

Diagnostic accuracy of technetium-99m-octreotide in imaging neuroendocrine tumors, Oman hospital experience with literature review

ABSTRACT

The aim of this observational cross-sectional study with retrospective review of the data is to evaluate the efficacy of using technetium-99m-octreotide (Tc-99m-OCT) in imaging neuroendocrine tumors (NETs) in our tertiary care hospital. A total of 58 patients had Tc-99m-OCT were identified in our database, from January 2013 to December 2016. Forty-one patients (age range of 15–75 years) meet our inclusion criteria, namely histopathology proven NETs, Tc-99m-OCT scan, computed tomography (CT), or magnetic resonance imaging (MRI) done in our institute for correlation. Twenty-three patients had true positive Tc-99m-OCT scan. In addition to the primary tumors, the octreotide scan revealed metastasis in the lung, liver, and retroperitoneal lymph nodes. The smallest lesion detected on octreotide scan was a 4-mm pulmonary nodule that was missed on lung window CT scan. The Tc-99m-OCT had 17 true negative, one false negative, and no false positive. The CT and MRI scans had 18 true positive, 17 true negative, 5 false negative, and one false positive. The overall sensitivity, specificity, accuracy, positive, and negative predictive values of Tc-99m-OCT scan were 96%, 100%, 97%, 100%, and 94%, respectively. Whereas those of CT and MRI were 78%, 94%, 85%, 94%, and 77%, respectively. Our diagnostic accuracy of Tc-99m-OCT is high. We recommend that, in addition to the conventional radiological investigations, Tc-99m-OCT scan, or other somatostatin receptor imaging (SSR) is a mandate for better and accurate staging of patients with NETs.

Keywords: Gallium-68, indium-111, neuroendocrine tumors, octreotide, somatostatin, technetium-99m

INTRODUCTION

Neuroendocrine tumors (NETs) are the uncommon type of tumors arising from the epithelial tissue of the neuroendocrine system.^[1] They can be either functioning or nonfunctioning type depending on the presence or absence of hormone and peptide secretions from the tumors. There are about 40–50 cases per million habitants which accounts for 0.5% of all adult cancers.^[1] The NET form 2% to 4% of the adults with cancer of unknown primary.^[2,3] Identifying the primary tumor in patients with NETs is crucial in the management of those patients even in the advanced stages with metastasis. Studies showed that resecting the primary tumor improves the quality of life and the overall survival in patients with NET even with metastatic disease.^[4,5]


As the NETs have increased the density of somatostatin receptors (SSTRs), it was possible to visualize those tumors

with radiolabeled somatostatin analogs. The imaging of NETs and other tumors with positive SSTRs started more than two decades back using (Indium-111-DTPA-[D-Phe¹]-Octreotide) (In-111-OCT).^[6] However, because

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the somatostatin analog is labeled with Indium-111, this enforced some limitations such as limited availability, high cost, higher radiation burden to the patient, and the overall suboptimal image quality.^[7] One and a half-decade back Decristoforo *et al.* described the development of a Tc-99m-labeled somatostatin analog (Tyr3-octreotide [TOC] and hydrazinonicotinic acid [HYNIC]).^[8] In their study, they found that Tc-99m-TOC had high tumor to background ratio and optimal imaging time, which was done as 1-day protocol as appose to the 2 days' protocols (4 and 24 h imaging) for In-111-OCT. With the advent of positron emission tomography/computed tomography (PET/CT), more positron emitting radiotracers were used to image the NETs, those include fluorine-18-fluoro-2-deoxy-D-glucose followed by 6-fluoro-(18F)-L-3,4-dihydroxyphenylalanine.^[9] However, Ga-68-DOTA-peptide PET/CT was found to be the most useful in imaging NETs including visualization, initial staging, and detection of relapse.^[10] It is also used to select patients who are likely to benefit from molecular radiotherapy, i.e., peptide receptor radionuclide therapy (PRRT), which consists of administration of radiotherapeutic Yttrium-90 (Y-90) or Lutetium-177 (Lu-177) versions of the same peptides used for imaging of inoperable NET.^[10] However, the latter is not readily available, hence most of the patients with NETs were scanned and operated based on the findings on multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) only.

MATERIALS AND METHODS

Patients

We introduce Technetium-99m instead of Indium-111 labeled octreotide in the last quarter of 2012. In our database, there were 58 patients who had technetium-99m-octreotide (Tc-99m-OCT) scans done between January 2013 and December 2016. Forty-one patients meet our inclusion criteria; that were histopathology proven somatostatin positive tumors, biochemical evidence of somatostatin tumors, Technetium-99m labeled octreotide scan, CT, and MRI. They were 21 males and 20 females with age range of 15–75 years (mean age of 42.7 years) [Table 1]. The findings on the Tc-99m-OCT scans were correlated lesion by lesion to the available MDCT and MRI scans.

Patients preparations

The patient should be off somatostatin receptor blocking agents for 72 h before the study. Occasionally, patients will be studied on somatostatin receptor blocking agents to assess the degree of suppression of uptake in a known lesion. In addition, the patients are advised to be on a liquid diet for 2 days before the scan with a mild laxative to be taken the evening before. On the day of the procedure, the patient

Table 1: Demographic details of the patients with the histopathology of the lesions postsurgery

n	Sex	Age	Histopathology
1	Male	72	Colon NET
2	Male	36	Poorly differentiated NET of duodenum
3	Male	26	Pancreatic insulinoma
4	Female	28	Paraganglioma
5	Female	31	Medullary thyroid cancer
6	Male	39	Metastatic malignant NET with no known primary
7	Male	30	Pancreatic Insulinoma
8	Female	28	Paraganglioma
9	Female	33	Medullary thyroid cancer
10	Male	41	MEN1 with pancreatic NET
11	Female	26	MEN 1 with pancreatic islet cell tumors
12	Female	63	Endobronchial NET
13	Male	41	Gastric gastrinomas and pancreatic islet cell tumor
14	Male	66	Poorly differentiated gastric NET
15	Female	47	MEN 1 with multiple NETs in stomach, duodenum and pancreas
16	Male	53	NET of the lung
17	Male	41	Pheochromocytoma of pancreas
18	Female	29	Metastatic NET with no known primary
19	Female	53	Gastric NET
20	Female	72	Carcinoid tumor of ileum
21	Female	58	Carcinoid tumor of colon
22	Male	33	Endobronchial carcinoid tumor
23	Male	60	Metastatic NET
24	Male	39	Pancreatic NET
25	Male	41	Pancreatic insulinoma
26	Female	26	Paraganglioma
27	Male	43	Appendix NET
28	Female	17	Appendix carcinoid
29	Male	31	Appendix carcinoid
30	Female	15	Appendix NET
31	Female	53	Gastric carcinoid
32	Male	59	Mesenteric carcinoid
33	Female	58	Small bowel NET
34	Male	12	Left lobe bronchus carcinoid
35	Female	72	Small bowel NET
36	Male	41	Pancreatic NET
37	Female	60	Gastric NET
38	Male	68	Colon NET
39	Female	17	Lung carcinoid
40	Male	43	Appendix NET
41	Female	25	Appendix carcinoid

NET: Neuroendocrine tumor; MEN: Multiple endocrine neoplasia

should fast until the end of the first scan but should be well hydrated. For breastfeeding mothers, they need to stop breastfeeding 12 h post-Tc-99m-OCT injection.^[11]

Preparation technetium-99m-labeled octreotide

The Tc-99m-OCT is prepared as per the instructions attached to the product kit. The octreotide kit consists of two vials; vial no - 1 contains 20 µg of HYNIC-Tyr-Octreotide TFA and vial no - 2 contains 10 µg (EDDA) as a stabilizing reagent.

The preparation starts by placing vial no - 1 in a suitable lead shielded container. This is followed by dissolving the content of vial no - 2 (EDDA) in 1 ml of saline and shaking it gently. Following that 0.5 ml from vial no - 2 (EDDA) is injected to vial no - 1 HYNIC-Tyr-(Octreotide). This step is followed by gentle shaking to dissolve the content of vial no - 1. 1ml of Tc-99m-sodium pertechnetate from the elution, which should be 2200 MBq (59.45 mCi), is injected to vial no - 1. The reconstituted vial no - 1 HYNIC-Tyr-(Octreotide) is then placed on the dry heater block which should be set at 80°. The vial should be boiled for 20 min using a breathing needle. The reconstituted vial is left to cool down at room temperature for 30 min. The radiopharmaceutical Tc-99m-HYNIC-Tyr-(Octreotide) should be used within 6 h.

Technetium-99m-octreotide scan

The dose used for adult patients is 740 MBq (20 mCi) Tc-99m-octreotide and the whole body, and static images are done at 2 and 4 h postradiotracer injection. The whole-body scan is performed using dual-head gamma camera, using image matrix of 256 × 1024 with speed of 8 cm/min and 5 min for each static image. The SPECT images are performed for the region of interest, as requested by the nuclear medicine physician, using 128 × 128 matrix, 1.45 zoom and 30 s per view for 32 frames.

This study was approved by the Ethics and Research Committee in our institution (MESRC-11/2015).

RESULTS

Out of the 41 patients who were included in this study, 23 showed single or multiple Tc-99m-OCT avid lesions. Most of our patients had either NET; some were known or with a strong family history of multiple neuroendocrine neoplasms (MEN) subtype I or II. Others had specific type of NET such as carcinoid tumors of bowel or bronchus, medullary thyroid cancer, islet cell tumors, and pheochromocytoma [Table 1].

The Tc-99m-OCT showed true positive results in 23 patients, whereas the CT and MRI showed true positive results in 18 patients. The Tc-99m-OCT showed one false-negative result in a patient with incidental finding of the left retroperitoneal mass, the histopathology of which was a well-differentiated paraganglioma. The CT and MRI, on the other hand, showed false-positive result in one patient with carcinoid tumor of the appendix, and few mesenteric lymph nodes and the patient was upstaged metastatic disease. The Tc-99m-OCT scan was performed to confirm the CT

findings, but it showed no uptake in the mesenteric lymph nodes, on 6 months' follow-up CT scan, the mesenteric lymph nodes resolved and the patient remained disease-free after 2 years of follow-up. Furthermore, the CT and MRI showed false-negative results in five patients, in which the Tc-99m-OCT scan detected metastasis in the bones, lung and retroperitoneal lymph nodes, resulting in upstaging of those patients [Table 2].

The octreotide scan SN, SP, PPV, and NPV were 96%, 100%, 100%, and 94%, respectively. On the other hand, the SN, SP, PPV, and NPV of the CT and MRI were 78%, 94%, 94%, and 77%, respectively. The Tc-99m-OCT showed significantly higher sensitivity and negative predictive value compared to those of CT and MRI. However, the specificity and positive predictive values of CT and MRI were not significantly lower than those of Tc-99m-OCT scan.

One of the patients in this cohort was a 47-year-old female who is known to have multiple endocrine neoplasia type 1 (MEN 1). She presented with severe diarrhea, and she was investigated for NET. The postcontrast CT scan of the abdomen and pelvis revealed no abnormality apart for a small, 7 mm, benign-looking preduodenal lymph node. She then had Tc-99m-octreotide scan which revealed focal uptake in the preduodenal lymph node and intense uptake in the proximal small bowel [Figure 1]. For further confirmation, the patient was sent overseas for Gallium-68-DOTA scan which revealed intense, abnormal uptake in the stomach, duodenum, pancreas, and preduodenal lymph node. The patient underwent Whipple's procedure, and the histopathology report came as multiple gastrinomas in the stomach, duodenum, pancreas, and one preduodenal metastatic lymph node. In a second patient, who was a 72-year-old male with known NET of the colon and a single metastasis to the liver, the postcontrast CT scan of chest and abdomen showed the known metastatic lesion in the liver with a small, 9 mm, mesenteric lymph node of query significance. The Tc-99m-octreotide scan showed octreotide avid lesion in the liver, focal uptake in the mesenteric lymph node and a small, 4 mm, octreotide avid lung nodule that was overlooked in the CT scan as it was solitary and small, denoting additional metastatic foci and changing the surgical management in

Table 2: Comparison between the technetium-99m-octreotide scan, computed tomography and magnetic resonance imaging scan results

	TP	TN	FP	FN
OCT scan	23	17	-	1
CT and MRI	18	17	1	5

OCT: Octreotide; CT: Computed tomography; MRI: Magnetic imaging resonance; TP: True positive; TN: True negative, FP: False positive, FN: False negative

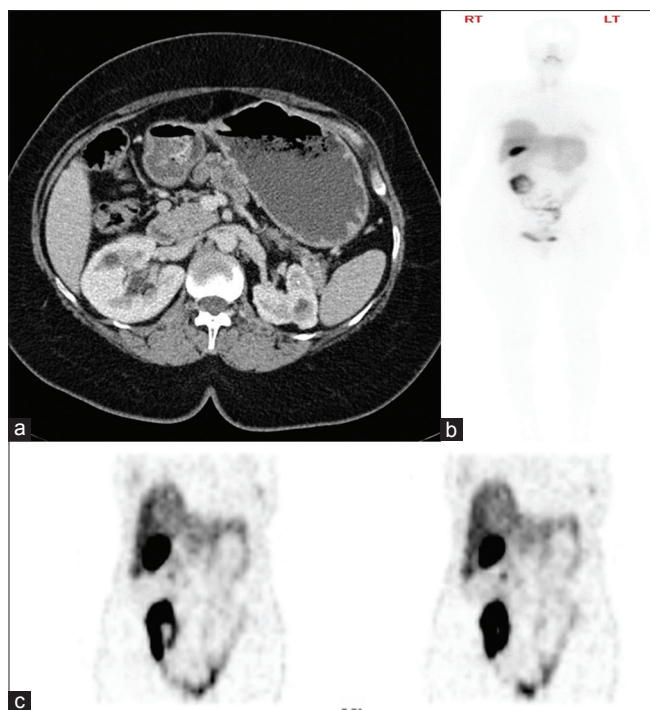


Figure 1: Tc-99m-OCT upstaged this patient with false-negative contrast-enhanced CT scan. Axial postcontrast CT scan image in (a) only found a 7 mm preduodenal lymph node, reported as benign looking (white arrow). The whole body of Tc-99m-OCT in (b) showed abnormal uptake in the small bowel (black arrow). Selected coronal images of the Tc-99m-OCT in (c) showed abnormal radiotracer uptake in the preduodenal lymph node (white arrow) and the proximal small bowel (black arrow). CT: Computed tomography; Tc-99m-OCT: Technetium-99m-octreotide

this patient [Figure 2]. Another patient who was 29-year-old female known as MEN1 and the postcontrast CT scan showed pancreatic lesion. The octreotide scan upstaged this patient by showing additional foci of octreotide avid lesions in the right breast and left distal femur in addition to the known lesion in the pancreas. Additional examples of octreotide scan upstaging the patients were in a 33-year-old female, known to have medullary thyroid cancer. Postcontrast CT chest that was done as part of the disease surveillance showed left-sided cervical lymph nodes only. However, the octreotide scan showed the uptake in the cervical lymph nodes in addition to focal uptake in the left clavicle. Reviewing the CT images revealed that there was a destructive lesion involving the distal aspect of the right clavicle, as this was at the tip of the field of view, it was overlooked on the CT scan.

DISCUSSION

Somatostatin is a peptide hormone made of 14 amino acids; it is normally found in the cerebral cortex, hypothalamus, brain stem, gastrointestinal tract, and the pancreas.^[6] To date, there are five known subtypes of somatostatin receptors (SSTR) that are expressed in various levels in NETs, SSTR 2 and 5

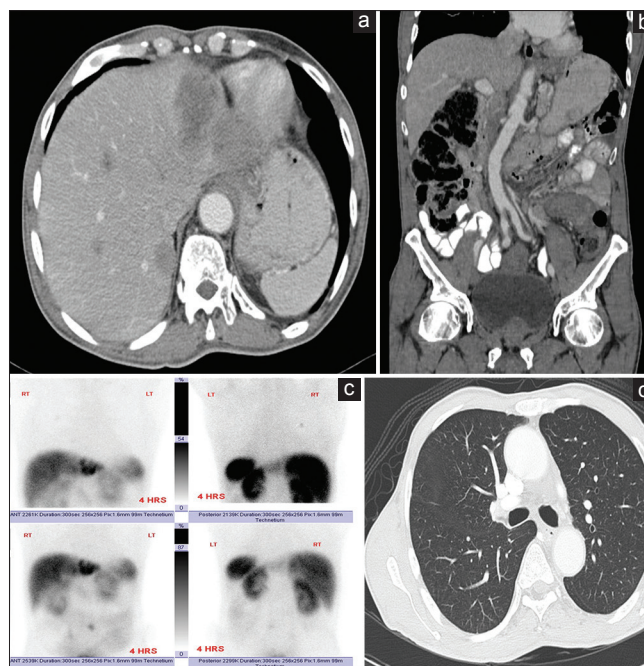


Figure 2: Tc-99m-OCT detected additional pulmonary nodule that was missed on CT scan. Axial CT scan image in (a) showed the metastatic lesion in the left liver lobe (white arrow). Coronal CT image in (b) showed the left retroperitoneal lymph node (white arrow). Static images of the Tc-99m-OCT in (c) showed the liver lesion (black arrow), the retroperitoneal lymph node (black arrowhead) and additional 4 mm pulmonary nodule that were missed on CT scan (white arrowhead). Axial lung window CT image in (d) showed the single pulmonary nodule (white arrow). CT: Computed tomography; Tc-99m-OCT: Technetium-99m-octreotide

are the most common with their frequency of expression in the NET ranging from 70% to 90%.^[12] Octreotide is the first somatostatin known analog; it is SST subtype 2 receptor agonists.^[13,14] Somatostatin receptor (SSR) imaging is used for; gastrointestinal and brain tissues evaluation, NETs, lung cancer, meningioma, and lymphoma. In addition, it is used before PRRT.

For decades radiolabeled somatostatin analog, (DTPA-[D-Phe¹]-Octreotide) – Indium-111 (In-111) was used in imaging NET.^[6] In our institution, indium-111-octreotide scans were not performed for years mainly due to the high cost and availability. Patients with NETs were staged and operated-on based on the findings on CT and MRI only. In 2012, we started using Tc-99m instead of In-111 for the octreotide scan, and this solved the issues of availability as the octreotide is readily available as a cold kit in our department. It is also much cheaper than buying the In-111-labeled octreotide; and the overall image quality with Tc-99m is much better than those with In-111. In both Tc-99m and In-111-labeled octreotide, the spleen is the highest exposed organ (the critical organ). The estimated absorbed dose of the spleen with Tc-99m-OCT in mGy/MBq is 0.030^[15] and that of In-111-OCT is 0.665.^[16] The risk-weighted equivalent dose to the whole body or

“effective dose” is measured in (mSv/MBq). The effective dose of Tc-99m-OCT is much less than that of In-111-OCT, 0.0056^[15] and 0.117,^[16] respectively [Table 3]. In addition, gamma Exposure rate at 1 cm from 1 mCi of Tc-99m is 720 mR/hr and that of In-111 is 3200 mR/h, i.e., the exposure of the workers from the In-111 is 4.4 times that of Tc-99m.

When comparing lesion by lesion detected by Tc-99m-OCT to those detected by MDCT and MRI, the octreotide study could detect all lesion except one, which was a well-differentiated paraganglioma. The sensitivity of octreotide in detecting NET was higher than that of MDCT and MRI (96% vs. 78%). The octreotide showed more lesions than MDCT and MRI which upstaged the patients and changed the management.

Reviewing the literature for Tc-99m-OCT, there were very few papers available, and the number of patients in this paper might be the largest mentioned in the literature so far. In the last decade, many centers shifted from conventional scintigraphy imaging for NET using In-111/Tc-99m labeled octreotide to PET/CT, particularly after the advent of Ga-68-DOTA peptides. Studies have shown the superiority of Ga-68-DOTA peptide PET/CT imaging over conventional SRS.^[17] In a study that included 109 patients with gastroenteropancreatic NETs, Ga-68-DOTA-NOC PET/CT showed sensitivity and specificity of 78.3% and 92.5%, respectively, for primary tumor and 97.4% and 100% for metastases. It was better than a conventional imaging modality for the detection of both primary tumor ($P < 0.001$) and metastases ($P < 0.0001$). It changed the management strategy in 21 patients (19%) and supported management decisions in 32 patients (29%).^[18]

Reasons for the preference of using Ga-68-DOTA include easy and economical synthesis of peptides which does not require a cyclotron, unlike In-111. Another important factor is the less imaging time (2 h for Ga-68-DOTA peptides, instead of the 4 h plus 24 h acquisition for In-111). When compared to the Tc-99m-OCT, both are imaged within 2 h, however, PET has higher spatial resolution compared to the single photon

emission computed tomography (SPECT) (3-6 mm versus 10-15 mm). Although in our study, the smallest lesion detected was 4 mm lung nodule, the Tc-99m-OCT missed multiple small lesions in the stomach and pancreas that were detected by Ga-68-DOTA PET/CT scan. In addition, DOTA-peptides have higher and broader affinity for SSTRs compared to octreotide. Finally, tracer uptake quantification in the region of interest can be achieved using PET.^[17]

CONCLUSION

In staging and follow-up patients with NETs, somatostatin receptor imaging (SSRI) is a mandate for better and accurate staging as well assessing the avidity of the primary tumor for future follow-up. In this study, we showed that the sensitivity and negative predictive values of Tc-99m-OCT scan is significantly higher than that of CT and MRI.

Using Tc-99m instead of In-111 had several advantages that include better availability, cheaper and higher quality images. This is in addition to less radiation exposure to both patients and nuclear medicine personnel. The introduction of PET imaging with ⁶⁸Ga and its labeling with DOTA compounds has cleared the way for somatostatin receptor imaging with a viable PET agent, with all the advantages compared to single photon imaging. This has revolutionized the current and future clinical practice for NET.^[19] The main limitation of the study is a retrospective data collection, and hence, all the patients included were known to have NETs, in addition, to the small sample size.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Table 3: The adult estimated absorbed dose in mGy/MBq and the effective dose in mSv/MBq of Technetium-99m-Octreotide and Indium-111-Octreotide

Organ	In-111-OCT (absorbed dose)	Tc-99m-OCT (absorbed dose)
Spleen	0.665 mGy/MBq	0.030 mGy/MBq
Kidney	0.488 mGy/MBq	0.021 mGy/MBq
Liver	0.109 mGy/MBq	0.012 mGy/MBq
Urinary Bladder	0.272 mGy/MBq	0.014 mGy/MBq
Thyroid	0.067 mGy/MBq	0.004 mGy/MBq
Effective dose (mSv/MBq)	0.117	0.0056

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