CT Enterography Evaluation of Small Intestine

Neuroendocrine Tumours and Correlation with $^{68}$Ga-DOTA-NOC PET/CT Findings

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Learning objectives

The objective of this presentation is to review and illustrate imaging findings of small intestine neuroendocrine tumours (NETs) on computed tomography (CT) enterography and to correlate with findings from $^{68}$Ga-DOTA-NOC PET/CT.

There are still no clear guidelines on which techniques to use for the diagnosis and follow-up of small intestine NETs.

CT Enterography is a useful well tolerated study for the evaluation of diseases affecting the mucosa and bowel wall while $^{68}$Ga-DOTA-NOC PET/CT allows for a more specific functional imaging since $^{68}$Ga-DOTA-peptides bind to the somatostatin receptors overexpressed on neuroendocrine tumour cells.
Background

Epidemiology

Gastrointestinal NETs incidence has been on the rise in the last 35 years. The reason for this increase is still unknown and nowadays the overall incidence is 1.9 new cases per 100,000 persons per year. According to a study published by Modlin et al:

- 41.8% occur in the small intestine;
- 27.4% occur in the rectum;
- 24.1% occur in the appendix;
- 8.7% occur in the stomach.

Incidence is similar on both genders and the mean age of diagnosis is about 61.4 years old.

Over 70% of small intestine NETs arise in the ileum, most frequently on the terminal ileum, and 58-64% of patients have metastatic disease at the time of diagnosis.

5-year survival rate for patients with small intestinal NETs is about 60.5%.

Clinical presentation

NETs are typically slowly growing tumours and can go undetected for many years. Small intestine NETs can occasionally be asymptomatic, however this tumours are frequently related with indolent nonspecific symptoms such as sporadic abdominal pain, nausea and vomits.

Carcinoid syndrome occurs in about 6-30% of patients and is comprised of diarrhoea, flushing, heart disease (right heart failure secondary to severe dysfunction of the tricuspid and pulmonary valves), bronchoconstriction and abdominal pain. This syndrome is largely related to the presence of hepatic metastatic disease.

Symptoms caused by localized disease are infrequent (gastrointestinal bleeding, small bowel obstruction or ischemia) and can occur due to desmoplastic reaction.

Pathologic features

This tumours arise from enterochromaffin cells that release serotonin. They arise in the submucosal layer and are usually well-limited intramural or polypoid lesions. About 26-30% are multifocal.
The primary lesion is usually small (< 3.5 cm), contrary to lymph node metastases, peritoneal implants and hepatic metastases which are typically large.

Subserosal and mesenteric infiltration of the primary tumour, in addition to mesenteric lymph node metastases, can lead to a mesenteric desmoplastic reaction.

According to WHO the grading system is based on the rate of proliferation (mitotic rate or Ki-67 index):

- Well differentiated (low grade, G1 - Ki-67 <2%);
- Moderately differentiated (intermediate grade, G2 - Ki-67 2-20%);
- Poorly differentiated (high grade, G3 - Ki-67 >20%).

**Imaging techniques - Radiologic**

Imaging has an important role on diagnosing, localizing, staging and evaluating tumour response but there is still no consensus on which are the best imaging techniques.

In the past enteroclysis was the most used exam, and is still used in some countries. Some advocate the use of endoscopic techniques such as colonoscopy, capsule endoscopy and double balloon enteroscopy.

CT alone has reports of very low sensitivity (0-6%) but nowadays most institutions use enterography/enteroclysis CT or enterography/enteroclysis MRI with excellent results.

One study from Kamoui et al reported that CT enteroclysis has better results but this technique leads to patient discomfort from nasojejunal intubation. CT enterography is a good alternative with high sensitivity and more tolerable.

**CT enterography findings**

The main finding for primary tumour is solitary or multiple polypoid hypervascular lesions or hypervascular wall thickening that shows marked enhancement in arterial phase.

Tumour infiltration and fibrosis can produce a kink or curvature of the intestinal wall that can lead to ischemia and is visible on CT scans.

Mesenteric bulky ganglionar metastases (58-64%) are frequently associated with desmoplastic reaction, creating retraction of the mesentery with a sunburst appearance and calcifications (70%). Bowel loops may be displaced, unusually separated, or sharply bent by the mesenteric retraction.
Hepatic (hypervascular sometimes with central cystic areas producing rimlike enhancement), pulmonary and osteoblastic skeletal metastasis can appear in advanced disease.

**Imaging techniques - Nuclear Medicine**

Nuclear medicine also has an important role in the diagnosis, staging and follow-up of these tumours. As NETs express somatostatin receptors (SR), scintigraphy and PET/CT techniques using radiolabeled somatostatin analogues have been developed for this purpose.

In the past Serotonin Receptors Scintigraphy (SRS) using a SPECT scan was the mainstay but nowadays more advanced techniques have been developed using Gallium-68 which can be labeled with chelators such as DOTA that binds to a short peptide analogue of somatostatin such as: NaI3-Octreotide (NOC), Phe1-Tyr3-Octreotide (TOC) and Tyr3-Octreotate (TATE).

The main difference between these three tracers is that, while all can bind to SR-2 and SR-5, only DOTA-NOC shows good affinity for SR-3. There is currently no evidence of a clinical impact of these differences and therefore no preferential use of one compound over the others can be advised, although a wide spectrum ligand (such as $^{68}$Ga-DOTA-NOC) may be preferred for imaging.

$^{68}$Ga-DOTA-NOC PET/CT findings

According to a study published by Naswa et al., $^{68}$Ga-DOTA-NOC uptake showed a sensitivity of 78.3% and a specificity of 92.5% for detection of gastropancreatoenteric NETs. The mean SUVmax of primary tumour lesions was 13.

$^{68}$Ga-DOTA-NOC uptake showed a sensitivity of 97.4% and a specificity of 100% for detection of metastasis and the mean SUVmax was 14.5.

According to this study $^{68}$Ga-DOTA-NOC PET/CT showed higher accuracy for detection of both primary and metastatic gastroenteropancreatic NETs when compared to conventional imaging.

Negative findings are also crucial to select the appropriate therapy since tumours that don't show $^{68}$Ga-DOTA-NOC uptake usually don't respond to somatostatin analogues.

**Therapeutic options**
Surgical resection of the primary tumour is a first-line therapy for early NETs. Due to the favorable prognosis of well differentiated NETs, spread disease also has indication for palliative resection of primary tumour and regional mesenteric lymph node metastasis.

In patients with isolated hepatic metastases or metastases limited to a single hepatic segment or lobe, metastasectomy, segmentectomy or lobectomy may be surgical options. For patients with multiple hepatic metastases trans-arterial embolization (TAE) or chemoembolization (TACE) may be considered to control growth and hormone-related symptoms and to improve chances of survival.

Medical palliative therapy with serotonin analogues also plays an important role since it controls hormone-related symptoms and causes a cytostatic tumour response, prolonging progression-free survival, although rarely results in tumour size reduction. When this therapy fails, for example on poorly differentiated NETs, other options include Interferon # (adverse effects have limited its use) and chemotherapy (disappointing results and substantial adverse effects).
Findings and procedure details

Correlation between techniques

To review and correlate these techniques we retrospectively evaluated 17 patients from our institution with suspected or known small intestine NETs who underwent both CT enterography and $^{68}$Ga-DOTA-NOC PET/CT for diagnostic or follow-up purposes between 2013 and 2016.

On Tables 1 and 2 we demonstrate CT enterography and $^{68}$Ga-DOTA-NOC PET/CT protocols used at our institution.

All 17 patients were diagnosed with ileal NETs, 9 were female, and the mean age of diagnosis was 60.3 years old.

15 of these ileal NETs were classified as well differentiated (G1) and 2 were classified as moderately differentiated (G2).

During follow-up:

- 6 patients had, or developed, carcinoid syndrome, one of which had carcinoid heart disease on diagnosis, 8 patients had indistinct symptoms (frequently vague abdominal pain) and only 3 were asymptomatic and diagnosed incidentally;
- One of these patients succumbed to illness (patient on Figure 6);
- All patients had hepatic metastasis on diagnosis and, for most of them, hepatic biopsy was the first clue to the presence of NET. 2 patients also had osteoblastic metastasis;
- 15 patients had detectable mesenteric lymph node metastasis and 4 of them had demonstrable desmoplastic reaction on CT enterography.

On Figures 1 to 6 we demonstrate examples on how the correlation between these techniques further aids on identifying the primary tumour and identifying the presence and extent of metastatic disease.

Therapeutic options and response evaluation

On most of our patients follow-up with CT enterography and/or $^{68}$Ga-DOTA-NOC PET/CT was done 6 months after diagnosis and annually thereafter, excluding hepatic CT scans to evaluate response after hepatic trans-arterial embolization.
Table 3 shows medical, surgical and interventional therapeutic options that our selected 17 patients were subjected to.

On the matter of hepatic trans-arterial embolization (TAE), it is still debatable if the addition of cytotoxic drugs (TACE) increases therapeutic effectiveness.

At our institution we use TAE to treat patients with multiple hepatic metastasis from small bowel NETs since in most cases it decreases biomarkers activity, reduces symptoms and improves progression-free survival.

Evaluation of response to hepatic embolization at our institution is usually done by measuring biomarkers activity and with arterial phase CT scan to demonstrate total volume reduction and reduction of arterial enhancement. On PET/CT follow-up, after TAE, functional changes can also be appreciated with decreased uptake of the radiolabeled tracer by hepatic metastasis.

On Figures 8 to 11 we show examples of response evaluation some of which also showing correlation between CT enterography and $^{68}$Ga-DOTA-NOC PET/CT findings.
### CT Enterography protocol used at our institution

Prepare 2 L of Polyethylene glycol solution to ingest according to this plan:
- 1500 mL, 60 minutes prior to exam;
- 250 mL, 25 minutes prior to exam;
- 250 mL, 15 minutes prior to exam.

Empty bladder and enter CT room.

Butylscopolamine (20 mg IV) 5 minutes prior to scanning.

**IV contrast media administration** (Omnipaque®, 120 mL at a rate of 3-4 mL/s).

Scanning begins 45 seconds after the initiation of contrast material injection (late arterial phase).

Axial reconstruction interval of 1mm and automatic coronal and sagittal reformatted images with 2 mm interval.

**Table 1**: CT Enterography protocol.

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**Table 2:** 68Ga-DOTA-NOC PET/CT protocol.

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Fig. 1: 59 year old male incidentally diagnosed with NET (occult primary) after colonoscopic polypectomy. (a.) Intense 68Ga-DOTA-NOC uptake of multiple small bowel lesions and a metastatic mesenteric lymph node confirming multifocal NET. (b.) Sagittal reformatted image of CT enterography demonstrating mulifocal hypervascular NET lesions in correlation with those demonstrated on PET/CT, one of which shows kinking of the intestinal wall (lowest arrow). (c.) Polypoid hypervascular polyp in the ascending colon.

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Fig. 2: 49 year old female with abdominal pain who had hepatic metastasis on ultrasound examination. CT enterography axial image showing mesenteric adenopathy with punctate calcifications and intense desmoplastic reaction - the so-called "sunburst" appearance.

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**Fig. 3:** 64 year old female incidentally diagnosed with NET (occult primary) when, during a total hysterectomy, surgeons encountered peritoneal implants. (a.) Intense 68Ga-DOTA-NOC uptake in the terminal ileum, the most frequent location of small intestine NET. (b.) CT enterography demonstrating the primary lesion, a hypervascular mass on the terminal ileum. This patient also had peritoneal implants and metastatic lymph nodes but no hepatic metastasis.

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Fig. 4: 58 year old female with vague abdominal complaints who had hepatic metastasis on an ultrasound examination. (a.) Intense 68Ga-DOTA-NOC uptake from metastatic lymph node. (b.) CT enterography shows mesenteric adenopathy with spiculated margins, calcifications and desmoplastic reaction.

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Fig. 5: 67 year old female with carcinoid syndrome. (a.) 68Ga-DOTA-NOC uptake on the terminal ileum and on multiple hepatic metastasis. (b.) Coronal reformatted image from CT enterography shows the primary tumour and an hepatic metastasis (with rimlike enhancement due to central necrosis) in correlation with PET/TC findings.

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Fig. 6: 78 year old female with an history of diarrhoea, weight loss and abdominal pain who had hepatic metastasis on CT scan. (a.) Intense 68Ga-DOTA-NOC uptake from osteoblastic metastasis of small intestine NET located on the right ilium, also shown on (b.) CT enterography. (c.) Hepatic metastasis with intense enhancement on arterial phase, one of which has substantial central necrosis. This patient succumbed to the disease 5 months after diagnosis.

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Table 3: Medical, surgical and interventional therapeutic options that, our selected 17 patients, were subjected to.

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Fig. 7: Image taken during TAE procedure showing multiple enhancing hepatic metastasis from small intestine NET.

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Fig. 8: 61 year old male with multiple hepatic metastasis from ileal NET (a./b.) that show intense arterial phase enhancement on CT enterography. 4 months after this CT scan the patient was submitted to TAE and 2 months later an hepatic arterial phase CT scan was performed to evaluate tumour response. (c./d.) Axial and coronal CT images showing marked decrease of arterial enhancement from hepatic metastasis in correlation with tumour response. In this patient, it was not possible to show correlation with PET/CT findings because, unlike the other cases, these hepatic metastasis didn't show significant 68Ga-DOTA-NOC or even FDG uptake (although both the primary tumour and lymph nodes' metastasis uptake 68Ga-DOTA-NOC).

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Fig. 9: 68 year old male with multiple hepatic metastasis that (on the left) show intense 68Ga-DOTA-NOC uptake. This patient was submitted to TAE and on follow-up PET/CT (on the right), after 1 year, there is markedly reduction of 68Ga-DOTA-NOC uptake, indicative of tumour response.

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Fig. 10: 63 year old male with vague abdominal pain and history of cholelithiasis with suspected biliary colic. On ultrasound he was discovered to have multiple hepatic metastasis later confirmed to be from ileal NET. Similarly to the case on Figure 9, after TAE, on follow-up PET/CT (on the right), after 1 year, there is markedly reduction of 68Ga-DOTA-NOC uptake from hepatic metastasis in correlation with positive tumour response to therapy.

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Fig. 11: 51 year old male with long-standing abdominal pain who after ultrasound examination was discovered to have multiple hepatic metastasis later confirmed to be from ileal NET. (a.) This patient was submitted to TAE and comparing diagnostic CT enterography (on the left) with post-TAE CT scan (on the right) there is a decrease on arterial enhancement of two, right lobe, hepatic metastasis. (b.) This patient had annual follow-up PET/CT (on the right), only 2 months after this post-TAE CT scan, that shows marked decrease of 68Ga-DOTA-NOC uptake. This case clearly shows good correlation between both techniques’ findings demonstrating good response to TAE treatment in this patient.

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Conclusion

While small bowel neuroendocrine tumours are on the rise, we now have additional means and techniques to improve both diagnosis and management of these rare tumours.

The therapeutic objective is to further improve patient symptoms and progression-free survival or even attempt cure of localized disease.

Combining and correlating features from both CT enterography and $^{68}$Ga-DOTA-NOC PET/CT findings further aids on identifying the primary tumour, identifying the presence and extent of metastatic disease and assessing therapeutic response.
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