Nucl Med Mol Imaging (2011) 45:197–202
DOI 10.1007/s13139-011-0097-5

ORIGINAL ARTICLE

Clinical Significance of Diffuse ^{18}F-FDG Uptake in Residual Thyroid Gland after Unilateral Thyroid Lobectomy

Hee-Sung Song · Su Jin Lee · Seok-Ho Yoon · Jandee Lee · Euy-Young Soh · Young-Sil An · Joon-Kee Yoon

Received: 22 April 2011 / Accepted: 30 June 2011 / Published online: 26 July 2011

Abstract
Purpose We investigated the clinical significance of diffuse uptake in remaining thyroid after unilateral lobectomy for thyroid cancer.
Methods A total of 144 thyroid cancer patients who underwent ^{18}F-FDG PET/CT after lobectomy were enrolled in the present study. The PET/CT images were evaluated for the presence of diffuse ^{18}F-FDG uptake with maximum SUV (SUVmax) >2.0 in the residual thyroid and placed into one of two groups: with diffuse uptake and without diffuse uptake group. Clinical, laboratory, and PET/CT parameters in both groups were compared. Correlations between SUVmax of thyroid and available parameters were analyzed.
Results Forty-two of 144 patients (29.2%) had diffuse thyroid uptake (mean SUVmax: 3.2±1.1). All patients with diffuse uptake and 96 (94.1%) without diffuse uptake were receiving thyroxine therapy (P=0.09). Thyroid function tests showed that most patients were euthyroid status (78.6 vs. 85.3%, P=0.36). TgAb levels were significantly higher in patients with diffuse uptake (338.0±664.6 vs. 57.3±46.4, P<0.0001). Mean attenuation values in the diffuse uptake group were significantly lower (72.2±15. vs. 97.0±16.0, P<0.0001). An inverse correlation was found between SUVmax and mean attenuation values of residual thyroid in all patients (r=−0.57, P<0.0001) and subgroup with diffuse uptake (r=−0.31, P<0.05).
Conclusion In this study, diffuse ^{18}F-FDG uptake in the residual thyroid after unilateral lobectomy was a relatively frequent finding and may be associated with chronic thyroiditis. This uptake is not influenced by thyroid status or thyroxine therapy. The ^{18}F-FDG uptake is inversely correlated with mean attenuation value of thyroid.

Keywords Diffuse thyroid uptake · FDG PET/CT · Thyroiditis · Thyroid lobectomy

H.-S. Song · S. J. Lee (✉) · S.-H. Yoon · Y.-S. An · J.-K. Yoon
Department of Nuclear Medicine,
Ajou University School of Medicine,
San 5, Woncheon-dong, Yeongtong-gu,
Suwon, Korea
e-mail: suesj202@ajou.ac.kr

J. Lee · E.-Y. Soh
Department of Surgery, Ajou University School of Medicine,
San 5, Woncheon-dong, Yeongtong-gu,
Suwon, Korea

Introduction

Incidental ^{18}F-FDG uptake in thyroid is not a common finding in both healthy subjects and cancer patients [1, 2]. The normal thyroid gland shows low to absent ^{18}F-FDG uptake, and it is not well visualized on whole body maximum intensity projection images [3, 4].

A thyroid lesion with focal ^{18}F-FDG uptake is likely to be malignant [5–9], whereas diffusely increased uptake in the thyroid gland is associated with several thyroid disorders including chronic thyroiditis, Graves' disease, and diffuse goiter [9–13]. Several studies have reported that incidence of diffusely increased ^{18}F-FDG uptake in the thyroid gland was 0.6–3.3%. Interestingly, Tateish et al. recently found that 20% of breast cancer patients in their study population showed diffuse thyroid uptake in PET/CT, which was significantly greater compared to the results of previous studies [14]. Although the precise mechanism for diffuse thyroid uptake is still unknown, the possibility of lymphocytic infiltration or active fibrosis formation related to chronic thyroiditis has been suggested [10, 11].

^{18}F-FDG PET is a noninvasive whole body imaging technique used to evaluate many kinds of malignant tumors. A recently developed integrated PET/CT, which

can provide both the metabolic and anatomic information of a cancer, has been shown to have better accuracy in tumor staging than conventional PET alone [15, 16]. One study investigated the clinical significance of diffuse thyroid uptake using both morphologic and metabolic data on ^{18}F-FDG PET/CT [14].

While PET/CT has been widely used in thyroid cancer patients for follow-up, we occasionally observe diffuse uptake in the residual thyroid gland after unilateral thyroid lobectomy. However, to our knowledge, the clinical implications of diffuse ^{18}F-FDG uptake in the residual thyroid gland have not been clarified in those patients. In this study, we investigated the incidence and clinical significance of diffuse ^{18}F-FDG uptake in the residual thyroid after unilateral lobectomy for well-differentiated thyroid cancer.

Materials and Methods

Study Subjects

The study was approved by the Institutional Review Board of our hospital. Study subjects were 149 well-differentiated thyroid cancer patients who underwent unilateral thyroid lobectomy and postoperative ^{18}F-FDG PET/CT scans from April 2008 to December 2010 in our hospital. Among them, five patients with focal thyroid uptake were excluded. Finally, a total of 144 patients were evaluated in the present study.

Clinical information and laboratory findings of the subjects were also reviewed retrospectively.

^{18}F-FDG PET/CT

After at least 6 h of fasting, PET/CT was performed on a scanner (Discovery ST; GE Healthcare, Milwaukee, WI, USA) 60 min after intravenous injection of 370 MBq of ^{18}F-FDG. Seven to eight frames (3 min/frame) of emission PET data were acquired in two-dimensional mode after noncontrast-enhanced CT images from the base of the skull to the upper thigh were taken (tube rotation time of 1 s per revolution, 120 kV, 60 mA, 7.5 mm per rotation, and acquisition time of 60.9 s for a scan length of 867 mm). CT-based attenuation-corrected PET images were reconstructed using an iterative method (ordered-subsets expectation maximization with two iterations and 30 subsets, field of view=600 mm, slice thickness=3.27 mm). Standardized uptake values (SUVs) were calculated based on injected dose and body weight. Two nuclear medicine physicians reviewed PET/CT images on an Advantage Workstation 4.4 (GE Healthcare). For the semi-quantitative analysis of ^{18}F-FDG uptake, a 10 mm circular region of interest (ROI) was placed at mid-pole level of the residual thyroid, and maximum SUV (SUVmax) was recorded. For mean attenuation values (Hounsfield units, HU) of the thyroid, a 10 mm circular ROI was drawn on noncontrast CT images of the PET/CT scans. Mean attenuation values of the residual thyroid were measured, and the number of patients with HU<80 was recorded. Diffusely increased ^{18}F-FDG uptake in the residual thyroid on the three-dimensional maximum intensity projection images with an SUVmax > 2.0 was considered a positive scan.

Laboratory Evaluation

Thyroid function tests were performed at the Department of Nuclear Medicine in all patients on the same day (n =109) as the PET/CT or within 1 month (n=35) of the PET/CT scan. Serum thyroid stimulating hormone (TSH) was measured by immunoradiometric assay using a sandwich type assay (TSH IRMA KIT, Beckman Coulter, Czech Republic). Serum free thyroxine (T4) was measured using a competition assay based on the principle of labeled antibody (FT4 RIA KIT, Beckman Coulter). Serum total triiodothyronine (T3) was performed using a competition assay (TOTAL T3 RIA KIT, Beckman Coulter). Serum thyroglobulin (Tg) was checked using Tg-S IRMA CT (RADIM, Rome, Italy). Serum anti-thyroglobulin antibody (TgAb) was measured with a radioligand assay for the quantitative determination of antibodies to Tg in human serum (B R A H M S anti-Tg RIA kit, Thermo Scientific, Hennigsdorf, Germany). Normal ranges of TSH, free T4, T3, Tg, and TgAb are 0.35–5.50 μlU/ml, 0.80–1.50 ng/dl, 60–181 ng/dl, 0–40 ng/ml, and 0–100 U/ml, respectively.

Statistical Analysis

All continuous variables are expressed as mean±SD. Univariate analyses of continuous variables were performed using unpaired t-tests. Univariate analyses of categorical variables were compared by chi-squared tests. Correlation analyses between SUVmax of the residual thyroid and available clinical and laboratory parameters or mean attenuation values were performed. P values<0.05 were considered statistically significant.

Results

^{18}F-FDG PET/CT scans were performed at an average of 19.5±16.5 months after operation (range: 1.0–83.9 months). During the PET/CT scan, 42 of 144 patients (29.2%) were found to have diffusely increased ^{18}F-FDG uptake in the residual thyroid gland. The clinical characteristics of the patients are summarized in Table 1. The subjects were 43.8±9.4 years old, and most were female (91%). All patients in the diffuse uptake group were receiving thyroxine therapy, as were 96 (94.1%) in

Table 1 Clinical characteristics of the patients

Data	With diffuse thyroid uptake (n=42)	Without diffuse thyroid uptake (n=102)	P value
Male/female (n)	2/40	11/91	NS
Age (years)	43.8±8.1	43.9±9.9	NS
Interval between operation and PET/CT (months)	15.9±12.2	20.3±17.9	NS
Interval between PET/CT and TFT (days)	−1.6±7.6	0.0±5.5	NS
Thyroxine therapy	100 %	94.1%	NS
Thyroid function state			
Hyperthyroidism	4 (9.5%)	10 (9.8%)	NS
Euthyroid	33 (78.6%)	87 (85.3%)	NS
Subclinical hypothyroidism	5 (11.9%)	5 (4.9%)	NS

TFT Thyroid function test, *NS* not significant

the group without uptake (P=0.09). When the thyroid status was compared between the two groups, the number of subclinical hypothyroidism, euthyroid, and hyperthyroidism patients was 5, 33, and 4 in the diffuse uptake group, respectively. Among the 102 patients without diffuse thyroid uptake, 5 demonstrated subclinical hypothyroidism, 87 were euthyroid, and the remaining 10 showed hyperthyroidism.

Figure 1 demonstrates an example of diffusely increased ^{18}F-FDG uptake in the right thyroid gland on PET/CT performed 9 months after left thyroid lobectomy.

Comparison of thyroid function tests revealed a significantly higher TgAb in patients with diffuse uptake than in patients without diffuse uptake (Table 2). On PET/CT scans, SUVmax was 3.2±1.1 in the diffuse uptake group. Mean attenuation values in the residual thyroid were significantly

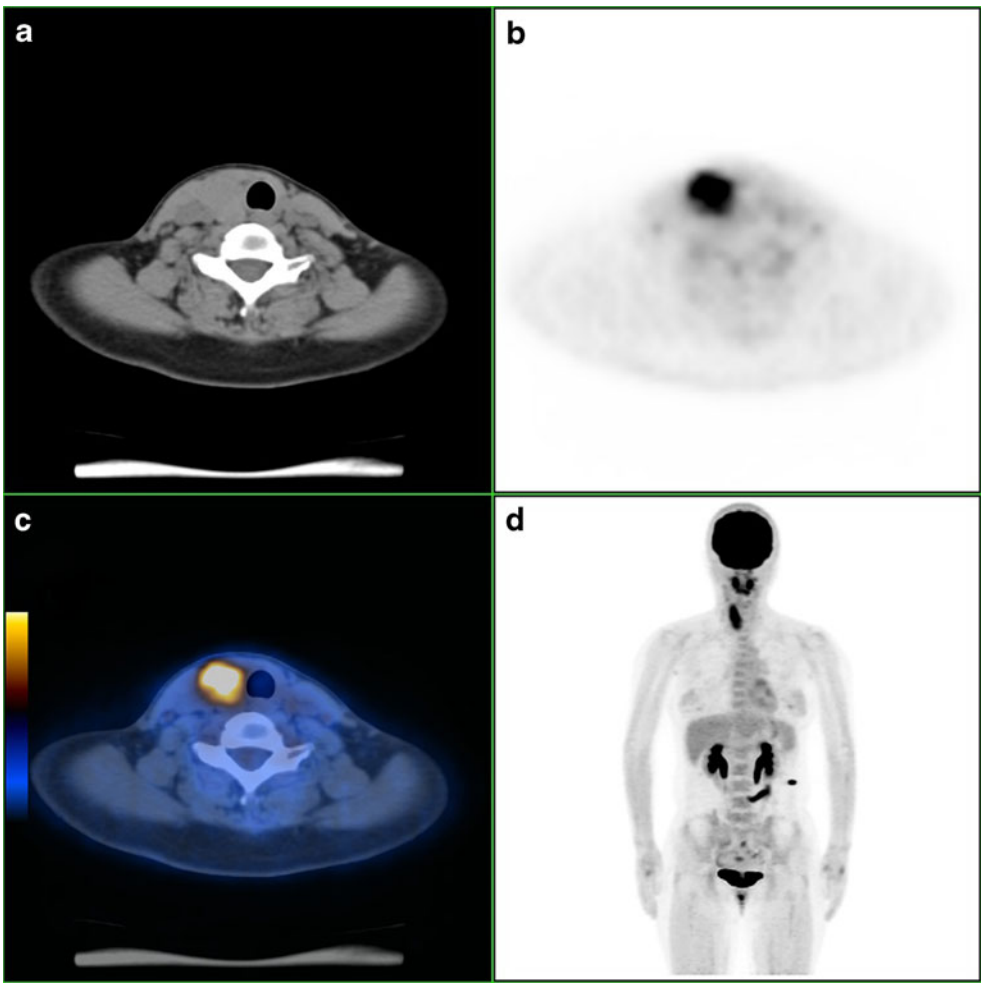

Fig. 1 ^{18}F-FDG PET/CT images of a 37-year-old female with papillary thyroid cancer. Unilateral thyroid lobectomy was performed 9 months before PET/CT scan. These images show diffusely increased ^{18}F-FDG uptake in the right thyroid lobe, and its SUVmax was 6.7. Her serum TgAb was 285 U/ml (normal range 0–100 U/ml) and Tg was 13.2 ng/ml (normal range 0–40 ng/ml). Shown are transaxial CT image (**a**), PET image (**b**), fused PET/CT image (**c**), and three-dimensional maximum-intensity-projection image (**d**)

Table 2 Comparison of thyroid function tests and PET/CT parameters

Data	With diffuse thyroid uptake (n=42)	Without diffuse thyroid uptake (n=102)	P value
Thyroid function test			
TSH	2.2±2.6	1.5±1.7	NS
Free T4	1.4±0.2	1.4±0.2	NS
T3	96.0±15.6	99.7±18.6	NS
Tg	4.1±6.7	4.2±9.3	NS
TgAb	338.0±664.6	57.3±46.4	<0.0001
PET/CT			
SUVmax	3.2±1.1	1.4±0.3	<0.0001
Mean attenuation value	72.2±15.1	97.0±16.0	<0.0001
HU<80	31 (73.8%)	15 (14.7%)	<0.0001

HU Hounsfield units, *NS* not significant

lower in patients with diffuse uptake than in patients without diffuse uptake. Furthermore, the number of patients with HU under 80 was significantly higher in the diffuse thyroid uptake group than in those without uptake.

Data regarding TgAb or ultrasonography for diagnosis of chronic thyroiditis were available in 26 of 42 patients (61.9%) with diffuse thyroid uptake, although definite diagnosis was impossible in the remaining 16 patients because of the retrospective nature of the study. However, data regarding TgAb elevation (TgAb>100), ultrasonography, and low attenuation value on CT (HU<80) revealed that chronic thyroiditis was suggested in 40 of 42 patients (95.2%) with diffuse uptake, whereas 24 of 102 patients (23.5%) without diffuse uptake might have the same disease.

An inverse correlation between SUVmax and mean attenuation values of residual thyroid was demonstrated in all patients (r=−0.57, P<0.0001; Fig. 2a) and in the subgroup with diffuse uptake (r=−0.31, P<0.05; Fig. 2b). However, no significant correlations were found between SUVmax and thyroid function tests in all patients or subgroups.

Discussion

The present study may be the first investigation to evaluate diffusely increased ^{18}F-FDG uptake in the remaining thyroid lobe in patients who had undergone unilateral thyroid lobectomy for carcinoma. We also assessed the relationship between SUVmax and mean attenuation values of thyroid, or other clinical parameters including thyroid function tests.

There have been several studies to evaluate diffuse ^{18}F-FDG uptake in both thyroid lobes. Kang et al. reported this finding in only 8 of 1,130 subjects (0.6%) including 999 cancer patients and 331 healthy subjects [6]. A 1.8% prevalence of diffuse thyroid uptake was reported by Chen et al. [9]. Yasuda et al. demonstrated diffuse ^{18}F-FDG uptake in the thyroid in 36 of 1,102 healthy subjects (3.3%) [10]. These results showed relatively similar incidence of diffuse thyroid uptake in the healthy subjects and cancer patients. However, Tateishi et al. recently found 29 of 146 breast cancer patients (20%) showed diffuse thyroid uptake in PET/CT, which was considerably greater than the results of previous studies [14]. They concluded that women with breast carcinoma had a high incidence of thyroid disorders. Interestingly, our study population had an overall 29.2% prevalence of diffuse ^{18}F-FDG uptake in the residual thyroid, which is significantly higher than that of most previous studies evaluated in both thyroid lobes.

Diffuse thyroid uptake is very likely secondary to thyroiditis and/or hypothyroidism. Several studies reported that most of the cases with diffuse thyroid uptake had

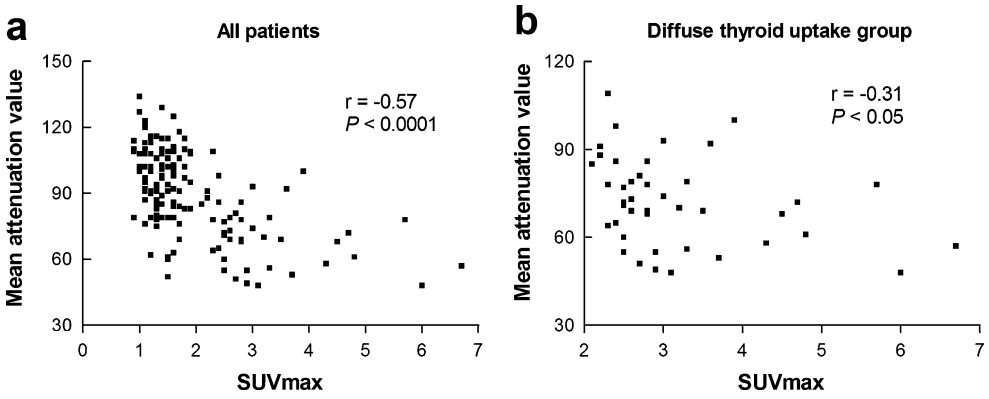

Fig. 2 Correlation between SUVmax and mean attenuation values of residual thyroid in all patients (**a**) and patients with diffuse uptake (**b**)

positive serum antithyroid antibody, and some had abnormal ultrasound findings suggestive of thyroiditis. Yasuda et al. reported that in 36 patients with diffuse uptake, 7 (19.4%) had hypothyroidism and 34 (94.4%) had positive antithyroid antibodies and/or abnormal ultrasound findings suggesting chronic thyroiditis [10]. Karntanis et al. found that 82 of 133 (61.7%) patients with diffuse thyroid uptake had chronic thyroiditis and/or hypothyroidism [11]. Chen et al. reported that among the 46 cases with diffuse uptake, 21 cases had thyroid function assays and/or ultrasound study, and a diagnosis of chronic thyroiditis was made in all 21 cases [9]. In the present study, data regarding antithyroid antibodies and ultrasonography for diagnosis of chronic thyroiditis were available in 61.9% with diffuse ^{18}F-FDG uptake. However, we also evaluated the mean attenuation values of the remnant thyroid in the CT portion of PET/CT. On CT scans, the normal thyroid gland has high attenuation (80–100 HU) because the normal thyroid gland concentrates iodine almost 100 times more than does the serum [17]. In inflammatory conditions, the thyroid gland shows low attenuation on CT because of follicular cell destruction and loss of iodine concentration [14, 18, 19]. Thus, data regarding TgAb elevation, ultrasonography, and low attenuation value of CT revealed that chronic thyroiditis was suggested in 95.2% of the diffuse uptake group, and this percentage is similar to the 94.4% found by Yasuda et al. [10]. Therefore, a possible explanation for diffuse uptake in the residual thyroid is mostly associated with chronic thyroiditis in the present study.

Diffuse thyroid uptake does not seem to be affected by hormone replacement therapy and thyroid function state. Karantanis et al. found that patients receiving thyroxine therapy for primary hypothyroidism could demonstrate diffusely increased ^{18}F-FDG uptake in their thyroid gland [11]. In agreement, most (95.8%) of our study population had already started thyroid hormone replacement therapy after unilateral thyroid lobectomy, and the thyroid function status was not significantly different between the two groups.

The relationship between SUVmax and serum TSH level was evaluated by Karantanis et al. in 138 patients with diffuse thyroid uptake [11]. They suggested that diffuse thyroid uptake might be associated with chronic thyroiditis, but no significant correlation between SUVmax and serum TSH level was found. Our study also demonstrated no significant correlation between SUVmax and serum TSH level. We observed that SUVmax was inversely correlated with mean parenchymal density of thyroid, and this finding is consistent with a recent report by Tateish et al. [14]. Based on histology in chronic thyroiditis, destruction of thyroid follicular cells causes a decrease in iodine content in the thyroid gland [14, 18].

The present study is limited by its retrospective nature; postoperative ultrasonography was performed in only 53 of 144 patients (36.8%), and histopathologic confirmation for chronic thyroiditis was not obtained. Of the antithyroid antibodies, only the TgAb level was available in this study because antiperoxidase antibodies and antimicrosomal antibodies were not evaluated as routine laboratory findings in thyroid cancer patients who underwent unilateral thyroid lobectomy. The number of patients in the present study population was relatively small. Finally, we could not evaluate the natural course of diffuse uptake in remnant thyroid lobe because of the short follow-up period.

In conclusion, this study demonstrates that diffusely increased ^{18}F-FDG uptake in the residual thyroid gland of patients who have undergone unilateral thyroid lobectomy is a relatively frequent finding and may be associated with chronic thyroiditis. This finding is not influenced by thyroid function status or the use of thyroid hormone replacement therapy. The ^{18}F-FDG uptake in the residual thyroid is inversely correlated with mean attenuation value. More data are needed to elucidate the natural course of diffuse uptake in the residual thyroid lobe.

Conflict of Interest We declare that we have no conflict of interest.

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