Diagnostic Imaging of abdominal neuroendocrine tumors. Imaging findings and usefulness of different techniques.

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Learning objectives

To review the findings and most frequent forms of presentation of abdominal neuroendocrine tumors (NETs) in Imaging Diagnosis Techniques.

To understand the role of diagnostic imaging in the diagnosis and management of these tumors.

Neuroendocrine tumors are a heterogeneous group of neoplasms. They originate in neuroendocrine cells of the neural crest, endocrine glands, islets or diffuse endocrine system. These cells during embryonic development are distributed almost throughout all the body, which is why NETs can be located in different organs. Neuroendocrine cells have the ability to release hormones, producing varied symptoms, are usually found in very advanced stages, when the disease has invaded different organs.
Background

NETs are characterized by heterogeneity in terms of cell lineage, anatomical location, imaging findings and potential biomarkers associated with hyper secretion syndromes, which often translates into a diagnostic and therapeutic challenge.
Findings and procedure details

NETs represent between 1.2 -1.5% of all gastrointestinal malignancies, with an incidence of 1.6-2 new cases per 100,000 people per year.

NETs settle more often in the digestive tract, mainly in the ileum, followed by the rectum and appendix. The most common form of detection is through its secondary findings or mesenteric lymph nodes metastases.

In the initial diagnosis of NETs CT or entero CT is used, for staging and monitoring of disease CT or MRI and scintigraphy with somatostatin receptors, with analogue SS + 99m (20 mCi). The use of ultrasound contrast may be considered in certain cases. (Figures 1-21).

The sensitivity and specificity of CT and MRI in the NET is comparable (93% and 88%), but MRI is more sensitive in liver metastases detection and CT in pancreatic head tumors. Overall the sensitivity increases with increasing tumor size and specificity decreases with lesions with atypical features.

Gastrointestinal NET

30% of NETs in gastrointestinal tract are located in the ileum, 2-3% in duodenum and jejunum. The primary tumor, multifocal in 26-40% of the cases, is manifested as small polypoid lesions, or hypervascular parietal concentric or asymmetrical thickening. Therefore they are not usually detectable with conventional CT or MRI techniques. CT and MR enterography or enteroclysis have demonstrated a high sensitivity (100% and 86-94% respectively) and specificity (96.2% and 95-98%). However, the most common form of detection is through their secondary findings, such as metastases or mesenteric lymph nodes. Mesenteric metastases are typically presented as contours heterogeneous spiculated mass (due to intense desmoplastic reaction), with or without central calcifications, usually near the primary tumor (Figure 22). This mass resembles sometimes to bicycle handlebars, in which the ends correspond to small bowel loops retracted by the mass.

Sometimes it is accompanied by intestinal obstruction and even venous ischemia due to involvement of mesenteric vessels. These lesions may pose differential diagnosis with other entities: mesenteric panniculitis, desmoid tumors or metastases from another origin. The metastatic lymph nodes are frequently located in the mesentry, retroperitoneum, paracardiac (most often right) and sometimes retrocrural and mediastinal. In advanced disease can be detected distant metastases in liver, lung, bone and occasionally brain. Metastases have also been described, although exceptionally, in breast and orbit.
The rectum is the second most frequent gastrointestinal localization (21-27%) experiencing a significant increase in incidence over the past three decades. Colon origin lesions are rare and larger (5cm), usually located, and its management is similar to conventional adenocarcinoma. Thoraco-abdominal CT is used as a diagnostic method of distant disease. In rectal tumors, endorectal ultrasound allows prior to surgery, to determine the degree of tumor invasion of the wall (T1, T2 or T3). Pelvic MRI is an accurate technique for assessing the degree of tumor infiltration of the mesorectal fat and adjacent structures (Figure 23).

Appendiceal NETs are the third most common gastrointestinal location after ileum and rectum (17-20%). In many cases, diagnosis is made after resection in acute abdomen. In the case that the excised tumor is larger than 2 cm, CT or MRI should be performed to assess distant disease. A review of the colon with colonoscopy or CT-colonoscopy is also necessary, because of the risk of synchronous neoplasia. This last technique consists in air or CO2 insufflation of the colon, prior preparation with residues free diet and performing MDCT with multiplanar reconstruction and volume rendering (Figure 24).

Duodenal tumors are rare, usually located in upper portion, and difficult to detect with CT and MRI due to their localization (40% and 50% intramural intraluminal) and small size (1-2 cm). Often presented as hypervascular intramural or intraluminal polypoid lesions. Gastric tumors correspond to 6-9% of gastrointestinal tumors. Of the three described types (I, II and III), types I and II are shown in CT as hypervascular submucosal lesions smaller than 2 cm, similar to other advanced polyps and gastric carcinoma (Figure 25). For detection adequate gastric distension with neutral oral contrast (water) is required. However, its diagnosis and invasion of the gastric wall is usually done by gastroscopy and endoscopic ultrasound. The type III are usually presented as solitary lesion larger than 2 cm in body and fundus.

**Pancreatic NETs**

They correspond to 7% of gastrointestinal tumors and 10% of pancreatic tumors. The majority (60-80%) are nonfunctioning tumors. Insulinoma is the most common functioning tumor (32%) followed by gastrinoma (9%).

Multidetector CT (MDCT) is the technique of choice for suspected pancreatic neoplasia. The sensitivity of MDCT varies between 67% and 94% with a specificity between 83-100%, significantly higher than those recorded in studies with older equipment (14-30%) values. The undetectable tumors with CT correspond to small lesions, usually insulinomas. Multiplanar reconstruction improves sensitivity. MRI has superior sensitivity between 74% and 94%, and a specificity between 78% and 100%. When MRI or CT are unable to detect the tumor, endoscopic ultrasound is the most sensitive technique to detect, especially in small lesions located in the head and duodenal frame, with a sensitivity range between 77-100%, with a 95% specificity. The transabdominal ultrasound with contrast, has a low sensitivity with a detection range between 20%
for small lesions and 80% for larger lesions. Preoperative ultrasound can improve intraoperative sensitivity to identify and detect small lesions and multiple lesions in more than 92-97% in patients with MEN-1 syndrome. It may be helpful with the palpation of the gland, although not sensitive in the detection of extrapancreatic lesions.

The functioning tumors are usually small and their existence is suspected by the symptoms they cause, such are the insulinomas and gastrinomas. In ultrasound usually appear as well-defined hypoechoic lesions with peripheral echogenic ring sometimes. In CT and MR they showed as small hypervascular lesions, best displayed in the late arterial phase (Figure 26). This behavior is similar to other hypervascular lesions such as metastases from another origin (renal cell carcinoma, serous cystadenomas solids) or intrapancreatic accessory spleen. Calcifications can be found mainly in the non-functioning tumors. In larger tumors, such as glucagonomas, they may present heterogeneous density. In MR these lesions are usually hypointense on T1 and hyperintense on T2 sequences with significant restrictions on DW sequences.

Gastrinomas are extrapancreatic lesions usually located in the so-called "gastrinoma triangle" (defined by the union of the pancreatic neck and body portion and third duodenal junction of the cystic and hepatic ducts) (Figure 27). VIPomas and glucagonomas, are less frequent and may be confused by CT or MRI with pancreatic ductal neoplasms.

The non-functioning tumors are usually larger, well defined and encapsulated with heterogeneous enhancement (due to existence of cystic degeneration, necrosis or fibrosis) and hypervascular ring in 90% (Figure 28). Sometimes they can be completely cystic. It is also detected more frequently intratumoral calcification (20%), which presence is often indicative of malignancy. In more aggressive tumors, as in pancreatic adenocarcinoma, retroperitoneum invasion and metastases in regional lymph nodes and liver can be seen. In this case the CT or MRI determine the locoregional staging and its relationship to adjacent vascular structures in order to establish its resectability or unresectability with the same parameters as in adenocarcinoma.

Metastases

NETs most frequently metastasize nodes and liver, followed by lungs, bone, peritoneum and mesentery, soft tissue and breast. Mesenteric metastases are typically presented as contours spiculated heterogeneous mass (due to intense desmoplastic reaction), with or without central calcifications, typically near the original tumor.

Ultrasound has a variable detection sensitivity in liver metastasis (14-88%) and specificity (92-100%). Ultrasound with intravenous contrast is very sensitive in detecting lesions less than 0.5 cm in size. The sensitivity of detection MDCT metastases ranges from 82-100% and a specificity 83-100%. MRI is superior to CT in detecting metastases with a mean sensitivity of 95% and specificity ranging from 88-100%. The combined use of dynamic contrast studies and diffusion sequences DW, improves lesion detection significantly. However, even with MRI only about 50% of existing liver damage are
detected, with a significant decrease in sensitivity lesions size less than 4 mm. In dynamic study (ultrasound contrast MDCT or MRI) lesions are hypervascular in arterial phase with washing portal phase (approximately 70%). Less frequently (15%) they have a progressive pattern or hypovascular enhancement like hemangiomas (10%). They can be found even in the same patient lesions of both types, hypervascular and hypovascular (Figure 2).

The detection of lymph node metastases by imaging techniques, mainly based on morphological criteria (minor axial diameter less than 1cm), are not sufficiently precise. 20-30% of the infiltrated lymph nodes have a lower diameter less than 1cm. There are also other causes of increased node size as the inflammatory component.

Detection of NET unknown origin

In patients with metastatic cancer of unknown primary origin, NET, mainly low-grade, are responsible for 11-14% of the cases. Although they are of poor prognosis, localization and resection of the primary tumor can prolong life expectancy 1-2 years. Biopsy of metastases, usually guided by ultrasound or CT confirms the neuroendocrine origin, and through specific markers may indicate the potential location of the primary tumor that most often is in the digestive tract. However, success in detecting the primary tumor by imaging is less than desirable, with a sensitivity of 0-22% with CT and 50% with CT-enteroclysis. CT detection of suspicious lymphadenopathy groups of malignancy, usually close to the primary tumor, may suggest its location.

Monitoring therapy of neuroendocrine tumors

NET's follow up requires a multidisciplinary management in which biochemical, radiological techniques, nuclear medicine and histological evidence are included. CT or MRI techniques are commonly used in the monitoring of neuroendocrine tumors with an interval of 3-6 months in low-grade tumors. After a year, semester controls. Then, in patients with stable disease controls can be annual.

The transabdominal ultrasound is not accepted as a therapy monitoring method. However, ultrasound contrast can be useful for liver assessment in patients where there is difficulty performing CT (allergy to contrast or renal insufficiency) or their results are equivocal.

Due to the specific characteristics of these tumors, follow up with CT must always be performed with the same technical protocol (contrast concentration, rate of administration, delay after contrast injection...) in order to reduce the variability of findings due to the technique. In fact the degree of contrast enhancement may be different based on these parameters, and simulate growth of lesions or appearance of new.

Normally the response evaluation of solid tumors is based on the so-called RECIST (Response Evaluation Criteria In Solid Tumors), based on the morphological changes (size and number of lesions). However, this system is not optimal for the monitoring of
NET, since they are mostly low graded, with a slow growth and after treatment, stability of the disease is usually observed rather than decrease of the tumor. Therefore, it is necessary to seek for other evaluation criteria in the treatment of these tumors.

Finally, in patients with genetic defect and high risk for NET, such as MEN-1 neurofibromatosis or Von Hippel-Lindau disease, transabdominal ultrasound or MRI are included as prevention protocols. The use of endoscopic ultrasound is also taken into account in MEN-1 patients for assessment of pancreatic tumors.
**Fig. 1**: CASE 1 MDCT. Axial images obtained unenhanced, arterial, late and portal phases. Hyperenhancing lesion is seen in IV liver segment with wash-out in late phase (arrow). Aortic Volume Rendering reconstruction, MIP mesenteric artery trunk and abdomen coronal image in portal phase.

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Fig. 2: CASE 2 Liver metastases of NET. (A) late arterial phase CT images: multiple hypervascular small lesions (arrowheads). (B) portal phase CT images: hypodense lesions visible in portal phase (arrow). (C) Liver MRI with axial T1-weighted phase with hepatocyte contrast: small hypointense nodule in segment VIII (arrow). (D) Contrast enhanced ultrasound in portal phase: multiple confluent hypoechoic nodules (arrow).

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**Fig. 3:** CASE 3 MRI normal liver sequences: T1 in-phase (A) and out-of-phase gradient echo images (B) with signal drop out indicative of fatty infiltration (*). T2 with fat suppression (C): Small quite intense nodule (long arrow) with respect to increased cerebrospinal fluid (CSF) signal intensity (short arrow). Sequences diffusion factor b0 (D) factor b600 (E) and ADC map (F): lesion that keeps the restriction E to D (thick arrows) unlike the CSF (small arrows).

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Fig. 4: CASE 4 T1 Dynamic sequences with hepatospecific paramagnetic gadolinium based contrast agent (interstitial and hepatocyte). Unenhanced (A), arterial (B), portal (C) and late hepatocyte phase images (D). Note in this last major enhancement of liver parenchyma and elimination through bile.

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Fig. 5: CASE 5 Enhanced ultrasound images. At baseline unenhanced study (A) a well-defined (arrow) hypoechoic node having homogeneous enhancement in arterial phase (B), isoechoic in portal phase (C) and late phase partial washing (D) is observed.

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**Fig. 6:** CASE 6 Abdominal MDCT. Coronal (A), axial images (B and C). Mesenteric mass with intense desmoplastic reaction (arrowhead). Parietal nodule in the proximal ileum that enhances after intravenous contrast administration, which could correspond to the primary neuroendocrine tumor (star).

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Fig. 7: CASE 6 Abdominal MDCT. Coronal and axial images where a globular uterus is seen with both annexes (arrowheads) enlarged and enhancement after intravenous contrast administration (A and B). Hyperenhancing peritoneal nodules (arrows) suggestive of peritoneal carcinomatosis (C, D and E).

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Fig. 8: CASE 6 Abdominal MDCT. Axial image of the liver in arterial phase (A) focal lesion in segment VI (arrow), isointense relative to liver parenchyma due to its rich blood supply. Axial liver venous phase image (B). Focal hypodense lesion relative to liver parenchyma (arrow). Lesion with characteristic semiology of hypervascular metastases. Axial retroperitoneal image (C) retroperitoneal lymphadenopathy (arrow).

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Fig. 9: CASE 6 Pelvis MRI, correlation with findings seen on MDCT. T1 sequence after intravenous contrast administration with fat suppression. Coronal image (A). Left ovary is increased in size and hyperintense (arrowhead). Hyperenhancing peritoneal nodule (arrow). Sagittal image (B). Peritoneal nodule (arrow). Axial pelvis image (C). Enlarged enhanced ovaries (arrowheads). Axial pelvis image (D) peritoneal nodule (arrow).

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Fig. 10: CASE 6 Pelvis MRI. T2-weighted sequence. Axial slices. Peritoneal slightly hyperintense nodules suggestive rectouterine recess (arrowhead) of peritoneal carcinomatosis.

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**Fig. 11:** CASE 6 Somatostatin receptor scintigraphy 99mTc. Radiopharmaceutical: 99mTc-Tektrotyd. Whole body scan (A) SPECT-CT (B). Ileal carcinoid tumor expressing somatostatin receptors (arrow).

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Fig. 12: CASE 6 Somatostatin receptor scintigraphy 99mTc. Radiopharmaceutical: 99mTc-Tektrotyd. (A) ileal carcinoid tumor (arrows). (B) Mesenteric and ovarian implants (arrows).

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Fig. 13: CASE 6 Abdominal MDCT biphasic. Increase of the number and size of liver metastases (circles) indicative of tumor progression.

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Fig. 14: CASE 6 Somatostatin receptor scintigraphy 99mTc. Radiopharmaceutical: 99mTc-Tektrotyd. Whole body scan (A). Left supraclavicular (B) and paratracheal uptake level (circles).

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Fig. 15: CASE 6 Somatostatin receptor scintigraphy 99mTc. Radiopharmaceutical: 99mTc-Tektrotyd. Liver metastases (A). Periaortic metastases (B). Peritoneal metastases (C) interaortocava metastases (D) (circles).

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**Fig. 16:** CASE 7 99mTc-MIBI scintigraphy. SPECT (A) SPECT-CT fusion images (B). Focus with mild activity in right thyroid lobe (circle).

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**Fig. 17:** CASE 7 99mTc-MIBI scintigraphy. Images SPECT-CT fusion. Focus with mild activity in right thyroid lobe (circle).

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Fig. 18: CASE 7 LAVA dynamic MRI sequences and T2-weighted and DWI. Axial unenhanced image (A) Axial images after administration of gadolinium (B). Coronal images after administration of gadolinium (C). Nodules at the 2nd portion of duodenum in duodenal-pancreatic junction and duodenal knee with contrast enhanced (arrowheads).

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**Fig. 19:** CASE 7 MRI T2-weighted sequence (A). Isointense nodule (arrowhead). Spreading sequence (B) with no restriction, no typical finding.

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Fig. 20: CASE 7 Somatostatin receptor scintigraphy 99mTc. Radiopharmaceutical: 99mTc-Tektrotyd. Whole body scan (A). SPECT-CT low dose (B). Localized lesion with high activity in duodenal knee (yellow arrow). Lesion with high activity in the second portion of the duodenum, in its lower area (red arrow). Compatible lesions with neuroendocrine tumors.

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Fig. 21: CASE 7 Somatostatin receptor scintigraphy 99mTc. Radiopharmaceutical: 99mTc-Tektrotyd. Third abdominal focus of activity of somatostatin receptors in the pancreatic tail adjacent to the lower pole of the spleen (purple arrow). Three abdominal foci activity (triangle). Lesions compatible with neuroendocrine tumors.

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Fig. 22: CASO 8 Ileal NET with mesenteric metastases (*) of spiculated morphology which causes retraction of adjacent loops (arrows) with wall thickening suspicious of vascular commitment.

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Fig. 23: CASO 9 MRI pelvic TNE T3N2 lower rectum. Axial (A) and sagittal images (B) T2. Rectal discreetly hyperintense mass invading mesorectal fat (*) with multiple regional lymph nodes (arrow) can be seen.

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Fig. 24: CASO 10 Appendiceal NETs patient who comes to the emergency department with pain in right lower quadrant. In ultrasound (B) thickened appendix (*) was observed. In CT (A) irregular wall thickening with mucosal enhancement (short arrows).

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Fig. 25: CASE 11 Gastric NETs Type II. Contrast enhanced CT in late arterial phase. Two hypervascular nodules in the gastric body and fundus (arrows) are seen.

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Fig. 26: CASE 12 Insulinoma in pancreatic tail. CT lesion is seen with homogeneous enhancement in late arterial phase (arrow).

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Fig. 27: CASE 13 Gastrinomas. Unenhanced CT images (A and B): small lesions in pancreato-duodenal area (arrows). T1 MRI contrast in the arterial phase (D) and portal coronal plane (C): homogeneous and early enhancement of these lesions is appreciated.

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**Fig. 28:** CASE 14 Nonfunctioning NETs in uncinate process of pancreas head (arrows). Pancreatic MRI. In dynamic study T1 without contrast (A) hypointense nodule rounded morphology is observed. In arterial (B), portal (C) and late phase images (D), progressive contrast enhancement is appreciated. In portal phase (C) slightly hypervascular ring is observed. T2 (E) Moderate hyperintensity is observed. DW sequence (F) presents significant restriction resulting in hyperintense lesion.

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Conclusion

NETs are a specific group of tumors considered in the differential diagnosis of suspected neoplasia.

It is important to know its characteristics, evolution, and major differences with other abdominal malignancies radiological findings.


