Better Way to Image and Manage Neuroendocrine Tumors: Role of 68Gallium DOTA-Peptide PET-CT Scan

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ABSTRACT

Neuroendocrine tumours (NETs) are especial entity of neoplasms arising from nervous and endocrine systems and involving variety of organs. Over expression of somatostatin receptors is an unique characteristic of these tumours. This allows molecular imaging to play a significant role in evaluation of NETs using somatostatin analogues. ^{111}In Pentetreotide scintigraphy has been playing a significant role as molecular imaging of choice to locate the primary tumor, evaluate extent of disease and plan for surgical management. Recently ^{68}Ga labelled peptides have emerged as promising PET tracers for scintigraphy of these tumours. Several recent studies have demonstrated the superiority of ^{68}Ga DOTA-Peptide PET-CT scan with a number of advantages over conventional somatostatin receptor scintigraphy.

Key Words: **Neuroendocrine tumours (NETs), ^{68}Ga DOTA-peptides, Positron Emission Tomography (PET).**

INTRODUCTION

Neuroendocrine tumors (NETs) comprise a heterogeneous group of malignancies with a very variable clinical expression and progression. These tumors can originate from endocrine glands such as the pituitary and adrenal medulla, as well as endocrine cell clusters in the thyroid or the pancreas and widely dispersed endocrine cells in the gastrointestinal and respiratory tract as well as skin (1). Though these tumors can arise in any of the aforementioned tissues, the most common primary sites are the lung, rectum and small bowel (2).

Historically, these tumors were thought to be extremely rare, though many recent studies have shown an increasing incidence (2-4). This increase has been ascribed, in part, to improved methods of diagnosis and greater disease awareness (3). Innovations in somatostatin receptor-based technologies have also pushed NET molecular diagnostics and therapeutics forward, improving the quality of life for many patients (5,6). They present unique properties that are important to consider for radiological and nuclear imaging, such as APUD-characteristics (amine precursor uptake and dearboxylation), as well as the expression of somatostatin receptors (7). This unique feature has enabled the field of nuclear medicine and molecular imaging to image these tumors with radiolabelled somatostatin analogues agent (8). Octreotide, a long-acting somatostatin analogue, was initially used in 1989 and since then it evolved as an important agent in the initial evaluation and management of NETs using molecular imaging techniques. The procedure offers a total body examination and a better staging of the disease (9). However, gamma imaging using ^{111}In-octreotide has several limiting factors which decreased the image quality and overall efficiency of the test. These include low image quality of Indium-111 isotope, increased physiological uptake which restricts detection of small lesions, prolonged imaging protocol and relatively high radiation dose to the patients (10, 11). Because of the small lesion size, variable anatomical location, and low metabolic rate; conventional imaging of such tumors is often difficult. Computed tomography (CT), ultrasound (US), and magnetic resonance imaging (MRI) are often unable to

characterize or sometimes unable to detect such tumors (12).

Recently, positron emission tomography/computed tomography (PET/CT) with 68Gallium (^{68}Ga)-labeled somatostatin analogues has shown excellent results for imaging of NETs and better results than conventional SSTR scintigraphy (13). This review discussed the valuable role of ^{68}Ga DOTA-Peptide PET/CT in management of neuroendocrine tumours and to compare it with coventional somatostatin receptor scintigraphy (SRS).

^{68}Ga LABELED SOMATOSTATIN ANALOGUES

^{68}Ga-labeled somatostatin analogues are generally short peptide analogues of somatostatin which are linked to the positron emitter ^{68}Ga by a bifunctional chelate, usually 1,4,7,10- tetraazacyclododecane -1,4,7,10-tetraacetic acid (DOTA). The ^{68}Ga-DOTA-peptides bind to the somatostatin receptors (SSTRs) overexpressed on NETs cells. Six different SSTRs have been identified (14). These are SSTR1, 2A, 2B, 3, 4, and 5. These SSTRs are G-protein coupled transmembrane receptors and are internalized after binding to specific ligand (14). Among these SSTR2 and 5 are predominantly overexpressed in NETs, while normal tissue majorly express SSTR3 and 5. Three major ^{68}Ga-DOTA-peptides are currently available for imaging: ^{68}Ga-DOTA-Phe1-Tyr3-Octreotide (TOC), ^{68}Ga-DOTA-NaI3-Octreotide (NOC), and ^{68}Ga-DOTA-Tyr3-Octreotate (TATE). All of them can bind to SSTR2 and SSTR5, while only DOTA-NOC shows good affinity for SSTR3 (15).

TRACER PREPARARTION AND ACQUISITION

With the help of ^{68}Ge/^{68}Ga generators, now the PET radiolabelled tracers can be made on-site independent of cyclotron and therefore less expensive for clinical practice. ^{68}Ga is eluted from the ^{68}Ge/^{68}Ga generator which immobilizes the parent radioisotope Germanium. The ^{68}Ga can be eluted using various concentrations of HCl (16). The long half-life of the mother radionuclide 68Ge (270.8 days) makes it possible to use the generator for approximately 6-12 months depending on use and can be eluted as early as every 3 hours (17).

Several different methods have been used for radiolabeling of DOTA-peptides with 68Ga, (for example ^{68}Ga DOTATATE) including pre-concentration and purification (cationic or anion exchange) method or fractionation method based on the feasibility and type of generator. In few methods post-processing purification by using ^{18}C Sep Pak purification to ensure removal of free ^{68}Ga. The quality control (including the endotoxin test, ^{68}Ge breakthrough, radionuclide identity test, osmolality test, pH test) of the ^{68}Ga-DOTATATE completes preparation of clinical dose of radiotracer. Nevertheless, the methodology of preparation of ^{68}Ga-DOTATATE is well characterized and standardized for clinical practice upon stringent quality control testing (17). Reubi et al. reported that the affinity of DOTATATE in binding SST2 to be approximately 10-fold higher than that of octreotide (18). The radiation exposure to the radiochemist is within limits prescribed (19). With availability of automated modules the synthesis has become safer.

The recommended dose of ^{68}Ga-DOTA-peptides is usually 132-222 M Bq (4-6 mCi), but should not be less than 100 MBq (20). PET/CT is acquired 45-60 minutes post injection, with the general consensus that best images are obtained at 60 minutes. Images are acquired from skull (must include the pituitary gland) to mid-thigh. Additional views can be taken as and when required. Use of intravenous contrast during CT part of PET/CT is controversial; with few studies advocate their use (21).

ADVANTAGES OF ^{68}Ga LABELED PEPTIDE IMAGING

^{68}Ga-DOTA peptide PET/CT offers several advantages over conventional SRS. These peptides are easier and cheaper to synthesize than standard

octreotide-analog based ligands, and does not require a cyclotron. PET-CT requires single time point image acquisition (1-2 h post injection vs OctreoScan, which requires patients to be scanned at 4 and 24 h post injection). Its superior spatial resolution derives from the fact that it measures the radiation from two photons coincidentally. SPECT, in comparison, measures the gamma radiation emitted from one photon directly. This results in different limitations of detection – millimeters for ^{68}Ga-PET compared with 1 cm or more for SPECT thus providing better visualization of small lesions (22). Also, the ^{68}Ga-DOTA-NOC has broad spectrum affinity for SSTRs (SSTR2, 3, and 5) as compared to 111In-Octreotide (SSTR2 only). Finally, PET provides the possibility of quantification of the tracer uptake in a given region of interest. This can be achieved by measuring the standardized uptake value (SUVmax) which can be used for response monitoring and prognostication (23, 24).

USEFULLNESS IN DIFFERENT NEURIENDICRINE TUMORS

^{68}Ga-DOTA peptide PET/CT has been shown to be extremely useful for imaging of gastrenteropancreatic neuroendocrine tumors (GEP-NETs). A meta-analysis by Treglia et al. evaluated 16 studies comprising 567 patients with GEP and thoracic NETs (25). They advised that this accurate technique should be considered as first-line diagnostic imaging methods in patients with suspicious thoracic and/or GEP NETs. Ambrosini et al. reviewed their experience of imaging GEP-NETs in 1,239 patients (26). The sensitivity was 92% and specificity was 98% for the detection of NET.

Pulmonary NETs are second most common site for NETs after GEP-NETs and account for 22-27% of such tumors. The WHO classification of pulmonary NETs classifies these neoplasms in order of increasing malignant potential into typical carcinoids, atypical carcinoids, and large cell and small cell NETs (27). Many studies in the past have explored ^{68}Ga-labeled somatostatin analogue PET/CT in patients with pulmonary NETs, often in conjunction with ^{18}F-FDG. Ambrosini et al. evaluated ^{68}Ga-DOTA-NOC PET/CT in 11 patients with bronchial carcinoid (28). PET/CT detected at least one lesion in nine of 11 patients and was negative in two. On a clinical basis, PET/CT provided additional information in nine of 11 patients leading to the changes in the clinical management of three of nine patients. Kayani et al. (29) compared ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT in 18 patients with pulmonary NET. In that series, typical carcinoids showed significantly higher uptake of ^{68}Ga-DOTA-TATE and significantly less uptake of ^{18}F-FDG than did tumors of higher grade ($P = 0.002$ and 0.005). In addition, ^{68}Ga-DOTA-TATE was superior to ^{18}F-FDG for discriminating endobronchial tumor from distal collapsed lung.

Paragangliomas are tumors that develop from endocrine cells derived from pluripotent neural crest stem cells and are associated with neurons of the autonomic nervous system. Those developing from adrenal medulla are most common (~90%) and called pheochromocytoma (30).

^{123}/^{131}I- Metaiodobenzyguanidine (MIBG) scintigraphy is currently the functional imaging method of choice for the localization of pheochromocytomas and paragangliomas. It provides high sensitivity and specificity, but is not without limitations (31). Win et al. (32) compared ^{68}Ga-DOTA-TATE PET with ^{123}I-MIBG in five patients with pheochromocytoma and showed that ^{68}Ga-DOTA-TATE PET showed more lesions, with higher uptake and better resolution. Maurice et al. (33) compared ^{68}Ga-DOTA-TATE PET with ^{123}I-MIBG in 15 patients with pheochromocytoma / paraganglioma. They recommended that ^{68}Ga-DOTA-TATE PET should be used as the first line investigation for paraganglioma and metastatic disease.

COMPARISON WITH CONVENTIONAL SRS

With the advent of ^{68}Ga-DOTA peptide PET/CT there is a trend toward shifting from conventional scintigraphy to PET/CT.

Many studies have already shown the superiority of ^{68}Ga-DOTA peptide PET/CT over conventional SRS for imaging NETs (34, 35).

Srirajaskanthan et al. (36) were the first group that compared the ^{68}Ga-DOTATATE to Octreoscan. They evaluated the diagnostic and management role of ^{68}Ga-DOTATATE PET imaging in patients with neuroendocrine tumors and negative or equivocal findings on ^{111}In-DTPA-octreotide scintigraphy. They showed that ^{68}Ga-DOTATATE PET was positive in 41 of these 47 patients (87.2%). No false-positive lesions were identified. ^{68}Ga-DOTATATE PET identified significantly more lesions than ^{111}In-DTPA-octreotide scintigraphy (168 versus 27 respectively, $P < 0.001$). Hofman et al. (37) studied the impact of ^{68}Ga-DOTATATE PET/CT for imaging neuroendocrine and other somatostatin expressing tumors and compared it to Octreoscan and conventional imaging. They demonstrated that 88% of ^{68}Ga-DOTATATE PET/CT studies were abnormal. Compared with conventional and In-111 octreotide imaging, additional information was provided by ^{68}Ga-DOTATATE PET/CT in 68% and 83% of patients, respectively.

Buchmann et al. (38) reported that ^{68}Ga-DOTATOC detected more than 279 NET lesions in 27 patients with histologically proven NETs, whereas SRS-SPECT detected only 157. The greatest number of lesions were detected in the liver. ^{68}Ga-DOTATOC found more than 152 hepatic lesions, while SRS-SPECT found only 105, resulting in a 66% concordance rate between the two modalities. The concordance for abdominal lymph nodes was worse at 40.1%. In this set of patients, the greater sensitivity of ^{68}Ga-DOTATOC resulted in an altered surgical plan in one patient.

Gabriel et al. (34) reported similar conclusions to Buchmann et al. (38) in their comparison study of ^{68}Ga-DOTATOC, SRS-SPECT and CT in 84 patients. They found the sensitivity and specificity of ^{68}Ga-DOTATOC to be 97% and 92%, respectively. For SRS-SPECT, the sensitivity was 52% and specificity 92%. The difference in sensitivities between these two modalities was statistically significant ($p < 0.001$). ^{68}Ga-DOTATOC provided new clinical information in 21.4% of patients, which resulted in altered surgical plans in three patients (surgery declined due to previously unknown widespread metastases).

DISCUSSION

Neuroendocrine tumors (NETs) arise from the diffuse neuroendocrine system, which is comprised of 17 different cell types that reside in skin, lung, the hepatobiliary system, the urogenital tract, thyroid and the gastrointestinal tract (39). These tumors (NETs) represent a considerable diagnostic challenge as their clinical presentation is protean, nonspecific and usually late, often when hepatic metastases are already evident (40). So tumor burden assessment often requires use of multiple imaging modalities. In their diagnostic workup, two critical issues are present: firstly, the need to identify tumor presence and, secondly, to define the primary location and assess regional and distant metastases. Imaging plays a pivotal role in diagnosis, staging, treatment selection and follow-up of NETs (41). 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) with ^{111}In-pentetreotide or, more recently, PET with ^{68}Ga-labeled somatostatin analogs (SSA), ^{18}F-DOPA and 11C-5-HTP (40).

Somatostatin receptor based imaging is the functional imaging of choice in diagnosis and managenent of NETS. The indications for somatostatin receptor-based imaging are: detection and localization of primary

NETs and their metastases, staging, follow-up for disease recurrence and to select patients for peptide receptor radionuclide therapy (42). Octreoscan using ^{111}In-pentetreotide is the only universally approved radiopharmaceutical for NET imaging so far (41). The use of ^{111}In-pentetreotide to localize, stage, restage as well as provide therapeutic indications was a major advance in NET management (42-45).

However, with the recent availability of PET imaging, ^{68}Gallium (^{68}Ga)-labeled somatostatin analogues has shown excellent results for imaging of NETs and better results than conventional SSTR scintigraphy (13). It has been demonstrated that ^{68}Ga-DOTA-peptide PET scan can dramatically improve the spatial resolution and lesion detectability compared to Octreoscan® or MIBG scintigraphy (46,47).

This provides several advantages over conventional scintigraphy. These include the simple and economical synthesis of the radio peptide 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 (48). The intrinsic multi planarity of the PET techniques and the co registration with high resolution CT produces low-dose, or preferably, diagnostic contrast enhanced scans, with an improved accuracy and image interpretation (49). Another advantage is the possibility of labeling and imaging the same peptide used for PRRT (50). ^{68}Ga-SSA-PET/CT has demonstrated a higher sensitivity than metabolic tracers, such as ^{18}F-DOPA and 11C-5-HTP, and is able to sensitively visualize difficult areas including bones, peritoneum, the heart or soft tissues (51, 52). It allows for localization, staging and restaging and provides therapeutic indications based on tumor SSR expression (24, 48). Moreover, it is able to modify the therapeutic management in >50% (24, 53). A recent study reported in the Journal of Nuclear Medicine, 2016 demonstrates that Ga-68 DOTATATE PET/CT scans are superior to ^{111}In-pentetreotide scans, the current imaging standard in the United States for detecting neuroendocrine tumors (NETS), and could significantly impact treatment management (54).

CONCLUSION

Neuroendocrine tumors are malignancies that can be diagnosed by variety of imaging modalities. Molecular imaging based on somatostatin receptor analogues is unique for this purpose. Recent studies demonstrate ^{68}Ga DOTA –peptide PET-CT scans as superior diagnostic tool in evaluating these tumors and have the capability to alter clinical decision making due to their superior sensitivity. It has the potential to be the first line of imaging for evaluating NETs.

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