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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and predominantly renal excretion, with only minimal hepatobiliary clearance (*3*).

This tracer has been extensively evaluated for imaging various tumors, including gastroenteropancreatic (GEP) neuroendocrine tumors, medullary thyroid carcinoma, lymphoma, breast carcinoma and small-cell lung cancer (*1,3–13*). Most studies have shown that ^{111}In-pentetreotide scintigraphy is a sensitive tool, providing good lesion-to-background contrast. However, quantitative data on tumor uptake, obtained noninvasively, and the pattern of tracer distribution in normal tissues have been reported and discussed in only limited numbers of patients (*3,4,6,14,15*). After registration of the tracer in many countries, more nuclear medicine physicians will be in a position to use it for clinical requests and will need appropriate reference standards regarding organ distribution, including normal variants. Indium-111-pentetreotide scintigraphy also has been presented as a decision-making tool for potential metabolic radiotherapy using alpha- or beta-emitter-labeled somatostatin analogs (*1,16*). In view of this, accurate knowledge of the uptake by target organs in quantitative terms is a prerequisite for a radiotherapy that is beneficial to tumors without being deleterious to normal organs.

The aim of the present study was to evaluate, both qualitatively and quantitatively the biodistribution of ^{111}In-pentetreotide in patients with suspected GEP neuroendocrine tumors (including patients subsequently proved to have no tumor) and in patients with lymphoma. Further, the influence of various parameters, including time of scanning, octreotide treatment, type of tumor and presence or absence of ^{111}In-pentetreotide-positive lesions, was assessed.

MATERIALS AND METHODS

Patients

Two groups of patients presenting with a high suspicion of GEP neuroendocrine tumor or lymphoma were included in the study.

Patients with GEP Neuroendocrine Tumor. The data were obtained from 45 consecutive patients enrolled in a clinical study of somatostatin receptor imaging (SRI) using ^{111}In-pentetreotide (*17*). All patients had normal renal function (plasma creatinine <133 μmole/liter), except for one with end-stage renal failure on hemodialysis who was analyzed separately. A final diagnosis of GEP tumor was retained in 36 patients on the basis of histological data (26 patients) and abnormal hormone levels (10 patients): carcinoid tumors in 19 patients, gastrinomas in 10, nonfunctioning islet-cell carcinomas in 3, insulinomas in 2 and multiple endocrine neoplasia type 1 syndromes (MEN-1) in 2. The SRI disclosed at least one tumor site in 31 of these patients. In the remaining eight patients (control group), no final diagnosis of GEP tumor could be made, and the scintigraphic findings were normal. Fifteen patients were receiving octreotide therapy (Sandostatine, Sandoz, Basel, Switzerland) regimens that varied from 150 to 1500 μg/day subcutaneously. The duration of drug administration ranged from 14 to 64 mo (median 37). Treatment was withdrawn 12 hr to 10 days (median 36 hr) before injection of the labeled somatostatin analog and was resumed only after completion of scintigraphy. A laxative treatment (bisacodyl, 7.5 mg orally) was given 8 hr after injection to reduce intestinal activity on the 24-hr images.

Patients with Lymphoma. Fifteen patients were selected on the basis of SRI showing at least one tumor site. This group included 10 patients with a newly diagnosed lymphoma and 5 with a confirmed relapse. Four patients had Hodgkin's disease and 11 non-Hodgkin's lymphoma (5, 2 and 4 patients with high-, intermediate- and low-grade histological findings, respectively, according to the Working Formulation). Laxatives were not systematically administered to these patients.

Radiopharmaceutical

[DTPA-D-Phe^1]octreotide was labeled with ^{111}In-Cl_3 according to the manufacturer's instructions (specific activity 14.6 GBq/μmole), and a dose of 214 ± 55 MBq (mean ± s.d.) was injected intravenously. Radiopharmaceutical purity, assessed by reversed-phase chromatography on Sep-Pak C18 cartridges (Waters, Millipore Corp., Milford, MA), was 98.0 ± 1.9%.

Scintigraphic Procedure

Planar (4 and 24 hr) and SPECT (24 hr) images were obtained using a large field of view gamma camera equipped with a medium-energy collimator and regularly checked for uniformity and count rate linearity. The pulse height analyzer windows were centered over the 173- and 247-keV photon peaks with a window width of 20%. Anterior and posterior views of at least 500 kcounts were recorded over the chest, abdomen and pelvis. Images of 50 to 200 kcounts were obtained from the anterior, left and right profile views of the head. Images were stored in a 128 × 128 matrix. In patients with GEP tumor, SPECT of the abdominal region was performed systematically. SPECT was performed in 10 patients with lymphoma (head in 1, chest in 5 and abdomen in 4). SPECT acquisitions were obtained following an elliptic orbit from 64 views of at least 40 sec and stored in a 64 × 64 matrix (pixel size 6.5 × 6.5 mm).

An in vivo displacement study was performed in three patients with GEP tumor who received an intravenous injection of cold octreotide after the 24-hr imaging session. A 20-min dynamic acquisition (1 min/frame) was started at the moment of a 1-min intravenous injection of 50 μg cold octreotide.

Qualitative Analysis

The frequency of visualization of the normal liver, spleen, kidneys, thyroid, pituitary, female breast, gallbladder and intestinal activity was determined at 4 and 24 hr after injection by consensus of two observers.

Quantitative Analysis

Total uptake in the liver, spleen, kidneys and tumors was estimated using the geometric mean of counts in regions of interest (ROIs) drawn on the anterior and posterior views. Corrected organ or lesion activity was obtained after subtraction of background activity determined in surrounding areas and normalization of image duration. Activity in the renal pelvis, often visible at 4 hr, was not included in the kidney ROI. Organs showing extensive superimposition or infiltration of tumor activity were excluded from the analysis. For attenuation correction, an effective coefficient of 0.09 cm^{-1} (determined from phantom studies) was used, and the mean patient thickness was obtained from lateral views or transverse SPECT slices. Total thyroid uptake was estimated from the anterior view only, and attenuation correction was performed using a constant organ depth of 2.6 cm (*18*). An aliquot of the injected material (~3.7 MBq) was imaged on the gamma camera under standard geometry at each imaging session and used to estimate the total injected dose. The total uptake in organs or tumor was expressed as a percentage of injected dose (%ID). Owing to the lack of accuracy in determining the pituitary contour, total pituitary uptake was not calculated.

Regional uptake in normal organs and tumor lesions was semiquantitated from transverse SPECT slices corrected for attenuation. Attenuation correction was performed using the analytical method described by Bellini et al. (*19*), which assumes that attenuation is constant throughout the body. An effective attenuation coefficient (μ) of 0.09 cm^{-1} was applied. This μ value was experimentally determined by means of a cylindrical phantom of

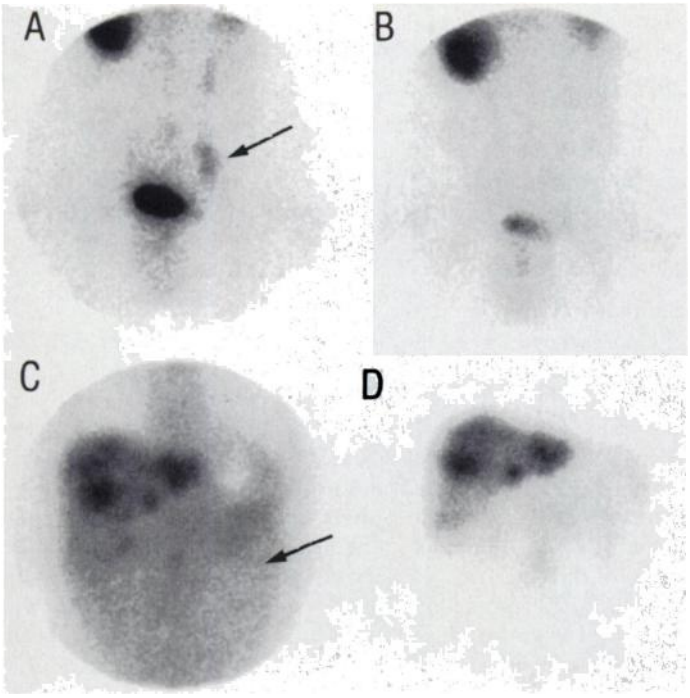

FIGURE 1. Anterior view of lower abdomen at 4 hr after injection shows activity in the left ureter (A [arrow]) that disappears after bladder emptying (B). Anterior views of the abdomen show abnormal background activity at 4 hr after injection representing transudation of ^{111}In-pentetreotide into the ascitic fluid (C [arrow]). This activity disappears at 24 hr (D).

30-cm diameter filled with a homogeneous ^{111}In solution. The patient contour was determined from transverse SPECT slices. The accuracy of the regional semiquantification method was further validated by a phantom study. Briefly, ^{111}In sources representing tumors of variable size, together with larger sources that mimicked ^{111}In-pentetreotide uptake by liver, spleen and kidneys, were placed in a water tank simulating the abdomen. The regional activity calculated over "organ" sources was 99% ± 7% of the expected activity. For the large tumor sources (diameter >3 cm), the regional uptake was close to the expected values (88% ± 8%). In smaller tumor sources (diameter ≤3 cm), we observed a systematic underestimation that could reach 50%. In patient studies, the mean voxel activity in organs was calculated from ROIs drawn over the central part of normal organs on at least four contiguous slices. Keeping in mind that quantification errors are maximum in small lesions, the smallest tumor lesions analyzed were at least visible on four contiguous slices. In these cases, lesion activity was determined from the middle slices. In large heterogeneous tumors, the ROIs were drawn over the site of maximum tumor activity. The mean voxel activity was finally normalized for volume and expressed as a percentage of injected dose (measured as described previously) per 100 ml of tissue (% ID/100 ml).

Data Analysis and Statistical Methods

Total and regional uptake values in normal organs and tumor lesions were analyzed according to the following parameters: scanning time, presence or absence of positive lesions, tumor type and influence of octreotide treatment before the scan.

Unless stated, results are given as mean ± s.d. Frequencies of organ visualization were compared between groups using the Fisher's exact test for nonparametric data. The Student's t-test for paired or unpaired data was used as appropriate, and correlations were calculated using linear regression analysis. A p value <0.05 was considered significant.

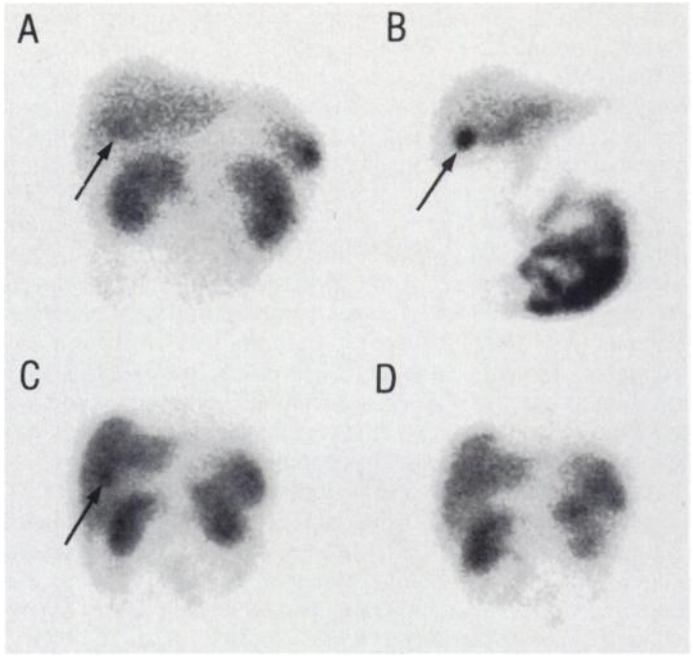

FIGURE 2. Anterior view shows ^{111}In-pentetreotide activity in the gallbladder (A and C [arrow]). This was confirmed in one patient by a ^{99m}Tc-HIDA image at 40 min (B [arrow]) and in another by repeat imaging performed after a meal, which shows the clearance of this activity (D).

RESULTS

Organ Visualization

The liver, spleen, kidneys and urinary bladder were visualized in all patients. Transient ureteral activity was occasionally observed at 4 hr after injection (Fig. 1A, B). In three patients with ascites, high background activity was observed over the abdomen at 4 hr after injection and disappeared at 24 hr (Fig. 1C, D). The frequency of visualization of the thyroid, bowel and pituitary was similar in all groups and higher at 24 hr than at 4 hr after injection (Table 1). Conversely, the female breast was more frequently observed at 4 hr than at 24 hr. Bowel activity was seldom seen at 4 hr, whereas it was observed in nearly all patients at 24 hr, including those who received laxatives. In 45 patients without focal liver involvement, the gallbladder was unambiguously visualized in 5 (2 at 4 hr and 4 at 24 hr) (Fig. 2).

Quantitative Analysis

Normal Organs. Total liver and spleen uptake remained stable between 4 and 24 hr, whereas kidney activity decreased with time; no differences were found between the three groups of patients except for the 4-hr spleen uptake, which was slightly higher in patients with lymphoma than the control group ($p = 0.04$) (Table 2). Mean uptake in liver, spleen and kidneys was not significantly different in patients with GEP tumor with an SRI-positive lesion compared with that in patients with GEP tumor with normal scintigraphic findings or control subjects. Total thyroid uptake was minimal, and in the eight patients with GEP tumor with visible uptake at 4 hr, the activity remained stable over time. Background activity measured over the lung area decreased by a mean of 69% ± 8% (range 44%–88%) between 4 and 24 hr. Regional uptake values in normal organs, calculated for a representative tissue sample at 24 hr (200–800 voxels, depending on organ size), were distributed over a wide range, without significant differences between groups (Table 3). On average, regional uptake was approximately three times higher in the spleen and kidneys than in the liver. In three patients with lymphoma with known spleen involvement, splenic uptake (7.1% ID, 12.4% ID and 18.7% ID) was two to

TABLE 1
Visualization of Normal Organs 4 and 24 Hours after Injection of Indium-111-Pentetreotide

	Control group		GEP group		Lymphoma group	
	4 hr	24 hr	4 hr	24 hr	4 hr	24 hr
Thyroid	1/7 (14%)	7/7 (100%)*	8/35 (23%)	31/35 (89%)*	6/12 (50%)	11/13 (85%)
Pituitary	2/8 (25%)	7/8 (88%)*	8/35 (23%)	25/35 (71%)*	3/11 (27%)	10/12 (83%)*
Bowel	5/8 (63%)	7/8 (88%)	3/35 (9%)	33/35 (94%)	4/14 (29%)	13/15 (87%)
Breast†	0/1 (0%)	0/1 (0%)	9/21 (43%)	4/21 (19%)*	4/6 (66%)	1/7 (14%)*

*$p < 0.05$, 4 hr versus 24 hr.
†Female patients only.

five times higher than that in control subjects (95% confidence interval 1.4–3.8% ID). One patient with end-stage renal failure and minimal urine output (<50 ml/24 hr) underwent hemodialysis at 42 hr after injection. Uptake of ^{111}In-pentetreotide in the liver and spleen amounted, respectively, to 13.6% ID and 27.3% ID at 16 hr after injection and 17.0% ID and 32.3% ID at 48 hr after injection (i.e., after dialysis). The dialysis fluid contained 28.6% of the injected dose.

Tumor Lesions. Total and regional uptake in tumors was highly variable (Table 4); however, in patients with GEP tumor, total tumor uptake calculated in 50 lesions at both 4 and 24 hr did not vary with time ($p = 0.90$). In contrast, total uptake in lymphoma lesions decreased between 4 and 24 hr from 0.49 ± 0.54% ID to 0.27 ± 0.28% ID ($n = 17$; $p = 0.045$). Intraindividual differences in regional uptake were also noted, in that tumor uptake measured over different sites could vary by a factor of up to 5 (intraindividual coefficient of variation 27% ± 21%; range 0.3%–77%, calculated in 17 patients with multiple lesions). Regional tumor uptake was lower in lymphoma than in GEP neuroendocrine lesions by a mean factor of 10, resulting in a tumor/liver ratio less than 1 for patients with lymphoma lesions (0.5 ± 0.2) and 5.0 ± 1.5 for GEP neuroendocrine tumors ($p < 0.0001$).

Effect of Octreotide. No statistical difference was observed between mean organ or tumor uptake in patients with or without octreotide treatment before the scan (Table 5). However, in the octreotide group a significant positive correlation was observed between the duration of octreotide therapy and liver or spleen uptake (Fig. 3). For kidneys, this correlation did not reach statistical significance (Fig. 3). No relationship could be found between the duration of octreotide withdrawal (12 hr to 10 days) and regional uptake in the liver ($r = -0.23$; $p = 0.42$), spleen ($r = 0.48$; $p = 0.08$) and kidneys ($r = -0.14$; $p = 0.65$). Cold octreotide injected 24 hr after tracer administration did not result in any significant change in activity of the liver, spleen, kidney and tumor in the three patients studied, indicating that excess unlabeled peptide was unable to displace the activity present at that time in the organs or tumor sites (Fig. 4).

TABLE 2
Comparison of 4- and 24-Hour Total Uptake of Indium-111-Pentetreotide in Normal Organs (%ID, mean ± s.d.)

	n*	4 hr	24 hr
Control group			
Liver	8	3.75 ± 0.98	3.46 ± 0.83
Spleen	8	2.48 ± 0.55	2.61 ± 1.42
2 kidneys	8	5.80 ± 1.75	4.71 ± 0.50
GEP group			
Liver	25	3.68 ± 1.27	4.15 ± 1.92
Spleen	29	2.85 ± 1.80	3.03 ± 1.94
2 kidneys	29	5.93 ± 2.66	5.22 ± 2.00†
Thyroid	8	0.04 ± 0.01	0.04 ± 0.01
Lymphoma group			
Liver	10	3.78 ± 1.14	3.42 ± 0.99
Spleen	9	3.84 ± 1.59‡	3.59 ± 1.57
2 kidneys	10	6.03 ± 2.38	4.59 ± 1.96†

*Number of organs in which uptake could be quantitated at 4 and 24 hr.
†$p < 0.005$, 4 hr versus 24 hr (paired t-test).
‡$p = 0.04$ versus control group (unpaired t-test).

DISCUSSION

The present retrospective study was intended to investigate the biodistribution of ^{111}In-pentetreotide both qualitatively and quantitatively. We used the data from consecutive patients referred for evaluation of GEP neuroendocrine tumors and lymphoma who underwent imaging using a standard acquisition protocol. Because excretion mainly occurs through the renal route, only patients with normal kidney function were analyzed. Eight patients were subsequently considered normal control subjects because no definite GEP tumor was diagnosed.

Qualitative Analysis

Accurate image interpretation requires an extended knowledge of normal organ distribution of the tracer. Uptake by the liver, spleen and kidneys was observed in all patients at 4 and 24 hr, in accordance with previous reports (*3,6,15*). This finding should be kept in mind when interpreting scans in patients with abdominal tumors. Activity in the urinary bladder can usually be easily identified, but problems may be anticipated when tumors are sought in the pelvic area. Activity in the ureters, especially at 4 hr is unusual but should not be mistaken for tumor uptake; if needed, repeat images may help to

TABLE 3
Regional Uptake in Organs with Physiological Uptake at 24 Hours (%ID/100 ml)

	n*	Mean ± s.d.	Range	Median
Control group				
Liver	7	0.16 ± 0.05	0.12–0.26	0.14
Spleen	7	0.67 ± 0.14	0.45–0.81	0.66
Kidney†	8	0.63 ± 0.17	0.47–0.88	0.58
GEP group				
Liver	32	0.21 ± 0.11	0.10–0.53	0.19
Spleen	32	0.81 ± 0.57	0.13–2.61	0.59
Kidney†	32	0.80 ± 0.40	0.29–2.08	0.73
Lymphoma group				
Liver	6	0.24 ± 0.14	0.11–0.47	0.19
Spleen	5	0.78 ± 0.20	0.50–1.03	0.77
Kidney†	5	0.68 ± 0.36	0.31–1.17	0.65

*Number of organs in which uptake could be quantitated.
†Mean value of the two kidneys.

TABLE 4
Total (%ID) and Regional (%ID/100 ml) Uptake of Indium-111-Pentetreotide in Tumor Lesions

	n*	Mean ± s.d.	Range	Median
GEP group				
Total uptake				
4 hr	56	1.61 ± 3.47	0.01–20.6	0.28
24 hr	61	1.48 ± 3.08	0.01–17.6	0.28
Regional uptake, 24 hr	72	0.96 ± 0.75	0.09–4.62	0.81
Lymphoma group				
Total uptake				
4 hr	17	0.49 ± 0.54	0.02–2.32	0.37
24 hr	18	0.29 ± 0.29†	0.002–0.78	0.14
Regional uptake, 24 hr	9	0.10 ± 0.08‡	0.04–0.30	0.07

*Number of tumors in which uptake could be quantitated.
†p = 0.004 and ‡p < 0.0001, GEP versus lymphoma group.

differentiate ureteric activity, which rapidly migrates, from tumor deposits. Despite the systematic use of laxatives, bowel activity was observed at 24 hr in nearly all patients. Bowel activity seemed reduced in those patients who received laxatives compared to those who did not (i.e., lymphoma group). In our experience, bowel activity at 24 hr could mask tumor activity or be misinterpreted for tumor uptake. Even though early images are characterized by a lesser contrast, bowel activity is infrequent and faint at this time, so that interpretation of abnormal abdominal uptake is more confident when both early and delayed images are available. Whether intestinal activity represents excretion of ^{111}In-pentetreotide by the biliary route or specific uptake by the intestinal wall, where low density of somatostatin receptors has been characterized (*20*), remains uncertain. Although ^{111}In-pentetreotide is known to undergo biliary excretion, the gallbladder could be visualized in only a small number of patients, most likely those who were still fasting at the time of scanning. Double-isotope imaging using a biliary agent may help to localize the gallbladder with certitude. More easily, repeat imaging after a meal may demonstrate gallbladder emptying and thereby rule out tumor uptake. The latter approach may not be valid in patients with chronic cholecystitis. Finally, activity in abdominal fluid can be expected in patients with ascites. This activity was only observed at 4-hr imaging and thus probably reflects transudation of the tracer into an expanded extracellular fluid rather than uptake by diffuse peritoneal implants.

TABLE 5
Influence of Octreotide Treatment Before Scintigraphy on Organ and Tumor Uptake of Indium-111-Pentetreotide at 24 Hours in Patients with GEP Tumors

	n*	No octreotide (mean ± s.d.)†	n*	With octreotide (mean ± s.d.)†
Total uptake (%ID)				
Liver	16	4.06 ± 1.36	9	4.31 ± 2.75
Spleen	17	3.44 ± 2.03	12	2.53 ± 1.74
2 kidneys	19	5.17 ± 1.84	10	5.32 ± 2.38
Tumor	28	1.07 ± 3.31	33	1.82 ± 2.89
Regional uptake (%ID/100 ml)				
Liver	18	0.20 ± 0.09	14	0.24 ± 0.13
Spleen	18	0.80 ± 0.50	14	0.84 ± 0.66
Kidneys‡	19	0.76 ± 0.39	13	0.86 ± 0.42
Tumor	37	0.96 ± 0.91	35	0.96 ± 0.54

*Number of organs or tumor lesions that could be analyzed.
†p = ns for all comparisons.
‡Mean value of two kidneys.

No specific organ uptake was visualized in the chest. However, early and diffuse breast uptake was noted in more than one third of the female patients. This activity does not seem to represent specific binding of the tracer to somatostatin receptors in the breast tissue because it could not be confirmed in most patients at 24 hr. We could not find any relationship with age or hormonal status. Thyroid and pituitary visualization was time dependent. However, total uptake in the thyroid did not vary between 4 and 24 hr, indicating that clear delineation was possible at 24 hr because of the reduction in background activity. Similarly, the improvement in pituitary visualization with time mainly reflects a reduction in the background activity of the cranial base. Because pituitary and thyroid are visualized at 24 hr in most cases, evaluation of diseases of these organs cannot be assessed by a qualitative approach but requires an accurate quantification (*21,22*).

Organ Uptake

Quantitative uptake by the liver, spleen and both kidneys amounted to 10%–15% ID, which is in the same range as previously published values (*3,15*). In contradiction to earlier reports, which described the release of tracer from organs (*6,23*), no difference was observed between 4 and 24 hr, indicating that uptake by these organs occurs early, without subsequent washout. This in turn suggests rapid internalization of the label. One exception is the kidney activity. Indeed, on early images, activity in renal calyces could be observed and may account for the slightly higher percentage injected dose measured at 4 hr than at 24 hr because this activity could not be excluded from the ROIs during the quantification procedure. Most renal uptake is related to cortical activity in the tubular cells (*24*), which can be inhibited by amino acids or other reuptake blocking agents (*25,26*). In view of dosimetric considerations, other than the urinary bladder, the spleen and kidneys, with a regional uptake three to five times higher than the liver, are the main target organs in all groups of patients. Absolute uptake by the thyroid is minimal (<0.05% ID). However, assuming an average thyroid weight of 18 g (*27*), this would represent 0.28% ID/100 ml. When the high radiosensitivity of the thyroid tissue is taken into account, the thyroid gland also represents a significant target organ. The visualization of the pituitary in 93% of the patients confirms that this gland might be a non-negligible organ for dosimetry, as previously reported (*3,15*). However, precise quantitative data on pituitary uptake are not yet available because of the small size of this organ, difficulties in reliable delineation and the lack of attenuation correction methods in the absence of SPECT data. Renal function should also be taken into account, as illustrated by the patient undergoing hemodialysis. Although ^{111}In-pentetreotide can be dialyzed, uptake values in the liver and spleen were completely out of range by comparison with those in the other patients. Definite uptake by normal bone marrow was not noted in the present series. Nevertheless, as recently shown in biopsy samples (*28*), bone marrow uptake averages 0.017% ID/100 g at 24 hr. This should result in a poor contrast in vivo signal that cannot be accurately quantitated. In addition, bone marrow activity is well in excess of blood activity, suggesting a specific cellular binding of the tracer (*28*). Thus, the generally accepted method of distinguishing bone

marrow activity from blood activity appears to be inadequate for this tracer. Therefore, systematic biopsies and a knowledge of the kinetics of uptake in bone marrow would be required for an accurate calculation of the radiation dose to the bone marrow.

Tumor Uptake

The presence or absence of ^{111}In-pentetreotide-positive tumors, regardless of tumor type, did not seem to influence the biodistribution of the tracer in normal organs. Thus, despite the interindividual variations in uptake as measured semiquantitatively, the dosimetric calculations for diagnostic scanning published previously can be used as a gross estimate of the radiation burden to patients (*3,14,15*). However, the contribution of tumor uptake to the radiation dose to normal organs (e.g., liver metastases) can only be determined from individual patient data. Furthermore, for the therapeutic administration of radiolabeled analogs, the dosimetry must be evaluated on a strictly individual patient basis. This is particularly true for tumor dosimetry. In terms of percentage injected dose, the total amount of material concentrated in tumor lesions is extremely variable, ranging from as little as 0.01% ID to more than 20% ID. Although tumor size was one of the factors explaining this variability, no correlation was found between total and regional uptake of ^{111}In-pentetreotide. Regional uptake itself varied from less than 0.1%–5% ID/100 ml. Although the accuracy of quantitative SPECT methods can be questioned, it is noteworthy that the values reported herein are within the same range of magnitude than those measured ex vivo by Forssell-Aronsson et al. (*28*) in tumors (0.05%–7.8% ID/100 g) and liver (0.24%–0.56% ID/100 g). In patients with GEP tumor, no washout from tumors was observed, which is consistent with internalization of the ^{111}In label into tumor cells. The hypothesis of label internalization is further supported by the chase experiment, showing no variation in tissue uptake after a bolus injection of cold octreotide at 24 hr. In patients with lymphoma, however, there was an apparent release of activity from tumor lesions over time. Indeed, the 50% higher activity observed in these patients at 4 hr compared with 24 hr could represent recirculation of nonanchored lymphocytes inside the germinal center, the zone of lymphoid tissue known to contain the maximum density of somatostatin receptors (*29*). However, this finding needs a cautious interpretation, as the delineation of the tumor tissue itself was hampered by the proximity of large vessels, especially in the mediastinum. SPECT data at 4 and 24 hr are needed in these patients to confirm this finding in terms of regional uptake.

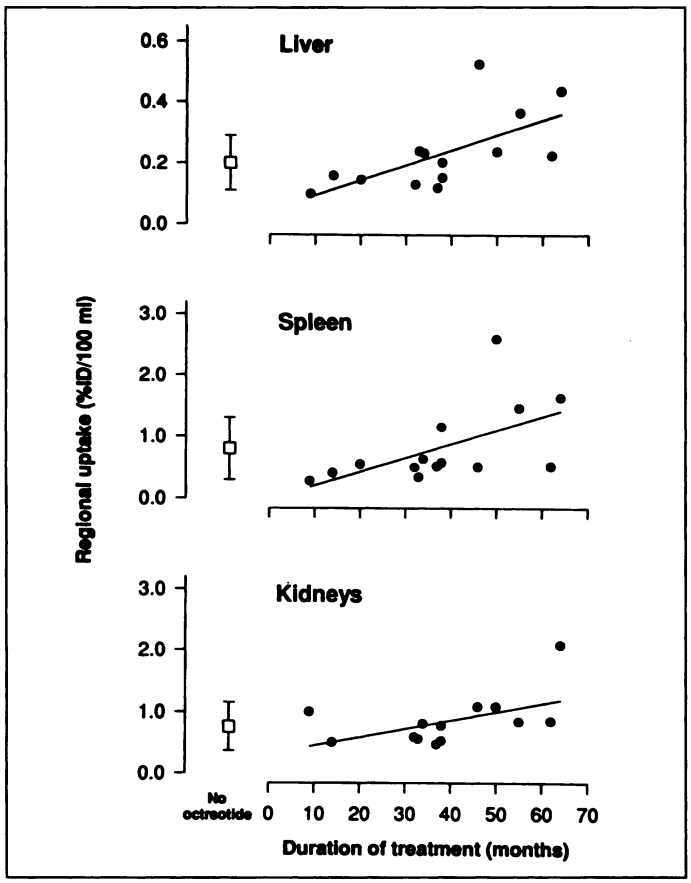

FIGURE 3. Effect of duration of octreotide therapy on uptake at 24 hr of ^{111}In-pentetreotide in liver ($r = 0.65$; $p = 0.012$), spleen ($r = 0.56$; $p = 0.036$) and kidneys ($r = 0.52$; $p = 0.068$). No octreotide = mean value ± s.d. in patients with GEP tumor ($n = 18$ for liver and spleen; $n = 19$ for kidneys) who did not receive octreotide therapy before scintigraphy.

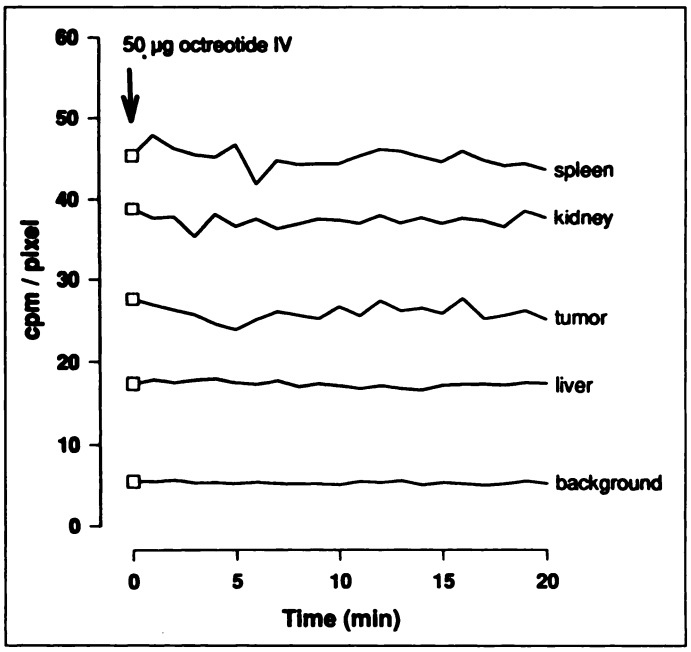

FIGURE 4. Representative time-activity curves obtained from ROIs drawn over normal organs and tumor tissue in one patient, before (open square) and after intravenous injection of cold octreotide (50 µg), 24 hr after injection of ^{111}In-pentetreotide.

No significant effect of octreotide administration before the scan (i.e., at the latest 12 hr before injection) was observed in either normal organ or tumor uptake. Clearly, in the GEP group, recent octreotide treatment did not preclude successful imaging of tumors (*17*). The correlation between octreotide treatment duration and uptake by the liver and spleen is weak but suggests depression of somatostatin receptor expression by these organs under octreotide therapy, followed by an upregulation for periods of treatment of more than several years. A longitudinal study is required to assess the individual response of patients to octreotide treatment in terms of sensitivity of the scan and in terms of biodistribution and dosimetry.

A major finding of the present study is the striking difference observed between uptake values of neuroendocrine tumors and lymphoma tissues. Although some overlap exists between regional uptake values for both groups, on average, regional uptake in GEP tumors was 10 times higher than that in lymphoma, leading to a mean tumor/liver ratio of 0.5. Although somatostatin receptors have been described in 70%–100% of lymphomas (*29*), their low density, as reflected in vivo by the low uptake values, and poor contrast may explain the reduced

sensitivity of lymphoma lesion detection as opposed to the constantly good results in GEP tumors. Also, SRI may not be sensitive enough to characterize the presence of somatostatin receptors in known lymphoma, in view of adjunctive therapy with octreotide. Finally, although metabolic therapy using radiolabeled somatostatin analogs can be reasonably envisioned for GEP tumors (*16*), it is doubtful that success can be anticipated in lymphoma.

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Technetium-99m-Sestamibi Uptake in Breast Tumor and Associated Lymph Nodes

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The aim of this study was to measure the accumulation of ^{99m}Tc-sestamibi in breast tumors and their axillary lymph nodes in patients undergoing scintimammography. **Methods:** Eighteen patients who were scheduled for breast surgery underwent scintimammography with 740 MBq of ^{99m}Tc-sestamibi on the day before the operation. The next morning, reinjection with 370 MBq was performed. Immediately after the surgical procedure, the ^{99m}Tc activity of the tumor samples and, when available, the related lymph nodes was measured in a gamma counter. The samples were weighed and prepared for histological analysis. The activity of each sample was normalized to the mean activity of normal tissue samples obtained from the same patient. **Results:** Among the 198 samples analyzed, the relative uptake of sestamibi was increased in 111 containing normal lymph nodes (1.80 ± 0.79 vs 1.00 ± 0.22, $p < 0.05$), as well as in the seven containing invaded lymph nodes (2.01 ± 0.83, $p < 0.01$) and, more dramatically, in the 22 with a carcinoma (5.64 ± 3.06, $p < 0.001$). In two patients with a benign lesion, both scintigraphy and counting demonstrated increased activity in the tumor. Four patients had negative scan results despite the presence of a malignant tumor and a more than fourfold increase of sestamibi concentration in two of them. **Conclusion:** Technetium-99m-sestamibi concentrates strongly in breast carcinoma, sometimes even when the scan results appear normal, and mildly in lymph nodes, especially when invaded; it also concentrates in some benign tumors, possibly in relation to the presence of epithelial hyperplasia.

Key Words: technetium-99m-sestamibi; breast tumors; lymph nodes

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