Detection of Bone Metastases in Patients with Endocrine Gastroenteropancreatic Tumors: Bone Scintigraphy Compared with Somatostatin Receptor Scintigraphy

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Scintigraphy with somatostatin analogs is a sensitive method for the staging and therapeutic management of patients with endocrine gastroenteropancreatic (GEP) tumors. The aim of this study was to compare prospectively somatostatin receptor scintigraphy (SRS) using $^{111}$In-pentetreotide with bone scintigraphy using $^{99m}$Tc-hydroxymethylene diphosphonate for the detection of bone metastases. **Methods:** One-hundred-forty-five patients with proven endocrine GEP tumors were investigated. Patients were classified according to the presence of bone metastases as indicated by CT, MRI or histologic data. Group I included 19 patients with confirmed bone metastases, and group II included 126 patients without bone metastases. **Results:** In group I, SRS was positive in all 19 patients with bone metastases, and bone scintigraphy was positive in 17 patients. Bone metastases were found to occur predominantly in patients with liver metastases. In group II, 5 patients had recent bone surgery for fracture or arthritis. SRS showed bone uptake in 4 of these patients, and bone scanning showed abnormal uptake in 5. In 7 of the remaining 121 group II patients, SRS was negative and bone scanning showed normal bone uptake suggesting bone metastases. The detection of bone metastases was of major prognostic value, because 42% of group 1 patients died during a 2-y follow-up. **Conclusion:** In patients with GEP tumors, the accuracy of SRS appears to be similar to that of bone scintigraphy for the detection of bone metastases.

**Key Words:** somatostatin receptor scintigraphy; bone scintigraphy; gastroenteropancreatic tumor; bone metastases


**T**herapeutic management of patients with endocrine gastroenteropancreatic (GEP) tumors depends on staging (1–5). Bone metastases are associated with poor prognosis and contraindicate surgical resection of primary tumor or liver metastases, chemotherapy or liver transplantation.

Somatostatin receptor scintigraphy (SRS) has been reported as a sensitive method, especially in the detection of primary tumors and liver metastases in patients with endocrine GEP tumors (6–13). SRS is one of the first-line imaging methods in the staging of endocrine GEP tumors. Only one other study reporting the comparative accuracy of both SRS and conventional bone scanning in patients with gastrinoma has been identified (14). The aim of this study was to compare prospectively the value of SRS and conventional bone scintigraphy in the detection of bone involvement in patients with proven endocrine GEP tumors, including Zollinger-Ellison syndrome (ZES), carcinoid tumors and other types of GEP tumors.

**MATERIALS AND METHODS**

**Patients**

The population included 145 consecutive patients (91 men, 54 women; mean age 54 ± 15 y; range 22–83 y) with histologically or biologically proven GEP tumors, including 78 patients with ZES, 30 patients with carcinoid tumors and 37 patients with other types of endocrine GEP tumors (4 functioning and 33 nonfunctioning endocrine tumors). Ninety-five patients were investigated within primary staging evaluation after the diagnosis of the endocrine GEP tumors. Fifty patients were investigated during the follow-up period for clinical or biologic recurrence of the disease after surgery (6 ± 1 y), after chemotherapy or after chemoembolization. Patients with previously known bone metastases were excluded. Fifty-five patients had known liver metastases (38%). The mean length of follow-up after SRS was 18 ± 2 mo (range 4–36 mo). All patients underwent SRS and bone scintigraphy within 4 wk of each other.

Final diagnoses of bone metastases were based on the results of all radiologic findings, i.e., CT, MRI or histology. The imaging modalities were used in patients with clinical symptoms (bone pain) or positive results from at least one scintigraphic procedure. In patients with multiple bone metastases, confirmation of metastatic bone involvement was not always available for all sites (but was available for at least one site). Patients therefore were classified into two groups according to the presence (group I [19

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Imaging

**Bone Scintigraphy.** Bone scintigrams were acquired using a double-head gamma camera (DST SMV, DST Sopha Medical Vision, Brie, France) with a technetium photopen centered on 140 keV ± 20%. Whole-body images were acquired 3 h after injection of 925 MBq $^{99m}$Tc-hydroxyethylene diphosphonate (Mallinkrodt Medical, Petten, The Netherlands), with a high-resolution parallel-hole collimator, with six or seven steps of more than 2 min. Additional static images were also acquired as required with a 256 × 256 matrix and at least 800 kcts.

**Somatostatin Receptor Scintigraphy.** A digestive preparation including a 3-d low-residue diet and a 24-h laxative procedure was applied before SRS to decrease bowel activity.

Scintigrams were acquired after injection of 135 MBq $^{111}$In-diethylenetriamine pentaaetic acid-D-Phe1-octreotide (Mallinkrodt Medical), using a single-head circular large-field-of-view rotating gamma camera (Apex Elscint System; Elscint, Haifa, Israel) or a double-head camera (DST SMV) with a medium-resolution parallel-hole collimator and a 256 × 256 word matrix with a preset time of at least 10 min. Acquisition was performed using both $^{111}$In photopeaks (171 and 245 keV).

Abdominal images were obtained in anterior and posterior views 4 h after injection. At 24 h, the acquisition systematically included anterior and posterior views of the head, chest and pelvis and anterior, posterior, lateral and oblique views of the abdomen. Additional lateral or oblique views of the chest or head were obtained when necessary. Delayed images of the abdomen were obtained systematically in the anterior and posterior views 30–48 h after injection. In cases of negative or doubtful images, acquisition time was increased from 15 to 20 min.

Abdominal SPECT was performed on 64 patients. Acquisition parameters were a double-iumdium peak acquisition, 64 projections over a 360° rotation, 60 s per step and a 64 × 64 matrix. Slices were reconstructed after backprojection using a Hann filter.

### Image Analysis

Scintigrams for each scintigraphic method were viewed separately and independently by two observers. For both scans, sites of recent surgery, trauma and known benign bone disease were not considered as metastatic bone sites; the results of bone scintigraphy and SRS in patients with such sites were analyzed separately. For each scintigraphic method, patients were classified as being with or without bone metastases. For bone scans, abnormally increased bone uptake was not automatically considered to represent metastatic disease: a typical pattern of osteoarthritis or degenerative bone disease was not categorized as metastatic. A consensus reading was obtained in each case of interobserver disagreement.

For both scans, if fewer than 10 bone hot spots were found, the sites were counted. If more than 10 bone hot spots sites were found, bone metastases were considered to be multiple. Diffuse uptake, especially in the axial skeleton and metaphyseal areas, was interpreted as bone marrow infiltration.

### Statistical Analysis

Qualitative data were compared by the $\chi^2$ test, and quantitative data were compared by the Student $t$ test. Differences between groups were considered significant when $P$ was < 0.05.

### RESULTS

#### Patients

Group I included 19 patients (mean age 50.8 y, range 22–83 y) with bone metastases, and group II included 126 patients (mean age 52 ± 3 y, range 24–79 y) without bone metastases according to the results of conventional imaging or histology (Table 1).

Among the group I patients, 5 had ZES (26%), 4 had carcinoid tumors (21%) and 10 had other types of endocrine tumors (53%; 1 functioning and 9 nonfunctioning). Among these patients, 17 of 19 (89%) had previously known liver metastases. Ten group I patients had no bone-related symptoms. The mean duration of disease from the diagnosis of endocrine GEP tumor to the discovery of bone metastases was 27 ± 8 mo (range 1–72 mo). No group I patient had recent bone surgery, trauma or arthritis.

Among the group II patients, 73 had ZES (58%), 26 had carcinoid tumors (21%) and 27 had other types of endocrine tumors (21%). Among these patients, 38 of 126 (30%) had previously known liver metastases. The mean duration of disease from the diagnosis of endocrine GEP tumor to scintigraphy was 34 ± 6 mo. Five patients had bone disease corresponding to known recent trauma (1 patient), recent bone surgery (2 patients) rheumatoid arthritis of the shoulder (2 patients).

#### Scintigraphic Results

**Group I.** SRS was positive in all 19 group I patients, and bone scintigraphy was positive in 17.

Both procedures were positive in 17 patients. In 12 patients, the bone metastases were multiple and metastatic diffusion was so great that the counting of sites was impossible. Bone metastases involved the skull, ribs, vertebral column and hip. In these patients with multiple bone metastases, both scans were discordant, but the uptake at the multiple tumoral sites evidenced by each investigation sometimes differed (Fig. 1). In the other 5 patients, bone metastases were limited, showing 11 concordant sites: sacrum (1 patient), lumbar spine and cotyle (1 patient), dorsal spine (1 patient), 3 hip sites (1 patient), 2 dorsal spine sites and 2 sternal sites (1 patient) (Fig. 2).

The results of the two imaging methods were discordant in 2 of 19 patients. SRS was positive, showing 5 sites, whereas bone scanning was negative. In the first patient,

#### Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Mean age (y)</th>
<th>ZES (%)</th>
<th>Carcinoid (%)</th>
<th>Other types (%)</th>
<th>Liver metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n = 19)</td>
<td>50.8</td>
<td>26%</td>
<td>21%</td>
<td>53%</td>
<td>95%</td>
</tr>
<tr>
<td>II (n = 126)</td>
<td>52</td>
<td>58%</td>
<td>21%</td>
<td>21%</td>
<td>30%</td>
</tr>
</tbody>
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*Group I: patients with bone metastases.
†Group II: patients without bone metastases.
ZES = Zollinger-Ellison syndrome.
SRS showed 3 metastatic sites (2 rib sites and 1 iliac crest site) (Fig. 3). In this patient the first bone scan was negative; 3 mo later, a second bone scintigram was positive but showed only 1 tumoral site of 3 (1 rib site). The last patient had lumbar and cotyle sites shown by SRS and confirmed by MRI, whereas bone scintigraphy was negative.

In 4 of the 19 group I patients, both conventional bone scintigraphy and SRS showed diffuse axial bone uptake suggesting bone marrow involvement, which was more evident with SRS than with conventional bone scintigraphy and was confirmed by biopsy in 2 patients and by follow-up in 1. In addition, SRS revealed additional liver tumors in 1 of these patients and mediastinal metastases in 5.

Bone metastases have been found to occur predominantly in patients with liver metastases (18 of 19 patients), and only 1 patient was found to have bone metastases without liver involvement. However, according to the therapeutic guidelines of our institution, the presence of bone metastases in these patients modified the treatment: hepatectomy (1 patient), liver transplantation (2 patients) and liver chemoembolization (14 patients) were canceled and chemotherapy or localized radiation were indicated.

The presence of bone metastases also had prognostic implications in this series. During follow-up, 8 of the 19 group I patients (42%) died. The mean survival between the disclosure of bone metastases and death was 14 mo (range 2–24 mo).

**Group II.** Of the 126 patients without bone metastases, 5 were known to have recent bone disease and were analyzed separately. In 4 of these patients, SRS and conventional bone scintigraphy concordantly showed bone uptake corresponding to a left femoral prosthesis placed 3 wk previously (1 patient), surgery of the skull for a pituitary tumor (1 patient) or rheumatoid arthritis of the shoulder (2 patients). In the fifth patient, SRS was negative, whereas conventional bone scintigraphy was positive, showing multiple hot spots corresponding to chest trauma known to have occurred 1 mo previously (Fig. 4).

In 7 of the remaining 121 patients, SRS and conventional bone scintigraphy were discordant. SRS was negative, and bone scintigraphy showed abnormal bone uptake suggesting bone metastases. Two patients presented with multiple bone sites, and 5 patients presented with limited sites (8 vertebral sites).

For 1 of the 2 patients with multiple bone sites on bone scanning and negative SRS, CT of the vertebral column was first performed 4 wk after bone scintigraphy and was negative. The patient was evaluated clinically and biologically during a follow-up of 1 y. MRI and SRS were performed at 1 y to confirm or rule out the presence of bone metastases and were consistently negative; the more likely diagnosis was metabolic disease (Fig. 5). Shortly after imaging, septicemia with bone sepsis developed in the second patient with multiple bone sites. In the 5 patients
FIGURE 2. Results of both procedures in 19 group II patients with bone metastases. SRS = somatostatin receptor scintigraphy.

FIGURE 3. Patient with nonsecreting endocrine tumor and liver metastases. (A) Bone scintigrams were negative. (B) $^{111}$In-pentetreotide scintigrams show 2 rib sites and 1 iliac crest site.
FIGURE 4. Patient with ZES and 3-mo-old chest trauma. (A) Abnormal bone scintigrams correspond to rib fractures. (B) $^{111}$In-pentetrotide scintigrams show negative findings.

FIGURE 5. Patient with ZES with liver metastases and with multiple-bone uptake on bone scintigrams (A), suggesting bone metastases, but negative findings on $^{111}$In-pentetrotide scintigrams (B). First CT of vertebral column was performed 4 wk after bone scintigraphy and was negative. MRI and $^{111}$In-pentetrotide scintigraphy performed 1 y later were consistently negative, confirming absence of bone metastases and suggesting metabolic disorder as likely diagnosis.
with limited bone sites on bone scintigraphy, radiologic findings confirmed that bone sites represented benign degenerative bone disease (Fig. 6).

DISCUSSION
Surgery is currently the major option for the treatment of patients with endocrine GEP tumors but cannot be curative in cases of metastatic spread at the time of diagnosis (1–5). The detection of bone metastases also has a significant impact on the prognosis, indicating short survival after diagnosis (11,15).

Bone metastases occur in 8%–13% of patients with endocrine GEP tumors and often are reported as multiple (11,14–22). In this study, bone metastases were found in 13% of the overall population of 145 patients with endocrine GEP tumor. Gibril et al. (14) reported bone metastases in 8 of 115 (7%) patients with ZES.

Bone metastases of gastrinoma have been reported predominantly in patients with liver metastases (11,14). In this study, in 18 of 19 patients (95%) with liver metastases, bone metastases were found that were previously known in 17 patients and revealed by SRS in 1.

However, the presence of bone metastases had therapeutic and prognostic implications. Differentiation between patients with extrahepatic or bone metastases is important for therapeutic management. In our institution, when extrahepatic or bone metastases are present, curative tumor surgery, hepatectomy, liver chemoembolization and liver transplantation are canceled. A more generalized therapy, such as chemotherapy and localized radiation, is considered.

The high rate of death (42%) and short survival times confirmed the poor prognosis associated with bone metastases in this study. These results agreed with those of Barton et al. (15), who reported six patients with malignant gastrinoma and bone metastases. Five of the six patients died after diagnosis of ZES (mean survival 3.3 y, range 1.0–7.0 y).

Before the use of 111In-pentetreotide scintigraphy, bone scans were required systematically when bone metastases were suspected. After the development of the new imaging modality, the question was whether to continue bone scanning along with 111In-pentetreotide scintigraphy.

Conventional bone scintigraphy is the most common imaging technique for the detection of bone metastases, especially because of its ability to assess the entire skeleton (23–25). However, a positive scan may require radiologic or histologic confirmation, because of low specificity. Furthermore, bone metastases in endocrine tumors may be lytic and may not be detected by bone scintigraphy. Because the expression of somatostatin receptors is probably not related to the lytic or osteoblastic character of the bone metastases, SRS should be accurate in the detection of bone metastases.

In this study, SRS detected 19 patients with confirmed bone metastases, and bone scintigraphy detected 17 patients with bone metastases. The difference in sensitivity between the two imaging procedures was minimal and not significant. In the literature, to our knowledge only one study reported comparable accuracy for both SRS and bone scanning. Gibril et al. (14), in a series of 115 patients with gastrinoma, reported that SRS accurately detected bone metastases of gastrinoma in 6 of 8 patients, whereas bone scintigraphy was positive in 5 patients. In contrast, there was a high rate of false-positive results with bone scintigraphy (47 patients).

The tracer uptake mechanism may explain in part the difference in the sites evidenced by the two modalities when bone metastases were multiple: bone scintigraphy expresses osteoblastic response, and SRS expresses the presence of somatostatin receptors in bone lesions (6,7). However, in areas such as the vertebral column, especially the last thoracic vertebra and the first lumbar vertebra, intense uptake of 111In-pentetreotide in the spleen, liver and kidneys may lead to underestimation of uptake. This can be seen in Figure 1 for one lower thoracic vertebra, where uptake is intense on bone scintigraphy and faint on SRS. In addition, the intense uptake of 111In-pentetreotide in the liver when metastases are present may lead to nonvisualization of rib metastases because of the superimposition of liver metastases when lateral views are not obtained, as seen in Figure 3.

Uptake of 111In-pentetreotide in nonmetastatic disease has been reported (7). In this study, uptake of 111In-pentetreotide was found after recent surgery or fracture in patients with arthritis. The difference in specificity between the two modalities was not significant.

It is important to note that 10 of 19 patients had no bone-related symptoms and that bone metastases were often multiple at the time of discovery. This suggests that diagno-

![Figure 6](https://example.com/6.png)

**Figure 6.** Patient with ZES and liver metastases. (A) Bone scintigram shows one vertebral hot spot falsely identified as metastatic. (B) 111In-pentetreotide scintigram was negative.
sis is often delayed and that a systematic noninvasive search for bone metastases in the staging process is needed, because their discovery has major therapeutic and prognostic implications. SRS is the most accurate imaging modality for the detection of liver and extrahepatic metastases in patients with endocrine GEP tumors (6–13). In addition, SRS sensitivity appears to be similar to that of bone scintigraphy for the detection of bone metastases.

**Study Limitations**

In this study, CT, MRI and histology were not performed systematically for the detection of bone metastases in all 145 patients. They were performed only when there was a clinical indication, i.e., a symptom or at least one positive scintigraphic result. Therefore, the sensitivity and specificity of both imaging procedures cannot be determined. However, this is a common approach in staging patients with GEP tumors. The number of patients with bone metastases in this study does not lead to a definitive conclusion. However, this was a large series of GEP tumors, which are relatively rare, and the prevalence of bone metastases (13%) was similar to that reported in the literature (8%–13%) (2,14,15).

**CONCLUSION**

In patients with endocrine GEP tumors, the accuracy of SRS, compared with bone scintigraphy, appears to be similar for the detection of bone metastases. The detection of bone metastases is a major prognostic factor, because nearly half the patients died during a 2-y follow-up. SRS should be the first imaging method in the staging of endocrine GEP tumors. It detects liver metastases and also ensures accurate bone metastasis detection and accurate staging, leading to more appropriate therapeutic decisions. However, the role that bone scanning should play in diagnosis in these patients needs to be evaluated in a larger series.

**REFERENCES**