Iodine-123-Vasoactive Intestinal Peptide Receptor Scanning in Patients with Pancreatic Cancer

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Recent data demonstrated a high sensitivity (>90%) in the visualization of primary/recurrent pancreatic cancer as well as metastases by means of ^{123}I-labeled vasoactive intestinal peptide (VIP). The aim of this study was to investigate the diagnostic value of radioiodinated VIP in patients suffering from adenocarcinoma of the exocrine pancreas. **Methods:** Sixty consecutive patients (26 women, 34 men; mean age 59 yr) with histologically verified pancreatic cancer were investigated in this study. Twenty-one patients presented with organ-confined malignancy (19 at study entry and 2 during follow-up after initial surgery developed tumor recurrence), while 25 patients had distant metastases along with the local malignancy, and 7 patients had liver metastases after resection of the primary lesion (6 on study entry and 1 during follow-up showed tumor development). In 5 of these patients, abdominal lymph node metastases were present at the time of scanning. Of 10 patients, who had undergone potentially curative surgery for their cancer, 7 remained free of disease during follow-up until death or for at least 6 mo. Iodine-123-VIP (150-200 MBq; ~1 μg VIP) was administered to all patients. Scintigraphic results were evaluated as compared to conventional radiologic imaging methods and surgical exploration. **Results:** Primary pancreatic tumors were visualized by ^{123}I-VIP in 19/21 patients (90%) with disease confined to the pancreas and in 8/25 patients (32%) suffering both from locoregional and disease metastatic to the liver. The overall ^{123}I-VIP scan sensitivity for primary pancreatic adenocarcinomas was 58% (27/46 scans). Liver metastases were imaged in 29/32 patients (scan sensitivity 90%) and abdominal lymph node metastases in 4/5 patients. In 5 patients, the VIP receptor scan indicated the malignant lesion before CT. In vitro results confirmed specific binding of ^{123}I-VIP to primary pancreatic tumor cells as well as to PANC1 adenocarcinoma cells. **Conclusion:** Iodine-123-VIP receptor scanning has the potential to offer additional information to augment diagnostic standard methods and could influence the decision-making process in the treatment of pancreatic cancer.

Key Words: vasoactive intestinal peptide; pancreatic cancer; radioimaging

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Adenocarcinoma of the pancreas is a common cause of cancer death (*1*). To date, the only therapeutic measure with curative potential is surgical intervention with total removal of apparently clinically malignant tissue. Despite improvement in terms of perioperative morbidity and mortality, the overall prognosis for patients diagnosed with pancreatic cancer remains poor, since even those individuals undergoing surgical resection have a very high risk of relapse (*2,3*). More than 80% of all patients die within the first year of diagnosis, and only about 3% of patients are still alive after 5 yr (*2,3*). One of the major obstacles in the treatment of this disease is the fact that pancreatic adenocarcinoma is almost always diagnosed at an advanced stage (*4*). This is due to the lack of specific symptoms or signs, and lesions smaller than 2 cm may escape detection by means of conventional radiologic imaging (*5*). Consequently, patients who can undergo a potentially curative resection remain the minority.

Sonography (and more recently endosonography) and CT scanning are the most widely applied methods for diagnosis and staging of pancreatic cancer (*5–7*). The most reliable and, thus, most widely applied modality for detection and imaging of pancreatic cancer remains CT scanning (*6*), while MRI still has to prove its advantage over conventional CT imaging (*8,9*). Scintigraphic methods, for the time being, continue to be experimental approaches, although the exploration of additional methods with the potential for early detection is clearly warranted.

Recently, it has been demonstrated that adenocarcinomas of the gastrointestinal (GI) tract express abundant numbers of receptors for vasoactive intestinal peptide (VIP) (*10–12*), including colorectal and pancreatic cancer (*12*). Iodine-123-labeling of VIP offers the opportunity of applying this peptide for in vivo localization purposes. In initial studies, the feasibility and safety of this novel peptide receptor scan has been demonstrated (*13–15*) showing the localization of most GI adenocarcinomas and liver metastases, including 20 patients suffering from pancreatic adenocarcinoma. As this tumor entity poses a diagnostic challenge, VIP receptor scanning results obtained in a total of 60 consecutive patients with pancreatic adenocarcinomas were evaluated compared with conventional radiologic imaging methods and surgical exploration results.

MATERIALS AND METHODS

Patients

Sixty consecutive patients (26 women, 34 men; mean age 59 yr) with histologically verified adenocarcinoma of the pancreas were included in this study (Table 1). Patients were administered neoadjuvant or adjuvant combined radiochemotherapy or were given palliative chemotherapy for metastatic disease. Histologic verification of the diagnosis was done in all patients by fine-needle biopsy or surgery before initiation of treatment. Patients older than 75 yr or individuals with severe concurrent illness such as psychiatric disorders, florid infections or a second malignancy were excluded from the study. All patients gave informed consent according to institutional guidelines. All patients had undergone conventional radiologic imaging by means of CT to confirm the presence or absence of cancer and to measure objectively the extent of the tumor burden at the time of radioimaging. The maximum time span between conventional imaging and application of ^{123}I-VIP was 4 wk. Before injection of the radiotracer, all patients had received full thyroid gland blockade with sodium perchlorate (400

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TABLE 1
Patient Characteristics

Characteristic	Number/size
No. of patients	60 (26 women, 34 men)
Median age	59 yr (range 30–75)
World Health Organization performance status	1 (range 0–2)
No. of patients with primary cancers/no metastases†	21
Diameter of primary lesions*	5 cm (range 2–8 cm)
Primary cancers/liver metastases†	25
Diameter of primary lesions*	8 cm (range 4–16 cm)
Diameter of liver lesions*	3 cm (range 1.5–10 cm)
No. of primary cancers/liver metastases†	7
Diameter of liver lesions*	3 cm (range 2–5.5 cm)
No. of primary cancers/no liver metastases†	

*Measured by conventional radiologic imaging (i.e., CT scan and ultrasound).
†After the end of follow-up.

mg three times daily for 3 days) and potassium iodide (2 × 65 mg for 2 days) starting the day before the injection of labeled VIP.

Nineteen patients presented with organ-confined malignancy, while 25 patients also had distant metastases along with the local malignancy, and 6 patients had liver metastases after resection of the primary lesion. In 5 of these patients, abdominal lymph node metastases were present at the time of scanning. Ten patients had undergone potentially curative surgery for their cancer and were free of disease at the time of radioimaging.

Nuclear physicians were blinded to the extent of the tumor spread until final evaluation of all scans at the end of the follow-up period. Final evaluation of all scans was performed independently by two nuclear medicine physicians using a yes-or-no-system for imaging of primary tumors and/or metastases. The opinion of a third nuclear medicine physician was considered when a consensus could not be reached. After initial CT imaging, all patients were followed until death or for at least 6 mo by CT repeated every 8 wk. Comparison with radioimaging results was performed after the end of the follow-up period. The rationale of this design was to minimize potential bias arising from lesions detectable by ^{123}I-VIP, but not by CT. Thus, focal VIP accumulation was found to indicate malignant tissue in the situation that corresponding CT lesions appeared during the follow-up period. Subsequently, a retrospective reading of all VIP-scans was performed and compared with the initial results of blind reading. Endpoints of the study were the numbers of true-positive and true-negative scans, as well as false-positive and false-negative scans compared with conventional imaging after the end of the follow-up period. If surgery was necessary, the results obtained during surgical exploration were also considered.

Preparation of Radioiodinated VIP

The preparation of ^{123}I-VIP has been reported earlier (*13,14*). In brief, VIP was generated by a peptide synthesizing machine and labeled with ^{123}I using a modified iodogen method. Iodine-123-VIP was purified by preparative high-performance liquid chromatography (HPLC) (column: reverse phase C18, 5 μm, 4 × 250 mm, eluent: 74% (volume/volume) aqueous 0.25 *M* triethylammonium-formiate, pH 3, 26% (volume/volume) acetonitrile at 1 ml/min) to obtain a high-specific activity. The column eluent passed through a scintillation radioactivity detector and ultraviolet (280 nm) detector in a series. The system was calibrated with unlabeled VIP and enabled collection of pure radioiodinated VIP, separated from unlabeled VIP, reagents and inorganic iodine species. The eluent was evaporated at reduced pressure. The product was dissolved in phosphate-buffered saline containing 0.1% (wt/vol) Tween 80 (Koch-Light Lab Ltd., Colnbroke, United Kingdom). The labeled product was analyzed by analytical HPLC (corresponding to the preparative system, however, using a dedicated analytical column) and zone electrophoresis (Whatman 3 mm paper, 0.1 barbital buffer, pH 8.6, using a field of 300 V for 10 min). The percentage of unbound iodine (<3% in all preparations) remained stable over at least 24 hr. The biological activity of labeled and unlabeled VIP was identical as determined by its ability to enhance cAMP formation, ^{32}P-adenosine triphosphate incorporation as well as ^{3}H-thymidine uptake (*13,14*). Before injection, ^{123}I-VIP was filtered through sterile Millex GV 0.2 μm (Millipore, Milford, MA) membranes. Iodine-123-VIP was administered as a single intravenous bolus injection in 3 ml 0.9% NaCl solution (150–200 MBq; ~ 1 μg VIP). In the initial 20 patients, blood pressures and heart rates were monitored before, during and 5 and 10 min after injection (*13*).

In Vitro Binding Studies

Binding studies were performed with the adenocarcinoma cell line PANC1, primary tumors (n = 6) and peripheral blood cells [platelets and peripheral mononuclear cells (PMNC)]. Assays were performed under essentially the same conditions as reported earlier for other tumor tissues (*16,17*) and cells (*14*). Cell membrane fractions were prepared according to Virgolini et al. (*14*) and Haegerstrand et al. (*16*). Saturation studies were done with intact cells or membrane fractions by incubating increasing concentrations of ^{123}I-VIP (0.01–100 n*M*) in the absence (total binding) and the presence of unlabeled VIP (100 n*M*, nonspecific binding), respectively. After incubation, the reaction mixture was diluted 1:10 with assay buffer (4°C), and rapidly centrifuged (5000 g, 10 min, 4°C) to separate membrane-bound from free ligand. The resulting pellet was washed twice with buffer and counted in a gamma counter for 1 min. Binding data were calculated according to Scatchard (*18*).

Gamma Camera Imaging and Analysis

Planar and SPECT acquisitions were performed with a large field-of-view gamma camera equipped with a low-energy, parallel-hole collimator. In most patients, sequential abdominal images were recorded every minute for 30 min (matrix 128 × 128 pixels). Thereafter, planar images in anterior, posterior and lateral views of three regions covering brain/neck, thorax and abdomen were acquired at 30 min, 2–4 hr (and in initial studies at 18–24 hr) after injection (matrix 256 × 256 pixels; 300–800 kcounts were acquired). For recording and visualization, standard techniques were applied. A three- (Picker Prism 3000) or one-head gamma camera (Picker Prism 1000) was used for SPECT imaging at 2–4 hr. Scanning was performed in a 360° circle in 6° steps, 30 sec per step. After processing by a dedicated computer (backprojection with a ramp filter, postfiltering with a low-pass filter), the data were reconstructed in three planes (coronal, sagittal and transaxial reconstruction).

RESULTS

Iodine-123-VIP Receptor Scanning in Pancreatic Cancer

After injection of ^{123}I-VIP, the lungs were the primary organ of accumulation, whereas only minimal activity was found in the GI tract. In all patients, VIP was tolerated without side effects apart from a short asymptomatic drop (10% maximum) in blood pressure (*13*). Primary pancreatic adenocarcinomas (Fig. 1) and/or liver metastases (Fig. 2) were visualized shortly after injection and were still visible at 2–4 (and 24) hr after application.

The overall sensitivity of ^{123}I-VIP receptor scanning for primary pancreatic adenocarcinomas was 58% (27 of 46 scans).

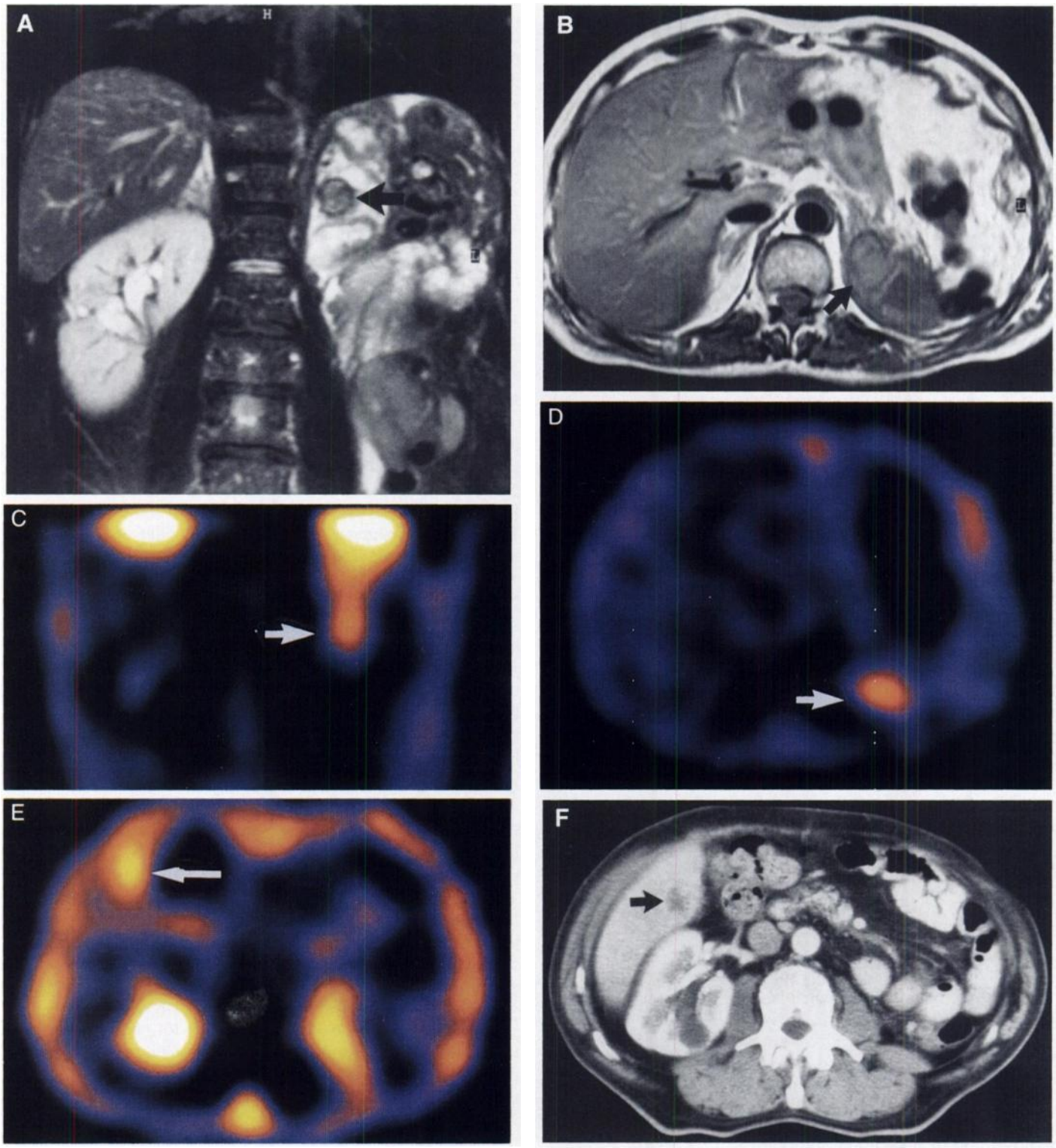

FIGURE 1. Primary pancreatic cancer as imaged by ^{123}I-VIP. Primary CT-negative tumor as seen by MRI on a coronary (A) and transverse (B) slice in a male patient with pancreatic cancer (arrow) who had undergone nephrectomy on the left side due to cystic kidney disease 12 yr before. SPECT reconstruction 4 hr postinjection of ^{123}I-VIP showing the pancreatic cancer (arrow) seen on a coronary (C) and transverse (D) slice. Single liver metastases in the same patient as seen on a coronary slice (E) after injection of ^{123}I-VIP and by CT (F).

However, the results for patients grouped by the presence of metastatic disease were as follows:

1. In patients with disease confined to the pancreas, the primary tumors were visualized in 19/21 patients (90%). The median diameter of lesions in these patients was 5 cm (range 2–8.5 cm), as judged by the largest tumor manifestation present in each patient.
2. In patients suffering both from locoregional and disease metastatic to the liver, the primary was imaged in 8/25 patients (32%). The median size of these neoplastic sites was 8 cm (range 4–16 cm, largest diameter) (Fig. 2).
3. Liver metastases were imaged in 29/32 patients (scan sensitivity 90%). The negative scans were obtained in one subject who had undergone Whipple's operation before relapse of the disease in the liver, while the other patients

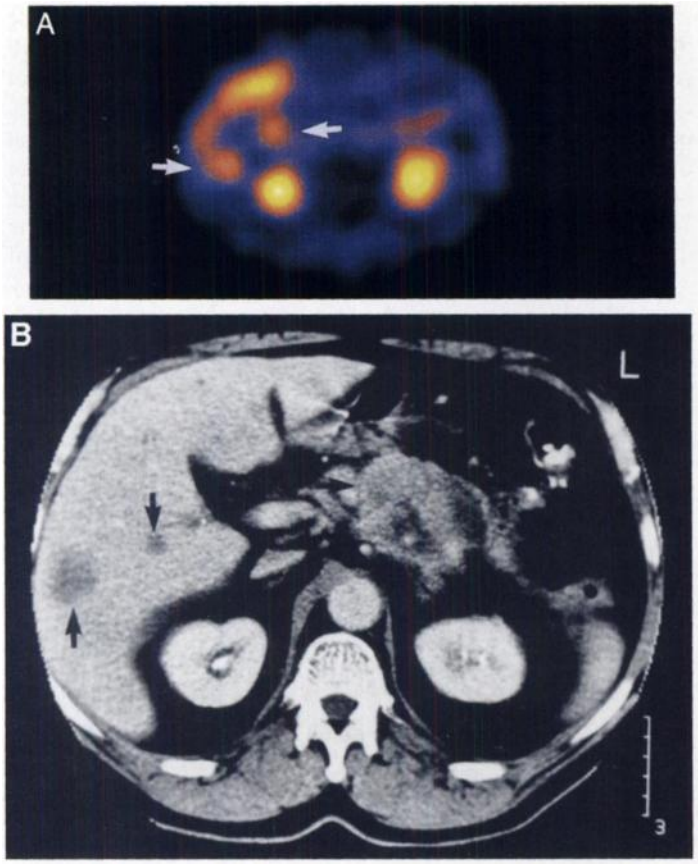

FIGURE 2. Iodine-123-VIP receptor image of liver metastases from pancreatic cancer. (A) Liver metastases (arrows) indicated by focal tracer accumulation, while the primary cancer (7 cm in diameter) was not detected by ^{123}I-VIP. (B) Corresponding CT image of liver lesions (arrows) also depicting the large pancreatic tumor.

had not been operated on due to the presence of liver lesions at the time of diagnosis.

4. Lymph node metastases were present in 5 patients at the time of VIP receptor scanning, and were successfully visualized in 4 patients.
5. Retrospective reading of VIP scans after the end of the follow-up period did not change the results obtained during the initial blinded evaluation.

Effect of Iodine-123-VIP Receptor Scanning on Staging

Of 10 patients who had surgery and were thought to be free of cancer at the scanning time, 7 had negative scans and did not develop recurrence as judged by CT during the follow-up period. However, 3 patients with positive VIP scans (2 local recurrences, 1 patient with liver lesions) without corresponding CT lesions also developed evidence of relapse as judged by conventional CT during the follow-up period (for localization of lesions at the end of follow-up see Table 1). Thus, recurrent disease was detected by ^{123}I-VIP before conventional methods had indicated the presence of cancer relapse in these 3 patients.

In one patient (63-yr-old man) with pancreatic primary cancer and no evidence for liver metastases by CT and MRI scanning, VIP receptor scanning indicated the presence of focal liver accumulation in addition to the pancreatic lesion (Fig. 1). However, follow-up by means of CT 6 wk later clearly demonstrated the presence of liver metastases corresponding to the focal lesion visualized by VIP receptor scanning.

In another patient (62-yr-old man), VIP receptor scanning showed focal tracer accumulation in the pancreatic region, while only edema of the pancreatic head adjacent to the diaphragm could be demonstrated by CT. CT was repeated 4 wk later and, due to a slight increase of the edematous lesion and suspected invasion of the diaphragm, fine-needle biopsy was performed. Histologic examination revealed the presence of malignant tissue, i.e., adenocarcinoma of the pancreatic head. Three weeks later, the patient developed ascites, with paracentesis giving cytologic evidence for malignant cells. He died 9 wk later despite initiation of chemotherapy.

Adenocarcinoma of the pancreatic head was detected in a 30-yr-old woman by CT scanning and was confirmed by surgical exploration. The tumor was estimated to be unresectable at that time due to the presence of lymph node involvement. The patient received combined radiochemotherapy (3 cycles of 400 mg/m ≤ fluorouracil Days 1–5, 200 mg/m≤ Leucovorin Days 1–5 and 20 mg/m≤ Cisplatinum Days 1–5, with a concomitant radiation dose of 55 Gy during the second and third cycle). The patient underwent ^{123}I-VIP receptor scanning 4 wk after the last cycle of chemotherapy. During whole-body scanning, a small focus was visualized in the pancreatic area, with no evidence of lymphatic or metastatic spread. CT scanning performed on the same day suggested significant tumor regression. However, the remaining enlargement could not be distinguished with certainty from scar-tissue, since disappearance of all lymph node enlargement was demonstrated by CT. During subsequent surgery, the small pancreatic lesion was completely removed. Intraoperative histopathology of multiple biopsies revealed no evidence for lymph node involvement, but the presence of the small cancerous lesion (2.5 cm in diameter) was confirmed.

TABLE 2
Binding of Iodine-123-VIP to PANC1 cells, Primary Tumors and Normal Cells

	B_{max} (sites/cell)	K_d (nM)	IC_{50} (nM)
Platelets	$2.2 \pm 0.4 \times 10^3$	1.0 ± 0.1	5.9 ± 1.2
PMNCs	$1.8 \pm 0.6 \times 10^{3*}$	0.09 ± 0.04	3.1 ± 1.4
	$15.1 \pm 2.5 \times 10^{3\dagger}$	1.5 ± 0.6	
PANC1	$2.2 \pm 0.5 \times 10^8$	1.2 ± 0.5	4.5 ± 2.9
	$6.7 \pm 1.0 \times 10^{8\dagger}$	4.0 ± 1.0	
Pancreatic cancer (n = 6)	$1.6 \pm 0.3 \times 10^{8*}$	1.2 ± 0.3	6.9 ± 3.6
	$12.4 \pm 2.5 \times 10^{8\dagger}$	4.3 ± 0.9	

*B_{max} and corresponding K_d of high affinity receptors.
†B_{max} and corresponding K_d of low affinity receptors.
Calculated conversion factor for primary pancreatic cancer from sites/milligram into sites/cell is 1.2×10^6 (i.e., 1 mg = 1.2×10^6 cells). PMNCs = peripheral mononuclear cells.

Iodine-123-VIP Receptor Binding In Vitro

In vitro data showed specific binding of ^{123}I-VIP to PANC1 cells and primary tumor specimens. In PMNCs, PANC1 cells and primary tumors, VIP bound to a class of high affinity receptors as well as low affinity receptors. As listed in Table 2, significantly ($p < 0.001$) higher numbers of ^{123}I-VIP receptors were expressed on malignant cells as compared with normal peripheral blood cells (platelets and PMNCs).

DISCUSSION

Pancreatic cancer is a disease that is almost uniformly fatal within a few months after diagnosis. Despite intensive investigational efforts, pathogenetic mechanisms still remain elusive, and only a few risk factors including cigarette smoking have been defined (*19*). Due to the lack of detectable precursor lesions and absence of characteristic early symptoms, the presence of malignant disease is usually diagnosed at an advanced stage and, therefore, is difficult to treat with curative

intent (*2,5*). CT and sonography still remain the mainstay of diagnosis and staging, and endosonography has gained widespread use more recently. However, one of the major shortcomings of these methods is a low sensitivity for small lesions (*2,5*). The aim of this study was to determine the exact performance of radioiodinated VIP (*13–15*) for imaging of pancreatic adenocarcinomas as compared to CT and/or surgery. The data obtained in our study suggest that peptide receptor scanning with ^{123}I-VIP can be considered as an approach complimentary to conventional methods for the imaging of pancreatic adenocarcinoma. Especially noteworthy are the results obtained in 5 of 60 patients (8.3%) investigated in this study, in whom VIP receptor scanning indicated recurrence of disease and/or metastatic liver spread before conventional methods. Possible changes in the choice of treatment modalities for pancreatic cancer after VIP receptor scanning suggest a profound effect in terms of quality of life and cost-effectiveness.

On a cellular level, the ability of radiolabeled VIP to visualize pancreatic carcinoma is due to the expression of cell surface binding sites for VIP (*13*). In fact, previous autoradiographic results (*12*) and binding studies performed in our laboratory (*20*) (Table 2) detected the presence of receptor-mediated binding in pancreatic tumor specimens and cell lines.

In this study, an overall scan sensitivity of 58% was obtained for primary panreatic cancers. However, subgroup analysis disclosed diverging results in two groups of patients. In the 21 patients who presented only with local cancer at the end of follow-up, 18 had their tumor successfully imaged, resulting in an overall sensitivity of 90% in this cohort. In contrast, only 32% of primary cancers (8 of 25) could be detected in patients with clinically manifest liver metastases at the time of scanning (Fig. 2). With regards to tumor size, the cancers in the latter group were larger (median size 8 cm, range 4–16 cm) than in the former (median diameter 5 cm, range 2–8 cm). Though we cannot offer a definite explanation for the different binding of ^{123}I-VIP to primary pancreatic tumors in patients with and without liver metastases, larger tumors tend to dedifferentiate and, therefore, to lose the ability to express surface receptors for VIP. In fact, the finding that highly differentiated gastroenteropancreatic tumors of neuroendocrine origin express VIP receptors in almost 100%, while undifferentiated tumors do so in only about 50% (*12*) is consistent with this hypothesis. Additionally, tumor cell necroses or changes in the blood supply of larger cancers might also influence either peptide tracer penetration or cell surface binding properties (*21*). These facts, however, could also explain the cases of patients with liver metastases (10% of all patients) who had a negative VIP scan. Furthermore, also our in vitro binding data with pancreatic tumor tissue obtained from small-sized tumors support the notion that small-sized tumors express abundant numbers of ^{123}I-VIP binding sites as opposed to normal peripheral blood cells (Table 2). Unfortunately, due to the fact that larger pancreatic tumors are usually not resected, we could not perform a direct comparison between in vitro receptor expression and in vivo binding results with regards to pancreatic tumor size.

These diverging results in the two subgroups deserve special emphasis, because our data suggest that ^{123}I-VIP receptor scintigraphy has the highest diagnostic accuracy in a cohort of patients who usually present a diagnostic problem with conventional radiologic imaging. Thus, ^{123}I-VIP receptor scanning may be applied as an additional and complementary method in the evaluation of presurgical patients with suspected cancer of the pancreas.

The diagnostic sensitivity for liver metastases achieved in our study was similar to that reported for conventional radiologic imaging by means of sonography or CT (*6,8*). Iodine-123-VIP is excreted preferentially through the kidneys. Thus, it does not concentrate in physiologic liver and biliary tissues, offering the opportunity of visualizing hepatic metastases. The smallest liver lesions imaged in our patients were in the range of 1.5 cm with the median size of liver metastases being 3 cm (range 1.5–10 cm). Although the early detection of disease metastatic to the liver may not directly translate into a prolongation of survival (*2*), this information, nevertheless, is of high importance for physicians involved in the management of such patients. There is an international consensus that patients with metastatic disease are best spared an operation (*2*), since extensive surgery does not affect overall survival in these patients and bears the risk of perioperative mortality and morbidity. The same holds true for the early detection of lymph node metastases and, in this study, VIP visualized abdominal lymph node metastases in 4/5 patients.

Previously, another peptide receptor scan using a radiolabeled, long-acting somatostatin analog, octreotide, has been used for imaging of GI tumors (*21*). However, whereas VIP scans were positive in a small cohort of patients with pancreatic exocrine tumors, negative imaging results were obtained by labeled octreotide (*13,21*). The most likely explanation for these negative in vivo results is a lack of high affinity receptors specific for octreotide on pancreatic adenocarcinomas (*22*). The VIP receptor scan was also superior to immunoscintigraphy in a recent study, in which a direct comparison of the monoclonal antibody ^{111}In-CYT-103 (OncoScint; CIS Biointernational, Paris, France) with ^{123}I-VIP was performed (*15*). Recently, promising results with the administration of fluorodeoxyglucose (FDG) for PET have been reported (*23,24*). Forthcoming investigations will have to be performed to evaluate the diagnostic value of VIP/SPECT and FDG/PET in a direct comparison.

Additionally, ^{123}I-VIP receptor scanning has promising potential for the clinical use in diagnosing and/or staging of pancreatic cancer. As demonstrated by five patients in our trial, ^{123}I-VIP receptor scintigraphy could possibly influence the decision making process in patients with verified or suspected cancer of the pancreas, due to its ability to visualize malignancy even in the absence of conventional radiologic proof.

CONCLUSION

Radioimaging with ^{123}I-VIP could provide valuable additional information to the available conventional radiologic imaging modalities for staging and early diagnosis of pancreatic cancer. In fact, the high sensitivity especially for small lesions and metastatic deposits might have a profound effect on clinical management of such patients.

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Location of a VIPoma by Iodine-123-Vasoactive Intestinal Peptide Scintigraphy

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A major problem in patients with small endocrine tumors is the difficulty in localizing the primary tumor site. Many endocrine tumors possess larger amounts of high affinity vasoactive intestinal peptide (VIP) binding sites compared with normal tissue or blood cells. We used radiolabeled VIP to localize the tumor site in a patient with Verner-Morrison syndrome (VMS). Under octreotide therapy, the VIP levels had declined in this patient, but a tumor site could not be detected by conventional techniques or by radiolabeled octreotide. However, using ^{123}I-VIP, the tumor was detectable in the pancreatic tail. Surgical resection of the tumor was followed by complete remission of the VMS. Expression of VIP binding sites in the tumor was confirmed by a radioreceptor assay and showed cross-competition between VIP and octreotide. The identity of the VIP binding site in the tumor was analyzed by Northern blotting and revealed the expression of somatostatin receptor subtype 3, which binds both somatostatin-14 and VIP with higher affinity than octreotide. Iodine-123-VIP scintigraphy would be an effective tracer to identity the tumor site in VMS patients.

Key Words: vasoactive intestinal peptide; Verner-Morrison syndrome; somatostatin; VIPoma; scintigraphy

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In 1958, Verner and Morrison described a syndrome of watery diarrhea and hypokalemia in a patient with an islet cell tumor (*1*). The substance responsible for this syndrome was identified in 1970 (*2*) and named vasoactive intestinal peptide (VIP).

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At presentation, VIP-secreting tumors (VIPomas) can be large and hypervascular (*3*). In approximately 20% of the well-documented cases, however, these tumors are small and cannot be localized by conventional techniques (*3*). These patients represent a serious challenge for clinicians since surgery is the only form of curative treatment.

Recently, somatostatin receptor (SSTR) scintigraphy using radiolabeled octreotide has detected small neuroendocrine tumors and has been used to detect VIPomas (*4,5*).

Based on the high level expression of VIP receptors on various tumor cells, we have demonstrated that ^{123}I-VIP scintigraphy provided excellent visualization of small gastrointestinal (GI) tumors expressing receptors for VIP (*6,7*). We describe here a patient with Verner-Morrison syndrome (VMS) in whom the VIPoma could not be localized by radiolabeled octreotide, but it was identified in the pancreatic tail before surgical resection by VIP scintigraphy using ^{123}I-labeled VIP.

CASE REPORT

In November 1994, a 38-yr-old man was referred because of a 4-yr history of therapy-refractory watery diarrhea, hypokalemia and dehydration. Since 1990, the patient had been having episodes of headache, diarrhea, hypotension and tachycardia associated with progressive malabsorption. In 1992 and 1993, he was hospitalized for hypokalemia (K+ = 1.6 mmol/liter) and acute renal failure. In January 1994, an elevated serum VIP level was measured (159 pmol/liter; normal value < 8 pmol/liter), and the diagnosis of VMS was established. Normal serum values for parathyroid hormone, insulin, C-peptide, gastrin and