

The Value of F18-FDG PET/CT in Medullary Thyroid Cancer Patients with Persistent Elevated Calcitonin Levels

Samuel Anane, Dr. hai jun bao , Gabriel Komla Adzika, Kofi Ayensu

ABSTRACT

Purpose of the Study: In this retrospective study, we reported our experience with FDG-PET/CT in evaluation of medullary thyroid cancer (MTC) patients with persistent elevated calcitonin levels.

Materials and Methods: A total of 33 F-18 FDG PET/CT scans and 9 somatostatin receptor imaging (SRI) (6 In-111 octreotide and 3 Ga-68 DOTATATE PET/CT) of 25 MTC patients with persistently elevated calcitonin levels, performed for staging and restaging, were analyzed retrospectively. The scans were compared lesion by lesion with histopathological data and other imaging methods. Because all patients had abnormally high calcitonin levels defined as persistent disease, negative F-18 FDG PET/CT scans accepted as false negative. Because there was no true-negative study, only sensitivity and positive predictive value (PPV) were calculated. Calcitonin levels and SUVmax values were assessed by Mann-Whitney U test and the ROC curve analysis.

Results: There were 11 true-positive, 11 false-positive and 11 false-negative F-18 FDG PET/CT scans. Sensitivity and PPV were 50% and 50% respectively. Difference of mean calcitonin level between true-positive cases and the others was nonsignificant. SUVmax of true-positive lesions were significantly higher than of the others. All 9 SRIs were negative.

Conclusions: FDG PET/CT scan appeared to be less sensitive. However, it should be considered that F-18 FDG PET/CT was performed to the patients with only no lesion had been detected by the other imaging modalities in this group. Because F-18 FDG PET/CT was not performed when a residual or recurrent lesion had clearly been detected before, sensitivity of 50% was considered to be acceptable.

Key words: medullary thyroid carcinoma, FDG, PET/CT, calcitonin, thyroid cancer

INTRODUCTION

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor that originates from parafollicular C cells of the thyroid gland and occurs both in hereditary (25%) and sporadic (75%) forms. In recent studies, MTC accounts for approximately 2-3% of all thyroid cancers, much lower incidence than previously reported (5%), because of the marked increase in the relative incidence of papillary thyroid carcinoma (PTC) over the past several decades. Parafollicular C cells produce several hormones or biogenic amines such as calcitonin, carcinoembryonic antigen (CEA), adrenocorticotrophic hormone (ACTH) and somatostatin. Among all of them, calcitonin and CEA are most valuable tumor markers for MTC (1, 2).

The only curative treatment option of MTC is surgical resection (total thyroidectomy and lymph node dissection) in patients without distant metastasis. The most frequent metastasis sites of MTC are cervical and mediastinal lymph nodes, lungs, liver and bone. The patients with distant metastasis would not be candidates for extensive loco-regional surgery with curative intent and show poor response to chemotherapy and radiation therapy. Therefore, the most important prognostic factor in patients with MTC is early diagnosis that facilitates early surgical intervention before metastatic spread (2, 3).

Measurements of the serum calcitonin level are important in the follow-up of patient with MTC. Two or three months after

surgery is the optimal time to determine the lowest level of serum calcitonin. Persistently or increasingly elevated calcitonin level is indicative for residual or recurrent disease in MTC patients (2). These patients are evaluated with conventional imaging methods such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine imaging methods with several types of radiopharmaceuticals such as indium-111 octreotide (In-111 octreotide), technetium-99m pentavalent dimercaptosuccinic acid (Tc-99m (V) DMSA), gallium-68 (Ga-68) labelled somatostatin analogues, fluorine-18 fluorodeoxyglucose (F-18 FDG), fluorine-18 dihydroxyphenylalanine (F-18 DOPA) (4-7). But no consensus has yet been reported on their selective use. In this study, we reported our experience with F-18 FDG positron emission tomography/computed tomography (PET/CT) in the evaluation of this specific group.

HUMAN LIFE CYCLE

To understand death, one must be able to know what life is about. Life is the ability of one to use (ATP) effectively to power the processes involved in the Human Life Cycle (HLC). The absence of this invites death which is a process that truncates the cycle. Given this, the organs that are crucial for the effective use of ATP are mostly involved in the common causes of death worldwide.

The human life cycle (HLC) includes the processes that travel from the intrauterine to old age. HLC involves many complex processes

that are very important at each stage of the cycle. The main source of energy for the cycle is ATP which can be produced more when there is an availability of oxygen. This because many aspects of cell metabolism revolve around ATP production and consumption (11). The production of ATP is much greater in the presence of oxygen. This is because eukaryotic cells use oxygen for the production of biochemical energy in the form of adenosine triphosphate (ATP). Also, any condition that competes for or impairs the production and usage of ATP by the body cells nourishes the environment for death to set in. Therefore, conditions that affect the lungs and the heart are more likely to impair ATP production because of their involvement in the distribution of oxygen throughout the body.

The following are the stages involved in the human life cycle; Intrauterine stage Infancy, Toddler, Childhood, Puberty, Adolescence, Adulthood, Middle age and old age which is the last stage of HLC. Each of these stages depends greatly on ATP to function properly. Also, the transition from one stage to another relies on the factors that affect the effective usage of ATP. The factors include the internal pathological factors which affect the normal physiology of the body such as diabetes, lung cancer, lung infection, etc. The external factors that cause the body to be in a state of shock. Examples of external factors are car accidents that cause excessive bleeding, drowning that causes impairment of oxygen usage, an animal bite which causes severe shock and so on.

MATERIALS and METHODS

Patients

We examined the patients who diagnosed with MTC and were performed F-18 PET/CT scans at Ege University Medicine Faculty, Department of Nuclear Medicine retrospectively. Between October 2011 and June 2018, 44 F-18 FDG PET/CT scans were performed on 25 patients (8 men, 17 women; mean age: 50.3 ± 13.7 years old; min: 23, max: 73 years) with MTC and persistently elevated calcitonin levels. Eleven PET/CT scans performed for treatment response were excluded from the study. All F-18 PET/CT scans (33 scans of 25 patients) included in the study were performed for localization of residual or recurrent disease and restaging. Before F-18 FDG PET/CT scans, all patients had undergone bilateral total thyroidectomy and had elevated serum calcitonin level (mean: 615 ± 667 pg/ml; min: 40, max: 2000 pg/ml) at the follow-up examinations. In 9 patients, somatostatin receptor imaging (SRI) (6 In-111 octreotide and 3 Ga-68 DOTATATE PET/CT scans) was also performed.

Imaging Protocol of F-18 FDG PET/CT

F-18 FDG PET/CT scans were performed after minimum of 6 hours fasting. Data acquisition started about 60 minutes after injection of 5-7 MBq/kg of F-18 FDG intravenously. The blood glucose levels of all patients were checked before radiopharmaceutical administration. All patients were scanned from the base of the skull to the mid thighs. The PET emission images were acquired for 2 min acquisition period at each bed position. CT images (90 kV and 120 mA, slice thickness of 5 mm) were used for attenuation correction and for anatomic localization. PET, CT, and PET/CT fused images were automatically generated by dedicated software

and shown on a workstation.

Image Interpretation

F-18 FDG PET/CT images were evaluated visually and semi-quantitatively. F18 FDG uptake was considered abnormal, if it had higher F-18 FDG uptake intensity than the background blood-pool or adjacent normal tissue. For semi-quantitatively analysis, the maximum standardized uptake value (SUVmax) of the lesions was measured in the region of interest by standard method (8).

Data analysis

The results of F-18 FDG PET/CT scans were compared lesion by lesion with histopathological data and clinical official reports of other imaging methods including neck and abdominal US, thorax CT and abdominal MRI.

Positive F-18 FDG PET scans were considered as true positive for local recurrence or metastasis if confirmed by one of the following criteria: (a) a positive histopathology result from fine needle aspiration biopsy or resection, (b) a detectable lesion was present at the corresponding site on follow-up conventional imaging studies when the histopathology results were not available, (c) a lesion size and/or metabolism increased on follow-up scans. Positive F-18 FDG PET scans were classified as false positive if imaging findings were not confirmed by either these 3 criteria. Because all calcitonin levels were abnormally high defined as persistent disease, F-18 FDG PET scans were accepted as false negative if any abnormal finding was not detected by F-18 FDG PET scan. When viewed from this aspect, because there was no true-negative study, only sensitivity and positive predictive value (PPV) were calculated.

Statistical analysis

Serum calcitonin levels and SUVmax values were assessed by Mann-Whitney U test. A P value less than 0.05 was considered as indicating a significant difference. The receiver operating characteristic (ROC) curve was performed for calculation the best cut-off point. Accuracy of the tests was measured by area under the curve (AUC).

RESULTS

A total of 33 F-18 PET/CT scans included in the study were performed on 25 patients for localization of residual or recurrent disease and restaging. All patients had undergone bilateral total thyroidectomy and have elevated serum calcitonin level (mean serum calcitonin level: 615 ± 667 pg/ml; min: 40, max: 2000 pg/ml) at the follow-up examinations. The mean clinical follow-up time was 50.3 ± 13.7 months (min: 2, max: 84 months) after F-18 FDG PET/CT scans.

Patients' characteristics, F-18 FDG PET/CT scan results and further details have been presented in Table 1. There were 11 true-positive, 11 false-positive and 11 false-negative F-18 FDG PET/CT scans. Because there was no true-negative results, specificity and negative predictive value were not calculated. Sensitivity and PPV were 50% and 50% respectively. The serum calcitonin mean level was 809 ± 775 pg/ml in true-positive cases, and 518 ± 602 pg/ml in other cases. Difference of mean serum calcitonin level between

true-positive cases and the others was nonsignificant ($p=0.29$). Somatostatin receptor imaging (6 In-111 octreotide and 3 Ga-68 DOTATATE PET/CT scans) of 9 patients with negative F-18 FDG PET/CT scans were also negative.

In 23 F-18 FDG PET/CT scans performed on 18 patients, 5 metastatic lymph nodes which had normal F-18 FDG uptake, 53 metastatic lymph nodes which had increased F-18 FDG uptake (SUVmax mean of metastatic lymph nodes: 6.1 ± 2.2) and 20 non-metastatic lymph nodes which had increased F-18 FDG uptake (SUVmax >2.5 , SUVmax mean: 3.7 ± 0.8) were detected. The mean SUVmax of metastatic lymph nodes was significantly higher than of non-metastatic lymph nodes ($p<0.05$). When we used the SUVmax cut-off value of 2.5, the sensitivity and specificity of F-18 FDG PET/CT for identification of lymph nodes were 91.4% and 10.0% respectively. Using the SUVmax cut-off value of 5.05 the sensitivity and specificity were found 72.4% and 100% respectively according to the ROC curve analysis. AUC of SUVmax was 0.83.

Multiple millimetric non-metabolic lung metastases were seen in 6 F-18 FDG PET/CT scans performed on 5 patients. Nineteen hypermetabolic metastatic bone lesions (SUVmax mean: 6.7 ± 2.9 ; min: 2.7, max: 12.4) were detected in 5 F-18 FDG PET/CT scans performed on 4 patients. Furthermore, the SUVmax level of at least one of metastatic bone lesion was higher than 5, in each F-18 FDG PET/CT scans detected metastatic bone lesion. Seven metastatic liver lesions (SUVmax mean: 4.5 ± 0.9 ; min: 3.6, max: 5.9) were detected in 5 F-18 FDG PET/CT scans performed on 4 patients. All metastatic liver lesions had F-18 FDG uptake equal to physiological liver uptake, except one lesion (SUVmax: 5.9).

DISCUSSION

The calcitonin is the most useful biochemical marker in the follow-up of medullary thyroid carcinoma. Persistently or increasingly elevated calcitonin level is biochemical evidence for residual or recurrent disease in underwent MTC patients (9). According to the American Thyroid Association, after surgery the patients with serum calcitonin level above 150 pg/ml should be evaluated by imaging procedures, including neck ultrasound, chest CT, contrast-enhanced MRI or three-phase contrast-enhanced CT of the liver, and bone scintigraphy, and MRI of the pelvis and axial skeleton (10). When there was a suspicious lesion or no lesion in these conventional methods, F-18 FDG, F-18 DOPA or somatostatin receptor PET/CT should be considered in patients with suspected residual or recurrent MTC (2).

In some studies, negative F-18 FDG PET/CT results in patients with elevated calcitonin levels were considered false-negative as in our study. The sensitivity of F-18 FDG PET/CT to detect recurrent or residual disease on a per patient basis analysis was reported to be from 41% to 62% in these studies (11-14). Our study showed that a sensitivity of F-18 FDG PET/CT was 50%, within the range of reported data. Conversely, other studies considered the same patients as true negative in the literature. The sensitivity of F-18 FDG PET/CT to detect recurrent or residual disease on a per patient basis analysis was reported to be from 65.7 to 93% in these studies (15-20). In a meta-analysis published by Treglia et al, a detection rate of F-18 FDG PET/CT was defined due to these

different considerations in the literature. The detection rate of F-18 FDG PET/CT in patients with recurrent or residual was reported 59 % on a per patient-based analysis in the meta-analysis (21).

According to the literature, the diagnostic performance of F-18 FDG-PET/CT increases in MTC patients with higher serum calcitonin level (14, 21). However, we didn't find a significant difference in serum calcitonin level between the true positive cases and the others. This observation may be related to the small number of cases in each group of our study.

In our study, the SUVmax mean of metastatic lymph nodes was found 6.1 ± 2.2 which is generally low compared with other cancer type and may reflect the slow growth rate and low proliferation index of MTC lesions and it agrees with literature data (12, 20, 22). However, we found that the mean SUVmax of metastatic lymph nodes was significantly higher than of non-metastatic lymph nodes. When we calculated the SUVmax cut-off value of 2.5, the specificity of F-18 FDG PET/CT for identification of lymph nodes was 10.0% which is below acceptable value. Nevertheless, using the SUVmax cut-off value of 5.05 the sensitivity and specificity were found 72.4% and 100% respectively.

As shown in the literature, F-18 FDG PET is low sensitive for lung and liver metastasis (10, 23, 24). In our study, all patients with multiple millimetric lung metastases had non-metabolic lung lesions. We observed only one slightly hypermetabolic metastatic liver lesion, other metastatic liver lesions were non-metabolic.

Somatostatin receptor PET/CT is a valuable imaging method for patients with neuroendocrine tumors and has a significantly higher diagnostic accuracy compared to somatostatin receptor scintigraphy (4, 25). The recent studies have shown that there was no significant difference between the sensitivity of F-18 FDG PET/CT and somatostatin receptor PET/CT. However, somatostatin receptor PET/CT is a useful complementary imaging method for patients with MTC and could be beneficial to identify the patients for somatostatin receptor-targeted radionuclide therapy (5, 7, 26). In our study, somatostatin receptor imaging (6 In-111 octreotide scintigraphy and 3 Ga-68 DOTATATE PET/CT scans) of 9 patients with negative F-18 FDG PET/CT scans were also negative.

Our study has several limitations. This is a retrospective study with a relatively small number of patients included as the disease is rare. According to the literature, the sensitivity of F-18 FDG PET/CT improves in patients with shorter the doubling time of serum calcitonin level (21, 27). Unfortunately, we couldn't calculate the doubling time of serum calcitonin level due to this information was not available for all patients. Additionally, we obtained no histopathological confirmation of some lesions. When histopathological data was not available, we have evaluated the patients with other imaging modalities during follow-up.

CONCLUSIONS

F-18 FDG PET/CT scan appeared to be less sensitive (50%) to find a residual or recurrent lesion in medullary thyroid carcinoma patients with persistently elevated calcitonin levels. However, it should be considered that F-18 FDG PET/CT was performed to the patients with only no lesion or a suspicious lesion had been

detected by the other imaging modalities in this group. Because F-18 FDG PET/CT was not performed when a residual or recurrent lesion had clearly been detected before, the sensitivity of 50% was considered to be acceptable.

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