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Author(s)	Nakamoto, Yuji; Sano, Kohei; Ishimori, Takayoshi; Ueda, Masashi; Temma, Takashi; Saji, Hideo; Togashi, Kaori
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Additional information gained by positron emission tomography with ^{68}Ga -DOTATOC for suspected unknown primary or recurrent neuroendocrine tumors

Yuji Nakamoto¹ · Kohei Sano^{2,3} · Takayoshi Ishimori¹ · Masashi Ueda^{2,3} · Takashi Temma² · Hideo Saji² · Kaori Togashi¹

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Abstract

Objective Positron emission tomography (PET)/computed tomography (CT) using ^{68}Ga -labeled 1,4,7,10-tetraazacyclododecane-*N,N',N'',N'''*-tetraacetic acid-D-Phe¹-Tyr³-octreotide (DOTATOC) has been used to detect neuroendocrine tumors (NETs). The purpose of this study was to investigate the clinical efficacy of DOTATOC-PET/CT for detecting clinically suspected NETs when conventional imaging modalities were negative or inconclusive, in terms of additional value.

Methods A total of 46 patients were analyzed retrospectively. Among them, 14 patients underwent a DOTATOC-PET/CT scan for detecting unknown primary tumors after histopathological confirmation of a NET at metastatic sites (group A): 7 patients for detecting metastasis or recurrence after surgery for NET because of their high hormone levels but with no recurrence detected by other imaging modalities (group B); the remaining 25 patients for detecting suspected NETs because their hormone levels were high with no history of histopathologically proven NET (group C). Additional information was assessed, according to each situation.

Results In group A, unknown primary tumors were suspected by DOTATOC-PET/CT in 8 of 14 patients (gastrointestinal/pancreatic NET in 7 patients, prostatic cancer in 1 patient), but prostatic cancer was not confirmed by histopathology (i.e., false positive). In group B, DOTATOC-PET/CT depicted lesions in six of seven patients, including nodal metastasis ($n = 5$) and liver metastasis ($n = 1$). In group C, DOTATOC-PET/CT did not demonstrate any abnormal foci except in one case of pancreatic NET. Additional information was obtained in 50, 86, and 4 % of cases, in groups A, B, and C, respectively.

Conclusions DOTATOC-PET/CT was useful for detecting NETs, especially when recurrence or metastases were suspected because of high hormone levels after surgery for a NET. It is unlikely, however, that additional information can be acquired in patients with no history of NET simply based on high hormone levels.

Keywords PET/CT · DOTATOC · Somatostatin · Neuroendocrine tumor

Introduction

Positron emission tomography computed tomography using ^{18}F -fluorodeoxyglucose (FDG-PET/CT) has been widely accepted for clinical tumor imaging [1]. Primary or metastatic lesions are depicted as a hypermetabolic area of glucose in many cancers, which is helpful for staging, restaging, and monitoring the response to therapy. Despite dramatic spread of FDG-PET/CT use during the past decade, neuroendocrine tumors (NETs), which commonly express somatostatin receptors, are often not FDG-avid, for which conventional FDG-PET/CT does not always provide useful information for therapeutic management. For these

✉ Yuji Nakamoto
ynakamo1@kuhp.kyoto-u.ac.jp

¹ Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine, 54 Shogoinkawahara-cho, Sakyo-Ku, Kyoto 606-8507, Japan

² Department of Patho-Functional Bioanalysis, Kyoto University Graduate School of Pharmaceutical Sciences, Kyoto, Japan

³ Radioisotopes Research Laboratory, Kyoto University Hospital, Kyoto, Japan

tumors, ^{111}In -octreotide has been used in Europe and the United States for somatostatin receptor scintigraphy [2, 3], but it is not routinely available in Japan.

^{68}Ga -labeled octreotide, including ^{68}Ga -labeled 1,4,7,10-tetraazacyclododecane- N,N',N'',N''' -tetraacetic acid- D -Phe 1 -Tyr 3 -octreotide (DOTATOC), has been used as a PET tracer for somatostatin receptor imaging mainly in Europe [4–6]. Compared with ^{111}In -labeled compounds, more promising results have been reported, especially for detecting lung or bone metastasis [7]. There have already been a few articles demonstrating the clinical efficacy of DOTATOC-PET/CT for unknown primary NETs [8, 9]. The data are limited, however, and the value of PET/CT with ^{68}Ga -labeled compounds clinically has not been investigated in Japan, although there has been one article that elucidated characteristics of NETs quantitatively with ^{111}In -labeled octreotide investigation [10]. Because it has been reported that there are large differences in the features of gastroenteropancreatic NETs in Japan and Western countries [11], the clinical efficacy of DOTATOC-PET/CT should be evaluated in a Japanese population.

The aim of this study was to evaluate the clinical usefulness of PET/CT using ^{68}Ga -DOTATOC in NET patients with suspected unknown primary or recurrent tumors in each situation when other conventional imaging modalities were negative or inconclusive, from a view point of additional information.

Patients and methods

Patients

A total of 46 consecutive patients (male/female ratio 12:34; mean age 56 years, range 27–80 years) who underwent DOTATOC-PET/CT at our institution were analyzed. The patients were divided into three groups according to their scanning records. In group A, PET/CT was performed after metastatic NETs were confirmed histopathologically, but primary tumors had not been identified by other imaging modalities. In group B, DOTATOC-PET/CT scan was performed to evaluate suspected recurrent lesions because of a high level of gastrin ($n = 5$), insulin ($n = 1$), or chromogranin A ($n = 1$) after they underwent curative surgery for histologically proven NETs. Conventional imaging tests were negative. In group C, NETs had been suspected based on laboratory data without definitive localization of primary sites by conventional imaging modalities. In this group, patients had been suspected of having NET because of high levels of gastrin ($n = 9$), adrenocorticotropic hormone (ACTH) ($n = 8$), insulin ($n = 5$),

5-hydroxyindoleacetic acid ($n = 2$), or chromogranin A ($n = 1$). We checked all patients who had not taken a long-acting octreotide analogue within 1 month before their DOTATOC-PET/CT scan. The ethics committee of our institution approved the study, and written informed consent was obtained from all patients.

PET scanning

PET/CT scanning was performed using a combined PET/CT scanner (Discovery ST Elite; GE Healthcare, Waukesha, WI, USA). This system integrates a PET scanner with multidetector-row CT (16 detectors) and permits acquisition of co-registered CT and PET images during a single examination. For DOTATOC-PET/CT scanning, approximately 130 MBq of ^{68}Ga -DOTATOC was injected intravenously, and whole-body PET/CT scanning was performed approximately 60 min after injection. Just before the PET/CT scanning, patients were requested to void the bladder. Initially, starting at the level of the thigh, the low-dose CT scans were acquired during shallow breathing, and scanning included the area from the upper thigh to the skull. Immediately after CT, a PET emission scan was acquired with an acquisition time of 3 min per bed position. For one patient in group A and two patients in group C, diagnostic CT scans were also performed 30 and 90 s after intravenous administration of 100 mL iopromide (Iopamiron 300; Nihon Beyer, Osaka, Japan) with an injection rate of 3 mL/s. The total acquisition time was 20–30 min. Unenhanced CT data were used for attenuation correction, and images were reconstructed using a commercial three-dimensional iterative reconstruction algorithm called VUE Point Plus (matrix 128×128 , interval 3.27 mm, 2 iterations, 14 subsets).

Image analysis

PET/CT images were interpreted visually by at least two board-certified radiologists/nuclear medicine physicians based on consensus. Focal moderate-to-intense uptake was regarded as abnormal, but accumulations of DOTATOC in some organs (e.g., pituitary gland, adrenal gland, accessory spleen) that were considered physiological [12] were excluded. As a quantitative analysis, standardized uptake values (SUVs) were calculated for each lesion if patients had abnormal foci, but quantitative values were not used for diagnostic criteria in this investigation. The findings were compared with the final diagnoses obtained by histopathological confirmation or clinical follow-up for at least 6 months.

Table 1 Patient profiles and PET/CT findings for each group

Pt. no.	Age/sex	Reason for scan	Lesion location	SUV _{max}	Size ^a (mm)	Standard reference
Group A						
1.	59/M	Liver mets.	Jejunum	19.7	17	Hx
2.	60/F	Liver mets.	–	–	–	f/u
3.	44/F	Nodal mets.	Jejunum	14.1	12	Hx
4.	30/F	Nodal mets.	Duodenum	28.0	14	f/u
5.	28/M	Liver mets.	–	–	–	f/u
6.	57/F	Liver mets.	–	–	–	f/u
7.	74/F	Liver mets.	Duodenum	11.4	12	Hx
8.	69/M	Bone mets.	Prostate ^b	14.6	44	Hx
9.	66/F	Liver mets.	Duodenum	8.3	21	f/u
10.	39/M	Nodal mets.	Jejunum	11.8	23	f/u
11.	59/F	Liver mets.	–	–	–	Hx ^c
12.	71/M	Liver mets.	–	–	–	f/u
13.	46/F	Bone mets.	–	–	–	f/u
14.	80/F	Liver mets.	Pancreas	10.0	18	f/u
Group B						
1.	63/F	Gastrin	Node	33.7	23	f/u
2.	57/F	Gastrin	Node	14.7	15	f/u
3.	68/F	Gastrin	Node	12.2	13	f/u
			Node	33.3	22	f/u
			Node	8.1	11	f/u
4.	27/M	Insulin	–	–	–	f/u
5.	51/F	Gastrin	Node	10.6	11	Hx
6.	37/M	Gastrin	Node	46.8	12	Hx
7.	43/M	Chromogranin A	Liver	70.1	24	Hx
			Liver	11.7	16	Hx
			Liver	7.9	9	Hx
Group C						
1.	55/F	Insulin	–	–	–	f/u
2.	77/F	5-HIAA	–	–	–	f/u
3.	61/F	Gastrin	–	–	–	f/u
4.	45/F	ACTH	–	–	–	f/u
5.	65/M	Gastrin	–	–	–	f/u
6.	77/M	Gastrin.	–	–	–	f/u
7.	61/F	Gastrin.	–	–	–	f/u
8.	78/M	5-HIAA	–	–	–	f/u
9.	71/F	ACTH	–	–	–	f/u
10.	77/F	Gastrin	–	–	–	f/u
11.	55/F	Gastrin	–	–	–	f/u
12.	57/F	ACTH	–	–	–	f/u
13.	61/F	ACTH	–	–	–	f/u
14.	66/F	ACTH	–	–	–	f/u
15.	37/F	Insulin	–	–	–	f/u
16.	45/F	Insulin	–	–	–	f/u
17.	71/F	Insulin	–	–	–	f/u
18.	35/F	Chromogranin A	–	–	–	f/u
19.	32/F	Gastrin	–	–	–	f/u
20.	51/F	ACTH	Pancreas	68.5	36	Hx
21.	57/F	Gastrin	–	–	–	f/u

Table 1 continued

Pt. no.	Age/sex	Reason for scan	Lesion location	SUV _{max}	Size ^a (mm)	Standard reference
22.	48/M	Gastrin	–	–	–	f/u
23.	30/F	Insulin	–	–	–	f/u
24.	68/F	ACTH	–	–	–	f/u
25.	65/F	ACTH	–	–	–	f/u

mets. metastasis, *ACTH* adrenocorticotrophic hormone, *5-HIAA* 5-hydroxyindoleacetic acid, *Hx* histopathology, *f/u* follow-up

^a Lesion diameter was measured on PET images when not clearly depicted by morphological modalities

^b Prostatic cancer was suspected, but biopsy demonstrated benign prostatic hypertrophy

^c A neuroendocrine tumor in the rectum was confirmed by endoscopic biopsy, but no uptake was observed by DOTATOC-PET/CT

Results

Patients' profiles and PET/CT findings are summarized in Table 1.

Group A

There were 14 patients who had been suspected of having a primary NET because of pathologically proven liver metastasis ($n = 9$), nodal metastasis ($n = 3$), or bone metastasis ($n = 2$). In four of nine patients with metastatic liver tumors, DOTATOC-PET/CT demonstrated positive findings, such as a suspected primary tumor in the duodenum ($n = 2$), jejunum ($n = 1$), and pancreatic tail ($n = 1$) with the maximum SUV (SUV_{max}) ranging from 2.8 to 19.7. One case in which a duodenal submucosal tumor was confirmed to be a primary NET is shown in Fig. 1.

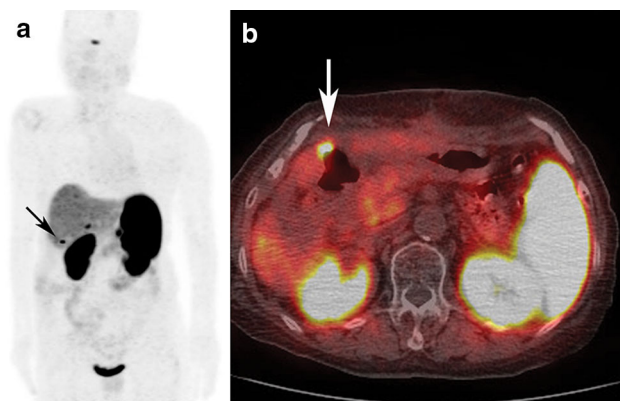


Fig. 1 A 74-year-old woman had a metastatic liver tumor. A maximum intensity projection DOTATOC-PET image (a) and a DOTATOC-PET/CT transaxial fused image (b) are shown. A liver tumor was resected prior to DOTATOC-PET/CT, with the histopathologic confirmation of a neuroendocrine tumor (NET). A primary site had not been identified by conventional imaging modalities, including enhanced CT, MRI, and FDG-PET/CT. DOTATOC-PET/CT revealed intense uptake corresponding to the duodenal wall (arrows). Biopsy was performed, and NET G2 was confirmed histopathologically

DOTATOC-PET/CT showed no abnormal findings for the remaining five patients. In three patients with nodal metastasis, DOTATOC-PET/CT revealed abnormal uptake in the duodenum ($n = 1$) and jejunum ($n = 2$). For two patients with bone metastasis, DOTATOC-PET/CT was negative in one patient but showed intense focal uptake in the prostate, suggesting prostatic cancer. In the other patient, the uptake was confirmed by biopsy to be due to benign prostatic hypertrophy. The primary site remained unknown. Thus, a final diagnosis of a gastroenteropancreatic NET was obtained in 7 of 14 patients (50 %) histopathologically ($n = 3$) and clinically ($n = 4$).

Group B

Seven patients in group B underwent surgery for a NET. They had undergone DOTATOC-PET/CT. Except for one patient with a high insulin level, DOTATOC-PET/CT depicted 10 lesions in six patients (seven nodal metastases in five patients, three liver metastases in one patient). The SUV_{max} of these lesions ranged from 7.9 to 70.1. Two patients had histopathological confirmation after surgery, whereas the remaining four patients were under follow-up with no surgical treatment. Thus, DOTATOC-PET/CT provided additional information in six of seven patients (86 %). A representative case of nodal metastasis is shown in Fig. 2.

Group C

A total of 25 patients who had been suspected of having NETs underwent DOTATOC-PET/CT. One patient with suspected ACTH-producing tumors underwent DOTATOC-PET/CT, which identified a pancreatic NET with SUV_{max} of 68.5 (Fig. 3), followed by surgical confirmation. For the remaining 24 patients, DOTATOC-PET/CT did not provide any clinically relevant additional information. The detection rate was significantly lower than in other groups (Fisher's exact test, $p < 0.01$).

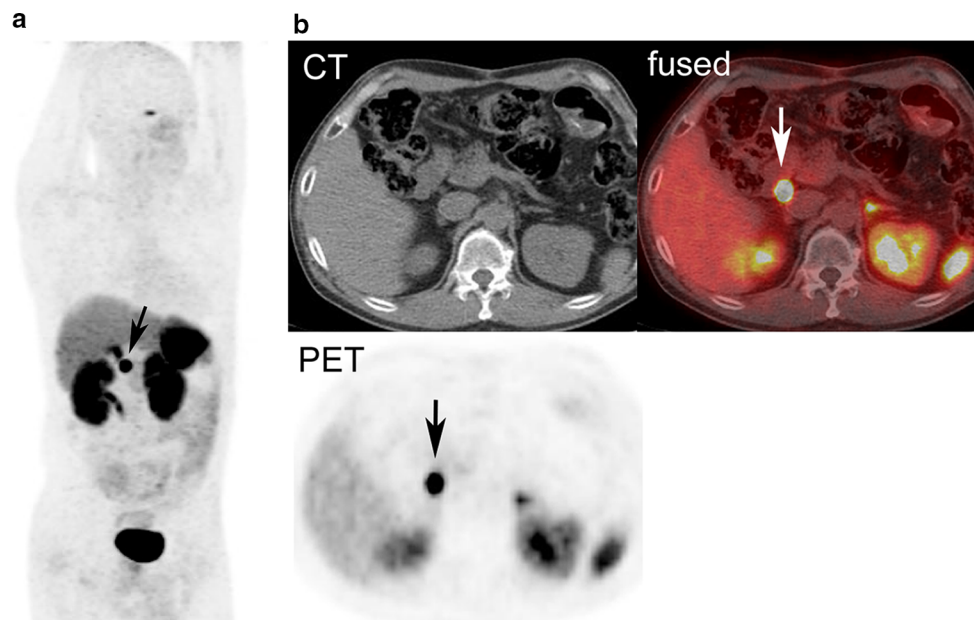


Fig. 2 A 37-year-old man had a history of surgical resection of a gastrinoma. DOTATOC-PET with a maximum intensity projection image (a) and CT, DOTATOC-PET, and DOTATOC-PET/CT transaxial images (b) are demonstrated. During the follow-up period,

the patient's serum gastrin level increased, but recurrence had not been identified on CT. Focal intense DOTATOC uptake corresponds to a subcentimeter node (arrows), which was confirmed as a nodal metastasis during surgery

Discussion

We demonstrated the clinical usefulness of ^{68}Ga -DOTATOC-PET/CT when a primary or metastatic lesion had been suspected, according to three situations. Additional information would be expected especially when hormone levels are high after surgery for histologically proven NETs, as is often the case with FDG-PET/CT being performed for restaging FDG-avid tumors. Its clinical value was limited, however, when hormone levels were high in patients without a history of NETs. According to meta-analyses [13, 14], the diagnostic performance of DOTATOC-PET/CT has been excellent, but it is thought to be influenced by clinical scenarios in which DOTATOC-PET/CT scans are performed.

Articles have been published that are limited to cases in which NETs had been confirmed histopathologically without identifying a primary tumor (corresponding to our group A) [8, 9]. Prasad et al. [8] reported that DOTANOC-PET/CT identified the primary tumor in 35 of 59 patients (59 %) with documented NETs but an unknown primary. In their report, the primary sites were mainly in the pancreas ($n = 16$), followed by the small intestine ($n = 14$). Naswa et al. [9] demonstrated that DOTANOC-PET/CT found 12 of 20 primary tumors (60 %) in NET patients with unknown primary tumors. The primary sites were mainly in the midgut (four in the duodenum, four in the ileum, one in the colon). In our series, DOTATOC-PET/CT revealed primary sites in half of the patients, which is

similar to the data from previous reports. Regarding detected primary sites, our findings were consistent with the results by Naswa et al. Pancreatic lesions were well evaluated by contrast-enhanced CT and magnetic resonance imaging at our institution. Therefore, it was a small number of cases in which the primary sites were located in the pancreas in this investigation.

One male patient had a bone metastasis from a NET, which was confirmed histopathologically. Prostatic cancer was suspected as the primary tumor because of intense uptake in the prostate gland on DOTATOC-PET/CT. Histopathological evaluation of biopsy tissue, however, did not confirm a prostatic cancer. It may be because of a sampling error, but DOTATOC accumulation in the prostate was extensive, and eight specimens were acquired, covering almost the entire prostate. This case was therefore regarded as giving false-positive results. It is known that somatostatin receptors are expressed not only in normal prostate glands, but also in the presence of prostatic cancer or prostatic hypertrophy [15, 16]. It is thought that accumulation in the prostate would be a pitfall when interpreting DOTATOC-PET/CT images.

DOTATOC-PET/CT was useful when hormone levels were high after surgery was undertaken for NETs. This situation is similar to that of cases in which FDG-PET was conducted because of suspected recurrence or metastasis after surgery with a high level of tumor markers. As the pretest probability is high and other imaging modalities (e.g., conventional CT or FDG-PET/CT) are negative, it is

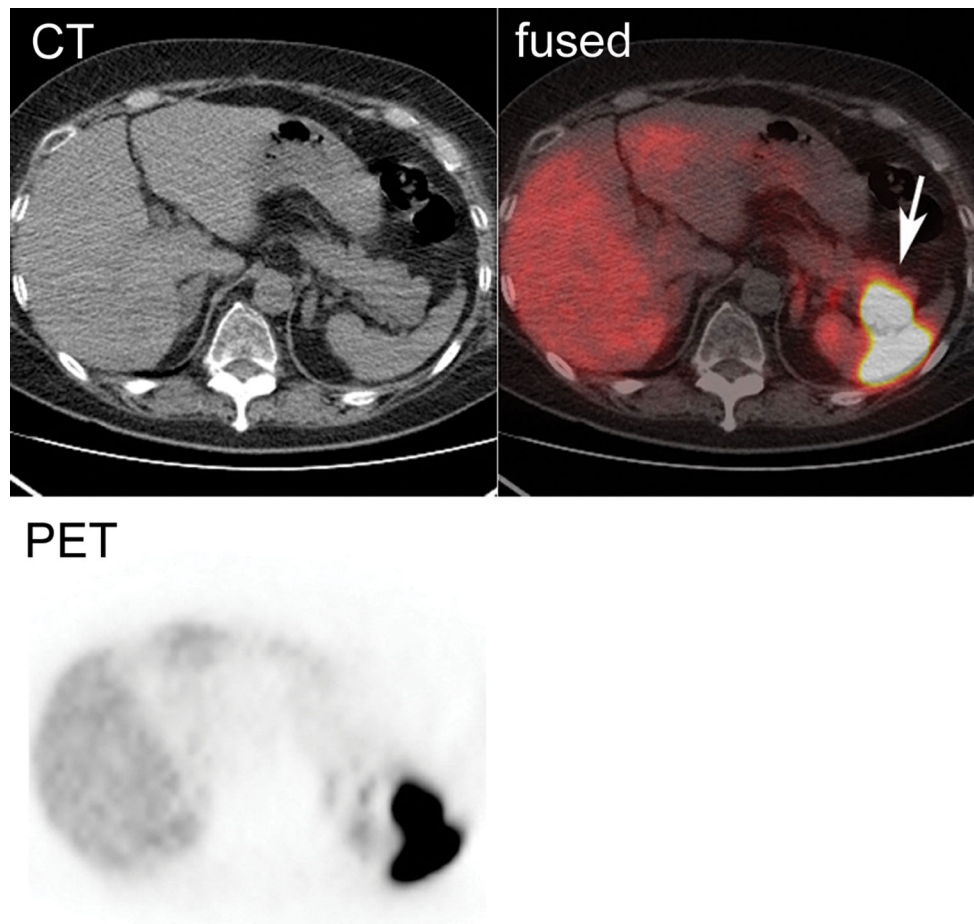


Fig. 3 A 51-year-old woman had a suspected ectopic ACTH-producing tumor. CT, DOTATOC-PET, and DOTATOC-PET/CT transaxial images are shown. Focal intense uptake is observed in the

pancreatic tail (*arrow*), suggesting a pancreatic NET that had not been identified by unenhanced CT. Surgery was performed, supplying pathological confirmation of NET G2

reasonable that DOTATOC-PET/CT would be expected to yield relevant information. As demonstrated in Fig. 2, a subcentimeter node can be detected by CT, but it is difficult to distinguish it from a benign inflammatory node. In addition, NET tumors usually grow slowly. The high accumulation of DOTATOC in a subcentimeter node is helpful for detecting a local recurrence or metastasis after NET surgery.

On the other hand, without a history of NET, DOTATOC-PET/CT might not provide helpful information simply because hormone levels are high. Some reasons can be considered. First, primary sites may be too small to be detected by morphologic imaging modalities. If lesions are extremely small, uptake tends to be underestimated because of a partial volume effect with PET. Also, when the primary site is in the upper abdomen or alimentary tract, the uptake could be easily influenced by respiratory motion and peristalsis. Second, it is not guaranteed that there is a

primary site because hyperfunctioning can cause high hormone levels (e.g., nesidioblastosis in suspected with an insulinoma or G-cell hyperplasia with a suspected gastrinoma). In addition, it has been reported that somatostatin receptor subtypes 2 and 5 are not well expressed in many insulinomas [17]. Thus, DOTATOC-PET/CT may have failed to depict the primary tumor.

One patient had been suspected of having an ACTH-producing tumor. Before DOTATOC-PET/CT scanning, the patient had undergone unenhanced CT, but enhanced CT performed after DOTATOC-PET/CT revealed a tumor in the pancreatic tail. Therefore, DOTATOC-PET/CT may be useful in such patients with high hormone levels if enhanced CT cannot be performed for some reason, including renal dysfunction.

There are some limitations in this investigation. First, the sample size is small. Also, histopathological confirmation was not obtained in all cases, so there may have

been some false-positive cases despite the fact that DOTATOC-PET/CT provided additional information. It is not ethically acceptable to acquire histopathologic confirmation of every lesion. Because this study was retrospective, the imaging modalities before DOTATOC-PET/CT became available were varied. For this reason, there may be selection bias in our population. The scan times ranged from 57 to 82 min (average 65 min) after injection of ^{68}Ga -DOTATOC. Based on the procedure guidelines, these scan times are considered normal after tracer administration [18], but the most optimal scanning time remains unknown. A different scanning time may alter the results.

Conclusion

Our data indicate that DOTATOC-PET/CT provided additional useful information, especially when recurrence or metastases were suspected because of high hormone levels after surgery for a primary NET. It did not yield any relevant information, however, in cases in which only the hormone levels were high.

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Conflict of interest There are no potential conflicts of interest relevant to this article.

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