Diagnostic Value of ^{68}Ga -DOTATATE PET/CT in Liver Metastases of Neuroendocrine Tumours of Unknown Origin

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Abstract

Purpose In neuroendocrine liver metastases of unknown primary, a multimodality approach is usually adopted and consists of transabdominal ultrasound, endoscopic ultrasound (EUS), computed tomography (CT), magnetic resonance imaging (MRI), nuclear medicine techniques, endoscopy and exploratory surgery. The purpose of the study is to evaluate the diagnostic value of ^{68}Ga -DOTATATE positron emission tomography (PET)/CT as part of a multimodality approach in neuroendocrine liver metastases of unknown primary.

Materials and Methods Six patients (M:F=5:1, age range 28–56 years) with immunohistochemically proven neuroendocrine liver metastases but inconclusive initial CT work-up were retrospectively analysed. Clinical finding, histopathology, comparative imaging and follow-up were used to validate the results when ethically justified.

Results ^{68}Ga -DOTATATE PET/CT identified the primary tumour in five out of six (83.3 %) patients: pancreas ($n=4$) and stomach ($n=1$). Out of three patients with indeterminate primary on initial CT, two patients were confirmed by ^{68}Ga -DOTATATE PET/CT. Absence of uptake in indeterminate primary of one patient was later confirmed negative by histopathology. In another three patients with undetected primary on initial CT, primary site was demonstrated in all patients with unsuspected metastases in two patients on ^{68}Ga -DOTATATE PET/CT. No further work-up was done to confirm the primary in patients with distant metastases. Change of management was observed in three out of six (50 %) patients. **Conclusion** Our small study indicates that ^{68}Ga -DOTATATE PET/CT is a promising diagnostic option in the multimodality

approach to neuroendocrine liver metastases of unknown primary origin.

Keywords Unknown primary · Neuroendocrine tumour · Liver metastases · ^{68}Ga -DOTATATE

Introduction

The incidence and prevalence of neuroendocrine tumours (NETs) have considerably increased over the past three decades [1]. Neuroendocrine liver metastases of unknown primary origin are not uncommonly encountered in clinical practice. They account for 5–10 % of total cases [2]. Primary hepatic NET is extremely rare and the diagnosis can only be made after primary tumours are excluded [3].

Neuroendocrine liver metastases has poorer prognosis [4]. Nonetheless, it is important to identify and surgically remove the primary tumour. This would prevent local complications, and facilitates effective treatment to the liver, leading to improved overall survival [5, 6].

As neuroendocrine cells can originate from gastroenteropancreatic tract, bronchopulmonary system, and less commonly skin, adrenal glands, thyroid and genital tract [7], localisation of primary is often challenging. As such, a multimodality approach comprised of radiological imaging, nuclear medicine imaging, endoscopy, and exploratory surgery is required to evaluate liver metastases of NETs of unknown origin. [2, 3]. ^{68}Ga -DOTATATE positron emission tomography (PET)/computed tomography (CT) is a promising diagnostic tool in such evaluation. The objective of the study is to evaluate the diagnostic value of ^{68}Ga -DOTATATE PET/CT in determining the primary of liver metastases of NETs of unknown origin.

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Materials and Methods

Six patients (M:F=5:1, age range 28–56 years) with histologically proven liver metastases of NETs, whereby the initial CTs were inconclusive for the primary were retrospectively analysed between June 2011 and Dec 2012. ^{68}Ga -DOTATATE PET/CT was performed as a part of the subsequent multimodality evaluation. Serum chromogranin A was performed in five patients prior to the study.

PET-CT imaging was performed on the dedicated GE Discovery ST scanner combining a PET unit and an eight-slice CT unit. No specific patient preparation. Patients were administered 148–185 MBq (mean, 160 MBq) of ^{68}Ga -DOTATATE intravenously. Image acquisition was performed 45–60 min post-injection with a whole-body field of view (brain to mid thigh).

Transmission CT images for attenuation correction were performed with the exposure factors for all examinations of 120 kVp and 80 mA in 0.8 s. Emission PET images were obtained in two-dimensional mode, at a rate of 4 min per bed position with a three-slice overlap between consecutive bed positions. Transaxial ^{68}Ga -DOTATATE PET data were reconstructed using ordered-subsets expectation maximisation with 2 iterations and 21 subsets. The CT data for PET were reconstructed to axial slices of 3.3 mm thick.

The images were reviewed by two experienced nuclear medicine physicians. Images were read independently. A positive lesion was defined as non-physiologically increased tracer uptake based on visual assessment with the consensus of the two physicians. The site and number of lesions and maximum standardised uptake value (SUV_{max}) were documented using spleen as a reference background activity. The unenhanced CT studies from the PET/CT acquisition were also used to document lesion characteristics.

Comprehensive evaluation including histopathology, comparative imaging and follow-ups was used to validate the diagnosis. Change in management was assessed by comparing recorded pre-PET/CT management plans with follow-up post-PET/CT management plans.

The study protocol was approved by the local ethics committee.

Results

The results of the findings are summarised in Table 1. The average time interval between the first liver biopsy-proven NET and ^{68}Ga -DOTATATE PET/CT was approximately 12 months. Three patients had liver metastases of NETs of unknown origin on the initial CTs, whereby the primaries were demonstrated by ^{68}Ga -DOTATATE PET/CT. Additional metastases other than liver were detected in two patients. As tissue confirmation was ethically unjustifiable, no further

work-up was done to confirm the primaries in these two patients with widespread metastases.

In three patients with ambiguous primaries on the initial CTs, ^{68}Ga -DOTATATE PET/CT confirmed those primaries in two patients where the primaries were located in the pancreas (Fig. 1). One patient with the initial suspected primary at the colon on CT was excluded by ^{68}Ga -DOTATATE PET/CT. The exclusion was validated by a subsequent negative histopathological examination on colonoscopic biopsy. In total, ^{68}Ga -DOTATATE PET/CT identified the primary tumours in five out of six (83.3 %) patients: pancreas ($n=4$) and stomach ($n=1$).

Out of the six patients, management plans were changed in three patients (50 %) on the basis of the ^{68}Ga -DOTATATE PET/CT result. Two patients with additional widespread metastases on ^{68}Ga -DOTATATE PET/CT were changed to palliative intent. One patient had distal pancreatectomy post-PET/CT. The management of the other three patients remained the same.

Discussion

In the evaluation of liver metastases of NETs, conventional anatomical imaging such as ultrasound, CT and MRI are commonly adopted as a preliminary search for the primaries. However, their sensitivities in detecting the primaries have been rather disappointing due to the high occurrence of their small size, variety of location and slow tumoural growth. The reported sensitivities for CT or MRI range only between 22 % and 45 % in detecting pancreatic NETs [2, 5]. As such, functional radionuclide studies are usually involved in the subsequent workout [8, 9].

The distinct characteristic of somatostatin receptors (SSTRs) over-expression especially subtype 2 (SSTR 2) in NET has resulted in the development of several selective radiolabelled somatostatin analogues that target these sites [10]. ^{111}In -DTPA-octreotide has been commercially used as one of these radiolabelled somatostatin analogues. Currently, ^{111}In -DTPA-octreotide (Octreoscan) single-photon emission computed tomography (SPECT) has been considered as a “gold standard” in detection, mapping as well as assessment of the eligibility for somatostatin analogues therapy in gastroenteropancreatic (GEP) NETs. However, it often fails to pinpoint the exact location of the primary tumour due to comparatively lack of spatial resolution and anatomical definition. Subsequent development of hybrid SPECT/CT somehow overcomes these challenges [11]; however, the sensitivity and resolution of gamma imaging is still inferior to PET [12].

The introduction of hybrid PET-CT technology using commercially available ^{68}Ga -labelled somatostatin radiotracer in the evaluation of NETs has overcome the weakness of both anatomical imaging and ^{111}In -DTPA-octreotide imaging. Although it has proven superior to CT, MRI and ^{111}In -DTPA-

Table 1 Summary of initial CT and liver biopsy findings, ^{68}Ga -DOTATATE PET/CT findings and final diagnosis

Age (years)/sex	CgA (ng/ml)	CT	Liver biopsy		^{68}Ga -DOTATATE PET/CT			Primary site evaluation	Final diagnosis
			Mitotic count (hpf)	Ki-67	Primary site (SUV_{max})	Liver (SUV_{max})	Additional lesion		
51/M	34.7	None	<1/10	N/A	Pancreas (81.7)	(35.7)	None	EUS biopsy	TP
56/M	41.9	None	<1/10	N/A	Stomach (13.9)	(15.8)	Bone	None	None
55/M	N/A	None	N/A	N/A	Pancreas (22.5)	(35.0)	Lung, lymph node, peritoneum	None	None
28/M	770	Pancreas	3/10	<2 %	Pancreas (14.7)	(20.6)	None	Distal pancreatectomy	TP
45/M	261	Pancreas	<1/10	N/A	Pancreas (10.5)	(8.2)	None	Follow-up and repeat PET/CT	TP
38/F	2,488	Rectum	1/10	<2 %	None	(21.3)	None	Colonoscopy biopsy	TN

CgA chromogranin A, SUV_{max} maximum standardised uptake value, N/A not available, TP true positive, TN true negative

octreotide for cancer staging in NET with a sensitivity of 97 %, specificity of 92 %, and an accuracy of 96 % [13–16], there are limited evidence on its use in NET metastases. By mirroring some of the published data [16–18], our results yield high diagnostic value of ^{68}Ga -DOTATATE PET/CT compared with CT in searching for the primary tumour in patients with known liver metastases of NETs. In our study, five out of six primary tumours were correctly identified. One patient with reported lesion on initial CT was correctly ruled out.

Using the WHO 2010 grading system [19, 20], all liver biopsies in our study demonstrated immunohistological evidence of well-differentiated low-grade NET (mitotic count <2/10 hpf or Ki-67 <2 %) despite clinical evidence of metastases. As cellular differentiation correlates with somatostatin receptor expression and hence ^{68}Ga -DOTATATE avidity [21], the use ^{68}Ga -DOTATATE PET/CT in the detection of metastatic NETs is feasible as evidence by high detection rate on both the liver and primary lesions in our observed data.

By using ^{68}Ga -labelled somatostatin PET/CT, quantitative assessment of somatostatin receptor density is achievable by measuring the tumour's standardised uptake value (SUV). The SUV value strongly correlates with expression of somatostatin receptor 2 (SSTR 2) [22, 23]. In our data, wide variation of SUV_{max} was noted in both the primary and metastatic liver lesions (range SUV_{max} 8.2–35.7 and 10.5–81.7, respectively). This indicates that the different degree of somatostatin receptor expression observed in well-differentiated tumours could be due to receptor down-regulation after somatostatin analogue therapy despite controversial results in the literature [24–26]. In our study, octreotide therapy was not disrupted. Using Pearson correlation analysis, a strong relationship was found between the detected primary SUV_{max} and liver lesion SUV_{max} ($r=0.697$, $p=0.98$). However, no correlation was found between SUV_{max} and chromogranin A level.

Because of the disease's rarity, the drawback of this study is limited sample size that hinders further evaluation. As poorly differentiated NET was not found in this study, the use of

Fig. 1 **a, b** Fused PET-CT image showed multiple foci of ^{68}Ga -DOTATATE avid lesions in both lobes of liver consistent with known liver metastases on CT. **c, d** While CT showed indeterminate lesion in the head of pancreas, high uptake of ^{68}Ga -DOTATATE (arrow) in the pancreatic head without additional lesion elsewhere established the diagnosis of primary pancreatic NET. This was later confirmed histologically by EUS biopsy

^{68}Ga -DOTATATE PET/CT and SUV evaluation in this particular group of patients remain unanswered. Nevertheless, in the well-differentiated NETs, the disease management was modified in 50 % of patients based on ^{68}Ga -DOTATATE PET/CT finding. These results support the use DOTATATE PET/CT in the current multimodal approach and should be performed early in the work-out.

In summary, ^{68}Ga -DOTATATE PET/CT has high diagnostic value in determining the primary site of liver metastases of NETs; and has significant impact on the management especially in well-differentiated metastatic lesions. Despite promising results, ^{68}Ga -labelled peptide PET/CT is still considered a new diagnostic option in a multimodality approach [27]. Prospective studies with a larger patient group including poorly differentiated tumour would be beneficial in the future.

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Conflict of Interest Statement Teik Hin Tan, Boon Nang Lee and Siti Zarina Amir Hassan declare that they have no conflict of interest.

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