Comparison of Octreotide Scintigraphy and Conventional Imaging in Medullary Thyroid Carcinoma

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We evaluated the clinical utility of positive somatostatin receptor scintigraphy in patients with medullary thyroid cancer (MTC). **Methods:** Twenty-four MTC patients with increased calcitonin levels underwent somatostatin receptor scintigraphy using ^{111}In-pentetreotide (120–200 MBq) with early (4 hr after injection) and delayed (24 hr) whole-body scans and liver SPECT imaging. In Group 1 (12 patients), conventional imaging modalities demonstrated the presence of tumor sites prior to somatostatin receptor scintigraphy; in Group 2 (12 patients), conventional imaging modalities were negative or inconclusive. **Results:** Somatostatin receptor scintigraphy had positive results in 9 of 24 patients (37%): of Group 1 patients, 7 of 12 had positive somatostatin receptor scintigraphy results. Of these patients cases, somatostatin receptor scintigraphy demonstrated several involved organs and tumor sites either identical (two patients) or smaller (five patients) in size than conventional imaging modalities. Only two patients in Group 2 had positive somatostatin receptor scintigraphy results which demonstrated significant mediastinal uptake previously classified as indeterminate on conventional imaging modalities. No new tumor site was identified nor were therapeutic options modified by the somatostatin receptor scintigraphy results. **Conclusion:** Somatostatin receptor scintigraphy only demonstrates part of tumor sites and cannot visualize small tumor sites (≤1 cm). We believe that somatostatin receptor scintigraphy has a limited role in the management of MTC patients.

Key Words: medullary thyroid carcinoma; indium-111-octreotide; scintigraphy

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Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor which arises from thyroid C-cells. The initial treatment consists of a total thyroidectomy with bilateral neck lymph node and upper mediastinum dissection (*1*). Normalization of serum calcitonin levels after surgery is a strong indicator that neoplastic tissue was totally removed. This is achieved, however, in only 20% of patients with clinical disease (*2*). Persistent elevated serum calcitonin levels in other patients indicate the presence of residual disease, which could, if localized, be treated by further surgery. A complete work-up, including ultrasonography, CT or MRI and bone scintigraphy frequently yields no positive evidence of localized tumors in these patients. Furthermore, due to previous surgical procedures, the significance of any abnormality may be ambiguous. Selective venous sampling catheterization appears to be a sensitive and specific tool for localizing the site of calcitonin production (*3*). This technique, however, is invasive and performed in only a few specialized centers. Presently, scintigraphic procedures using metaiodobenzylguanidine (*4*), ^{201}Tl-chloride (*5*), 99mTc-V-DMSA (*6*) or monoclonal antibodies directed against calcitonin (*7*) or carcinoembryonic antigen (*8*) have not demonstrated clinical utility in such patients.

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Somatostatin receptor scintigraphy, using a radiolabeled somatostatin analog (octreotide), has proven to be an efficient method for detecting tumor sites in a variety of neuroendocrine tumors (*9*). Positive findings have been reported in 65%–90% of MTC patients (*10–12*). The role of somatostatin receptor scintigraphy in the imaging strategy of these patients remains unclear, mainly because comparisons with standardized conventional imaging modalities have not been performed systematically. Furthermore, only a few patients with elevated serum calcitonin levels and negative or inconclusive conventional imaging modalities have been studied.

Therefore, we studied 24 MTC patients with either clearly identified metastases or negative or indeterminate conventional imaging modalities results despite increased calcitonin levels. We then compared the roles of somatostatin receptor scintigraphy and conventional imaging modalities in the diagnosis of tumor sites and recorded modifications in therapeutic options based on somatostatin receptor scintigraphy results.

METHODS

Patients

Twenty-four consecutive patients, with histologically proven MTC, seen in our institute between May 1993 and December 1994, were included in this prospective study. No selection criteria were used. There were 13 men and 11 women, with a mean age of 48 yr (range 32–72 yr). Familial MTC was diagnosed in five and multiple endocrine neoplasia type 2a in two patients. Twenty-three patients had elevated basal calcitonin levels (mean 6313 pg/ml; range 42–51650 pg/ml) measured by a monoclonal immunoradiometric assay (normal <10 pg/ml) (*13*). One patient with an undetectable basal calcitonin level had a positive pentagastrin test (calcitonin: 478 pg/ml). Serum carcinoembryonic antigen (CEA) level (normal <7 ng/ml) was normal in four patients and elevated in 20 patients (mean 442 ng/ml; ranges 13–4530 ng/ml).

Previous treatments included total thyroidectomy with lymph node dissection in all patients, external radiotherapy to the neck and mediastinum in nine, interferon therapy in three and chemotherapy in three.

Patients were assigned to one of two groups according to conventional imaging modalities results as reevaluated by an experienced radiologist (J. Le): Group 1 included 12 patients with tumor sites on conventional imaging modalities. Their serum calcitonin ranged from 1070 to 51650 pg/ml (Table 1). Group 2 included 12 patients with either no (six patients) or doubtful (six patients) tumor sites on conventional imaging modalities; their basal serum calcitonin ranged from <10 to 5760 pg/ml (Table 2). All patients gave informed consent for somatostatin receptor scintigraphy.

TABLE 1
Comparison of Conventional Imaging Modalities, Somatostatin Receptor Scintigraphy and Selective Venous Sampling Catheterization in MTC patients with Previously Known Tumor Sites (Group 1)

Patient no.	Serum		CIM results	SRS results	SVSC results
	Ct (pg/ml)	CEA (ng/ml)			
1	51,650	4530	Lung (n = 7), Mediastinum (n = 7), Liver (n = 4), Bone (n = 2)	Lung (n = 4)	ND
2	6610	164	Neck (n = 1), Liver (n = 6)	Liver (n = 3)	ND
3	2184	53	Neck (n = 1), Mediastinum (n = 1)	Mediastinum (n = 1)	L. Mediastinum gdt R. Iliac gdt*
4	9989	659	Liver (n = 2), Bone (n = 1)	Liver (n = 1), Bone (n = 1)	ND
5	2320	91	Neck (n = 5), Doubtful (n = 5), Lung (n = 7), Liver (n = 4)	Liver (n = 1)	ND
6	11,350	424	Lung (n = 7)	Negative	ND
7	2235	103	Liver (n = 7)	Negative	ND
8	21,900	2327	Liver (n = 7)	Negative	ND
9	9511	14	Liver (n = 2), Doubtful (n = 1)	Negative	ND
10	1070	16	Liver (n = 4)	Liver (n = 4)	ND
11	7750	153	Neck (n = 2), Mediastinum (n = 5), Doubtful (n = 5)	Negative	ND
12	5700	98	Neck (n = 1)	Neck (n = 1)	ND

*Bone metastases were discovered 12 mo later at RMI.

Ct = calcitonin; CIM = conventional imaging modalities (involved organs and number of metastases in each involved organ found by conventional and additional imaging modalities); SRS = somatostatin receptor scintigraphy (abdominal SPECT was performed in all patients, except Patient 8); SVSC = selective venous sampling catheterization; gdt = gradient; ND = not done.

Imaging

Neck palpation and standardized conventional imaging modalities, including chest radiography, bone scintigraphy and liver ultrasonography were performed in all patients as part of the routine follow-up protocol. Additional imaging methods included neck ultrasonography (16 patients), CT of the chest (17 patients), abdomen (3 patients) or bones (2 patients), which were performed according to clinical status, calcitonin and CEA levels and to complement conventional imaging modalities findings. Chest CT was systematically performed when conventional imaging modal-

TABLE 2
Comparison of Conventional Imaging Modalities, Somatostatin Receptor Scintigraphy and Selective Venous Sampling Catheterization in MTC Patients with Doubtful or Unknown Tumor Sites (Group 2)

Patient no.	Serum		CIM* results	SRS results	SVSC results
	Ct (pg/ml)	CEA (ng/ml)			
1	1200	5	Mediastinum (n = 1, doubtful)	Mediastinum (n = 1)	L. Mediastinum gdt
2	3950	30	Mediastinum (n = 2, doubtful)	Mediastinum (n = 2)	ND
3	584	22	Neck: doubtful	Negative	ND
4	69	2	Liver (n = 7, doubtful)	Negative	R. Neck. gdt
5	509	33	Liver (n = 2, doubtful)	Negative	Suprahepatic gdt and R. neck gdt.
6	<10 (478)**	3	Mediastinum (n = 2) Doubtful	Negative	ND
7	5760	41	Negative	Negative	ND
8	171	13	Negative	Negative	Negative
9	502	33	Negative	Negative	ND
10	500	16	Negative	Negative	R. Mediastinum gdt
11	151	22	Negative	Negative	Negative
12	42	4	Negative	Negative	R. Neck. gdt

*Results of calcitonin after pentagastrin test.

CT = calcitonin; CIM = conventional imaging modalities (involved organs and number of metastases in each involved organ found by conventional and additional imaging modalities); SRS = somatostatin receptor scintigraphy (abdominal SPECT was performed in all patients, except Patients 4, 5, 6, 7 and 9); SVSC = selective venous sampling catheterization; gdt = gradient; ND = not done.

ities remained negative. Selective venous sampling catheterization was performed in eight patients (*3*). In fact, selective venous sampling catheterization is considered the most sensitive and specific tool for localizing neoplastic foci. All gradients equal to or above 1.2 were considered to be significant. Results were compared separately to somatostatin receptor scintigraphy. Since the growth rate of most MTCs is slow, imaging modalities and somatostatin receptor scintigraphy were performed within 6 mo.

Indium-111-DTPA-Phe1-octreotide (120–200 MBq) was injected intravenously. No adverse reaction was noted. Quality control revealed a labeling yield of more than 98% in each batch. A 30-min dynamic neck, chest and upper abdomen was started immediately after injection (60 images of 30 sec, approximately 2 million total counts). Whole-body anterior and posterior scans were obtained 4, 24 and, if necessary, 48 hr after injection (scanning at 10 cm/mn, yielding a total of approximately 2 million, 1.6 million and 1 million counts, respectively). Abdominal SPECT was performed at 24 hr in 18 patients (64 projections of 20 sec over 360°; approximately 2,000,000 total counts). A large field of view gamma camera equipped with a medium-energy collimator was used.

Somatostatin receptor scintigraphy and conventional imaging modalities results were independently re-examined by two of us (J. Lu and J. Le). Radioactivity accumulation was considered as abnormal if present at different times. Somatostatin receptor scintigraphy results were scored using a yes-or-no system. Somatostatin receptor scintigraphy was defined as positive when at least one abnormal tumor site was visualized. In our study, the term "doubtful" identifies patients in whom conventional modality images cannot be definitely classified to be of tumoral origin because of a low tumoral burden, isolated occurrence or if differentiation from normal tissue (i.e., the thyroid) or postsurgical fibrosis was not possible. Numbers of involved organs and sites (metastases) at each organ visualized by each technique were recorded as well as tumor sites discovered by somatostatin receptor scintigraphy and modifications of therapeutic options after somatostatin receptor scintigraphy. To simplify data analysis, the maximal number of metastases in a given organ was arbitrarily set to seven.

RESULTS

Somatostatin receptor scintigraphy was positive in 9 of 24 patients (37%). Seven of 12 patients (60%) in Group 1 had positive somatostatin receptor scintigraphy scans and only two of the seven patients with positive findings had similar results on somatostatin receptor scintigraphy and conventional imaging modalities. Overall, somatostatin receptor scintigraphy visualized fewer tumor organs (8/19) and metatastic sites (16/72) than conventional imaging modalities in these seven patients, when clearly abnormal tumor organs and sites on conventional imaging modalities are considered (Table 1). Furthermore, the intensity of abnormal uptake was low in the majority of patients. Organ-by-organ analysis showed a low sensitivity of somatostatin receptor scintigraphy in all organs studied when compared to conventional imaging modalities: only 50% of the liver and bone, 33% of chest and 25% of neck (excluding normal thyroid remnants) involvements were visualized. Furthermore, the number of sites in a given involved organ as visualized with somatostatin receptor scintigraphy was underestimated when compared to conventional imaging modalities in all patients but two (Fig. 1). Hepatic SPECT performed in 11 patients confirmed the diagnosis of hepatic metastases in one patient who presented with one doubtful hepatic site on conventional imaging modalities and discovered three hepatic foci of uptake in another patient in whom planar views had previ-

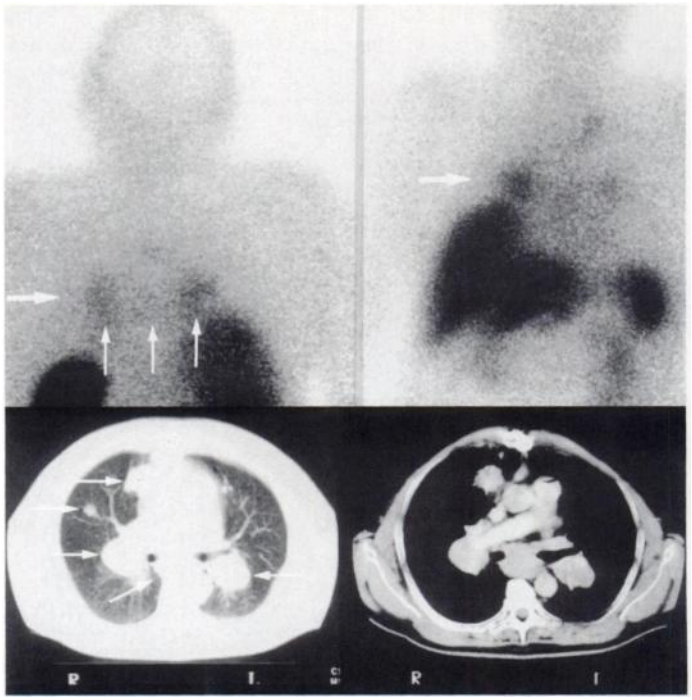

FIGURE 1. Somatostatin receptor scintigraphy anterior (A) and posterior views (B) of the neck and chest in a patient with disseminated metastases in the mediastinum and lungs. Somatostatin receptor scintigraphy demonstrates three abnormal thoracic foci, including one with weak hilar uptake (thin arrows). In comparison, chest CT performed at the hilar level (large arrow) demonstrates the presence of five metastases (thin arrows).

ously identified only one hepatic focus. SPECT provided no new information in the other nine patients, despite knowledge of hepatic metastases in six of them. No new information was discovered by somatostatin receptor scintigraphy when compared to conventional imaging modalities and therefore therapeutic options were not modified.

In Group 2, somatostatin receptor scintigraphy was positive in only two of the 12 patients with negative or doubtful conventional imaging modalities. It demonstrated an isolated mediastinal uptake (Fig. 2) in two patients with a 1 cm mediastinal mass at chest CT scan. A significant mediastinal gradient was found at selective venous sampling catheterization in one of these two patients, which resulted in further surgery and excision of a paratracheal lymph node metastasis. In the other patient, the uptake was too low to induce any modification in therapeutic options. Another chest CT scan performed 1 yr later showed a mediastinal mass of 3 cm in diameter. SPECT studies of the liver performed in seven patients yielded no

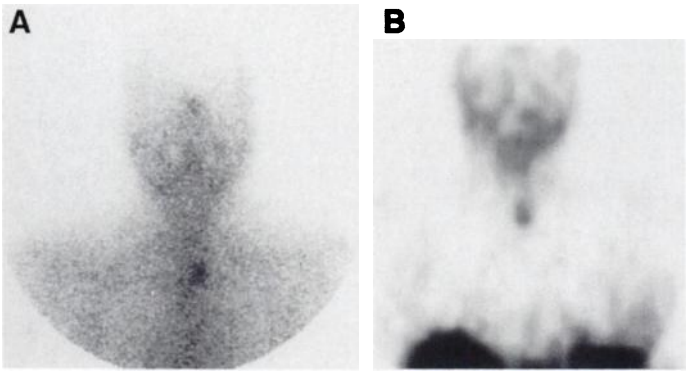

FIGURE 2. Somatostatin receptor scintigraphy anterior view (A) and coronal section (B) of the neck and chest shows pathological mediastinal uptake. Chest CT scan depicted a mass. Surgical finding was a lymph node metastasis.

FIGURE 3. Somatostatin receptor scintigraphy anterior view of the neck and chest demonstrates diffuse mediastinal uptake in a patient who had previously received external irradiation to the neck and mediastinum.

additional information. Also, no additional data were available from the dynamic studies in any of the 24 patients.

An abnormal accumulation of radioactivity was found in three patients and considered to be unrelated to the tumoral disease: in two patients who had undergone previous irradiation to the neck and mediastinum, diffuse mediastinal accumulation of radioactivity was observed (Fig. 3). Chest CT did not detect a mediastinal tumor mass in either patients. This feature delineates the field of external radiation to the mediastinum and corresponds to a radiation-induced pneumonitis with an enlarged pulmonary pleura on the chest CT scan. A pelvic focus was observed in one patient, which corresponded to a uterine fibroma.

Selective venous sampling catheterization performed in eight patients showed a calcitonin gradient in six: in two of two patients with known secondary sites and in four of six patients with unknown or doubtful secondary sites. It confirmed known tumor sites in all patients and found new tumor sites in four. Somatostatin receptor scintigraphy was positive and concordant with known tumor sites in only two of these six patients who had positive selective venous sampling catheterization, but it showed fewer sites in one of these two cases.

DISCUSSION

In patients with disseminated disease and positive results from conventional imaging modalities, we found that somatostatin receptor scintigraphy had a sensitivity (60%) similar to previously reported results (*10–12*).

False-negative somatostatin receptor scintigraphy results have already been reported in MTC patients, mainly in the liver (*10–12*). The present study confirms these results and demonstrates that false-negative somatostatin receptor scintigraphy results are not restricted to the liver but can be observed in all organs. Since standardized conventional imaging modalities was performed in all patients, this study quantifies the sensitivity of somatostatin receptor scintigraphy for each organ: 50% of liver and bone, 33% of chest and 25% of neck involvement were visualized. Many parameters may influence the comparison between somatostatin receptor scintigraphy and conventional imaging modalities results, including the extent of conventional imaging modalities performed prior to somatostatin receptor scintigraphy and the experience of the radiologist. Conventional imaging modalities performed in our study was standardized and complete and no unknown focus was discovered with somatostatin receptor scintigraphy. In contrast to previous series, somatostatin receptor scintigraphy permitted the discovery of unknown foci in a few MTC patients, but even this did not induce any subsequent modification in therapeutic options. Discrepancies between studies could also be explained by difference in tumor volume at the time of somatostatin receptor scintigraphy and extent of previous treatment. In particular, extent of previous lymph neck node dissection could modulate somatostatin receptor scintigraphy results.

In patients with an isolated increase of serum calcitonin levels, somatostatin receptor scintigraphy was positive in only two patients with indeterminate CT images of the mediastinum because of the relatively small tumor size (1 cm). Both patients had positive somatostatin receptor scintigraphy. In one patient, radiolabeled octreotide uptake was too low to induce additional imaging modalities or therapy. The presence of a lymph node metastasis was confirmed 1 yr later on the CT scan. In the other patient, the lymph node depicted on the CT scan was highly suspect, and we did believe that somatostatin receptor scintigraphy provided additional relevant information. Selective venous sampling catheterization was performed in parallel in one of these two patients, the results of which supported our view in that a CT gradient was demonstrated. A lymph node was found at surgery. Neither abdominal SPECT nor dynamic studies detected small tumor masses in these patients. Despite the possibility that false-positive conventional imaging modalities results cannot be excluded, somatostatin receptor scintigraphy results in MTC patients with inconclusive results from conventional diagnostic tests confirms the poor performance of somatostatin receptor scintigraphy in the detection of tumor masses. In our study, somatostatin receptor scintigraphy provided far less information than selective venous sampling catheterization despite abdominal SPECT studies in most patients. Dörr (*11*) pointed out the interest of chest SPECT in patients with elevated serum calcitonin levels. In fact, 65% (13/20) of his patients had positive chest SPECT scans despite negative planar images. Moreover, SPECT abnormalities were concordant with selective venous sampling catheterization gradients in most patients. The exact extent of conventional imaging modalities performed in these patients was not accurately defined. It was also not mentioned whether or not both techniques were independently examined. Furthermore, histological results were concordant with previous somatostatin receptor scintigraphy in only two of the four reoperated sites. Therefore, the clinical interest of such positive foci detected only by SPECT is still a matter of debate.

Clearly, abnormal but not tumoral foci of radioactive uptake with this new scintigraphic imaging technique has been reported (*12*). We identified increased mediastinal uptake, already reported by Krenning et al. (*14*) in two patients who had received external radiotherapy to the neck and mediastinum (Fig. 3). An enlarged pleura was observed in these patients at CT scan, similar to that observed in patients after mediastinal irradiation for other conditions. Such uptake could explain some of the foci previously reported and should be considered as false-positive uptake.

Our results corroborate in vitro studies (*16*), but somatostatin

receptors were expressed in only 35% of MTC and most tumor sections exhibited low receptor density (*16*). The present study is further proof of the good relationship between in vitro and in vivo studies for detecting somatostatin receptors in neuroendocrine tumors (*10,15*). Our results are also in accordance with the absence of antitumoral results demonstrated in MTC patients treated with a somatostatin analog (*17*). Therefore, we believe that symptomatic effects of somatostatin analogs should be explored by somatostatin analog test rather than somatostatin receptor scintigraphy in the clinical management of patients with MTC.

CONCLUSION

Somatostatin receptor scintigraphy did not improve tumor staging patients or detect small (≤1 cm) tumor masses in our series of patients with MTC. We believe that octreotide scintigraphy should not become part of the routine imaging strategy for MTC patients.

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Indium-111-Pentetreotide Uptake in Endocrine Tumors and Lymphoma

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The biodistribution of ^{111}In-pentetreotide was assessed in patients with gastroenteropancreatic (GEP) neuroendocrine tumors or lymphoma and in control patients and analyzed as a function of scanning time, presence or absence of tumor uptake, tumor type and previous octreotide treatment. **Methods:** Patients underwent imaging 4 and 24 hr after injection of approximately 200 MBq ^{111}In-pentetreotide. The frequency of organ visualization was assessed on planar views. Total organ and tumor uptake (% injected dose [ID]) was determined using the geometric mean method and regional tissue uptake (% ID/100 ml) by semiquantitative SPECT. **Results:** Liver, spleen, kidneys and urinary bladder were visualized in all patients. Thyroid, bowel and pituitary were more often visualized at 24 hr than at 4 hr. Activity in the gallbladder, breast, ureters and ascites was only occasionally observed. Total liver, spleen and thyroid uptake was stable over time, whereas kidney activity decreased slightly. At 24 hr, regional uptake was threefold lower in the liver than in the spleen or kidneys and was similar in the three groups. In patients with long-term octreotide therapy, a positive correlation was found between the duration of octreotide therapy and liver or spleen uptake. Total and regional tumor uptake showed high intraindividual and interindividual variations. Total tumor activity was stable over 24 hr in patients with GEP and decreased in those with lymphoma. The mean regional tumor uptake was 10-fold lower in patients with lymphoma than in those with GEP. Cold octreotide injected 24 hr after tracer administration did not result in any displacement of organ and tumor activity. **Conclusion:** Organ uptake seems not to be influenced by the presence of ^{111}In-pentetreotide-positive lesions or by tumor type. Tumor uptake is highly variable among patients and clearly lower in patients with lymphoma than in those with GEP. The widespread of uptake values in tumors indicates that radiotherapy using radiolabeled somatostatin analogs may not be applicable to all patients with ^{111}In-pentetreotide-positive tumors.

Key Words: indium-111-pentetreotide; quantification; endocrine tumors; lymphoma

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Over the past years, somatostatin receptor imaging has been introduced for in vivo evaluation of tumors, especially those of neuroendocrine origin, which are known to bear high-affinity somatostatin receptors (*1,2*). The procedure is now performed using ^{111}In-pentetreotide, a DTPA-coupled somatostatin analog, characterized by easy and efficient labeling, fast clearance

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