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SOMATOSTATIN RECEPTOR SCINTIGRAPHY OF CARCINOID TUMOURS USING THE [^{111}In-DTPA-D-Phe^{1}]-OCTREOTIDE

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Somatostatin-receptor scintigraphy using the ^{111}In-labelled somatostatin-analogue octreotide ([^{111}In-DTPA-D-Phe^{1}]-octreotide) was performed in 40 patients with carcinoid tumours. In 31/40 patients, this scintigraphy proved positive compared with the 33/40 patients whose tumours were disclosed on CT scans. In addition, 18 previously unidentified lesions were detected with this scintigraphy. Two of these lesions represented previously undetectable primary tumours. It is concluded that somatostatin receptor scintigraphy using [^{111}In-DTPA-D-Phe^{1}]-octreotide has a future role in the staging of patients with carcinoid disease.

Somatostatin was first described in 1973 and has been shown to have endocrine and paracrine regulating functions (1, 2). Somatostatin receptors are expressed in large amounts on carcinoid tumour cells (3). The first initial attempt to treat patients with carcinoid-related symptoms with somatostatin was performed in 1978 (4). However, natural somatostatin has a very short half-life and a somatostatin analogue, octreotide, with a longer half-life, has been developed. Octreotide is currently used in the treatment of carcinoid-related symptoms as a single drug (5) or in combination (6). Radiolabelled octreotide, using the ^{123}I-Tyr^{3}-octreotide or the [^{111}In-DTPA-D-Phe^{1}]-octreotide, has shown good properties for the scintigraphic visualization of tumours expressing somatostatin receptors (7–11). The ^{123}I-Tyr^{3}-octreotide is excreted via the hepatobiliary system and is of limited value for detection of intra-abdominal lesions. The [^{111}In-DTPA-D-Phe^{1}]-octreotide is excreted via the kidneys, thus making it more suitable for the diagnosis of pathological uptakes in the abdomen. In the course of an international multi-centre study, aimed at assessing the tumour-seeking capabilities of the [^{111}In-DTPA-D-Phe^{1}]-octreotide, 40 patients with carcinoid tumours were investigated, using a scintigraphic technique. The results were compared with findings at CT scans, bone scan and, in one case, ultra-sound combined with biopsy.

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Material and Methods

Patients. Forty patients (24 women and 16 men) with either histologically verified carcinoid tumour or with elevated biochemical markers, indicating the presence of carcinoid tumour, were investigated. The diagnosis was histopathologically verified in 37 patients. The diagnosis in the remaining 3 patients was based on elevated hormone levels. Five of the 40 patients had foregut and 35/40 midgut carcinoids. The median age of the patients was 57 years (range 24–78).

Imaging procedures. In order to avoid artefacts, caused by the slight excretion of [^{111}In-DTPA-D-Phe^{1}]-octreotide via the hepato-biliary system into the intestine and colon, the patients were routinely administered laxatives, beginning on the day of the administration of the [^{111}In-DTPA-D-Phe^{1}]-octreotide and continuing throughout the study.

Lyophilized [DTPA-D-Phe^1]-octreotide and the ^{111}In-chloride were obtained in separate vials from the manufacturer (Mallinckrodt Medical, Petten, Netherlands). The ^{111}In-chloride (244 MBq) was added to the lyophilized [DTPA-D-Phe^1]-octreotide (20 μg) and incubated for 30 min at room temperature. The labelling yield was controlled with reversed phase chromatography using SEP-PAK (10). The labelling yield always exceeded 97%. After labelling, 2 ml of sterile isotonic sodium chloride solution was added to the vial to make the injection volume more practical to handle. The patients received 139–220 MBq of the ^{111}In-labelled octreotide solution (3.5–4.5 ml) as an intravenous (i.v.) bolus injection. Planar anterio-posterior whole-body images, with the exception of the extremities, were collected 4 and 24 h after injection. Lateral images were obtained from the head for a better visualization of the pituitary. Twenty-four hours after injection, SPECT (Single Photon Emission Tomography) was performed over the abdomen and, if uptakes regarded as pathological were detected in the thorax, a SPECT study of the thorax was performed. A gamma scintillation SPECT-camera, delivered by Nuclear Diagnostics (Hägersten, Sweden and London, UK) and equipped with a medium-energy general purpose collimator, was used. The collection of original data for SPECT images was performed using a 64-step rotation of 360° in a 64 × 64 word matrix. Energy windows of 173 and 247 keV ±10% were used. The collection time for each angle was 30–40 s which gave a total of about 40 000 counts/angle. For the reconstruction of SPECT images, a Wiener filter was applied to the original data.

Comparison of scintigraphic data and conventional investigational modalities. Reconstructed SPECT images of the abdomen were compared with CT scans of the abdomen. A Somatom II (Siemens) was used for performing CT scans. In cases where the CT was performed for the first time, the procedure included an investigation both with and without i.v. contrast and with 8 mm thick contiguous slices. The optimal conditions for tumour visualization, i.e. with or without contrast, were then individually selected for the subsequent CT investigations, which were performed with 8 mm thick slices and at 8 mm increments. Most of the patients included in the protocol had previously undergone investigations with CT and the comparative CT was thus performed with 8 mm thick slices and 8 mm increments. Each CT scan was reviewed blindly by an experienced radiologist (H.A.). The acquisition data from the [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphies were processed and interpreted blindly by a separate investigator (J.-E.W.). The tumour lesions discovered with the two techniques were then compared, one by one, with each other. In some instances, the CT scans were performed before the [^{111}In-DTPA-D-Phe^1]-octreotide investigation, and vice versa. The time interval between these two investigations was generally less than 4 weeks. Patients who had pathological skeletal uptake on [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy also underwent a bone scintigraphy using ^{99}mTc-HDP. Areas of uptake in soft tissues, detected in the [^{111}In-DTPA-D-Phe^1]-octreotide investigations, were verified both by clinical investigation and CT scan.

Results

[^{111}In-DTPA-D-Phe^1]-octreotide uptake pattern in normal organs. The uptake pattern in normal organs is described elsewhere (11). Briefly, a slight uptake is seen in the pituitary and in the thyroid. The slight uptake in the liver is seen as a haze in the scintigraphic images. The spleen has a varying uptake and the kidneys always display an intense uptake due to the excretion of the [^{111}In-DTPA-D-Phe^1]-octreotide via this route. In the 4-h post-injection images a slight uptake in the shoulder joints and in the nipples is seen in certain patients. This pattern of uptake is not seen in the 24-h post-injection images.

[^{111}In-DTPA-D-Phe^1]-octreotide uptake in tumour lesions. A comparison between the results obtained from the [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy and those visualized by CT, bone scan and, in one case, ultrasound in combination with biopsy, is presented in the Table. A total of 40 patients were investigated yielding a total of 115 pathological lesions detected with the [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy. Tumour lesions tend to confluence, especially in cases with extensive metastatic spread to the liver. In these cases problems arise when attempting to compare the number of [^{111}In-DTPA-D-Phe^1]-octreotide uptakes with the number of lesions seen on CT. In cases with confluent or partly confluent multiple

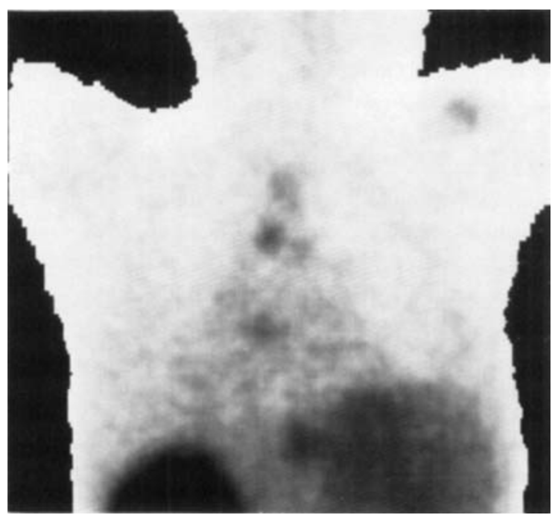

Figure. Dorsal view of the thorax of a patient with disseminated carcinoid disease. The image was collected 4 h after injection of the [^{111}In-DTPA-D-Phe^1]-octreotide. A marked uptake corresponding to the spleen is seen at the bottom left of the image. Pathological uptakes are seen in the vertebral column and in the right shoulder.

metastases, and where the [^{111}In-DTPA-D-Phe^1]-octreotide uptake corroborated the results obtained at CT, the number of metastases was denoted >5 (Table). False negative pathological uptakes were detected in 6 patients, amounting to 11 lesions. In two of these patients, CT-verified liver metastases showed no uptake in subsequent [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy. In these cases the metastases were seen as defects in normal liver

Table

The diagnosis of each investigated patient shown together with the hormonal status, histological verification, number of lesions detected in the [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy, the number of false negative uptakes and the number of new pathological manifestations of the disease detected with the [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy

Patient number	Diagnosis	Pos. horm.	Hist. ver.	Number of lesions in scintigraphy	False neg.	Number of new lesions detected by scintigraphy
1	fc	+	+	>5	0	1#
2	fc	+/−	+	0	0	0
3	fc	+	+	0	0	0
4	fc	+	+	0	3***	0
5	fc	+	+	0	0	0
6	mc	+	−	1	0	1**
7	mc	+	−	0	0	0
8	mc	+	−	>5	0	0
9	mc	+	+	3	1***	1****
10	mc	+	+	>5	0	1****
11	mc	+	+	>5	0	0
12	mc	+	+	>5	0	4#/****
13	mc	+	+	>5	0	0
14	mc	+	+	0	0	0
15	mc	+	+	3	0	0
16	mc	+	+	>5	0	0
17	mc	+	+	0	2***	0
18	mc	+	+	3	2***	0
19	mc	+	+	2	0	0
20	mc	+	+	>5	0	0
21	mc	+	+	1	0	0
22	mc	+	+	>5	0	0
23	mc	+	+	3	0	0
24	mc	+	+	>5	0	0
25	mc	+	+	>5	0	0
26	mc	+	+	1	0	0
27	mc	+	+	5	0	0
28	mc	+	+	3	0	0
29	mc	+	+	0	0	0
30	mc	+	+	0	0	0
31	mc	+	+	3	0	0
32	mc	+	+	2	0	0
33	mc	+	+	5	>1***	1*
34	mc	+	+	4	0	1****
35	mc	+	+	2	2***	2****
36	mc	−	+	4	0	1*
37	mc	+	+	2	0	0
38	mc	+	+	>5	0	0
39	mc	+	+	>5	0	5#/****
40	mc	+	+	3	0	0

Pos. horm. = elevated hormonal levels in serum
Hist. ver. = histological verification
fc = foregut carcinoid tumour
mc = midgut carcinoid tumour
* = primary tumour found at scintigraphy
** = liver metastases identified by scintigraphy, verified by ultrasound and biopsy
*** = located in the liver
**** = located in the skeleton
# = located in soft tissue

background activity. All false negative manifestations were located in the liver. In 9/40 patients, previously unknown manifestations of the disease were detected, corresponding to 16% of the pathological uptakes registered with scintigraphy. (See example in the Figure.) In 2 cases the scintigraphy revealed the primary tumour, located in the caecal area in both cases. Extended retrospective analysis also revealed the tumours in the CT scans. One patient, previously operated radically for a carcinoid tumour, now presented with elevated hormonal levels but a negative CT scan of the liver. The [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy was positive in the right liver lobe. An ultrasound-guided biopsy verified the diagnosis. In 6 cases, previously unidentified skeletal metastases in 9 locations were found and, in 3 patients, soft tissue metastases were seen in 6 locations.

Discussion

Somatostatin receptor scintigraphy using the [^{111}In-DTPA-D-Phe^1]-octreotide seems to be a safe and useful technique for visualizing carcinoid tumours. No adverse effects of the drug were registered during the study. The number of patients positive at scintigraphy and CT scanning was similar, making the detection rate almost equal. In addition, scintigraphy provides a view of the whole body, enabling the detection of a total of 18 previously unknown lesions. With the addition of SPECT, the localization of the individual tumour lesions can be further analyzed. An earlier study registered discrepancies with respect to the [^{111}In-DTPA-D-Phe^1]-octreotide uptake at different tumour sites of equal size in the patients with endocrine pancreatic disease (11). Interestingly, such differences were also found in 2 patients (Nos. 18 and 35) in this study. One explanation for this could be differences in the bioavailability of the drug, due to parameters, such as vascularity, perfusion, etc. Another possibility could be heterogeneity in the tumour areas with respect to the expression of somatostatin receptors. This may explain the false negative lesions, which were all located in the liver, as seen in the [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy. All lesions, except in patient 33, were large enough to be detected in SPECT as defects in normal liver uptake. The uptake seen in the nipples in certain patients may be explained by a higher blood perfusion in the nipples and subsequently higher vascular background in these areas. The uptake seen in the shoulders in the 4-h post-injection images may also partly be explained by an increased vascularity in combination with an inflammatory process since activated lymphocytes express somatostatin receptors (12). There were no false positive findings in this study. However, in another study (11), a false positive uptake was detected. This was located in a wound that was in the process of healing after sternotomy. The future use of the [^{111}In-DTPA-D-Phe^1]-octreotide must be further analyzed but the presence of false negative manifestations in patients indicates that the scintigraphy is unable to 'compete' with CT scan. In contrast to CT, the importance of biological relevance has to be scintigraph appreciated when using the [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy. What is actually detected is the expression of somatostatin receptors in tumour cells and not the tumour cells as such, as in CT examinations. Consequently, additional information is obtained when compared with conventional methods only measuring volume. This piece of information may be of special importance in the staging and treatment of these tumours.

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