

Somatostatin Receptor Imaging In Recurrent Medullary Thyroid Cancer

L Freudenberg, E Eising, R Görge, A Bockisch

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Abstract

This study was performed to evaluate the clinical value of somatostatin receptor scintigraphy (SRS) in the diagnostic management of patients having recurrent medullary thyroid cancer (MTC).

In 22 patients with recurrent MTC after primary surgical intervention, 33 SRS were performed. Planar imaging was carried after i.v. administration of 180 MBq of [¹¹¹In]-DTPA-D-Phe¹-octreotide (Octreoscan®), SPET of the neck and thoracic regions. The scintigraphical results were compared with the tumor markers human calcitonin (hCT), CEA, other imaging methods, histological findings, and clinical follow-up.

In 36% (8/22) of the cases, SRS was concordant to the defined gold standard in the detection or exclusion of tumor tissue. If patients with liver metastases are excluded, SRS was positive in hCT levels >6.4 ng/ml and in hCT/CEA ratios >0.38.

SRS can only be recommended to clear up equivocal findings especially in patients having sufficiently elevated titers of hCT levels and hCT/CEA ratios.

INTRODUCTION

Medullary thyroid carcinoma (MTC) originates in the calcitonin-secreting cells of the thyroid gland and represents 4-9% [1] of thyroid carcinomas. In 75% of the patients, the sporadic form of the disease can be observed whereas the remaining 25% have the hereditary form [2, 3]. Up to now, the genetic defects could be detected on the chromosome 10q11.2 [4].

Human calcitonin (hCT) has been proven as the most reliable marker for primary, residual and recurrent medullary thyroid carcinoma [5, 6]. In this context, the pentagastrin-test is an important diagnostic tool.

An exact determination of the tumor spread is mandatory because surgery is the only curative treatment modality with a five-year-survival rate of 70% [7], but only about a half of the patients will be primarily in remission after total thyroidectomy and neck dissection [8,9,10,11,12]. This is caused by the early nodal spread which is reported in 35 % of the patients [13, 14], the presence of distant metastases in 10-20% of the patients at the time of diagnosis, and the resistance to chemotherapy and radiotherapy [15].

By autoradiographical methods the presence of positive somatostatin receptor staining has been reported in

40%-60% of primary medullary thyroid cancers [16].

Previously published sensitivities of in-vivo SRS are varying between 57% and 72% [17,18,19,20,21]. With regard to these differences and to the relatively high costs of SRS (comparing to CT and MRT) we want to report our results of SRS imaging in patients having recurrent MTC and compare those findings with other localization procedures, pathological and biochemical assessment.

PATIENTS AND METHODS

PATIENTS

22 patients (8 female, 14 male, age 32-73 yrs. (mean: 51.3, SD: 12.1 yrs.) with suspicion of recurrent MTC after primary surgical intervention underwent 33 SRS examinations. 18 patients suffered from the sporadic and 4 from the hereditary form of the disease (Tab. 1). Because the extent of surgical intervention has influence on SRS findings, the collective of patients was divided into three groups:

- Group 1 (n=8): patients treated by thyroidectomy alone
- Group 2 (n=11): patients who received additional neck dissection

- Group 3 (n=3): patients treated as Group 2 with additional mediastinal resection of lymphatic metastases

Figure 1

Table 1: Data of patients

Basic data										Lab results	
Pat. #	Age	Sex	Disease			previous treatment			hCT	CEA	
			sp	fam	pTNM	THYR	ND	MED		ng/ml	
1	25	F	+	-	-	+			>10.0	2145.0	
2	41	M	+	-	T4N1bM	+	+		16.9	-	
3	66	M	+	-	-	+			24.4	1.6	
"	"	"				+			39.0	2.4	
4	48	F	+	-	TxN1M1	+	+		8.8	-	
5	47	M	+	-	T3N1aM	+	+		1.8	11.0	
6	32	M	+	-	-	+	+		12.0	706.0	
7	39	F	+	-	T4NxMx	+	+		29.9	19.4	
8	60	M	+	-	T4N1aM	+	+		>10.0	-	
"	"	"				+	+		>10.0	315.0	
9	59	M	+	-	T2N1M0	+	+		0.8	9.7	
"	"	"				+	+		0.7	12.4	
10	53	M	+	-	T2bN1ANx	+	+	+	0.1	7.2	
11	30	M	+	-	T4N1Mx	+	+		6.1	398.0	
12	62	M	+	-	T3N0M0	+			0.9	2.7	
13	33	F	+	-	T2N1M0	+			6.2	32.0	
14	53	F	+	-	T2aNxMx	+			1.0	8.5	
"	"	"				+			1.3	7.7	
15	64	F	+	-	T3bN1Mb	+	+		0.7	4.3	
"	"	"				+	+		0.9	7.0	
16	53	M	+	-	T4aN1M	+	+	+	3.4	6.9	
"	"	"				+	+	+	3.5	-	
"	"	"				+	+	+	-	-	
17	44	M	+	-	T3bNxMx	+	+	+	0.2	0.9	
"	"	"				+	+	+	0.1	1.6	
18	73	M	+	-	T2aN1Mb	+			1.5	11.4	
"	"	"				+			0.2	3.4	
19	48	F	+	-	-	+	+		1.0	11.6	
"	"	"				+			1.5	-	
20	58	M	+	-	T2aN1aM0	+			3.8	-	
"	"	"				+			5.6	157.0	
21	66	M	+	-	T2bN1Mb	+	+		7.2	113.0	
22	49	F	+	-	-	+	+		2.9	157.0	

Figure 2

Pat. #	Imaging			Other localization methods			Histo.
	outcome (SRS score)	judgement	US	CT	NMR		
1	none (1)	f.n.	liver	liver	-	-	
2	mediast. (5)	r.p.	-	none	none	-	
3	cervical, bone (5)	r.p.	cervical	-	bone	pos.	
"	progress (5)	r.p.	-	-	-	-	
4	lung (5)	r.p.	liver	lung, liver	-	pos.	
5	bone (3)	f.p.	liver, cervical	liver	tibia	neg.	
6	none (1)	f.n.	liver	-	liver	pos.	
7	lung (4)	r.p.	-	lung	-	-	
8	none (3)	f.n.	liver	liver	-	-	
"	none (2)	f.n.	liver	-	liver	-	
9	none (1)	f.n.	-	lung	-	-	
"	none (1)	r.n.	cervical	cervical, lung	-	-	
10	none (1)	r.n.	none	none	-	-	
11	none (2)	f.n.	-	liver, lung, med.	-	pos.	
12	none (3)	f.n.	cervical	-	-	pos.	
13	none (1)	f.n.	cervical	-	cervical	pos.	
14	none (3)	r.n.	cervical	none	-	-	
"	none (1)	r.n.	cervical	cervical	-	-	
15	none (2)	r.n.	none	-	-	-	
"	none (1)	r.n.	cervical	none	-	-	
16	cervical (5)	r.p.	cervical	none	-	pos.	
"	none (1)	f.n.	none	-	-	-	
"	none (1)	f.n.	none	-	none	-	
17	none (1)	r.n.	none	none	-	-	
"	none (1)	r.n.	none	-	-	-	
18	cervical (4)	r.p.	cervical	-	-	pos.	
"	none (1)	r.n.	none	-	none	-	
19	none (2)	r.n.	none	none	-	-	
"	none (2)	r.n.	none	-	-	-	
20	none (1)	f.n.	none	-	-	-	
"	none (2)	f.n.	none	bone	-	pos.	
21	bone, lung (4)	r.p.	-	bone, lung	-	pos.	
22	none (2)	f.n.	-	liver	-	-	

Legend: - : not performed
 + : performed
 none: performed, but with negative result
 (1) .. (5): SRS score (see text)
 bold: SRS-positive patients
 THYR: thyroidectomy
 ND: neck dissection
 MED: mediastinotomy

METHODS

IMAGING

Planar whole body images were obtained with a double-headed Siemens Bodyscan® gamma camera, additional planar images and SPET with a single-headed Siemens Orbiter® or Siemens MultiSPECT3® gamma camera. For SPET, a step-and-shot acquisition mode, 360° circular orbiting, 64 x 64 matrix size, 64 views, and a zoom factor of 1 were used. All images were acquired in supine position.

For SRS both cameras were equipped with a medium energy parallel hole collimator. SPET was performed with 30 sec./view. A nine-point smooth prefiltering was chosen beside a ramp filter for reconstruction. Planar imaging of the whole body was carried out at 30 min., 4h, 24h, and 48h after i.v. administration of 180 MBq of [¹¹¹In]-DTPA-D-Phe¹-octreotide (Octreoscan®), SPET of the neck and thoracic regions was performed at 24 and 48 h p.i..

EVALUATION

For further comparison especially with the tumor markers, it was necessary to score the scintigraphic findings. The following 5-point score was applied:

1. no pathologic findings
2. probably not pathologic
3. equivocal
4. probably pathologic
5. sure pathologic.

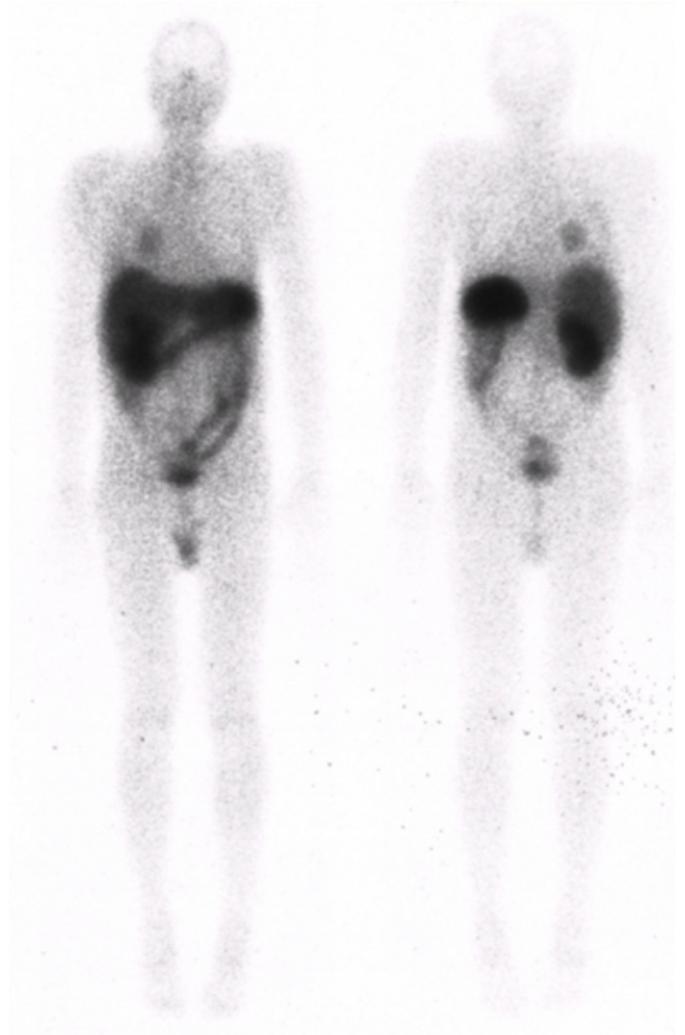
The scintigraphical results were compared with tumor markers (human calcitonin (hCT), CEA, hCT/CEA-ratio [18], imaging (e.g., penta-DMSA scintigraphy, ultrasound of the neck, computer tomography and/or NMR), histological findings, and the clinical follow-up (over a mean time period of 18 months).

RESULTS

As indicated in Tab. 1, 8 images were detected as probably or sure pathologic (score 4 or 5) by the SRS whereas 25 images showed no suspicious accumulation (score 1 - 3). In none of the 7 patients with liver metastases, the SRS was able to detect the hepatic manifestation, whereas US and/or CT led to a detection of liver metastases in 7 cases. SRS showed pulmonary metastases in 3 cases and bone metastases in 2 cases. Figure 1 shows the example of a patient with SRS positive pulmonary metastasis (patient 7). In 4 patients, SRS was useful for the decision of a cervical surgical intervention.

Figure 3

Figure 1: Whole-body-SRS (48h p.i., anterior view left, posterior view right) of patient 7 showing intense pathologic tracer-uptake in the left lung representing a pulmonary metastasis.



False positive results were obtained once in SRS (right tibia with no signs of infection or malignancy in the biopsy). On the other hand SRS led to false negative results in all locations of liver metastases and in two examinations of a patient with lung metastases (diagnosed by CT), two times in detecting bone metastases in the same patient (positive histology), in two patients (two examinations) with histologically proven cervical metastases and two times in one patient with elevated hCT level with 3.5 ng/ml. A correct negative outcome was stated in 3 examinations.

Considering the small number of examinations, a sensitivity of 36% could be calculated for SRS. After exclusion of patients with liver metastases the sensitivity increased to 50%.

GROUP-RELATED RESULTS

In group 1, SRS indicated 3 cervical lymph node metastases, 1 pulmonary tumor manifestation (see figure 1) , and 2 bone metastases, whereas both scintigraphical examinations failed in the detection of local recurrences. In this group, the (mean/SD) levels of hCT amounted to 9.1 ± 12.1 ng/ml and the CEA titer to 9.8 ± 9.7 ng/ml (hCT/CEA: 0.93). One patient showed liver metastases on US and CT.

In group 2, SRS was able to detect three pulmonary tumor manifestations. In this group with the most frequent (6/7) presence of liver metastases, hCT level was 6.2 ± 7.4 ng/ml (CEA: 147.9 ± 211.2 ng/ml). In this group the hCT/ CEA ratio of 0.035 was the lowest.

In group 3, no other tumor manifestation could be found with SRS nor with other localization methods. In these patients, the mean hCT level was the lowest of all groups with 1 ± 1.7 ng/ml (CEA: 3.2 ± 3.5 ng/ml; hCT/CEA: 0.31). No patient of this group showed liver metastases on CT or US.

RELATION OF THE SRS FINDINGS AND THE TUMOR MARKERS

Comparing the positive and negative SRS results with the the levels of hCT and CEA and the hCT/CEA ratios, it could be expected that the hCT levels (16.4 ± 4.8 ng/ml) were higher in the patients with positive findings (SRS-score 4 and 5) than in those with negative or equivocal (score 1, 2, and 3) findings (hCT: 3.4 ± 0.77 ng/ml).

The CEA levels increased with negative results, probably due to the lower grade of tumor differentiation. The mean CEA levels of the negative group amounted to 199.9 ± 110.1 ng/ml (hCT/CEA ratio: 0.1 ng/ml) and for the positive group 25.8 ± 17.7 ng/ml (hCT/CEA ratio: 5.6).

As shown in table 2, the scored findings of SRS were correlated with the levels of hCT (figure 1), CEA, and the hCT/CEA ratio:

- Four cases with sure pathological findings showed a mean hCT level of 20.9 ng/ml, a CEA level of 3.63 ng/ml, and a hCT/CEA ratio of 10.7.
- In patients with probably pathological findings these values amounted to 12.9 ng/ml for hCT, 48 ng/ml for CEA, and 0.58 for the hCT/CEA ratio.
- Patients with negative scintigraphical findings showed a significant lower average concentration

of hCT of 0.98 ng/ml (group 3), 2.2 ng/ml (group 2), and 1.6 ng/ml (group 1). The hCT/CEA ratios were averaged for the three groups by 0.23, 0.10, and 0.11.

Figure 4

Table 2: Scintigraphic score vs. levels of hCT, CEA, and the hCT/CEA ratio

SRS findings		Tumor markers (mean/SEM)		
Score	n (exam.)*	hCT [ng/ml]	CEA [ng/ml]	hCT/CEA
5	4	20.9 / 7.4**	3.6 / 1.7	10.70 / 5.1**
4	3	12.9 / 8.7	47.9 / 32.6	0.58 / 0.48
3	2	1.0 / 0.1	5.6 / 2.9	0.23 / 0.11
2	4	2.2 / 1.2	57.0 / 49.7	0.10 / 0.04
1	11	1.6 / 0.6	9.1 / 3.1	0.11 / 0.03

Legend: *) not including the examinations of patients with liver metastases
**) significant difference to score group 1 (hCT/CEA ration marginal)

Note: Data of patients with known liver metastases were not included in this table.

The mean serum concentration of hCT and CEA were 6.6 ng/ml and 159.7 ng/ml respectively, the hCT/CEA ratio amounted to 1.4. In 16 cases with negative scintigraphical findings, no increase of tumor markers could be stated in the averaged follow-up of 18 months and no tumor was found with other diagnostic methods (CT, US, and NMR). Comparing the intervals of confidence (mean \pm 2 SEM) in table 2, a significant difference in the levels of hCT and the hCT/CEA ratio can be stated between the patients with an SRS score of 1 and 5. For CEA alone, no clear differences between the patients having different SRS scores could be found. All scintigraphical examinations performed at hCT levels exceeding 6.4 ng/ml revealed a positive result, whereas all SRS failed below a threshold of about 1.5 ng/ml in hCT (and hCT/CEA ratios of < 0.064).

DISCUSSION

As expected, ultrasonography was very sensitive in detection of cervical lymph node metastases, but a presence of tumor tissue (with surgical consequences for the patient) could only be stated if further scintigraphical imaging or fine needle aspiration confirmed the diagnosis. In 4/10 of our patients with visible cervical lymph nodes on ultrasound, SRS was positive, which was histologically confirmed after a subsequent surgical intervention.

Because it is known, that SRS often fails in detection of liver metastases in MTC patients[20], US and CT remain the diagnostic procedures of primary choice for this question. In three cases with pulmonary metastases, the SRS was positive

prior to CT, which stresses the value of the SRS in the therapeutic management of the patients (avoidance of unnecessary surgical interventions in cases with disseminated pulmonary metastases).

If patients with known metastases 'only' in the liver are included, we could localize tumor manifestation with SRS only in 36% (8/22) of our patients. These results are confident to the findings of BAUDIN [22], who calculated a sensitivity of 37% in 24 patients. He examined 10 patients with liver metastases. In 6 cases with metastases in the liver only, SRS failed and the lesions could be detected only with other imaging methods.

These results were poorer than the findings of other studies (table 3) [18, 20,21,22] with a reported sensitivity of 57% - 65% (table 3). One reason may be, that 5/17 patients in the study of KWEKKEBOOM et al. [18] were examined before any surgical intervention. If these patients are excluded, the sensitivity decreases to 58%. Furthermore only 2/7 patients had no other tumor locations than liver metastases and in these two cases SRS was negative.

FRANK-RAUE et al. [21] have reported a 'sensitivity' of 57%, but this estimation was based on lesions and not individuals. If the sensitivity is calculated in the latter way, a value of only 32% would result.

It seems that the fact of 'solitary' liver metastases decreases the sensitivity of SRS and represents the cause for the wide spread of reported 'sensitivities' additionally to the small number of patients in all studies.

Figure 5

Table 3: Literature data of previous treatment, tumor markers, and sensitivities

Study [Author]	SRS [n]	previous treatment		tumor markers (mean/SEM)			Sensitivity positive SRS (n/n)
		thyroide ctomy [n]	no surgical interventi on [n]	hCT [ng/ml]	CEA [ng/ml]	hCT/CEA ratio	
Kwekkeboom et al.	17	12	5	169/82	506/228	0.34/0.32	65 % (11/17)
Frank-Raue et al.	28	28	0	8.5/2.7	101/41	0.19/0.08	32 % (9/ 28) [57 % (12/28)*]
Baudin et al.	24	24	0	6.1/2.3	369/206	0.07/0.03	37 % (9/24)
present study	33	33	0	6.6/1.6	180/85.6	1.4/0.8	36 % (8/22)

Legend: *) sensitivity as defined by the authors

PROPOSALS FOR INDICATION OF SRS

Considering the high costs of the SRS we tried to select the

patients who could benefit from the additional localization procedure with SRS. As shown only in patients with higher levels of hCT or high hCT/CEA-ratios, SRS could give additional information on tumor manifestation. Low hCT levels may be associated with minimal disease and SRS has been reported to fail in detection of small tumor sites of up to 1 cm in diameter [22]. Previous studies [16] showed a preferential labelling for somatostatin receptors on highly differentiated tumors. As described [16, 18, 20], a high hCT/CEA ratio suggests a sufficient differentiation and therefore a presence of somatostatin receptors for labelling. On the other hand, a low hCT/CEA ratio implies a poorer differentiation of MTC and therefore a limitation of the SRS as diagnostic tool.

CORRESPONDENCE TO

Dr. med. Lutz S. Freudenberg, M.A., M.B.A.
 Department of Nuclear Medicine
 University of Duisburg/Essen
 Hufelandstrasse 55
 D-45122 Essen
 Germany
 Tel: +49 / 201 723-2032
 Fax: +49 / 201 723-5964

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Author Information

Luts S. Freudenberg

Department of Nuclear Medicine, University of Duisburg/Essen

Ernst G. Eising

Department of Nuclear Medicine, University of Duisburg/Essen

Rainer Görge

Department of Nuclear Medicine, University of Duisburg/Essen

Andreas Bockisch

Department of Nuclear Medicine, University of Duisburg/Essen