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Original article

Somatostatin receptor scintigraphy with In-111 octreotide in the detection of gastroenteropancreatic carcinoids and their metastases

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SUMMARY

Background: Carcinoid tumours are a very rare malignancy most frequently arising in the gastrointestinal tract. The method of choice for detection of these tumours is somatostatin receptors scintigraphy (SRS). The aim of the present study was to evaluate the diagnostic sensitivity and accuracy of this technique in the detection of gastroenteropancreatic carcinoid tumours and their metastases in comparison with conventional imaging methods.

Methods: In 24 patients with confirmed carcinoids and 7 under investigation SRS was performed. The results were compared with those of conventional imaging methods (chest X-ray, upper abdominal US, chest CT, upper and lower abdominal CT) and other combinations.

Results: SRS visualized primary or metastatic sites in 71.0% of cases vs 61.3% of conventional imaging. The diagnostic sensitivity of the method was higher in patients with suspected lesions (85.7% vs 57.1%). SRS was less sensitive in the detection of metastatic sites (78.9% vs 84.2%). The metastatic sites undetectable by SRS were all in the liver. Between several imaging combinations, the combinations chest X-ray/upper abdominal CT/SRS and chest CT/upper abdominal CT/SRS showed the highest sensitivity (88.75%) in terms of the number of detected lesions. The combinations chest X-ray/upper abdominal US/SRS and chest CT/upper abdominal US/SRS yielded a similar sensitivity (82%).

Conclusions: SRS imaging is a very sensitive method for the detection of gastroenteropancreatic carcinoids but is less sensitive than US and CT in the detection of liver metastases. Between several imaging combinations, the combination chest x-ray/upper abdominal CT/SRS showed the highest sensitivity.

Key words: Somatostatin receptors scintigraphy, gastroenteropancreatic carcinoids, cost effectiveness

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INTRODUCTION

The carcinoid tumour -argentaffinoma- is a member of a very exclusive neoplastic family known as neuroendocrine or amine precursor uptake and decarboxylation (APUD) tumours.

The carcinoid tumour has been found to arise from almost every organ and system derived from the primitive endoderm, but most frequently originats from the gastrointestinal (G.I.), tract, accounting for approximately half of all GI endocrine tumours.[1]

Over 95 per cent of all GI carcinoids are located in only three sites: The appendix, the rectum and the small intestine.

Irrespective of their location, carcinoids are capable of producing one or more of the following substances: 5-hydroxy-tryptamine (serotonin), gastrin kinin-peptides, histamine, catecholamines and glucagon. Some of them

induce systemic manifestations known as the carcinoid syndrome characterized by flushing, diarrhea, right-sided heart disease and wheezing.[2,3]

Carcinoid tumours are rare (incidence: about 2/100,000 people)[4] and malignancy –that is, mainly, liver metastases- may be encountered in 10-60% of cases depending on the site of the primary tumour.[5,6] Metastases are observed in less than 2% of carcinoids 1 cm or less in size. In contrast, nearly all carcinoids 2 cm or greater show evidence of metastatic spread.[1]

Tumour localization is essential since surgery remains the optimal treatment in most patients without metastases.[7,8]

Curative surgery is difficult since primary tumours are frequently very small (<1 cm) and potentially undetectable by conventional imaging. When liver metastases occur, the staging of these patients is essential for therapeutic manipulation.

Tumour localization for accurate staging and therapeutic management justifies the use of new imaging techniques such as somatostatin receptor scintigraphy (SRS).[9,10]

Since the introduction of somatostatin receptor imaging in 1989,[9] many reports on the usefulness and limitation of this technique have been published.

It has been shown by autoradiography using 125-I-labeled octreotide that endocrine tumours of GI tract and especially carcinoids possess somatostatin receptors.[11,12,13] When octreotide is labeled with radio-nuclides such as 123-I[14,15] or ^{111}In the specific receptor binding can be exploited for the scintigraphic in vivo demonstration of receptor-expressing tumours.[9,10,16]

The radiolabelled analog ^{111}In-DTPA-octreotide, also known as Octreoscan, is cleared by the renal rather than the hepatobiliary route, thus causing less artifacts on hepatic and mesenteric imaging.[17,18]

PATIENTS AND METHODS

In a total number of 31 patients (18 M, 13 F, age ranged between 27-73 years) SRS ^{111}In-Pentatreotide was performed during the period from April 1997 to October 2002 at "Saint Savvas" Cancer Hospital (Section of Nuclear Medicine), Athens, Greece. Their data are listed in Table 1.

Inclusion criteria required histologic or cytologic confirmation of a present or previously operated abdominal carcinoid or, for patients with suspected tumours, a history of carcinoid syndrome-related signs and symptoms with an additional elevation of urinary 5-HIAA. All patients gave informed consent to participation in the study, which was approved by the ethics committee of our hospital.

Seven patients were under investigation for suspected carcinoids in different sites (caecum, appendix, small intestine, pancreas) while the remaining 24 had histologically/cytologically confirmed tumours; in 10 of them the primary lesion had been excised. All gastric carcinoids were type II or "mixed cellular composition" gastric carcinoid tumours.

Seven patients were treated by octreotide prior to SRS. In all but 3 cases therapy was withdrawn 36 hours prior to somatostatin receptor imaging, in order to lift the blockade of SRS. In the remaining 3 patients the three-day withdrawal period was clinically impossible. The administration dose of octreotide in these patients was 0.5 mg daily.

A low-residue diet was started 3 days prior to SRS and stopped at the end of the imaging procedure. Twelve hours before the injection of the tracer, a mild laxative was administered to minimize the false positive results, because a small quantity of the administrated dose undergoes hepatobiliary excretion.

Patients were well hydrated prior to radioactive drug administration to increase renal clearance and to reduce radiation uptake to the thyroid, kidneys, bladder and other target organs. All individuals in our study had normal thyroid and renal function.

^{111}In-Pentetreotide (Octreoscan, Mallinckrodt Medical BV, Petten, Holland) is supplied as a two vial kit. The first contain ^{111}-In as ^{111}-In Cl_3 diluted in 1.1 ml hydrochlorid acid and the other lyophilised pentetreotide. After reconstitution the pH of the final product is between 3.8 and 5. This product may be diluted with normal saline solution because the dilution will raise the pH slightly.

After an incubation period of 30 minutes at room temperature, and before administration, we performed Instant Thin Layer Chromatography (ITLC) for quality control. The dose for a planar investigation was 111 MBq (3.3 mCi) of Octreoscan.

The radiolabelled somatostatin analog was administered as an intravenous bolus and no side effects were observed after i.v. injection.

Whole body scanning and planar images were obtained with a large field of view gamma camera

Table 1.

Pt	Sex	Age	Primary tumour site	Metastases	Carcinoid syndrome Related signs and symptoms	SRS Primary sites	SRS Meta-stases	Conventional imaging methods Primary sites	Conventional imaging methods Meta-stases
Patients with confirmed tumours									
1	F	69	Stomach			-	-	-	-
2	M	58	Stomach			+	-	-	-
3	M	55	Duodenum			-	-	-	-
4	M	55	Small intestine	Liver		+	+	-	+
5	F	69	Small intestine			+	-	-	-
6	M	33	Appendix	Lymph nodes		+	+	-	-
7	F	27	Appendix			-	-	-	-
8	M	39	Appendix	Liver-Lymph nodes	Diarrhoea	+	+	+	+
9	M	59	Caecum			-	-	+	-
10	F	64	Caecum			+	-	-	-
11	M	69	Rectum			+	-	-	-
12	F	57	Rectum			+	-	-	-
13	F	49	Pancreas	Liver-Lungs	Diarrhoea	+	+	+	+
14	M	58	Pancreas	Liver-Lymph nodes	Flushes diarrhoea	+	+	+	+
Patients previously operated									
15	F	42	Stomach	Liver			+		+
16	M	34	Appendix	Liver			-		+
17	M	36	Appendix	Lymph nodes			+		+
18	F	40	Appendix	Liver-Lymph nodes			+		+
19	M	69	Small intestine	Lymph nodes			+		+
20	M	61	Small intestine	Liver			+		+
21	F	67	Caecum	Lymph nodes			+		+
22	F	56	Colon	Liver			-		+
23	M	72	Rectum	Liver-Lymph nodes			-		+
24	M	59	Pancreas	Liver			-		+
Patients with suspected carcinoid tumours									
25	M	34	Sus.Appendix		Flushes	-	-	-	-
26	F	33	Sus.Appendix		Diarhoea	+	-	-	-
27	M	51	Susp. small Intestine	Liver	Diarrhoea flushes	-	+	-	-
28	M	62	Susp.Caecum		Diarhoea	+	-	+	-
29	M	61	Susp.Caecum	Liver-Lymph nodes	Diarr. flushes	+	+	+	-
30	F	71	Susp.Caecum	Liver	Diarr.flushes	+	+	+	+
31	F	73	Sus.Pancreas	Liver-Lungs	Diarr. flushes	+	+	+	+

(Siemens) equipped with a medium- energy, parallel-hole collimator. The pulse-height analyser windows are centered over both ^{111}-In peaks (172 KeV and 245 KeV) with a window width of 20%. Data from both windows are added to the acquisition frames. Images are obtained 24 and sometimes 48 hours after tracers administrations.

The scintigraphic results were compared with those obtained by other imaging methods, including:

1. Chest X-Ray, performed on all patients.
2. Upper abdominal ultrasonography, performed on all patients.
3. Chest CT scan, performed on all patients.
4. Upper and lower abdominal CT scans, performed on all patients.

Magnetic resonance imaging of the abdomen and digital abdominal angiography were performed in a few cases, but because of the small number of patients these

imaging techniques were not taken into acount.

Statistical analysis

The statistical comparison between SRS and conventional imaging methods for the detection of primary and metastatic sites, globally and in each group of patients, was performed using McNemar's test based on discordant pairs. A P value ≤ 0.05 was considered significant.

RESULTS

SRS imaging visualized the primary tumour or metastatic sites in 22 (71.0%) out of 31 patients who had a histologically-cytologically confirmed carcinoid tumour or were under investigation for highly suspected carcinoids (16/24-66.7% and 6/7-85.7% respectively) (Figure 1).

Conventional imaging was positive in 19 (61.3%) patients (4/7- 57.1% with suspected carcinoids and 15/24-62.5% with known tumours). Thus, SRS provided additional detection sites compared with conventional imaging methods even though the global detection rate (71.0% vs 61.3%) was quite similar. Detection of primary sites is 33.3% higher with SRS than conventional methods (71.4% vs 38.1% respectively, p=0.039). The primary lesions were detected by SRS in 15 (71.4%) out of 21 patients. Octreoscan scintigraphy failed to detect primary tumours in 6 patients (28.6%), 4 with known lesions (stomach, duodenum, appendix, caecum) and 2 under investigation (appendix, small intestine).

The 6 lesions (≤0.7 cm) that were not visualized after injection of ^{111}In-Pentetreotide were detected by endoscopy (3) or surgery (3) and were diagnosed by histology. Only one out of 6 lesions was visualized by conventional imaging methods (patient No 9). Further analysis of the results from each group of patients with residual primary tumour did not reveal any statistically significant difference between the two methods (p>0.05).

The positive detection rate in metastatic sites was similar for SRS and conventional imaging methods: 48.4% and 51.6% respectively, p>0.05.

In the overall population of 19 patients with metastatic disease, SRS detected metastatic lesions in 15 cases (78.9%) (Figures 2,3) and failed to visualize metastatic sites in 4 patients (21.1%), all in the liver and subsequently detected by ultrasonography and CT scans. On the other hand, conventional imaging visualized metastases in 16 (84.2%) patients with a detection rate 5.3% higher than that of SRS.

False negative results of SRS and conventional imaging methods for primary and metastatic tumour sites

Figure 1. Carcinoid tumour of appendix (patient No 26).

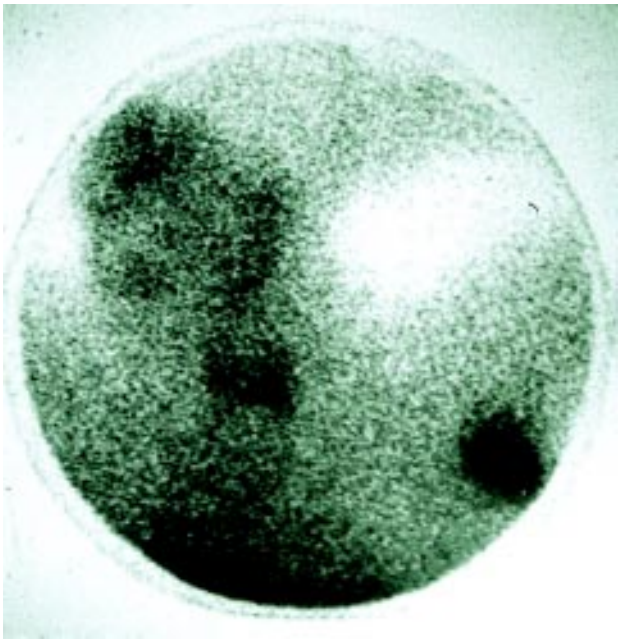

Figure 2. Metastatic sites in the abdominal lymph nodes from a previously operated carcinoid.

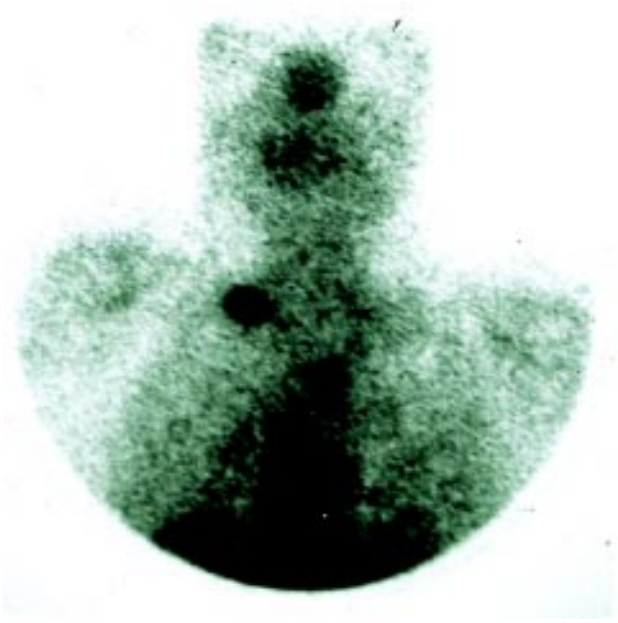

Figure 3. Metastatic sites in axillary lymph nodes (patient No 6).

in patients with known and suspected carcinoids are shown in tables 2 and 3.

Comparison of 8 imaging combinations showed that the combination of chest X-Ray / upper abdominal CT scan / SRS and chest CT scan / upper abdominal CT scan / SRS achieved the highest sensitivity in the detection of primary and metastatic lesions (88.75% for each one).

The combination of chest X-Ray/upper abdominal ultrasonography/SRS and chest CT/upper abdominal ultrasonography/SRS also yielded a similar sensitivity (82% for each one in terms of the number of detected lesions).

DISCUSSION

Carcinoids are often indolent, asymptomatic, slow growing tumours and clinically silent for years.[3] The vast majority do not cause symptoms until complications (e.g. intestinal obstruction) or symptoms and signs of the carcinoid syndrome occur. This syndrome occurs in less than 10% of cases and may be present in patients with midgut carcinoid tumours with liver metastases and also in some patients with foregut carcinoids. Patients with hindgut carcinoids do not exhibit the carcinoid syndrome.

The final diagnosis is not easy, unless bioptic material is examined for the secretory peptide chromogranin or the neuron-specific enolase.[19,20]

Due to their multiple localizations and their small size, images of carcinoid tumours are difficult to obtain even with the most sophisticated conventional imaging techniques.[21,22,23] MRI, CT scan and ultraso-nography are very sensitive in the detection of liver metastases, but seem to be less sensitive in the diagnosis of extrahepatic sites.[24,25,26]

It is known that the carcinoid tumours have a high expression of somatostatin receptors.[27,28] More than 90% of patients with midgut carcinoids expess somatostatin receptors detected by autoradiography with iodinated somatostatin analogues as ligands, while the somatostatin receptor expression in foregut carcinoid tumours is less frequent.[29]

Table 2. False negative results of SRS and conventional imaging methods for primary sites

			Patient No	**%**
SRS	Known carcinoids	4/14 patients	1, 3, 7, 9	28.57
	Suspected carcinoids	2/7 patients	25, 27	28.57
Conventional	Known carcinoids	10/14 patients	1-7, 10-12	71.42
Imaging Methods	Suspected carcinoids	3/7 patients	25, 26, 27	42.85

Table 3. False negative results of SRS and conventional imaging methods for metastatic sites

			Patient No	**%**
SRS	Known carcinoids	4/24 patients	16, 22-24	16.66
	Suspected carcinoids	0/7 patients	-	0
Conventional				
Imaging Methods	Known carcinoids	1/24 patients	6	4.16
	Suspected carcinoids	2/7 patients	27, 29	28.6

Five different subtypes of somatostatin receptors have been cloned. Somatostatin receptor subtype 2 binds the somatostatin analogues used in the clinical practice with high affinity. Subtypes 3 and 5 have an intermediate affinity while subtypes 1 and 4 have low affinity for the available somatostatin analogues.[30]

SRS is a very sensitive method for the demonstration of receptor-positive tumours and their metastases and its diagnostic usefulness in patients with abdominal carcinoid tumours has already been reported.[31,32]

In our study, SRS imaging visualized the primary or metastatic sites in 22 out of 31 patients with gastrointestinal and pancreatic carcinoid tumours (detection rate 71.0%) and the results are in concordance with other previously published reports.[31,32,33]

Conventional imaging was positive in 19 out of 31 patients (detection rate 61.3%).

Our results demonstrate that SRS, compared with conventional imaging, provides major additional information.

More interestingly, SRS was positive in 71.4% of the primary tumour sites, with a statistical significant difference ($p=0.039$) compared with conventional imaging methods. Lebtahi et al also reported similar results (75%) in a similar group of 38 patients.[34]

Conventional imaging modalities (ultrasonography and upper abdominal CT) are more sensitive in the detection of hepatic metastases. On the other hand, SRS is more sensitive in the detection of extrahepatic metastatic sites and provides additional information on previous unsuspected localizations. Schillaci et al, in a group of 18 patients with abdominal carcinoid tumours, reported similar results.[35]

It is thus clear that the combination of several conventional imaging techniques with SRS is the method of choice for better evaluation of patients with carcinoid tumours. For individuals with carcinoid tumours of the digestive tract, gastrointestinal endoscopy is a first line diagnostic tool.

In our study, 2 (chest X-Ray/upper abdominal CT scan/SRS, chest ST/upper abdominal CT scan/SRS) out of 8 combinations of imaging modalities yielded an overall sensitivity of 88.75% in the detection of primary and metastatic carcinoid sites.

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