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Indium-111-DTPA-octreotide scintigraphy in patients with carcinoid tumor

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Background. *The aim of the study was the evaluation of clinical utility and comparison of ^{111}In-DTPA-octreotide receptor scintigraphy (SRS) with conventional imaging modalities (CIM) in the detection of carcinoid tumor.*

Patients and methods. *Fourteen patients with pathohistologically proven diagnosis of carcinoid tumor and one patient with clinical suspicion of carcinoid tumor were investigated by SRS. SRS was performed for localization of primary tumor, recurrence or estimation of spread of the disease after CIM had been completed.*

Whole body scans and single photon emission computed tomography (SPECT) were acquired 6 and 24 h after the application of radiopharmaceutical. The intensity of nonspecific radiopharmaceutical uptake in the bowel was assessed semiquantitatively by a score using whole body scans.

Results. *The evaluation was done for patients and for tumor sites. The sensitivity, specificity, and positive and negative predictive values for patient evaluation were 89%, 100%, 100% and 80%, respectively for both CIM and SRS, whereas for tumor sites, these parameters were 69%, 100%, 100% and 82% for CIM, and 88%, 100%, 100% and 92% for SRS. Intensity score of nonspecific ^{111}In-octreotide bowel accumulation was 0.92 and 2.01 for 6 and 24 h scans respectively ($p < 0.01$).*

Conclusion. *^{111}In-octreotide scintigraphy should be included in the diagnostic algorithm for the patients with clinical suspicion of carcinoid and for the assessment of patients with proven carcinoid tumor.*

Key words: carcinoid tumor-radionuclide imaging; indium radioisotopes, octreotide, DTPA; ^{111}In-octreotide scintigraphy, diagnosis; nonspecific bowel accumulation

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Introduction

Indium-111-DTPA-octreotide (^{111}In-pentetreotid) is a radiolabeled octapeptide somatostatin analogue. It binds to somatostatin receptors in normal tissues and in a variety of tumors and inflammatory diseases.[1] Of five known somatostatin receptor subtypes, ^{111}In-octreotide exerts the highest affinity to the receptor subtype II and to a much lesser extent to the receptor subtype V.[2] A high percentage of carcinoid tumors express somatostatin receptors in vitro, specifically the subtype II, enabling their visualization by ^{111}In-octreotide scintigraphy (SRS) in patients.[3-5] The rationale for introducing SRS into clinical practice is a relatively low sensitivity of conventional imaging modalities (CIM) for extrahepatic sites of carcinoid tumors.[6] SRS adds diagnostic and therapeutic information to conventional imaging modalities and laboratory procedures in carcinoid patients.[7] Indeed, several factors influence the sensitivity of SRS, including the density and subtype of the receptor expressed by the tumor, radioligand receptor affinity and tumor size.[8] Unspecific bowel activity due to the biliary excretion of radiopharmaceutical may affect tumor to background ratio in imaging setting.[9,10] Clinical utility and comparison of SRS with CIM in the detection of carcinoid tumor are evaluated. Semiquantitative assessment of changing intensity of unspecific bowel accumulation during scanning procedure is addressed, too.

Patients and methods

Patients

Fifteen patients (7 male and 8 female) mean age 49 years (range 23-70) were referred to SRS for clinical suspicion of carcinoid tumor, recurrence, assessment of spread of disease or in vivo estimation of somatostatin receptor activity. All patients except one had pathohystologically proven diagnosis of carcinoid tumor either of primary site or of metastasis. On the basis of knowledge of primary site of carcinoid tumor prior to scintigraphy, the patients were divided into Group A: 10 patients with known primary site; and Group B: 5 patients with unknown primary site.

Two patients were on somatostatin therapy which was not withdrawn before scintigraphy.

Methods

Whole body scans in anterior and posterior projection and a single photon emission computed tomography (SPECT) of the abdomen, and the thorax when appropriate, were obtained 4-6 and 24 h after i.v. application of 111-145 MBq ^{111}In-octreotide on large, rectangular field of view by gamma camera equipped with high energy collimator and linked to an appropriate computer. The pulse height analyzer windows with a width of 20% were centered over 172 keV and 245 keV photon peaks of ^{111}In. For whole body scintigrams, the scanning speed was 10 cm/min and the data were collected in 128 word matrix. A 360° rotation ECT in steps of 6° lasting for 60 s was performed using 128 word matrix. Back projection algorithm applying a ramp filter was used on prefiltered data with Butterworth filter of order 5 and cut-off frequency 0.50 to 0.25.

The presence of unspecific uptake of radiopharmaceutical in the small and large intestine on anterior whole body scans was assessed by an intensity score; 0 for its absence, 1 for intensity smaller than the liver, 2 for intensity equal to the liver and 3 for intensity bigger than the liver (Figure 1).

CT of the abdomen was performed in all patients, whereas abdominal ultrasound, upper gastrointestinal series, bowel enema, CT of the thorax, bronchoscopy, bronchial lavage and bone x-ray were performed in some only.

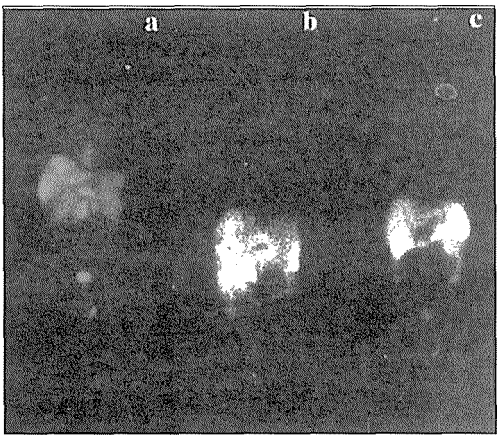

Figure 1. Intensity of nonspecific ^{111}In-octreotide bowel accumulation. **a:** Grade 0-1. **b:** Grade 2. **c:** Grade 3. Multiple pathologic hepatic and extrahepatic ^{111}In-octreotide accumulation in **a** and **b**. Physiologic ^{111}In-octreotide accumalation in **c**.

For both imaging modalities, 3 categories of lesions were searched for: the primary site of carcinoid, liver metastases and extrahepatic metastases. Liver metastases, regardless the number, were considered as single lesion.

Biological markers of tumor metabolism were not systematically investigated.

For statistical analysis of scintigraphy scores, a paired t-test was applied. For the evaluation of a diagnostic test, usual formulas were used.[11]

Results

Group A

Results of CIM

All 10 patients had pathohystologically proven primary tumor, and in 9, the primary tumor was surgically removed. In the remaining patient, an unresectable carcinoid of the pancreatic head was found on operation. Five patients had liver metastases and only one patient had extrahepatic metastasis in the spleen. Extrahepatic lesions were detected by conventional imaging in 3 patients: in one, an enlargement of right suprarenal gland was observed, the second had a thyroid nodus and a renal cyst and the third had a renal cyst (Table 1).

Table 1. Site of primary tumor and liver metastases detected by conventional imaging modalities (CIM) in Group A patients

Site	No. of patients	No. of patients with liver metastases
bronch	2	2
gastric polyp	3	0
ascending colon	1	1
appendix	2	0
caecum	1	1
pancreas	1	1

Results of SRS

^{111}In-pentetreotid scintigraphy revealed a carcinoid of the pancreas head in the patient with inoperable tumor. In other 9 patients, scintigraphy was negative at the site of the primary tumor. In 4 of 5 patients who had liver metastases scintigraphy was positive. The known spleen metastasis was visualized by scintigraphy. In 3 patients, scintigraphy revealed 3 additional lesions nonvisualized by conventional imaging: periaortic lymph nodes (Figure 2), mediastinal lymph nodes and a left clavicular metastasis.

Group B

Results CIM

Four patients in this group had proven liver metastases. In one of these patients, CT revealed an enlargement of the left suprarenal gland. Another patient had bilateral adnexectomy and omentectomy for metastatic carcinoid tumor. The patient with clinical suspicion of carcinoid syndrome had negative work up by conventio-

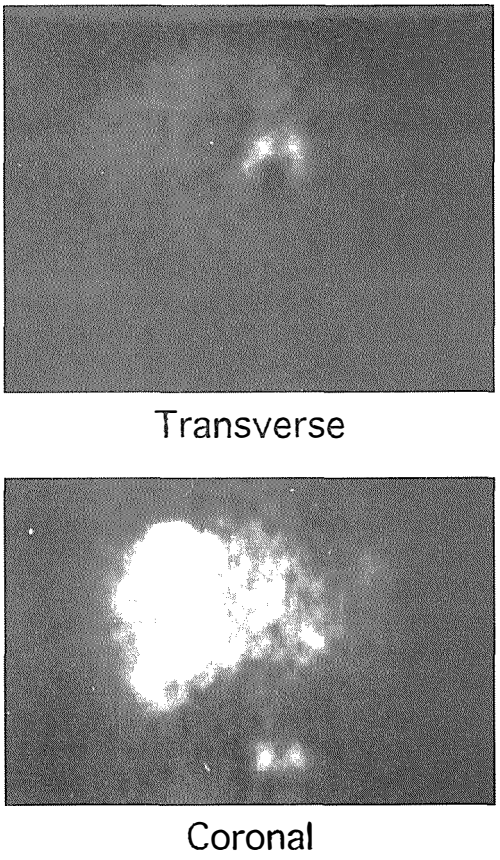

Figure 2. ^{111}In-octreotide SPECT of abdomen. Unsuspected paraaortic lymph node metastases in patient with liver metastases from coecal carcinoid. **a.** transversal and **b.** coronal slice.

nal imaging modalities except for elevated 5-hydroxyindol-acetic acid in one urine specimen.

Results of SRS

One out of 4 patients with liver metastases had scintigraphy after extirpation of a solitary liver metastasis. In the remaining 3 patients, the liver metastases were visualized by scintigraphy. In all 4 patients, SRS revealed 4 sites of extrahepatic accumulation, of which 2 were in the thorax and 2 in the abdomen; one carcinoid was removed from small intestine (Figure 3) and a tumor of the thymus was found on repeated CT. The remaining two sites in 2 patients have not been characterized yet, but the scintigraphic pattern suggests a tumor uptake.

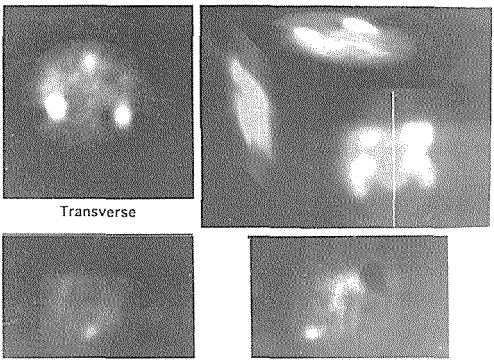

Figure 3. ^{111}In-octreotide SPECT of abdomen. Small intestine carcinoid.

In both groups, none of the extrahepatic solid lesions detected by CIM has demonstrated any uptake of radiopharmaceutical on scintigraphy, and none has yet been proven to represent a metastasis of carcinoid tumor. The comparison and summary of CIM and SRS findings are given in Table 2 and Table 3.

In 5 patients included in the final analysis (1 group A, 4 groups B), the primary tumor was not removed or its site was unknown prior to SRS. In all 5 patients, the uptake of

Table 2. Comparison of conventional imagingmodalities (CIM) findings and corresponding ^{111}In-octreotide accumulation on scintigraphy (SRS) in Groups A and B

	CIM	SRS
primary site	1	5*
liver metastasis	8	7
spleen metastasis	1	1
lymph node metastasis	0	2
bone metastasis	0	1
renal cyst	2	0
thyroid nodule	1	0
suprarenal mass	2**	0

* 2 sites not confirmed by CIM or surgery
** unknown ethiology

^{111}In-pentetreotid was present on possible sites of primary tumor. In 3 out of these 5 patients, the primary site of tumor has been confirmed by surgery or CT. Due to a proportionally small number of patients with primary tumor in the study population, primary tumors were evaluated together with extrahepatic lesions.

In 13 patients, 39 sites could be confirmed to bear carcinoid or to be free of tumor. Nine patients and 16 sites were tumor-bearing, 4 patients and 23 sites were tumor-free. On the basis of these data, sensitivity, specificity, and predictive positive and negative values of conventional imaging modalities and ^{111}In-pentetreotid scintigraphy were calculated.

The sensitivity, specificity, positive and negative predictive values of CIM for detection of disease in a patient were 89% 100%, 100% and 80% respectively. The same parameters of CIM for detection of a single lesion were 69%, 100%, 100% and 82%, respectively. The sensitivity, specificity, positive and negative predictive values of SRS for the detection of disease in a patient were 89%, 100%, 100% and 80%, respectively whereas, for the detection of a single lesion, these parameters were 88%, 100%, 100% and 92%, respectively (Table 4).

In 2 of 13 (15%) patients, the treatment strategy was changed on the basis of positive scintigraphic findings.[12,13] The primary tumor was removed in a patient with liver metastases from group B and a contemplated liver transplantation was rejected for unsuspected extrahepatic spread in a group A patient (Figure 3).

Intensity of unspecific bowel accumulation was significantly higher ($p < 0.01$) on whole body scans at 24 h p.i. than after 6 h p.i. (score 2.01 vs. 0.93 respectively).

Discussion

In this study, the sensitivity, specificity, positive and negative predictive values were equal for both CIM and SRS, when considering the presence of the disease in a patient (Table 4). The result of sensitivity for CIM, which is in the range of 71%-91%,[14,15] in our case can be explained on the basis of inclusion criteria. In 14 out of 15 patients, the diagnosis was established before scintigraphy. On the other hand, at the time of presentation, 50% of patients had liver metastases which were diagnosed by CT or ultrasound. CIM missed a patient with

Table 3. Summary of ^{111}In-octreotide scintigraphy and conventional imaging modalities (CIM) results in Groups A and B

	CIM			^{111}In		
	Group A	Group B	Total	Group A	Group B	Total
primary site	1	0	1	1	4	5
liver metastasis	5	3	8	4	3	7
extrahepatic lesion	5	1	6	4	0	4

Table 4. Evaluation of conventional imaging modalities and ^{111}In-octreotide scintigraphy in carcinoid tumor

	per patient		per lesion	
	CIM	In-111	CIM	In-111
sensitivity	89%	89%	69%	88%
specificity	100%	100%	100%	100%
positive predictive value	100%	100%	100%	100%
negative predictive value	80%	80%	82%	92%

clinical suspicion of carcinoid in whom SRS revealed a mediastinal accumulation, subsequently confirmed by repeated CT as mediastinal tumor, presumably thymoma. The sensitivity of SRS was in the expected range of 73% to 89% for the patients with carcinoid tumors.[8,9,14] SRS missed a liver metastasis.

SPECT was positive in 7 of 8 patients with liver metastases (sensitivity 88%). This is in accordance with a recent report[16] and supported by previous studies indicating the superiority of SPECT (Figure 4.) over planar imaging in detecting liver metastases.[15,17]

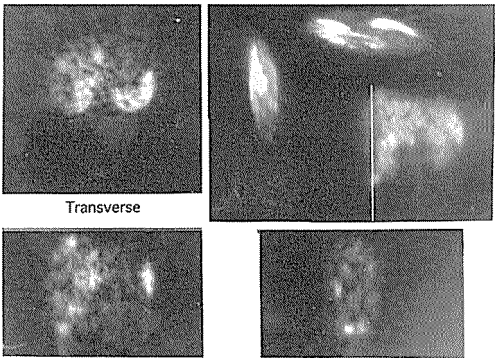

Figure 4. ^{111}In-octreotide SPECT of the liver. Tansversal, coronal and sagital slices. Multiple liver metastases in patient with bronchial carcinoid.

The sensitivity and negative predictive value for the detection of a single lesion were in favor of scintigraphy, on the account of detecting more primary and solid extrahepatic lesions (Tables 2 and 3). These SRS results are comparable to the results of previous studies.[14,16,18] Factors affecting relatively low sensitivity of SRS for primary carcinoid sites are discussed elsewhere,[15,16,19] adding to them site or even origin of carcinoid tumor. In vitro studies of carcinoid tumor receptor affinity for radiolabeled somatostatin analogues revealed that grater proportion of bronchial carcinoids had lower affinity for radioligand examined in comparison to carcinoids of midgut origin.[5] Further, in vivo sensitivity for primary carcinoid site in the studies where patients with carcinoids of foregut and midgut origin were included detection was about 50%.[16,19] Indeed, in the studies enrolling only patients with carcinoids of midgut origin the sensitivity for the detection of primary site of carcinoids ranged from 70% to 87%.[18,20]

In 2 patients, scintigraphy was performed under somatostatin treatment, which did not the preclude the detection of liver and extrahepatic metastases. This contradicts the report of Schillaci[5,21] and supports the observations that somatostatin treatment in carcinoid patients indeed enhances the tumor to background ratio.[22,23]

The specificity of SRS can be compromised by nonspecific bowel accumulation due to biliary excretion, the intensity of which significantly increases on 24 h scintigrams making patients preparation with laxatives mandatory in non diarrhea patients.9 The variations in shape and position of the spleen and kidneys and concomitant diseases expressing somatostatin receptors are further potential sources of false positive findings.[1,24,25] Two patients with an enlargement of suprarenal glands on CT and negative SRS were excluded from the final analysis because the nature of the lesions had not been established yet. If these lesions were confirmed not to represent carcinoid spread, this would indicate that unrelated suprarenal masses in carcinoid patients could cause false positives on conventional imaging modalities.

Conclusion

^{111}In-octreotide scintigraphy encompasses the whole body and can be advocated as an imaging modality of choice in patients suspected of having carcinoid tumor, especially in the search for primary site and extrahepatic spread. In patients with documented disease high predictive value of positive and negative

scintigraphic findings justifies its use in the evaluation of the spread of the disease. Bowel preparation with laxatives before SRS is recommended. Further investigations on affinity for binding of somatostatin analogues, depending on carcinoid origin, can be proposed.

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