Comparison of Radiolabeled Octreotide and Meta-Iodobenzylguanidine (MIBG) Scintigraphy in Malignant Pheochromocytoma

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Methods: The results of in vivo somatostatin scintigraphy were correlated with those of MIBG from 14 patients, aged 22–66 yr, with metastatic pheochromocytoma (10 patients), malignant paraganglioma (3 patients) and metastatic ganglioneuroblastoma (1 patient). Twelve patients had elevated catecholamine excretion. A dynamic study and serial whole-body scans (4–48 hr) were obtained after injection of 130–187 MBq of ^{111}In-DTPA-Phe-1-octreotide. When indicated, SPECT imaging was done. The results were compared to MIBG scans obtained after a diagnostic or a therapeutic dose. **Results:** Three patients with more than 20 tumor sites on MIBG scans had only 1–9 sites on ^{111}In-octreotide scintigraphy. Two patients had no MIBG uptake but one had lung uptake on octreotide scintigraphy. In the other 9 patients with a total of 41 foci of MIBG uptake, 33 sites of ^{111}In-octreotide uptake are found. All positive images with octreotide scintigraphy were seen at or before 4 hr, but the contrast improved at 24 hr. Uptake intensity was lower with ^{111}In-octreotide than MIBG and the number of tumor sites was higher with MIBG. However, seven foci were positive only on octreotide scintigraphy and six of them could not be confirmed by other imaging modalities. **Conclusion:** Use of octreotide to identify somatostatin receptors seems promising, especially when results from MIBG scans are negative. Moreover octreotide images could aid in determining a treatment regimen as well as establishing the extent of disease and prognosis.

Key Words: malignant pheochromocytoma; indium-111-octreotide; meta-iodobenzylguanidine

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Tumors derived from neuroectodermal chromaffin tissue are rare and generally associated with catecholamine overproduction. They may arise from the adrenal medulla (pheochromocytomas and ganglioneuroblastomas) or from sympathetic paraganglia (para-aortic paragangliomas or extra-adrenal pheochromocytomas).

Malignant behavior characterized by local invasion or by the presence of chromaffin tissue in sites where it is normally absent, i.e., bone, liver and lung occurs in about 10% of pheochromocytomas and more frequently in para-aortic paragangliomas (28%–42%) (*1–4*). The malignancy must be distinguished from a multicentric disease which is possible with this kind of tumor. More than 40% of the patients do not have metastases at the time of initial surgery, but metastases are discovered during prolonged follow-up by combining urinary measurement of catecholamines and derivatives with the results of the MIBG scintigraphy (*5–7*). MIBG uptake is found in 90% of these tumors and is the most sensitive tool for in vivo localization of neoplastic foci (*1,8*). The presence of somatostatin receptors in these tumors has been demonstrated in vitro (*9,10*); successful in vivo localization with ^{111}In-octreotide scintigraphy has recently been reported (*10,11*).

In this study, octreotide images were obtained from 14 patients with malignant tumors arising from chromaffin cells. Image results were compared with MIBG scintigraphy as well as ultrasound, CT or MRI, and bone scintigraphy.

MATERIALS AND METHODS

Patients

Octreotide imaging was performed on 14 patients (9 male, 5 female, mean age 41.4 yr, range 22–66 yr) because of its potential benefit (Table 1). The delay from initial diagnosis of tumor until ^{111}In-octreotide scintigraphy varied from 6 mo to 24 yr (mean 7.6 yr). Histological confirmation of chromaffin tumor was obtained in all patients either before or after scintigraphy. Malignancy was ascertained by local invasion or by the finding of chromaffin tissue at sites where it is normally absent (bone, liver, lung and lymph nodes). This led to the diagnosis of malignant pheochromocytoma in 10 patients, malignant paraganglioma in three patients (one metastatic and two locally invasive) and of metastatic ganglioneuroblastoma in one patient. Patient 10, who had undergone surgery for a bilateral malignant pheochromocytoma, also had undergone surgery for four local relapses and a cervical paraganglioma.

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TABLE 1
Clinical, Biological and Therapeutic Characteristics

Patient no.	Age (yr)	Sex	Histological type	Delay from diagnosis	Tumor primary site	Metastatic locations	Catecholamine excretion*	Surgery	MIBG therapy†	Chemo-therapy‡	Radio-therapy
1	39	M	Pheochromocytoma	16 yr	Right adrenal	Bones, testis	NMN:37549	+	11.1 GBq	−	−
2	44	M	Pheochromocytoma	7 yr	Left adrenal	Bones, parotid	normal	+	14.8 GBq	+	+
3	42	M	Pheochromocytoma	8 yr	Right adrenal	Bones	NMN:75400	+	−	−	+
4	29	M	Pheochromocytoma	4 yr	Right adrenal	Bone, lung	NMN:3611	+	−	+	−
5	43	F	Pheochromocytoma	1 yr	Left adrenal	Lung	normal	+	−	+	−
6	44	M	Pheochromocytoma	5 yr	Zuckerkandl organ	Bones	NMN:19379	+	14.8 GBq	−	−
7	66	F	Pheochromocytoma	24 yr	Right adrenal	Bones, liver	NMN:10596	+	3.7 GBq	−	+
8	39	F	Pheochromocytoma	13 yr	Left adrenal	Bones	NMN:5443	+	3.7 GBq	−	−
9	39	F	Pheochromocytoma	3 yr	Left adrenal	Lymph nodes	NMN:13519 MT:139704	−	−	−	−
10	22	M	Pheochromocytoma	13 yr	Bilateral adrenals	Unknown sites	NMN:5918	+	−	−	−
11	46	M	Paraganglioma	7 yr	Retroperitoneal	Retroperitoneal	NMN:5988	+	22.2 GBq	−	−
12	43	M	Paraganglioma	4 yr	Retroperitoneal	Lung, liver	NMN:132110	−	−	−	−
13	25	F	Multiple paraganglioma	6 mo	Retrocaval	Latero-aortic, cervical	NMN:12920	−	−	−	−
14	59	M	Ganglio neuroblastoma	1 yr	Right adrenal	Bones, lung, liver, lymph nodes	dopamine:2931 MT:1936	+	−	+	−

*NMN (normetanephrine) = <2000 nmol/24 hr; MT (methoxytyramine) = <1600 nmol/24 hr; Dopamine = <1800 nmol/24 hr.
†cumulative doses of ^{131}I-MIBG.
‡Etoposide-cisplatin. Patient 2 also received doses of cyclophosphamid-vincristine-deticene.
+ = surgery occurred.
− = surgery did not occur.

Conventional imaging, excluding MIBG scintigraphy, showed that the tumor was disseminated in 12 patients. Patient 11 had a retroperitoneal inoperable paraganglioma and Patient 10 had an increased urinary excretion of catecholamines and metabolites, but no other evidence of disease. Conventional imaging discovered bone metastases in eight patients, lung metastases in four, liver metastases in three, soft-tissue metastases (testis and parotid gland) in two, lymph node metastases in two and abdominal tumors in five patients.

Eleven patients had previous surgery on the primary tumor. Three had surgery and external radiotherapy on bone metastases. Six patients had received treatments with ^{131}I-MIBG, four with chemotherapy and two with somatostatin analogs, which were stopped 6 mo before scintigraphy.

Urinary excretion of catecholamines and metabolites was elevated in 12 patients and normal in two (Patients 2, 5).

Octreotide and MIBG Imaging

Each patient underwent octreotide scintigraphy; data from MIBG imaging were available within a period of 1–14 wk before or after octreotide scintigraphy (mean = 3.5 wk).

Indium-111-DTPA-Phe-1-octreotide (130–187 MBq) was injected intravenously. Quality control by chromatography revealed a labeling yield superior to 98% in each preparation. No adverse reaction was observed after injection. A 30-min dynamic study was started immediately after injection (60 images for 30 sec, 2,000,000 total counts). A whole body anterior and posterior scan was obtained at 4, 24 and 48 hr after injection (scanning at 10 cm/mn, yielding a total of 2,000,000, 1,600,000 and 1,000,000 counts, respectively). When indicated, SPECT imaging was performed 24 hr (64 projections of 20 sec over 360°) after octreotide imaging. Anterior and posterior views were obtained using a large field of view gamma camera equipped with a medium-energy collimator.

A diagnostic dose of either ^{123}I-MIBG (74 MBq) or ^{131}I-MIBG (37 MBq) was injected into nine patients (Patients 2–5, 8, 10 and 12–14) prior to imaging. Patient 10 received 370 MBq of ^{131}I-MIBG after an equivocal result with ^{123}I-MIBG. All patients were given Lugol's solution for 3 days before and 4 days after MIBG administration. A whole-body anterior and posterior scan was done at 24 hr after injection of ^{123}I-MIBG and at 48 hr, 72 hr and 7 days after injection of ^{131}I-MIBG.

A therapeutic dose of ^{131}I-MIBG (3.7 GBq) was administered to four patients (Patients 1, 6, 7 and 11) and an MIBG scan was obtained. All patients were given Lugol's solution for 7 days before and 1 mo after i.v. injection of MIBG. A baseline diagnostic ^{123}I-MIBG scan was available for all patients, up to 1 yr before ^{131}I-MIBG treatment. A whole-body anterior and posterior scan was obtained at 2 and 5 days after i.v. using a home-made, double-probe rectilinear scanner equipped with a high-energy collimator. All patients except two (Patients 1 and 11) had ^{111}In-octreotide scintigraphy before MIBG treatment. For one patient (Patient 9), the two types of MIBG imaging were done within a 1 wk interval.

Images were interpreted blindly by three observers (JL, AM, FT) in the following way: The uptake of ^{111}In-octreotide or MIBG was assessed for each site. If present, its intensity was compared to the background of the liver and quoted as:

+ if less intense than the liver
++ if equal to the liver
+++ if more intense than the liver

TABLE 2
Octreotide and MIBG Scintigraphy Results

Patient no.	Octreotide: No. of uptake foci	Octreotide: Intensity	Diagnostic MIBG: Isotope (dose)	Diagnostic MIBG: No. of uptake foci	Diagnostic MIBG: Intensity	Post-therapeutic ^{131}I-MIBG: Dose	Post-therapeutic ^{131}I-MIBG: No. of uptake foci	Post-therapeutic ^{131}I-MIBG: Intensity
1	1	+				3.7 GBq	>20	++/+++
2	9	+/++	^{123}I (74 MBq)	>20	+++	—		
3	5	+	^{123}I (74 MBq)	>20	+++			
4	0	0	^{123}I (74 MBq)	0				
5	1	+	^{123}I (74 MBq)	0				
6	4	+				3.7 GBq	6	++/+++
7	2	+				3.7 GBq	5	+
8	3	+	^{123}I (74 MBq)	3	++			
9	2	+				3.7 GBq	7	+
10	1	+	^{131}I (370 MBq)	1	+			
11	1	+				3.7 GBq	1	+++
12	4	+++	^{123}I (74 MBq)	6	+++			
13	3	+/++	^{131}I (37 MBq)	2	+++			
14	13	++/+++	^{123}I (74 MBq)	10	++/+++			

+ = low
++ = medium
+++ = high

The number of uptake sites on ^{111}In-octreotide and MIBG scans was recorded separately. Results of ^{111}In-octreotide and MIBG then were compared.

RESULTS

Octreotide scintigraphy demonstrated abnormal accumulation of radioactivity in 13 of the 14 patients (93%). Comparison with MIBG results is summarized in Table 2.

For Patients 1, 2 and 3 MIBG scintigraphy demonstrated more than 20 foci of increased uptake (Fig. 1). Most of the foci corresponded to bone metastases. Octreotide scintigraphy showed abnormal accumulation in only 1, 9 and 5 sites. The intensity of ^{111}In-octreotide uptake was lower than with MIBG. Soft tissue lesions (testis or parotid gland) were demonstrated by both methods.

Patients 4 and 5 had no MIBG uptake in their primary or metastatic sites (lung, bone and lymph nodes). No uptake of octreotide was found in Patient 4. Octreotide scintigraphy showed one focus of lung uptake in Patient 5 (Fig. 2). It corresponded to a lung metastasis, confirmed by biopsy, whereas the primary abdominal tumor was not visualized.

Patients 6–14, who had a limited number of tumor sites, showed a total of 41 foci of MIBG uptake. Octreotide scintigraphy were positive in all these patients and demonstrated a total of 33 sites. All foci of octreotide uptake were seen at 4 hr after injection but contrast improved at 24 hr.

Twenty-six foci were positive on both MIBG and oc-

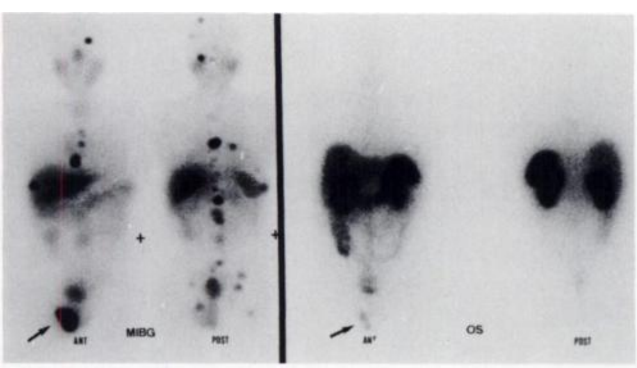

FIGURE 1. MIBG images from Patient 1 who has a malignant pheochromocytoma. (Left) Anterior and posterior views show multiple foci corresponding to bone metastases (vertebrae, ribs and skull) and a metastasis to the right testis (arrow). (Right) Anterior and posterior views of octreotide scintigraphy, demonstrating only an abnormal accumulation on testicular localization (arrow) contrasting with the absence of visualization of bone metastases.

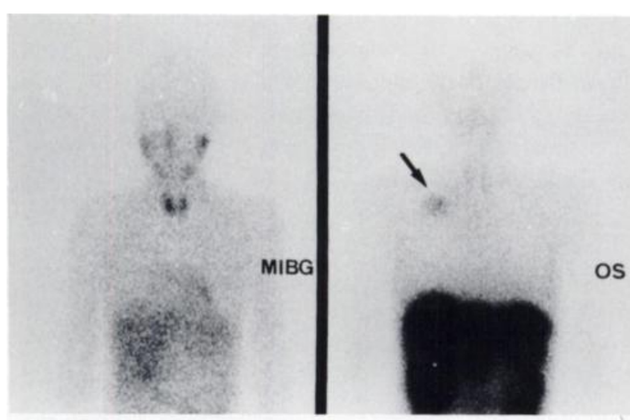

FIGURE 2. Patient 5 with a malignant pheochromocytoma. Presentation as in Figure 1. No abnormal uptake is seen on MIBG scan but octreotide scintigraphy demonstrates a right lung metastasis (arrow).

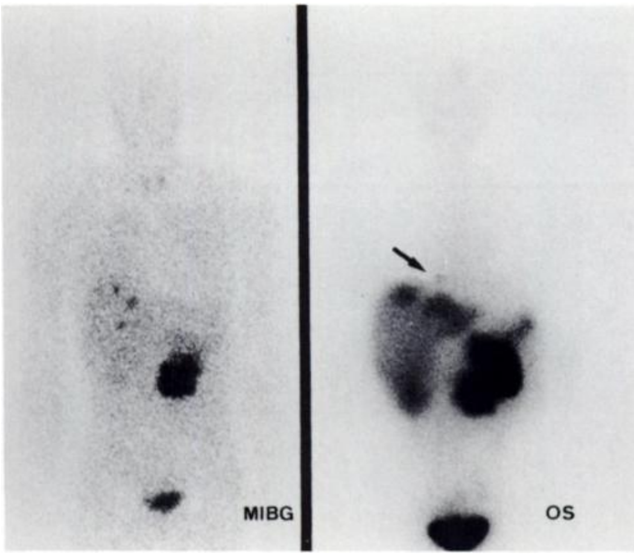

FIGURE 3. Patient 12 with a malignant paraganglioma. Presentation as in Figure 1. MIBG scintigraphy clearly demonstrates the primary tumor and hepatic metastases. Octreotide scintigraphy demonstrates the primary tumor (below the left kidney) and hepatic metastases images different (size, topography and number) from those obtained with MIBG. In addition, a cardio-diaphragmatic right pulmonary metastasis (arrow) is demonstrated only by octreotide scintigraphy.

treotide scans and were confirmed by morphological imaging modalities.

Fifteen foci were positive only with MIBG and consisted of 2 bone metastases, 12 liver metastases and 1 abdominal lesion. Only 1 of these 15 foci was not demonstrated by CT scan. It was a supracardiac focus in Patient 10 who had elevated urinary excretion of catecholamines.

Seven foci were positive only with octreotide scan. One focus corresponded to a pulmonary lesion visible on CT scan (Fig. 3). The other 6 foci (1 abdominal, 2 cervical and 3 pelvic foci) could not be confirmed by any other imaging modality (ultrasonography, CT and MRI scans and bone scintigraphy), even after a 6 mo follow-up (Fig. 4).

Generally, both the intensity of uptake and the number of uptake sites were lower with labeled octreotide than with MIBG. In particular, the MIBG scan was more sensitive for the detection of bone involvement.

A comparison between diagnostic and post-therapeutic MIBG images in Patients 1, 6, 7, 9 and 11 shows the following results: in Patient 9, diagnostic MIBG scintigraphy performed 1 wk before MIBG treatment demonstrated 3 abdominal foci and post-therapeutic scan demonstrated 7 foci (3 abdominal, 3 liver and 1 cervical lymph node). Octreotide scan showed only one abdominal lesion and the cervical lymph node. No difference between the diagnostic and post-therapeutic MIBG scintigraphies was noted for the other patients, except in Patient 7 whose post-therapeutic MIBG scan demonstrated a lumbo-aortic focus not seen on the diagnostic MIBG scan.

DISCUSSION

Currently, radiolabeled somatostatin analogs (^{123}I-Tyr-3-octreotide or ^{111}In-DTPA octreotide) have been used in more than 1000 patients (*12*). Various pathologies have been studied: gastro-entero pancreatic endocrine tumors (*13–17*), other neuroendocrine tumors (Merkel's tumor, medullary thyroid cancer and small cell bronchial cancer), lymphomas, renal cancer, pulmonary adenocarcinoma, breast cancer and inflammatory diseases (*12,18–25*). However, all positive results are expressed in terms of relative sensitivity (that is compared to a "reference diagnostic method" or a combination of several diagnostic methods) and of relative specificity (when biopsy is unavailable for each site demonstrated by somatostatin scintigraphy). Although evidence exists for the targeting of somatostatin membrane receptors of type II (competition with cold somatostatin, autoradiography, correlation between somatostatin scintigraphy and in vitro assay of receptors), the clinical relevance of a positive site on somatostatin scintigraphy is still a matter of debate due to the possibility of non-tumoral uptake.

For pheochromocytomas or thoraco-abdominal (para-aortic) paragangliomas, few data are available comparing results of octreotide and MIBG scintigraphies. Most of the tumoral sites in our patients were demonstrated by MIBG and confirmed by other conventional imaging modalities. Only Patient 10, who had already been operated for bilateral adrenal pheochromocytomas and a cervical paraganglioma, presented at the time of octreotide scan with an overproduction of catecholamines without any other evidence of disease. This new functional imaging method could result in a potential benefit for these patients by improving staging, providing an additional prognostic factor and predicting the outcome of a treatment with somatostatin analogs. In vitro autoradiography studies have demonstrated the presence of somatostatin receptors in 37 of 51 (73%) pheochromocytomas (including 6 malignant tumors) and 13 of 14 (93%) paragangliomas, without any precision on the receptor density (high or low) in these two types of tumors (*9*). Plouin et al. suggested that the density of somatostatin receptors is lower in malignant pheochromocytomas and para-aortic paragangliomas than in benign pheochromocytomas (*26*). The presence of somatostatin receptors for related tumors such as neuroblastomas could be correlated with the favorable prognosis of the disease (*10,27*).

The comparison between octreotide and MIBG scans, in our study, shows a higher sensitivity of both diagnostic and post-therapeutic MIBG scans regarding the number of uptake foci, except in Patient 14 with a ganglioneuroblastoma. The contrast and intensity of uptake were also higher with MIBG. These differences were particularly visible in bone metastases and in hepatic or abdominal lesions, which occurred frequent in our patients. This is in agreement with another series (*1*) where bone metastases were found in 8 of 14 patients and hepatic or abdominal lesions

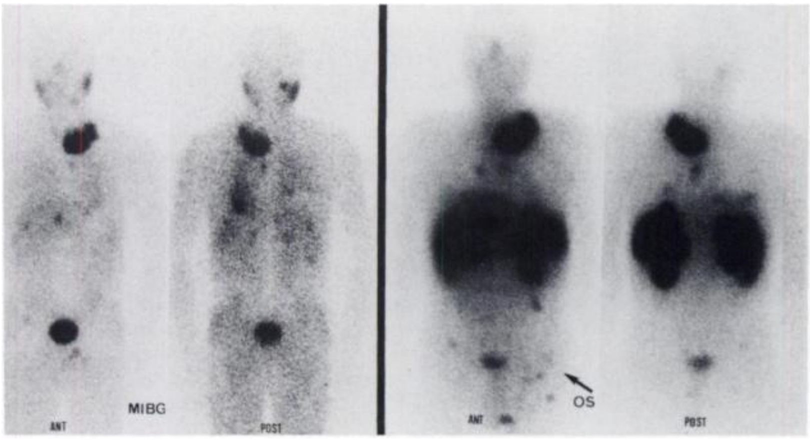

FIGURE 4. Patient 14 with a malignant ganglioneuroblastoma. Presentation as in Figure 1. Multiple foci corresponding to already known tumor sites (CT scan): a left cervical lymph node, bilateral lung metastases, a right pterygo-maxillar metastasis, costal metastases and liver metastases. Three pelvic foci are visible only on octreotide scintigraphy (arrow) and could not be explained.

in 7 of 14. The other soft-tissue tumor sites (testicular and parotid gland) were seen with both tracers (2 of 14 patients). Octreotide scan demonstrated positive images in 3 of 4 patients with lung metastases seen on CT scan and MIBG was positive in only 1 patient; this agrees with the results of another study which found octreotide scan to be more sensitive than MIBG for detecting lung and lymph node metastases (*28*). Some uptake foci are difficult to assess due to abdominal artifacts, renal and hepato-splenic uptake and sometimes biliary excretion, so that both 4-hr and 24-hr images are necessary. Dynamic images acquired during the first 30 min after injection show only a few early foci of uptake. Tomoscintigraphy did not reveal additional uptake sites but provided a better spatial localization of some uptake foci. Results of diagnostic MIBG scintigraphies in our patients seem comparable to those obtained after a therapeutic dose of MIBG (except for 2 patients) but this does not affect the comparison between MIBG and octreotide results.

Our results differ from those reported in the literature. For paragangliomas of head and neck, 50 of 53 (94%) lesions were visualized (*11*); however, these tumors are different from chromaffin and catecholamine secreting paragangliomas and have a lower MIBG detection rate (54%) (*29*). Concerning adrenal pheochromocytoma, Krenning et al. (*12*) reported 12 of 14 (86%) positive octreotide scintigraphies, however the benign or malignant nature of the disease was not mentioned. Mabille et al. (*30*) reported four patients with malignant pheochromocytoma who showed a good concordance in both ^{111}In-octreotide and ^{131}I-MIBG post-therapy images. Our MIBG results are consistent with those of the literature which reports a sensitivity of 92% and a specificity of 100% (*8*). Most authors group paraganglioma with pheochromocytomas, because the former have the same histological biological and clinical features (*31*).

A number of points remain unanswered. The lower sensitivity of octreotide scan compared to MIBG may reflect the influence of previous treatments such as radiotherapy (including MIBG metabolic radiotherapy) and chemotherapy on the density of somatostatin receptors. Although no data seem to exist in the pathology of malignant pheochromocytoma, positive in vitro receptors in patients with malignant lymphoma after chemotherapy or radiotherapy have been reported (*22*), as well as positive octreotide images in patients with small cell bronchial carcinoma after chemotherapy (*21*). This suggests that these treatments had no detectable effect on somatostatin receptors. Patients 9, 12 and 13 did not receive any treatment before octreotide scintigraphy.

The anatomical localization (bone and soft tissues) of tumor sites may influence the expression or the density of somatostatin receptors as well as cellular differentiation. A local production of somatostatin by tumor cells has been demonstrated in some tumors and can lead to competition with radioactive somatostatin analogs. We have no direct evidence in our study that somatostatin analog images truly corresponded to somatostatin receptors, although Patient 2, who had a positive octreotide scintigraphy, showed an improvement following somatostatin therapy (octreotide 500 μg/day, symptomatic improvement and a moderate clinical response of a palpable tumor). The significance of a positive somatostatin uptake associated with no MIBG uptake is not clear: Patient 12 corresponded to a pulmonary lesion confirmed by CT, and in six other cases the foci seen on somatostatin scintigraphy have not yet been confirmed by other imaging modalities. They correspond either to very small tumors sites or to non-tumoral lesions including inflammatory processes. It has been found that lymphocytes have somatostatin receptors not only in malignant lymphomas but also in benign inflammatory infiltrates (*25*). For these reasons, to date, isolated positive octreotide images have no therapeutic consequences in the absence of histological confirmation.

Finally, the contribution of octreotide scintigraphy in pheochromocytoma and paraganglioma, particularly in their malignant form, although not yet assessed, may be of predictive value with regard to the secretory or tumoral response to nonradioactive somatostatin therapy as has already been described for gastro-entero-pancreatic tumors. The better detection of some tumor sites, particularly in lungs and soft tissues, and the definition of two patient populations with or without somatostatin analog uptake may refine prognosis and therapeutic management, and probably be the base for further development of an agent for metabolic radiotherapy targeting somatostatin receptors.

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