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Review

Contemporary nuclear medicine imaging of neuroendocrine tumours

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Neuroendocrine tumours (NETs) are rare, heterogeneous, and often hormonally active neoplasms. Nuclear medicine (NM) imaging using single photon- and positron-emitting radiopharmaceuticals allows sensitive and highly specific molecular imaging of NETs, complementary to anatomy-based techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI). Somatostatin-receptor scintigraphy is a whole-body imaging technique widely used for diagnosis, staging and restaging of NETs. The increasing availability of hybrid single-photon emission CT (SPECT)/CT cameras now offers superior accuracy for localization and functional characterization of NETs compared to traditional planar and SPECT imaging. The potential role of positron-emission tomography (PET) tracers in the functional imaging of NETs is also being increasingly recognized. In addition to 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG), newer positron-emitting radiopharmaceuticals such as ^{18}F-dihydroxyphenylalanine (DOPA) and ^{68}Ga-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) peptides, show promise for the future. This article will summarize the role of current and emerging radiopharmaceuticals in NM imaging of this rare but important group of tumours.

Introduction

Neuroendocrine tumours (NETs) comprise a rare, heterogeneous group of hormonally active neoplasms with variable natural history and prognosis.[1,2] They are derived from endocrine stem cells of the amine precursor uptake and decarboxylation (APUD) system, and have the potential to cause clinical syndromes due to hypersecretion of biogenic amines and polypeptides.[3–5] Although their annual incidence is increasing due to greater awareness, earlier detection and the availability of more sensitive biochemical evaluation, diagnosis remains challenging and is often delayed for a mean duration of up to 9 years due to non-specificity or lack of symptoms.[2] Consequently, metastatic disease at diagnosis is frequent and detection can be problematic due to the small size of both primary and metastatic lesions.[2,3,6] This review article will briefly outline the classification of NETs, followed by a synopsis of the current and emerging radiopharmaceuticals that are

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available for NET imaging, and finally, provide a practical overview of the evidence, strengths, and limitations of single-photon and positron emitting radiotracers in the imaging of different groups of NETs.

Classification of NETs

For practical purposes [including selection of the appropriate nuclear medicine (NM) imaging technique], NETs have traditionally been divided into enterochromaffin tumours, chromaffin tumours, and medullary thyroid cancer (MTC).

Enterochromaffin NETs

Enterochromaffin NETs are derived from enteroendocrine cells within the epithelial lining of the digestive and respiratory tracts. They were previously classified based on secretory activity as carcinoid tumours (50% of NETs) with the classical triad of flushing, hypotension and diarrhoea, or non-carcinoid tumours, (e.g., gastrinomas, glucagonomas, insulinomas, and vasoactive intestinal peptide-producing tumour (VIPomas)), and also by site: bronchial (respiratory), foregut (oesophagus to pancreas), midgut "classic" carcinoid (jejunum to right colon, gonads), and hindgut (transverse colon to rectum). However, this older classification system was somewhat arbitrary leading to heterogeneous groups of NETs with highly variable biological behaviour being incorporated into inappropriate categories for the purposes of prognosis and management. Recent revisions to the classification system propose NETs be grouped according to their *differentiation*, how closely they resemble their non-neoplastic counterparts, and *grade*, a measure of their biological aggressiveness and malignant potential based upon mitotic rates and Ki-67 index.[1,3] For example, the World Health Organization (WHO) criteria distinguish well-differentiated NETs, including low and intermediate grades, and high-grade poorly differentiated neuroendocrine carcinomas. This method of classification when combined with staging systems, such as the AJCC TNM 7th edition, more appropriately reflects the prognosis of NETs and guides therapeutic management.

Chromaffin NETs

Chromaffin NETs are derived from sympathomedullary cells within post-ganglionic sympathetic neurons, which secrete catecholamines.[7] The majority of these cells are located in the adrenal medulla or in an extra-adrenal location near the coeliac axis or aortic bifurcation (e.g., organ of Zuckerkandl).[4,5] Those arising in the adrenal gland are termed phaeochromocytomas (PHAEO), while those arising from extra-adrenal tissues are paragangliomas (PGLs). Patients with PHAEO may present with hypertension and symptoms of biogenic amine excess.[2,7] PHAEO occurs in 0.5% of hypertensive patients and 4% of incidentally discovered adrenal masses.[4] PGLs are generally intra-abdominal in 85%, thoracic in 15%, and cervical in 1–3% of patients.[4] Cervical PGLs have a different clinical behaviour as they are usually of parasympathetic origin, do not contain chromaffin cells, and are frequently non-secretory.

Genetic testing may be positive in 12–25% of apparently sporadic cases of PHAEO with association to hereditable syndromes, including multiple endocrine neoplasia (MEN) type 2, neurofibromatosis type 1, von Hippel–Lindau syndrome, tuberous sclerosis,[4,5,8] and Carney's triad [gastrointestinal stromal tumour (GIST), pulmonary chondroma, and/or functioning extra-adrenal paraganglioma]. In familial cases due to germline mutations of succinate dehydrogenase subunits B,C,D (SDHB, SDHC, SDHD), bilateral PHAEO is common and two-thirds have metastatic disease.[4] As many as 50% of extra-adrenal paragangliomas are due to SDH mutations.[5] Another NET derived from chromaffin cells is neuroblastoma, which is a highly malignant neural crest tumour, the majority of which (>97%) occur in children <10 years, and which represents the second most common solid malignancy in childhood.[9]

Medullary thyroid cancers

Medullary thyroid cancers (MTC) are derived from parafollicular (C cells) of the thyroid, which originate from the neural crest. They frequently secrete calcitonin and carcinoembryonic antigen (CEA), which are used as tumour biomarkers. MTC comprise between 3–12% of all thyroid cancers and may be sporadic in 70–80% of patients or inherited in 20–30%.[10] Inherited MTC is associated with germline mutations of the RET proto-oncogene and manifests as multiple endocrine neoplasia (MEN) type 2A and 2B, or as an isolated familial syndrome.

Primary treatment consists of total thyroidectomy with central compartment nodal dissection. MTC is an indolent disease and at diagnosis 35–50% of patients may already have neck or mediastinal nodal spread with 10–15% presenting with distant metastases to lung, bone, liver, or other sites.[10] After surgery up to 40% of patients will have residual or recurrent disease. Recurrence is indicated by elevated serum calcitonin levels, although both morphological and NM techniques have limited sensitivity for detection of low-volume disease. MTC remains a difficult tumour to image with no single imaging technique having unequivocally demonstrated superior accuracy.

Single-photon emitting and positron-emitting radiopharmaceuticals for neuroendocrine tumour imaging

Somatostatin-receptor imaging

Somatostatin is a regulatory peptide, with affinity for G-protein-coupled membrane-bound somatostatin receptors (SSTR) subtypes 1–5, including 2A and 2B, which are overexpressed in NETs.[6,11,12] Peptide-based imaging with somatostatin analogues has advantages of high specificity, good tissue penetration, rapid clearance, and low antigenicity, and is considered a first-line imaging technique for NETs.[11] Additionally it provides evidence for targeting of