Clinical value of technetium-99m-labeled octreotide scintigraphy in local recurrent or metastatic medullary thyroid cancers: a comparison of lesions with ^{18}F -FDG-PET and MIBI images

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Aim Various studies have been conducted for determining the most optimal method for the early diagnosis of local recurrent or distant metastatic thyroid cancers. The aim of this study was to evaluate the clinical utility of technetium-99m (Tc-99m)-labeled octreotide derivatives in the detection of recurrence or distant metastases in medullary thyroid cancer patients and to compare the lesions with those detected using ^{18}F -fluorodeoxyglucose (^{18}F -FDG)-PET and Tc-99m MIBI studies in the same patient group.

Patients and methods Sixteen medullary thyroid cancer patients [two male and 14 female; mean age 52.0 ± 14.1 years (range 13–72 years)] were included in this study. All patients underwent a whole-body scan 1 and 4 h after injection with octreotide derivatives and single photon emission computed tomography images were taken of the sites suspicious for metastasis. The lesions seen in Tc-99m HYNIC octreotide studies were compared with those seen in ^{18}F -FDG-PET and Tc-99m MIBI studies.

Results Among the Tc-99m-labeled octreotide scintigraphy studies, nine were evaluated as true positive (56.2%) and one was evaluated as false positive (6.2%); six were false negative (37.5%). In 16 patients, the total number of lesions seen on octreotide scintigraphy was 21. Thirteen of the 16 patients underwent ^{18}F -FDG-PET imaging. Of the 13 patients studied, 10 showed true-positive (76.9%) and three showed false-negative (23.1%)

results. The total number of lesions seen on ^{18}F -FDG-PET was 23. The Tc-99m MIBI study yielded positive results in seven of 16 patients (43.7%) and negative results in nine patients (56.3%). The total number of lesions on Tc-99m MIBI was 12.

Conclusion The Tc-99m-labeled somatostatin receptor scintigraphy analogs HYNIC-tyrosine octreotide and HYNIC-TATE are useful imaging alternatives in somatostatin receptor-expressing thyroid cancers. Radiolabeling using these analogs is easy and they are readily available for routine use. *Nucl Med Commun* 34:1190–1195 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Nuclear Medicine Communications 2013, 34:1190–1195

Keywords: ^{18}F -fluorodeoxyglucose-PET, HYNIC-TATE, HYNIC-tyrosine octreotide, octreotide scintigraphy, Tc-99m MIBI

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Received 25 June 2013 Revised 2 September 2013
Accepted 5 September 2013

Introduction

Medullary thyroid carcinoma originates from para-follicular cells and secretes calcitonin [1]. After surgery, elevated calcitonin levels indicate the presence of metastatic or recurrent disease and the patient has to undergo multiple imaging procedures. An early diagnosis of local recurrence or distant metastases of medullary thyroid carcinoma can be achieved using several conventional imaging modalities [e.g. ultrasonography (USG), computed tomography (CT), MRI, and nuclear medicine imaging procedures such as positron emission tomography/CT (PET/CT), scintigraphy with different types of radiopharmaceuticals (technetium-99m (Tc-99m) MIBI, Tc-99m DMSA-V, thallium-201), and scintigraphy with radiolabeled receptor ligands (octreotide scintigraphy)] [2].

Somatostatin scintigraphy is most commonly used in the evaluation of somatostatin receptor-positive tumors such as carcinoid tumor, gastroenteropancreatic tumors (gastrinoma, insulinoma, glucagonoma, VIPoma), pheochromocytoma, paraganglioma, neuroblastoma, lung cancer (both small-cell and non-small-cell types), differentiated and medullary thyroid cancer, central nervous system tumors (meningioma, glioma, hypophyseal adenoma), lymphoma (both Hodgkin's and non-Hodgkin's type), breast cancer, ovarian cancer, and Merkel cell tumors. There is variable uptake in these tumors on somatostatin scintigraphy [3]. The half-life of natural somatostatin is short (1–2 min); therefore, many synthetic somatostatin analogs (octreotide, lanreotide, vapreotide, and depreotide) were developed. There are five different subtypes of somatostatin receptors, and natural somatostatin can

bind to all of them. The synthetic somatostatin analog octreotide can strongly bind to somatostatin receptor subtype 2 and weakly to subtype 5 [4].

Most medullary thyroid cancers express somatostatin receptors. Indium-111 (In-111) octreotide somatostatin receptor scintigraphy has been used to detect sites of recurrent or metastatic focus. There are several advantages of Tc-99m-labeled octreotide scintigraphy over In-111 octreotide scintigraphy. Image properties and image quality are better with Tc-99m than with In-111; further, whole-body images are taken at the first and fourth hours on the same day on using Tc-99m, whereas patients given an In-111-labeled radiopharmaceutical have to come the next day for 24th-hour imaging. Further, the radiation dose to the patient is lower on Tc-99m scintigraphy.

^{18}F -Fluorodeoxyglucose (^{18}F -FDG)-PET plays a crucial role in the detection of residual tumor or metastatic disease in patients with medullary thyroid cancer. Fasting is necessary before ^{18}F -FDG injection, and diabetic patients should have regulated blood glucose levels. PET/CT with ^{18}F -FDG has been proven to be better than other diagnostic tools in the detection of cervical and mediastinal lymph node metastases in medullary thyroid cancer [5].

The aim of this study was to evaluate the clinical utility of Tc-99m-labeled octreotide scintigraphy in the detection of tumor recurrence or metastases in patients with medullary thyroid carcinoma and to compare the lesions with those detected using PET/CT and Tc-99m MIBI studies.

Patients and methods

The study was approved by the local ethical committee and all patients gave informed consent before inclusion. Sixteen thyroid cancer patients [mean age 52.0 ± 14.1 years (range 13–72 years)] who presented at our department and were diagnosed with medullary thyroid cancer with elevated calcitonin levels were included in this study. Two patients (13%) were male and 14 (87%) were female. All patients had undergone total thyroidectomy 1–12 years earlier and were diagnosed with medullary thyroid carcinoma. In all patients, octreotide scintigraphy, MIBI scintigraphy, and ^{18}F -FDG-PET/CT imaging were performed within a 2–14-day time interval. None of these patients received any further therapy during these studies. All patients underwent a whole-body scan 1 and 4 h after injection with octreotide derivatives, and single photon emission computed tomography (SPECT) images were acquired of the sites suspicious for metastases. The lesions seen on Tc-99m HYNIC-octreotide studies were compared with those seen in ^{18}F -FDG-PET and Tc-99m MIBI studies.

The somatostatin analog Tc-99m HYNIC-TATE (HYNIC⁰, Tyr³, Thr⁸) octreotide, using ethylenediamine-

N,N' -diacetic acid as a coligand, was prepared in a sterile environment, boiled in water for 10 min, and left at room temperature for 15 min to cool. Each patient received an intravenous injection of 350–444 MBq (9–12 mCi) as a radiopharmaceutical. Whole-body scanning was carried out 1 and 4 h after injection, and SPECT images were acquired at the fourth hour. Images were acquired with a double-head gamma camera (Nucline Spirit DH-V; Mediso, Budapest, Hungary) using a low-energy high-resolution collimator. A 140 keV energy peak $\pm 10\%$ energy window was selected. SPECT images of the cervical region, mediastinum, lungs, and other suspicious locations observed on whole-body scanning were taken.

^{18}F -FDG-PET imaging was performed with a six-slice multidetector CT integrated high-resolution PET scanner (Biograph LSO HI-REZ PET/CT; Siemens, Chicago, Illinois, USA). A minimum of 4 h of fasting and good hydration were maintained and blood glucose levels of each patient were measured using a glucometer (Medisense Optium; Xceed Abbott Diabetes Care Inc., Alameda, California, USA) before radiopharmaceutical injection. Anxious patients and especially young female patients received 5 mg of diazepam to reduce brown fat activity, following which they rested at room temperature. ^{18}F -FDG [370–703 MBq (10–19 mCi)] was administered to patients with blood glucose levels lower than 150 mg/dL. After the injection, the patients rested for a further 45–60 min in a quiet, comfortable room for biodistribution and ideal tumor uptake of the radiopharmaceutical. Before imaging, all patients were asked to urinate to reduce urinary vesicle activity. First topogram images, then noncontrast low-dose CT images from the vertex to 1/3 of the upper portion of the thigh, and finally PET images were acquired while the patients lay in the supine position.

For Tc-99m MIBI imaging, 370–740 MBq (10–20 mCi) radiopharmaceutical was administered. Early images were taken 10–15 min after injection and late images were taken 2–3 h later with a dual-head gamma camera (Nucline Spirit DH-V; Mediso) using a low-energy high-resolution collimator and selecting a 140 keV energy peak $\pm 10\%$ window for Tc-99m.

Octreotide scintigraphy, ^{18}F -FDG-PET, and MIBI scintigraphy images were evaluated by two separate nuclear medicine physicians at different times who were blinded to clinical data and the results of other imaging methods. The lesions observed in the images were divided into five anatomical groups: cervical (including the thyroid region), mediastinal, lung, bone, and abdomen and other regions. Images were compared for each lesion. The χ^2 -test was used to determine whether there was a significant association between these imaging methods. The sensitivity, specificity, and number of lesions were determined for each imaging method.

Findings

Sixteen patients had sporadic medullary thyroid cancer. On Tc-99m-labeled octreotide scintigraphy, nine cases were evaluated as true positive (56.2%) and one was evaluated as false positive (6.2%); six were false negative (37.5%). In the 16 patients, the total number of lesions seen on octreotide scintigraphy was 21 (Table 1).

Thirteen of the 16 patients underwent ^{18}F -FDG-PET imaging; of the 13 cases 10 were true positive (76.9%) and three were false negative (23.1%). The total number of lesions seen on ^{18}F -FDG-PET was 23.

Tc-99m MIBI scintigraphy revealed seven of 16 positive cases (43.7%) and nine (56.3%) negative cases. The total number of lesions seen on Tc-99m MIBI was 12 (Figs 1 and 2).

Discussion

Somatostatin scintigraphy is used to detect the primary tumor focus for staging, preparation of therapy protocol, and assessment of therapy response in neuroendocrine tumors and in breast, brain, colon, and lung carcinomas [6]. The aim of somatostatin scintigraphy is to visualize tumors and tissues that express somatostatin receptors. In-111-labeled octreotide scintigraphy is the most common method for visualizing lesions with somatostatin receptors. In-111 octreotide was discovered by Krenning *et al.* [7] in the Netherlands, and octreotide scintigraphy was introduced as a reliable noninvasive imaging tool for detection of somatostatin receptor-expressing tumors. In-111 has some disadvantages with

respect to its supplement, high cost, suboptimal imaging properties, and low resolution because of its medium energy and relatively high radiation dose to the patient. For this reason, new somatostatin analogs are being labeled with Tc-99m instead. In our study, we used the new somatostatin analog HYNIC-TATE labeled with Tc-99m.

It might be difficult to find a remnant or recurrent tumor focus in medullary thyroid cancer patients with high postoperative serum calcitonin levels. Detection of recurrence or distant metastasis is crucial for clinical assessment and selection of candidates for reoperation. Conventional methods such as neck USG, abdominal USG, spiral CT, and MRI are being used to detect recurrence or distant metastasis. However, sensitivity of all of these anatomical imaging modalities may be low because of postoperative changes and limited imaging properties. Scintigraphic modalities, such as Tc-99m MDP, thallium-201 chloride, Tc-99m MIBI, Tc-99m tetrofosmin, In-111 octreotide, and ^{18}F -FDG-PET/CT, are the nuclear medicine whole-body imaging modalities for the detection of recurrence or metastatic disease in this group of patients.

Medullary thyroid carcinoma is a type of neuroendocrine tumor, which expresses somatostatin receptor subtype 2 (30–50%) and subtype 5 to a lesser extent [8]. Because of its somatostatin receptor expression, In-111 octreotide scintigraphy had been used to detect recurrence in medullary thyroid carcinoma patients with high levels of calcitonin and carcinoembryonic antigen. Kwekkeboom *et al.* [9] reported the sensitivity of somatostatin scintigraphy to be 65% in medullary thyroid carcinoma detection.

De Groot and colleagues compared In-111 octreotide scintigraphy with ^{18}F -FDG-PET in 26 medullary thyroid carcinoma patients with high levels of calcitonin. ^{18}F -FDG-PET could detect malign focus in 13 of 26 patients (50%), whereas In-111 octreotide scintigraphy was positive for four of 21 patients. When lesions were compared, ^{18}F -FDG-PET could detect 53 lesions and In-111 octreotide scintigraphy could detect 12. Sensitivity of ^{18}F -FDG-PET and In-111 octreotide scintigraphy was 96 and 41%, respectively [10].

In the study by Parisella and colleagues, the aim was to detect recurrence and distant metastasis with Tc-99m tyrosine octreotide (HYNIC-TOC) in five patients with high levels of calcitonin after total thyroidectomy. Tc-99m TOC scintigraphy showed positive results in all five patients, and a total of 15 lesions were detected. When In-111 octreotide scintigraphy was performed in the same patient group, only three patients were found to be positive, and eight lesions were detected. All five patients were ^{18}F -FDG-PET positive, and a total of 11 lesions were detected with PET. Parisella *et al.* [11] found more

Table 1 Characteristics and results of patients with medullary thyroid cancer

Patient number	Sex	Age	Calcitonin	SRS	PET	MIBI	Vf
1	M	71	312	Med (TP)	Absent	Med (TP)	O
2	F	13	22	N (FN)	Absent	N (FN)	R/follow-up
3	F	54	135	Cer (TP)	Cer (TP)	Cer (TP)	O
				Med (TP)	Med (TP)	Med (FN)	
4	F	57	142	Cer (TP)	Cer (TP)	Cer (TP)	O
5	M	50	1016	Cer (TP)	Cer (TP)	Cer (TP)	R/O
				Med (TP)	Med (TP)	Med (TP)	
				Lung (TP)	Lung (TP)	Lung (FN)	
6	F	55	75	Cer (TP)	Cer (TP)	Cer (TP)	O
7	F	46	500	N (FN)	Absent	N (FN)	R
8	F	51	120	Med (TP)	Med (TP)	N (FN)	O
9	F	49	188	Med (TP)	Med (TP)	N (FN)	R/O
				Lung (TP)	Lung (TP)		
10	F	50	116	Med (FP)	N (FN)	N (FN)	R/O
11	F	58	105	N (FN)	N (FN)	N (FN)	R/follow-up
12	F	39	130	Cer (TP)	Cer (TP)	Cer (TP)	O
13	F	71	214	N (FN)	N (FN)	N (FN)	R/follow-up
14	F	45	240	Cer (TP)	Cer (TP)	Cer (TP)	R/O
				Med (TP)	Med (TP)	Med (TP)	
				Lung (TP)	Lung (TP)	Lung (FN)	
15	F	72	360	N (FN)	Cer (TP)	N (FN)	R/O
16	F	51	96	N (FN)	Ser (TP)	N (FN)	R/O

Cer, cervical region/thyroid gland; FN, false negative; FP, false positive; med, mediastinum; N, normal; O, operation; R, radiology; SRS, somatostatin receptor scintigraphy; TP, true positive; Vf, verification.

Fig. 1

^{18}F -FDG-PET MIP, axial PET, axial CT, and axial fusion images of a 51-year-old female patient with medullary thyroid cancer who had high calcitonin levels. PET/CT images show increased ^{18}F -FDG uptake in the mediastinum (arrow). After the operation, pathology results confirmed medullary thyroid cancer metastases. CT, computed tomography; ^{18}F -FDG, ^{18}F -fluorodeoxyglucose.

lesions using octreotide scintigraphy compared with ^{18}F -FDG-PET.

Lodish *et al.* [12] found that In-111 octreotide scintigraphy is less sensitive than conventional imaging modalities in detecting the full extent of metastatic

disease in children and adolescents with hereditary medullary thyroid carcinoma.

In the study by Czepczyński and colleagues, octreotide scintigraphy using Tc-99m HYNIC-TOC showed 20 true-positive, four true-negative, one false-positive, and seven

Fig. 2

SPECT images of Tc-99m HYNIC octreotide scintigraphy in a 51-year-old female patient with medullary thyroid carcinoma. There is increased uptake in the mediastinum (arrow), which is the same lesion in PET/CT slices. CT, computed tomography; SPECT, single photon emission computed tomography; Tc-99m, technetium-99m.

false-negative results in a total of 26 medullary thyroid cancer patients. They found the sensitivity of octreotide scintigraphy with Tc-99m HYNIC-TOC to be 74.1% and the specificity to be 80.0%, demonstrating that these results were better than those obtained by other imaging methods [13].

In our study, octreotide scintigraphy was true positive in nine of 12 patients, and a total of 21 lesions were visualized. Ten of 13 patients showed true-positive results on ^{18}F -FDG-PET, and a total of 23 lesions were

detected. MIBI was true positive in seven of 16 patients, with a total of 12 lesions detected.

When we compare the total effective doses of these imaging methods, Tc-99m-labeled octreotide imaging is seen to involve the lowest radiation dose to the patients. Grimes *et al.* [14] reported the mean effective dose of Tc-99m HYNIC-TOC to be 4.6 ± 1.1 mSv. The effective dose of ^{18}F -FDG-PET/CT and whole-body Tc-99m MIBI imaging for adults is 0.019 (0.070) and 0.015 (0.056) mSv/MBq (rem/mCi), respectively [15,16].

Conclusion

Tc-99m-labeled somatostatin scintigraphy is an easy and promising imaging modality in medullary thyroid carcinoma patients with high levels of calcitonin. In comparison with In-111 octreotide scintigraphy, its availability and application is easier. Further, it has better image resolution and involves less radiation exposure to the patient. It has a higher sensitivity and a greater ability to detect lesions compared with MIBI; however, compared with ^{18}F -FDG-PET, its sensitivity in detecting lesions is lower. Nevertheless, it can be used as an alternative imaging method when ^{18}F -FDG-PET is not available. In addition, it is recommended when ^{18}F -FDG-PET results are found to be negative. Our study suggests that Tc-99m-labeled octreotide could be considered an alternative to In-111-labeled octreotide, and further evaluation with larger numbers in a sufficiently powered study to enable statistical analysis should be undertaken.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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