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The clinical impact of ^{18}F-FDG PET in papillary thyroid carcinoma with a negative ^{131}I whole body scan: a single-center study of 108 patients

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Objective: To assess whether FDG PET could localize the recurrent or metastatic lesions in papillary thyroid cancer patients with negative radioiodine scan. ***Methods:*** Whole body PET was performed after injecting 370–555 MBq of ^{18}F-FDG in 108 patients, who were suspected of having recurrence or metastasis and whose ^{131}I whole body scans were negative. Recurrence or metastasis occurred in 63 patients by pathology or clinical assessment, whereas 45 patients remained in remission. ***Results:*** FDG PET revealed recurrence or metastases in 59 patients (sensitivity 93.7%), whereas thyroglobulin (Tg) levels were elevated in 41 (sensitivity 65.1%). In 35 of 45 patients in remission, FDG PET was negative (specificity 77.8%). When patients positive for antithyroglobulin antibody were excluded, the sensitivity and specificity of serum Tg became 84.8% and 46.9%, respectively. Compared to Tg measurement, FDG PET detected more metastatic lesions in cervical lymph nodes. Of 40 patients with a negative radioiodine scan showing diffuse hepatic uptake, metastases occurred in 23 patients and remission in 17. FDG PET showed 100% sensitivity and 76.5% specificity in the detection of recurrence in these 40 patients. ***Conclusion:*** FDG PET is useful for localizing recurrent or metastatic lesions in ^{131}I scan-negative thyroid cancer patients. In particular, it is superior to serum Tg measurement for identifying metastases to cervical lymph nodes. We recommend its use in cases of negative radioiodine scan with diffuse hepatic uptake.

Key words: papillary thyroid cancer, ^{18}F-fluorodeoxyglucose (^{18}F-FDG), positron emission tomography (PET), ^{131}I whole body scan, thyroglobulin (Tg)

INTRODUCTION

THE PRIMARY TREATMENT for differentiated thyroid cancer (DTC) consists of surgical thyroidectomy, subsequent radioiodine ablation therapy for remnant tissues, and T_4 therapy for TSH suppression. Patients with DTC generally have a good prognosis. [1] However, patient follow-up is needed for life because of the high incidence of recurrence or metastases. Radioiodine scans and serum thyroglobulin (Tg) measurements are the most commonly used methods for monitoring thyroid cancer patients.[2–6]

DTC may transform over time and lose some or all of its ability to take up and retain ^{131}I, and may not be visualized on ^{131}I whole body scan.[7,8] In such patients, the precise localization of recurrent or metastatic sites is essential to define the therapeutic strategy, more specifically, surgical treatment whenever possible, or palliative methods. Since conventional imaging procedures such as ultrasonography, computerized tomography (CT) or magnetic resonance imaging (MRI) are of limited value when the normal anatomy is altered by surgery, several scintigraphic methods such as ^{201}Tl, ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin, and FDG PET have been proposed.[9–12]

The use of FDG PET has been established in various cancers, and this modality is now valuable for managing thyroid cancer. Several studies have shown that, in DTC, FDG PET can be used to detect recurrence or metastases

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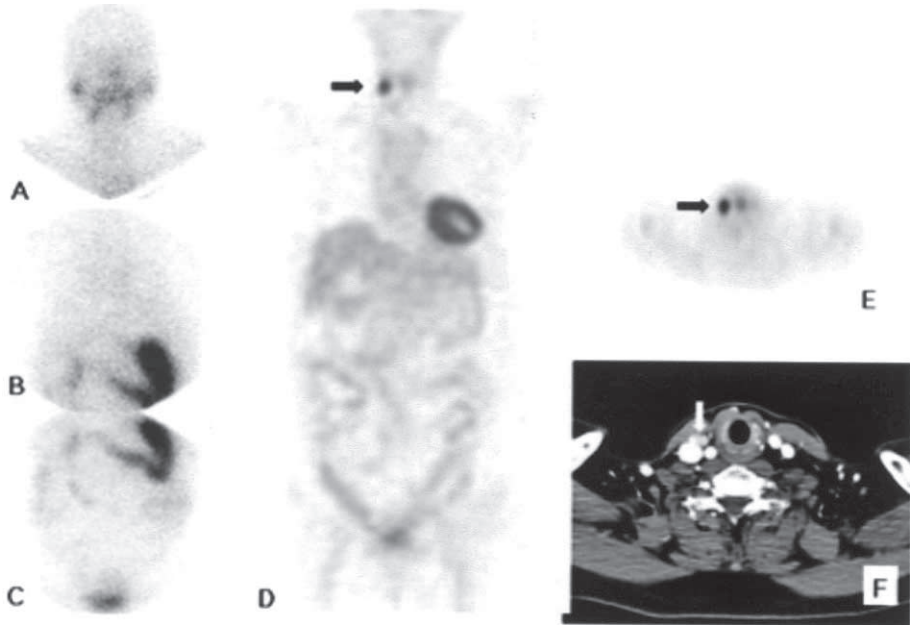

Fig. 1 ^{131}I whole-body scan, ^{18}F-FDG PET images, and a neck CT image of a 69-year-old female patient with papillary thyroid cancer. A–C: ^{131}I whole-body scan showing no functioning metastases. D and E: ^{18}F-FDG PET images showing increased ^{18}F-FDG uptake (*black arrow*) in the right neck. F: Axial computed tomography scanning of the neck showing a necrotic lymph node (*white arrow*) at the matched level in the transaxial ^{18}F-FDG PET image.

with a high degree of sensitivity (80%–90%), which is especially valuable in patients that do not take up radioactive iodine.[13–16] However, the number of these patients is small, and the clinical value of FDG PET for the follow-up of thyroid cancer patients remains controversial.

Therefore, we performed this study to assess the usefulness of FDG PET in 108 papillary thyroid cancer patients with a negative ^{131}I whole body scan.

MATERIALS AND METHODS

Patients

All patients with differentiated thyroid carcinoma were treated by total or near total thyroidectomy followed by successful ablation of the normal thyroid remnant with 1.11–3.7 GBq ^{131}I. In a postoperative care program implemented by the Department of Nuclear Medicine, Seoul National University, serum levels of thyroglobulin and antithyroglobulin antibody were measured every 6 months, and I-131 whole body scan, chest x-ray and neck ultrasonography were performed every year. If necessary, neck CT or chest CT was added. During the follow-up period, FDG PET was recommended when the serum level of Tg or anti-Tg antibody became elevated or other anatomic images showed suspicious lesions with negative iodine scan. We reviewed the records of 108 papillary thyroid cancer patients that were suspected of having recurrence or metastases clinically, with negative iodine whole-body scans, and that had undergone a FDG PET scan between 1995 and 2002. Eighty-six females and 22 males were included in the analysis. Their ages ranged from 20 to 73 years; mean ± standard deviation (SD) was 49.0 ± 11.7 years. Follow-up time was at least 1 year in all patients.

^{131}I whole body scan

^{131}I whole body scans were performed 2 days after the administration of ^{131}I (74–111 MBq), under endogenous thyrotrophin stimulation (TSH level higher than 30 m*U*/*l*), using a large field-of-view gamma camera (ON 410; Ohio Nuclear, Solon, OH) equipped with a medium-energy parallel-hole collimator, with a 20% symmetric window centered at 364 keV. Anterior images of the neck, chest, and abdomen were obtained, each accumulating 100,000 counts. Images were evaluated by two experienced nuclear medicine physicians for remnant thyroid uptake, and recurrent or metastatic lesions and diffuse hepatic uptake.

FDG-PET imaging

FDG PET scans were performed using an ECAT EXACT 47 scanner (Siemens-CTI, Knoxville, TN) under thyroxine replacement therapy. After an overnight fast, 370–555 MBq ^{18}F-FDG was administered intravenously, and whole-body emission scans were obtained 60 minutes later. Images were visually interpreted by two experienced nuclear medicine physicians. Abnormal uptake was defined as any focus of increased uptake greater than the surrounding normal tissue, or when the standardized uptake

value (SUV) was ≥3.0. Regions of uptake were divided into four areas: cervical lymph node, lung, mediastinum, and bone. The FDG findings were compared retrospectively with conventional imaging findings obtained within 6 months.

Laboratory criteria

Serum Tg levels were measured on thyroid replacement hormone therapy (TSH suppression). In 83 patients, Tg measurements were repeated when thyroid replacement was withdrawn (TSH stimulation). The assay used in our laboratory is an immunoradioassay and uses commercial kits; HTGK-2 (Sorin Diagnostics, Saluggia, Italy) and HENNING test anti Tg (Brahms Diagnostica, GmbH, Berlin, Germany). A serum Tg level of higher than 2.0 ng/m*l* on TSH stimulation (defined as a TSH >30 mIU/*l*) or higher than 1.0 ng/m*l* on TSH suppression (defined as a TSH <0.1 mIU/*l*) was considered abnormal, and a serum antithyroglobulin antibody measurement of >200 U/m*l* was also considered abnormal.

Confirmation of metastasis

Metastasis was confirmed by pathology in 28 patients. In the other 35 patients, the final classification was based on the clinical outcome and the biological follow-up, together with all imaging findings (chest x-ray, sonography, or CT).

Statistical analysis

The sensitivity and specificity of FDG PET and serum thyroglobulin measurement were calculated. Statistical analysis was performed using McNemar's test. The proportion of metastatic sites detected by FDG PET and ^{131}I whole-body scan was compared using the chi-square test. A p value <0.05 was considered statistically significant.

Table 1 Detectabilities of FDG PET and serum Tg level in 108 papillary thyroid cancer patients with negative radioiodine scan

Measurement	Result	Metastasis	No metastasis
FDG PET	Positive	59	10
	Negative	4	35
Thyroglobulin	Positive	41	17
	Negative	22	28

Table 2 Detectabilities of FDG PET and TSH stimulated serum Tg level in 83 papillary thyroid cancer patients with negative radioiodine scan

Measurement	Result	Metastasis	No metastasis
FDG PET	Positive	50	8
	Negative	2	23
Thyroglobulin	Positive	36	14
	Negative	16	17

Table 3 Profiles of serum thyroglobulin and antithyroglobulin antibody in 108 papillary thyroid cancer patients

Profiles	Metastasis	No metastasis
Thyroglobulin positive		
Anti-Tg Ab positive	2	0
Anti-Tg Ab negative	39	17
Thyroglobulin negative		
Anti-Tg Ab positive	15	13
Anti-Tg Ab negative	7	15

Anti-Tg Ab, antithyroglobulin antibody

RESULTS

Among 63 patients having metastases, FDG PET identified metastases in 59 patients (sensitivity 93.7%, Fig. 1), and serum Tg levels were elevated in 41 patients (sensitivity 65.1%). Twenty of the 22 metastatic cancer patients with normal Tg levels showed positive FDG PET. In 35 of 45 patients in remission, FDG PET was negative (specificity 77.8%). Serum Tg levels were normal in 28 of 45 patients (specificity 62.2%) (Table 1). On comparing FDG PET results with serum Tg measurements, the sensitivity of FDG PET was found to be significantly higher ($p < 0.0005$). There was no statistical difference between the specificities of FDG PET and serum Tg ($p = 0.17$). When the result of TSH stimulated Tg was compared with FDG PET in 83 patients (Table 2), FDG PET still showed higher sensitivity (96.2%) than that of Tg (72%) in identification of metastases. In 23 of 31 patients

Table 4 Relationship between the profiles of serum thyroglobulin and antithyroglobulin antibody and positive sites by FDG PET

Profiles	Cervical lymph node	Mediastinum	Lung	Bone
Thyroglobulin positive				
Anti-Tg Ab positive	2	1	0	0
Anti-Tg Ab negative	35	11	9	4
Thyroglobulin negative				
Anti-Tg Ab positive	12	3	1	0
Anti-Tg Ab negative	6	1	0	0

Anti-Tg Ab, antithyroglobulin antibody

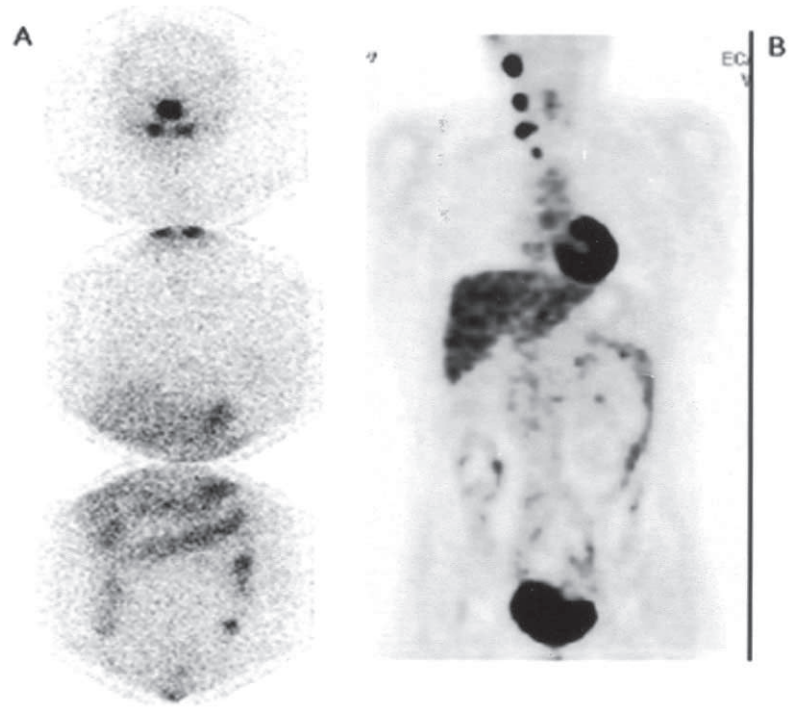

Fig. 2 ^{131}I whole-body scan and ^{18}F-FDG PET image of a 41-year-old female with papillary thyroid cancer. A: The ^{131}I whole-body scan shows diffuse uptake in the liver without functioning metastases. B: Coronal view of ^{18}F-FDG PET showing multiple increased ^{18}F-FDG uptakes in the right neck.

Table 5 Comparison of FDG PET and serum Tg level detectabilities in 40 patients with diffuse liver uptake on ^{131}I whole-body scan

Measurement	Result	Metastasis	No metastasis
FDG PET	Positive	23	4
	Negative	0	13
Thyroglobulin	Positive	15	5
	Negative	8	12

in remission, FDG PET was negative (specificity 74.2%). Serum Tg levels were normal in 17 patients (specificity 54.8%).

False positive FDG PET results were obtained in 10 patients, two cases confirmed by biopsy or chest x-ray were of tuberculosis, one was reactive hyperplasia by aspiration cytology, and seven were negative in images by CT, bone scan, and repeated PET.

Fifteen of 22 metastatic cancer patients with normal serum Tg levels had elevated antithyroglobulin antibody levels (Table 3). When patients with positive antithyroglobulin antibody were excluded, the sensitivity and specificity of serum Tg became 84.8% and 46.9%, respectively. In this case, the sensitivity of Tg was not statistically different from that of FDG PET.

FDG PET identified cervical lymph node metastasis in 55 patients (93.2%), mediastinal metastasis in 16 (27.1%), lung metastasis in 10 (16.9%), and bone metastasis in 4 (6.8%) (Table 4). Compared to Tg measurement, FDG PET detected more metastatic lesions in cervical lymph nodes. In cases with a positive FDG PET, Tg sensitivities for distant metastases in lung or bone, or for cervical lymph nodes were 92.9% and 69%, respectively.

Of the 108 patients, ^{131}I whole body scan revealed diffuse hepatic uptake without remnant or metastatic lesions in 40 patients (Table 5). Twenty-three of these patients were found to have metastatic lesions by FDG PET (sensitivity 100%, Fig 2), and 15 patients by Tg (sensitivity 65.2%). Eight metastatic patients with normal Tg levels showed positive FDG PET. The sensitivity of FDG PET was significantly higher than that of serum Tg ($p = 0.0068$).

DISCUSSION

After FDG uptake in the metastases of differentiated thyroid cancer (DTC) was first reported in 1987 by Joensuu and Ahonen,[17] several indications for FDG PET have been suggested in DTC. The differential diagnosis of thyroid nodule, preoperative staging, detection of recurrence, and the prediction of prognosis by FDG PET have been tried.[18] Among these indications, many investigators have studied the role of FDG PET in the detection of recurrence or metastases.

In terms of detecting the recurrent or metastatic lesions of DTC, radioiodine whole body scan and FDG PET show

different patterns. Some investigators have reported the alternating uptake pattern of ^{131}I and FDG by DTC, the so-called "flip-flop" phenomenon.[19–21] Whereas positive ^{131}I uptake in the absence of FDG uptake is associated with a high degree of differentiation, FDG uptake in the absence of radioiodine uptake suggests dedifferentiation. Therefore, there appears to be agreement that FDG PET is useful for detecting metastatic lesions negative by radioiodine whole body scanning.[13] A multicenter study reported by Grunwald et al.[20] showed that the overall sensitivity of FDG PET is 75%, and that this increased to 85% when patients with negative ^{131}I scan were included. In our study, the sensitivity of FDG PET in the detection of recurrence or metastases is somewhat higher than those of previous reports. The reason may be that all patients of this study were papillary thyroid cancer patients showing somewhat dedifferentiation compared to follicular cancer.

Basic research has supported the usefulness of FDG PET in recurrent or metastatic thyroid cancer with negative radioiodine scan. Kim et al.[22] found that the expressions of sodium/iodide symporter and glucose transporter-1 genes in DTC display an inverse relationship and reflect cancer differentiation. The level of expression of glucose transporter-1 was found to be higher in less differentiated carcinomas than in well-differentiated carcinomas, which supports the clinical usefulness of FDG PET in moderate to poorly differentiated DTC with a negative radioiodine scan.

We found that the sensitivity of FDG PET was higher than that of serum Tg measurement in both TSH suppressed and stimulated states. Twenty-two patients with metastatic disease had undetectable Tg level, and FDG PET detected an abnormality in 20. One reason for false negative Tg measurements is the presence of antithyroglobulin antibody. When the patients with positive antithyroglobulin antibody were excluded, the sensitivity of Tg increased to 84.8%, which was not statistically different from that of FDG PET. However, Westbury et al.[23] reported Tg false negative cases without antithyroglobulin antibody, which supports our observation. Our results indicate that FDG PET is effective in patients with elevated or undetectable Tg levels.

We found that FDG PET is useful for detecting metastases to the regional lymph nodes. In cases of positive FDG PET, Tg sensitivity for metastases to the cervical lymph nodes was 69%. And, compared to Tg, FDG PET detected more metastatic lesions in the cervical lymph nodes. Dietlein et al.[20] also reported that the degree of FDG PET uptake varied in different organs, and is highest in the cervical lymph nodes and lowest in small pulmonary metastases. Due to the inefficacy of radioiodine therapy for cervical lymph node metastases without ^{131}I-avidity, surgical methods are necessary, if possible. Our result is concordant with previously published data,[13,21] and adds to growing evidence, which indicates that FDG PET is helpful in defining cervical lymph node metastases before surgical management.

Several studies have reported that diffuse liver uptake of radioiodine is related to residual thyroid tissue or functioning metastases, while other studies have noted that diffuse hepatic uptake is a benign finding without clinical importance.[24–27] Chung et al.[24] suggested that when there is liver uptake without uptake by the remnant thyroid or evidence of metastasis, hidden metastases might be suspected. However, its clinical importance is still debated. In our study, the radioiodine scans of 40 patients without uptake in the thyroid bed showed diffuse hepatic uptake. Of these patients, 23 patients (57.5%) were proven to have metastases. In fact, the rate of hidden recurrence or metastases in cases with diffuse hepatic uptake in this study was almost the same as in a previous report.[24] All these 23 metastatic lesions were revealed by FDG PET (sensitivity 100%, specificity 76.5%) and 8 of these 23 patients had undetectable Tg levels. Therefore, we suggest that FDG PET should be recommended for patients with diffuse radioiodine liver uptake.

Our results suggest that FDG PET identifies metastatic lesions with high accuracy in papillary thyroid cancer with a negative radioiodine scan, regardless of Tg level. In particular, FDG PET can be used as a first-investigation tool in patients with a negative radioiodine scan and diffuse hepatic uptake.

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