Nucl Med Mol Imaging (2018) 52:119–124
DOI 10.1007/s13139-017-0496-3

ORIGINAL ARTICLE

ISSN (print) 1869-3482
ISSN (online) 1869-3474

Impact of ^{68}Ga-DOTA-Peptide PET/CT on the Management of Gastrointestinal Neuroendocrine Tumour (GI-NET): Malaysian National Referral Centre Experience

Teik Hin Tan[1] · **Ching Yeen Boey**[2] · **Boon Nang Lee**[2]

Received: 4 January 2017 / Revised: 23 August 2017 / Accepted: 13 September 2017 / Published online: 8 December 2017

Abstract
Purpose The National Cancer Institute is the only referral centre in Malaysia that provides ^{68}Ga-DOTA-peptide imaging. The purpose of this study is to determine the impact of ^{68}Ga-DOTA-peptide PET/CT on the management of gastrointestinal neuroendocrine tumours (GI-NET).
Materials and Methods A cross-sectional study was performed to review the impact of ^{68}Ga-DOTA-peptide (^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC) PET/CT on patients with biopsy-proven GI-NET between January 2011 and December 2015. Suspected NET was excluded. Demographic data, tumoral characteristics, change of disease stage, pre-PET intended management and post-PET management were evaluated.
Results Over a 5-year period, 82 studies of ^{68}Ga-DOTA-peptide PET/CT were performed on 44 GI-NET patients. The most common primary site was the rectum (50.0%) followed by the small bowel, stomach and colon. Using WHO 2010 grading, 40.9% of patients had low-grade (G1) tumour, 22.7% intermediate (G2) and 4.5% high (G3). Of ten patients scheduled for pre-operative staging, ^{68}Ga-DOTA-peptide PET/CT only led to therapeutic change in three patients. Furthermore, false-negative results of ^{68}Ga-DOTA-peptide PET/CT were reported in one patient after surgical confirmation. However, therapeutic changes were seen in 20/36 patients (55.6%) scheduled for post-surgical restaging or assessment of somatostatin analogue (SSA) eligibility. When ^{68}Ga-DOTA-peptide PET/CT was used for monitoring disease progress during systemic treatment (sandostatin, chemotherapy, everolimus and PRRT) in metastatic disease, impact on management modification was seen in 19/36 patients (52.8%), of which 84.2% had inter-modality change (switch to everolimus, chemotherapy or PRRT) and 15.8% had intra-modality change (increased SSA dosage).
Conclusions ^{68}Ga-DOTA-peptide PET/CT has a significant impact on management decisions in GI-NET patients as it can provide additional information on occult metastasis/equivocal lesions and supply the clinician an opportunity to select patients for targeted therapy.

Keywords ^{68}Ga-DOTA-peptide · ^{68}Ga-DOTA-TATE · PET/CT · Neuroendocrine tumour

Introduction

Neuroendocrine tumours (NETs) are a heterogenous group of neoplasms with characteristic features of somatostatin receptor (SSTR) over-expression [1]. As targeted somatostatin receptor-based therapy is recognised as an important component in the treatment for NETs, the ability to demonstrate and predict the response to these therapies is extremely useful [2, 3]. Hence, functional imaging, which specifically targets these receptors, plays a pivotal role in the detection, mapping, monitoring as well as treatment planning of these diseases.

^{68}Ga-DOTA peptides are a group of PET tracers that specifically bind to SSTR [4]. Three main peptides are available: TOC, NOC and TATE [4]. The main difference among these peptides is the variable affinity to SSTR subtypes. All peptides show good affinity to SSTR 2 and 5, whereas only -NOC shows additional good binding to SSTR 3 [5]. However, there

✉ Teik Hin Tan
teikhin.tan@gmail.com

[1] Nuclear Medicine Centre, Sunway Medical Centre, No 5, Jalan Lagoon Selatan, 74500 Bandar Sunway, Selangor, Malaysia

[2] Department of Nuclear Medicine, National Cancer Institute, No 4, Jalan P7, Presint 7, 62250 Putrajaya, Malaysia

is currently no evidence of a clinical impact of these differences on receptor binding affinity, and therefore there is no indication suggesting the preferential use of one compound over the others [6].

Recently, somatostatin receptor scintigraphy (SRS), which was previously regarded as the gold standard somatostatin receptor imaging in gastro-entero-pancreatic neuroendocrine tumours (GEP-NET), has been largely replaced by ^{68}Ga-DOTA-peptide PET/CT. This substitution is expected as ^{68}Ga-DOTA-peptide PET/CT is found to provide simpler patient preparation and a lower radiation dose to the patient, and, most importantly, it provides superior image quality, which results in higher sensitivity in detecting GEP-NET as compared to SRS [7, 8].

As high detection rates do not necessarily translate into a change in the therapeutic approach, few studies have addressed the impact of ^{68}Ga-DOTA-peptide PET/CT on the management of neuroendocrine tumours [9, 10]. This study aims to establish the local data on the role of ^{68}Ga-DOTA-peptide PET/CT on the management of gastrointestinal neuroendocrine tumours (GI-NET) in the Malaysian population.

Materials and Methods

Patients

Patients with histologically proven GI-NET who underwent ^{68}Ga-DOTA-peptide PET/CT at the National Cancer Institute between January 2011 and December 2015 were included in this study. Suspected NET based on symptoms alone without histological confirmation, cases of NET with unknown primary and pancreatic NETs were excluded from this study. Reasons for excluding pancreatic NETs were due to their distinct presentation, symptom and treatment characteristics.

The histopathological report, other investigations/imaging (i.e. ultrasound, CT, endoscopy), indication for ^{68}Ga-DOTA-peptide PET/CT and pre-PET management strategies were examined.

Based on their indication for ^{68}GaDOTA-peptide PET/CT, patients were categorised into three groups: pre-operative staging, post-operative restaging and monitoring of systemic treatment response. In the post-operative restaging group, patients would undergo surgical resection based on conventional imaging modalities. ^{68}GaDOTA-peptide PET/CT was performed after the surgery for further re-staging. The reasons for such practice are the long waiting time for ^{68}GaDOTA-peptide PET/CT appointments and that surgical resection of the primary tumour remains the mainstay of treatment even in the presence of metastatic disease.

In the first and second groups, the pre-PET disease stage, post-PET disease stage and treatment modification post-PET were analysed. The stage of the patient was determined using the American Joint Committee on Cancer (AJCC) staging system.

In the third group, PET/CT was performed to assess treatment response in patients receiving some form of systemic therapy such as cold octreotide therapy, everolimus, chemotherapy or peptide receptor radionuclide therapy. Apart from using the Response Evaluation Criteria in Solid Tumours(RECIST) 1.1, new non-physiological uptake detected on ^{68}Ga-DOTA-peptide PET/CT was considered as disease progression in this study. Raised chromogranin A levels or worsening of symptoms were not considered to indicate disease progression in this study.

The study was approved by the local ethics committee and adhered to Good Clinical Practice guidelines.

Radiopharmaceutical Preparation

Throughout the study period, either DOTA-TOC or DOTA-TATE peptide was used. ^{68}Ga-DOTA-peptide PET/CT service was started in June 2010 using ^{68}Ga-DOTA-TATE as radiotracer. In October 2013, ^{68}Ga-DOTA-TOC replaced ^{68}Ga-DOTA-TATE. In November 2015, we switched back to ^{68}Ga-DOTA-TATE.

Both ^{68}Ga-DOTA-TATE and ^{68}Ga-DOTA-TOC were prepared using similar methods. ^{A} ^{68}Ge/^{68}Ga generator was eluted using 0.05 M HCl. ^{68}Ga was then mixed with a reactive vial containing 25 ug of DOTA-TATE or DOTA-TOC. Synthesis was carried out at approximately 90 °C for 10 min. Then, the reactive vial was allowed to cool to approximately 50 °C; 0.3 ml of 1 M HEPES buffer was then mixed into the reactive vial. Activity of the final product was measured and time recorded.

^{68}Ga-DOTA-peptide PET/CT Imaging Protocol

Cold octreotide therapy was not withheld and no specific patient preparations were required prior to imaging. Activities administered were between 148 to 185 MBq (4–5 mCi). Imaging was performed 45 to 60 min post-injection of the 68Ga-DOTA-peptide. PET/CT imaging was acquired on a GE Discovery ST scanner with a PET unit and eight-slice CT unit from vertex to mid-thigh. The CT component was carried out without contrast with exposure factors of 120 kVp and 80 mA in 0.8 s. Emission PET images were acquired in 3D mode with 4 min per bed position and three-slice overlap between consecutive bed positions. The PET data were reconstructed using iterative reconstruction and the CT images were reconstructed to axial slices of 3.3 mm thickness.

An experienced nuclear medicine physician examined PET/CT images. Positive uptake was based on visual assessment of areas that showed non-physiological increased tracer uptake. The maximum standardised uptake value (SUVmax) corrected for body weight was also documented.

Results

A total of 44 patients with histologically proven GI-NET underwent ^{68}Ga-DOTA-peptide PET/CT during the study period, comprising 16 females and 28 males with a median age of 55 years (range 19–73). Of the tumours, 27.3% arose from the foregut, 15.9% from the midgut and 26.8% from the hindgut. Based on the World Health Organisation (WHO) histopathology grading, 40.9% of patients had grade 1 NET, 22.7% had grade 2 NET, 4.5% had grade 3 NET and in 31.8% of patients the grading was unknown. The chromogranin level (cutoff taken at 94 ng/ml) was elevated on presentation in 20.5% of patients, increasing in trend in 45.5% and never raised in 13.6%; the levels were unknown in 61.4% of patients (Table 1).

From the 44 patients, 82 studies of ^{68}Ga-DOTA-peptide PET/CT were performed. Frequency of scans performed per patient is shown in Table 1. Of 82 ^{68}Ga-DOTA-peptide PET/CTs performed, 36 examinations were performed using ^{68}Ga-DOTA-TATE, and the remaining 46 were performed using ^{68}Ga-DOTA-TOC.

A wide range of SUVmax was demonstrated in tumoral lesions with the SUVmax of tumoral lesions in the soft tissue range (9.6 to 76.8), node (3.3 to 64.7), liver (9.2 to 66.6), adrenal gland (9.7 to 23.1), bone (2.8 to 61.1) and extra-orbital muscle (8.5 to 19.7). Interestingly, no lung metastasis was detected.

In the first group of patients, the staging of five (50%) of the ten patients who had ^{68}Ga-DOTA-peptide PET/CT for pre-operative staging were changed following PET, whereby one patient was upstaged and the remaining four were downstaged. In the downstaged group, three patients (30%) who were initially diagnosed with metastatic disease had a change in decision for primary tumour resection only. The remaining one downstaged patient was shown to have a false-negative PET/CT on subsequent EUS study. This patient had D1 tumour, which measured 1.5 cm in size and invaded the submucosa. Subsequent biopsy results showed a WHO grade 1 neuroendocrine tumour. In per patient analysis, the sensitivity and specificity were 87.5% and 100% respectively, whereas in per lesion analysis, the sensitivity and specificity were 94.1% and 90.0% respectively.

In the second group of patients, a total of 19 (52.8%) of 36 patients who had ^{68}Ga-DOTA-peptide PET/CT for post-operative restaging had their staging changed. Ten patients were upstaged and nine were downstaged. Twenty patients (55.6%) had their therapy changed and 11 patients (30.6%) had no change in therapy. The remaining five patients (13.9%) were lost to follow-up (Table 2). This included commencement of octreotide therapy, repeat surgery, palliative radiotherapy and adoption of a watch-and-wait strategy.

In the third group of patients, a total of 36 patients had ^{68}Ga-DOTA-peptide PET/CT for monitoring of treatment response. Seventeen patients (47.2%) showed disease progression, whereas 19 patients (52.8%) showed stable disease. A total of 19 patients (52.8%) had a significant change in their therapy (Table 3). This was either commencement/change in dosage of octreotide therapy, starting chemotherapy/everolimus or peptide receptor radionuclide therapy.

It is worth noting that the therapeutic alteration decision was not based on imaging alone. As NET is considered a slow-growing tumour, some clinicians adopt a conservative approach, whereas some opt for therapeutic change even in stable metastatic disease.

Table 1 Patient chracteristics

Characteristics		*n* = 44
Gender, n (%)	Female	16 (36.4%)
	Male	28 (63.6%)
Age, median years (range)		55 (19–73)
Primary site, n (%)	Foregut-stomach 7, doudenum 5	12 (27.3%)
	Midgut-small bowel (4), appendix (3)	7 (15.9%)
	Hindgut-rectal 22, sigmoid 2, colon 1	25 (56.8%)
WHO grading, n (%)	G1	18 (40.9%)
	G2	10 (22.7%)
	G3	2 (4.5%)
	Unknown	14 (31.8%)
Raised CgA (ng/ml), n (%)	High on presentation	9 (20.5%)
	From normal to high	2 (45.5%)
	Never raised	6 (13.6%)
Cutoff value: <94	Unknown	27 (61.4%)
Number of times scanning performed per patient	1	24
	2	10
	3	5
	4	3
	5	1
	6	1

Discussion

To date, five studies have demonstrated a high impact of ^{68}Ga-DOTA-peptide PET/CT in the management of NET, ranging from 19.0% to 60.0% (Table 4) [9–13]. Our findings were consistent with these results, where an impact on management was seen in 30% in the pre-treatment group and approximately 50% in the post-treatment group (including both the post-operative restaging group and post-systemic treatment group).

In patients who had ^{68}Ga-DOTA-peptide PET/CT for pre-operative assessment, there was a substantial change in their disease staging post-PET. As an adjunct to conventional imaging (multiphase CT/ MRI/ EUS), ^{68}Ga-DOTA-peptide

Table 2 Impact on post-operative ^{68}Ga-DOTA-peptide PET/CT on staging and management (n = 36)

Impact on stage	19 (52.8%)
Upstaging	10
Downstaging	9 (including 2 false negatives)
Impact on therapy	20 (55.6%)
Omit further Tx	6
Start cold octreotide	11
Re-surgery	2
Palliative RT	1
No impact on therapy	11 (30.6%)
Unknown impact because lost to follow-up	5 (13.9%)

PET/CT offers further delineation on the N and M staging and characterises equivocal lesions detected on CT or MRI. However, the impact of ^{68}Ga-DOTA-peptide on the treatment approach was less striking. This is partly due to the fact that the change of disease stage may not necessarily be followed by a change of the treatment strategy especially in patients with known disseminated disease. Furthermore, ^{68}Ga-DOTA-peptide PET/CT could be falsely negative in small lesions. Hence, conventional imaging for initial staging still remains mandatory as it provides precise anatomical information and guides biopsy.

The impact of ^{68}Ga-DOTA-peptide PET/CT on both stage and management change was particularly evident when it was performed for post-operative restaging purposes. This was partly due to more accurate patient re-stratification and subsequently led to additional or no treatment. It was also interesting to note that 25% of patients had their disease down-staged, which subsequently led to omission from further treatment in 16% of patients. This indicates that ^{68}Ga-DOTA-peptide PET/CT has an important role in excluding disease, which prevents unnecessary treatment and saves costs. However, we should keep in mind the possibility of false-negative findings, which were also noted in this study. In this study, two patients demonstrated false-negative results on ^{68}Ga-DOTA-peptide PET/CT as one patient had small lesions and another patient harboured a WHO grade 3 de-differentiated tumour. Due to potential false-negative findings on ^{68}Ga-DOTA-peptide PET/CT, which may result in a negative impact, further analysis of the patient outcomes is needed in future studies.

Table 3 Impact of ^{68}Ga-DOTA-peptide PET/CT on the surveillance and monitoring response post-chemo/sandostatin/everolimus/PRRT (n = 36)

PET/CT showed progression	17 (47.2%)
PET/CT showed non-progression	19 (52.8%)
Impact on therapy	19 (52.8%)
Start octreotide	2
Increase octreotide dosage	3
Start chemotherapy	4
Start everolimus	3
Start PRRT	7
No impact on therapy	16 (44.4%)
Continue sandostatin dosage	11
Continue everolimus	1
Continue PRRT	4
Unknown impact because lost to follow-up	1 (2.8%)

Table 4 Studies on impact of ^{68}Ga-DOTA-peptide PET/CT in the management of NET

Studies	Number of patients	Percentage change of intended management, %
Ambrosini et al. [11]	90	36.2%
Hofman et al. [10]	59	Intermodality change 47%
Hermann et al. [12]	88	60%
Naswa et al. [9]	109	19%
Skoura et al. [13]	728	40.9%

By identifying tumours with somatostatin receptor expression, ^{68}Ga-DOTA-peptide PET/CT is particularly useful in identifying patients who will likely benefit from cold octreotide or peptide receptor radionuclide therapy [3, 14]. However, somatostatin receptor expression in NET is heterogenous and dynamic, especially the evolution of tumoral characteristic from somatostatin receptor expression to glucose hypermetabolism over time [15, 16]. Therefore, dual tracer PET/CT using both ^{68}Ga-DOTA-peptide and 18F–FDG has been suggested to allow real-time comprehensive assessment of overall tumoral characteristics and stage, particularly high grade 2 and grade 3 tumours (Fig. 1).

Regarding the surveillance and monitoring of the treatment response group, ^{68}Ga-DOTA-peptide PET/CT influenced patient's stage and management in half of the studied population. Although the use of standardised uptake values (SUV) for treatment monitoring is uncertain and requires further studies [14, 17], the high sensitivity of ^{68}Ga-DOTA-peptide PET/CT has placed it in an important position in identifying occult new lesions during follow-up, which might not be demonstrated by CT. However, current standard response criteria have proven suboptimal for the assessment of the antiproliferative effect of many targeted agents, particularly in the context of slow-growing tumours such as well-differentiated NETs [18]. Again, tumoral heterogeneity may hinder the use of single agent ^{68}Ga-DOTA-peptide PET/CT during follow-up. We suggest performing a dual tracer approach at the initial staging, followed by a single tracer for future monitoring

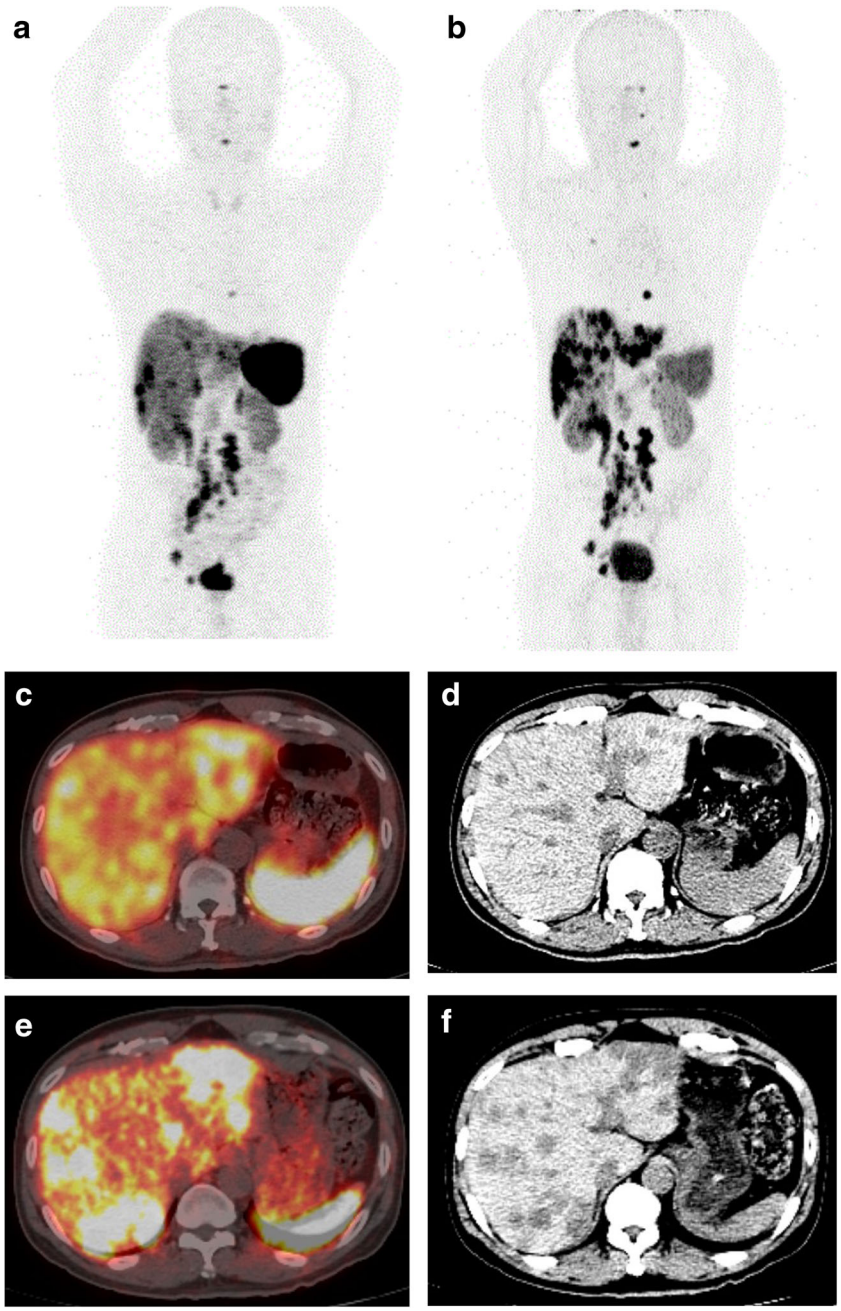

Fig. 1 A 51-year-old male with rectal NET who underwent low anterior resection. Post-surgery Ga-DOTATATE PET/CT showed extensive somatostatin receptor-avid metastases in the liver, abdominal and pelvic lymph nodes, and bones (A, C and D). He was started on subcutaneous long-acting octreotide. Six months later, his Ga-DOTATATE PET/CT showed progression of disease particularly in the liver (B, E and F). He was subsequently referred for peptide receptor chemoradionuclide therapy (PRCRT)

if no glucose hypermetabolism lesion is demonstrated on ^{18}F–FDG PET/CT. However, more studies are needed to establish the appropriate use of the dual tracer approach with consideration of initial histopathological grading and subsequent tumour progression.

As this is a cross-sectional cohort study, the main drawbacks would include unavailable or missing data due to loss to follow-up. The evolving classification, diagnosis and treatment algorithm of NETs also contribute to the difficulties faced in this study. For example, the use of the Ki67 index for tumour grading was only used routinely in recent years. In addition to this, many centres adopt diverse diagnostic and treatment strategies because of limitations in specialties, resources and experience.

Conclusion

In conclusion, ^{68}Ga-DOTA-peptide PET/CT has a significant impact on management decisions in GI-NET patients as it can provide additional information on occult metastasis/equivocal lesions and give the clinician an opportunity to select patients for targeted therapy.

Acknowledgments We are grateful to Dr. Asmayani Khalib and all our staff for their assistance in this study. We also thank the Director General of the Ministry of Health of Malaysia for permission to publish this paper.

Compliance with Ethical Standards

Conflicts of Interest Teik Hin Tan, Ching Yee Boey and Boon Nang Lee declare that they have no conflicts of interest.

Ethics Statement Informed consent was obtained from all patients for being included in the study. This study is approved by the local ethics committee.

Ethics Approval All procedures performed in studies were in accordance with the ethical standards of the national Medical Research and Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent This retrospective study was approved by the national ethics committee, and the requirement to obtain informed consent was waived.

References

1. Reubi JC, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumors: molecular basis for in vivo multireceptor tumour targeting. Eur J Nucl Med Mol Imaging. 2003;30:781–93.
2. Kulkarni HR, Baum RP. Theranostics with Ga-68 somatostatin receptor PET/CT: monitoring response to peptide receptor radionuclide therapy. PET Clin. 2014;9:91–7.
3. Kulkarni HR, Baum RP. Patient selection for personalized peptide receptor radionuclide therapy using Ga-68 somatostatin receptor PET/CT. PET Clin. 2014;9:83–90.
4. Deppen SA, Liu E, Blume JD, et al. Safety and efficacy of 68Ga DOTATATE PET/CT for diagnosis, staging, and treatment management of neuroendocrine tumors. J Nucl Med. 2016;57:708–14.
5. Antunes P, Ginj M, Zhang H, Waser B, Baum RP, Reubi JC, et al. Are radiogallium-labelled DOTA-conjugated somatostatin analogues superior to those labelled with other radiometals? Eur J Nucl Med Mol Imaging. 2007;34:982–93.
6. Ambrosini V, et al. 68Ga-labelled peptides for diagnosis of gastroenteropancreatic NET. Eur J Nucl Med Mol Imaging. 2012;39:S52–60.
7. Buchmann I, Henze M, Engelbrecht S, Eisenhut M, Runz A, Schäfer M, et al. Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2007;34:1617–26.
8. Krausz Y, Freedman N, Rubinstein R, Lavie E, Orevi M, Tshori S, et al. 68Ga-DOTA-NOC PET/CT imaging of neuroendocrine tumors: comparison with ^{111}In-DTPA-octreotide (OctreoScan®). Mol Imaging Biol. 2011;13:583–93.
9. Naswa N, Sharma P, Kumar A, Nazar AH, Kumar R, Chumber S, et al. Gallium-68-DOTA-NOC PET/CT of patients with gastroenteropancreatic neuroendocrine tumors: a prospective single-center study. AJR Am J Roentgenol. 2011;197:1221–8.
10. Hofman MS, Kong G, Neels OC, Eu P, Hong E, Hicks RJ. High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. J Med Imaging Radiat Oncol. 2012;56:40–7.
11. Ambrosini V, Campana D, Bodei L, et al. ^{68}Ga-DOTANOC PET/CT clinical impact in patients with neuroendocrine tumors. J Nucl Med. 2010;51:669–73.
12. Herrmann K, Czernin J, Wolin EM, et al. Impact of ^{68}Ga-DOTATATE PET/CT on the management of neuroendocrine tumors: the referring physician's perspective. J Nucl Med. 2015;56:70–5.
13. Skoura E, Michopoulou S, Mohmaduvesh M, et al. The impact of ^{68}Ga-DOTATATE PET/CT imaging on management of patients with neuroendocrine tumors: experience from a National Referral Center in the United Kingdom. J Nucl Med. 2016;57:34–40.
14. Kratochwil C, Stefanova M, Mavriopoulou E, et al. SUV of [68Ga]DOTATOC-PET/CT predicts response probability of PRRT in neuroendocrine tumors. Mol Imaging Biol. 2015;17:313–8.
15. Kayani I, Bomanji JB, Groves A, Conway G, Gacinovic S, Win T, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and 18F-FDG. Cancer. 2008;112(11):2447–55.
16. Oh S, Prasad V, Lee DS, Baum RP. Effect of peptide receptor radionuclide therapy on Somatostatin receptor status and glucose metabolism in neuroendocrine tumors: Intraindividual comparison of Ga-68 DOTANOC PET/CT and F-18 FDG PET/CT. Int J Mol Imaging. 2011;2011
17. Gabriel M, Oberaurl A, Dobrozemskyl G, et al. 68Ga-DOTA-Tyr3-octreotide PET for assessing response to somatostatin-receptor-mediated radionuclide therapy. J Nucl Med. 2009;50:1427–34.
18. Garcia-Carbonero R, et al. Imaging approaches to assess the therapeutic response of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): current perspectives and future trends of an exciting field in development. Cancer Metastasis Rev. 2015;34:823–42.