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Localization of neuroendocrine tumours with [^{111}In]DTPA-octreotide scintigraphy (Octreoscan): a comparative study with CT and MR imaging

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Summary

A wide variety of neuroendocrine tumours express somatostatin receptors, and can be visualized by radiolabelled somatostatin analogue scintigraphy. To investigate the value of [^{111}In]-octreotide scintigraphy (Octreoscan), 48 patients (37 with proven carcinoid, pancreatic endocrine and medullary carcinoma of thyroid tumours, 11 with neuroendocrine syndromes multiple endocrine neoplasia (MEN-I) and Zollinger-Ellison syndrome (ZES) were examined with ^{111}In-DTPA-D-Phe^{1}-octreotide. Scintigrams were obtained at 24 and 48 h, and the results were compared with CT and magnetic resonance imaging (MRI). Thirty-five of 48 patients had positive [^{111}In]-octreotide scintigraphy (23/25 (92%) carcinoids, 8/9 (89%) PETs, 4/11 (36%) MEN-I & ZES). Of the 42 lesions located by conventional imaging techniques, 37 (88%) were also identified by Octreoscan. Unexpected lesions (40 sites), not detected by CT or MR imaging were found in 24/48 (50%) patients. [^{111}In]-octreotide scintigraphy has a higher sensitivity for tumour detection, and is superior to MR imaging and CT scanning in the identification of previously unsuspected extraliver and lymph node metastases. It may also be helpful for the localization of clinically suspected tumours in patients with MEN-I and ZES.

Introduction

Primary neuroendocrine tumours (NETs) are often small and grow slowly. This often makes their identification and localization difficult, especially in the early stages. NETs in the gastroenteropancreatic system are especially difficult to localize, due to their anatomical and multiple functional characteristics. Unfortunately, metastases are already present at the time of diagnosis in most cases.[1] For both diagnosis and management purposes, identification of the primary tumour and metastases is mandatory.

Conventional radiological techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and angiography are well established as advanced tools for the identification of NETs. CT scanning is highly accurate and non-invasive. MRI has been shown to be effective for detecting tumours in both the liver and pancreas and is more sensitive than CT.[2,3] However, these techniques also have limitations for localizing and staging tumours. For CT scanning to be useful for the detection of NETs, advanced dynamic scanning techniques with rapid contrast injection are required. Contrast enhancement of the peritumour vessels permits identification of tumour involvement of the adjacent arterial and venous structures, and also identifies tumours greater than 2 cm in diameter and metastases of regional lymph nodes or in the liver. Approximately 30–75% of solitary gastrinomas may be detected at CT scanning.[4] However, the pancreas

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is one of the most difficult abdominal organs to visualize, even by MR imaging. Although pancreatic endocrine tumours have significantly longer T1 and T2 relaxation times compared to normal pancreas tissue, the potential advantage of the improved tissue contrast of MR imaging has been overshadowed by the presence of motion artifacts. Because of these, small pancreatic endocrine tumours are not detected, and the sensitivity is less than 50%.[5] Because pancreatic endocrine tumours are frequently vascular, contrast agents such as gadolinium-DTPA can improve imaging. A report by Semelke has suggested that MR imaging with dynamic gadolinium enhancement and fat suppression may be superior to CT in detecting small (<1.5 cm in diameter) pancreatic tumours.[6] In addition, a major drawback of CT scanning and MR imaging is that only suspected specific anatomical sites such as the abdomen or chest are usually imaged.

The recent observation that the cell surfaces of NETs express somatostatin receptors has led to the development of new localization techniques. ^{111}In-[DTPA-D-Phe^1] octreotide scintigraphy (Octreoscan) has been reported to be the most effective diagnostic tool for the localization of primary tumours and their metastases in patients presenting with the clinical and biochemical features of NETs.[7,8] The sensitivity and specificity of ^{111}In-[DTPA-D-Phe^1]octreotide scintigraphy have been studied either by comparing this procedure with other radiological techniques or in patients with various types of APUD cell tumours.[9–11]

The aim of the present study was to evaluate [^{111}In]-octreotide scintigraphy in localizing primary and metastatic neuroendocrine tumours, and to compare these imaging characteristics with those of CT scanning and MR imaging.

Methods

Forty-eight patients with known or clinically suspected NETs were investigated between October 1993 and January 1996. Thirty-seven patients had immunohistologically-proven neuroendocrine tumours. The group consisted of 25 patients with carcinoid tumours (16 gut, 8 lung and 1 ovarian; 14 women and 11 men); 9 patients with pancreatic endocrine tumours (PETs) (3 gastrinomas, 2 insulinomas, 1 VIPoma and 3 tumours of undetermined type; 4 women and 5 men); and 3 patients with metastatic medullary carcinoma of thyroid (MCTs) (1 woman and 2 men). The mean age of the patients was 56.1 years (range 6–78 years). Thirty-three patients had had the primary tumours surgically removed, and four patients had the histopathological diagnosis established by ultrasound-guided biopsy. At the time of the study, 28 patients who underwent surgical resection of a primary tumour had recurrent disease: metastatic liver disease was found in 18 patients, mediastinal metastases in four patients, abdominal and/or pelvic lymph nodes in three patients, and bony metastases in four patients. All 37 patients underwent hormone marker evaluation by radioimmunoassay. Besides urinary 5-HIAA and 5-HT, plasma pancreastatin, neurokinin A, pancreatic polypeptide, gastrin, insulin, vasoactive intestinal peptide, glucagon and somatostatin were analysed in carcinoid and PET patients. Plasma calcitonin, calcitonin-gene-related peptide and pancreatic polypeptide were measured in MCT patients.

In addition, in another group of 11 patients, the diagnosis of multiple endocrine neoplasia type I (MEN-I) ($n=3$) and Zollinger-Ellison syndrome (ZES) ($n=8$) were based on the clinical features, family history and elevated hormone levels. The clinical characteristics of these patients are presented in Table 1.

Some patients had received either chemotherapy, radiotherapy, or omeprazole treatment, and 12/48 patients had been treated with somatostatin analogues. Somatostatin treatment was stopped 3 days before the octreotide scintigraphy.

Lyophilized somatostatin analogue DTPA-D-Phe^1-octreotide and ^{111}In-chloride were obtained in separate vials from the manufacturer (Mallinckrodt Medical). They were conjugated on site, and the labelling yield was controlled by SEP-PAK reversed-phase chromatography. The accepted labelling efficacy was $>97\%$. At 24 and 48 h, following the intravenous administration of ^{111}In-labelled octreotide (mean adult dose 185 MBg), scintigraphy was performed using a large-field gamma camera equipped with a medium energy collimator. On each occasion, a series of 500 000-count images was acquired, including the head, neck, thorax, abdomen and pelvic in anterior and posterior projections. Tumour visualization was determined and correlated with biphasic (arterial and venous) helical CT scanning for each patient. Helical scanning with dynamic enchancement with 90 ml of 300 mg% non-ionic contrast medium with 5 mm reformatting was used. For pancreatic studies (as opposed to abdomen, i.e. liver/pancreas, peritoneal cavity) water was used in preference to oral contrast.

MR imaging was performed on a Sigma 1.5 T MRS 1000 superconducting imaging system (GE). In each patient, two pulse sequences were employed: a T1-weighted spin-echo (SE) sequence and a T2-weighted SE sequence. Additional T2-weighted SE images of patients were obtained immediately after a bolus intravenous administration of 0.1 mmol/kg Gadopentetate with a 10 mm section thickness and a 5.0 or 10 mm intersection gap.

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Table 1 Clinical characteristics of patients with neuroendocrine tumours

Type of patients	*n*	Sex (F/M)	Mean (range) age (years)	Pre-localization (Primary/metastases) (n)	Primary tumour resection (n)
Carcinoid	25				
Gut	16	9/7	61.9(33–78)	L(12), ALN(2), Bo(2)	13
Lung	8	4/4	54.1(29–74)	Med(3), Bo(1), Lu(2)	4
Ovarian	1	1/0	64.0	L(1)	1
Gastrinoma	3	0/3	28.7(6–45)	Pan(2), L(1)	2
Insulinoma	2	1/1	62.0	L(1)	2
VIPoma	1	0/1	59.0	L(1)	1
Undetermined	3	3/0	52(33–62)	Pan(3), ALN(1)	2
MEN-I	3	2/1	48.0(30–69)	Pan(1)	0
ZES	8	3/5	58.7(42–73)	Pan(1)	0
MCT	3	1/2	55.3(47–62)	L(2), Med(1), Bo(1)	3

L, liver; ALN, abdominal lymph node; Bo, bone; Med, mediastinum lymph node; Lu, lung; Pan, pancreas.

Results

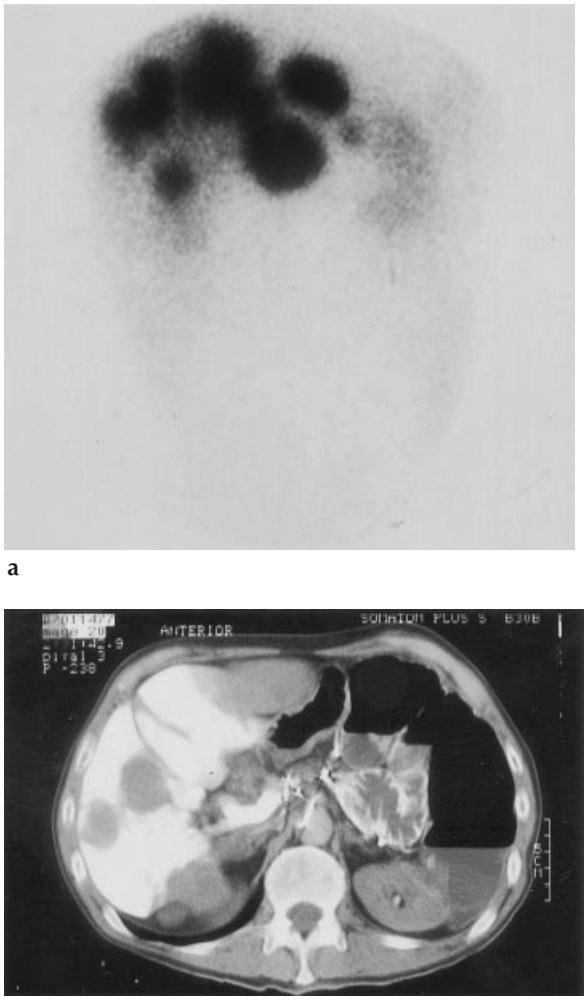
Patients

Carcinoid tumours

Primary and metastatic lesions were identified by CT and MR imaging in 19/25 patients with proven carcinoid tumours. Of these 19 patients, 18 had positive [^{111}In]-octreotide scintigraphy. The false negative Octreoscan patient had both the symptoms and the biochemical evidence of a metastatic neuroendocrine tumour, and three metastatic lesions in the liver (diameter varied from 1–4 cm) which were detected by MR imaging and CT scanning. Apart from the visualization of known lesions, previously unrecognized sites were found in 9/19 patients by scintigraphy. In the remaining six of the 25 patients, five were found to have previously unsuspected liver, para-aortic lymph node, pulmonary or bone lesions on scintigraphy, which were not identified using conventional imaging techniques. The diagnosis was subsequently confirmed surgically in two patients, and on percutaneous needle biopsy in three. In one further patient with resected carcinoid tumours of the ileum, Octreoscan, MR imaging and CT scanning were concordantly negative.

Pancreatic endocrine tumours (PETs)

Eight of nine patients with primary or metastatic pancreatic endocrine tumours had positive scintigraphy, but liver metastases in one patient with histologically-proven insulinoma remained undetected. One patient with a previously resected pancreatic VIPoma demonstrated widespread metastases in both lobes of the liver by all imaging procedures (Figure 1). In another patient, octreotide scintigraphy demonstrated a large lobulated mass lying in the tail of the pancreas, with multiple liver and para-aortic lymph-node metastases; enhanced CT scanning



a

b

Figure 1. a ^{111}In-octreotide planar anterior scintigram of the abdomen in a 60-year-old man with a resected pancreatic VIPoma showing extensive tumour uptake in the liver. **b** Enhanced CT scanning confirming multiple metastatic diseases in the liver.

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revealed the pancreatic and liver lesions, but no lymph-node abnormality. Biopsy subsequent to the scintigrams showed a neuroendocrine tumour in the pancreas secreting insulin, gastrin and glucagon, widespread metastatic lesions in the liver and multiple extra-liver lymph-node metastases.

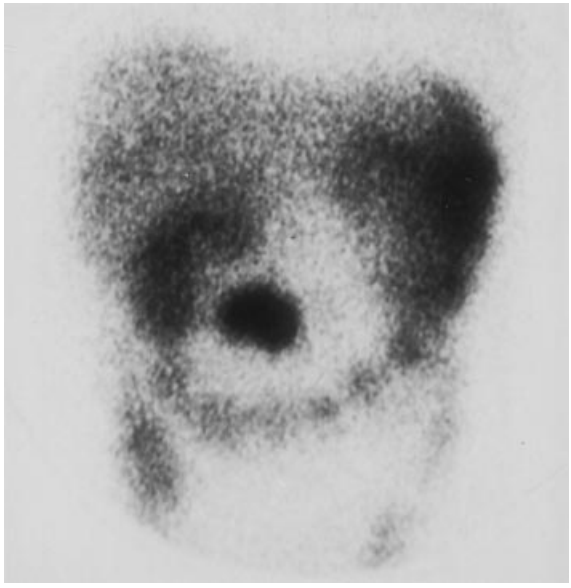
Medullary carcinoma of the thyroid (MCT)

Three MCT patients, with multiple liver and mediastinal lymph-node involvement identified on MR imaging and CT scanning had negative octreotide scintigraphy, the only identified lesion was a probable small-bone metastasis.

In the remaining 11 patients (8 with Zollinger-Ellison syndrome, 3 with MEN-I syndrome), tumours were identified by octreotide scintigraphy in four patients (3 ZES, 1 MEN-I), which were confirmed by MR imaging in 3 patients (2 ZES, 1 MEN-I), and by CT in one patient with ZES. One patient with a long history of Zollinger-Ellison syndrome showed an abnormal increased octreotide uptake in the region of the head of the pancreas. This lesion was confirmed by MR imaging and CT scanning, and later a gastrinoma was proven at surgery (Figure 2). In another 45-year-old patient with MEN-I syndrome, two primary tumours were found at surgery, one pancreatic, the other duodenal. Octreotide scintigraphy identified one tumour in the tail of the pancreas in a number of small lesions in the liver and multiple para-aortic lymph nodes. In another two patients with ZES, one patient had evidence of a tumour deposit in the tail of the pancreas on Octreoscan and the tumour was consequently confirmed at surgery; the other patient who had an abnormal liver deposit had two biopsy-confirmed hepatic deposits from a gastrinoma, but the primary tumour was not visualized. In the remaining seven patients, who all had significant clinical signs and strong biochemical characteristics, no primary or metastatic lesions were found using any of these three imaging procedures.

Lesions

Altogether 42 tumour lesions were detected by CT and MR imaging. The distribution of these lesions included liver ($n=17$) (multiple metastatic lesions in the liver were counted as one lesion), abdominal/mediastinal lymph node ($n=6$) (more than five sites were counted as five lesions, less than five sites were counted as one lesion), lung ($n=2$), bone ($n=10$), and pancreas ($n=7$). Of the 42 localizations, 37 were also identified by [^{111}In]-octreotide scintigraphy. The five false-negative studies on Octreoscan were observed where the lesions occurred in liver ($n=3$), mediastinum ($n=1$) and bone ($n=1$), they were from one carcinoid, one insulinoma and three MCTs.



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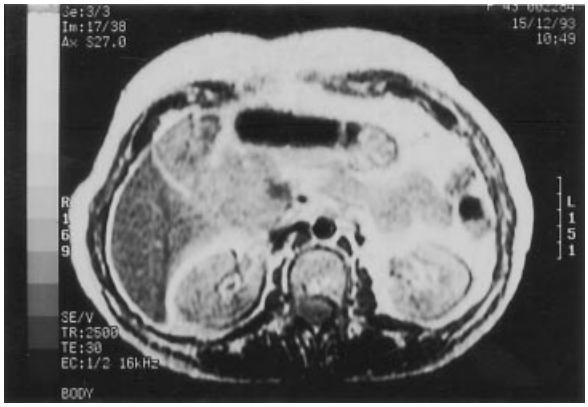

b

Figure 2. a ^{111}In-octreotide planar anterior scintigram of the abdomen in a 43-year-old woman with long history of Zollinger-Ellison syndrome, showing an abnormal uptake in the head of the pancreas. **b** MR imaging demonstrating that a lesion lay in the head of the pancreas; a gastrinoma was consequently confirmed by surgery.

However, more widespread disease: (4 liver lesions, 34 abdominal/mediastinal/peripheral lymph nodes, and 3 pancreatic sites) which was not suspected or identified by conventional imaging was recognized by scintigraphy. Overall, the detection rate of octreotide scintigraphy was 91% of the liver lesions, 98% of lymph nodes, 100% of the lung, 89% of the pancreas and 30% of bone. The detection rate of [^{111}In]-octreotide scintigraphy, MR imaging and CT scanning in localization of primary and metastatic diseases in NET patients is summarized in Table 2. The overall sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of Octreoscan were determined for each tumour type on the basis of the histological proof in Table 3. However, the three patients with MCT were not

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Table 2 Comparison of the detection rate of various imaging procedures for localisation of primary and metastatic lesions

Tumour site	Number of lesions (MRI + CT + SRI)	Detection rate (%)		
		MRI	CT	SRI
Liver	21	12/15* (80)	17/21 (81)	19/21 (91)
Abdominal/Mediastinal lymph node	40	1/34* (3)	6/40 (15)	39/40 (98)
Lung	3	ND	2/3 (67)	3/3 (100)
Bone	10	10/10 (100)	2/3 (67)	3/10 (30)
Pancreas	9	6/9 (67)	6/9 (67)	8/9 (89)
Total	83	29/68 (43)	33/76 (44)	72/83 (87)

SRI, somatostatin receptor scintigraphy; MRI, magnetic resonance imaging; CT, computed tomography; ND, not detected. * Number of lesions for which MRI was performed.

Table 3 Results of MRI, CT and SRI in patients with a variety of NETs

Type of tumours	No. of patients (with pathology)	Detection rate (%)			SRI			
		MRI	CT	SRI	Sensitivity	Specificity	PPV	NPV
Carcinoid	25 (24)	13/16* (81%)	19/25 (76%)	23/25 (92%)	95%	100%	84.6%	50%
Gastrinoma	3 (3)	2/2* (100%)	2/3 (67%)	3/3 (100%)	100%	100%	100%	100%
Insulinoma	2 (2)	0/1* (0)	2/2 (100%)	1/2 (50%)	66.7%	ND	100%	ND
VIPoma	1 (1)	1/1 (100%)	1/1 (100%)	1/1 (100%)	100%	ND	100%	ND
Undetermined	3 (3)	0/3 (0)	1/2* (50%)	3/3 (100%)	100%	0	66.7%	ND
MCT	3 (3)	2/3 (67%)	3/3 (100%)	0/3 (0)	ND	ND	ND	ND
MEN-I	3 (1)	1/3 (33%)	0/3 (0)	1/3 (33%)	50%	0	50%	0
ZES	8 (3)	2/7* (29%)	1/7* (14%)	3/8 (38%)	75%	0	75%	0

SRI, somatostatin receptor scintigraphy; MRI, magnetic resonance imaging; CT, computed tomography; ND, not determined; PPV, positive predictive value; NPV, negative predictive value. * Number of patients who had MRI or CT performed.

included in the calculations, because of the false-negative Octreoscan studies.

There was no significant correlation between age and positive octreotide scintigraphy in our patients. In the group of patients aged <60 years, 19/25 (76.0%) patients had positive scintigraphy; while in those over 60 years, 16/23 (69.9%) had positive scintigrams ($p>0.05$). Long-term somatostatin analogues treatment did not appear to influence the outcome of the scintigram in our 12 patients who had taken this therapy.

Discussion

Somatostatin receptor scintigraphy has been shown to be useful in identifying primary tumours and distant metastases in most patients with NETs. [^{111}In]-octreotide scintigraphy was highly sensitive and specific for somatostatin-receptor positive tumours, especially in comparison with CT and MR scanning. In our series, the sensitivity of octreotide scintigraphy for detecting carcinoid was 95%, and that for PET was 90.6%. This is therefore comparable to the 85% to 95% sensitivity reported in the literature.[12–14] In the total of 83 tumour lesions, 33 (44%) were demonstrated by CT scanning, 29 (43%) by MR imaging, and 72 (87%) by [^{111}In]-octreotide scintigraphy. This demonstrated the variable detection rate previously reported by Zimmer *et al.*,[30] in which metastatic upper gastrointestinal tract neuroendocrine tumour sites were detected with octreotide scintigraphy (52%), with MR imaging (24%) and with CT scanning (36%); and by Carnaille *et al.*,[15] in which 72% of carcinoid tumour sites were identified by Octreoscan. For the former, the lower detection rate is probably because only tumours of the foregut type were studied, and the tumours were relatively small.[30]

The great advantage of octreotide scintigraphy is that it can cover all body regions. Conventional imaging using CT or MRI will normally only examine areas of high clinical suspicion (e.g. thorax, upper abdomen, etc.). In a review, Lambert *et al.*[13] described a group of 39 patients with gastroenteropancreatic neuroendocrine tumours in which 37 primary tumours and previously unknown metastases (95%) were detected by octreotide scintigraphy. In our 37 histologically-verified NETs, 50% of patients

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had previously unexpected lesions detected (40 previously unrecognized liver, mediastinal and extra-abdominal lymph-node metastases being found). In this particular group, all two pancreatic, four liver lesions and 11 lymph-node metastases were confirmed, either by subsequent surgery or by biopsy. The remaining lesions will be followed-up by Octreoscan or by conventional imaging methods. However, in contrast to MR imaging, the detection rate of Octreoscan in carcinoid bony metastases was low in our series (30%).

The precondition for the accumulation of somatostatin analogues in the scintigram is the presence of somatostatin receptors on the tumour cells. Using a receptor binding assay and *in vitro* autoradiography, saturable and high-affinity somatostatin receptors have been identified on most human tumours, especially on neuroendocrine tumours.[16,17] In a group of 62 carcinoid patients, 54 tumours (87%) were shown to contain somatostatin receptors.[18] A strong correlation between the presence of high numbers of high-affinity somatostatin analogue-binding sites on the tumour tissue with both the inhibitory effects of somatostatin analogue, Sandostatin on hormone secretion, and somatostatin receptor scintigraphy has also been demonstrated.[13,18] Moreover, most carcinoids, gastrinomas and VIPomas have shown evidence of a high diagnostic success rate in somatostatin receptor scintigraphy.[19,20] A similar detection rate was found in our group of carcinoids and PETs, only one metastatic carcinoid and one insulinoma not being detected on scintigraphy. Insulinomas were reported to express somatostatin receptors at a rate of 72% *in vitro*,[21] but only 46% of insulinoma could be recognized on [^{111}In]-octreotide scintigraphy.[22] Our results from two insulinoma patients are consistent with these observations. Medullary carcinoma of thyroid is known to bear somatostatin receptors at a relatively low level compared with other NETs. [21]In our study, all three MCTs were false-negative on scintigraphy. This may be explained by somatostatin receptor negativity in the tumour tissues, or because of heterogeneity and low receptor density. Recently, five somatostatin receptor subtypes (SSTR1–5) have been cloned and characterized.[23] Since then, different functional properties for various SSTRs have provided a pharmacological basis for their binding specificity on target tissues. Specific binding to SSTR2 correlates with positive [^{111}In]-octreotide scintigraphy.[24] Therefore, the false-negative phenomenon for MCT may be explained by the lack of SSTR2 on their tumour cells. Our results suggest that tumour uptake of radiolabelled somatostatin analogues is dependent on their somatostatin receptor type and functional state rather than the location and size of the tumours.

Apart from above 37 histologically-proven NETs, 11 ZES and MEN-I patients were also involved in this study. MEN-I is characterized by the familial association of parathyroid, pancreatic islet, and pituitary hyperplasia or neoplasia.[25] Parathyroid tumour and pancreatic islet-cell tumours are important features of MEN-I.[26,27] Approximately 60% of islet-cell tumours in MEN-I patients secrete gastrin, resulting in the ZES which has been reported to be the cause of morbidity and mortality in this group of patients.[28] Optimum therapy for MEN-I and ZES is the resection of the primary tumour, and the control of the symptoms due to hormone overproduction. Therefore, early identification and assessment of the extent of tumour is becoming increasingly important. In the present study, the detection rate of patients with Octreoscan was 36.4%, that with MRI was 27%, and that for CT was as low as 9%. Although we found that octreotide scintigraphy is superior to MRI and CT in the detection of clinically-suspected tumours, the results are less sensitive than previously reported,[29] when 39/48 (81%) patients with ZES showed abnormal tracer uptake on the scintigraphy. This could be explained by the small size of the tumours we investigated, as well as by the receptor types contained. More recently, endoscopic ultrasonography has been claimed as the most sensitive imaging method to localize difficult PETs, with a sensitivity of 79% for gastrinomas and 93% for insulinomas,[10] but the method is still limited, as it does not localize extra pancreas and extrahepatic lesions. As a non-invasive, functional imaging technique, [^{111}In]-octreotide scintigraphy can play a useful screening role in patients with MEN-I and ZES.

[^{111}In]-octreotide scintigraphy is becoming increasingly available, and our results help to define the potential role of this scintigraphy in detecting carcinoids, pancreatic endocrine tumours, and medullary thyroid tumours, as well as tumours in MEN-I and ZES patients. [^{111}In]-octreotide scintigraphy has a higher sensitivity for tumour detection, and it is superior to MR imaging and CT scanning in identification of previously unsuspected extrahepatic and lymph-node metastases. For the localization of clinically-suspected tumours in patients with MEN-I and ZES, [^{111}In]-octreotide scintigraphy may be the primary choice of imaging techniques, although the cost of Octreoscan is high.

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References

1. Solcia E, Capella C, Fiocca R, Cornaggia M, Bosi F. The gastroenteropancreatic endocrine system and related tumours. *Gastroenterol Clin North Am* 1989; **18**:671–93.

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2. Reinig JW, Dwyer AJ, Miller DL, White M, Frank JA, Sugarbaker PH, Chang AE, Doppman JL. Liver metastasis detection: comparative sensitivities of MR imaging and CT scanning. *Radiology* 1987; **162**:43–7.
3. Chezmar JL, Nelson RC, Small WC, Bernardino ME. Magntic resonance imaging of the pancreas with gadolinium-DTPA. *Gastrointest Radiol* 1991; **16**:139–42.
4. Wank SA, Doppman JL, Miller DL, Collen MJ, Maton PN, Vinayek R, Slaff JI, Norton JA, Gardner JD, Jensen RT. Prospective study of the ability of computed tomography to localize gastrinomas in patients with Zollinger-Eliison syndrome. *Gastroenterology* 1987; **92**:905–12.
5. Steiner E, Stark DD, Hahn PF, Saini S, Simeone JF, Mueller PR, Wittenberg J, Ferrucci JT. Imaging of pancreatic neoplasms: comparision of MR and CT. *Am J Roentgenol* 1989; **152**:487–91.
6. Semelke RC, Cumming MJ, Shoenut JP, Magro CM, Yaffe CS, Kroeker MA, Greenberg HM. Comparison of dynamic contrast-enhanced CT and MR imaging with dynamic Gadolinium enhancement and fat suppression. *Radiology* 1993; **186**:799–802.
7. Krenning EP, Kwekkeboom DJ, Reubi JC, Hahen PM, Eijck CHJ, Oei HY, Lambert SWJ. ^{111}In-octreotide scintigraphy in oncology. *Digestion* 1993; **54(suppl 1)**:84–7.
8. Scherubl Bader M, Fett U, Hamm B, Schmidt-Gayk H, Koppenhagen K, Dop FJ, Riechen EO, Wiedenmann B. Somatostatin-receptor imaging of neuroendocrine gastroenterohepatic tumours. *Gastroenterology* 1993; **105**:1705–9.
9. Bohuslavizki KH, Brenner W, Gunther M, Eberhardt J-U, Jahn N, Tinnemeyer S, Wolf H, Sippel C, Clausen M, Gatzemeier U, hense E. Somatostatin receptor scintigraphy in the staging of small cell lung cancer. *Nucl Med Commun* 1996; **17**:191–6.
10. Zimmer T, Stolzel U, Bader M, Koppenhagen K, Hamm B, Buhr H, Riecken EO, Wiedenmann B. Endoscopic ultrasonography and somatostatin receptor scintigraphy in the preoperative localisation of insulinomas and gastrinomas. *Gut* 1996; **39**:562–8.
11. Jamar F, Fiasse R, Norbert L, Pauwels S. Somatostatin receptor imaging with indium–111-pentetreotide in gastroenteropancreatic neuroendocrine tumours: safety, efficacy and impact on patient management. *J Nucl Med* 1995; **36**:542–9.
12. Kvols L, Brown M, O'Connor M, *et al*. Evaluation of radiolabeled somatostatin ananlogue (I–123 octreotide) in the detection and localization of carcinoid and islet tumours. *Radiology* 1993; **187**:129–33.
13. Lamberts SWJ, Reubi JC, Krenning EP. Validation of somatostatin receptor scintigraphy in the localization of neuroendocrine tumours. *Acta Oncol* 1993; **32**:167–70.
14. Kwekkeboom DJ, Krenning EP, Bakker WH, Oei HY, Kooij PPM, Lamberts SWJ. Somatostatin analogue scintigraphy in carcinoid tumours. *Eur J Nucl Med* 1993; **20**:283–92.
15. Carnaille B, Nocaudie M, Pattou F, Huglo D, Deveaux M, Marchandise X, Proye C. Scintiscans and carcinoid tumours. *Surgery* 1994; **116**:1118–22.
16. Moyse E, Le Dafniet M, Epelbaum J, Pagesy P, Peillon K, Kordon C, Enjalbert A. Somatostatin receptors in human growth hormone and prolactin-secreting pituitary adenomas. *J Clin Endocrinol and Metabol* 1985; **61**:98.
17. Reubi JC, Krenning E, Lamberts SWJ, Kvols L. In vitro detection of somatostatin receptors in human tumours. *Digestion* 1993; **54(suppl 1)**:76–83.
18. Reubi JC, Kvols LK, Nagorney DM, Heitz PU, Charboneau JW, Reading CC, Moertel C. Detection of somatostatin receptors in surgical and percutaneous needle biopsy samples of carcinoids and islet cell carcinomas. *Cancer Res* 1990; **50**:5969–77.
19. Hammond PJ, Arka A, Peters AM, Bloom SR, Gilbey SG. Localization of metastatic gastroenteropancreatic tumours by somatostatin receptors scintigraphy with [^{111}In-DTPA-D-Phe^1]-octreotide. *Q J Med* 1994; **87**:83–8.
20. Ramage JK, Williams R, Buxton-Thomas M. Imaging scecondary neuroendocrine tumours of the liver: comparison of I^{123} metaiodobenzylguanidine (MIBG) and I^{111}-labelled octreotide (Octreoscan). *Q J Med* 1996; **89**:539–42.
21. Reubi JC, Kvols L, Krenning E, Lamberts SWJ. *In vitro* and *In vivo* detection of somatostatin receptors in human malignant tissues. *Acta Oncologica* 1991; **30**:463–8.
22. Krenning EP, Kwekkeboom DJ, Pauwels S, Kvols LK, Reubi JC. Somatostatin receptor scintigraphy. *Nuclear Med Annual* 1995:1–50.
23. Raynor K, Murphy WA, Coy DH, Taylor JE, Moreau JP, Yasuda K, Bell GI, Reisine T. Cloned Somatiostation receptors: identification of subtype-selective peptides and demonstration of high affinity-binding of linear peptides. *Mol Pharmacol* 1993; **43**:838–44.
24. John M, Meyerhof W, Richter D, Waser B, Schaer JC, Scherübl H, *et al*. Positive soamtostatin receptor scintigraphy correlates with the presence of soamtostatin receptor subtype 2. *Gut* 1996; **38**:33–9.
25. Wermer P. Genetic aspects of adenomatosis of endocrine glands. *Am J Med* 1954; **16**:363–71.
26. Marx SJ, Spiegel AM, Levine MA, Rizzoli RE, Lasker RD, Santora AC, Downs RW Jr, Aurbach GD. Famial hypocalciuric hypercalciemia; the relation to primary parathyroid hyperplasia. *N Engl J Med* 1982; **307**:416–26.
27. Thakker RV, Ponder BAJ. Multiple endocrine neoplasia. In: Sheppard MC, ed. *Clinical Endocrinology and Metabolism*. London, Bailliere Tindall, 1988:1031–67.
28. Eberle F, Grun R. Multiple endocrine neoplasia, type 1 (MEN 1). *Ergebnisse der Innern medizin und Kinderheilkunde* 1981; **46**:76–149.
29. de Kerviler E, Cadiot G, Lebtahi R, Faraggi M, Leguludec D, Mignon M. Somatostatin receptor scintigraphy in forty-eight patients with the Zollinger-Ellison syndrome. *Eur J Nucl Med* 1994; **21**:1191–7.
30. Zimmer T, Ziegler K, Bader M, Fett U, Hamm B, Riecken E-O, Wiedenmann B. Localization of neuroendocrine tumours of the upper gastrointestinal tract. *Gut* 1994; **35**:471–5.

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