

# Radiolabeled Somatostatin Analog Scintigraphy in Differentiated Thyroid Carcinoma

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After intravenous administration of a radiolabeled somatostatin analog (octreotide), an image of the thyroid gland is frequently observed; few data are available, however, on somatostatin receptors in epithelial thyroid cells assessed *in vitro* and on images of differentiated thyroid carcinoma (DTC) with pentetotide scintigraphy. **Methods:** In four patients with metastatic thyroid carcinoma, whole-body scintigraphy was performed 4 to 48 hr after injection of 110 MBq of  $^{111}\text{In}$ -pentetotide. The results were compared to data obtained with other imaging modalities, including scintigraphy performed after administration of a therapeutic dose of  $^{131}\text{I}$ . **Results:** There were positive foci in distant metastases on  $^{111}\text{In}$ -pentetotide scintigraphy. Pentetotide scintigraphy was positive in two patients with an "insular" form of DTC, one of whom had a positive (faintly)  $^{131}\text{I}$  scan. Of the other two patients with papillary DTC without radioiodine uptake, only one exhibited a certain degree of pentetotide scintigraphy positivity in distant metastases. **Conclusion:** These results show promise for exploration of insular thyroid carcinoma and suggest that these carcinomas may possess functional differentiation features, including somatostatin receptors.

**Key Words:** thyroid cancer; thyroglobulin; somatostatin receptors; pentetotide

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The uptake of a labeled somatostatin analog (octreotide) has been described in most neuroendocrine tumors, malignant lymphomas and in some breast and kidney adenocarcinomas (1-3). Radiopharmaceutical accumulation is observed in the normal thyroid gland, but initial *in vitro* studies did not demonstrate somatostatin receptor uptake in epithelial thyroid cells (1). We evaluated the uptake of pentetotide in patients with distant metastases from differentiated thyroid carcinoma (DTC) as a functional imaging modality.

## CASE REPORT

A 52-yr-old man (Patient 1) with an insular form of thyroid carcinoma (4) had a large iliac bone metastasis at diagnosis in

August 1992. This metastasis was partially resected and a total thyroidectomy with neck dissection was performed in November 1992, revealing a right thyroid tumor of 4 cm in diameter with capsular invasion and extension into surrounding tissues and involvement of four lymph nodes.

In December 1992, radioiodine treatment (3.7 GBq of  $^{131}\text{I}$ ) was administered, but a post-therapeutic whole-body scan obtained 5 days later disclosed no uptake in the metastases. Technetium-99m-diphosphonate bone scintigraphy, on the other hand, showed multiple foci of uptake corresponding to bone lesions (ribs, vertebrae, sacrum, right humerus), which were confirmed by CT. Between January and April 1993, external radiotherapy was delivered to the patient's painful sites and locations at risk of pathological fracture and also to the cervico-mediastinal region. In June 1993, a tracheal recurrence was diagnosed which caused acute dyspnea. It was treated by adrenocortical steroid treatment and tracheotomy. In the presence of this progressive disease and the lack of an effective therapeutic modality, we wanted to see whether palliative treatment such as octreotide therapy, apparently free of major side effects, could be useful for this patient (5,6). Radiolabeled octreotide scintigraphy was performed to determine the presence of somatostatin receptors in tumor sites.

## Scintigraphic Procedure

A whole-body scan was obtained 4, 24 and 48 hr after intravenous injection of 110 MBq  $^{111}\text{In}$ -pentetotide. The images were obtained using a large field of view gamma camera equipped with a medium-energy collimator. The number of foci exhibiting uptake and their intensity (compared to hepatic uptake) were recorded.

## RESULTS

Octreotide scintigraphy was positive in Patient 1, showing uptake of  $^{111}\text{In}$ -pentetotide in some metastatic sites (Fig. 1). The number of foci showing uptake, however, was lower than the number of known metastatic sites (first and second left ribs, left scapula, lumbar and cervical spine, left pubis, left femoral diaphysis, the upper part of the right humerus, local cervical recurrence), and the uptake intensity was lower than the physiological hepatic uptake.

## Additional Cases

The positive results obtained with Patient 1 prompted us to study three other patients with distant metastases from DTC. The clinical, histological, biological and scintigraphic characteristics of the four patients are summarized in Table 1.

As with Patient 1, Patient 2 had an insular form of thyroid carcinoma (4) and Patients 3 and 4 had a common form

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**FIGURE 1.** Patient 1. (Left) Anterior view of  $^{111}\text{In}$ -pentetreotide whole-body scan with several foci on right humerus, first left rib, cervical and lumbar vertebrae. (Right) Posterior view of  $^{111}\text{In}$ -pentetreotide scintigraph with foci corresponding to the same lesions.

of papillary carcinoma (7). Immunohistochemistry was performed and staining was positive for thyroglobulin and cytokeratin (KL1) in all patients, and positive for neuron-specific enolase in some cells in Patients 1, 2 and 4. Immunostaining with chromogranin A and somatostatin in Patients 1, 2 and 4 was negative. Serum thyroglobulin levels were elevated during thyroxine suppressive treatment. A post-therapeutic whole-body scan was obtained 5 days after administration of 3.7 GBq (100 mCi) of  $^{131}\text{I}$  in the patients after thyroxine withdrawal. This scan disclosed metastatic uptake only in Patient 2. Pentetreotide scintigraphy was performed within a 6–12-mo interval after the

**TABLE 2**  
Pentetreotide Scintigraphy Results

Patient no.	Pos. sites*	Intensity <sup>†</sup>	Localization
1	5	+ / + +	Bones
2	3	+	Lymph node, lung, adrenal
3	0	0	None
4	4	+	Pleura, lung, mediastinal nodules

\*Number of radiolabeled octreotide uptake foci.  
<sup>†</sup>Uptake intensity compared to physiological uptake in liver: + if inferior to the liver and ++ if equal to the liver.

negative iodine scan while patients were undergoing thyroxine therapy.

Localization of metastases in the four patients was assessed by conventional imaging modalities (CT, ultrasound, bone scintigraphy). The diagnosis was histologically confirmed by surgery on bone metastases (iliac bone for Patient 1) or biopsy of lymph node, lung and adrenal gland (Patients 2, 3, 4). A biopsy was not performed for the other metastatic sites; their metastatic nature was confirmed with conventional imaging modalities. The results are summarized in Table 2.

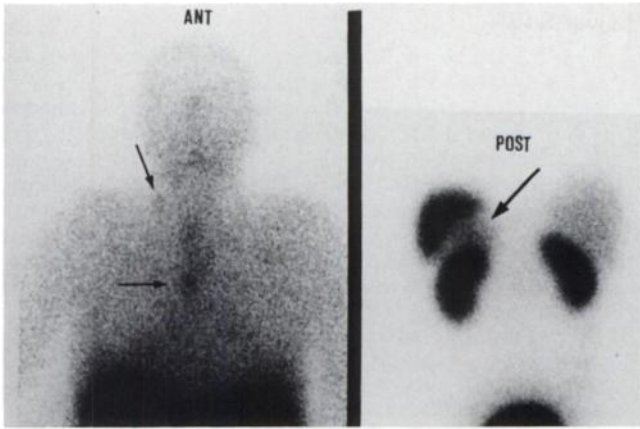
Patient 2 showed metastatic uptake of  $^{111}\text{In}$ -pentetreotide (Fig. 2) similar to that already described for Patient 1. The number of foci exhibiting tracer uptake, however, was lower than the number of known metastatic sites. Uptake was higher in Patient 1 than in Patient 2. In both patients, it was lower or equal to that of the liver. No uptake was found in the metastases of Patient 3. Patient 4 showed uptake in the chest, corresponding to pleura and faint uptake of  $^{111}\text{In}$ -pentetreotide in the macronodular lung metastasis (Fig. 3). Although multiple cytological examinations of pleural fluid were performed in this patient, no evidence of malignancy was discovered. As already de-

**TABLE 1**  
Clinical, Biological, Histological and Scintigraphic Characteristics

Patient no.	Age (yr)	Sex	Pathological type	Immunological staining	Metastatic sites	Tg* (ng/ml)	Iodine scan
1	52	M	insular	Tg + /NSE + /chr A - KL1 + /SMS -	bone, lymph nodes	21,000	-
2	64	M	insular	Tg + /NSE + /chr A -/ KL1 + SMS -	lung, lymph nodes, adrenal gland	60,000	+
3	52	M	papillary	Tg + /NSE - /chr A - / KL1 + /SMS nd		120	-
4	64	M	papillary	Tg + /NSE + /chr A - / KL1 + /SMS -	lung, mediastinum	800	-

\*Thyroglobulin blood level.

Tg = thyroglobulin; NSE = neuron-specific enolase; chr A = chromogranin A; KL1 = cytokeratin; SMS = somatostatin; nd = not done.



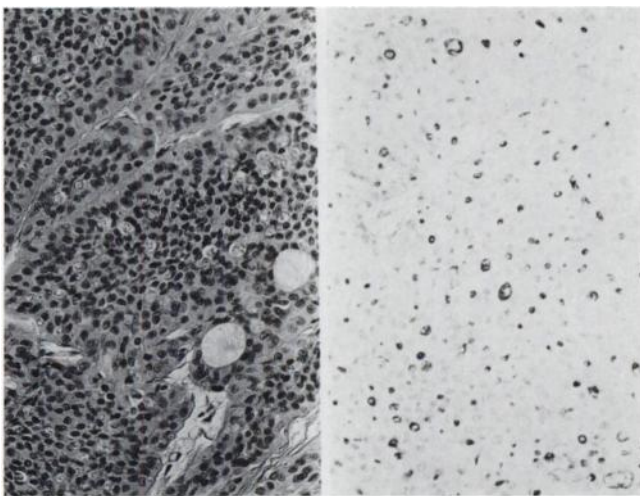
**FIGURE 2.** Patient 2. (Left) Anterior view of  $^{111}\text{In}$ -pentetreotide whole-body scan with foci corresponds to a right cervical lymph node and a mediastinal metastasis (arrows). (Right) Posterior view of whole-body scan with a left adrenal metastasis (arrow).

scribed, uptake of octreotide can correspond to inflammatory lesions (1).

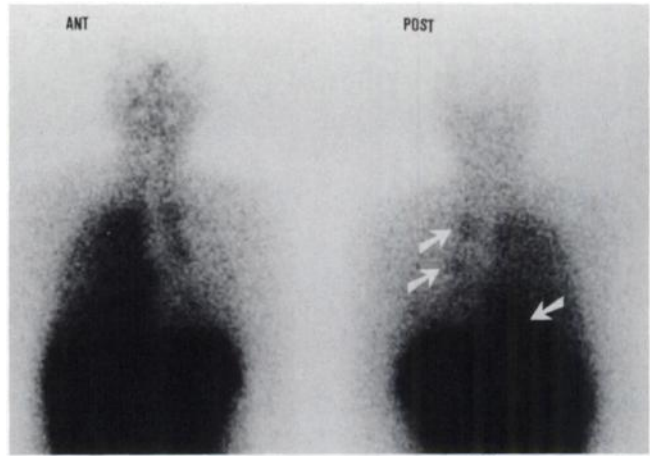
We compared the pentetreotide scintigraph of Patient 2 with the patient's  $^{131}\text{I}$  whole-body scan. Diffuse pulmonary uptake was observed in both lungs with  $^{131}\text{I}$ , but there was no adrenal uptake.

## DISCUSSION

Clinical evaluation of pentetreotide scintigraphy did not include patients with DTC because somatostatin receptors were not clearly visualized in vitro in DTC (1). Recent studies, however, have shown that somatostatin inhibits basal and TSH-stimulated adenylate cyclase activity in normal and neoplastic human thyroid tissues (8) and that octreotide inhibits cell growth and protease activity in papillary and follicular thyroid carcinomas (9). A recent study demonstrated ligand binding to somatostatin receptors in



**FIGURE 4.** Photomicrograph (250 $\times$ ) corresponds to the thyroid tumor in Patient 1. (Left) Architectural pattern of insulae and presence of small follicles. (Right) Positive staining for thyroglobulin at the neoplastic follicular level and of the cytoplasm of many tumor cells.



**FIGURE 3.** Patient 4. (Left) Anterior view of  $^{111}\text{In}$ -pentetreotide scintigraphy with diffuse right-sided pulmonary uptake probably corresponds to pleura. (Right) Posterior view of whole-body scan with positive uptake in the right basal nodule and two nodules of the para-mediastinal region of the left lung (arrows).

membranes and cell lines of human thyroid carcinoma but did not identify which of the receptor subtypes were expressed (10).

During pentetreotide scintigraphy, radioactivity accumulates in normal and diseased thyroids, but it is unclear which mechanism is responsible for this accumulation: somatostatin receptors were demonstrated in medullary thyroid carcinoma and on activated lymphocytes in Grave's II disease (1). Insular thyroid carcinoma is a poorly-differentiated thyroid cancer histologically defined as the "formation of solid clusters (insulae) of tumor cells containing a variable number of small follicles; small size and uniformity of tumor cells, consistently present mitotic activity; capsular and blood vessel invasion and frequent necrotic foci" (4) (Fig. 4). Immunohistochemistry is positive for thyroglobulin and radioiodine uptake has been found in some, but not in all insular carcinomas (4,11). Patient follow-up provided evidence that this tumor type is an aggressive and often lethal form of DTC. In the study of Carcangiu et al. (4), 80% of patients (21/25) developed metastases (64% in cervical nodes, 20% in mediastinal nodes, 44% in the lung and 36% in bone). Approximately 30% of papillary thyroid carcinoma fail to take up radioiodine, making it impossible to perform scintigraphic imaging with  $^{131}\text{I}$  (12).

Our results suggest the clinical efficacy of pentetreotide scintigraphy in DTC as follows:

1. Pentetreotide scintigraphy could be useful for imaging tumor sites when there is no  $^{131}\text{I}$  uptake in patients with elevated thyroglobulin levels and negative  $^{131}\text{I}$  post-therapeutic scans.
2. Uptake in tumor sites could signify the presence of somatostatin receptors, thus increasing the chance of using some form of octreotide therapy in patients with metastases who cannot be treated by other modalities.

3. Pentetreotide scintigraphy could provide data on the aggressiveness of the disease, such as those reported for neuroblastoma (13).

In conclusion, our results suggest that pentetreotide scintigraphy could play a role in the exploration of DTC, especially when radioiodine uptake is absent or low.

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