

Incremental Diagnostic Value and Impact on Patient Management of Somatostatin Receptor Scintigraphy with Indium-111-Pentetreotide in Gastroenteropancreatic Neuroendocrine Tumors

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Key Words

Indium-111-pentetreotide · Gastroenteropancreatic neuroendocrine tumors · Somatostatin receptor scintigraphy

Abstract

Objective: To evaluate the efficacy of somatostatin analog scintigraphy with indium-111-pentetreotide and its overall impact on management in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NET). **Subjects and Methods:** Twenty-two consecutive patients with a proven or clinically suspected GEP-NET with or without proven metastases were imaged at 24 and 48 h after injection of ¹¹¹In-pentetreotide. The scintigraphic findings were compared with results from conventional imaging methods. The final diagnosis was based on histopathological and surgical findings and complementary radiology. **Results:** Somatostatin receptor-positive lesions were found in 20 of the patients, whereas conventional methods were positive in 18 patients. Additionally, 13 new tumor sites were discovered by somatostatin receptor scintigraphy in 5 patients (liver: 6; chest: 2; bone: 1; abdomen: 4). The surgical therapeutic strategy was changed in 7 patients (32%). **Conclusions:** Our data reinforced that scintigraphy with ¹¹¹In-pentetreotide repre-

sents the imaging modality of choice in the initial evaluation of GEP-NET. It is highly accurate and can identify clinically unsuspected lesions and optimize the overall staging. It also guides optimal therapy choice and most importantly identifies patients with inoperable or metastatic disease who might be candidates for high-dose targeted therapy.

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Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NET) are relatively rare tumors which manifest as a syndrome related to uncontrolled hormone secretion by functioning tumors, or as nonspecific symptoms related to the mass effect of nonfunctioning tumors, with an overall incidence of 3–4.5 per 100,000 [1]. The first manifestations of the disease seriously affect patient prognosis. The tumors most commonly metastasize to the liver, and the presence of hepatic metastases is known to decrease the 5-year survival rate [2].

Surgery is widely accepted as first-choice therapy. In fact, even in patients with liver metastases, resection is now considered a safe procedure [3]. Cytoreductive surgery can represent a potentially curative treatment when

metastases are still resectable [4]. For nonresectable metastases, other treatments are used, such as interferon- α and somatostatin analog therapy, cytotoxic chemotherapy, hepatic arterial embolization or chemoembolization, and even liver transplantation [5].

Accurate localization of the primary tumor is particularly important for appropriate management. Assessment of the extent of the tumor and disease progression is essential for making decisions about resectability and tumoricidal therapy. Many conventional imaging methods, including ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), selective arteriography and selective intra-arterial secretin stimulation with venous sampling, already exist for the localization of GEP tumors [6]. Several studies have shown that the primary lesions as well as metastases of well-differentiated GEP-NET express somatostatin receptors, especially subtype 2 [7].

Indium-111-pentetreotide binds to somatostatin receptor subtype 2 and can be used for imaging purposes [8]. Somatostatin receptor scintigraphy (SRS) is routinely performed to localize the primary tumor, evaluate disease extension, determine the receptor status as a predictor of response to octreotide therapy, and monitor treatment effects in patients selected for targeted radionuclide therapy. The reported sensitivity of SRS is 80–90%, and it has been found to be superior to other diagnostic imaging methods in identifying and assessing the staging of GEP tumors, except for insulinoma [9]. SRS has been shown to upstage disease in 10–43% of patients with a modification of previous therapeutic options in some cases [10–12]. The purpose of this study was to prospectively evaluate the ability of ^{111}In -pentetreotide scintigraphy in the detection and localization of GEP-NET and the overall impact of this diagnostic modality on patient management.

Subjects and Methods

Twenty-two patients (12 males, 10 females; mean age: 56 ± 13 years; range: 27–76 years) with proven or clinically suspected GEP-NET were prospectively included in the study. During the initial diagnostic process, 19 patients with suspected GEP-NET were included in the study, while in 3 patients, the primary tumor had already been resected prior to initial SRS, but they had not received any other form of therapy. Written consent was obtained from all patients. Final diagnoses for patients considered to have a GEP tumor or metastases were based on the results of complementary radiology (CT, MRI, arteriography or endoscopic sonography) or of surgery and histology as obtained from the medical records of the patients.

^{111}In -Pentetreotide Imaging

A mean dose of $110 \pm 10 \text{ MBq}$ ^{111}In -pentetreotide containing $10 \mu\text{g}$ somatostatin analog was administered immediately after its specific radiochemical purity had been checked by chromatography. Scintigraphic planar images were acquired using a double-headed camera with a medium-energy, parallel-hole collimator, a 256×256 matrix and a preset time of 10–15 min. Acquisition was performed using both ^{111}In photopeaks (171 and 245 keV). Whole body images were obtained at 24 h after injection. Additional lateral and oblique views were obtained when considered necessary. Delayed static images of the abdomen were systematically obtained in the anterior and posterior views at 48 h after injection.

Single-photon emission computed tomography (SPECT) was performed after planar imaging. The SPECT acquisition parameters were: a double-indium peak acquisition, 64 projections over a 360-degree rotation, 40–60 s per step, and a 64×64 matrix. Tomographic slices were obtained using iterative reconstruction (2 iterations, 8 subsets) with Hanning postfilter reconstruction.

Image Interpretation

The scintigraphic images were visually analyzed, separately and independently for each scintigraphic method, by two experienced nuclear medicine physicians (H.A.K. and S.U.) who were blinded to the patients' clinical information. A consensus reading was obtained in cases of interobserver disagreement. The images were evaluated for the presence or absence of abnormal uptake.

Results

Out of the 22 patients, histopathologically, 12 had carcinoid tumor, 3 had gastrinoma, 2 had insulinoma and 1 had glucagonoma, while 4 were determined to be non-functional islet cell carcinoma (table 1). ^{111}In -pentetreotide scintigraphy showed abnormal findings in 20 (91%) out of 22 patients ($p < 0.005$), while combined conventional imaging procedures (CT, MRI, arteriography or endoscopic sonography) were positive in 18 patients. Additionally, 13 new tumor sites were discovered by SRS in 5 patients (liver: 6; chest: 2; bone: 1; abdomen: 4) (table 1).

The presence of liver metastases was confirmed by histopathological examination in 10 of 22 GEP tumor patients (45%). SPECT ^{111}In -pentetreotide scintigraphy (fig. 1) was true positive in 9 of the above 10 patients, while planar and conventional imaging procedures were true positive in 6 and 7 patients, respectively. Thirty-nine sites (in 10 patients) were detected by ^{111}In -pentetreotide scintigraphy, and 30 sites (in 7 patients) were detected by conventional imaging procedures.

The surgical therapeutic strategy was changed in 7 patients (32%) as a direct result of SRS findings. In 3 patients, SRS showed only 1 or 2 liver metastases, and curative surgery of the primary tumor along with liver surgery was therefore thought to be a valid option. SRS revealed extra-

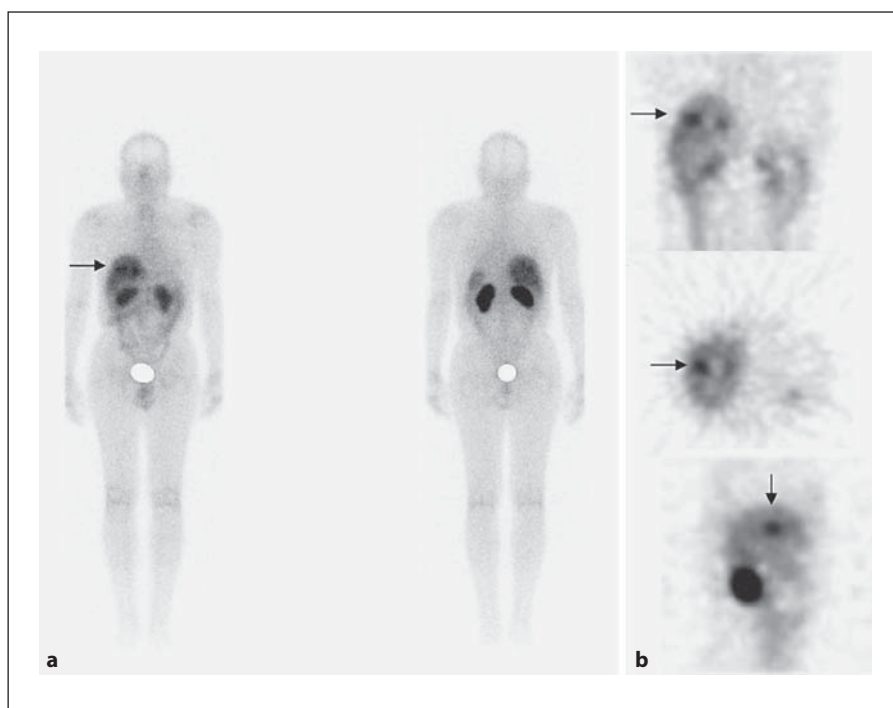


Fig. 1. ^{111}In -pentetreotide. **a** Whole body images. **b** SPECT images. Multiple focal areas of increased tracer uptake in the liver (arrows) suggest metastases.

Table 1. Patient characteristics, SRS findings and their impact on management

Patient No.	Age, years	Sex	Primary tumor type	SRS		
				finding sites	impact on surgery	therapeutic decision
1	60	M	islet cell pancreatic tumor	pancreas	surgery confirmed	surgery
2	46	F	islet cell pancreatic tumor	pancreas, liver, abdomen ¹	surgery rejected	octreotide therapy + chemotherapy
3	65	F	gastrinoma	pancreas, stomach, abdomen ¹	surgery rejected	octreotide therapy + chemotherapy
4	67	F	insulinoma	pancreas	surgery confirmed	surgery
5	39	M	carcinoid	ileum	surgery confirmed	surgery
6	27	M	gastrinoma	pancreas	surgery confirmed	surgery
7	56	M	carcinoid (R)	liver ²	surgery confirmed	surgery twice ² + octreotide therapy started
8	47	M	islet cell pancreatic tumor	pancreas	surgery confirmed	surgery
9	55	F	carcinoid (R)	liver ²	surgery confirmed	surgery ² + octreotide therapy started
10	64	F	carcinoid	rectum	surgery confirmed	surgery
11	58	M	carcinoid (R)	liver ²	surgery confirmed	surgery ² + octreotide therapy started
12	72	M	carcinoid	ileum, liver, mesenteric nodes ¹	surgery rejected	octreotide therapy + chemotherapy
13	68	M	carcinoid	no lesion	-	surgery
14	39	F	glucagonoma	pancreas	surgery confirmed	surgery
15	65	F	islet cell pancreatic tumor	pancreas	surgery confirmed	surgery
16	72	F	carcinoid	liver ²	surgery confirmed	no surgery ³ , octreotide therapy started
17	49	M	carcinoid	ileum, liver, chest ¹	surgery rejected	octreotide therapy + chemotherapy
18	32	M	carcinoid	rectum	surgery confirmed	surgery
19	58	M	insulinoma	no lesion	-	surgery
20	76	F	carcinoid	liver ²	surgery confirmed	no surgery ³ , octreotide therapy started
21	55	M	gastrinoma	pancreas	surgery	surgery
22	62	F	carcinoid	ileum, liver, chest ¹ , bone ¹	surgery rejected	octreotide therapy + chemotherapy + radiotherapy

R = Primary tumor already resected prior to initial SRS.

¹ Confirmed new sites identified by SRS. ² Another curative liver surgery was performed as a direct result of SRS. ³ Surgery not performed due to poor medical condition.

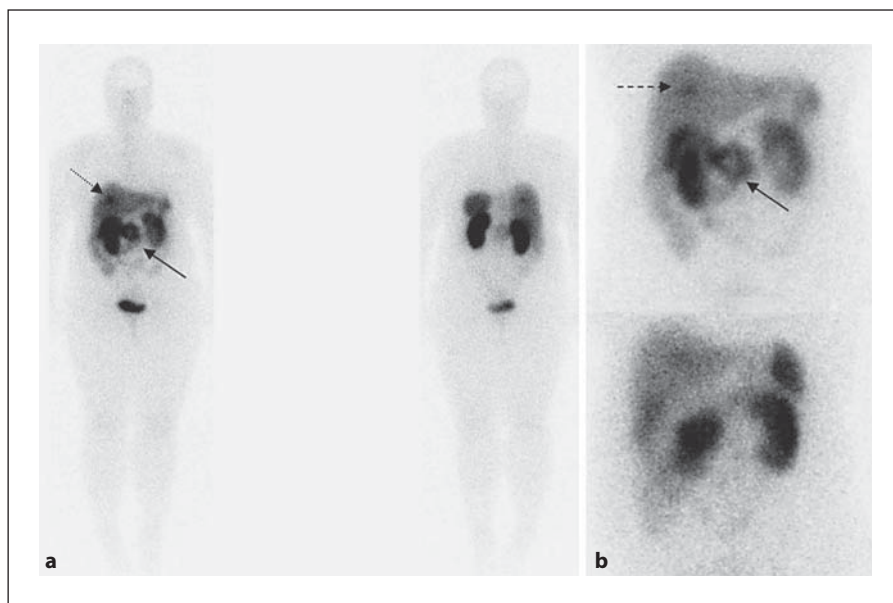


Fig. 2. ^{111}In -pentetreotide whole body images (a) and spot view of the abdomen (b) show focal areas of increased tracer uptake at the mid abdomen (primary site at the pancreas; solid arrows). Focal areas of increased tracer uptake are also seen in the liver, suggesting metastases (dashed/dotted arrows).

hepatic metastases in 4 patients, and in these patients, the curative surgery was abandoned (fig. 2, 3).

Twenty patients were positive by SRS and therefore susceptible to benefit from octreotide therapy. Following scintigraphy, octreotide therapy was started in 12 patients. In 5 cases, the clinician did not consider octreotide therapy. Three patients underwent curative surgery in the form of removal of the primary tumor and associated resectable liver metastases.

Discussion

In our study, SRS proved to be of major clinical significance, and it altered the surgical therapeutic strategy for 7 patients (32%). Our results are in agreement with those by Lebtahi et al. [13], who confirmed previous reports [13, 14] that SRS is able to induce a change in the clinical management of a significant proportion of 21–53% of patients with GEP tumors. Therefore, performing SRS has become essential for the proper management of patients with different types of GEP tumors, and it is now recommended as the initial imaging modality for these neoplasms [14].

GEP tumors are characterized by a high to very high incidence and density of somatostatin receptors of the sst_{2A} type. The very high sensitivity of SRS permits the detection of not only very small primary tumors but also small metastases, which explains why it often modifies patient classification and therapeutic strategy [15]. The

impact of SRS on patient management is manifold as it may detect resectable tumors that would be unrecognized by conventional imaging techniques and may prevent surgery in patients whose tumors have metastasized to a greater extent but the lesions are still too small to be characterized by conventional imaging. SRS is also used to select patients for cold octreotide therapy. The whole body imaging technique may provide valuable information about unsuspected metastatic disease. SRS is also important for assessing patients' suitability for radiolabeled somatostatin analog therapy and for monitoring the response to that therapy.

In our study, 13 new tumor sites were discovered by SRS in 5 patients, thus leading to a change in classification of these patients similar to that described by Chiti et al. [12], who reported that SRS detected new lesions in 28% of cases and modified the therapeutic schedule in 21%. The surgical therapeutic strategy was changed in 7 patients (32%) as a direct result of SRS findings.

^{111}In -pentetreotide SRS is a sensitive method of localizing liver metastases in patients with GEP tumors, with a reported sensitivity of 80–100% [16, 17]. Our study is in agreement with previous reports that SPECT is more sensitive for the detection of focal lesions than planar and conventional imaging. SPECT has better contrast resolution than planar imaging, which accounts for its enhanced sensitivity [18]. Nevertheless, despite this high sensitivity to most GEP tumors, the ability of SRS to visualize tumor sites *in vivo* is closely related to their size

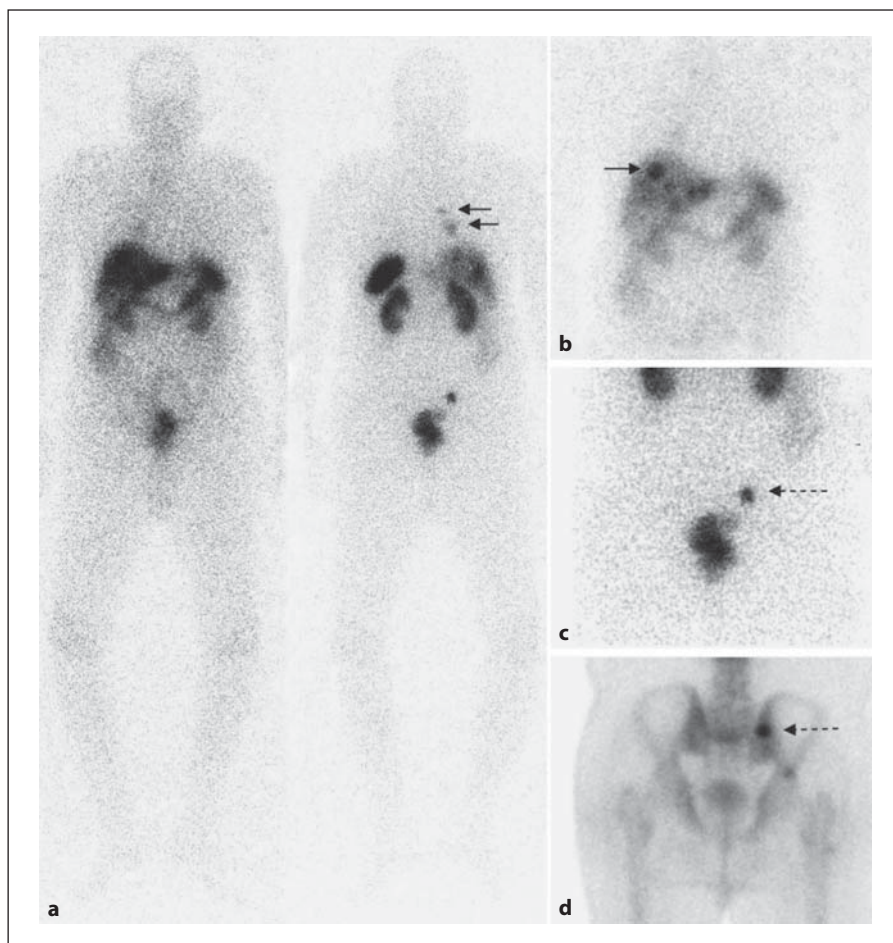


Fig. 3. a, b ^{111}In -pentetreotide whole body images and spot view image show multiple focal lesions at the posterior mediastinum and in the liver (solid arrows). **c** SRS discovered bone metastases at the right sacroiliac joint (dashed arrow). **d** The corresponding bone scan also shows this uptake in the right sacroiliac joint (dashed arrow).

and is limited especially for lesions of ≤ 1 cm (both primary and metastatic lymph-nodal and hepatic lesions) [19]. Moreover, other limiting factors are modifications in local tumor blood supply, unlabeled endogenous somatostatin resulting in competition with – or downregulation of – the somatostatin receptors, and expression of receptor subtype pattern with less affinity for the radioligand [20]. In our study, the specificity of SRS imaging was 100% (no false-positive case). The reported specificity of SRS is high (90%), but it can be significantly affected by the physiologic biodistribution of the radiopharmaceutical related to the receptor status of target tissues or to its elimination route via the kidneys and gastrointestinal tract [21]. Because SRS like other radionuclide images lacks anatomical definition, which frequently makes it difficult to precisely localize a focus of abnormal accumulation and identify structures displaying normal activity, the fusion of SPECT and CT images might resolve this problem by improving image interpretation [22].

^{18}F -fluorodeoxyglucose positron emission tomography (PET) frequently fails to visualize tumors with a low proliferation rate, such as NET [23]. The development of new PET radiopharmaceuticals for detecting NET is of great interest [24, 25]. ^{68}Ga -DOTATOC PET is one of the promising new tools for evaluating patients with NET, showing a high diagnostic accuracy superior to conventional SRS. It is likely that this tracer will be routinely used in the near future [26].

Conclusions

In our study, SRS substantially changed the management of a number of patients. SRS is a useful diagnostic tool which is very reliable for correct staging and in selecting the most appropriate therapeutic strategy, especially for patients with liver metastases.

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