Localization of Neuroendocrine Tumors Using Somatostatin Receptor Imaging With Indium-111-Pentetreotide (OctreoScan)

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Studies have shown $^{111}$In-pentetreotide to be an effective imaging technique for accurate localization and staging of neuroendocrine tumors of the gastrointestinal system.

**Background:** Many imaging methods have been used to detect neuroendocrine tumors of the gastrointestinal system. There is no gold standard for identifying the location of primary tumors and their potential metastases, and most conventional imaging techniques cannot detect tumors less than 1.0 cm in size.

**Methods:** The authors have investigated the use of $^{111}$In-pentetreotide as an imaging agent for abdominal neuroendocrine tumors.

**Results:** The agent is cleared rapidly by the kidneys and is primarily excreted intact with a biologic half-life of six hours. The largest radiation burden is to the spleen and kidneys. A nine-center study conducted in Europe involved 365 patients with gastroenteropancreatic neuroendocrine tumors that were also imaged by other methods. The results of $^{111}$In-pentetreotide were in agreement with those obtained by other methods for 79% of tumor locations. An additional 110 tumor localizations were detected that were not seen with conventional methods. The smallest gastrinoma imaged by $^{111}$In-pentetreotide was a 4-mm duodenal tumor.

**Conclusions:** Scintigraphy with $^{111}$In-pentetreotide is effective in visualizing various somatostatin receptors characteristic of neuroendocrine tumors of the gastrointestinal tract. Insulinomas, however, are not well imaged. Concurrent computed tomography scanning is advised to minimize the risk of missing liver metastases.

**Introduction**

The optimal management of patients with neuroendocrine tumors of the gastrointestinal system requires accurate tumor localization and staging. Various imaging methods that have been evaluated include ultrasonography, computed axial tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography, selective arteriography, transhepatic portal venous sampling, and secretin angiography. These techniques are applied with various indications. Regardless of the type, no single method or combination of methods has emerged as a gold standard for identifying the location of primary tumors and predicting the presence and extent of metastases. Most conventional imaging techniques cannot detect tumors less than 1.0 cm in size. Preoperative localization of the primary tumor increases the probability that the tumor will be found at laparotomy and thus increases the chance of cure.

Many neuroendocrine tumors contain high-affinity somatostatin receptors[1] (Please see hard copy of journal for Table 1), which is the basis for somatostatin radioreceptor imaging. In 1989, Krenning et al[2] introduced the first somatostatin-based radiopharmaceutical, $^{123}$I-TYR3-octreotide. It was effective in identifying metastatic extra-abdominal neuroendocrine tumors but, due to a high hepatic clearance and secretion into the bile, was of limited value for localizing small intraabdominal or intrahepatic tumors. Many of the limitations of $^{123}$I-TYR3-octreotide are overcome with $^{111}$In-pentetreotide. $^{111}$In-pentetreotide is excreted primarily by the kidneys with minimal physiologic uptake in the liver. Background activity in the right upper quadrant is more favorable for localizing neuroendocrine tumors, which have a propensity for this location, particularly gastrinomas. $^{111}$In-pentetreotide is a proton-rich nuclide that decays by electron capture to cadmium 111 with a physical half-life of 2.83 days. The principal photons used for detection and imaging studies are a 171.3-keV gamma radiograph with an abundance of 90.4% and 245.4 keV gamma ray with an abundance of 94% per disintegration.

**Pharmacology**

After injection, $^{111}$In-pentetreotide is cleared rapidly by the kidneys. Only approximately 2% of the injected dose undergoes hepatobiliary excretion. Within 10 minutes following injection, approximately 33% of the dose remains in circulation. At four hours, 10% of the injected dose is still in circulation, and at 24 hours, less than 1% of the dose remains circulating. This rapid clearance serves to enhance the tumor-to-background ratio, and the relatively low hepatobiliary clearance facilitates abdominal imaging. Analyses of urine and blood samples have shown that $^{111}$In-pentetreotide is primarily excreted intact with a biologic half-life of six hours.[2]

**Dosimetry**

The largest radiation burden from $^{111}$In-pentetreotide is delivered to the spleen and kidneys. A standard dose of 6 mCi (222 mGy) delivers approximately 14.5 rads
Patient Preparation

There are no patient diet restrictions for $^{111}$In-pentetreotide imaging study. The patient may take any medication except octreotide acetate. Patients must discontinue use of this pharmaceutical for 72 hours before administration of $^{111}$In-pentetreotide. To enhance renal clearance, patients are hydrated with two 8-oz glasses of water before injection. The recommended intravenous dose is 6 mCi (222 MBq) of $^{111}$In-pentetreotide. Patients are asked to use a laxative program generally consisting of four bisacodyl (Dulcolax) tablets of 5 mg each, 10 fluid ounces of magnesium citrate solution, and three packets of natural psyllium fiber.

Imaging Protocol

Initially at our center, we routinely obtained four hour images. However, we found that images obtained at higher resolution at 24 hours and, if needed, at 48 hours provided superior information. Therefore, scintigraphic images are obtained at 24 hours after injection. Images consist of whole-body anterior and posterior planar images by using a high-resolution 250-word matrix, a medium-energy general-purpose (MEGP) collimator, and a scan speed of 8 cm per minute. Additionally, digital planar spot images were obtained at 600 seconds per view by using a 250-word matrix and a MEGP collimator. Single photon emission computed tomography (SPECT) images of the upper abdomen are obtained in all patients. These images are essential to evaluate the region of the pancreas and duodenum because of the high competing signal from the kidneys, the spleen, and sometimes the gallbladder. A multihead camera is preferred to reduce imaging time. Radiologists have performed our studies with a dualhead camera by using MEGP collimation, 128 x 128-word matrix, 60 steps, and 40 to 50 seconds per step. When a three-head camera was used, we imaged 40 steps so that in each instance, 120 data sets were collected for reconstruction. Forty-eight-hour images were obtained as needed for review by the physician but were not standard. For example, 48-hour images may be needed to resolve the question of residual bowel or gallbladder activity vs tumor or to further evaluate the question of an abnormality shown on a 24-hour image.

Imaging Results

The results of a nine-center study conducted in Europe involving a total of 365 patients with proven or high clinical suspicions of gastroenteropancreatic neuroendocrine tumors are listed in Table 2.[3] (Please see hard copy of journal for Table 2.) The data compare $^{111}$In-pentetreotide localizations with lesions identified by other imaging modalities including CT, ultrasound, MRL angiography, or biopsy. True-positives were lesions detected by both $^{111}$In-pentetreotide imaging and by one of these other means. True-negatives had no evidence of neuroendocrine tumor with either $^{111}$In-pentetreotide or other methods. Overall, the results of $^{111}$In-pentetreotide were in agreement with those obtained by other methods, including biopsy, for 79% of tumor localizations (401 of 508). $^{111}$In-pentetreotide detected an additional 110 tumor localizations not seen with conventional methods. Of the 40 localizations that underwent biopsy, 37 were subsequently confirmed as tumors (true-positives). Three localizations were subsequently determined to be false-positives, and the remaining 70 localizations were unconfirmed. Overall, $^{111}$In-pentetreotide yielded information about previously unknown tumor localizations in 28% of patients. This statistic is remarkable because all of these patients were thoroughly evaluated before entering the study.

The general results at The Ohio State University Medical Center are listed in Table 3.[3] (Please see hard copy of journal for Table 3.) These data are remarkable because of the number of surgically confirmed localizations, as well as the fact that there are more instances of positive $^{111}$In-pentetreotide-negative CT results than negative $^{111}$In-pentetreotide-positive CT results. Figs 1-3 (Please see hard copy of journal for Fig 3A&B) demonstrate examples of $^{111}$In-pentetreotide images compared with images using other techniques.[3,4]

A specific study at our center of localization of gastrinoma consisted of 12 patients with histologic confirmation of gastrinoma. In these patients, 30 discrete foci of intrahepatic and extrahepatic tumors were detected at operation. CT scanning detected three of the nine pancreaticoduodenal lesions, whereas eight of these nine extrahepatic primary tumors were imaged by $^{111}$In-pentetreotide scanning. No false-positive scans were noted. The sensitivity of CT scanning for detection of metastatic disease was 56% compared with 94% for the $^{111}$In-pentetreotide scan. Successful CT imaging was highly dependent on tumor size. No tumor smaller than 1 cm was imaged by CT scan, whereas four of five lesions less than 1 cm were imaged by $^{111}$In-pentetreotide. The smallest gastrinoma imaged by $^{111}$In-pentetreotide was a 4-mm duodenal tumor.

Conclusions

$^{111}$In-pentetreotide, a relatively new radiopharmaceutical, has shown considerable success in the visualization of various somatostatin receptor-positive neuroendocrine tumors of the gastrointestinal tract. The sensitivity of scintigraphy is high for localizing neuroendocrine tumors except in the case of insulinoma. We currently recommend $^{111}$In-pentetreotide scintigraphy as the first localization technique for neuroendocrine tumors. Since a drawback of this technique is occasional failure to identify liver metastases, we recommend concurrent CT scanning.
References


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