68Ga-labelled somatostatin analogues (SSA) PET CT imaging in Neuroendocrine tumours

Kiran Kumar J.K.

Neuroendocrine tumours are derived from embryonic neural crest tissue found in the hypothalamus, pituitary gland, thyroid gland, adrenal medulla, and gastrointestinal tract. Enteropancreatic tumours (carcinoid tumours, gastrinoma, glucagonoma, vasoactive intestinal peptide [VIP]- related tumours [VlPomas], poorly differentiated neuroendocrine tumours), sympathoadrenal tumours (phaeochromocytoma [PHEO], paraganglioma), multiple endocrine neoplasia (MEN) syndromes (type 1 MEN, type 2 MEN), and medullary thyroid carcinoma (MTC). The sites most affected in neuroendocrine tumours are the gastrointestinal tract in about 65% of cases followed by bronchopulmonary tract, which accounts for about 25%. Presentation with metastases is found in 22% of the cases. Gastroenteropancreatic NETs are typically classified on the basis of the Ki-67 proliferation index or the mitotic count Well-differentiated (G1 and G2) NETs are relatively indolent and High-grade (G3) poorly differentiated neuroendocrine carcinomas (NECs) are typically much more aggressive and nearly always metastatic at diagnosis.

The radio pharmaceuticals used for imaging neuroendocrine tumours are either similar in molecular structure to the hormones that the tumours synthesise or incorporated into various metabolic and cellular processes of the tumour cell.

Theoretically, radionuclide-labelled somatostatin could bind to neuroendocrine tumours that contain somatostatin receptors, thereby facilitating the identification and imaging of the tumour and, potentially, of tumour metastases.

Somatostatin is a naturally occurring hormone that acts by binding to SSTR, a receptor that is overexpressed on most NETs. There are S predominant subtypes of SSTR, type 2 being the most commonly expressed in NETs.[1]

TABLE I: World Health Organisation Classification 20l7

Characteristic	Well-Differentiated (Neuroendocrine Tumour)			Poorly Differentiated (Neuroendocrine Carcinoma)
Grade	G1	G2	G3	G3
Ki-67 index (%)	≤3	3-20	20-50	> 50

Imaging plays a pivotal role in diagnosis, staging, treatment selection and follow-up of NETs. Current diagnostic methods include morphologic modalities such as computed tomography (CT), magnetic resonance imaging (MRI), transabdominal ultrasound (US), endoscopic US (EUS) and intraoperative US (IOUS).

Nuclear medicine imaging or molecular imaging consists of scintigraphy including single photon emission computed tomography (SPECT)

Consultant & Head, Dept. of Nuclear Medicine & PET -CT, BHIMS, 12 New Marine Lines, Mumbai-400 020.

with ^{111}In-pentetreotide or, more recently, PET with 68Ga-labelled somatostatin analogues (SSA), ^{18}F-DOPA and ^{11}C-5-HTP. Combination of anatomic and functional techniques is routinely performed to optimise sensitivity and specificity.[2]

Imaging Techniques

US: Transabdominal US is often the first technique utilised for NET imaging. US allows for easy guidance of the biopsy needle for fine needle aspiration cytology.

Improved techniques, including contrast-enhanced US (CEUS), EUS and IOUS have allowed for an increase in sensitivity.

CT/MRI : Principal methods used for the detection of the primary tumour, describing its local extent, staging of locoregional and distant metastases, as well as for the assessment of therapeutic response. Since neuroendocrine lesions and their metastases are usually hypervascular, they enhance in the late arterial phase after contrast medium injection on CT and MRI.[3]

MDCT can localise the primary tumour, assess the extent of disease, characterise the architectural relationships with the surrounding structures and be used to reassess the disease following treatments. The better soft-tissue contrast of MRI, as compared to CT, is particularly useful to detect liver metastases.[4] MRI is particularly advantageous in localising primary pancreatic tumours and for staging and restaging liver lesions. The sensitivity for pancreatic NETs ranges from 69 to 94% for CT, 74 to 94% for MRI and is >80% for EUS coupled with biopsy.[8-13] The sensitivity for locating a primary small intestine NET is 100% for CT enteroclysis and 86-94% for MRI.[5]

Limitations

Long duration of MRI scan. Difficulty in reassessment of small-volume disease. Difficult assessment of small thoracic lesions on MRI. Difficult in reassessment of large-volume disease (poor demarcation, coalescence). Difficulty in capturing modifications in slow-growing tumours. Difficulty in defining response (e.g. RECIST) if necrosis/ fibrosis/ haemorrhage occurs without a marked decrease in tumour size.

Nuclear medicine imaging or molecular imaging

Besides localisation, staging and restaging of primary and metastatic tumours, molecular imaging allows for the functional characterisation of lesions and the therapy selection with cold or radiolabelled SSA (PRRT). Functional imaging has a clinical impact in terms of modification of the therapeutic strategy and of prognosis.

SPECT/CT: The radiolabelled SSA III In-pentetreotide is the most commonly used agent for SRS. Generally has >75% for gastroenteropancreatic and bronchial tumours.

The major limitation of conventional SRS with III Inpentetreotide is the low spatial resolution.

68 Ga-SSAPET/CT: The approach to the molecular imaging of NETs has been revolutionised by the introduction of PET with the 68 Ga-labelled octreotide derivatives DOTATOC, DOTATATE and DOTANOC (68Ga-SSA-PET/ CT). The

advantages are simple and economical synthesis of the radiopeptide from an on-site 68 Ge/ 68 Ga generator eluate, the single-day procedure, the possibility of semiquantification of the activity in a given region of interest as the 'SUV', the higher spatial resolution with the detection of 4 to 6 mm lesions and, finally, the better dosimetry.[6]

Hofmann et al in 2001, studied eight patients with histologically proven carcinoid tumours who underwent III In-octreotide scintigraphy and 68Ga-DOTATOC PET. Forty lesions were identified with CT and/or MRI. III In octreotide planar and SPECT imaging identified only 85% whereas 68Ga, DOTATOC PET identified 100% of these lesions. Furthermore, it also detected 30% more lesions. The tumour to non-tumour uptake ratios with 68Ga-DOTATOC PET ranged from >3:1 for liver III (In-octreotide: 1.5:1) to100:1 for CNS.[7]

They concluded that using Ga-DOTATOC PET results in high tumour to non-tumour contrast, low kidney accumulation and yields higher detection rates as compared to In-octreotide scintigraphy.[7]

The overall sensitivity of 68 Ga-SSA-PET/CT for NETs is >90%, while the specificity ranges from 92 to 98%.

Gastroenteropancreatic Neuroendocrine Tumours

68 Ga-SSA-PET/CT is indicated for staging after histologic diagnosis of NETs. Up to 20% of patients with NETs have unknown primaries after initial workup. In one prospective study, the primary tumour was found in 38% of patients who were imaged with SSTR PET.

For N staging: 68Ga-DOTATOC PET/CT showed higher sensitivity than whole-body MRI for metastatic lymph nodes (100% vs 73%). Mesenteric lymph nodes are the second most common metastatic site of small bowel NET, with the liver being first. Albanus et al. compared a combination of 68Ga-DOTATATE PET and contrast-enhanced CT with stand alone contrast-enhanced CT in 54 patients with NETs and found that, on a per-patient basis, contrast-enhanced PET/CT achieved a higher sensitivity (92% vs 64%) and specificity (83% vs 59%) for lymph nodes.

For M staging: Common sites of metastatic spread in GEP NETs are liver, peritoneum, lung and bone. Gallium-68 DOTATATE PET/ CT has good diagnostic accuracy to detect distant metastases and can have significant impact on patient management. Frilling et al. examined 52 patients with NET and found that 68Ga-SSA PET identified additional liver metastases, extrahepatic disease, or both that were undetected by CT or MRI in 22 of the 33 patients with liver metastases.[9]

SSTR PET should be used to guide surgical planning and to rule out extensive extra abdominal disease in patients before undergoing hepatic cytoreductive procedures. SSTR PET can demonstrate noninvasively that an uncharacterised mass is SSTR-positive and therefore most likely an NET. SSTR PET is indicated for routine imaging and follow-up. lf a patient did not undergo SSTR PET before surgical resection, a single SSTR PET examination should be considered to complete staging

postoperatively. SSTR PET can be used to clarify whether a suspected lesion is an NET and represents true progression or recurrence.

There are specific instances in which SSTR PET is clearly preferred: at initial diagnosis, when selecting patients for PRRT, and for localisation of unknown primaries.

68 Ga-SSA-PET/CT has demonstrated a higher sensitivity than metabolic tracers, such as 18 F-DOPA and 11 C-5-HTP, and is able to sensitively visualise difficult areas including bones, peritoneum, the heart or soft tissues.[10] Moreover, it is able to modify the therapeutic management in >50%.[11]

68Ga-DOTATATE PET performed better in extra-adrenal tumours and in SDHD positive cases of phaeochromocytoma.

18 FDG PET may instead be considered for imaging of high G2 NETs with Ki67 >15-20% for which SRS and 68 Ga-SSA-PET/ CT may be unreliable. Typically, high-grade NECs have lower SSTR expression, as evidenced by less tracer uptake on SSTR,-PET, and are better imaged with FDG PET. The increased glucose metabolism, expressed as standardised uptake value (SUV), can provide predictive information in terms of overall survival and progression free survival (PFS). NETs that exhibited increased metabolic activity had a significantly lower disease control rate (100 vs. 76%) and PFS (32 vs. 20 months) after PRRT compared to 18 FDG-negative tumours.

Significant tumour heterogeneity can occur in patients, with the coexistence of both well-differentiated and poorly differentiated tumours; in this case, a combination of F18-FDG and SSTR PET can be helpful in characterising disease.

18 F-DOPA,: which measures neuroendocrine metabolism, High sensitivity, especially for carcinoids. Alternative or a problem-solving tool when SR1 is negative.

Conclusion

Gallium-68 DOTATATE PET/ CT is an advanced functional imaging modality for assessment of well-differentiated NETs. It should be the preferred imaging modality for initial diagnosis, selection of patients for PRRT, and localisation of unknown primary tumours.

The NCCN guideline has added 68Ga-DOTATATE PET/CT as an appropriate test in the management of NETs. ln combination with FDG PET/CT, 68Ga-DOTATATEPET/ CT can noninvasively assess tumour heterogeneity especially in G2 and G3 NETs for personalised management of patients.

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Statin-associated muscle symptoms: beware of the nocebo effect

Patient-reported statin intolerance, predominantly due to statin-associated muscle symptoms (SAMS), is a common and difficult-to-manage condition affecting millions of patients worldwide.

However, the development of SAMS does not necessarily signify statin intolerance since statin therapy might not always be pharmacologically involved. Moreover, some patients with SAMS might be able to tolerate a lower dose than the dose that leads to SAMS, longer dose intervals, or an alternative statin.

Ajay Gupta and colleagues report a highly relevant study in The Lancet in support of the fact that statins do ***not*** significantly increase the risk of muscle pain.

The main finding was that no excess of muscle-related AEs was reported among patients receiving atorvastatin therapy during the blinded randomised period (298 [2.03% per annum] in the atorvastatin group vs 283 [2.00% per annum] in the placebo group.

The excess of muscle-related AEs associated with atorvastatin therapy only when the comparison was non-blinded, is consistent, at least in part, with a nocebo effect.

The term nocebo was coined by Walter Kennedy in 1961 to denote the counterpart to the use of placebo. The nocebo effect reflects changes in human psychobiology involving the brain, body, and behaviour rather than drug toxicity. Reports of SAMS might result from patients' perceptions about statins in light of negative press reports of statin use or even to or understanding of warnings about statin-associated side effects.

Fewer patients could possibly report SAMS with statins if they receive the medication blindly than if they receive it open label, or they might have SAMS even if they received a placebo, indicating a highly improbable pharmacological basis. Since the nocebo effect occurs frequently and is under-recognised in clinical practice, physicians should be informed of how to recognise and manage this effect. Evidence from the Understanding Statin Use in America and Gaps in Education survey, seeking predictors of statin adherence, switching, and discontinuation, underlines the importance of a trustful physician-patient relationship, since only a few patients will believe that their SAMS are of psychogenic origin.

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