GEP-NETs update

Functional localisation and scintigraphy in neuroendocrine tumours of the gastrointestinal tract and pancreas (GEP-NETs)

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Abstract

For patients with neuroendocrine tumours (NETs) of the gastrointestinal tract and pancreas (GEP) (GEP-NETs), excellent care should ideally be provided by a multidisciplinary team of skilled health care professionals. In these patients, a combination of nuclear medicine imaging and conventional radiological imaging techniques is usually mandatory for primary tumour visualisation, tumour staging and evaluation of treatment. In specific cases, as in patients with occult insulinomas, sampling procedures can provide a clue as to where to localise the insulin-hypersecreting pancreatic NETs. Recent developments in these fields have led to an increase in the detection rate of primary GEP-NETs and their metastatic deposits. Radiopharmaceuticals targeted at specific tumour cell properties and processes can be used to provide sensitive and specific whole-body imaging. Functional imaging also allows for patient selection for receptor-based therapies and prediction of the efficacy of such therapies. Positron emission tomography/computed tomography (CT) and single-photon emission CT/CT are used to map functional images with anatomical localisations. As a result, tumour imaging and tumour follow-up strategies can be optimised for every individual GEP-NET patient. In some cases, functional imaging might give indications with regard to future tumour behaviour and prognosis.

Introduction

Neuroendocrine tumours (NETs) of the gastrointestinal tract and pancreas (GEP) (GEP-NETs) constitute a heterogeneous group of diseases (1, 2, 3). According to the current WHO grading system, GEP-NETs can be classified according to their Ki-67 proliferation index (MIB-1 staining) into grade 1 (G1), with a Ki-67 index amounting to, or <2%, G2 with a Ki-67 index between 3 and 20% and G3 with a Ki-67 index higher than 20% (4, 5). Grading correlates well with the clinical course of patients harbouring these GEP-NETs (6, 7, 8, 9). In addition, clinical features such as the primary localisation of these GEP-NETs, the secretion of excessive amounts of hormones or peptides by these GEP-NETs and the metastatic spread, as reflected by staging of these GEP-NETs, also

Invited Author’s profile

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determine their clinical manifestations and contribute to their prognosis (1, 10, 11).

Various imaging modalities can be used to localise GEP-NETs (12). Conventional imaging modalities include transabdominal ultrasound (US) and endoscopic US (EUS), computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy. These techniques are used to localise primary GEP-NETs and to determine their metastatic spread. Functional imaging can be used to study physiological and chemical processes and changes in chemical composition, including metabolism, and also (changes in) blood flow and absorption. Molecular imaging can be used for the visualisation and follow-up of processes at the molecular and cellular level in the intact patient without disturbing them (12, 13). Sampling procedures aim to localise functional GEP-NETs by measuring appropriate hormonal gradients in the blood, both before and sometimes after the local or systemic i.v. or intra-arterial administration of stimulatory agents.

This review summarises the current status of the different molecular imaging and sampling methods that can be applied for the diagnosis and localisation of the different GEP-NETs.

Somatostatin receptor scintigraphy

Most GEP-NET cells show a high expression of high-affinity somatostatin receptors (14). Five different somatostatin receptor subtypes (SSTRs, namely SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5) have been cloned and characterised (14, 15). The subtype sst2(a) is expressed in more than 80% of GEP-NET cells. This receptor subtype is important with regard to its ability to bind the current commercially available somatostatin analogues (SSAs) and the radio-labelled SSAs (14, 16). Other ssts are also involved, but their expression is generally lower on GEP-NET cells (14).

Historically, ¹¹¹In-pentetreotide (OctreoScan) is in use for somatostatin receptor scintigraphy (SRS) (13) (Fig. 1). This radiopharmaceutical preferentially binds to sst2(a) and with decreasing lower affinities to also sst3 and sst1 (2, 14, 17). Planar and single-photon emission CT (SPECT) images are generally obtained 24 and 48 h after injection of this radiopharmaceutical (2, 18, 19). For a detailed protocol, the reader is referred to the literature (18, 19). The reported overall sensitivity of SRS for well-differentiated (grades 1 and 2) GEP-NETs is also more than 80%. Combining SRS and SPECT–CT allows functional localisation to be correlated with anatomic localisation. SRS plays an important role in the localisation of primary GEP-NETs and their metastases and can also be used for the monitoring of treatment responses in patients with these tumours in combination with conventional – anatomic – imaging (CT and MRI). SRS with ¹¹¹In-pentetreotide has been used to predict the clinical efficacy of current commercially available SSAs and for the selection of patients for peptide receptor radionuclide therapy (PRRT) using β-radiation-emitting SSAs (20, 21, 22, 23).

Physiological uptake of radiolabelled SSAs occurs in pituitary, thyroid, kidneys, liver and spleen (18). False-positive SRS in GEP-NETs might occur in patients with accessory spleen(s), infections, adrenal medullary tumours and sometimes in the uncinate process of the pancreas (13).

The sensitivity of SRS is generally lower in:

- Small tumours with a diameter generally < 1 cm, due to insufficient tumour-to-background uptake ratios of radioactivity (13);
- non-metastasised insulinomas (sensitivity < 50%), reflecting the generally low sst2(a) expression in this specific group of benign pancreatic NETs (13, 24); and
- NETs or neuroendocrine carcinomas (NECs) with a high Ki-67 index, reflecting dedifferentiation and loss of ssts; in these cases, ¹⁸F-fluorodeoxy-o-glucose (¹⁸F-FDG) positron emission tomography (PET) might be a better option for total body imaging (see below) (25).
Other radiolabelled SSAs with varying affinities for the different ssts are either still under investigation or already being used in a few centres. When compared with $^{111}$In-pentetreotide, $^{99m}$Tc-labelled SSAs are cheaper and include $^{99m}$Tc-depreotide, which preferentially binds with high affinity to sst$_{2(a)}$, sst$_3$ and sst$_5$ (26), and $^{99m}$Tc-vapreotide, which preferentially binds with high affinity to sst$_{2(a)}$ and sst$_3$ and with lower affinity to sst$_3$ and sst$_4$ (27). $^{111}$In-DOTA-lanreotide, $^{99m}$Tc-HYNIC-TOC and $^{99m}$Tc-HYNIC-TATE have more or less similar sst-binding affinities as $^{111}$In-pentetreotide and the comparison of imaging with these compounds have shown similar results (28, 29, 30).

**PET: PET/CT using $^{68}$Ga-DOTA-labelled SSAs**

In the recent decade, PET/CT using $^{68}$Ga-DOTA-labelled SSAs has been introduced for the diagnostic work-up of GEP-NETs. Three different $^{68}$Ga-DOTA-labelled SSAs are used in clinical practice: DOTANOC, DOTATATE and DOTATOC (13, 31, 32, 33, 34). These compounds differ with regard to their individual affinity for the different ssts. $^{68}$Ga-DOTATATE has a high affinity for sst$_{2(a)}$, $^{68}$Ga-DOTATOC has a high affinity for sst$_{2(a)}$ and sst$_5$ and $^{68}$Ga-DOTANOC is sst$_{2(a)}$, sst$_3$ and sst$_5$ specific (13, 31, 32, 33, 34). Somatostatin receptor PET/CT using $^{68}$Ga-DOTANOC, $^{68}$Ga-DOTATATE or $^{68}$Ga-DOTATOC is superior to SRS SPECT–CT showing higher sensitivities for GEP-NET lesion detection (more than 90%), particularly due to a better special resolution or better sst affinities (13, 31, 32, 33, 34). These compounds are also more ‘patient friendly’, as they allow for imaging 1–3 h within i.v. injection (13, 31, 32, 33, 34). New $^{68}$Ga-DOTA-labelled SSAs for PET imaging include $^{68}$Ga-DOTAVAP and $^{68}$Ga-DOTALAN (27). In the near future, it can be expected that somatostatin receptor PET(–CT) will increasingly replace SRS SPECT(–CT). Currently, these techniques are not available in every centre.

**Metaiodobenzylguanidine scintigraphy**

Metaiodobenzylguanidine (MIBG – iobenguane) is taken up and stored by the catecholamine-secreting cells of the sympathetic and parasympathetic systems. Radioiodinated MIBG, $^{123}$I-MIBG (or $^{131}$I-MIBG) is a guanethidine analogue that shares structural features with noradrenaline. At low concentrations, $^{123}$I-MIBG (or $^{131}$I-MIBG) is transported over the plasma membrane by the noradrenaline transporter or it enters the cell by passive diffusion. Within the cells, the vesicular monoamine transporters accumulate $^{123}$I-MIBG in catecholamine-storing granules (35). $^{123}$I-MIBG scintigraphy is generally used for imaging of functional pheochromocytomas, paragangliomas and neuroblastomas (36). However, $^{123}$I-MIBG (or $^{131}$I-MIBG) scintigraphy has a lower sensitivity than SRS for the imaging of NETs of the gastrointestinal tract (sensitivity ~50%) and pancreas (sensitivity <10%). However, in those patients with metastatic, inoperable, GEP-NETs and high uptake on MIBG scintigraphy, palliative treatment with $^{131}$I-MIBG might be considered (37, 38, 39, 40).

False-positive $^{123}$I-MIBG scintigraphy has been demonstrated in adrenocortical adenoma, adrenocortical carcinoma, angiomyolipoma and gastrointestinal stromal tumours (36).

**FDG PET: PET/CT**

$^{18}$F-FDG PET provides images based on variations in glucose metabolism between normal, non-pathologic, and malignant cells and tissues. Patients in whom $^{18}$F-FDG PET has to be performed should fast for at least 6 h and blood glucose levels should be routinely assessed. Images are acquired 60–90 min after i.v. injection of $^{18}$F-FDG (13). Variable $^{18}$F-FDG uptake might be caused by muscle contractions, fasting, ‘brown fat’ activation and infections (41).

High $^{18}$F-FDG uptake is usually associated with more aggressive GEP-NETs and a less favourable prognosis. The value of this imaging modality in most grades 1 and 2 GEP-NETs is limited, because of their limited growth velocity and, therefore, low glucose utilisation (13, 25, 42). However, in grade 3 NECs, it might have additional value, especially in those cases where SRS is negative (13, 25, 43, 44). $^{18}$F-FDG PET might also have a role in the prediction of the GEP-NET and lung-NET responses to PRRT with $^{177}$Lu-octreotate. No tumour progression was found at follow-up in GEP-NET and lung-NET patients with a negative $^{18}$F-FDG PET finding treated with PRRT. However, patients with both a grade 2 NET and a positive $^{18}$F-FDG PET finding showed a less favourable disease course after PRRT, which in clinical practice might lead to changes in the therapeutic approach in this particular subgroup of GEP-NET patients (45).

**DOPA PET: PET/CT**

The efficacy of fluorine-18-l-3,4-dihydroxyphenylalanine ($^{18}$F-DOPA) PET/CT is based on co-secretion of dopamine and hormones or peptides by GEP-NETs. In these cells, l-DOPA is converted by the enzyme l-DOPA decarboxylase
to dopamine. In comparative studies, {superscript}18{subscript}F-DOPA PET showed the highest sensitivity (98%) as compared with SRS and {superscript}11{subscript}C-5-hydroxy-L-tryptophan (11C-5-HTP) PET for the detection of NETs of the gastrointestinal tract, but not of the pancreas (13, 46). {superscript}18{subscript}F-DOPA PET tumour uptake reflects metabolic activity in NETs of the gastrointestinal tract (47). {superscript}18{subscript}F-DOPA PET/CT also has an important role in the diagnosis of congenital hyperinsulinism (OMIM #601820), especially for the identification of focal forms (41, 48, 49, 50, 51, 52) (Fig. 2).

**5-HTP PET**

{superscript}11{subscript}C-5-HTP is a radiolabelled precursor in the serotonin synthesis. The short half-life of the {superscript}11{subscript}C radiolabel and complex synthesis considerably limits the worldwide availability and clinical use of {superscript}11{subscript}C-5-HTP PET. In comparative studies, {superscript}11{subscript}C-5-HTP PET showed the highest sensitivity (96%) for the detection of pancreatic NETs as compared with CT, SRS and {superscript}18{subscript}F-DOPA PET (13, 41, 46, 53, 54). {superscript}11{subscript}C-5-HTP PET was shown to be particularly useful for detecting small pancreatic NETs and early recurrences of pancreatic NETs (Fig. 3).

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**Gastrin receptor scintigraphy**

Cholecystokinin 2 (CCK2) receptor expression has been demonstrated in a high percentage of medullary thyroid carcinomas (MTCs). Several CCK2 receptor-binding radiopeptides have been developed for scintigraphy: {superscript}111{subscript}In-DOTA-CCK, {superscript}99{subscript}mTc-demogastrin and {superscript}111{subscript}In-DOTAMG11 (55, 56, 57). Particularly, {superscript}99{subscript}mTc-demogastrin scintigraphy appeared to be most promising as a diagnostic tool in patients with (metastatic) MTC (55). {superscript}68{subscript}Ga-DOTA-minigastrin was developed for PET imaging of CCK2 receptor-positive tumours. {superscript}68{subscript}Ga-DOTA-minigastrin PET/CT showed an almost 97% sensitivity for the detection of tumour deposits in patients with MTC (56). In comparison, the detection rate of MTC with SRS is only 65% (58). As GEP-NETs also express CCK2 receptors, this imaging modality was also tested in a variety of GEP-NETs showing an overall tumour detection of almost 74% for {superscript}68{subscript}Ga-DOTA-minigastrin PET (59).

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**Glucagon-like peptide 1 receptor imaging**

The glucagon-like peptide 1 receptor (GLP1R) is mainly expressed on the pancreatic β-cells and is therefore an
Vasoactive intestinal peptide receptor scintigraphy

$^{123}$I-labelled vasoactive intestinal peptide (VIP) receptor scintigraphy generally has lower sensitivity than SRS for GEP-NET localisation and is, therefore, generally not recommended for the diagnostic work-up of GEP-NETs (74, 75, 76).

Sampling

Insulinoma

Preoperative localisation of a benign (non-metastatic) sporadic insulinoma within the pancreas can be challenging. Several non-invasive localisation techniques are available, including: US, CT, MRI, SRS, $^{68}$Ga-DOTA-labelled SSA PET/CT, MIBG scintigraphy, 5-HTP PET, DOPA PET, GLP1R imaging as well as semi-invasive and invasive procedures, such as EUS, intraoperative US, pancreatic angiography, transhepatic portal venous sampling and selective intra-arterial calcium stimulation of insulin release by injection into the major pancreatic arteries with hepatic venous sampling (ASVS) for insulin gradients. ASVS for insulin gradients has been reported to be the most sensitive preoperative localising technique for pancreatic insulinomas. However, as opposed to benign insulinomas, malignant insulinomas often lack GLP1R (60). Conversely, malignant insulinomas often do express sst2, which can be targeted using SRS (24, 60, 61, 62, 63, 64, 65, 66). In various studies, GLP1R scintigraphy using $^{111}$In-DOTA-exendin-4 successfully detected benign insulinomas (60, 67, 68, 69, 70). This radiopharmaceutical can also be successfully applied for the intraoperative localisation of these benign tumours (68).

Another radiopeptide used for targeting the GLP1R is (Lys(40)(Ahx-HYNIC-$^{99m}$Tc/EDDA)NH$_2$)-exendin-4. GLP1R imaging using this compound has been studied in MTCs (71) and benign insulinomas (72). $^{68}$Ga-DOTA-exendin-3 is a promising tracer to visualise insulinomas with PET (73).
insulinomas with reported successful localisation rates of 65–100% (77, 78, 79, 80, 81) (Fig. 4).

Administration of a hyperosmolar concentration of calcium gluconate into the vessels supplying the tumour will cause a release of insulin (and any other hormone secreted by that NET) into the portal venous system, resulting in a several-fold increase in insulin in blood samples obtained from the hepatic veins. The common hepatic artery (CHA), gastroduodenal artery (GDA), superior mesenteric artery (SMA) and splenic artery are injected and an appropriate rise in the level of insulin in samples obtained from the hepatic vein after the administration of hyperosmolar calcium gluconate into the CHA, GDA or SMA will localise a lesion in the head of the pancreas, while a positive response following splenic artery injection predicts a lesion in the body or tail of the pancreas (77, 78, 79, 80, 81).

**Sampling**

**Gastrinoma**

Ninety per cent of gastrinomas occur within the ‘gastrinoma triangle’. This is the area bounded by the junction of the neck and body of the pancreas medially, the junction of the second and third parts of the duodenum inferiorly and the junction of the cystic and common bile ducts superiority. SRS is the initial localisation study of choice, as this investigation, together with CT and EUS, will detect more than 90% of gastrinomas (82, 83, 84, 85). Therefore, the role of angiography and ASVS using secretin or calcium gluconate for localising gastrinomas is less clear-cut than in insulinomas. ASVS will provide both anatomical and functional information about the site of the gastrinoma and can be particularly useful for the difficult localisation of a sporadic duodenal gastrinoma (86, 87, 88).

**Sampling**

**Ectopic adrenocorticotrophin secretion**

Bilateral sampling of the petrosal or cavernous sinuses for adrenocorticotrophin (ACTH) measurements before and after stimulation with corticotrophin-releasing hormone (CRH) is necessary in a 40-year-old woman with ACTH-dependent Cushing’s syndrome and negative pituitary MRI findings in whom diagnosis of a typical ACTH-secreting lung carcinoid in the right lower lobe was made and a curative resection was performed. (A) Bilateral inferior petrosal sampling for ACTH before and after stimulation with CRH. The figure shows no gradients between ACTH measurements in both inferior petrosal sinuses and a peripheral vein. This is illustrative for ectopic ACTH secretion. A positive ACTH response to CRH stimulation was observed, indicative of the presence of CRH receptors on the bronchial carcinoid. Open circle, right inferior petrosal sinus; grey shaded circle, peripheral vein; and black shaded circle, left inferior petrosal sinus. (B) Coronal OctreoScan image showing the pathologic uptake in the lower lobe of the right lung (arrow). (C) Transverse CT image showing the pathologic lesion (arrow), previously considered as a blood vessel.
after the administration of corticotrophin-releasing hormone (CRH) has become an established and widely used diagnostic procedure in patients with ACTH-dependent Cushing’s syndrome, especially in those cases with a negative or equivocal pituitary MRI finding (89, 90, 91, 92, 93) (Fig. 5). As the petrosal or cavernous sinuses are in close proximity to the anterior pituitary, basal and CRH-stimulated ACTH levels in the blood from the inferior petrosal or cavernous sinus are generally higher than in the peripheral blood in the case of a pituitary source of ACTH overproduction. The lack of an appropriate ACTH gradient between the blood samples from the petrosal or cavernous sinuses and the peripheral blood vessels is indicative of an ectopic (non-pituitary) ACTH-secreting tumour (generally a NET). However, attempts to localise such an ectopic tumour by means of sampling several peripheral blood vessels for ACTH have generally turned out to be disappointing. Only a few case reports exist in which ACTH-secreting bronchial NETs could be localised using pulmonary arterial sampling (94, 95). However, generally CT, MRI and the different scintigraphy and PET techniques, as mentioned above, are more successful in the localisation of (occult) ACTH-producing extra-pituitary tumours (89, 90, 91, 92, 93).

**Recommendation flow charts with regard to GEP-NET-specific imaging**

- Patients with well-differentiated (grades 1 and 2) NETs of the digestive tract: US, CT/MRI, SRS and DOPA PET.
- Patients with well-differentiated (grades 1 and 2) clinically non-functioning NETs of the pancreas: US, CT, EUS, MRI, SRS and HPT PET.
- Patients with insulinoma: US, CT, EUS, MRI, HTP PET, GLP1R imaging, SRS and ASVS.
- Patients with duodenal or pancreatic gastrinoma: SRS, US, CT, EUS, MRI, HTP PET and ASVS.
- Patients with other functioning pancreatic tumours: US, CT, EUS, MRI, SRS and HPT PET.
- Patients with poorly differentiated (grade 3) GEP-NECs: CT and FDG PET.

**Future directions**

Molecular imaging will continue to play an important role in the diagnosis and follow-up of GEP-NETs. It is apparent that PET techniques will gradually replace SPECT. New somatostatin receptor radioligands are being developed for clinical imaging. Not only somatostatin receptor agonists but also receptor antagonists are being studied (96). Other peptide receptors might also be interesting targets for receptor imaging, such as the gastrin-releasing peptide or bombesin receptors (97, 98, 99).

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