

# Somatostatin Receptor Scintigraphy in Localization of Pancreatic Neuroendocrine Tumors: A Preliminary Study

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## ABSTRACT

**Objective:** To study the ability of somatostatin receptor scintigraphy using Tc-99m-hydrazinonicotinyl-Tyr<sup>3</sup>-octreotide (Tc-99m-HYNIC-TOC) for localization of pancreatic neuroendocrine tumors.

**Methods:** Five patients (3 female, 2 male; age range: 53 to 80 years; mean age: 65 years) with either histologically proven or clinically suspected insulinoma were studied. Ten mCi of Tc-99m-HYNIC-TOC were intravenously injected. Whole body scans were obtained 2 and 4 hours after injection. SPECT/CT studies of areas of interest were performed after the 4-hour whole body image. Scintigraphic findings were correlated not only with the results of conventional imaging methods, including computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound but also through 1-year clinical follow-up.

**Results:** The Tc-99m-HYNIC-TOC study showed true-negatives in two patients suspected of insulinoma proven by intraoperative ultrasound in one case and 1-year clinical follow-up with no evidence of hypoglycemia in the other patient. Abnormal Tc-99m-HYNIC-TOC accumulation was demonstrated in three patients with pancreatic tumors. Additional metastatic lesions to lung and bone were detected in one patient formerly diagnosed of malignant insulinoma with multiple liver metastases.

**Conclusion:** Tc-99m-HYNIC-TOC SPECT/CT imaging may provide more accurate staging of pancreatic neuroendocrine tumors than conventional imaging. It is an optional technique to recruit patients for somatostatin analogs therapy.

**Keywords:** Technitium-99m-HYNIC-TOC, scintigraphy, SPECT/CT, pancreatic neuroendocrine tumors

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Neuroendocrine tumor is a rare and heterogeneous group of neoplasms originating from endocrine cells which are characterized by the presence of secretory granules and the ability to produce biogenic amines as well as polypeptide hormones.<sup>1</sup> These tumors originate from endocrine glands such as the adrenal medulla, the pituitary and the parathyroids as well as endocrine islets within the thyroid or the pancreas and dispersed endocrine cells in the respiratory and gastrointestinal tract.<sup>2</sup> The neuroendocrine tumors of the gastroentero-pancreatic tumors include insulinomas, gastrino-

mas, carcinoids, glucagonomas and VIP-omas which have different degrees of aggressiveness and occur in ectopic sites.<sup>3</sup> Because these tumors are frequently small, it is very difficult to localize them with conventional methods.<sup>4,5</sup>

The majority of neuroendocrine tumors express somatostatin receptors so they can be targeted with radiolabeled somatostatin analogs in vivo. Somatostatin receptor scintigraphy with In-111-octreotide has been one of the standard procedures for imaging neuroendocrine tumors.<sup>6</sup> The limitations of this technique are due to the use of In-111 as the radiolabeler with its limited availability, high cost, medium gamma energy leading to suboptimal image resolution and relatively

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high radiation burden to the patient.<sup>7</sup> Tc-99m-HYNIC-TOC, a new somatostatin analog reported by Decristoforo et al, has been developed as an alternative radiopharmaceutical.<sup>8,9</sup>

The Thailand Institute of Nuclear Technology has got a grant from the International Atomic Energy Agency to develop this radiopharmaceutical for clinical use in Thailand. The ability of scintigraphy using this radiopharmaceutical for diagnosis and localization of pancreatic neuroendocrine tumors has been studied. In the present study, the authors reported 3 true positive cases of pancreatic neuroendocrine tumors localized by Tc-99m-HYNIC-TOC.

## MATERIALS AND METHODS

Five patients (3 female, 2 male; age range: 53 to 80 years; mean age: 65 years) with either histological proven or clinically suspected neuroendocrine tumors were studied. The clinical study was approved by the Ethics Committee of the Faculty of Medicine Siriraj Hospital (Si 117/2550) and all patients gave their informed consents before inclusion.

Tc-99m-HYNIC-TOC was prepared using a kit formulated by the Thailand Institute of Nuclear Technology. The preparation was the same technique as described by Decristoforo et al.<sup>9</sup> The chemical purity of the preparation was more than 95%. Each patient received approximately ten mCi of Tc-99m-HYNIC-TOC intravenously. Whole body scans were performed 2 and 4 hours after injection with a dual-headed camera (Infinia: General Electric) equipped with a low-energy high resolution parallel-hole collimator, 15% energy window centered at 140 keV. It took about 30 minutes for the whole body scan. For SPECT/CT acquisition, the same dual-headed gamma camera was used. Acquisition parameters were: 64x64 matrix size, 25 second/projection, 60 projections. SPECT/CT of the abdomen was performed after the 4-hour whole body image in all patients and of the chest in one patient. All patients had undergone at least 1 of 3 conventional imaging modalities (CT, MRI and ultrasonography).

Any area of focal tracer accumulation exceeding normal regional tracer uptake was rated a pathological finding (positive tumor uptake). Scintigraphic findings were classified as true-positive, true-negative, false-positive or false-negative according to the gold standard (histopathology or other imaging methods during follow-up after scan) and also through 1-year of clinical follow-up.

## RESULTS

The Tc-99m-HYNIC-TOC study showed true-negative in two patients. They were a 53-year-old male and a 76-year-old female who presented with hypoglycemia. The studies were done due to clinically suspected insulinoma. The negative results in these two cases were proven by intra-operative ultrasound in one case, while the other showed no evidence of hypoglycemia during the 1-year clinical follow-up. The authors found three true-positive cases.

### Case 1

A 62-year-old female with a huge neuroendocrine tumor in the left upper abdomen confirmed by fine

needle aspiration was sent for an evaluation of the status of somatostatin receptors in the tumor. A somatostatin-expressing tumor attached to the pancreatic body with involvement to the spleen was depicted on Tc-99m-HYNIC-TOC SPECT/CT scans (Fig 1).

### Case 2

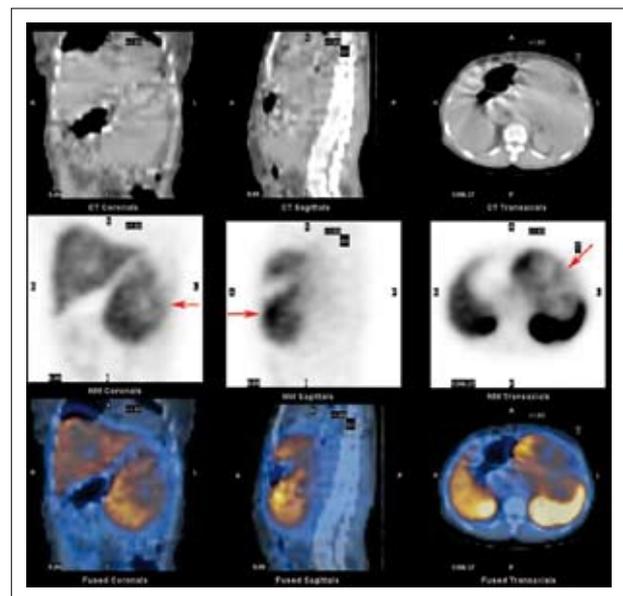
An 80-year-old female was suspected of insulinoma due to fasting hypoglycemia. MRI of the abdomen appeared unremarkable but transesophageal ultrasound showed a 5-mm hypoechoic mass at the pancreatic body. A suspicious finding at the tail of the pancreas was detected on Tc-99m-HYNIC-TOC SPECT/CT imaging (Fig 2). A laparoscopic distal pancreatectomy confirmed a 0.6 cm neuroendocrine tumor at the tail of the pancreas.

### Case 3

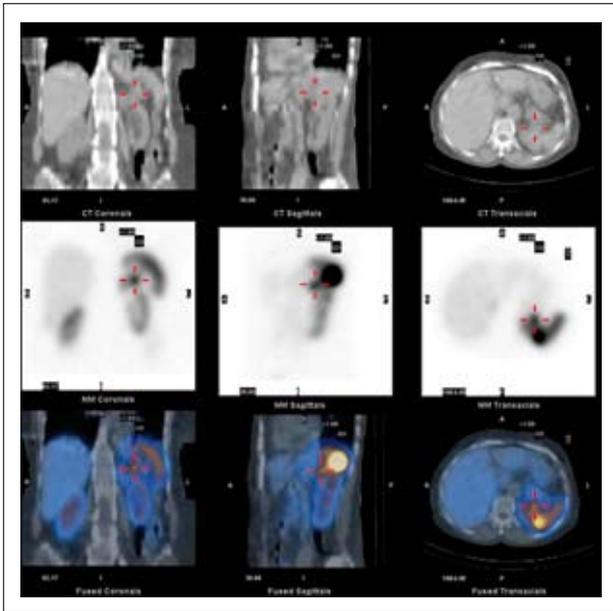
A 53-year-old male with multiple hepatic metastases from malignant insulinoma at the head and body of the pancreas status post chemoradiation and radiofrequency ablation for hepatic metastases was sent for restaging. Tc-99m-HYNIC-TOC SPECT/CT scan showed a primary tumor in the pancreas and multiple liver metastases (Fig 3). Multiple areas of abnormal uptake were additionally shown in the right chest from the masses in the right lung and hilum which correlated with CT images (Fig 4). Enhanced radioactivity accumulation was demonstrated in the left lower abdomen and was confirmed to be bony metastasis at the left acetabulum on CT scan (Fig 5).

## DISCUSSION

Conventional imaging modalities such as CT, MRI and endoscopic ultrasound have been accepted for the diagnosis and follow-up of pancreatic insulinoma although their sensitivities are less than optimal.<sup>10</sup> The challenge of these tumors is due to their small size and multiplicity. The most effective method to localize them



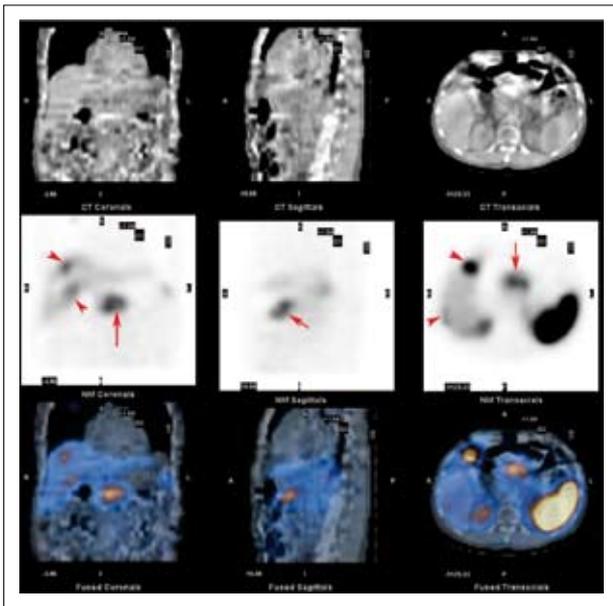
**Fig 1.** SPECT/CT of the abdomen using Tc-99m-HYNIC-TOC [upper panel: CT images, middle panel: SPECT images and lower panel: fusion images] showed a somatostatin-avid pancreatic tumor with invasion to spleen (arrow).



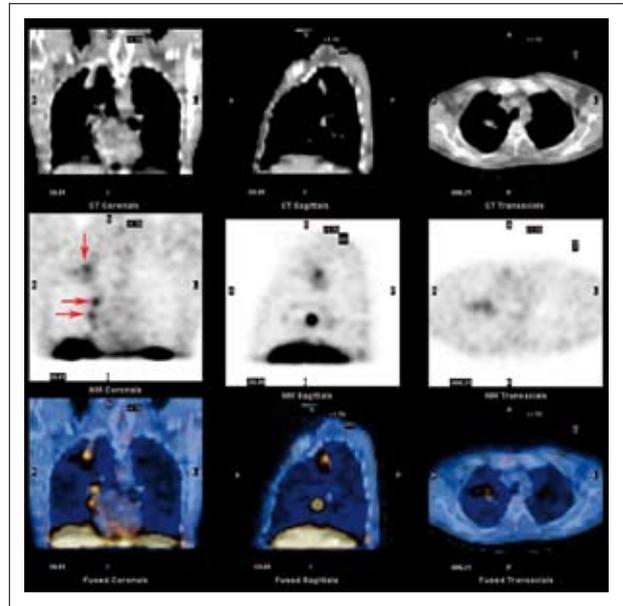
**Fig 2.** SPECT/CT images of the abdomen demonstrated abnormal uptake at the tail of the pancreas.

is probably intra-operative palpation and intra-operative ultrasound.

Various radiopharmaceuticals have been proposed for the diagnosis of neuroendocrine tumors based on specific uptake mechanism.<sup>1,11</sup> Radiolabeled metaiodobenzylguanidine (MIBG) uses an active amine uptake mechanism (uptake-1) in the cell membrane and is stored in the intracellular catecholamine storing granules.<sup>1,11</sup> More than 70% of well-differentiated pancreatic endocrine tumors express somatostatin receptors, so only the tumors with these receptors may be detected by radiolabeled somatostatin analog scan. This somatostatin analog scan uses the interaction with somatostatin receptors on the cell membrane of neuroendocrine



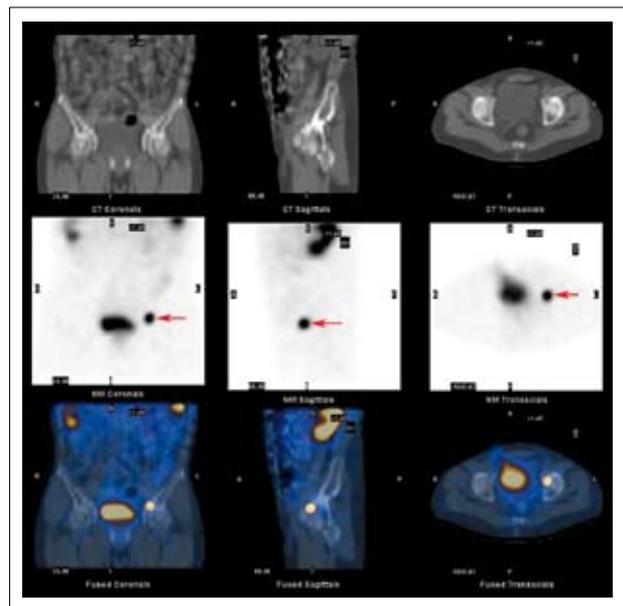
**Fig 3.** SPECT/CT images of the upper abdomen demonstrated the uptake in mid upper abdomen from the primary tumor of the pancreas (arrow) and the intense uptake in multiple liver metastases (arrow heads).



**Fig 4.** SPECT/CT images of the chest demonstrated abnormal uptake in the right upper lung mass and right hilum (arrows).

tumors. In-111-octreotide has been used as the first choice radiopharmaceuticals for visualization of somatostatin analog receptors.<sup>6</sup> The sensitivity of In-111-octreotide scan for the detection of gastroentero endocrine tumors and clinically nonfunctioning pancreatic endocrine tumors varies between 75-100%.<sup>12</sup> Tc-99m-HYNIC-TOC was reported to be used as an alternative agent with the sensitivity, specificity and accuracy for all gastro-entero-pancreatic neuroendocrine tumors of 80%, 94.4% and 82.9%, respectively.<sup>13</sup> In the presence of a pancreatic mass, a negative somatostatin analog scan suggests a pancreatic adenocarcinoma or a poorly differentiated endocrine pancreatic tumor.<sup>1</sup>

From the five patients in our study, Tc-99m-HYNIC-TOC showed two true-negative and three true-positive cases. Whole body scan seemed useful for



**Fig 5.** Bony metastasis at left acetabulum was detected on SPECT/CT images of the pelvis (arrow).

detection of distant metastases as previously unknown metastases in the chest and pelvis were detected in patient no. 3. Fusion SPECT/CT images significantly improved the localization of abnormal radioactivity accumulation. Apart from localization of the tumor, Tc-99m-HYNIC-TOC may be used with an intra-operative gamma probe if surgery is considered. Tc-99m-HYNIC-TOC can also be used to select the appropriate patient for therapy with radiolabeled somatostatin analogs.

## CONCLUSION

Tc-99m-HYNIC-TOC SPECT/CT technique may be an alternative procedure for diagnosis and follow-up of pancreatic neuroendocrine tumors. Fusion images improve SPECT interpretation and allow precise localization of lesions. This procedure will also be beneficial in selecting appropriate patients for somatostatin analogs therapy.

## ACKNOWLEDGEMENTS

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