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Somatostatin analogue scintigraphy in carcinoid tumours

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Abstract. Scintigraphy with iodine-123 or indium-111 labelled somatostatin analogue (octreotide) was performed in 52 patients diagnosed as, suspected of, or at risk of having carcinoid tumours. In 32 of 37 (86%) patients in whom histologically proven carcinoids were still present, known tumour sites were visualized. Using ^{123}I-coupled octreotide, 24 of 40 (60%) known extrahepatic sites were visualized, whereas all of 12 (100%) extrahepatic lesions were visualized after injection of ^{111}In-coupled octreotide. Known liver metastases were not distinctly visualized with octreotide scintigraphy in 12 of 24 patients. In all but two of these cases, an even distribution of radioactivity in the liver was observed. This is most probably due to the fact that these liver metastases accumulated about as much radioactivity as does normal liver tissue. Previously unsuspected localizations or sites not recognized with other imaging techniques were found in 20 of the 37 patients. In 3 of 11 patients who were thought to have been surgically cured, and in 4 of 4 patients who were suspected of having carcinoids, octreotide scintigraphy showed abnormal accumulation of radioactivity. Histological or radiological evidence that additional sites noticed on octreotide scintigrams indeed represented tumour tissue was obtained in ten patients. Visualization of the carcinoids did not depend on the site of the tumour or on the presence or absence of hormonal hypersecretion, as measured by urinary 5-hydroxyindoleacetic acid and serum α-subunit concentrations. Apart from its use for tumour localization, octreotide scintigraphy, in consequence of its ability to demonstrate somatostatin receptor positive tumours, could be used to select those patients with the carcinoid syndrome who are likely to respond favourably to octreotide treatment.

Key words: Carcinoid – Octreotide scintigraphy – Somatostatin

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Introduction

Carcinoid tumours, which stem from enterochromaffin cells, may arise throughout the body, but occur most often in the gastrointestinal tract and in the lung [1]. The carcinoid syndrome, characterized by flushing, diarrhoea, right-sided heart disease and wheezing is usually associated with carcinoids of the small bowel that are metastatic to the liver.

High numbers of high-affinity somatostatin binding sites have been found on carcinoid tumours [2–4]. Chronic treatment with the somatostatin analogue octreotide (Sandostatin) causes relief of symptoms and a decrease in urinary 5-hydroxyindoleacetic acid (5-HIAA) levels in most patients with the carcinoid syndrome [5–8].

We recently described the in vivo visualization of carcinoids after injection of a somatostatin analogue coupled to iodine-123 [9, 10]. Subsequently, an easier technique of in vivo visualization of somatostatin receptors using a somatostatin analogue coupled to indium-111 was developed [11–13]. In this study, we report the results of scintigraphy with ^{123}I- or ^{111}In-labelled octreotide in 19 and 33 patients, respectively, who were suspected to have carcinoids. The results of octreotide scintigraphy are compared with the outcomes of other imaging techniques which were used in the diagnosis or follow-up of the patients.

Materials and methods

Patients. Fifty-two patients in whom ^{123}I- or ^{111}labelled octreotide scintigraphy was performed, were studied. Inclusion required either histological confirmation of a carcinoid tumour of a present or previously operated lesion, or a history of carcinoid syndrome-related signs and symptoms. In all patients, data on previous symptomatology and treatment had to be present. Histologically proven carcinoids were present in 37 patients, 11 patients had undergone seemingly radical surgery and four patients were suspected to have carcinoids. The results of [^{123}I-Tyr^3]-octreotide scintigraphy in 13 patients of this series have been previously described in brief [10]. All patients gave informed consent to participation in the study, which was approved by the ethics committee of our hospital.

Methods. The somatostatin analogues [Tyr^3]-octreotide (204-090) and [DTPA-D-Phe^1]-octreotide (215–811) were obtained from Sandoz, Basel, Switzerland. [Tyr^3]-octreotide was iodinated as described previously [14]. [DTPA-D-Phe^1]-octreotide was coupled to ^{111}In as described elsewhere [11].

The in vivo visualization of somatostatin receptor-positive tumours after injection of [^{123}I-Tyr^3]-octreotide has been described previously [9, 10, 15, 16]. Drawbacks of this in vivo receptor imaging technique are the scarce availability of chemically pure ^{123}I and the high abdominal background of radioactivity, caused by principal clearance of this analogue via the liver [12]. Therefore, an ^{111}In-labelled somatostatin analogue has been developed. This analogue is excreted mainly via the kidneys, 90% of the dose being present in the urine 24 h after injection. Because of its relatively long effective half-life, ^{111}In-octreotide is a radionuclide-coupled somatostatin analogue which can be used to visualize somatostatin receptor-bearing tumours efficiently after 24 and 48 h, when interfering background radioactivity is minimized by renal clearance [12, 13].

[^{123}I-Tyr^3]-octreotide (248–555 MBq) was injected in 19 patients, and [^{111}In-DTPA-D-Phe^1]-octreotide (248–360 MBq) was injected in 33 patients. Planar images were obtained with a large-field-of-view gamma camera (Counterbalance 3700 and ROTA II, Siemens Gammasonics, Erlangen, Germany) equipped with a 190-keV parallel-hole collimator when [^{123}I-Tyr^3]-octreotide was injected, and with a medium-energy collimator when [^{111}In-DTPA-D-Phe^1]-octreotide was injected. Static images were obtained 4 and 24 h after injection of the ^{123}I-coupled somatostatin analogue, and 24 and 48 h after injection of the ^{111}In-coupled somatostatin analogue, because the background radioactivity at those times is low. Preset counts for images obtained 4 h after injection of the ^{123}I-coupled somatostatin analogue or 24 h after injection of the ^{111}In-coupled somatostatin analogue were 300000 for the head and neck, and 500000 for the remainder of the body; preset time was 15 min for images obtained 24 h after injection of the ^{123}I-coupled somatostatin analogue or 48 h after injection of the ^{111}In-coupled somatostatin analogue [13].

To define the tumours as visualized during this scanning procedure, we used a simple yes-or-no system. In each patient, the two subsequent scans (i.e. 4 and 24 h after injection of the ^{123}I-coupled somatostatin analogue, and 24 and 48 h after injection of the ^{111}In-coupled somatostatin analogue) were compared. As a rule, and especially in the abdomen, accumulation of radioactivity at an abnormal site was considered to represent somatostatin receptor binding only if it was present on the scintigrams of both standard imaging time points. We discarded images obtained up to 20 min after injection of ^{123}I-coupled octreotide since it may be argued that hot spots observed at that time might be due to hypervascularization of the tumour. The scintigrams from all 52 patients were re-examined by two of us (EPK, HYO), without knowing the patient's identity, medical history, or outcomes of other investigations. If the interpretations differed, they were discussed until agreement was reached.

In order to compare the number of lesions demonstrated with conventional imaging techniques with those visualized during octreotide scintigraphy, the images were divided into parts easily recognizable on scintigrams, i.e. the head and neck, chest, upper abdomen, lower abdomen (division line: lower edges of the kidneys) and extremities.

The routine radiological examinations which were used in the diagnosis or follow-up of the patients (i.e. any combination of CT scan, ultrasonography, bone scan and chest X-ray) had been carried out in a number of hospitals. In most patients, however, CT scanning with a slice thickness of 12 mm had been performed.

In some patients, a technetium-99m microcolloid scan of the liver (185 MBq; Albu-Res, Solco, Birsfelden, Switzerland) was made after octreotide scintigraphy.

Urinary 5-HIAA was measured using a fluorimetric method. Serum α-subunit concentrations were measured by radioimmunoassay using antibodies purchased from UCB (Brussels, Belgium). The sensitivity of the α-subunit assay was 0.3 μg/l and the intra- and interassay coefficients of variation were <6% and <11%, respectively [17].

Results

Between June 1988 and December 1990 octreotide scintigraphy was performed in 52 patients diagnosed as, suspected of, or at risk of having carcinoid tumours. At physical examination, 19 had hepatomegaly and two had right-sided heart valve insufficiency. The patients' symptomatology and past treatment are listed in Table 1. At the time of scanning, two patients used serotonin antagonists, three were being treated with octreotide (100, 200 and 400 μg daily, respectively) and two were receiving interferon-α. Octreotide therapy was discontinued at least 1 day before the injection of labelled octreotide and was resumed after the images had been made.

Histologically proven carcinoid tumours were present in 33 patients, whereas in four patients the removal of the tumour or its metastases was known to be incomplete peroperatively (Tables 1–3). In 11 patients (patients 18, 19 and 40–48) a seemingly complete removal of the tumour had been achieved (Tables 2, 3). Patients 49–52 were suspected to have carcinoids because of flush-like

Table 1. Clinical features and medical history of 52 patients

Patient	Sex	Age	Supposed primary tumour site	Site of previous surgery	Other therapy[b]	Flushes	Diarrhoea	5-HIAA (μmol/day	α-Subunit (μg/l)
1	M	53	Small intestine	Liver, peritoneum[a]	Octr, RT, IF	No	Yes	272[c]	0.7
2	F	64	Common bile duct	Common bile duct[a]	None	No	No	13	2.7
3	F	62	Unknown	None	^{131}I-MIBG	No	Yes	183[c]	–
4	M	75	Unknown	None	Octr	Yes	Yes	2045[c]	–
5	M	38	Unknown	None	^{131}I-MIBG, IF	Yes	Yes	110[c]	0.9
6	M	23	Unknown	None	Chemo	Yes	Yes	952[c]	–
7	F	50	Small intestine	Small intestine[a]	Chemo, ^{131}I-MIBG, Octr	Yes	Yes	1255[c]	–

Table 1. (continued)

Patient	Sex	Age	Supposed primary tumour site	Site of previous surgery	Other therapy[b]	Flushes	Diarrhoea	5-HIAA (μmol/day)	α-Subunit (μg/l)
8	M	75	Unknown	None	None	Yes	Yes	1274[c]	–
9	M	67	Small intestine	None	Octr	Yes	No	42	–
10	F	51	Unknown	None	None	No	No	111[c]	–
11	M	65	Unknown	None	None	No	Yes	206[c]	–
12	M	69	Stomach	Stomach	None	No	No	39	–
13	M	77	Small intestine	Small intestine, sigmoid[a]	None	Yes	No	1054[c]	–
14	M	65	Small intestine	Small intestine	None	No	No	–	0.8
15	M	24	Unknown	None	RT, Chemo	No	No	162[c]	12.0[c]
16	F	56	Unknown	None	Octr, Chemo, IF	No	No	482[c]	4.3[c]
17	M	65	Lung	None	None	No	No	45	–
18	F	43	Lung	Lung	None	Yes	No	23	–
19	M	19	Appendix	Appendix	None	No	Yes	28	–
20	M	64	Middle ear	Middle ear[a]	None	No	No	260[c]	1.3[c]
21	F	72	Lung	None	None	No	No	13	1.6
22	M	67	Lung	None	None	No	No	–	0.7
23	F	55	Stomach	None	None	Yes	No	–	4.3[c]
24	M	51	Duodenum	Duodenum: papillotomy[a]	None	No	No	–	5.0[c]
25	M	57	Unknown	Explorative laparotomy	Octr, IF	No	Yes	97[c]	0.8
26	M	60	Unknown	Humerus[a]	None	No	No	120[c]	1.0
27	F	74	Small intestine	Small intestine[a]	None	Yes	Yes	156[c]	1.6
28	F	55	Gall-bladder	Gall-bladder, colon[a]	Chemo	No	Yes	–	2.7
29	M	63	Lung	Lung	None	Yes	Yes	257[c]	66.5[c]
30	M	70	Unknown	None	None	No	No	48	0.9
31	M	61	Lung	Lung	None	No	Yes	151[c]	180.0[c]
32	F	69	Unknown	None	None	No	No	702[c]	2.8
33	M	74	Unknown	None	None	No	Yes	624[c]	1.1
34	F	64	Small intestine	None	IF	No	Yes	136[c]	1.6
35	M	71	Small intestine	Small intestine[a]	None	Yes	No	205[c]	2.3[c]
36	M	69	Lung	Lung[a]	None	Yes	No	111[c]	3.7[c]
37	M	74	Unknown	None	Octr	Yes	No	92[c]	2.9[c]
38	M	58	Duodenum	Duodenum, pancreas[a]	None	No	No	16	1.1
39	F	46	Appendix	Appendix, ovary[a]	None	No	No	[d]	1.3
40	M	68	Rectum	Rectum	None	No	No	20	1.4[c]
41	F	69	Small intestine	Small intestine, inguinal canal	None	No	No	16	1.7
42	F	61	Small intestine	Small intestine	None	No	No	40	2.8
43	F	48	Lung	Lung	None	No	No	22	–
44	F	16	Pancreas	Pancreas	None	No	No	16	0.6
45	F	81	Small intestine	Small intestine	None	No	No	3	0.5
46	F	68	Ovary	Ovary	None	No	No	–	3.6
47	F	47	Caecum	Appendix, caecum	None	No	No	–	0.6
48	M	60	Rectum	Rectum	None	No	No	16	1.1
49	M	48	Unknown	None	None	Yes	Yes	44	0.8
50	M	55	Unknown	None	None	No	No	35	0.9
51	M	71	Unknown	None	None	No	No	60[c]	1.6[c]
52	M	61	Unknown	None	None	Yes	No	36	0.7

Octr, Octreotide therapy; RT, radiotherapy; IF, interferon therapy; ^{131}I-MIBG, iodine-131 metaiodobenzylguanidine; Chemo, chemotherapy; –, not measured

[a] Operation known to be incomplete peroperatively

[b] Non-surgical therapy has been listed chronologically

[c] Abnormal value. Normal values: 5-HIAA: <50 μmol/day; α-subunit: men 0.4–1.1 μg/l, premenopausal women 0.3–2.3 μg/l, postmenopausal women 1.3–4.0 μg/l

[d] Value reported within the normal range

Table 2. Results of conventional imaging and ^{123}I-labelled octreotide scintigraphy in 19 patients

Patient	Conventional imaging	Visualization of supposed tumour sites[a,b]	
		Conventional imaging	Octreotide scintigraphy
1	CT (thorax, abdomen, spine), bone scan, chest X-ray	Lungs (m)[c], thoracic spine (m), ribs (m)	Thorax (m)[c]
2	CT/US (abdomen), chest X-ray	Common bile duct[c]	Upper abdomen (1)[c], *lower abdomen (3)*
3	CT/US (thorax, abdomen), chest X-ray	Retroperitoneal lymph nodes[c]	Upper abdomen (1)[c], *supraclavicular left (1)*
4	CT/US (thorax, abdomen), chest X-ray	Liver (m)[c],	Liver (m)[c] *supraclavicular left (2), upper abdomen (1)*[c]
5	CT/US (abdomen)	Liver (m)[c]	Liver (m)[c]
6	CT (skull base), US (upper abdomen) bone scan, chest X-ray	Cervical spine (1), liver (m)[c]	Neck (1), liver (m)[c]
7	CT/US (thorax, abdomen), chest X-ray	Supraclavicular left lymph node (1), para-aortic lymph nodes, liver (m)[c]	Supraclavicular left (1), upper abdomen (1), liver (m)[c]
8	CT/US (neck, thorax, abdomen) chest X-ray	Liver (m)[c], ileum (1, equivocal), *para-aortic and mesenteric lymph nodes*	Liver (m)[c], *lower abdomen (1), neck (2), supraclavicular left (1), axilla (1)*
9	CT/US (thorax, abdomen), chest X-ray	Supraclavicular left lymph nodes, mediastinum and pleura (m), para-aortic lymph nodes, *liver (1)*[c]	Supraclavicular left (1), thorax (m), upper abdomen (1)
10	CT (abdomen), chest X-ray	Colon and caecum (3), ileum (2 equivocal lesions), *liver (m)*[c]	Lower abdomen (3)
11	US (upper abdomen), chest X-ray	Lung (1)[c], *liver (2)*	Thorax (1)[c], liver (1)
12	US (abdomen)	Stomach (1)[c], abdominal wall (1)[c] *liver (m)*	Upper abdomen (1)[c], lower abdomen (m)[c]
13	CT/US (skull, abdomen)	Lower abdomen (2), *liver (m)*	Lower abdomen (2)
14	CT (abdomen)	*Liver (1)*[c]	None
15	CT (abdomen), bone scan, X-ray (skull, chest, spine)	*Spine (m), ribs (m), liver (m)*[c]	None
16	CT/US (abdomen), chest X-ray	*Lung (1), hilum of lung (1), liver (m)*[c], *lower abdomen (1)*	Cold spots, liver
17	CT (thorax, abdomen), chest X-ray	*Lung (1)*[c]	None
18	CT/US (thorax, abdomen), chest X-ray, bone scan	None	None
19	US (upper abdomen)	None	None

CT, CT scan; US, ultrasonography

[a] The number of lesions visualised is cited within parentheses when 4 or less. m: 5 or more lesions

[b] Italics: sites not recognized with imaging technique(s) applied in the other column

[c] Histologically proven tumour

Table 3. Results of conventional imaging and ^{111}In-labelled octreotide scintigraphy in 33 patients

Patient	Conventional imaging	Visualization of supposed tumour sites[a,b]	
		Conventional imaging	Octreotide scintigraphy
20	CT (head), US (upper abdomen), chest X-ray	Middle ear (1)[c]	Head (1)[c]
21	CT (thorax, abdomen), chest X-ray	Hilum of lung (1)[c], mediastinum (1)[c]	Thorax (2)[c]
22	CT/US (thorax, abdomen), chest X-ray	Lung (1)[c]	Thorax (1)[c]
23	CT/US (upper abdomen), chest-X-ray	None (gastroscopy: 4 polypoid tumours[c])	*Upper abdomen (1)*[c]
24	CT/US (upper abdomen), chest X-ray	Duodenum (1)[c]	Upper abdomen (1)[c], *liver (m)*
25	CT/US (abdomen), chest X-ray	Retroperitoneal lymph nodes[c], small bowel (swollen walls)	Upper abdomen (1)[c], lower abdomen (1), *supraclavicular left (1), thorax (1)*
26	CT/US (abdomen), bone scan, chest X-ray	Left humerus[c]	Left arm[c]/scapula (1), *lower abdomen (1)*
27	CT (abdomen), chest X-ray	Retroperitoneal lymph nodes[c]	Upper abdomen (1)[c], *Supraclavicular left (1), thorax (2)*
28	CT/US (abdomen), chest X-ray	Upper abdomen (1, equivocal)	*Upper abdomen (1)*
29	CT/US (thorax/abdomen), chest X-ray	Hilum of lung (1), liver (m)[c]	*Thorax (2)*, liver (m)[c]
30	CT/US (abdomen), chest X-ray	Liver (m)[c]	Liver (m)[c], *lower abdomen (2)*
31	CT (head), US (abdomen), bone scan	Liver (m)[c]	Liver (m)[c], *lower abdomen (1)*
32	US (upper abdomen), chest X-ray	Liver (2)[c]	*Liver (m)*[c], *upper abdomen (1), lower abdomen (3)*
33	CT/US (abdomen), chest X-ray	Liver (2)[c]	Liver (1)[c], upper abdomen or liver (1), *thorax (3), lower abdomen (2)*
34	CT/US (abdomen), chest X-ray	*Liver (m)*[c]	Liver (3)[c], *submandibular (1), thorax (2), lower abdomen (1)*
35	CT/US (abdomen), chest X-ray	Gallbladder (1), *Liver (1)*	Gallbladder (1), *lower abdomen (4)**
36	CT/US (abdomen), chest X-ray	*Liver (m)*[c]	*Upper abdomen (1), lower abdomen (1)*
37	CT (abdomen), chest X-ray	*Liver (4)*[c]	*Lower abdomen (1)*[c]
38	US (upper abdomen)	*Liver (m)*	*Upper abdomen (1)*
39	CT/US (abdomen)	*Liver (m)*	Cold spots, liver
40	CT/US (thorax, abdomen), chest X-ray	Retroperitoneal lymph node (1)	*Thorax (1), upper abdomen (3)*
41	CT/US (abdomen)	Ascending colon or lymph node (1)	Upper abdomen (1)
42	US (upper abdomen)	None	*Upper abdomen (1)*
43	US (abdomen), chest X-ray	None	None
44	CT/US (abdomen)	None	None
45	CT/US (abdomen), chest X-ray	None	None

Table 3. (continued)

Patient	Conventional imaging	Visualization of supposed tumour sites[a,b]	
		Conventional imaging	Octreotide scintigraphy
46	US (abdomen), chest X-ray	None	None
47	US (abdomen)	None	None
48	CT/US (thorax, abdomen), chest X-ray	None	None
49	CT/US (abdomen), chest X-ray	Upper abdomen (1)	Upper abdomen (1)
50	CT (upper abdomen)	Duodenal diverticulum	Upper abdomen (1)
51	CT/US (abdomen), chest X-ray	Caecum (1)	Lower abdomen (1)
52	CT (abdomen)	None	*Upper abdomen (1)*

CT, CT scan; US, ultrasonography

[a] The number of lesions visualized is cited within parentheses when 4 or less. m: 5 or more lesions

[b] Italics: sites not recognized with imaging technique(s) applied in the other column

[c] Histologically proven tumour

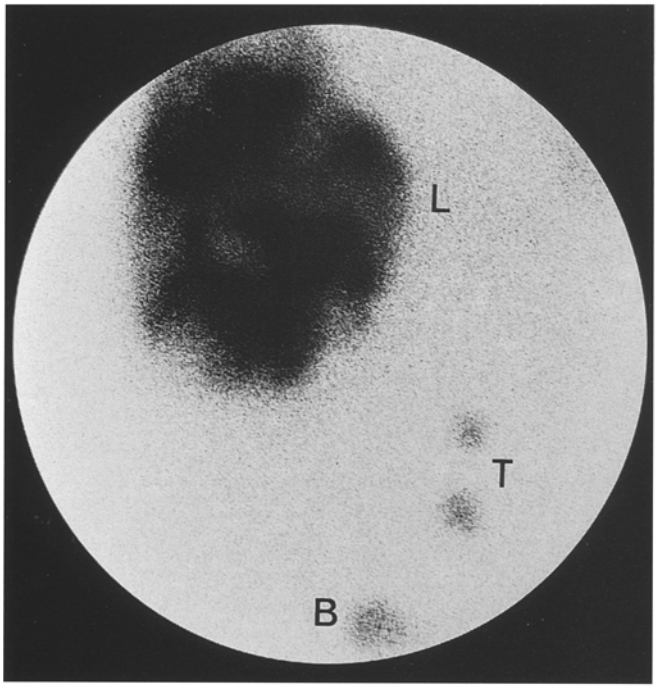

Fig. 1. Scintigraphy of the anterior abdomen in patient 30, 48 h after injection of ^{111}In-labelled octreotide. *L*, Liver; *T*, supposed tumour sites; *B*, urinary bladder

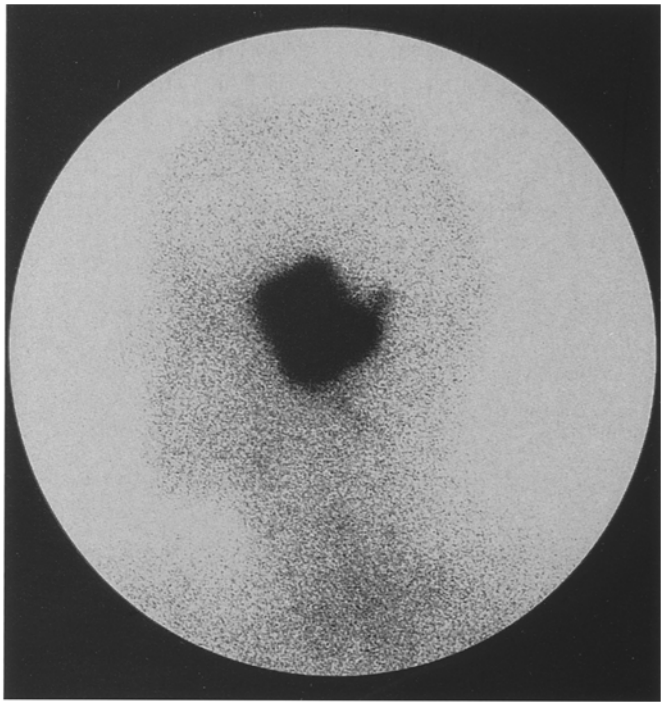

Fig. 2. Left lateral image of the head of patient 20, 48 h after injection of ^{111}In-labelled octreotide

attacks accompanied by elevated urinary 5-HIAA levels; in these four patients no histological proof of a carcinoid tumour had been obtained.

^{123}I-labelled octreotide or ^{111}In-labelled octreotide was injected in 19 and 33 patients, respectively. Accumulation of radioactivity at supposed tumour sites was found in 39 patients (Tables 2, 3). Figure 1 shows irregular distribution of radioactivity in the liver and two spots of radioactive accumulation in patient 30, 48 h after injection of ^{111}In-labelled octreotide. The uptake of labelled octreotide in a rare case of a carcinoid of the middle ear (in patient 20) is shown in Fig. 2. Tumour sites in the liver and abdomen in patient 33 are presented in Fig. 3.

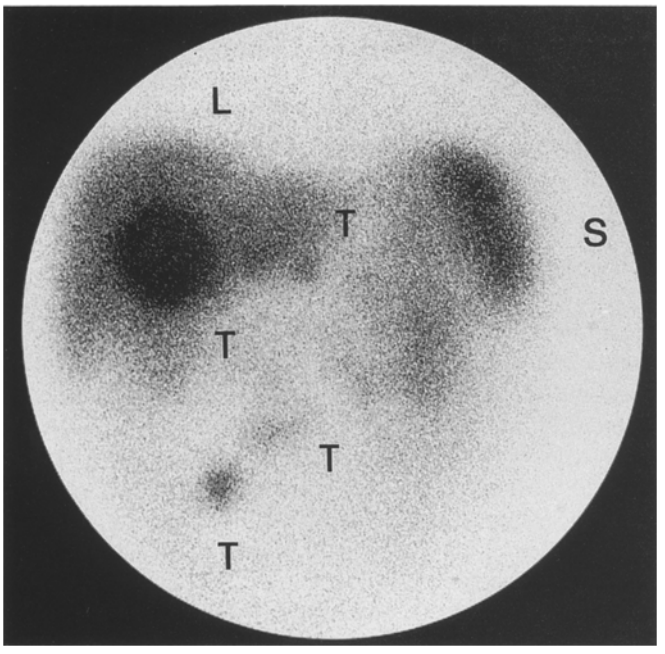

Fig. 3. Anterior image of the abdomen of patient 33, 48 h after injection of ^{111}In-labelled octreotide. *L*, Liver; *S*, spleen; *T*, supposed tumour sites – the top one just in or below the left liver lobe, one in the right liver lobe and two at lower abdominal localizations

Patients with proven carcinoids

Counting liver metastases and also lymph node groups as one lesion, and more than five lesions in one part of the body as five lesions, 52 extrahepatic and 24 hepatic sites were visualized with conventional imaging techniques in the 37 patients who either had histologically proven tumours present or in whom not all tumour had been removed during surgery. Nineteen of 27 (70%) localizations in the head, neck and thorax, and 17 of 25 (68%) extrahepatic abdominal localizations were visualized. Twenty-four of 40 (60%) known extrahepatic lesions were visualized in patients in whom ^{123}I-coupled octreotide was injected, and 12 of 12 (100%) known extrahepatic lesions were visualized in patients in whom ^{111}In-coupled octreotide was injected ($P<0.01$, Fisher's exact test). The 16 known extrahepatic lesions that were not visualized after injection of ^{123}I-coupled octreotide were present in four patients (patients 8, 15, 16 and 17, Table 2). Patients 15 and 16 had been treated with chemotherapy and radiotherapy, and chemotherapy and interferon, respectively, within the 12 months preceding octreotide scintigraphy. However, such treatment within a year before somatostatin receptor imaging had also been given in patients 1, 5, 25 and 34, in whom known lesions did accumulate labelled octreotide.

Accumulation of radioactivity at previously unsuspected localizations or sites not recognized with other imaging techniques was found in 4 of 17 patients (12 sites) in whom ^{123}I-coupled octreotide was injected, and in 16 of 20 patients (36 sites) in whom ^{111}In-coupled octreotide was injected.

Octreotide scintigraphy revealed presumed tumour spots in 22 of 24 patients with elevated urinary 5-HIAA, and in seven of eight patients with normal urinary 5-HIAA. In addition, octreotide imaging was positive in eight of ten patients with elevated serum α-subunit, and in 15 of 16 patients with normal serum α-subunit ($P>0.05$ for both markers; Fisher's exact test) (Tables 1–3).

In 12 of 24 patients who had liver metastases, no liver hot spots were detected using octreotide scintigraphy, whereas CT scanning and/or ultrasonography clearly demonstrated hypodensities (Tables 2, 3). The diameter of the liver metastases in these patients varied from 1 to 5 cm, whereas it ranged from 1 to 8 cm in those in whom liver hot spots were seen. In two of these patients (patients 16 and 39), cold spots were seen during octreotide scintigraphy. A comparison between octreotide scintigraphy and ^{99m}Tc-colloid scintigraphy of the liver in patient 13 (Fig. 4) reveals that the liver metastases, visible as cold spots on the colloid scintigram, accumulated ^{123}I-labelled octreotide, although to a lesser degree than the physiological accumulation in normal liver tissue.

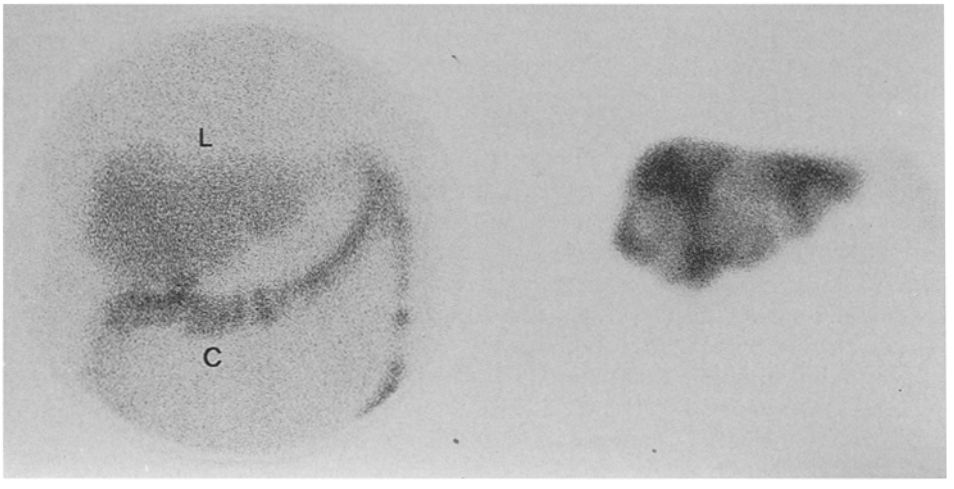

Fig. 4. Anterior image of the abdomen, 24 h after injection of [^{123}I-Tyr^3]-octreotide (*left panel*) and ^{99m}Tc-colloid scintigraphy of the liver (*right panel*) in patient 13. *L*, Liver; *C*, colon. Note that the cold spots on the *right panel* take up labelled octreotide (*left panel*)

Surgically "cured" patients

In 3 out of 11 patients who were thought to be surgically cured, octreotide scintigraphy showed abnormal accumulation of radioactivity. In patient 40, subsequent CT scanning of the abdomen demonstrated a retroperitoneal lymph node with a diameter of 1 cm in the upper abdomen; contrast-enhanced thin-slice CT scanning of the thorax, however, revealed no abnormalities which could explain the clearly visible accumulation of radioactivity in the lower left lung during octreotide scintigraphy. In patient 41, a CT scan performed 5 months after octreotide scintigraphy, because of the abdominal hot spot seen during the latter investigation, showed a hypodensity with a diameter of 1.5 cm near or in the ascending colon. In patient 42, no follow-up imaging was available.

Patients suspected of having carcinoids

In all four patients who were suspected to have carcinoids, an abnormal accumulation of radioactivity in the abdomen was observed during octreotide scintigraphy. In patient 49, CT scanning demonstrated a lesion with a diameter of 2 cm ventromedial to the right kidney. Repeated octreotide scintigraphy, 5 and 12 months after the initial imaging, demonstrated a persisting abnormal accumulation of radioactivity at the same site. In patient 50 the spot of radioactive accumulation during ^{111}In-octreotide scintigraphy coincided with a duodenal diverticulum according to CT scanning. In patient 51, CT scanning subsequent to octretoide scintigraphy revealed a hypodensity in the caecum; during colonoscopy, however, no abnormality was observed. In patient 52, no abnormalities were seen during CT scanning.

Confirmation of additional tumour localizations

In four patients in whom octreotide scintigraphy demonstrated more presumed abdominal tumour localizations than did conventional imaging techniques, histological confirmation for these additional sites was obtained afterwards. In patient 37, liver metastases, but also small tumour deposits in the ileum, were found during surgery. Autopsy performed 7 and 8 months after octreotide scintigraphy, respectively, revealed multiple tumour deposits in the abdomen in patient 2 and a tumour in the ileum in patient 4. In patient 23, histologically proven carcinoids of the stomach could be visualized with octreotide scintigraphy, but not with CT scan and ultrasonography. In two other patients (patients 27 and 32), localizations that were seen on octreotide scintigrams and were not detected with other imaging techniques performed at that time were much later confirmed by conventional imaging techniques. In patient 27, a chest X-ray performed 2 years after octreotide scintigraphy demonstrated a lesion in the left lung top, a site where octreotide scintigraphy had previously suggested tumour deposit. In patient 32, ultrasonography, performed 1 year after octreotide scintigraphy, demonstrated swollen walls in the sigmoid, whereas during somatostatin receptor imaging abnormal accumulation of radioactivity in the lower abdomen had been noticed.

Discussion

In contrast to bronchial carcinoids, small bowel carcinoids are often hard to localize by CT scanning [7]. Imaging of carcinoid tumours using ^{131}I-metaiodobenzylguanidine has a sensitivity of 40%–60% [18–20]. By contrast, ^{123}I- or ^{111}In-octreotide scintigraphy demonstrated presumed tumour sites in 32 of 37 patients (86%) with histologically proven carcinoid tumours present, whether localized in the lung or in the gastrointestinal tract. In five patients, no uptake of radiolabelled octreotide was observed at any of the tumour sites. In three of these patients, the tumours were localized in the chest. However, in six other patients carcinoid localizations in the lung did accumulate radioactivity. Apparently, the localization of the tumour is not a determining factor in the visualization of carcinoids with labelled octreotide.

Elevated serum α-subunit levels have been reported in patients with carcinoids [21, 22]. Also, in rectal carcinoids it has been shown that immunoreactivity for serotonin and α-subunit is present in the same cell [23]. In our series, the absence or presence of serotonin or α-subunit production by the tumour, as reflected in elevated urinary 5-HIAA or serum α-subunit concentrations, was not related to the outcome of octreotide scintigraphy, as carcinoids could be visualized both in patients with and in patients without elevated urinary 5-HIAA or serum α-subunit levels.

A significantly higher percentage of extrahepatic sites were visualized in patients in whom ^{111}In-octreotide was injected, as compared to those in whom ^{123}I-octreotide was injected. However, 13 of 16 extrahepatic lesions that were not visualized during ^{123}I-octreotide scintigraphy were present in two patients who had had recent radiotherapy and chemotherapy. Though carcinoid localizations were visualized in other patients who had also recently been treated in this way, it cannot be excluded that recent chemotherapy and radiotherapy influenced the somatostatin receptor status of the tumours in these two patients. In three patients who were treated with octreotide, this treatment was discontinued at least 1 day before injection of labelled octreotide. In all three patients, the carcinoids clearly accumulated radioactivity. This could mean either that discontinuation of octreotide therapy for 1 day is sufficient to make somatostatin receptors available for binding of labelled octreotide, or, alternatively, that not all somatostatin receptors are occupied during octreotide treatment.

In 12 of 24 patients who had liver metastases, the

metastases were not detected using octreotide scintigraphy, whereas CT scanning and/or ultrasonography clearly demonstrated hypodensities. Metastases visualized as cold spots in the normal distribution of radioactivity in the liver were present in only two patients. These metastases can therefore be regarded as truly somatostatin receptor negative. In the other ten patients, however, an even distribution of radioactivity in the liver was observed. As the diameter of the liver metastases in these patients did not differ from that observed in patients whose liver metastases were visualized, and as, moreover, other tumour sites in the same patients clearly accumulated labelled octreotide, it must be assumed that these liver metastases accumulated about as much radioactivity as does normal liver tissue. Single photon emission tomography studies might be useful in this respect, as an irregular distribution of radioactivity was observed in three of four patients in whom planar images showed an even uptake of liver radioactivity (data not shown).

Apart from the visualization of known lesions, previously unsuspected localizations or sites not recognized with other imaging techniques were found in 20 of 37 patients with proven carcinoids. Although the conventional imaging regime used was not the same in each patient, CT scanning with a slice distance of 12 mm of parts of the body in which octreotide scintigraphy suggested tumour deposits had been performed in 15 of 20 patients. In most patients the additional sites which were seen on octreotide scintigrams were localized in the abdomen. The finding of more abdominal tumour sites using octreotide scintigraphy is of special interest as the primary localization of intestinal carcinoids is often not detected with other imaging techniques [7]. In this respect, results obtained with the ^{111}In-labelled somatostatin analogue, demonstrating unsuspected abdominal spots in 12 of 20 patients, seeemed superior to those obtained with ^{123}I-labelled octreotide, which showed unsuspected abdominal sites in only 4 of 17 patients. Also, in two patients, extrahepatic abdominal tumour sites demonstrated with CT scanning or ultrasonography could not be visualized with ^{123}I-octreotide scintigraphy. This is probably because ^{123}I-octreotide is excreted into the bile, which causes a high background of radioactivity in the abdomen [14]. By contrast, ^{111}In-octreotide is excreted mainly via the kidneys, leaving the upper abdomen with less background radioactivity [12, 13].

The specificity of octreotide scintigraphy for carcinoids may be questioned, especially in those cases in which tumour deposits were suggested with octreotide scintigraphy, but could not be demonstrated with CT scanning. In one patient, the spot of radioactive accumulation during ^{111}In-octreotide scintigraphy coincided with a duodenal diverticulum on CT scanning, but it is not known whether carcinoid tissue was present in the diverticulum. However, in ten patients in whom octreotide scintigraphy suggested more tumour deposits than CT scanning, histological or radiological evidence was obtained that the sites of accumulation of radioactivity indeed represented tumour tissue.

Unfortunately, our series included only two patients with a carcinoid of the appendix. Recurrence of these tumours after appendectomy has been reported to depend on the size of the tumour. In a long-term study of 150 patients with carcinoid tumours of the appendix, Moertel et al. [24] found no metastases from tumours <2.0 cm in largest dimension, whereas metastases were observed from 3 of 14 lesions ≥ 2 cm and 4 of 9 lesions ≥ 3 cm. The authors conclude that right hemicolectomy seems justified in young patients with tumours ≥ 2 cm who have a low risk of operative morbidity or mortality. Octreotide scintigraphy in these patients might provide useful additional information.

Apart from its use for tumour localization, octreotide scintigraphy can also be used to differentiate those patients who have somatostatin receptor positive tumours from those who have somatostatin receptor negative ones. Treatment with octreotide may cause relief of symptoms and a decrease in urinary 5-HIAA levels in patients with the carcinoid syndrome [5–8]. In patients with the carcinoid syndrome, octreotide scintigraphy, in consequence of its ability to demonstrate somatostatin receptor positive tumours, could be used to select those patients who are likely to respond favourably to octreotide treatment.

In conclusion:

1. In the majority of patients with carcinoid tumours, these tumours could be visualized using octreotide scintigraphy.
2. Visualization of carcinoid tumours during octreotide scintigraphy did not depend on tumour site or presence or absence of hormonal hypersecretion.
3. Known liver metastases were not distinctly visualized with octreotide scintigraphy in half of the patients. This is most probably due to the fact that the liver metastases in these patients accumulated about as much radioactivity as does normal liver tissue.
4. ^{111}In-octreotide scintigraphy seemed superior to ^{123}I-octreotide scintigraphy in detecting extrahepatic carcinoid lesions.
5. Using octreotide scintigraphy, previously unsuspected localizations or sites not recognized with other imaging techniques were found in the majority of patients. In 10 of 27 patients, histological or radiological evidence was obtained that these additional sites indeed represented tumour tissue.
6. Apart from its use for tumour localization, octreotide scintigraphy, in consequence of its ability to demonstrate somatostatin receptor positive tumours, could be used to select those patients with the carcinoid syndrome who are likely to respond favourably to octreotide treatment.

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