypovascular insulinomas.
Fig. 17: Fig. 17. 33-year-old male with MEN 1 and clinical manifestations of insulinoma. CT demonstrates 3 small hypervascular nodules on the head and body of the pancreas (arrows).
Fig. 18: 72-year-old female who was operated of a duodenal NET in 2007. CT shows a hypervascular nodular lesion of 6 mm in the uncinate process (short arrow) not visible in the venous phase. It was diagnosed finally, clinically and pathologically, as gastrinoma.
**Fig. 19:** Fig. 19. 78-year-old female in study of metastatic NET. CT demonstrates 9 nodular lesions, most of them in the pancreatic head, where produced ectasia (short arrow) of the Wirsung and accessory duct (long arrow). Pathologic analysis revealed a "well-differentiated" multifocal gastrinoma. A nodule in the choledochal wall (arrowhead) that produced biliary tree dilation was also seen. Curve VR CT image may be helpful to improve the diagnosis of these small lesions.
Fig. 20: Fig. 20. 49-year-old male with MEN 1 who was operated of pancreatic gastrinoma with uptake in octreotide scintigraphy and gastrine elevated. On CT it is observed one nodular hypervascular lesion in the tail of the pancreas (arrowhead), an extrapancreatic nodule between the uncinate process and duodenum with similar characteristics (long arrow) and 7 small hyperenhancing lesions in the mucosal of 2° and 3° duodenal portions (short arrows). One of them was localized in the "gastrinoma triangle" and other in the Vater papila producing minimal biliar dilation. RM shows one duodenal lesion. The great spatial resolution afforded by multi-detector CT improve the visualization of small lesions and makes it the technique of choice.
**Fig. 21:** Fig. 21. Patient with RHC pain and diarrhea. US shows a hypoechoic lesion in the neck of the pancreas (arrow). This behaviour is also demonstrated on the contrast-US. The diagnosis was a gastrinoma NET.
**Fig. 22:** Fig. 22. The gastrinoma triangle is defined for the biliar duct (upper limit), 2ª and 3ª duodenal portions (lower limit) and the pancreatic neck and body (medial limit) confluence.
**Fig. 23:** Fig. 23. 74-year-old male with paraneoplastic syndrome who presented focal hyperechoic lesions and a mass in the head of the pancreas on US. CT shows a large heterogeneous mass with small calcifications (arrows) in the head of the pancreas that produced atrophy of the pancreas and Wirsung dilation, invaded celiac trunk, liver metastases and large mesenteric and retroperitoneal adenopathies with cystic and necrotic components.
**Fig. 24:** Fig. 24. 53-year-old male with resection of the body and tail of the pancreas because a "poorly-differentiated" nonfunctioning pancreatic NET. CT demonstrated tumoral recurrence in the body of the pancreas, with malignant behaviour: large size and celiac trunk invasion (arrow).
Conclusion

- Gastroenteropancreatic neuroendocrine tumors must be considered as a part of the differential diagnosis in certain clinical settings or in the presence of imaging findings that radiologist have to know. So it is important to use an adequate study protocol.

- In our series we have obtained better results in the detection and characterization of TNE with MDCT than MRI and other imaging techniques, so in our experience we consider MDCT the imaging modality of choice in the management of these tumors.

- Although classically they have been described as small hypervascular tumors, it is necessary to remember that there is some variability in the way of presentation.

- We have found tumors with manifestations in the mesentery or intestinal serous in which the anatomopathologic analysis of the adjacent removed intestinal segment wasn't able to localize the primary nidus tumor, indicating the small size that these lesions can take. On the other hand, we have ruled out numerous patients with metastatic carcinoids because it was impossible to verify the origin of the primary tumor, so it is possible to speculate that a proportion of them could have an ileal origin.

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References


