NEUROENDOCRINE TUMORS: CHOOSING APPROPRIATE IMAGING METHODS

Liliana Gheorghe¹, Irina Jari¹*, Manuela Ursaru¹, D. Negru¹,
Cipriana Ștefănescu², A. Naum²
“Grigore T. Popa” University of Medicine and Pharmacy Iasi
Faculty of Medicine
1. Department of Surgical Sciences (II)
2. Department of Morpho-functional Sciences
*Corresponding author. E-mail: irina.jari@umfiasi.ro

NEUROENDOCRINE TUMORS: CHOOSING APPROPRIATE IMAGING METHODS
(abstract): With an overall increased incidence in general population neuroendocrine tumors (NETs) are often late diagnosed. Symptoms are nonspecific and almost 50% of all patients have regional or distant metastases at the time of diagnosis. This article provides an overview of the current state of the imaging modalities used for primary tumor visualization, staging and follow-up. Detection of NETs and patient monitoring relies mainly on anatomical imaging such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US) under certain conditions. Molecular imaging techniques in combination with CT or MRI (hybrid imaging) greatly benefit patient management, including better localization of occult tumors and better staging. Octreoscan or somatostatin receptors (SSTRs) scintigraphic imaging in combination with CT represents the standard diagnostic of NETs in most countries. However, it is rapidly surpassed by SSTRs PET/CT with 68Ga-labelled somatostatin analogues with a superior spatial resolution and faster imaging (one-stop shop principle). Other more specific tracers are 18F-L-DOPA, 11C-L-DOPA and 11C-5-hydroxytryptophan, which have demonstrated excellent results in previously published studies. Diagnosis of patients with NETs is a complex process and, it is unlikely that any single diagnostic modality to be effective. Thus, NET diagnosis is a process utilizing a variety of methods including blood, urine and tumor tissue samples in combination with anatomical or hybrid imaging for localization, delineation and staging of the disease. Diagnostic approach to patients with NETs should focus on including hybrid imaging methods, which might play an important role in the future. Keywords: NEUROENDOCRINE TUMORS, ANATOMIC IMAGING, FUNCTIONAL IMAGING.

Neuroendocrine tumors (NETs) include a variety of malignancies that can arise from neuroendocrine cells throughout the body. They can store and secrete different peptides and neuroamines that cause characteristic hormonal syndromes, often late diagnosed (1, 2). Nonspecific symptoms are characteristic to the disease, and almost 50% of all patients have regional or distant metastases at the time of diagnosis (3). NETs can arise in many different areas of the body and are most often localized in the gastrointestinal tract (70%) and the bronchopulmonary system (25%), with substantial variations in both clinical presentation and tumor biology. NETs are mainly spo-
Neuroendocrine tumors: choosing appropriate imaging methods

...radic but may occur in a familial context of autosomal dominant inherited syndromes such as MEN1, MEN2, Von Hippel-Lindau disease, neurofibromatosis type 1 and multiple tuberous sclerosis. The annual incidence of clinically significant neuroendocrine tumors is approximately 2.5-5 per 100,000 (4, 5).

**Anatomic imaging.** Ultrasonography (US) is frequently used in the evaluation of gastroenteropancreatic neuroendocrine tumors (GEP-NETs), with a low success rate, between 13–27%. It is valuable for the localization of pancreatic and liver metastases and particularly in the preoperative assessment of patients (fig. 1).

Endoscopic US (EUS) could be an excellent imaging modality to detect pancreatic NETs, with pooled sensitivity and specificity of 87 and 98%, respectively. US performed intraoperatively combined with intraoperative palpation could raise the sensitivity up to 91% (6).

Computed tomography (CT) is the most commonly used technique for primary tumor localization, staging, therapeutic monitoring, and follow-up of patients with NETs. Triple-phase intravenous contrast-enhanced CT (early arterial, portal-venous, and equilibrium) is usually performed (fig. 2). In primary NETs, the average sensitivity of a CT scan is 73%. A better sensitivity of 80% in detecting NET metastases is reached for liver metastases and 75% sensitivity for extrahepatic metastases (7).

**Magnetic resonance imaging (MRI)** findings provide a broad spectrum of information for both primary and metastatic tumors. On non-contrast MRI they can be hypointense or isointense on T1-weighted images. Metastases to the liver are typically hyperintense on T2-weighted images. A primary tumor is best identified on dynamic gadolinium contrast images (fig. 3). MRI may be superior to CT regarding liver lesion characterization but may not be as useful in the identification and follow-up of extrahepatic disease (13). A study comparing MRI, CT and standard somatostatin receptor scintigraphy (SSR) reported 95.2% sensitivity for MRI, 78.5% sensitivity for CT and 49.3% sensitivity for the OctreoScan in detecting hepatic metastases (8, 9).

**Functional imaging.** These techniques depict the somatostatin receptor status, metabolic activity, or specific amine or peptide regulatory profile. The human somatostatin receptor family consists of 5 subtypes each differentially distributed throughout the body (SST1-SST5).

The radiolabeled somatostatin analogue (SSA) 111 In-pentetreotide is the most commonly used agent in somatostatin receptor scintigraphy. The tracer is commercially available as 111In-DTPA-D-Phe1-octreotide (Octreoscan, Mallinckrodt Medical, St. Louis, MO, USA) and used for scintigraphic localization of primary and metastatic neuroendocrine tumors that express somatostatin receptors subtype 2 and 5 (fig. 4) (10).
Fig. 2. Computed tomography of insulinoma of the pancreas. Typically, insulinomas are hyper vascular (arrow) and demonstrate more enhancement than normal pancreatic parenchyma during the arterial phase.

Fig. 3. Liver metastases from a neuroendocrine tumor (arrows) CT (A) versus MRI (B). The hyper vascular liver metastases are more clearly observed on the T1w gadolinium enhanced MRI (B) compared to the arterial phase CT (A).
Neuroendocrine tumors: choosing appropriate imaging methods

Fig. 4. Octreotide (111 In-pentetreotide) anterior and posterior images obtained at 24 hours. Increased activity is depicted in the pancreatic region corresponding to a neuroendocrine carcinoma. No distant metastases were visualized.

Alternatively, iodine metaiodobenzylguanidine (\(^{131}\)I /\(^{123}\)I MIBG) scintigraphy is an imaging test that confirms the presence of and monitors primary or metastatic pheochromocytoma (PCC) and paragangliomas (PGLs), and certain other NETs (neuroblastoma) (fig. 5).

False-negative results could occur with extra-adrenal tumors. Several drugs, such as opioids, tricyclic antidepressants, and antihypertensive drugs like labetalol can also affect MIBG uptake, leading to less intense or false-negative scans. MIBG scintigraphy performs poorly for head and neck PGLs and may also miss metastatic disease. \(^{131}\)I MIBG imaging is performed after 24 hours, 48 hours and, if necessary, at 72 hours; only planar views are obtained. \(^{123}\)I MIBG scintigraphy is performed after 24 hours and, if necessary, at 48 hours; single-photon emission computed tomography (SPECT) can be performed (11).

Hybrid imaging. \(^{18}\)F-18 FDG PET/CT. Positron emission tomography (PET) together with CT, using \(^{18}\)F-fluorodeoxyglucose (FDG PET/CT) has limited usefulness in NETs due to their low metabolic activity. \(^{18}\)F-FDG PET/CT may instead be considered for imaging of high-grade NETs (poorly-differentiated), where the relationship between standardized uptake value (SUV) and overall survival can provide predictive information regarding overall survival and progression (fig. 6) (12).

Fig. 5. Pheochromocytoma: US reveals a large echogenic lesion with calcifications on the right adrenal gland (arrow) (A). 131 I-MIBG scan shows a dark sphere (B, C).

\(^{18}\)F-DOPA PET/CT. \(^{18}\)F-DOPA (L-3, 4-dihydroxy-6-18F-fluorophenylalanine), fluorodopa (FDOPA) is a tracer which depicts catecholamine metabolism and
exhibits an intense concentration in NETs, independent of somatostatin receptor. The main indication for FDOPA may be for the patients with insulinoma or paraganglioma. The reported sensitivity and specificity rates of [18F] DOPA PET or PET/CT for the diagnosis of thoracic and gastroenteropancreatic NETs were 77% and 95%, respectively (13). In patients with pheochromocytoma or paraganglioma the rates were 92% (sensitivity) and 92% (specificity), respectively.

**PET/CT Imaging with Somatostatin Analsogs.** The introduction of somatostatin receptor PET/CT, somatostatin analogs (SSA) labeled with gallium-68 (Ga-68-DOTA-peptides) has allowed an accurate imaging of SSTRs by PET. DOTA peptide PET/CT has a significant role in the staging of well-differentiated gastroenteropancreatic tumors. It is recommended for clinical use in the initial diagnosis and for the evaluation of tumor response. The overall sensitivity of 68Ga-SSA-PET/CT for NETs is >90%, while the specificity ranges from 92 to 98%. The clinical impact of differences in SSTR binding affinity has not been proven, and therefore no preferential use of one compound over the others can be advised (14).

![Fig. 6.](image)

**Fig. 6.** Upper row: Patient with bronchopulmonary carcinoid, Ki-67 30-40%. Positive FDG PET uptake at the tumor level (B, arrow).

Bottom row: Liver metastases from a neuroendocrine tumor of midgut origin, Ki 67 10%. Faint FDG uptake (maximum SUV, 2.5 and 2.9 g/ml, E, arrows).
Neuroendocrine tumors: choosing appropriate imaging methods

**Future techniques.** Other investigational tracers include $^{18}$F-labeled amine, $^{18}$F-fluorothymidine (FLT) and $^{11}$C-labeled precursors, such as levodopa and serotonin, but the clinical experience is still limited (27).

There is great interest in the emergence of the so-called pan-receptor somatostatin analogs. Pasireotide (SOM230) is a novel multi receptor-targeted somatostatin analog with high binding affinity for SST receptor subtypes 1, 2, 3, and 5.

**CONCLUSIONS**

Our overview suggests that a single diagnostic test will not be effective to assess the NETs. The diagnosis will use a variety of methods including blood and urine tests and tumor biopsy in combination with anatomical and molecular imaging for localization, delineation, and staging of the disease, as the basis for optimal selection of therapy.

Future advances in NET diagnosis need to consider two realities. Firstly, the proper approach focused on validation of the present techniques. Secondly, a long-term strategy to develop a multilevel integration scheme of biologic and genomic diagnosis to provide added value to the imaging techniques. Thus, a fusion product of molecular and genomic information with tumor imaging is likely to be the essence of future NET diagnosis.

**REFERENCES**


CARDIOTOXICITY OF LEVOFLOXACIN AND CIPROFLOXACIN

Fluoroquinolones are a class of antibiotics widely used in the treatment of common bacterial infections and are unusual because they are synthesized, not isolated from living organisms. One potentially serious adverse effect is prolongation of QT interval that may lead to torsades de pointes or ventricular arrhythmias. A group of researchers did a study on animals using Wistar albino rats. The study was divided into two experiments to determine the effects of levofloxacin and ciprofloxacin on rats with acute myocardial dysfunction (AMI) induced by isoproterenol (sixty rats into five groups of twelve rats each) and rats without AMI (twenty five rats into five groups of five rats each). They analysed the changes in ECG pattern, the serum level of cardiac enzymes and the histopathologic features in the myocardium. In rats without AMI, the ECG pattern and the heart beats were normal but the rats with MI presented an abnormal pattern with specific change in ST segment and abnormal Q waves. The level of lactate dehydrogenase was increased in both experiments. The creatine kinase-MB activity was increased compared to the saline controls, however in the MI experiment treatment with any dose of levofloxacin or large dose of ciprofloxacin (300 mg/kg) the CK-MB activity was significantly increased. The histopathologic findings in cardiac sections, stained with hematoxylin and eosin, revealed different degrees of inflammatory cell infiltration, cardiomyocyte degeneration, intermuscular edema, loss of the cardiac striations and hemorrhage as an effect of levofloxacin and ciprofloxacin. The conclusion of the study was that it is important to monitor patients with a history of cardiac disease requiring treatment with these antibiotics (Ahmed M. Abdelradya, Sawsan A. Zaitoneb, Noha E. Faragd, et al. Cardiotoxic effect of levofloxacin and ciprofloxacin in rats with/without acute myocardial infarction: Impact on cardiac rhythm and cardiac expression of Kv4.3, Kv1.2 and Nav1.5 channels. Biomedicine & Pharmacotherapy 2017; 92: 196-206).

Alexandra Mirela Ciocan