Molecular medicine imaging of neuroendocrine tumours

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Introduction

Neuroendocrine tumours (NETs) are a diverse, highly heterogeneous group of neoplasms derived from endocrine cells found in the neural crest. NETs typically display endocrine metabolism and slow growth, while displaying a wide range of presentations and clinical symptoms. Demonstrating typically small lesions, with varying anatomical localisation, diagnosis is typically in the advanced stages of tumour development. Molecular medicine provides a unique role in both the diagnosis and treatment of NETs.

The diagnosis of NET is dependent upon clinical features, raised tumour biomarkers within the blood and urine, imaging of primary tumours and/or sites of metastasis and histopathologic results from tissue samples.

Commonly used imaging modalities include conventional radiology (computed tomography (CT), magnetic resonance imaging (MRI) and transabdominal ultrasonography (US)), selective angiography, nuclear imaging techniques (e.g. somatostatin receptor imaging) and endoscopic US (EUS). Triple-phase CT and MRI are routinely used to provide anatomical localisation of primary tumour sites and initial staging of disease.

Despite the heterogeneous nature of NETs, common characteristics exist among them. These tumours may possess special secretory granules, producing biogenic amines and polypeptide hormones, and express somatostatin receptors. Between 33-50% of NETs have active amine/hormone production and may be classified as functional tumours.

It is the shared characteristics of NETs that allows molecular imaging tracers to specifically target this wide range of neoplasms for imaging and treatment. This article aims to outline the most commonly used imaging methods for NET within molecular medicine.

Scintigraphy of neuroendocrine tumours

Initially NET imaging within molecular medicine was largely undertaken as planar images acquired using a gamma camera. Despite good sensitivity, this methodology offered poor spatial resolution and limited anatomical information. The introduction of combined modality SPECT/CT imaging addressed both of these limitations, allowing for greater spatial resolution and anatomical localisation of uptake. This resulted in greater diagnostic power due to the complementary nature of these two modalities.

The two most commonly used NET tracers suitable for imaging via SPECT/CT are 123I- Metaiodobenzylguanidine (MIBG) and 111In-pentetreotide (Octreoscan). MIBG is a radiotracer analogue of noradrenaline which can be labelled with either 111In or 11C, allowing for both diagnostic and therapeutic functions. MIBG undergoes active uptake into catecholamine secreting tumours upon which it is retained within the secretory granules common within NETs. MIBG has been routinely used in the imaging of pheochromocytoma and paraganglioma since the mid-1990s. 111In-pentetreotide represents the most successful analogue developed for use in somatostatin receptor scintigraphy. While NETs commonly exhibit a high expression of somatostatin receptors, the short plasma half-life (one to three minutes) of this hormone has called for synthetic analogues to be developed to facilitate imaging. This tracer provides a measure of the expression of somatostatin receptors upon NET cells, which is independent of cell metabolism, allowing for assessment of slowly progressing tumours unsuitable for other imaging agents (such as 18F-FDG.) High expression of somatostatin receptors is generally indicative of a well differentiated disease.

Despite the success of somatostatin receptor scintigraphy, it is not without limitations. The poor imaging characteristics of 111In-pentetreotide limit spatial resolution, which can be problematic for the detection of the small lesions typical of NETs. Physiological uptake in the spleen, liver and kidneys may reduce the visibility of lesions within and potentially obscure NET uptake. The sensitivity of this tracer is also reduced in patients with high levels of plasma somatostatin, either due to octreotide therapy or endogenous production by the tumour. Further to these issues, Indium is not widely available and is costly as it must be manufactured via cyclotron.

The development of 68Ga-DOTA peptides represent a group of positron-emitting somatostatin analogues used in PETCT, with each tracer within the group targeting a different expression of somatostatin receptors found upon NETs. These tracers offer an increased diagnostic value for somatostatin receptor NETs over both CT imaging and somatostatin receptor scintigraphy. 68Ga-DOTA peptides offer lower patient doses,
shorter protocol times and superior imaging qualities than that of $^{111}$In peptides. These advantages result in $^{68}$Ga-DOTA peptide imaging altering clinical management of patients in 70% of cases.

PETCT somatostatin receptor imaging is available at specialist centres via the $^{68}$Ge/$^{68}$Ga generator; this allows local pharmacies to produce $^{68}$Ga-DOTA peptide doses as required for the 9-12 month lifetime of the generator.

The improved image quality and quantitative abilities of $^{68}$Ga-DOTA peptides allows for accurate visualisation of lesions within areas of high uptake (such as the liver and spleen). However, while $^{68}$Ga-DOTA peptides have excellent sensitivity, false positive results may be caused by inflammation, presence of a splenunculus or by variable physiological uptake (often observed within the pancreatic head).3

The imaging of catecholamine secreting tumours is also possible by PETCT. $^{18}$F-DOPA is an amino acid-based tracer that enters the catecholamine metabolic pathway of natural L-DOPA. This metabolic pathway is active in many neuroendocrine tumours. As biogenic amine-producing neoplasms present strongly upregulated amino acid transporters in order to supply the increased demand for amine precursors, $^{18}$F-DOPA is able to visualise amine-producing NETs. This tracer is limited by difficult synthesis and high cost, but may be useful in regions where $^{68}$Ga-DOTA peptides are unavailable.

A further advantage of PETCT imaging of NETs exists in the form of the widely available $^{18}$F-FDG, a positron emitting glucose analogue. While most NETs display slow growth, and by extension low glucose metabolism, poorly differentiated disease may vary from this trend and present higher growth rates. Such tumours are suitable for glucose metabolism imaging using $^{18}$F-FDG PETCT. Presence of $^{18}$F-FDG avid lesions is strongly indicative of a worse prognosis.4

Peptide receptor imaging, via both SPECT/CT and PETCT, is important in staging as it may detect resectable NETs that could be missed with conventional imaging techniques. Furthermore, it may prevent surgery in patients whose tumours have metastasised to a greater extent than could be detected with conventional imaging alone. Moreover, staging may also be used to select patients for PRRT with $^{111}$In-, $^{90}$Y- or $^{177}$Lu-labelled peptide analogues.

Areas of future development

The future of NET imaging within molecular medicine is rapidly developing, with many avenues in which advancement is possible. Technical developments in diagnostic equipment and tracers look to substantially improve NET imaging. With novel PETCT somatostatin analogues utilising $^{64}$Cu in development, there is the potential for additional, delayed imaging of NETs at 24 hours post injection. As this isotope possesses excellent imaging characteristics, image quality and spatial resolution look set to improve. While equipment improves with the development of multi-modal PETMR, this looks to further increase the sensitivity and specificity of somatostatin analogue PET studies, as each modality provides complementary anatomical and functional information.

As we come to understand the heterogeneity of metastatic disease within individual patients, molecular imaging becomes better equipped to target specific tumour subtypes. An example of this is seen in insulinomas, a NET subtype displaying difficult diagnosis due to small lesion size (<2cm) and low somatostatin receptor expression. Molecular imaging can overcome this difficulty by the use of Ga$^{68}$ DOTA-Extendin-4, a PETCT glucagon-like peptide-1 (GLP-1) agonist tracer, as insulinomas display an overexpression of the GLP-1 receptor. This allows a personalised approach to medicine providing diagnostic results, with excellent sensitivity, in otherwise barely detectable insulinomas.

Alternative imaging routes are also being explored, with the advent of somatostatin receptor antagonist based tracers. In a paradigm shift from the currently utilised agonist based tracers, antagonist agents such as $^{111}$In-DOTA-BASS have been seen to demonstrate greater tumour uptake levels, with longer retention times, in preclinical trials. As these exciting new antagonist tracers are suitable for both diagnostic and therapeutic roles, the future of NET imaging and therapy looks bright within molecular medicine.

References


Figure 1

Planar and SPECT/CT imaging of phaeochromocytoma using 123I-MIBG. Note the normal appearance of planar WB image (A), however SPECT/CT imaging revealed a left phaeochromocytoma due to superior spatial resolution and anatomical localisation (B).
Figure 2
A normal MIP $^{68}$Ga-DOTA-NOC peptide image, areas of physiological uptake demonstrated within the pituitary gland, liver, spleen, adrenals and the urinary tract (both kidneys and urinary bladder).

Figure 3
Low metabolic activity $^{18}$F-FDG MIP (A) and markedly positive $^{68}$Ga-DOTA-NOC MIP images (B) of the same NET patient, showing extensive bone, liver, nodal, left orbit and peritoneal metastases. Liver biopsy showed a ki67 index of 18%. Given the less avid metabolic uptake, this patient would be considered for PRRT after clinical assessment.