SPECT Improves Accuracy of Somatostatin Receptor Scintigraphy in Abdominal Carcinoid Tumors

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Abdominal carcinoid tumors are often small and difficult to localize. Somatostatin receptors have been detected in carcinoids, thus enabling their in vivo visualization by scintigraphy with ^{111}In pentetreotide, a radiolabeled somatostatin analog. The aim of this study was to determine the value of ^{111}In-pentetreotide SPECT in the detection of abdominal carcinoids and to compare these results with the outcomes from planar scans and conventional imaging techniques. **Methods:** Eighteen patients with a present, or previously operated, abdominal carcinoid were evaluated. Abdominal SPECT scans were acquired 4 hr postinjection of ^{111}In-pentetreotide and multiple planar views were performed at 4, 24, and 48 hr. **Results:** No adverse reactions were observed after radiopharmaceutical injection. In 13 of 18 patients, abnormal sites of uptake were found by SPECT, which localized 9 abdominal extrahepatic lesions (in 7 patients) and 33 hepatic lesions (in 10 patients). No pathologic accumulation was seen in the five patients considered in complete remission after surgery. Planar scans visualized 5 abdominal extrahepatic sites (in 4 patients) and 21 liver tumor sites (in 7 patients), while conventional procedures detected 3 abdominal extrahepatic lesions (in 2 patients) and 30 hepatic lesions (in 7 patients). **Conclusion:** Indium-111-pentetreotide scintigraphy is a safe and practical procedure. SPECT appears to be more sensitive than planar scintigraphy and conventional methods to detect abdominal carcinoids: it can increase the number of visualized tumor sites and that of patients with positive findings and may therefore have a role not only in the mapping of tumor spread but also in therapeutic decisions.

Key Words: abdominal carcinoid tumors; SPECT; somatostatin receptor scintigraphy; indium-111-pentetreotide

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Carcinoid tumors are neoplasms of neuroectodermal origin which frequently express somatostatin binding receptors (*1*). They usually show a slow growth, are often small and difficult to localize with conventional imaging techniques (*2,3*): therefore, many of these tumors remain clinically silent for several years, and usually diagnosis cannot be made until the typical syndrome occurs (*4*). Therapy with a somatostatin analog (octreotide) is able to control clinical symptoms in the majority of patients and in some cases may inhibit tumor growth (*5,6*).

Isotopic scans using radiolabeled metaiodobenzylguanidine (MIBG) or a radioiodinated synthetic analog of somatostatin (^{123}I-Tyr-3-octreotide) have been used for carcinoid detection (*7–10*). Recently, an ^{111}In-labeled analog pentetreotide has been developed (*11,12*). The diagnostic usefulness of ^{111}In-pentetreotide scintigraphy in patients with abdominal carcinoid tumors has already been reported (*13,14*). However, SPECT has so far been performed only occasionally, and the value of this imaging technique has not yet been completely established. Our study therefore evaluated and compared abdominal SPECT and planar scintigraphy in patients with carcinoids. Furthermore, the scintigraphic results were compared with the outcomes of other imaging modalities such as CT and MRI.

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MATERIALS AND METHODS

Patients

Eighteen patients (8 men, 10 women, age 15–69 yr, mean age 53.6 ± 15.5 yr) were studied. Their data are listed in Table 1. In all patients, histological diagnoses of a present or previously operated abdominal carcinoid were made; in thirteen patients the primary tumor had been removed, and six presented with the clinical syndrome. At the time of scanning, three patients were under treatment with octreotide; the therapy was withdrawn 1 wk before scintigraphy.

To ensure better cleansing of the bowels, and thereby avoid interfering background radioactivity of the intestinal contents, a laxative was administered to all patients 1 day before the injection of ^{111}In-pentetreotide and continued for 48 hr, according to the manufacturer's recommendations. Moreover, the patients were encouraged to drink amply after the tracer injection so as to support the bowel-cleaning process and renal elimination.

CT and MRI of the abdomen were performed within 1 mo of the scintigraphic investigation. Urinary 5-hydroxyindoleacetic acid (5-HIAA) was determined in all patients.

The scintigrams were interpreted independently by two nuclear medicine physicians who were unaware of the results of any previous investigations. Informed consent was obtained from each patient for each diagnostic procedure performed.

Radiopharmaceutical

Pentetreotide was labeled with $^{111}InCl_3$ (~250 MBq). After an incubation period of 30 min, the preparation was diluted with 1–2 ml of 0.9% saline solution and then injected intravenously. Quality control of the product was performed by chromatography. The labeling yield exceeded 97% in each preparation.

Scintigraphy

Images were obtained with a large field of view gamma camera equipped with a medium-energy collimator. Two 20% energy windows were centered on the ^{111}In photon peaks (173 keV and 247 keV).

Five hundred thousand count planar images (128 × 128 word matrix) were acquired for chest and abdomen in anterior (A) and posterior (P) projections at 4, 24 and 48 hr postinjection. Images of the rest of the body (500,000 counts or 15 min acquisition time, A and P), including the head and neck region and the lower abdomen (down to the midthigh region), were performed 24 hr after injection. SPECT images were acquired over the abdomen at 4 hr using these parameters: (a) 64 × 64 word matrix; (b) 64 projections (rotation of 360°) and (c) 50–60 sec acquisition time per projection. Prefiltration was performed using a Wiener filter on original

TABLE 1
Patient Data

Patient no.	Sex	Age (yr)	Final diagnosis	Previous surgery	Urinary 5-HIAA (mg/day)
1	F	62	Foregut	No	—
2	F	46	Foregut	Yes	—
3*	F	49	Hindgut	Yes	—
4	F	15	Midgut	Yes	—
5	M	69	Midgut	Yes	—
6	M	60	Hindgut	Yes	—
7	F	38	Foregut	No	45†
8	M	48	Hindgut	Yes	15
9	F	69	Foregut	No	—
10	F	68	Midgut	Yes	—
11	M	65	Midgut	No	50†
12	F	48	Midgut	Yes	60†
13	M	59	Foregut	Yes	—
14	M	66	Foregut	Yes	51†
15	M	37	Midgut	No	50†
16	F	32	Hindgut	Yes	—
17	F	68	Midgut	Yes	13†
18	M	65	Midgut	Yes	—

*Patient 3 had plasma PP = 875 pg/ml (n.v. < 200).
†Carcinoid syndrome.
— = normal values (<10 mg/day).

data for SPECT image reconstruction. The filtered data were then reconstructed with a Ramp filter.

Statistical Analysis

No statistical analysis was made due to the small patient population.

RESULTS

No side effects were observed after i.v. injection of ^{111}In-pentetreotide.

Results are shown in Table 2. Figures 1 and 2 summarize the abdominal findings.

No pathologic focal accumulation of ^{111}In-pentetreotide was found in the five patients with both negative radiological and biochemical findings and whose primary tumors had been previously resected.

In 13 patients, abnormal sites of ^{111}In-pentetreotide uptake were found by SPECT, which localized 9 abdominal extrahepatic lesions (in 7 patients) and 33 hepatic lesions (in 10 patients). Conventional imaging techniques detected tumor localizations in 8 patients: 3 abdominal extrahepatic lesions (in 2 patients) and 30 hepatic lesions (in 7 patients). Planar images visualized tumor sites in 9 patients: 5 abdominal extrahepatic lesions (in 4 patients), 21 hepatic lesions (in 7 patients) and 4 extra-abdominal lesions (in 2 patients).

All abdominal extrahepatic sites previously detected by conventional imaging procedures were confirmed by SPECT, which also revealed six unsuspected localizations (in six patients). Twenty-nine of 30 known liver metastases (only two of three in Patient 13) visualized by conventional images were confirmed by SPECT, which also identified three single liver lesions (Patients 3, 8, and 17) and another hepatic localization (three instead of two) in Patient 18.

Compared to planar imaging, abdominal SPECT localized 16 additional tumor sites (4 extrahepatic lesions and 12 liver lesions) in 10 patients. Planar scintigraphy demonstrated 2 more abdominal extrahepatic localizations than conventional imaging modalities, but only 21 of 30 liver metastases could be detected. When compared with the 24- and 48-hr scans, the number of lesions detected on the 4-hr planar images were identical.

The two patients with negative radiological findings (both had had their primary tumors removed) and a single liver hot spot detected by SPECT had slightly increased urinary 5-HIAA (Patient 8) or elevated plasma pancreatic polypeptide (Patient 3).

After scanning, histological confirmation was made in the seven patients in whom ^{111}In-pentetreotide scan showed more presumed abdominal tumor sites than conventional imaging procedures (by endoscopy in Patients 1 and 9; by liver biopsy in Patients 3 and 8; by surgery in Patients 11, 15 and 17). In Patient 7, the pancreatic localization detected by ^{111}In-pentetreotide was confirmed 1 yr later by MRI. In Patient 18, the mediastinal and third hepatic lesions revealed by scintigraphy were also visualized by CT 7 mo later. In Patient 12, the pathological skeletal uptake in three unsuspected extra-abdominal sites (two ribs and left femur) were also observed on a bone scan performed 6 mo later using ^{99m}Tc-methylene diphosphonate.

There was no correlation between tumoral uptake of ^{111}In-pentetreotide and urinary 5-HIAA levels; in six patients with normal urinary 5-HIAA, scintigraphic imaging was positive.

DISCUSSION

Carcinoids are slow-growing tumors and may be symptomless and clinically silent for years (*4*). The carcinoid syndrome occurs in less than 10% of patients. Even in the presence of liver metastases, the final diagnosis is not easy, unless biopsy material is examined for the neuronal glycolytic enzyme neuron-specific enolase (*15*) or the secretory peptide chromogranin (*16*).

Primary abdominal tumors are often small and difficult to localize, even when the most sophisticated conventional imaging techniques (CT and MRI) are applied (*17*). In two different series, including 15 patients with gastrointestinal carcinoids, Picus et al. (*18*) and McCarthy et al. (*19*) showed that only six of nine primary lesions found later at surgery were revealed by CT. In addition, other primary lesions could not be detected by CT or at laparatomy. MRI is very sensitive in the detection of liver metastases but seems to be less sensitive in the diagnosis of extrahepatic sites (*20*). According to Li et al. (*21*), no differential diagnosis of liver metastases of carcinoid tumors from other metastases based on MRI signal intensity is possible.

Iodine-131- or iodine-123-MIBG has been used to obtain images of endocrine tumors and to visualize carcinoids (*7,22*). However, previous reports have demonstrated that a significant number of carcinoid tumors cannot be depicted by MIBG scintigraphy (*7,23,24*).

It is known that most carcinoids contain high-affinity somatostatin receptors (*1*) and that treatment with a somatostatin analog (octreotide) permits controlled hormone secretion and, in single cases, is able to inhibit tumoral growth (*6,25*). Recently, radiolabeled analogs of somatostatin have been used for the in vivo localization of carcinoid and other endocrine tumors (*9*). Bomanji et al. (*26*) have shown the usefulness of ^{123}I-labeled somatostatin analog Tyr-3-octreotide (TOCT) as a complement to [^{123}I]MIBG for detecting metastatic carcinoids. Nevertheless, the high hepatobiliary uptake and clearance of ^{123}I-TOCT, with the subsequent abdominal interference due to gut activity, may deteriorate the imaging within 2 hr, a fact which is hardly overcome by the use of laxatives. Due to its relatively long effective half-life and low clearance through the hepatobiliary system, ^{111}In-pentetreotide can be used to effi-

TABLE 2
Scintigraphic Results

Patient no.	^{111}In-pentetreotide SPECT	^{111}In-pentetreotide planar	Conventional imaging
1	Upper abdomen (1)	—	—
2	—	—	—
3	Liver (1)	—	—
4	—	—	—
5	—	—	—
6	—	—	—
7	Upper abdomen (1), liver (m)	Liver (m)	Liver (m)
8	Liver (1)	—	—
9	Upper abdomen (1)	—	—
10	Lower abdomen (1)	Lower abdomen (1)	Small bowel (1)
11	Upper abdomen (2), lower abdomen (1), liver (m)	Upper abdomen (1), lower abdomen (1), liver (3)	Ileum (1), paraortic lymph node (1), liver (m)
12	Liver (m)	Liver (2), skeleton (3)	Liver (m)
13	Liver (2)	Liver (1)	Liver (3)
14	Liver (m)	Liver (m)	Liver (m)
15	Lower abdomen (1), liver (m)	Lower abdomen (1), liver (3)	Liver (m)
16	—	—	—
17	Lower abdomen (1), liver (1)	Lower abdomen (1)	—
18	Liver (3)	Liver (2), mediastinum (1)	Liver (2)

Number in parentheses are the sites detected; m = 5 or more sites; — = none. Upper and lower abdomen division line: lower edges of the kidneys.

ciently localize endocrine abdominal tumors even at 24 or 48 hr. However, due to renal clearance of the radiopharmaceutical (*27*), the background radioactivity is also low after 4 hr, and this favors the use of ^{111}In-pentetreotide in abdominal SPECT, which is more sensitive than planar imaging (*28*).

The best timing for abdominal SPECT imaging has not been definitively established. In this study, SPECT was performed after 4 hr, at a time when the abdominal region will be less affected by the presence of intestinal radioactivity (mainly in the colon at 24 hr) excreted through the bile and mostly present, even if a laxative had been previously administered or an enema given to the patient to clean the bowels (*29*). In other reports, SPECT is generally performed at 24 hr in patients with gastroenteropancreatic neuroendocrine tumors (*30,31*) because of a much lower background radioactivity and a relatively long effective half-life in the tumor (*31*). SPECT proves to be of the utmost importance, particularly when tumors are small, located in the abdomen and not visualized on planar scans (Fig. 3), as an overprojection by other tissues and/or organs (liver, spleen, kidneys and intestines) which show some variable individual accumulation of ^{111}In-pentetreotide (*27*). SPECT is also useful in the study of the liver, which always shows ^{111}In-pentetreotide uptake. Focal accumulations may be located near the surface or in the depth of the liver; in addition, SPECT allows the distribution of radioactivity in a region to be detected without the interference caused by overlying or underlying activity (Fig. 4).

However, in the interpretation of SPECT studies, it can be difficult to find the precise anatomic sites of localization of the radiopharmaceutical in some cases. By combining the anatomic localizing capability of CT and MRI with SPECT images through image fusion, a more accurate identification of disease sites can be made. Image fusion has been used for improved understanding of brain imaging (*32*) and radiation treatment planning (*33*); more recently, for the analysis of radiolabeled monoclonal antibodies (*34*), and, in various clinical studies, in the field of oncology (*35*). The application of SPECT and CT/MRI image fusion in ^{111}In-pentetreotide studies will allow better anatomic localization of abnormal SPECT activity.

When compared with the results of Kwekkeboom et al. (*13*), the systematic use of abdominal SPECT might explain the higher diagnostic sensitivity demonstrated in this study, especially in the detection of liver involvement. SPECT is mandatory when abdom-

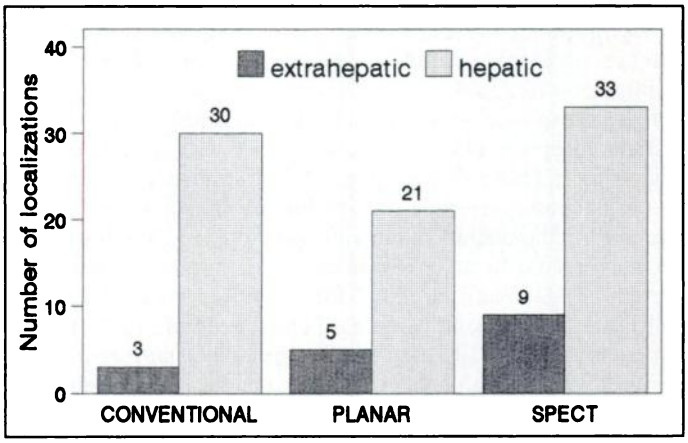

FIGURE 1. Total number of abdominal localizations (divided into extrahepatic and hepatic) detected using conventional imaging techniques (CONVENTIONAL), planar (PLANAR) images and tomographic (SPECT) images with ^{111}In-pentetreotide. Five or more liver sites are counted as five sites.

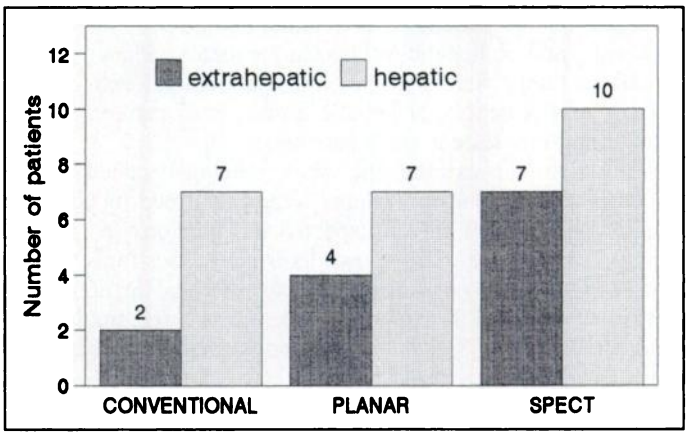

FIGURE 2. Total number of patients with positive abdominal findings (divided into extrahepatic and hepatic) detected using conventional imaging techniques (CONVENTIONAL), planar images (PLANAR) and tomographic (SPECT) images with ^{111}In-pentetreotide.

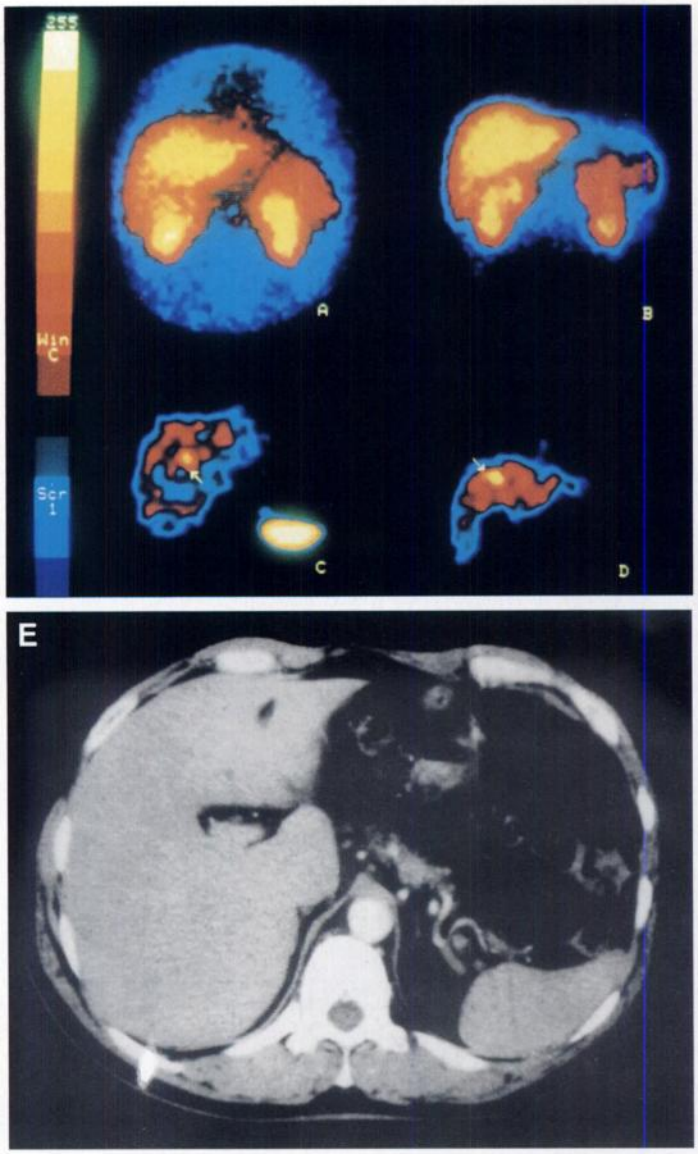

FIGURE 3. Patient 8. Abdominal 4-hr (A) and 24-hr (B) planar scintigraphic images do not show any site of abnormal uptake. Four-hour SPECT imaging localizes a single liver hot spot: transaxial (C) and coronal (D) slices. CT scan (E) shows no tumor site.

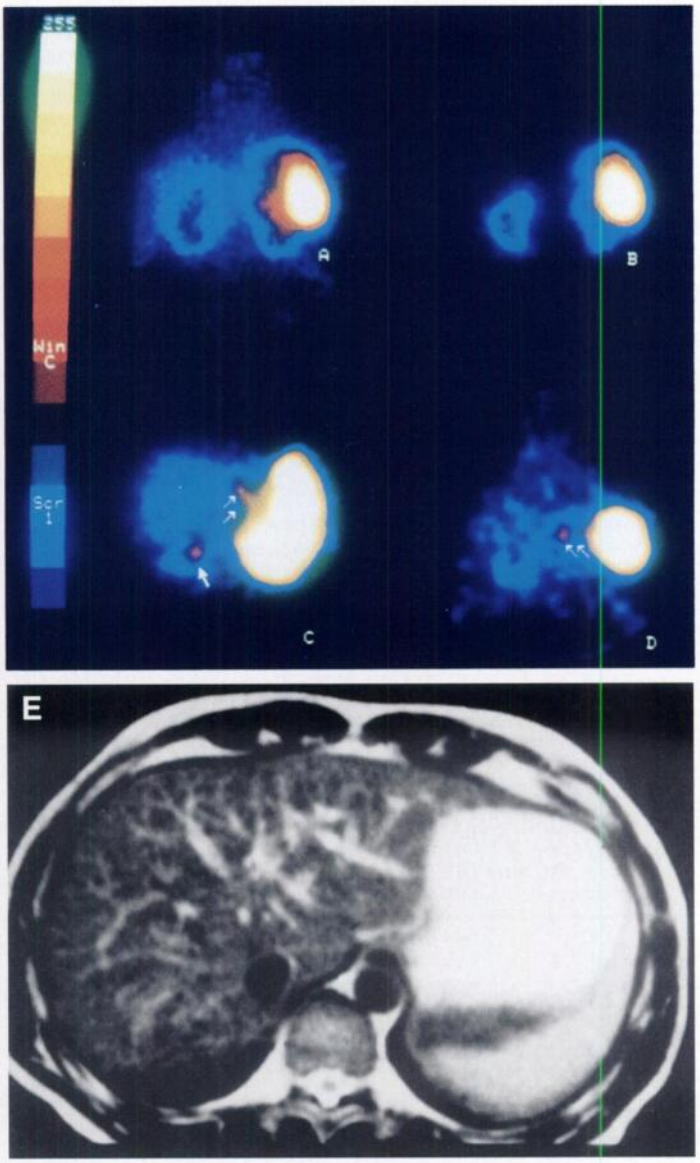

FIGURE 4. Patient 1. Abdominal planar scintigraphic images—both at 4 (A) and 24 hr (B)—do not show any site of abnormal uptake. Four-hour SPECT—transaxial (C) and coronal (D) slices—localizes one focus (double arrow) near the spleen (the single arrow in the transaxial image shows the normal uptake in the right kidney). MRI (E) shows no tumor site. Gastric biopsy specimens during endoscopy performed 1 mo after scintigraphy revealed a carcinoid of the stomach.

inal localizations are to be detected: nine (six extrahepatic and three liver hot spots) previously unknown sites (not visualized with other conventional imaging procedures) were found in 9 of 13 patients with abnormal ^{111}In-pentetreotide accumulation.

Planar scans showed two abdominal extrahepatic lesions not detected by CT and MRI, but failed to visualize 9 of 30 known liver metastases. When compared with planar scintigraphy, SPECT imaging could localize a greater number of both hepatic (33 versus 21) and extrahepatic abdominal sites (9 versus 5). Furthermore, abdominal SPECT visualized more single lesions (two extrahepatic and two hepatic) than planar scans and other conventional imaging techniques, thus increasing the number of patients (13 versus 9) with positive scintigraphic findings. For this reason, SPECT can diagnose abdominal involvement of carcinoid tumors at an early stage.

CONCLUSION

Our data indicate that ^{111}In-pentetreotide SPECT is a noninvasive diagnostic procedure that can successfully localize abdominal carcinoids and their metastases: it is more sensitive than other conventional imaging methods and planar scintigraphy, not only in detecting primary tumors, but also in assessing liver and abdominal extrahepatic involvement. Although we evaluated a relatively small number of patients and further studies in a larger series are required, our results suggest that ^{111}In-pentetreotide SPECT could be an early diagnostic method to accurately stage tumor extension in abdominal carcinoids. Moreover, due to its capacity to demonstrate in vivo somatostatin receptors, ^{111}In-pentetreotide could be a useful tool to select those patients with carcinoid syndrome who would possibly benefit from octreotide therapy.

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Bone Scintigraphy Evaluated in Diagnosing and Staging Langerhans' Cell Histiocytosis and Related Disorders

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An analysis of patients with proven Langerhans' cell histiocytosis (LCH) was undertaken with the aim of evaluating the role of bone scintigraphy in the diagnosis and staging of LCH. **Methods:** Radiographic skeletal surveys and whole-body bone scintigraphy study results were reviewed for all patients treated at the Mayo Clinic in Rochester, Minnesota during 1965–1994 with histologic proven LCH. All available studies were then reported in a randomized and blinded fashion. **Results:** Of the 73 patients with the histologic diagnosis, 56 (76%) had a definite lesion reported on radiographs and subsequent biopsy-proven bone involvement. For this population, the sensitivity and specificity of radiographic survey were 100% and 61%, respectively, compared to 91% and 55% for bone scintigraphy. Solitary bone lesions were reported on 21 radiographic surveys and 24 bone scintigrams. For solitary lesions, radiograph sensitivity and specificity were 95% and 73%, respectively, compared to 88% and 77% for bone scintigraphy. Bone scintigraphy receiver operating characteristic curves showed the region of greatest diagnostic accuracy to be skull, facial bones and mandible (88% sensitivity, 52% specificity). Radiation dosimetry to adult reproductive organs was less favorable for radiographic skeletal survey compared to bone scintigraphy. **Conclusion:** Our results support the use of radiographic skeletal survey in the initial diagnosis of LCH. Bone scintigraphy may have a role in monitoring a patient's progress in which the initial scintigram and radiographic survey show good correlation.

Key Words: bone scintigraphy; Langerhans' cell histiocytosis

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The diverse group of diseases associated with Langerhans' cell proliferation encompass a disparate group of clinical presentations, clinical courses and responses to treatment. They all display, however, abnormal proliferation of histiocytes, the cell class to which the Langerhans' cell belongs. Only recently has the classification and nomenclature of these diseases been standardized. The recommended term, Langerhans' cell histiocytosis (LCH) represents diseases that were previously known as eosinophilic granuloma, histiocytosis X, Langerhans' cell granulomatosis and classified into unifocal or multifocal subtypes (*1*). Syndromes such as Hand-Schuller-Christian disease

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