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Risk of Malignancy in Thyroid Incidentalomas Identified by Fluorodeoxyglucose-Positron Emission Tomography

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Background: Thyroid incidentalomas detected by 2-deoxy-2-^{18}F-fluoro-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) have been reported in 1% to 4% of the population, with a risk of malignancy of 27.8% to 74%. We performed a retrospective review of FDG-avid thyroid incidentalomas in cancer screening subjects and patients with nonthyroid cancer. The risk of malignancy in thyroid incidentaloma and its association with the maximal standardized uptake value (SUV_{max}) in ^{18}F-FDG PET/CT were evaluated to define the predictor variables in assessing risk of malignancy.

Methods: A total of 2,584 subjects underwent ^{18}F-FDG PET/CT for metastatic evaluation or cancer screening from January 2005 to January 2010. Among them, 36 subjects with FDG-avid thyroid incidentalomas underwent further diagnostic evaluation (thyroid ultrasonography-guided fine needle aspiration cytology [FNAC] or surgical resection). We retrospectively reviewed the database of these subjects.

Results: Of the 2,584 subjects who underwent ^{18}F-FDG PET/CT (319 for cancer screening and 2,265 for metastatic evaluation), 52 (2.0%) were identified as having FDG-avid thyroid incidentaloma and cytologic diagnosis was obtained by FNAC in 36 subjects. Of the subjects, 15 were proven to have malignant disease: 13 by FNAC and two by surgical resection. The positive predictive value of malignancy in FDG-avid thyroid incidentaloma was 41.7%. Median SUV_{max} was higher in malignancy than in benign lesions (4.7 [interquartile range (IQR), 3.4 to 6.0] vs. 2.8 [IQR, 2.6 to 4.0], P=0.001).

Conclusion: Thyroid incidentalomas found on ^{18}F-FDG PET/CT have a high risk of malignancy, with a positive predictive value of 41.7%. FDG-avid thyroid incidentalomas with higher SUV_{max} tended to be malignant.

Keywords: Thyroid gland; Incidental findings; Fluorodeoxyglucose F18; Positron-emission tomography; Thyroid neoplasms; Prevalence

INTRODUCTION

Thyroid nodules come to clinical attention when noted by the patient, as an incidental finding during routine physical examination, or during a radiologic imaging, such as carotid doppler, neck computed tomography (CT), or positron emission tomography (PET). Their clinical importance is primarily related to the need to exclude thyroid cancer, which accounts for 4.0% to

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6.5% of all thyroid nodules [1,2].

Thyroid incidentalomas are nonpalpable thyroid nodules defined as newly identified thyroid lesions encountered during imaging procedures. Nonpalpable nodules have approximately the same risk of malignancy as palpable nodules. In some circumstances, especially nodules discovered by PET/CT, the risk of malignancy may be higher [3,4].

As a molecular imaging modality, 2-deoxy-2-^{18}F-fluoro-D-glucose (^{18}F-FDG) PET/CT can detect a wide variety of tumor sites. Abnormal incidental findings, including thyroid lesions, are not uncommon because of the nonspecific physiologic properties of FDG, as well as the range of the scan. As the use of PET/CT becomes more common, the discovery of thyroid incidentalomas with focal FDG uptake will increase [5].

Focal thyroid incidentalomas detected by ^{18}F-FDG PET/CT have been reported in 1% to 4% of known cancer patients and the normal healthy population, with positive predictive values for underlying thyroid malignancy of 27.8% to 74% [4,6-9]. However, the prevalence of malignancy in thyroid nodules detected incidentally by ^{18}F-FDG PET/CT has not been fully characterized, and several issues remain. For example, it is controversial whether the semiquantified index maximal standardized uptake value (SUV_{max}) can differentiate between malignant and benign thyroid nodules [10-13].

In this study, we performed a retrospective review of our institutional experience of FDG-avid thyroid incidentaloma in healthy subjects undergoing cancer screening and patients with nonthyroid cancer. The risk of malignancy in FDG-avid thyroid incidentaloma and its association with SUV_{max} in ^{18}F-FDG PET/CT were evaluated to define the predictor variables in assessing the risk of malignancy.

METHODS

Subjects

Data from Korean patients who underwent ^{18}F-FDG PET/CT for metastatic evaluation or cancer screening at Soonchunhyang University Bucheon Hospital from January 2005 to January 2010 were analyzed retrospectively. We performed ^{18}F-FDG PET/CT for two different purposes: metastasis evaluation in patients with known or suspected cancer and cancer screening in asymptomatic healthy subjects who have no previous history of malignancy. A total of 2,584 subjects underwent ^{18}F-FDG PET/CT (319 for cancer screening and 2,265 for metastatic evaluation), and 52 subjects were identified as having focal thyroid FDG uptake. Thirty-six subjects with FDG-avid thyroid incidentalomas underwent further diagnostic evaluation in the form of fine needle aspiration biopsy (FNAB) or surgical resection (Fig. 1). All subjects who underwent further histologic evaluation, except for one, also had a thyroid ultrasonography (US) scan. This study was approved by the Institutional Review Board of Soonchunhyang University Bucheon Hospital.

Imaging protocol and interpretation

All patients underwent whole-body or torso PET/CT using one of two first-generation scanners: Biograph2 (Siemens Medical Solutions, Erlangen, Germany) or Gemini (Philips Medical Systems, Milpitas, CA, USA). Patients fasted for at least 6 hours before the scan. Prior to injection of ^{18}F-FDG, the blood glucose concentration was verified as <180 mg/dL. PET/CT was commenced 1 hour after intravenous injection of 7.4 MBq (0.2 mCi) of ^{18}F-FDG per kg body weight. Scans, including PET and nonenhanced CT, were acquired from the skull base to the proximal thigh from six to eight bed positions. The patient was placed in the supine position with both arms at the sides. PET was performed using an acquisition time of 150 seconds per bed position. CT was performed using a 5-mm slice thickness, 50 mAs, and 130 kVp. CT data were used for attenuation cor-

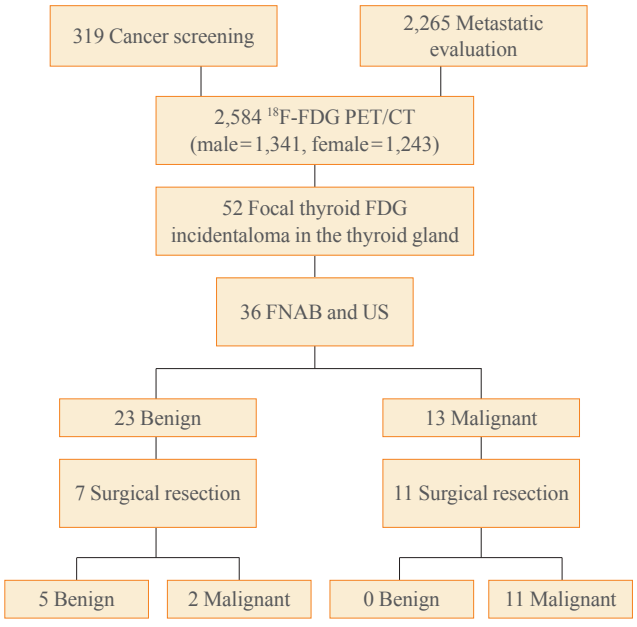

Fig. 1. Selection of patients from those who underwent 2-deoxy-2-18F-fluoro-D-glucose positron emission tomography/computed tomography (18F-FDG PET/CT) for cancer screening and metastatic evaluation was based on the presence of focal FDG-avid thyroid incidentaloma. FNAB, fine needle aspiration biopsy; US, ultrasonography.

rection. PET images were reconstructed using a standard three-dimensional iterative algorithm (ordered subset expectation maximization [OSEM]), providing axial, sagittal, and coronal planes. OSEM reconstruction using two iterations and eight subsets and a postreconstruction Gaussian filter of 5 mm full width at half maximum were applied for matrix sizes of 128×128, resulting in an image size of 5.3×5.3 mm.

All ^{18}F-FDG PET/CT images were analyzed by one of three experienced nuclear medicine physicians. Thyroid incidentaloma was defined as focal thyroid uptake identified incidentally on ^{18}F-FDG PET/CT study. Focal uptake was defined as FDG uptake in less than one lobe of the thyroid gland.

Statistical analysis

Statistical analyses were performed using SPSS version 19.0 (IBM Co., Armonk, NY, USA). Results are expressed as the means±SD or medians (interquartile range [IQR]). Student *t* test, the Mann-Whitney *U* test, and the chi-square test were used to compare PET/CT findings between benign and malignant thyroid lesions (Student *t* test and Mann-Whitney *U* test for mean comparisons, and chi-square test for group comparisons of categorical variables). To determine the correlation between SUV_{max} and tumor size in thyroid US, Spearman correlation coefficient was calculated. All analyses were two-sided. A $P<0.05$ was deemed to indicate a statistically significant difference.

RESULTS

Of the 2,584 subjects who underwent ^{18}F-FDG PET/CT (319 for cancer screening, 2,265 for metastatic evaluation), 52 (2.0%) were identified as having focal FDG uptake in the thyroid (Fig. 2). Among these 52 patients, further evaluation was not performed on 16 subjects because of refusal of additional workup, loss to clinical follow-up, or extensive disease of another underlying primary malignancy. These cases were excluded. Finally, 36 patients (12 males and 24 females; mean age, 63.4±10.9 years; range, 40 to 80 years; 28 patients with suspected or known cancer, eight healthy subjects who underwent ^{18}F-FDG PET/CT for cancer screening) who underwent FNAC for further diagnostic evaluastion were included in the analysis. All subjects who underwent further histologic evaluation, except for one, also had a thyroid US scan and had their tumor size determined by measurement of the longest diameter.

Cytologic diagnosis was obtained by fine needle aspiration cytology (FNAC). Among the 13 subjects with suspected malignancy based on FNAC, 11 underwent surgical resection. One subject who did not undergo surgical resection had suspected metastatic squamous carcinoma from known esophageal cancer for which surgery was not indicated, and another subject refused to undergo surgery. The subjects who underwent surgery were proven to have malignant disease, which in all 11 subjects was papillary carcinoma. Meanwhile, among the

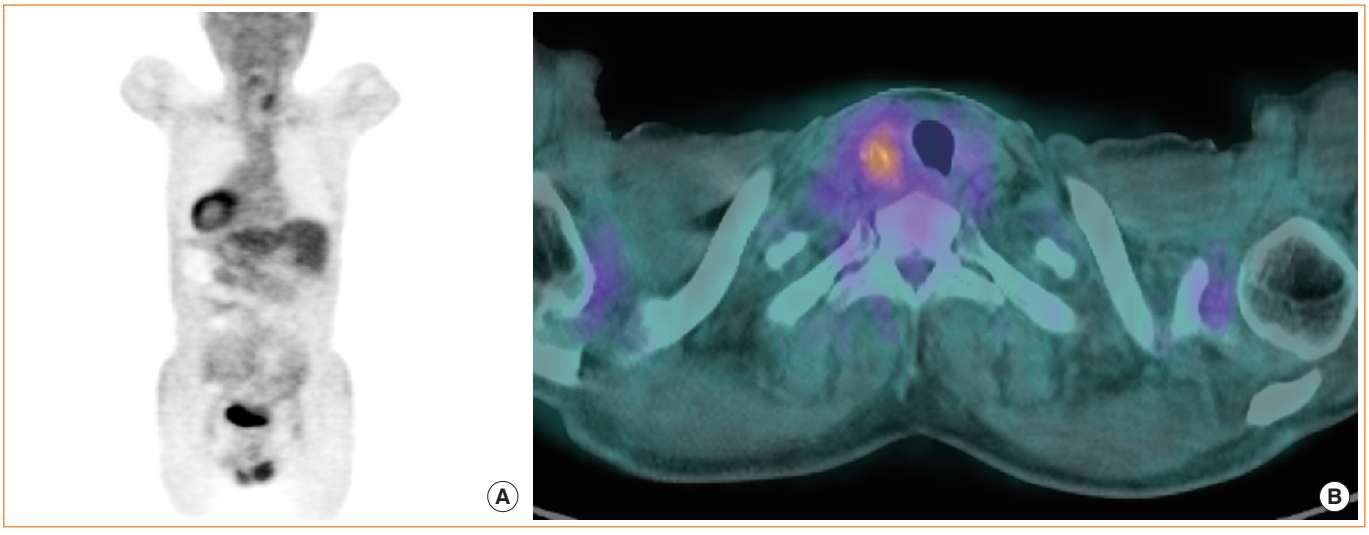

Fig. 2. A 60-year-old man with underlying sigmoid colon cancer. (A) A focal fluorodeoxyglucose-avid lesion with calcification was incidentally detected in the right lobe of the thyroid (posterior-anterior view). (B) Fusion axial positron emission tomography/computed tomography image showing a hypermetabolic lesion and calcification in the right lobe of the thyroid gland (maximal standardized uptake value=2.6).

Table 1. Summary of 36 Patients with Focal Fluoro-D-Glucose-Avid Thyroid Incidentalomas

No.	Sex/Age	SUV_{max}	Tumor size, cm[a]	FNAB	Final diagnosis (after surgery)
1	F/54	3.1	1.9	Papillary carcinoma	Papillary carcinoma
2	M/60	2.6	3.5	Follicular neoplasm	
3	F/62	5.5	1.5	Papillary carcinoma	Papillary carcinoma
4	M/50	6.6	2.3	Follicular neoplasm	
5	F/71	5.1	0.8	Papillary carcinoma	Papillary carcinoma
6	F/78	7.5	1.1	Follicular neoplasm	Follicular carcinoma
7	M/65	4.7	0.8	Papillary carcinoma	Papillary carcinoma
8	F/53	5.6	2.1	Benign follicular nodule	
9	F/70	3.4	1.2	Papillary carcinoma	Papillary carcinoma
10	M/63	3.9	1.0	Follicular neoplasm	
11	F/69	3.5	1.0	Papillary carcinoma	Papillary carcinoma
12	F/53	2.8	1.6	Nodular hyperplasia	
13	M/46	2.0	0.4	Nodular hyperplasia	
14	F/53	3.0	1.3	Papillary carcinoma	Papillary carcinoma
15	F/80	2.0	1.8	Follicular neoplasm	
16	F/69	2.6	0.6	Follicular neoplasm	
17	F/50	4.2	2.9	Nodular hyperplasia	Nodular hyperplasia
18	F/78	2.6		Thyroiditis	
19	M/77	2.9	1.8	Nodular hyperplasia	Nodular hyperplasia
20	F/65	2.8	3.6	Nodular hyperplasia	
21	F/40	2.6	0.8	Nodular hyperplasia	
22	M/73	6.0	4.0	Metastatic squamous carcinoma	
23	M/60	2.8	2.6	Nodular hyperplasia	
24	M/58	2.8	1.1	Nodular hyperplasia	
25	F/71	8.2	1.1	Papillary carcinoma	Papillary carcinoma
26	F/77	5.0	2.1	Follicular neoplasm	Nodular hyperplasia
27	F/46	2.4	1.1	Follicular neoplasm	
28	F/70	7.6	0.8	Papillary carcinoma	Papillary carcinoma
29	F/67	3.1	1.8	Follicular neoplasm	Nodular hyperplasia
30	F/53	4.3	4.2	Papillary carcinoma	Refused surgery
31	M/56	2.2	1.6	Follicular neoplasm	Nodular hyperplasia
32	F/71	7.6	2.5	Follicular neoplasm	
33	M/79	3.3	1.3	Papillary carcinoma	Papillary carcinoma
34	F/78	3.3	3.4	Nodular hyperplasia	
35	M/62	5.8	1.1	Nodular hyperplasia	Papillary carcinoma
36	F/54	4.5	1.2	Papillary carcinoma	Papillary carcinoma

SUV_{max}, maximal standardized uptake value; FNAB, fine needle aspiration biopsy; F, female; M, male.
[a]Tumor size was determined by measurement of the longest diameter on thyroid ultrasonography.

23 subjects with suspected benign disease based on FNAC, seven subjects underwent surgical resection (follicular neoplasm or suspicious for a malignancy on thyroid US finding) and two lesions were proven to be malignant (one follicular carcinoma and one papillary carcinoma) (Fig. 1). The remaining five lesions were nodular hyperplasias. The subject shown to have follicular carcinoma by surgical resection had been thought to have a follicular neoplasm based on FNAC. The subject shown to have papillary carcinoma had had suspected nodular hyperplasia based on FNAB; however, thyroid US made us suspect malignancy and a BRAF gene mutation test was positive. Therefore, surgical resection was performed and

Table 2. Clinical Characteristics of Fluoro-D-Glucose-Avid Thyroid Incidentalomas (n=36)

Characteristic	All	Malignant (n=15)[a]	Benign (n=21)	P value
Age	63.4±10.9	65.6±8.9	61.8±12.2	0.150
Sex				0.721
Male	12	4	8	
Female	24	11	13	
SUV_{max}	3.4 (2.8–5.4)	4.7 (3.4–6.0)	2.8 (2.6–4.0)	0.001
Tumor size, cm	1.5 (1.1–2.3)	1.2 (1.0–1.5)	1.8 (1.1–2.6)	0.158

Values are expressed as mean±SD or medians (interquartile range). Student t test and the Mann-Whitney U test were used for comparisons of means, and the chi-square test was used for group comparisons of categorical variables.
SUV_{max}, maximal standardized uptake value.
[a]Malignant lesions were defined by histologic confirmation by fine needle aspiration biopsy (n=13) or surgical resection (n=2).

this subject was finally proven to have a malignancy.

Of the 23 subjects with suspected non-malignant lesions, 11 were shown by FNAB to have follicular neoplasms; follicular carcinoma could not be excluded. However, surgical resection was not performed in all of these cases; therefore, the final diagnosis was not confirmed. The 12 subjects without follicular neoplasms had benign lesions: one benign follicular nodule, 10 nodular hyperplasias, and one case of thyroiditis (Table 1).

The positive predictive value of malignancy in FDG-avid thyroid incidentaloma was 41.7% (15 of 36 subjects). The prevalence of malignancy was 0.58% (15 of 2,584 subjects) and was higher in the cancer screening group than in patients with suspected or known cancer (0.94% vs. 0.53%).Comparisons of PET/CT findings between benign and malignant thyroid lesions detected incidentally on PET/CT scans are shown in Table 2. Age and sex had no relevance to malignancy. Median SUV_{max} for FDG-avid thyroid incidentalomas was 3.4 (IQR, 2.8 to 5.4). Median SUV_{max} for benign and malignant lesions was 2.8 (IQR, 2.6 to 4.0) and 4.7 (IQR, 3.4 to 6.0), respectively, which suggests a trend for FDG-avid thyroid incidentalomas with higher SUV_{max} values to be malignant. The difference was statistically significant in the current study (P=0.001; Mann-Whitney U test). The median tumor size (longest diameter in thyroid US) for FDG-avid thyroid incidentalomas was 1.5 cm (IQR, 1.1 to 2.3). The median tumor size for benign and malignant lesions was 1.8 cm (IQR, 1.1 to 2.6) and 1.2 cm (IQR, 1.0 to 1.5), respectively, and there was no statistical significance (P=0.158; Mann-Whitney U test). To determine the correlation between SUV_{max} and tumor size, Spearman's correlation coefficient was calculated. There was no correlation between SUV_{max} and tumor size (Spearman correlation coefficient=0.052; P=0.767).

DISCUSSION

Thyroid carcinoma accounts for 1% of all malignant tumors. It is the most frequent endocrine cancer and is usually characterized by a favorable prognosis and long-term survival [14,15]. About 5% of thyroid nodules are thyroid cancer. Thyroid incidentalomas have become increasingly common with the development and more frequent use of highly sensitive imaging modalities [16]. The more widespread use of ^{18}F-FDG PET/CT for cancer staging, restaging, and treatment response monitoring has increased the incidence of thyroid incidentalomas identified by ^{18}F- FDG PET/CT [17].

Prevalence rates of thyroid incidentalomas detected by ^{18}F-FDG PET/CT have been reported, and results show that thyroid incidentalomas are relatively frequent, with a rate of 0.2% to 8.9% [10,18-20]. However, the prevalence of malignant thyroid nodules detected incidentally by ^{18}F-FDG PET/CT has not yet been fully characterized and varies widely (range, 10.3% to 80.0%) [6-8,11,21-25]. At our institution, the prevalence of FDG-avid thyroid incidentalomas and the risk of malignancy of thyroid incidentalomas were 2.0% and 41.7%, respectively. These data are similar to those from previous studies and slightly higher than previous Korean values. The very high prevalence of malignancy justifies further work-up, such as US and FNAB [8,20,21].

Because of the high cost of ^{18}F-FDG PET/CT, it is generally not used for cancer screening in asymptomatic healthy subjects. Therefore, the prevalence of incidentalomas in these subjects is unclear [10]. In contrast, a higher prevalence in cancer screening subjects than in patients with suspected or known cancer has been reported in some studies (Kang et al. [7], 3.0% vs. 1.9%; Yang et al. [10], 3.1% vs. 2.3%). In our study, ^{18}F-FDG PET/CT detected 12 unexpected thyroid malignancies in 28 patients with suspected or known cancer and three thyroid malignancies in eight healthy subjects who underwent ^{18}F-FDG PET/CT for cancer screening. The prevalence of malignancy in FDG-avid thyroid incidentalomas was similar in patients with suspected or known cancer (42.0%) and in cancer screening patients (37.5%) in our study. However, other studies suggest that PET/CT is useful in detecting unexpected second primary cancers [26].

SUV_{max} is a semiquantitative parameter that reflects metabolic activity, but it is not a specific marker of malignancies. Many thresholds have been proposed to distinguish benign from malignant lesions, but no safe cutoff has been identified. In fact, approximately half of studies report a statistically significant difference between SUV_{max} for benign lesions and the value for malignant ones, whereas the other half show the opposite [18,21,27]. In this study, median SUV_{max} was significantly higher in malignant lesions than in benign ones (4.7 [IQR, 3.4 to 6.0] vs. 2.8 [IQR, 2.6 to 4.0], P=0.001). This study supports the view that SUV_{max} is a helpful diagnostic tool to discriminate benign from malignant nodules.

At our institution, all subjects who underwent further histologic evaluation, except for one, also underwent thyroid US and had their tumor size determined by measurement of the longest diameter. Tumor size is known as an important factor that affects FDG uptake. When tracer uptake in small tumors is measured, large biases can be introduced by the partial-volume effect. If a tumor is small, FDG uptake can be underestimated because of the partial-volume effect [28]. In this study, Spearman's correlation coefficient was calculated to determine the correlation between SUV_{max} and tumor size. There was no correlation between SUV_{max} and tumor size (Spearman correlation coefficient=0.052; P=0.767).

Our study has several limitations that must be taken into account. First, follicular neoplasms of the thyroid are defined as follicular carcinomas, follicular adenomas, and nodules of goiters. Surgical resection was not performed in all of these cases; therefore, the final diagnosis was not confirmed. So, some cases of follicular neoplasms may be thyroid malignancies, and the prevalence of malignancy in thyroid incidentaloma may have been underestimated. Second, SUV_{mean} was not evaluated. Third, because our study population was a cohort of patients cared for in a single center, the results might have been affected by selection bias. Nonetheless, this single-center study had the advantage of having a high degree of consistency regarding laboratory and imaging data and histological diagnosis.

In conclusion, thyroid incidentalomas found on ^{18}F-FDG PET/CT in patients with suspected or known cancer and healthy cancer screening subjects have a high risk of malignancy, with a positive predictive value of 41.7% for underlying thyroid malignancy. There was a trend for FDG-avid thyroid incidentalomas with higher SUV_{max} to be malignant. Given the risk of malignancy, patients with FDG-avid thyroid incidentaloma should receive a tissue diagnosis and proper management.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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