Functional imaging in neuroendocrine tumours

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By Dr S Reynolds, MRCP MSc
Dr A-M Quigley, MRCP, FRCR, MSc
Dr S Navalkissoor, MRCP, MSc
Royal Free Hospital, London

Neuroendocrine tumours (NETs) are a heterogeneous group of tumours arising from neuroectodermal cells. The incidence of neuroendocrine tumours has increased five-fold in the last three decades from 1/100,000 to 5/100,000.1 As these tumours can be slow-growing, the prevalence of patients with NETs has also markedly increased.1

NETs may be functioning, secreting biologically active peptides, causing a syndromic presentation (e.g. gastrinoma secreting gastrin). Alternatively, they can be non-functioning and usually present secondary to the mass effect of the tumour which frequently manifests as abdominal pain, jaundice and cachexia. NETs also have similarities in their ability to take up and store neuroamines and express peptide receptors. These features can be exploited both for imaging and therapy.

It has become standard practice to include functional imaging in the work-up of patients with neuroendocrine tumours. The first of these functional diagnostic agents used for imaging of NETs was described in the late 1970s, with 123I-meta-iodobenzylguanidine (mIBG).2 Somatostatin receptor (SSR) peptide imaging was introduced in the late 1980s.3 These remain the two principle functioning imaging mechanisms in NETs.

mIBG

Metaiodobenzylguanidine (mIBG) is an alkylguanidine (catecholamine analogue) and has similar properties to that of noradrenaline. It is concentrated by an active amine uptake mechanism in the cell membrane of sympathomedullary tissues and stored within cytoplasmic catecholamine storage vesicles4 and is dependent on the expression of VMAT 1 and VMAT 2 genes.

mIBG has been labelled both with 123I and 131I. The preferred imaging agent is 123I-mIBG on account of its more favourable dosimetry and superior image quality, due to higher photon flux and shorter image acquisition times. High photon flux and energy also allow single photon emission tomography (SPECT), which is essential for the separation of overlapping structures and allowing depth perception, thus improving both sensitivity and spatial resolution. The development of hybrid imaging has permitted anatomical localisation of functional SPECT data, thereby improving diagnostic accuracy.

123I-mIBG is well established in the scintigraphic detection of catecholamine secreting tumours (phaeochromocytoma and paraganglioma), with overall sensitivity approximating 90%.123I-mIBG scintigraphy also identifies metastatic disease in the skeleton, lymph nodes, lung and peritoneum. It can identify and characterise sub-centimetre tumours escaping detection by CT due to small size and close proximity to other structures.4

In childhood neuroblastoma, 123I-mIBG has a major role in staging, re-staging post-treatment, post-surgical residual tumour detection, treatment response monitoring and early diagnosis of recurrence. It can also detect metastatic involvement in bone, soft tissue and bone marrow. Overall detection accuracy is around 90%.

131I-mIBG may detect gastroenteropancreatic NETs (GEP-NETs) as well as bronchial NETs. Positivity is approximately 60% and, thus, insufficient to be used for staging. Although 111In-pentetreotide is generally accepted to have a higher positivity rate in NETs, it has been shown that in 17% of 115 patients, more lesions were seen on mIBG while 5% that were 123I-mIBG positive had a negative 111In-pentetreotide study.7

However, if a patient has good tumour uptake of 123I-mIBG on a diagnostic study, they may be suitable for targeted radionuclide therapy with 131I-mIBG. mIBG can also selectively concentrate in medullary thyroid cancer as this tumour is derived from C cells, which also originate from the neural crest. While specificity is high (>95%), sensitivity is rather low (34%). Targeted radionuclide therapy with 131I-mIBG has been utilised when uptake has been high.8

Some drugs, such as sympathomimetics, antidepressants, labetalol and certain calcium antagonists, compete for the type 1 transport mechanism and can interfere with tumour mIBG uptake and should be withdrawn prior to radiopharmaceutical administration.9 Thyroid blockade with potassium iodide should be also be performed to minimise thyroid irradiation by free 131I or 123I.

Somatostatin receptor (SSR) imaging

Somatostatin receptors are expressed on a number of normal cells, including the pituitary, thyroid, spleen, kidney and peripheral nervous system. In addition, several tumours have been found to express somatostatin receptors (SSR), with a high incidence and density of receptors found particularly in NETs.10 Five SSRs have been identified, of which the SSR-2 receptor and, to a lesser extent SSR-5, are most commonly expressed in NETs.

The main indications for SSR imaging are to accurately stage disease, follow-up and re-stage patients with known disease. SSR analogue uptake is also useful in selecting patients for treatment with 'cold' somatostatin analogues. It is essential when considering radio-targeted therapy.

SRS imaging agents

111In-DTPA-Octreotide

111In-DTPA-Octreotide (also known as 111In-Pentreotide), is commercially marketed as Octreoscan and was the first SSR imaging agent that became popular globally.11 In has a half-life of 68 hours with two discrete energy peaks of 173 and 247KeV. Octreotide predominantly has affinity for SSR-2 (the most commonly over-expressed receptor in NETS), SSR-5 and some (considerably lower) affinity for SSR-3. The European Neuroendocrine Tumour Society (ENETS) has recommended that 111In-DTPA-Octreotide imaging be performed at 4 and 24 hours (during which time there is reduction in hand activity by renal and gut clearance) post-administration of tracer.12 This agent has become the most widely used diagnostic imaging agent of SSRs worldwide and remains the gold standard. The recommended administered activity is 185-222MBq in adults and 5MBq/kg in children (ENETS). The effective patient whole-body dose is 0.054mSv/MBq.10

Recommended imaging techniques involve planar imaging (whole-body or multiple static acquisitions) together with SPECT imaging, the use of which increases the sensitivity of detecting disease around the pancreas and liver.12 More recently, with multi-modality imaging becoming increasingly more widely used, SPECT/CT has been incorporated with whole-body studies, with improved localisation of abnormal uptake.

Uptake with 111In-DTPA-octreotide is present in the majority of patients with NETs (>80%), the major exceptions being insulinomas (sensitivity <70%) and poorly differentiated NETs, due to reduced expression of somatostatin receptors.13
PET agents

**18F-FDG**

**18F-FDG** is taken up by metabolically active cells. NETs do not demonstrate increased FDG uptake due to the majorit


ty of them having relatively low metabolic activity, i.e. similar to surrounding healthy tissue. **18F-FDG**-PET may, however, be taken up by NETs that have de-differentiated or by those that have a high proliferative index.

**68Ga** agents

Imaging with **68Ga** has recently gained popularity. **68Ga** has a convenient physical half-life of 68 minutes and decays by positron emission. It is produced via a **68Ge-68Ga** generator and, as such, has the advantage of being independent of a cyclotron. A **68Ge-68Ga** generator lasts 7-9 months. The short half-life allows completion of the study within 2-3 hours of tracer administration.

**68Ga** linked somatostatin analogues have demonstrated affinity to SSRs and have been evaluated in vivo with several DOTA-related labelled somatostatin analogues, the most commonly utilised being DOTATATE, DOTANOC and DOTATOC. The main differences between these compounds are small changes in the peptide side chain which result in differing affinity to the SSR subtypes.

The advantages of **68Ga** somatostatin PETCT imaging over **111In**-pentetreotide include the improved resolution and sensitivity of PET over SPECT, imaging with a one day protocol. **68Ga**-DOTATATE has increased affinity for SSR-2 (which is the most predominant over-expressed receptor in NETs) than In-pentetreotide. In a recent study, **68Ga**-DOTATATE changed the management in 36/51 (70%) of patients who had either no uptake (35 patients) or low grade uptake (15 patients) on **111In**-octreotide. These patients were found to have a positive **68Ga**-DOTATATE scan as part of their staging, enabling them to be treated with cold or radiolabelled somatostatin analogues.

Other PET tracers

Other PET tracers used to diagnose NET include **11C** and **18F** labelled with Dihydroxyphenaline (L-DOPA). As L-DOPA is an amine precursor, it is taken up and decarboxylated by NET cells. Carbidopa is given as pre-treatment to block aromatic amino-acid decarboxylase (AADC) and decrease the urinary excretion of tracer. 5-hydroxy-L-tryptophan (5-HTTP) PET labelled with **11C** is another agent that has been used, which has been found to be useful for small lesions. However, **11C** has a short half-life of 20 minutes, necessitating an on-site cyclotron.

Conclusion

Nuclear medicine imaging plays a vital role in the management of patients with NET from staging through to assessment for treatment and follow-up. Some of the tracers used for imaging can be used therapeutically following substitution of the various isotopes for ones that are more suited to targeted radionuclide therapy. In recent years there has been considerable development of new tracers, notably the **68Ga** labelled somatostatin analogue PET tracers. The expansion of hybrid imaging (combining nuclear medicine and cross-sectional techniques), further seeks to improve diagnostic utility of functional imaging.

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References

**CASE 1**

In Octreotide whole body (images A and B) and SPECT/CT (images D and E) in a patient with a pancreatic NET. Image C shows multiple liver metastases on CT. Tracer uptake seen in a pelvic node (small arrow and image D). Uptake in lytic metastasis in pubic symphysis (large arrow and image E).

**CASE 2**

$^{123}$I-mIBG SPECT/CT images from a patient with metastatic phaeochromocytoma. Small nodule of $^{123}$I-mIBG avid tissue lying anterior to left kidney (arrows).
CASE 3

$^{111}$In-Octreotide and $^{68}$Ga Octreotate on a patient with NET. Very minimal uptake in liver on $^{111}$In-Octreotide (images A and C), compared with extensive uptake on $^{68}$Ga Octreotate (images B and D).

CASE 4

$^{123}$I-mIBG (A) and $^{131}$I-mIBG post-therapy image (B) from a patient with a small bowel carcinoid. CT scans from same patient showing solid metastatic deposit in liver (C and small arrow) and large cystic metastasis (D and large arrow).
CASE 5
Medullary carcinoma thyroid: ${}^{18}$F-DOPA and FDG. Patient A has a relatively slow growing tumour and has more uptake with the $^{18}$F-DOPA than $^{18}$F-FDG. Patient B has a more rapidly growing tumour and has more uptake with the $^{18}$F-FDG. Images courtesy of Professor Pirjo Nuutila, Yrku PET Centre University of Turku, Finland.

CASE 6
${}^{99m}$Tc-Hynic-Tate whole body images showing multiple sites of uptake within the liver. Note the improved target to background ratio on the four hour images.

CASE 7
A. Fused image from ${}^{68}$Ga Octreotate PETCT of a patient with pancreatic NET showing tracer uptake in a peritoneal deposit (small arrow) and a para-aortic lymph node (large arrow). B. CT image showing peritoneal deposit which could easily be overlooked as unopacified small bowel.