Human Biodistribution of $^{[111}\text{In}]$Diethylenetriaminepentaacetic Acid-(DTPA)-\(\text{D-}[\text{Phe}^1]\)-octreotide and Peroperative Detection of Endocrine Tumors

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Abstract

Requisites for preoperative and intraoperative tumor localization with $^{[111}\text{In}]$diethylenetriaminepentaacetic acid-D-[\text{Phe}^1]$\text{octreotide scanning were explored in 23 patients with endocrine tumors (15 carcinoids, 4 insulinomas, and single cases of gastrinoma, medullary thyroid carcinoma, aldosteronoma, and paraganglioma). The patients were subjected to Octreoscan single photon emission computed tomographic examination prior to surgery and well counter investigation of nuclide uptake in tumors and normal tissues sampled at surgery. Somatostatin receptor-positive tumors demonstrated efficient nuclide accumulation with mean tumor: blood radioactivity ratios of 180–370 (for carcinoids and insulinomas), compared with tissue: blood ratios of 302 for spleen, 42 for liver, and <10–15 in other normal tissues (pancreas, small intestine, and mesenteric fat). Inefficient preoperative visualization of lesions was related to inconspicuous size, as for primary intestinal carcinoids, tiny liver metastases, and a single small insulinoma. High background activity, pronounced tumor fibrosis, and meager accumulation of tracer also interfered with visualization. Tumor deposits in organs with low background activity (such as carcinoid mesenteric metastases and endocrine pancreatic tumors) were generally most readily detected. Intraoperative investigations with hand-held gamma detector probes were disturbed by obvious high background activity. These investigations revealed two preoperatively unrecognized primary intestinal carcinoids, which, however, were both palpable during surgery. These studies, therefore, had little impact on the surgical strategy.

Introduction

The peptide somatostatin was first described in 1973 (1), and its general inhibitory effects were found to include suppression of hormone release from various neuroendocrine tumors (2, 3). The short half-life of native somatostatin limited its clinical applications and led to the synthesis of analogues with longer biological half-lives (4). Also, these analogues could block hormone secretion and alleviate symptoms in patients with endocrine tumors (5–8). Because autoradiographic studies revealed a high content of somatostatin receptors in many endocrine tumors, including carcinoids and endocrine pancreatic tumors (9, 10), methods were developed for tumor targeting in vivo. It was demonstrated that $^{[111}\text{In}]$DTPA-D-[\text{Phe}^1]$\text{octreotide in combination with SPECT was particularly efficient in visualizing endocrine tumors (11–13). Subsequent experience, however, demonstrated that some of the small endocrine tumors still could fail detection by this scintigraphy, a well-known phenomenon in other scintigraphic tumor-tracing methods.

With the aim of enhancing the sensitivity and resolution of scintigraphic methods, gamma-sensitive manual probes have been developed and evaluated with radiolabeled monoclonal antibodies as tumor-seeking agents (14, 15). These studies have revealed that successful detection depends crucially on the tumor:background signal ratio. To analyze requirements for preoperative scintigraphy and intraoperative scintillation of somatostatin receptor-positive tumors, we investigated the uptake of $^{[111}\text{In}]$DTPA-D-[\text{Phe}^1]$-octreotide in endocrine tumors and surrounding normal tissues sampled at surgery. The intraoperative efficacy of two commercially available hand-held probes also has been evaluated in relation to the preoperative SPECT imaging.

Materials and Methods

Twenty-three patients (10 women and 13 men), ages 42–78 years (mean, 65 years), scheduled for routine operations of endocrine tumors, were included in the study. Fifteen of them had midgut carcinoid tumors with metastases, five had endocrine pancreatic tumors (four insulinomas and one gastrinoma), and single patients had primary aldosteronism due to adrenal cortical adenoma, multiple cutaneous metastases from a previously operated paraganglioma, and medullary thyroid carcinoma. Seven patients with midgut carcinoids had been treated with somatostatin analogues for 5–12 months prior to the investigation. This therapy was discontinued invariably 72 h before scintigraphy. All patients but the one with medullary thyroid carcinoma were preoperatively investigated by abdominal CT (Somatotom DR2; Siemens; i.v. contrast enhancement, 8-mm slice thickness) and percutaneous US (Acuson 128; 3.5 MHz). All patients gave informed consent to participate in the study, which was approved by the local ethics committee.

Imaging Procedure. Lyophilized DTPA-D-[\text{Phe}^1]$-octreotide and $^{[111}\text{In}]$chloride were obtained in separate vials (Mallinkrodt Medical, Petten, The Netherlands), and labeling was performed as described previously (16). The $^{[111}\text{In}]$chloride was added to the lyophilized DTPA-D-[\text{Phe}^1]$-octreotide (20 μg) and incubated for 30 min at room temperature. The labeling yield was controlled with chromatography using Sep-Pak (17). In short, a small aliquot of the $^{[111}\text{In}]$labeled pentetreotide was applied to the top of a 1.0 × 1.5-cm column (Sep-Pak C18) and eluted with 5 ml distilled water (fraction A) followed by 5 ml methanol (fraction B). The radioactivity in individual fractions as well as the residual activity in the column were measured with a scintillation well counter (CRL-15; Capintec, Pittsburgh, PA). The labeling yield always exceeded 97% as calculated by the formula: $\frac{\text{fraction B (fractions A + B + column) }}{100}$. Prior to injection, 2 ml sterile NaCl solution (9 mg/ml) were added to the vial to make the volume more practical to handle.

The procedure of $^{[111}\text{In}]$DTPA-D-[\text{Phe}^1]$-octreotide scanning has been described previously (16, 18). To avoid artifacts caused by intestinal isotope accumulation, the patients received laxatives routinely on the day of the $^{[111}\text{In}]$DTPA-D-[\text{Phe}^1]$-octreotide administration and throughout the study. The patients obtained 111–244 megabequerels $^{[111}\text{In}]$labeled pentetreotide as a 3.5–4.5-ml i.v. injection. Planar anteroposterior whole-body images, extremities excluded, were collected 4 and 24 h thereafter. In all but two cases, SPECT was performed over the areas of interest. A gamma scintillation SPECT camera (Nuclear Diagnostics, Hägersten, Sweden) equipped with a medium-energy general collimator was used. The collection of original data for SPECT images used a 64-step rotation of 360° in a 64 × 64-word matrix and energy windows of 173 and 247 keV ± 10%. The signal accumulation time for each angle was 30–40 s, giving a total of about 40,000 counts/angle. A Wiener filter was applied to the original data for the image reconstruction. The patients underwent surgery within 12–48 h after receiving the $^{[111}\text{In}]$DTPA-D-[\text{Phe}^1]$-octreotide injections.

Intraoperative Measurement. Eleven of the patients (nine with carcinoid tumors, one patient with insulinoma, and one with metastasizing paraganglioma) were recruited for intraoperative measurement. This was performed with a hand-held gamma radiation detector probe covered with a sterile plastic tube after incision and overview of the surgical field. Two probes were tested, both equipped with a CsI scintillator, collimator, and shield in lead and a standard calibration for $^{111}\text{In}$. They were connected to a count-rating system in which c/s were shown on the display and documented manually. Seven cases were examined with the Tec-Probe 2000 (Stratec Electronic, Birkenfeld, Germany). The probes were controlled with a personal computer and a communicates with a dot matrix printer. In this way, the probe counts could be evaluated and evaluated together with preoperative SPECT images.

1 Presented at the “Fifth Conference on Radioimmunodetection and Radioimmuno-therapy of Cancer,” October 6–8, 1994, Princeton, NJ. This study was supported by the Swedish Cancer Society.

2 To whom requests for reprints should be addressed.

3 The abbreviations used are: DTPA, diethylenetriaminepentaacetic acid; SPECT, single photon emission computed tomography; CT, computed tomography; US, ultrasound; ID, injected dose; c/s, counts/second.
performed. The tissue:blood radioactivity ratio and the percentage of injected teric metastases were larger and frequently visualized by scintigraphy.

The fourth glomerate of multiple small liver metastases gave the image of a metastasis. Larger liver metastases were not detected generally, however, and sometimes a con tumors measured invariably less than 20 mm in diameter, and no such patients with midgut carcinoids, 12 of whom had liver metastases at radiology and/or the subsequent operation. This comprised all 15 metastatic tumors were sent for histopathological examination. The specimens were fixed in 10% buffered formalin and were paraffin embedded, after which 5-μm thin sections were stained with the van Gieson, hematoxylin and eosin, Grimelius, and Masson stains, as well as with monoclonal chromogranin A antibodies (LK 2H10; Boehringer-Mannheim, Mannheim, Germany) using the avidin-biotin technique (Vector Laboratories, Burlingame, CA). Endocrine pancreatic tumors were also examined immunohistochemically for the presence of insulin, glucagon, somatostatin, pancreatic polypeptide, vasoactive intestinal polypeptide, and gastrin (19). All neoplasms but the adrenal cortical tumor exhibited the expected argyrophilia and chromogranin immunoreactivity, and the intestinal carcinoids were invariably Masson positive. The endocrine pancreatic tumors were insulin or gastrin reactive, and the medullary thyroid carcinoma was immunostained for calcitonin. The parenchymal content in carcinoids and pancreatic tumors was analyzed by point sampling using an ocular grid.

Results

Preoperative Scintigraphy. The preoperative octreotide scintigraphy was considered positive in patients who had unequivocal tracer localization to at least one tumor site, being verified with conventional radiology and/or the subsequent operation. This comprised all 15 patients with midgut carcinoids, 12 of whom had liver metastases at scintigraphy (Table 1). At surgery, the primary intestinal carcinoid tumors measured invariably less than 20 mm in diameter, and no such lesions were detected preoperatively. However, neighboring mesenteric metastases were larger and frequently visualized by scintigraphy (Fig. 1). Ovarian metastases in one patient were indistinguishable from those in the mesentery. Larger liver metastases were demonstrable frequently by preoperative scintigraphy (Fig. 2). Smaller metastases were not detected generally, however, and sometimes a conglomerate of multiple small liver metastases gave the image of a single large lesion. In three of the four patients with insulinoma, the primary lesion was visualized by scintigraphy (Fig. 3). The fourth insulinoma failed visualization with preoperative scintigraphy as well as with CT and US. In the single patient with gastrinoma, the primary lesion and liver metastases were detected with Octreoscan. The aldo-
able count rates (Table 2), and the registrations were disturbed easily by probe movements. Background values in the thigh were low (1–10 c/s; mean, 3 c/s). Count rates of primary carcinoid tumors measuring <10 mm in diameter were no higher than the normal small intestine, and only two primary lesions exceeding this size were detectable. The carcinoid mesenteric metastases (n = 9; 20–50 mm in diameter) demonstrated higher count rates than the surrounding mesentery. The count rates of liver metastases were variable, some being lower than the macroscopically normal liver; others exceeded this activity by up to three times. One insulinoma was 3 cm in diameter and displayed a count rate (85 c/s) less than twice the value of the surrounding pancreas (54 c/s). Count rates for normal organs varied considerably, with the highest values for the kidneys, spleen, and liver. The cutaneous metastases from paraganglioma measured 8–15 mm in diameter and were not detected with the hand-held probe. The Gammed 2 probe was similar to the Tecprobe 2000 with respect to size, weight, and counting system, and it seemed to provide generally lower count rates. Altogether, 15 of 21 tumors investigated were recognized with the probes.

Radioactivity and Morphology of Tissue Samples. Analysis of tissue specimens with the well counter displayed variable radioactivity ratios toward blood for the macroscopically normal organs (Table 3). Especially, the spleen and, to a lesser extent, the liver showed the highest ratios but also a considerable variation between the patients. The normal pancreas and the small intestine had lower tissue:blood ratios, and these values were especially modest in intraabdominal and s.c. fat as well as striated muscle. The standardized uptake in the normal tissues mirrored essentially the tissue:blood ratio (Fig. 4). On average, this uptake was highest in spleen (0.054% ID/g), lower in liver (0.0067% ID/g) and pancreas (0.0042% ID/g), and less in small intestine, fat, and muscle.

The tumor:blood radioactivity ratio averaged 183 in the primary carcinoid lesions and was slightly higher in the mesenteric and liver metastases (Table 4). These ratios varied considerably between the individual tumors, and this was particularly evident among the four insulinomas. In Fig. 5, the standardized nuclide uptake is presented for the different tumors and the most neighboring normal tissues. The radioactivity in primary carcinoid tumors and mesenteric metastases (0.003–0.069% ID/g) was approximately 10 times greater than the normal intestine and mesenteric fat. For carcinoid liver metastases (0.012–0.059% ID/g), the discrepancy was sometimes less impressive but still about six times higher than the surrounding normal liver. Analysis of multiple lesions in individual patients supported that primary carcinoid tumors had generally lower standardized radioactive uptake than the metastases to the mesentery and liver. In the endocrine pancreatic tumors (0.009–0.254% ID/g), the uptake was 20 times that of the normal pancreatic tissue. This relationship included the gastrinoma, with an uptake of 0.0560% ID/g and a tumor:blood radioactivity ratio of 240. The uptake in the paraganglioma metastases (tumor:blood ratio, 18) also displayed a marked difference to normal skin (0.0097 versus 0.0009% ID/g). The normal adrenal gland, including both cortex and medulla, had a higher tissue:blood ratio (ratio, 74) than the aldosteronoma (ratio, 9.7), which displayed a tumor uptake of 0.002% ID/g. The medullary thyroid carcinoma demonstrated a tumor:blood ratio of 85.

At histopathological examination, the individual tumor specimens exhibited variable architecture, particularly with respect to the degree of fibrosis (Fig. 6). In primary carcinoid tumors and their liver metastases, the parenchyma sometimes occupied more than 90% of the section, whereas it was less than 20% in some mesenteric and ovarian carcinoid metastases (Table 5). The endocrine pancreatic tumors displayed similar variability (data not shown).

Discussion

Carcinoids and endocrine pancreatic tumors exhibit high-affinity binding sites for somatostatin, and octreotide scintigraphy has been reported to visualize tumor sites in 80–90% of patients harboring these lesions (12, 13). Initially, [125I-Tyr3]octreotide was used for scintigraphy (20, 21), but later [111In-DTPA-d-Phe1]octreotide in combination with SPECT was found to be more efficient (12). This method can detect lesions that are occult with other imaging tech-
Intraoperative registrations for primary tumors, metastases, and normal organs obtained with two different hand-held gamma detector probes. The single patient with paraganglioma is accounted for in the text.

<table>
<thead>
<tr>
<th>Probe</th>
<th>Primary tumor</th>
<th>Metastases</th>
<th>Liver</th>
<th>Spleen</th>
<th>Small intestine</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tec-Probe 2000 (6 patients)</td>
<td>62</td>
<td>97</td>
<td>80</td>
<td>149</td>
<td>11</td>
<td>118</td>
</tr>
<tr>
<td>Mean</td>
<td>24.8</td>
<td>20.8</td>
<td>16.1</td>
<td>111</td>
<td>0.7</td>
<td>17.5</td>
</tr>
<tr>
<td>SE</td>
<td>16–120</td>
<td>20–180</td>
<td>24–130</td>
<td>50–247</td>
<td>10–12</td>
<td>40–190</td>
</tr>
<tr>
<td>Gammed 2 (4 patients)</td>
<td>62</td>
<td>44</td>
<td>70</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>21.5</td>
<td>17.0</td>
<td>31.5</td>
<td>10.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>17–120</td>
<td>13–92</td>
<td>14–160</td>
<td>18–60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3. Scintigraphic three-dimensional reconstructed SPECT image over the upper abdomen 24 h after administration of Octreoscan. The image represents a slightly caudal view, and a pathological uptake (arrow) represents an insulinoma.

Intraoperative registrations (counts/second) for primary tumors, metastases, and normal organs obtained with two different hand-held gamma detector probes. The single patient with paraganglioma is accounted for in the text.
Table 3  

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Mean</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen (4)</td>
<td>302</td>
<td>147.9</td>
</tr>
<tr>
<td>Liver (11)</td>
<td>42</td>
<td>8.3</td>
</tr>
<tr>
<td>Bile (5)</td>
<td>47</td>
<td>17.5</td>
</tr>
<tr>
<td>Gall bladder (4)</td>
<td>16</td>
<td>3.2</td>
</tr>
<tr>
<td>Pancreas (4)</td>
<td>14.2</td>
<td>6.8</td>
</tr>
<tr>
<td>Small intestine (13)</td>
<td>12.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Intraabdominal fat (13)</td>
<td>8.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Subcutaneous fat (21)</td>
<td>2.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Muscle (17)</td>
<td>0.9</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 3  Tissue:blood ratio for normal tissues

**Note:** Tissue:blood radioactivity ratios in normal tissues. Numbers of patients within parentheses.

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Figure 4  Percent radioactivity of injected dose/g (mean, SE) in normal tissues. Numbers of patients contributing tumor specimens are in parentheses.

Table 4  Tumor:blood ratios

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Mean</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary tumors (11)</td>
<td>183</td>
<td>47.4</td>
</tr>
<tr>
<td>Mesenteric metastases (10)</td>
<td>208</td>
<td>47.4</td>
</tr>
<tr>
<td>Liver metastases (7)</td>
<td>208</td>
<td>21.7</td>
</tr>
<tr>
<td>Ovarian metastasis (1)</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Insulinoma, primary tumors (4)</td>
<td>369</td>
<td>(29–961)</td>
</tr>
</tbody>
</table>

**Note:** Tumor:blood radioactivity ratios in tumors and metastases obtained during peroperative sampling. Numbers of patients in parentheses.

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Figure 5  Percent radioactivity of injected dose/g for tumors and surrounding normal tissues. Numbers of patients contributing tumor specimens are in parentheses.

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Manual gamma detector probes may increase theoretically the sensitivity of octreotide scanning. Such probes have been used efficiently with other radioactive markers in the neck and abdomen (29, 30). However, the presently investigated probes were shielded insufficiently for optimal use with the \(^{111}\)In-labeled analogue. The peroperative probe measurements identified tumors of at least 2 cm, provided the nuclide uptake was 5–10 times that of the surrounding normal tissue. This included two primary tumors, which were detectable only by this method (and surgical palpation). Metastases located within or close to the liver, the spleen, or the kidneys were not identified with the peroperative technique. Our conclusion is that lesions detected by the presently examined intraoperative probes need to be rather large, and the method was not considered to provide new information that impacted on the surgical strategy. The \(^{111}\)In nuclide is probably not ideal for intraoperative detection of lesions. Lower \(\gamma\)-radiation energies, as associated with \(^{99}\)Tc or \(^{125}\)I, may be preferable, because they should be more attenuated in normal tissue and thereby reduce disturbance from heavy background radioactivity. This is a possible reason why \(^{125}\)I has been applied successfully in intraoperative tracing of thyroid tissue at total thyroidectomy (31) and for demonstration of dissemination in colorectal tumors (14). Hand-held probes apparently need more efficient collimator and shielding and,
tion to the multitude of investigated primary and metastatic lesions. In this context, the present biodistribution study may aid in calculations of dose distributions for, e.g., $^{111}$In-labeled octreotide for such treatments.

### References


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