Added value of gastrin receptor scintigraphy in comparison to somatostatin receptor scintigraphy in patients with carcinoids and other neuroendocrine tumours

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Abstract

Gastrin receptor scintigraphy (GRS) is a new imaging method primarily developed for the detection of metastases of medullary thyroid carcinoma (MTC). As gastrin-binding CCK₂ receptors are also expressed on a variety of other neuroendocrine tumours (NET), we compared GRS to somatostatin receptor scintigraphy (SRS) in patients with NET. SRS and GRS were performed within 21 days in a series of 60 consecutive patients with NET. GRS was directly compared with SRS. If lesions were visible on GRS but not detectable by SRS, other imaging modalities (MRI, CT) and follow-up were used for verification. Of the 60 evaluable patients, 51 had carcinoid tumours, 3 gastrinomas, 2 glucagonomas, 1 insulinoma and 3 paragangliomas. The overall tumour-detection rate was 73.7% for GRS and 82.1% for SRS. In the 11 patients with negative SRS, GRS was positive in 6 (54.5%). Based on the number of tumour sites detected and the degree of uptake, GRS performed better than SRS in 13 patients (21.7%), equivalent images were obtained in 18 cases (30.0%) and SRS performed better in 24 (40.0%) cases. In six of the SRS positive patients, 18 additional sites of tumour involvement could be detected. Overall, GRS detected additional tumour sites in 20% of the patients. Localisation of the primary tumours or their functional status had no influence on the outcome of imaging. GRS should be performed in selected patients as it may provide additional information in patients with NET with equivocal or absent somatostatin uptake.

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Introduction

Somatostatin receptor scintigraphy (SRS) is a successful nuclear medicine procedure for the detection of neuroendocrine tumours (NET) and their metastases. It is considered as the diagnostic method of choice in several tumour entities (Krenning *et al.* 1993, Modlin & Tang 1997, Ricke *et al.* 2001). The method is based on specific binding of radiopeptides mainly to the somatostatin receptor subtype 2 (sstr2) overexpressed

by tumour cells (Lamberts *et al.* 1990). Residualising labels have been introduced to improve image quality (Bakker *et al.* 1991). In radiopeptide scintigraphy, these labels usually consist of radiometal–chelator complexes bound to the respective peptides. After specific binding and internalisation, the complexes are retained inside the cell (metabolic trapping) while activity in blood and other tissues decreases. This results in high tumour-to-background ratios.

Radiopeptide imaging has a considerable impact on patient management in the range of 25–50% (Lebtahi *et al.* 1997, Termanini *et al.* 1997). However, some patients show low or even absent uptake in SRS. Especially, patients with medullary thyroid carcinoma (MTC) are often sstr2-negative. As recurrent MTC can chemically be diagnosed by pentagastrin stimulation testing, a radiopeptide has been developed for targeting the pentagastrin-binding CCK₂ receptor. This peptide has shown first promising results in imaging of recurrent and occult MTC (Behr *et al.* 1999a,b, Gotthardt *et al.* 2006).

The CCK₂ receptor is also expressed in other NET, such as gastrointestinal NET (Reubi & Waser 2003). Therefore, the use of a CCK₂ receptor-binding compound may provide additional diagnostic information. We compared the results of SRS and gastrin receptor scintigraphy (GRS) in a series of patients with neuroendocrine tumours.

Materials and methods

Patients and study design

We included a series of consecutive patients who underwent staging for histologically verified NETs between July 2001 and July 2003 at the university hospital in Marburg. All patients underwent GRS and SRS within 21 days to guarantee for comparability. All patients had given written consent for participation in the study. The study was approved by the local ethics committee and the radiation protection authorities.

Scintigraphic imaging protocol

Somatostatin receptor scanning and gastrin receptor scanning

Four and 24 h after injection of 150–200 MBq ¹¹¹In-DPhe¹-DTPA-Octreotide (OctreoScan, Tyco Healthcare, Neustadt/Donau, Germany) or ¹¹¹In-DTPA-DGlu¹-minigastrin (DTPA-DGlu¹-minigastrin synthesised by Bachem, Weil am Rhein, Germany), anterior and posterior planar whole body images were obtained. A Siemens dual-head gamma camera (E CAM, Siemens, Hoffman Estates, IL, USA) was used, equipped with medium energy parallel hole collimators. The scanning speed was set to 7 cm/min. For imaging, the compound was labelled with a specific activity of 55 GBq/μmol, the radiochemical purity of the labelled minigastrin was always >95% (HPLC) as described previously (Behe *et al.* 2005, Behr *et al.* 1999a,b).

Other imaging techniques

Computed tomography

A Siemens Somatom 2 scanner was used. Using an automated power injector (70/120 ml volume, flow rate 2–3 ml/s), non-ionic contrast medium (Iopamidol 300; Solustrast, Bracco-Byc Gulden, Konstanz, Germany) was administered intravenously. Slices of 3–8 mm were obtained at 4.5 or 12 mm increments from skull base to jugulum and from lung apex to pubic symphysis.

Magnetic resonance imaging

Scans were acquired using a 1.0 T scanner (Magnetom Expert, Siemens, Erlangen, Germany) with commercially available gradients capable of a 1200 μs rise time and 20 mT/m maximum gradient strength using a body array coil. A T2 weighted axial turbo spin echo sequence (TR/TE 2730/138 ms, SL 6 mm) and an axial T1 weighted fast low angle shot gradient sequence (TR/TE 134/6 ms, FA 70°, SL6) were used prior to and after injection of the contrast agent (Gd-DTPA (Magnevist), 0.1 mmol/kg, flow of 1 ml/s), and a coronal true fast imaging with steady-state precession sequence (TR/TE 10.22/4.7 ms, SL 5 mm).

Evaluation of SRS and GRS

SRS and GRS images were evaluated independently by two observers who were experienced specialists in nuclear medicine. The observers were blinded with respect to patient identity, extent of disease and results of other imaging procedures, only the tumour type was known. In case of discordance, the differences were discussed together and settled (consensus reading).

As patient management depends more on involvement of a region (e.g. left liver lobe resection if right liver lobe is not involved) than on the total number of metastases, a regional assessment of tumour localisations was performed (cervical region, lung, supraclavicular, upper and lower limbs, liver, pelvis (all specified by involved side), peritoneal, retroperitoneal, cervical/thoracic/lumbar spine, mediastinal, mesenterial, pancreas and skull).

GRS was directly compared with SRS as it is the established standard technique for scintigraphic imaging of NETs. If foci were negative on SRS but positive on GRS, CT and MRI as described previously as well as follow-up were used for verification of these findings according to the method described by Juweid *et al.* (1996). Using these imaging modalities, foci had to be depicted in a typical manner to be rated as true-positive findings. As GRS would be underscored if it is true-positive while SRS is false-negative, it is necessary to verify such lesions by other techniques. As histologic evaluation of all detected lesions is not ethical, this is the

best approach to the problem of verification of findings false-positive in the standard of comparison.

Octreotide uptake was assessed in comparison with liver uptake using a modification of the score of Krenning *et al.* (1993) (1, lower than; 2, equivalent to and 3, higher than liver). The gastrin uptake was visually evaluated in comparison with SRS as 1, lower; 2, equivalent or 3, higher. If SRS was negative, gastrin uptake was determined in comparison with the thyroid uptake in analogy to the score described previously. For both SRS and GRS, the average uptake was calculated. The final score was derived from multiplication of the average tumour uptake value and the number of tumour sites detected.

Ki67 as a marker of tumour proliferation was documented as high (>10%), intermediate (2–10%) or low (<2%). Ki67 and the grading (high/intermediate/low differentiation) of the tumour as determined by histology were used for the determination of a possible correlation to the outcome of GRS and SRS (GRS better, SRS better or SRS and GRS equal).

Statistical analysis

Descriptive statistics were used giving a tumour-detection rate for comparison of SRS with GRS. As only histological evaluation of all lesions would allow

adequate calculation of specificity of an imaging method, specificity has not been determined. κ -Statistics were used to evaluate the inter-rater reliability for gastrin and somatostatin scanning. The correlation of the results of scintigraphy with Ki67 expression and grading was determined by Pearson's correlation coefficient. Correlation between outcome of scintigraphy and functional status/localisation of the tumours was determined in the same manner (paragangliomas were excluded from this evaluation).

Results

Patients

From July 2001 to July 2003, 122 GRS and SRS scans of 61 consecutive patients with NETs (27 female, 33 male; mean age 47.7 ± 11.4 years) were eligible for the study. GRS and SRS scans performed during follow-up of these 60 patients or scans not performed within the time limit of 21 days were not analysed. One patient thought to have a pulmonary carcinoid that proved to be small cell lung cancer later was excluded from the study.

Of the 60 evaluable patients, 51 had carcinoid tumours, 3 gastrinomas, 2 glucagonomas, 1 insulinoma and 3 paragangliomas. The majority of patients

Table 1 Comparison of GRS and SRS for all patients and for the subgroups

	No. of patients	Percentage of patients
Comparison of GRS/SRS in all patients with NET, 224 tumour sites		
No. of lesions detected: GRS 165; SRS 184		
Tumour detection rate: GRS 73.7%; SRS 82.1%		
GRS > SRS	13	21.7
GRS = SRS	18	30.0
GRS < SRS	24	40.0
GRS- and SRS-negative	5	8.3
SRS-negative	11	18.3
GRS-positive from SRS-negative	6/11	54.5
Comparison of GRS/SRS in patients with carcinoids		
No. of lesions detected: GRS 159; SRS 173		
Tumour detection rate: GRS 78.2%; SRS 85.2%		
GRS > SRS	12	27.5
GRS = SRS	16	13.7
GRS < SRS	20	58.8
SRS-negative	7	13.7
GRS-positive from SRS-negative	4/7	57.1
Comparison of GRS/SRS in patients with functional pancreatic NET		
No. of lesions detected: GRS 5; SRS 4		
Tumour detection rate: GRS 71.4%; SRS 57.1%		
GRS > SRS	2	33.3
GRS = SRS	1	16.7
GRS < SRS	1	16.7
GRS- and SRS-negative	2	33.3
GRS-positive and SRS-negative	2/4	50.0
GRS-positive from SRS-negative	2/4	50.0

($n=54$) had known metastatic disease, four had recurrent disease after R₀ resection of the primary, one had local recurrence after R₁ resection, and one had no known metastases after R₀ resection.

Side effects after the injection of minigastrin matched with those of pentagastrin testing (i.e. nausea, flush, tickling and hypotension) and were generally mild. In two patients, more severe side effects were observed (decrease in blood pressure to levels of approximately 80 over 50 mmHg), both recovering quickly without intervention.

Figure 1 Patient with a carcinoid of the smaller intestine, metastases to liver, mediastinum and paraaortic lymph nodes. High uptake in the paraaortic and liver lesions can be seen on GRS (a), anterior and (b), posterior view. On SRS (c), anterior and (d), posterior view), the large lesion in the liver is barely visible.

Figure 2 Patient with a metastasised carcinoid of the pancreatic tail. GRS (a) shows relatively low uptake into the bone metastases in the shoulder girdle and no uptake in the liver metastases. In contrast, SRS is strongly positive in all lesions (b); all scans are 24 h scans, anterior view left, posterior view right.

Figure 3 Patient with a bronchial carcinoid with metastases to lung, lymph nodes, liver and bone. GRS is positive (a), including uptake in liver metastases; (b) shows a differently windowed detail image of the liver. SRS is negative (c); all scans are 24 h scans, anterior view left, posterior view right.

Comparison of somatostatin and gastrin scans

The total number of involved sites was 224. GRS detected 165 and SRS 184. The overall tumour-detection rate was thus 73.7% for GRS and 82.1% for SRS. In 11 patients with negative SRS, GRS was positive in 6 (54.5% of SRS-negative patients). In 6 of the SRS-positive patients (12.2% of 49 SRS-positive patients), GRS was able to detect 18 additional sites of tumour involvement. Therefore, GRS detected tumour sites missed by SRS in 12 patients (20%). Average tumour uptake values were 1.8 ± 1.1 in SRS and 1.5 ± 1.0 in

Figure 4 Patient with a metastasised carcinoid of the ileum. While GRS is positive (a) showing lesions in the liver and the left mediastinum, SRS is negative (b); all scans are 24 h scans, anterior view left, posterior view right).

Table 2 Patient characteristics and per patient analysis of imaging

No.	Age	Sex	Diagnosis	Receptor status	Result	Active
1	55	f	Carcinoid (mg)	S-pos./G-neg.	S>G	y
2	65	m	Carcinoid (fg)	S-pos./G-pos.	S=G	n
3	37	m	Carcinoid (fg)	S-pos./G-pos.	S>G	n
4	33	f	Paraganglioma	S-pos./G-neg.	S>G	
5	47	m	Gastrinoma	S-neg./G-neg.	Negative	y
6	38	m	Carcinoid (fg)	S-pos./G-pos.	S<G	y
7	51	f	Carcinoid (mg)	S-pos./G-pos.	S=G	y
8	30	f	Gastrinoma	S-neg./G-neg.	Negative	y
9	24	f	Carcinoid (fg)	S-pos./G-pos.	S>G	y
10	50	f	Carcinoid (mg)	S-pos./G-pos.	S=G	n
11	37	m	Paraganglioma	S-pos./G-pos.	S>G	
12	42	f	Carcinoid (fg)	S-pos./G-pos.	S>G	n
13	46	m	Carcinoid (fg)	S-pos./G-pos.	S<G	n
14	28	f	Carcinoid (fg)	S-pos./G-pos.	S<G	y
15	17	f	Carcinoid (fg)	S-pos./G-pos.	S=G	n
16	70	f	Carcinoid (fg)	S-pos./G-pos.	S>G	n
17	49	m	Glucagonoma	S-neg./G-pos.	S<G	y
18	68	m	Carcinoid (unclear)	S-pos./G-pos.	S>G	n
19	50	f	Carcinoid (mg)	S-pos./G-pos.	S>G	y
20	57	f	Carcinoid (fg)	S-pos./G-pos.	S>G	n
21	41	m	Carcinoid (fg)	S-pos./G-pos.	S=G	n
22	39	f	Carcinoid (unclear)	S-pos./G-pos.	S>G	n
23	59	m	Carcinoid (unclear)	S-pos./G-pos.	S<G	n
24	49	f	Carcinoid (fg)	S-pos./G-pos.	S=G	n
25	38	m	Carcinoid (mg)	S-pos./G-pos.	S>G	n
26	39	f	Carcinoid (hg)	S-pos./G-neg.	S>G	n
27	39	m	Carcinoid (fg)	S-pos./G-pos.	S>G	n
28	66	m	Carcinoid (mg)	S-pos./G-pos.	S=G	y
29	41	f	Carcinoid (mg)	S-neg./G-pos.	S<G	n
30	40	m	Carcinoid (mg)	S-pos./G-pos.	S>G	n
31	56	f	Carcinoid (mg)	S-pos./G-neg.	S>G	y
32	56	m	Carcinoid (mg)	S-pos./G-neg.	S>G	y
33	49	f	Carcinoid (fg)	S-pos./G-pos.	S=G	n
34	56	f	Carcinoid (mg)	S-neg./G-neg.	Negative	y
35	61	m	Carcinoid (mg)	S-pos./G-pos.	S<G	y
36	38	f	Carcinoid (mg)	S-pos./G-pos.	S<G	y
37	50	m	Carcinoid (mg)	S-pos./G-pos.	S=G	n
38	50	f	Carcinoid (unclear)	S-pos./G-pos.	S=G	y
39	48	m	Gastrinoma (MEN I)	S-pos./G-neg.	S>G	y
40	53	m	Carcinoid (fg)	S-pos./G-pos.	S=G	n
41	53	m	Carcinoid (mg)	S-pos./G-pos.	S=G	y
42	43	f	Carcinoid (fg)	S-pos./G-pos.	S<G	n
43	40	m	Carcinoid (fg)	S-neg./G-pos.	S<G	n
44	25	m	Carcinoid (mg)	S-pos./G-pos.	S>G	y
45	49	m	Carcinoid (mg)	S-neg./G-pos.	S<G	y
46	55	f	Paraganglioma	S-pos./G-neg.	S>G	
47	42	m	Carcinoid (fg)	S-pos./G-pos.	S>G	n
48	55	m	Carcinoid (unclear)	S-pos./G-pos.	S=G	y
49	62	m	Carcinoid (mg)	S-pos./G-pos.	S>G	y
50	63	f	Carcinoid (hg)	S-neg./G-neg.	Negative	n
51	49	f	Carcinoid (fg)	S-pos./G-neg.	S>G	n
52	31	f	Glucagonoma	S-pos./G-pos.	S=G	y
53	62	m	Carcinoid (fg)	S-pos./G-pos.	S>G	n
54	50	f	Carcinoid (fg)	S-neg./G-pos.	S<G	n
55	47	m	Carcinoid (fg)	S-pos./G-pos.	S=G	n
56	60	m	Carcinoid (mg)	S-pos./G-pos.	S=G	y
57	48	f	Carcinoid (mg)	S-pos./G-pos.	S=G	n
58	58	m	Carcinoid (unclear)	S-pos./G-pos.	S=G	y
59	52	m	Carcinoid (mg)	S-neg./G-neg.	Negative	y
60	55	f	Insulinoma	S-neg./G-pos.	S<G	y

The localisation of the primary is characterised by (hg) for hindgut, (mg) for midgut, (fg) for foregut and unclear if the localisation is not known. In the last column, the functional status of the tumours is provided (functionally active or not).

GRS. According to the score from average tumour uptake and number of detected tumour sites, GRS was better than SRS in 13 patients (21.7%) and equivalent images were obtained in 18 cases (30.0%), while SRS performed better in 24 (40.0%) of the patients (the rest of the patients was negative in SRS and GRS). Especially in carcinoids, GRS scored higher in 27.5% of the patients due to the detection of more tumour sites or higher uptake. In these patients, GRS showed a detection rate of tumour sites of 78.2% and SRS of 85.2%. The complete results for all subgroups of tumour types are shown in Table 1, patient examples are shown in Figs 1–4.

κ -Statistics showed a high inter-rater reliability of 0.82 for SRS and 0.87 for GRS. Histological grading (high/intermediate/low differentiation) of the tumour was available in 36 patients with NET and Ki67 values in 32. In 27 patients, both Ki67 and grading had been determined. Ki67 values and tumour grading were missing in patients whose primary pathology had not been done in our institution. There was no significant Pearson's correlation between the results of scintigraphy and the grade of tumour differentiation ($r=0.028$, $P=0.873$), but there was a weak inverse correlation of GRS and SRS both being positive and the rate of Ki67 expression ($r=0.411$, $P=0.019$). Therefore, no conclusion can be drawn that GRS is preferable as first-line imaging modality in a certain group of patients.

No correlations between the performance of GRS or SRS and the localisation of the primary (foregut, midgut and hindgut; data of 42 patients with known localisation of the primary, $r=-0.211$, $P=0.18$) or the functional status of the NET ($r=-0.004$, $P=0.98$) was observed in the patients with gastrointestinal NET. The three patients with paragangliomas were all SRS positive, but only one was GRS-positive (Table 2).

Discussion

Our study demonstrates that GRS may provide additional information on patients with NET, especially if somatostatin uptake is missing. GRS detected additional tumour sites in 20% of all patients, half of which were negative in SRS. This indicates that minigastrin-binding CCK₂ receptors can be present in patients with missing somatostatin receptor expression (i.e. expression of the subtypes binding Octreotide). Apart from imaging, an alternative to Octreotide could also be helpful when exploring the possibilities for optimization of peptide receptor radiotherapy (PRRT) by choosing the peptide with the more favourable tumour uptake, especially in patients showing low or missing Octreotide uptake.

Figure 5 Anterior planar 24-h gastrin scan from a patient with small cell lung cancer. Uptake into the tumour and metastases is high (a), arrows while the somatostatin scan was negative (b), darker window, enlarged.

Furthermore, it may be possible to increase the efficacy of PRRT using a cocktail of peptides targeting different receptors (Reubi & Waser 2003).

Most of the radiopeptides introduced in clinical medicine or tested in clinical trials so far, are peptides also mainly targeting sstr2 and sstr5. Thus, their additional value in comparison to Octreotide with respect to targeting of new receptors is limited. The potential additional value of other non-sstr targeting peptides is abated by other properties, such as an unfavourable biodistribution with high background for example (Virgolini et al. 1994, 2002, Blum et al. 2000, Decristoforo et al. 2000, Hassenius et al. 2000, Reubi et al. 2000, Grewal et al. 2002, Janssen et al. 2002, De Visser et al. 2003, Gotthardt et al. 2004).

A possible advantage of gastrin scanning is that it can be performed in patients under therapy with long-acting somatostatin analogues without restriction as Octreotide is not known to interact with the CCK₂ receptor.

In the patient with a small cell lung cancer who had been excluded from the study because the diagnosis of a pulmonary carcinoid proved to be wrong, high uptake of gastrin in comparison with Octreotide was present (Fig. 5). GRS might thus also be of value in patients with small cell lung cancer (SCLC) where SRS does not perform well (Reisinger et al. 1998). This question should also be addressed in future studies.

In conclusion, GRS appears to add value in scintigraphic imaging in a subset of patients with NET. Gastrin scanning seems to be helpful if somatostatin scanning is negative, equivocal or showing low tumour uptake. Therefore, ¹¹¹In-DTPA-DGlu¹-minigastrin will not replace DPh¹-Octreotide in NET patients but should be positioned as an additional imaging modality in selected patients. Further studies have to be performed to address questions such as specificity of GRS in comparison with SRS or whether it may be of value in SCLC.

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