Chapter 23
Clinical Efficacy of PET/CT Using ^{68}Ga-DOTATOC for Diagnostic Imaging

Yuji Nakamoto, Takayoshi Ishimori, and Kaori Togashi

Abstract Positron emission tomography/computed tomography (PET/CT) using ^{68}Ga-labelled DOTA^{0}-Tyr^{3} octreotide (DOTATOC) is one of the diagnostic imaging tools in somatostatin receptor scintigraphy. There have been many studies demonstrating the clinical usefulness of this diagnostic imaging method, especially for detecting neuroendocrine tumors (NETs). It often yields clinically relevant information for determining therapeutic management in NET patients. However, we have found that the usefulness of the information provided depends on the clinical situation; for example, it was considered especially helpful when recurrence/metastasis was suspected after surgery for histopathologically proven NET. In addition to NETs, DOTATOC PET/CT sometimes provides useful information in patients with tumor-induced osteomalacia (TIO), in which fibroblast growth factor 23 produced by a mesenchymal tumor causes hypophosphatemia, resulting in osteomalacia. As these mesenchymal tumors frequently express somatostatin receptors, DOTATOC PET/CT would be expected to detect causative lesions in TIO. Furthermore, many renal cell carcinomas (RCC) are not FDG avid. DOTATOC PET/CT could be helpful for detecting unexpected lesions when recurrence or metastasis is suspected after surgery for RCC. DOTATOC PET/CT is also able to reveal additional findings even in sarcoidosis, an inflammatory disease. The clinical value of DOTATOC PET/CT is discussed, based on our clinical experience.

Keywords PET/CT • DOTATOC • Neuroendocrine tumor • Tumor-induced osteomalacia

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23.1 Current Status of Somatostatin Receptor Scintigraphy in Japan

In diagnostic imaging of cancers, positron emission tomography (PET) using ^{18}F-labeled fluorodeoxyglucose (FDG) has been widely accepted clinically for staging and restaging, monitoring therapy response, and detecting unknown primary sites. However, there are some tumors for which FDG PET/CT does not provide relevant information owing to their insufficient FDG avidity. Such tumors include well-differentiated neuroendocrine tumors (NETs), which often cannot be identified as hypermetabolic areas on FDG PET/CT [1]. A major characteristic of NETs is that they express somatostatin receptors. For scintigraphy targeting such receptors, a radiolabeled octreotide, which has high affinity for somatostatin receptors and is very stable in vivo, has been used in Europe and the United States. Compounds labeled with ^{111}In or ^{99m}Tc are used as tracers for single photon emission computed tomography (SPECT), and tracers labeled with ^{68}Ga are used for PET.

^{111}In-pentetreotide (OctreoScan) is a commercially available radiopharmaceutical. It is routinely used clinically in Europe and the United States. However, it is not currently approved for use in Japan (as of July 2015), although clinical trials were conducted about the year 2000. Patients must travel to Europe to receive this examination or personally arrange importation of this radiopharmaceutical to enable them to undergo scintigraphy in one of several academic institutions. The number of patients with gastroenteropancreatic NETs is relatively small compared with the number with other common cancers, but its incidence has been increasing [2] so that it is becoming a serious issue. In our institution, PET/CT with ^{68}Ga-DOTATOC for somatostatin receptor scintigraphy has performed since 2011. More than 300 patients have had this examination here over the last 4 years.

23.2 Usefulness in NET According to Clinical Situation

There have been many reports demonstrating the clinical usefulness of PET/CT with ^{68}Ga-DOTATOC or other ^{68}Ga-labeled PET tracers in NETs. It has been reported that it is superior to FDG PET/CT in well-differentiated NET and medullary thyroid cancer [3–5] and scintigraphy using ^{111}In-labeled compounds [6]. Its diagnostic accuracy, including sensitivity and specificity, is reasonably high (more than 90 %) according to a few meta-analyses [7, 8]. However, there are some patients with high hormone levels, indicating the presence of NETs, in whom DOTATOC PET/CT reveals no additional information.

We investigated the clinical value of DOTATOC PET/CT in relation to the clinical situation [9]. We divided patients into three groups: groups A, B, and C. In group A, PET/CT was performed after metastatic NET had been confirmed histopathologically, but the primary tumor had not been identified by other conventional imaging modalities. In group B, PET/CT was performed to evaluate suspected

recurrent lesions due to high hormone levels after the patient had undergone curative surgery for histologically proven NET. Conventional imaging had been negative before DOTATOC PET/CT. In group C, NET was suspected based on laboratory data without definitive localization of the primary site by conventional imaging.

In group A, there were 14 patients who were suspected of having a primary NET because of pathologically proven liver metastasis (9 patients), nodal metastasis (3 patients), or bone metastasis (2 patients). In four of the nine patients with liver metastasis, DOTATOC PET/CT demonstrated positive findings, indicating a suspected primary tumor in the duodenum (2 patients), jejunum (1 patient), and pancreatic tail (1 patient) with the maximum standardized uptake value (SUVmax) ranging from 2.8 to 19.7. DOTATOC PET/CT showed no abnormal findings in the remaining five patients. In three patients with nodal metastasis, DOTATOC PET/CT revealed abnormal uptake in the duodenum (1 patient) and jejunum (2 patients). In two patients with bone metastasis, DOTATOC PET/CT was negative in one but showed intense focal uptake in the prostate in the other, suggesting prostate cancer. However, the uptake was found, by biopsy, to be due to benign prostatic hypertrophy. Thus, a final diagnosis of a gastroenteropancreatic NET was obtained in 7 of the 14 patients (50 %).

In group B, seven patients underwent surgery for a NET. Except for one patient with a high insulin level, DOTATOC PET/CT detected ten lesions in six patients with the SUVmax ranging from 7.9 to 70.1. Two patients had histopathological confirmation after surgery, and the remaining four patients were followed up with no surgical treatment. Thus, DOTATOC PET/CT provided additional information in six of seven patients (86 %). PET/CT imaging in a representative patient with nodal metastasis is shown in Fig. 23.1.

In group C, a total of 25 patients with suspected NET due to high hormone levels underwent DOTATOC PET/CT. A pancreatic NET with SUVmax 68.5 was clearly shown by DOTATOC PET/CT in a patient with a suspected ACTH-producing tumor, followed by surgical confirmation. In the remaining 24 patients, DOTATOC

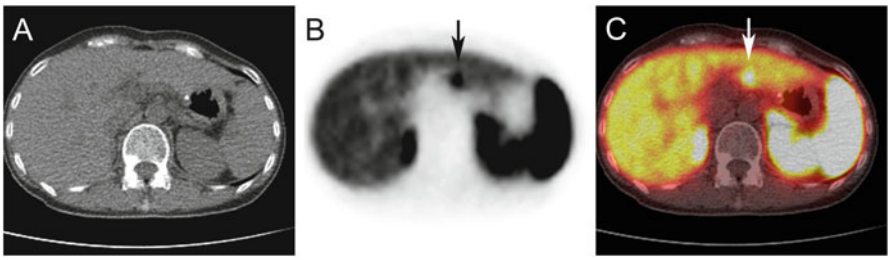

Fig. 23.1 A 51-year-old woman with suspected recurrent gastrinoma. Axial CT (**a**), DOTATOC PET (**b**), and fused (**c**) images are shown. A duodenal gastrinoma was removed by surgery, but recurrence was suspected because of rising serum gastrin levels. Intense focal uptake around the lateral segment of the liver is apparent on the DOTATOC PET and fused images (*arrows*). A lymph node metastasis was confirmed by surgery

PET/CT did not provide any additional clinically relevant information. The detection rate was significantly lower than in the other groups (Fisher's exact test, $p < 0.01$).

We concluded that DOTATOC PET/CT is useful for detecting NET, especially when recurrence or metastases are suspected because of high hormone levels after surgery for a primary NET and that it is hardly helpful in patients in whom only the hormone levels are high and the tumor has not been localized.

It is reasonable that DOTATOC PET/CT would be expected to yield relevant information when recurrence or metastasis is suspected due to high hormone levels after surgery for a functioning NET, since the pretest probability is high. In the patient shown in Fig. 23.1, a small lymph node was visualized retrospectively on contrast-enhanced CT (figure not shown), but it was difficult to distinguish from a benign inflammatory node on the basis of size. In addition, it would take time to confirm the characteristics during follow-up owing to its slow growth. The high accumulation of DOTATOC in a subcentimeter node is considered a useful finding for raising the suspicion of recurrence or metastasis after surgery for NET. Conversely, among the patients without a history of NET, only in one patient was DOTATOC PET/CT helpful, and it was negative in the remaining 24 patients. Some reasons might be considered. Primary sites may be too small to be detected by imaging modalities. If lesions are extremely small, uptake of DOTATOC could be underestimated because of the partial volume phenomenon. Also, when the primary tumor is located in the upper abdomen or alimentary tract, uptake could easily be influenced by respiratory motion or peristalsis, resulting in underestimation of uptake. In addition, high hormone levels do not always mean the presence of NET because hyperfunctioning can cause high hormone levels, e.g., nesidioblastosis in hyperinsulinemia or G-cell hyperplasia in hypergastrinemia. Furthermore, it has been reported that somatostatin receptor subtypes 2 and 5 are not well expressed in many insulinomas [10]. For these reasons, DOTATOC PET/CT may fail to show the primary tumor.

Peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-labeled or ^{90}Y-labeled octreotide has been used to treat NETs in Europe. To stratify patients according to their expected response to therapy, somatostatin receptor scintigraphy, including DOTATOC PET/CT, can be considered. However, we have no sufficient data so far on this subject because PRRT has not yet been performed in our country.

23.3 Localization of Causative Lesions in Tumor-Induced Osteomalacia

It is known that DOTATOC PET/CT is useful not only in the imaging of NETs but also in other diseases. Tumor-induced osteomalacia (TIO) is considered a suitable target for somatostatin receptor scintigraphy. TIO, which is also known as oncogenic osteomalacia, is a rare paraneoplastic syndrome. Phosphaturic mesenchymal

tumors secrete fibroblast growth factor 23 (FGF-23), causing hypophosphatemia due to suppression of the reabsorption of phosphorus in the proximal renal tubule and activation of vitamin D synthesis. Consequently, these tumors cause osteomalacia. Total resection of this mesenchymal tumor is essential to achieve complete cure, but localization of the causative lesions remains a challenge because they are usually small, slow growing, and are located at peculiar sites. Therefore, somatostatin receptor scintigraphy can be expected to be useful because these tumors often express somatostatin receptors [11].

There have been several studies investigating the potential usefulness of somatostatin receptor scintigraphy for detecting these mesenchymal tumors. As a preliminary evaluation in our institution, DOTATOC PET/CT has been performed for this purpose. We analyzed 14 patients (5 men and 9 women, mean age 46 years) with TIO who underwent DOTATOC PET/CT. All these patients had been suspected of having TIO due to hypophosphatemia (<2.5 mg/dl) and a high serum FGF-23 level (49–1,020 pg/ml). Overall, DOTATOC PET/CT showed 12 sites of abnormal uptake in eight patients. However, three lesions corresponding to bone were found to be fractured or pseudofractured, i.e., false-positive. Therefore, nine lesions in seven patients were finally considered to be the cause of the TIO. These lesions were located in the sphenoid bone, spine, rib, pelvic bone, tibia, and muscles. In the remaining six patients, DOTATOC PET/CT was negative. One patient is shown in Fig. 23.2. The serum FGF-23 levels in seven patients with true-positive DOTATOC PET/CT findings tended to be higher than in patients who had no causative tumor detected, but the difference was not significant. FDG PET/CT revealed only two abnormal foci in this population. Our preliminary data suggest that DOTATOC PET/CT would be a useful noninvasive technique for localizing causative tumors in patients with TIO and that fractures or pseudofractures caused by osteomalacia can be a pitfall in interpreting DOTATOC PET/CT images.

This is one of the hot topics in somatostatin receptor scintigraphy. Chong et al. found that ^{111}In-octreotide SPECT(/CT) was better than FDG PET/CT in detecting primary mesenchymal tumors causing TIO, with a sensitivity of 95 % [12]. Jing et al. showed the clinical value of ^{99m}Tc-HYNIC-TOC with a sensitivity of 86 % [13]. Other studies have demonstrated 100 % sensitivity of DOTATATE PET/CT in detecting causative lesions, although the number of cases is small [14–16]. In our experience, DOTATOC PET/CT does not always show the causative lesions, but this noninvasive technique may be considered even when TIO is suspected and the results of venous sampling are positive, because unexpected lesions can sometimes be detected by DOTATOC PET/CT.

23.4 Restaging in Renal Cell Carcinoma

Renal cell carcinoma (RCC) may be a target for somatostatin receptor scintigraphy because some recurrent or metastatic lesions from RCC are not FDG avid [17] and it has been reported that OctreoScan shows RCC metastasis [18]. At this time, experience with DOTATOC PET/CT in RCC is limited [19]. We have performed a

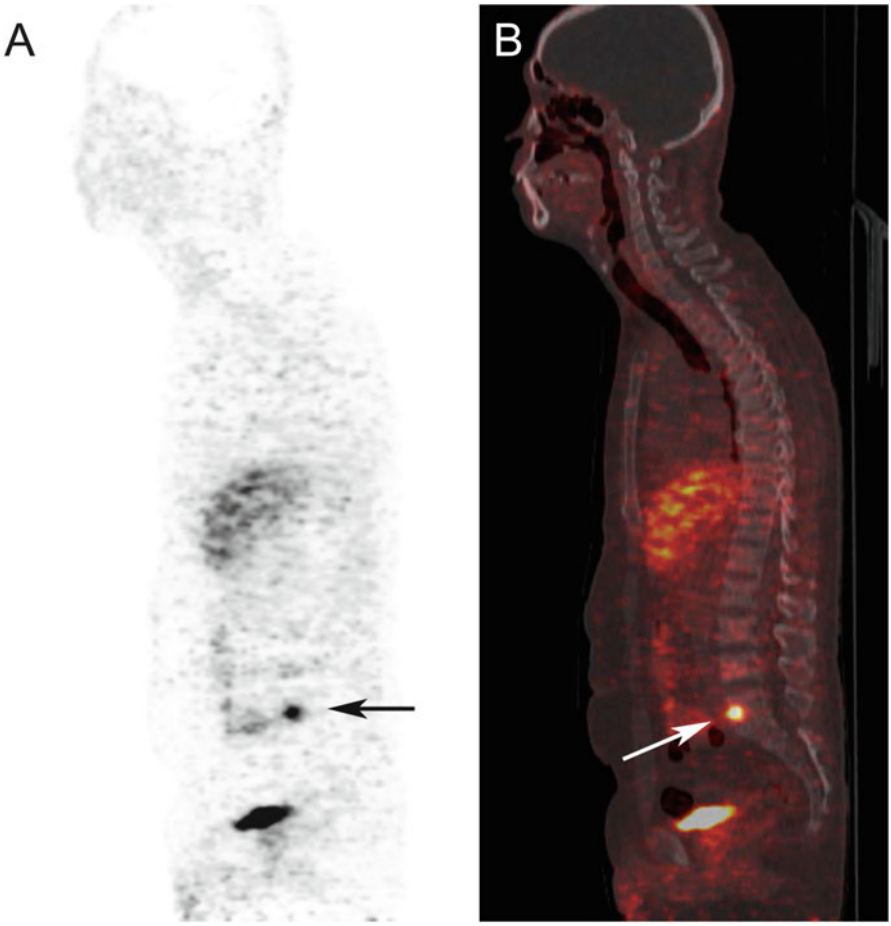

Fig. 23.2 A 54-year-old man with tumor-induced osteomalacia. Sagittal DOTATOC PET (**a**) and fused (**b**) images are shown. This patient was suspected of having tumor-induced osteomalacia due to his high FGF-23 level and hypophosphatemia. Intense focal uptake in the lumbar spine is apparent on the DOTATOC PET and fused images (*arrows*). The lesion was resected, and the patient's phosphorus level returned to normal

preliminary evaluation of the clinical efficacy of DOTATOC PET/CT in patients with suspected recurrent RCC after surgery. Seven consecutive patients who had surgery for histologically proven RCC and who were suspected of having recurrence of RCC underwent DOTATOC PET/CT for restaging. We retrospectively reviewed the PET/CT images and compared available FDG PET/CT findings. In this investigation, there were 18 recurrent or metastatic lesions in seven patients. Of the 18 lesions, 13 in six patients with clear-cell carcinoma were clearly shown on DOTATOC PET/CT, with SUVmax ranging from 2.8 to 23.3 (average 9.7). Excluding 2 of 13 lesions that were not assessed by FDG PET/CT, only three lesions were positive on FDG PET/CT. Four lesions were negative on DOTATOC PET/CT, but positive on FDG PET/CT in a patient with papillary carcinoma.

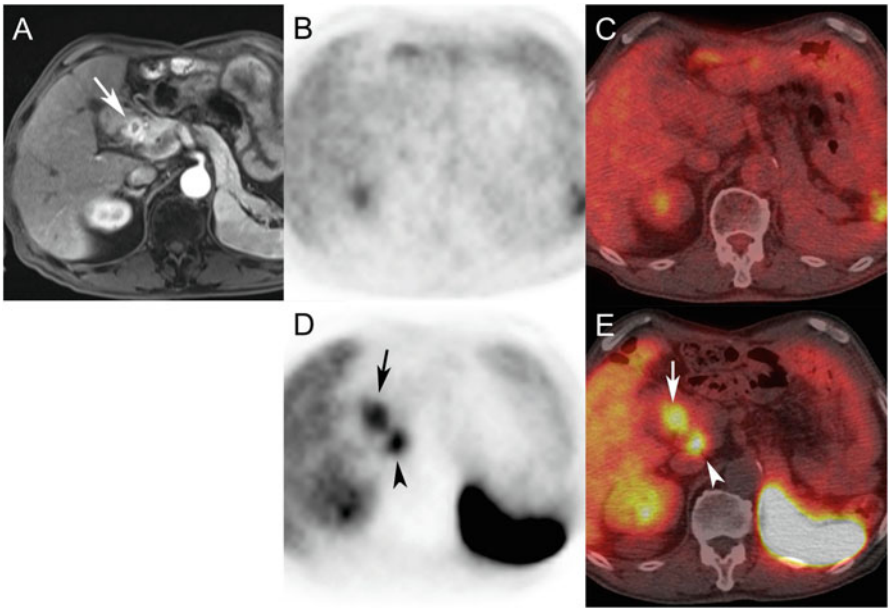

Fig. 23.3 A 76-year-old man with a hypervascular pancreatic tumor. Contrast-enhanced MR (**a**), FDG PET (**b**), FDG PET/CT (**c**), DOTATOC PET (**d**), and DOTATOC PET/CT (**e**) images are shown. The contrast-enhanced MR image (**a**) shows a well-enhanced mass in the pancreatic head (*arrow*). The FDG PET image (**b**) shows no abnormal uptake corresponding to this lesion, but the DOTATOC PET (**d**) and the DOTATOC PET/CT (**e**) images show DOTATOC accumulation in this tumor (*arrows*). A pancreatic neuroendocrine tumor and pancreatic metastasis from renal cell carcinoma was suspected. The final diagnosis was metastatic pancreatic tumor from renal cell carcinoma. Physiological uptake in a part of pancreas is also seen on the DOTATOC PET images (*arrowheads*)

Overall, the sensitivities of DOTATOC PET/CT and FDG PET/CT were 86 % and 67 %, respectively, on a patient basis and 72 % and 56 %, respectively, on a lesion basis, in our population.

A hypervascular tumor seen in the pancreas in a patient with a history of RCC may be difficult to differentiate from pancreatic NET and metastasis from RCC (Fig. 23.3). However, when inconclusive findings are obtained by conventional imaging, DOTATOC PET/CT would be useful for detecting unexpected additional metastatic lesions, just as FDG PET sometimes provides useful information if FDG-avid tumors are present.

23.5 Sarcoidosis

As somatostatin receptors are expressed on activated lymphocytes, it is expected that sarcoidosis, an inflammatory disorder, may also be visualized. The use of somatostatin receptor scintigraphy with ^{111}In-pentetreotide in patients with

sarcoidosis was investigated in one study [20]. The somatostatin receptor imaging was able to demonstrate active granulomatous disease in the patients with sarcoidosis, and pathological uptake of radioactivity in the parotid glands during imaging was correlated with higher serum ACE concentrations. However, the efficacy of somatostatin receptor imaging in sarcoidosis has not yet been established, and there are few articles regarding the clinical utility of DOTATOC PET/CT in sarcoidosis. In our experience, DOTATOC PET/CT reveals a similar or greater number of lesions than a conventional gallium scan. As compared with FDG PET/CT, uptake may be lower in involved nodes, but DOTATOC PET/CT could be useful for evaluating involvement of the myocardium in patients with cardiac sarcoidosis, because physiological uptake in the myocardium can make FDG PET/CT images difficult to evaluate. A representative patient with sarcoidosis is shown in Fig. 23.4.

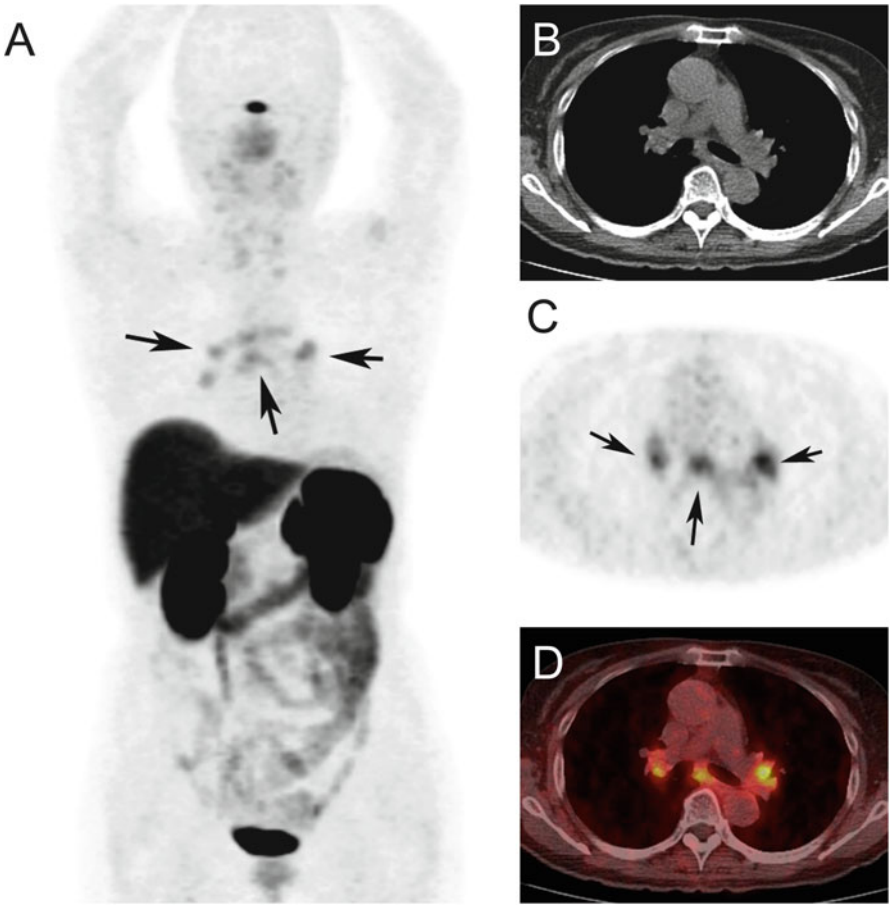

Fig. 23.4 A 65-year-old woman with suspected sarcoidosis. A maximum intensity projection image (**a**) and axial CT (**b**), DOTATOC PET (**c**), and fused (**d**) images are shown. Moderate to intense uptake of DOTATOC is observed in hilar and mediastinal lymph nodes (*arrows*)

23.6 Conclusion

DOTATOC PET/CT is a useful imaging modality for detecting NETs, as has been reported in many articles; however, its efficacy depends on the clinical situation. It may be helpful especially when recurrence or metastasis is suspected after surgery of NET, but additional information might not be obtained simply when hormone levels are high. DOTATOC PET/CT is also considered helpful for identifying causative lesions in TIO, although fracture or pseudofracture can be a pitfall. DOTATOC PET/CT could have a clinical impact in restaging of RCC or in detecting involved lesions in sarcoidosis, but further investigations with more patients are required.

Conflict of Interest None.

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