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【 CASE REPORT 】

Pancreatic Hamartoma Difficult to Diagnose Preoperatively

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Abstract:
Abdominal ultrasonography in a 70-year-old woman showed a hypoechoic mass, 14 mm in diameter, in the pancreatic body. Computed tomography showed a mass with contrast effect in the pancreatic body. Test results for endocrine factors or tumor markers were normal. The initial consideration was nonfunctional pancreatic neuroendocrine tumor. Over 8 years of monitoring, the tumor diameter increased to 18 mm, until pancreatic tumor enucleation was performed. The postoperative diagnosis was pancreatic hamartoma, a rare type of benign pancreatic tumor. The preoperative diagnosis of pancreatic hamartoma is difficult, but consideration must be given to the possibility of hamartoma when encountering pancreatic tumors.

Key words: pancreatic hamartoma, pancreatic neuroendocrine tumor

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Introduction

A hamartoma is an abnormality of tissue structural composition due to either a non-tumoral congenital anomaly or an error of postnatal tissue development, resulting in a localized mass formation. It is very rare for a hamartoma to develop in the pancreas.

We herein report a case of pancreatic hamartoma that was difficult to diagnose preoperatively.

Case Report

In Year X-8, the patient, a 70-year-old woman, underwent abdominal ultrasonography during a health checkup and was found to have a hypoechoic mass measuring 14 mm in diameter in the pancreatic body. She was therefore referred to our hospital for a complete examination and treatment. Various tests suggested a nonfunctional pancreatic neuroendocrine tumor, but no action was taken other than monitoring the progression, as requested by the patient. Over time, the mass grew to 18 mm, and in Year X, in consultation with the patient, surgery was performed.

With respect to her medical history, the patient had hypertension and insomnia. She was under treatment with losartan potassium and zolpidem. She had no allergies, there were no significant signs with respect to lifestyle or family history, and during hospitalization no abnormalities in her physical signs were noted. Lab tests during the hospital stay showed no abnormalities in the blood cell count, blood chemistry, coagulation, tumor markers, or endocrinology results (Table 1).

Abdominal computed tomography (CT) showed a round mass with a high density in the delayed phase in the pancreatic body, projecting outside the pancreas. In the early phase, the contrast effects were similar to those in the pancreatic parenchyma, but during the portal phase, these effects were more marked than in the pancreatic parenchyma, indicating delayed enhancement (Fig. 1). Over 8 years of monitoring, the diameter increased from 14 to 18 mm. Abdominal magnetic resonance imaging (MRI) showed a low signal intensity on T1-weighted imaging, high signal intensity with T2-weighted imaging, and minor diffusional limitation on diffusion-weighted imaging (Fig. 2).

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Table 1. Laboratory Findings.

Hematology		Biochemistry				Tumor markers	
WBC	5,330 /μL	TP	7.1 mg/dL	BUN	17 mg/dL	CA19-9	2.0 U/mL
RBC	447×10⁴ /μL	Alb	4.5 g/dL	Cr	0.64 mg/dL	CEA	3.6 ng/mL
Hb	13.9 g/dL	T-Bil	0.6 mg/dL	Na	139 mEq/L		
Ht	40.3 %	D-Bil	0.1 mg/dL	K	4.2 mEq/L	Endocrinology	
Plt	20×10⁴ /μL	AST	23 IU/L	Cl	103 mEq/L	Insulin	3.4 μU/mL
		ALT	18 IU/L	CRP	0.09 mg/dL	Gastrin	121 Pg/mL
Coagulation		LDH	201 IU/L				
PT	99 %	γ-GT	17 IU/L				
PT-INR	0.99	ALP	206 IU/L				
		AMY	73 IU/L				

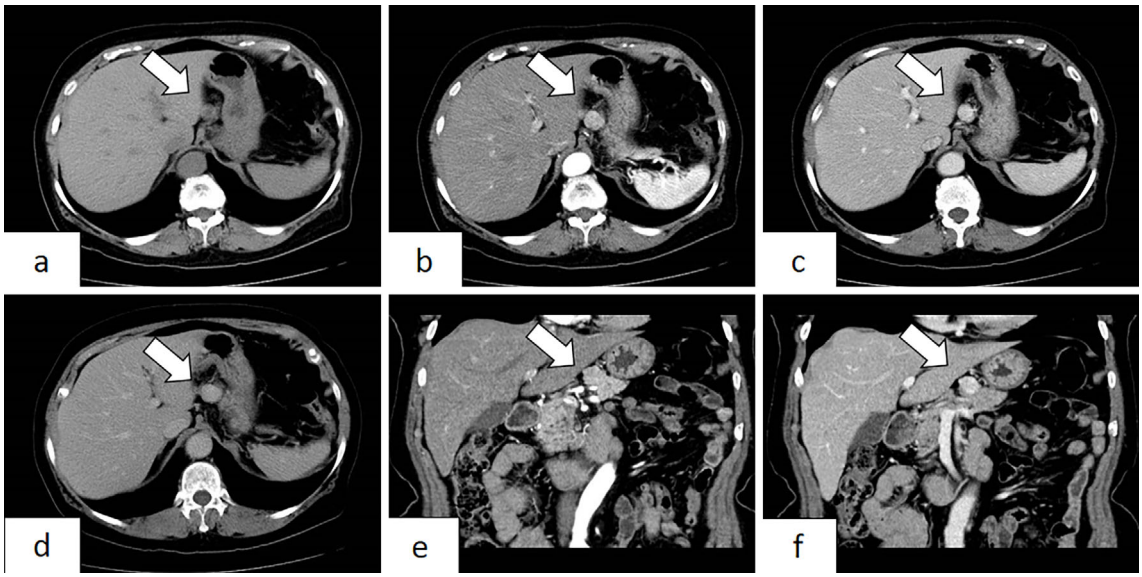

Figure 1. Abdominal contrast-enhanced computed tomography findings. In the pancreatic body, a round mass with a high density in the delayed phase extending outside the pancreas was found (arrow). In the early phase, the contrast effects were approximately the same as in the pancreatic parenchyma, whereas in the venous phase, they were greater, indicating delayed enhancement. (a) Plain phase, (b) early phase, (c) venous phase, (d) delayed phase, (e) early phase, coronal section, (f) delayed phase, coronal section.

Endoscopic ultrasonography showed a hypoechoic mass with clear borders and regular margins, measuring 16×12.3 mm, in the pancreatic body. The distance between the tumor and the main pancreatic duct was 3 mm (Fig. 3-a). Sonazoid-enhanced endoscopic ultrasonography showed both the early and delayed phases to be hypovascular in the tumor compared with the surrounding pancreatic parenchyma. This contrasts with the findings seen in typical neuroendocrine tumors (Fig. 3-b). After discussion with a surgeon, it was decided that endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) would not be performed because of the risk of EUS-FNA-related adverse effects, such as pancreatitis.

Although the contrast signs shown by endoscopic ultrasonography were atypical, the lesion was a pancreatic tumor with contrast effect, so the first suggested diagnosis was nonfunctional pancreatic neuroendocrine tumor, and in compliance with the patient's request, we performed surgery for diagnostic therapy. Since the main pancreatic duct ran close to the tumor, a transnasal pancreatic duct drainage tube was positioned endoscopically, and pancreatic tumor enucleation was performed. The histopathological findings were that the lesion was an elastically hard, yellow, phyllodes tumor that was visually evaluated to measure 19×16×14 mm. In histological terms, it was considered to have resulted from the dense proliferation of the small pancreatic ducts, and widespread collagen fiber hyperplasia was found between the pancreatic ducts. No atypia of pancreatic duct epithelial cells was found, but hyalinization of the pancreatic duct wall was marked. No islets of Langerhans or peripheral neural fibrous tissues were found inside the lesion. Chromogranin A and synaptophisin, characteristic neuroendocrine tumor markers, were negative. Therefore, the final diagnosis was pancreatic hamartoma (Fig. 4).

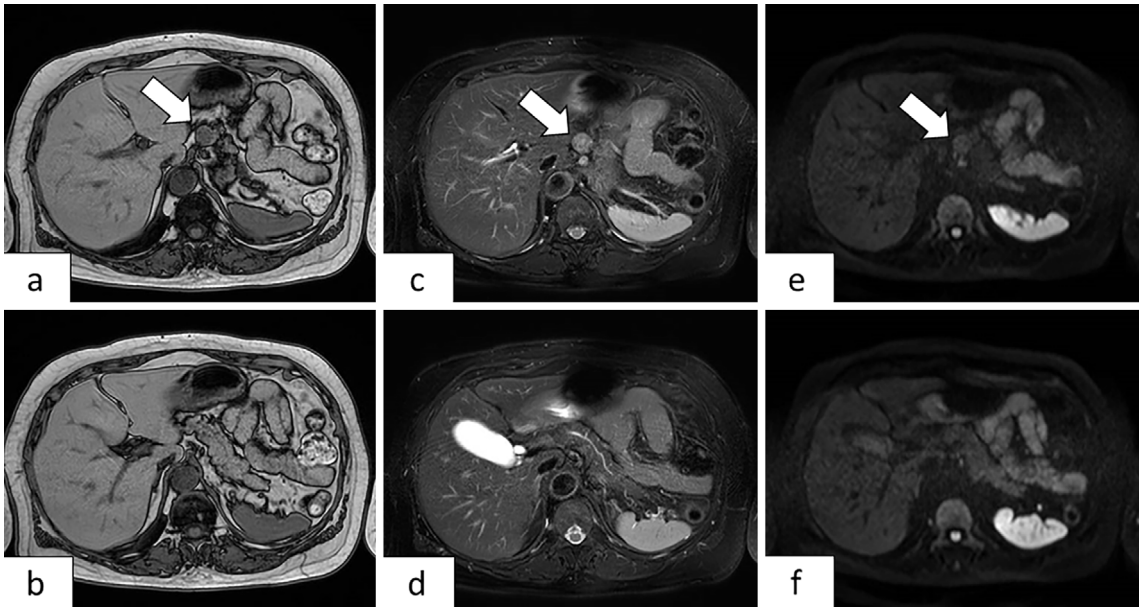

Figure 2. **Abdominal MRI findings. A low signal intensity was found with T1-weighted imaging (a, b), high signal intensity with T2-weighted imaging (c, d), and minor diffusional limitation with diffusion-weighted imaging (e, f). The signal of the tumor is clearly different from that of the surrounding pancreatic parenchyma.**

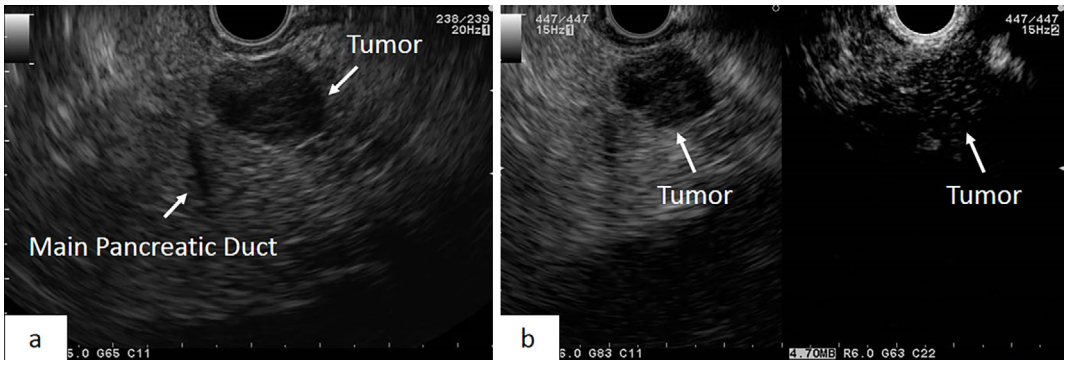

Figure 3. **Endoscopic ultrasonography findings. (a) From the stomach, a hypoechoic tumor measuring 16×12.3 mm was found in the pancreatic body, with the pancreatic duct running close to it. There was no posterior echo enhancement or lateral shadows of the tumor. (b) Left: fundamental B-mode, right: contrast mode. The early and delayed phases are hypovascular compared with the surrounding pancreatic parenchyma.**

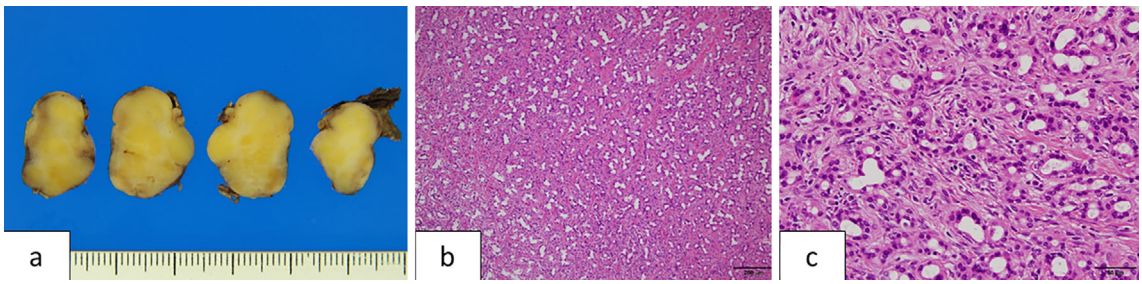

Figure 4. **The histopathological evaluation. (a) Gross slices of a fixed specimen. (b) Hematoxylin and Eosin (H&E) staining (×100), (c) H&E staining (×400).**

Table 2. Clinical Features of Pancreatic Hamartoma.

age, years; mean (range)	51.5 (0.6-78)
sex	M 24 F 22
symptoms	asymptomatic: 19 abdominal pain: 15 abdominal discomfort: 2 weight loss: 1 hypoglycemic events: 1 jaundice: 1 NR: 7
location	head: 29; body: 7; tail: 8 diffuse, multiple: 2
size, cm; mean (range)	4.1 (0.9-19)
preoperative diagnosis	NET: 8 SPT: 6 PDAC: 4 ACC: 2 liposarcoma: 1 lipoma: 1 epidermoid cyst: 1 mass forming pancreatitis: 1 SCN: 1

NR: not reported, NET: neuroendocrine tumor, SPT: solid pseudopapillary tumor, PDAC: pancreatic ductal adenocarcinoma, ACC: acinar cell carcinoma, SCN: serous cystic neoplasm

Discussion

Hamartoma is a type of histological anomaly that develops in association with quantitative or structural abnormalities during the developmental process of normal structural tissues. It most commonly occurs in the lung and breast and is very rare in the pancreas, with pancreatic hamartoma being reported to account for <1% of cases (1).

Pancreatic hamartoma was first reported in 1977 (2), and cases have occasionally been reported since. A search of the PubMed database with the keywords "pancreatic hamartoma" rendered 46 cases, including the present case, of which 4 were children and 42 were adults (1-26) (Table 2). The mean age of the patients was 52.5 years (range: 0.6 to 78), and the men:women ratio was 24:22, with most diagnoses made either by chance or because of abdominal pain. The sites of the hamartoma within the pancreas were the head, body, tail, and multiple sites in 29, 7, 8 and 2 patients, respectively, and the tumor diameter varied widely, from 0.9 to 19 cm. In all cases, the correct diagnosis was made by surgery or autopsy. Suggested preoperative diagnoses were pancreatic neuroendocrine tumor, solid pseudopapillary tumor, pancreatic ductal adenocarcinoma, acinar cell carcinoma, liposarcoma, lipoma, epidermoid cyst, mass forming pancreatitis, and serous cystic neoplasm, but no reports of the preoperative diagnosis of hamartoma were found.

There are no characteristic signs of pancreatic hamartoma in diagnostic imaging. Pancreatic hamartoma is classified histopathologically as being of solid type or solid-and-cystic type, and the signs of the solid type include (i) a pattern of delayed enhancement on imaging; (ii) with MRI, low signal intensity on T1-weighted imaging, high signal intensity on T 2-weighted imaging, and no diffusional limitation on diffusion-weighted imaging; and (iii) no accumulation shown by fluorodeoxyglucose positron emission tomography/CT. However, it is difficult to distinguish hamartomas from pancreatic neuroendocrine tumors (1). Typically, pancreatic neuroendocrine tumors appear as round, solid, and hypervascular and are visualized during the early arterial phase with washout during the portal venous phase on contrast-enhanced CT (27). Contrast-enhanced CT is highly accurate for detecting pancreatic neuroendocrine tumors, with a sensitivity range of 63-82% and specificity range of 83-100%. However, the sensitivity is decreased to 34% in tumors smaller than 1.5 cm in size (28-30), and tumors often show various contrast patterns on contrast-enhanced CT, depending on the vascularity and fibrosis (31). The imaging findings in the present patient were similar, with delayed enhancement considered to reflect fibrosis in the pancreatic hamartoma. This made it impossible to distinguish it from other lesions, including pancreatic neuroendocrine tumors.

Somatostatin receptor scintigraphy (SRS) is the standard test for a neuroendocrine tumor diagnosis (32). Since SRS is a test that reflects the expression of somatostatin receptors, not all neuroendocrine tumor cases are positive, but in cases of neuroendocrine tumors showing atypical imaging findings, it can aid in differentiation from other pancreatic tumors. However, there have been no reports of SRS for pancreatic hamartoma. Since pancreatic hamartoma is associated with either quantitative or structural abnormalities of normal pancreas cells, the somatostatin receptor expression may be similar to that of normal pancreatic tissue. Therefore, pancreatic hamartomas may show a physiological accumulation on SRS similar to normal pancreatic tissue. In the present case, SRS may have helped distinguish the tumor from NET, but SRS was not performed because this case occurred before SRS was covered by insurance.

All reported cases of pancreatic hamartoma have been diagnosed by surgery or autopsy. In recent years, EUS-FNA has been performed with some subjects, and if a case is considered difficult to distinguish by diagnostic imaging, EUS-FNA should be performed. While the preoperative diagnostic imaging findings were not typical, pancreatic neuroendocrine tumor was deemed the most likely diagnosis in this case. Therefore, after discussion with surgeons, EUS-FNA was not performed, and surgery was performed instead. However, in hindsight, we should have performed EUS-FNA for this pancreatic tumor, as this would have allowed us to identify the lesion as hamartoma and thus avoid surgery.

As reported previously, the preoperative diagnosis of pancreatic hamartoma is difficult, so despite it being a benign disease, surgical treatment is often selected. In connection

with the discriminatory diagnosis of pancreatic tumors, it is now considered important to recognize the existence of pancreatic hamartoma. Not only CT or EUS but various other diagnostic modalities, including EUS-FNA and SRS, are also needed. Furthermore, as experience with more patients accumulates, we expect a preoperative diagnostic method to be established, making it possible to avoid surgical treatment.

The authors state that they have no Conflict of Interest (COI).

References

1. Han YE, Park BJ, Sung DJ, et al. Computed tomography and magnetic resonance imaging findings of pancreatic hamartoma: a case report and literature review. Clin Imaging **52**: 32-35, 2018.
2. Anthony PP, Faber RG, Russell RC. Pseudotumors of the pancreas. Br Med J **1**: 814, 1977.
3. Noltenius H, Colmant HJ. Excessive hyperplasia of the exocrine pancreatic tissue and Wernicke's encephalopathy. Med Klin **72**: 2155-2158, 1977.
4. Izbicki JR, Knoefel WT, Müller-Höcker J, et al. Pancreatic hamartoma: a benign tumor of the pancreas. Am J Gastroenterol **89**: 1261-1262, 1994.
5. Wu SS, Vargas HI, French SW. Pancreatic hamartoma with Langerhans cell histiocytosis in a draining lymph node. Histopathology **33**: 485-487, 1998.
6. McFaul CD, Vitone LJ, Campbell F, et al. Pancreatic hamartoma. Pancreatology **4**: 533-537, 2004.
7. Pauser U, Kosmahl M, Kruslin B, et al. Pancreatic solid and cystic hamartoma in adults: characterization of a new tumorous lesion. Am J Surg Pathol **29**: 797-800, 2005.
8. Pauser U, da Silva MT, Placke J, et al. Cellular hamartoma resembling gastrointestinal stromal tumor: a solid tumor of the pancreas expressing c-kit (CD117). Mod Pathol **18**: 1211-1216, 2005.
9. Nagata S, Yamaguchi K, Inoue T, et al. Solid pancreatic hamartoma. Pathl Int **57**: 276-280, 2007.
10. Sampelean D, Adam M, Muntean V, et al. Pancreatic hamartoma and SAPHO syndrome: a case report. J Gastrointestin Liver Dis **18**: 483-486, 2009.
11. Durczynski A, Wiszniewski M, Olejniczak W, et al. Asymptomatic solid pancreatic hamartoma. Arch Med Sci **7**: 1082-1084, 2011.
12. Kawakami F, Hara S, Itoh T, et al. Multiple solid pancreatic hamartomas: A case report and review of the literature. World J Gastrointest Oncol **4**: 202-206, 2012.
13. Ho-Hyun K, Chol-Kyoon C, Young-Hoe H, et al. Pancreatic hamartoma diagnosed after surgical resection. J Korean Surg Soc **83**: 330-334, 2012.
14. Kersting S, Janot MS, Munding J, et al. Rare solid tumors of the pancreas as differential diagnosis of pancreatic adenocarcinoma. JOP **13**: 268-277, 2012.
15. Yamaguchi H, Aishima S, Oda Y, et al. Distinctive histopathologic findings of pancreatic hamartomas suggesting their "hamartomatous" nature: a study of 9 cases. Am J Surg Pathol **37**: 1006-1013, 2013.
16. Addeo P, Tudor G, Oussoultzoglou E, et al. Pancreatic hamartoma. Surgery **156**: 1284-1285, 2014.
17. Inoue H, Tameda M, Yamada R, et al. Pancreatic hamartoma: a rare cause of obstructive jaundice. Endoscopy **46**: 157-158, 2014.
18. Zhang J, Wang H, Tang X, Jiang Q, Wang C. Pancreatic hamartoma, a rare benign disease of the pancreas: a case report. Oncol Lett **11**: 3925-3928, 2016.
19. Matsushita D, Kurahara H, Mataki Y, et al. Pancreatic hamartoma: a case report and literature review. BMC Gastroenterol **16**: 3, 2016.
20. Murakami T, Yamazaki M, Yamazaki K, et al. A distinctive myoepithelial hamartoma of the pancreas histologically confirmed in the mother of a previously reported patient. Pancreatology **16**: 464-468, 2016.
21. Nagano H, Nakajo M, Fukukura Y, et al. A small pancreatic hamartoma with an obstruction of the main pancreatic duct and avid FDG uptake mimicking a malignant pancreatic tumor: a systematic case review. BMC Gastroenterol **17**: 146, 2017.
22. Tanaka M, Ushiku T, Ikemura M, et al. Pancreatic lipomatous hamartoma. Am J Surg Pathol **42**: 891-897, 2018.
23. Nahm CB, Najdawi F, Reagh J, et al. Pancreatic hamartoma: a sheep in wolf's clothing. ANZ J Surg **89**: E265-E267, 2019.
24. Shin DH, Rho SY, Hwang HK, et al. A case of pancreatic hamartoma pathologically confirmed after robot-assisted pancreaticoduodenectomy. Ann Hepatobiliary Pancreat Surg **23**: 286-290, 2019.
25. Toyama K, Matsusaka Y, Okuda S, et al. A case of pancreatic hamartoma with characteristic radiological findings: radiological-pathological correlation. Abdom Radiol (NY) **45**: 2244-2248, 2020.
26. Katayama H, Azuma K, Koneri K, et al. A typical case of resected pancreatic hamartoma: a case report and literature review on imaging and pathology. Surg Case Rep **6**: 107, 2020.
27. Paulson EK, McDermott VG, Keogan MT, et al. Carcinoid metastases to the liver: role of triple-phase helical CT. Radiology **206**: 143-150, 1998.
28. Sundin A. Radiological and nuclear medicine imaging of gastroenteropancreatic neuroendocrine tumours. Best Pract Res Clin Gastroenterol **26**: 803-818, 2012.
29. Herwick S, Miller FH, Keppke AL. MRI of islet cell tumors of the pancreas. Am J Roentgenol **187**: W472-W480, 2006.
30. Lingaku Lee, Tetsuhide Ito, Robert T. Jensen. Imaging of pancreatic neuroendocrine tumors: recent advances, current status and controversies. Expert Rev Anticancer Ther **18**: 837-860, 2018.
31. Rodallec M, Vilgrain V, Couvelard A, et al. Endocrine pancreatic tumours and helical CT: contrast enhancement is correlated with microvascular density, histoprognostic factors and survival. Pancreatology **6**: 77-85, 2006.
32. Krenning EP, Bakker WH, Kooij PP, et al. Somatostatin receptor scintigraphy with indium-111-DTPA-D-Phe-1-octreotide in man: metabolism, dosimetry and comparison with iodine-123-Tyr-3-octreotide. J Nucl Med **33**: 652-658, 1992.