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The assessment of incidental thyroid lesions on 18F-fluorodeoxyglucose positron emission tomography/computed tomogrophy: A single centre experience

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ABSTRACT

Objective: The aim of the present study was to evaluate the prevalence of thyroid lesions detected by ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) incidentally, determine malignancy risk and its relationship with maximal standardized uptake value (SUVmax) and FDG uptake pattern.
Methods: Between February 2009 and February 2014, a total of 12713 patients underwent ^{18}F-FDG PET/CT. Incidental thyroid uptake was seen in 710 patients and further diagnostic evaluation was performed on 147 patients with focal or diffuse FDG uptake. The ^{18}F-FDG PET/CT findings of these patients and their association with malignancy were retrospectively reviewed.
Results: The prevalence of thyroid incidentalomas detected by ^{18}F-FDG PET/CT was 5.6% (710/12713). Of the 147 patients who underwent biopsy or thyroid surgery, histology was benign in 99 and malign in 48 patients. The malignancy risk of incidental thyroid lesions was calculated as 32.7% (48/147). The median SUVmax was 2.9 (0.6–27.4) in benign group, whereas 11.8 (2.4–72.9) in malign group and the difference between these groups was statistically significant ($p < 0.001$). According to the ROC analysis, a SUVmax above 6 was more likely to be malign with statistical significance ($p < 0.001$). The sensitivity, specificity, positive predictive value and negative predictive value were 87.4%, 81.7%, 70.1% and 93% respectively.
Conclusion: The malignancy risk of incidental thyroid lesions on ^{18}F-FDG PET/CT is high. Although it is obvious that higher SUVmax values are tended to be malign, an overlap between benign and malign groups is still remaining. In case of absence of clinical contraindications, further examination should be recommended.

1. Introduction

The thyroid lesions identified by radiological imaging studies for non-thyroid disease are defined as thyroid incidentalomas.[1] In recent years ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography in combination with CT (^{18}F-FDG PET/CT) has been used for not only staging, but also monitorization of treatment response in malignancies.[2] Incidental FDG uptake outside of target lesions, including thyroid lesions, is not rare because of the nonspecific physiologic properties of FDG.[3]

The rate of thyroid incidentalomas detected by ^{18}F-FDG PET/CT was reported as 1.1–4% for the population including both cancer patients and healthy people. Thyroid cancer risk was 14–60% for this population.[4–14] The differentiation between benign and malign thyroid lesions according to the PET/CT findings has been the subject of many studies. It has been reported that the maximal standardized uptake value (SUVmax) of malign thyroid lesions was higher than benign lesions.[5–9,14–19] Several SUVmax cutoff values have been reported for distinguishing benign thyroid lesions from malign lesions in these studies.[4,8,9,17–19]

The aim of our study was to perform a retrospective review of FDG-avid incidental thyroid lesions in non-thyroid cancer patients.

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We assessed the prevalence and the malignancy risk of incidental thyroid uptake in a large series of ^{18}F-FDG PET/CT. In addition to the uptake pattern, we also investigated whether SUVmax cutoff value could differentiate benign from malign lesions.

2. Material and methods

2.1. Study population

We reviewed retrospectively 12713 non-thyroid cancer patients who underwent ^{18}F-FDG PET/CT at the Department of Nuclear Medicine, Gazi University Hospital between February 2009 and February 2014. Among them, 710 patients were diagnosed as having incidental thyroid uptake, focal uptake in 533 and diffuse uptake in 177. The inclusion criteria were as follows[1]: all patients who were yielded diagnosis of cancer[2]; no previous history or diagnosis of thyroid cancer[3]; incidentally found focal or diffuse thyroid lesions on ^{18}F-FDG PET/CT[4]; histopathologically proven thyroid lesions by fine needle aspiration biopsy (FNAB) or surgical resection[5]; patients with sufficient samples on cytology. Consequently, of these 710 patients, 147 patients whose thyroid incidentaloma was histopathologically proven were included in the study. Demographic characteristics of the patients, FDG uptake pattern and the SUVmax of thyroid incidentalomas were recorded. The current study was approved by the ethics committee of Gazi University.

2.2. ^{18}F-FDG-PET-CT procedure

All PET/CT scans were performed in the Nuclear Medicine Department of Gazi University. The standard PET/CT protocol required a minimum 6 h of fasting of patients whose blood glucose levels were below 160 mg/dl, intravenous injection of 0.1 mCi/kg of FDG and a 60 min delay post-injection before the start of imaging. During the uptake phase patients laid still in a warm room. Whole body PET/CT scans were acquired using a GE Discovery STPET/CT scanner (General Electric Medical Systems, Milwaukee, WI, USA) starting from the mid-thigh up to the top of the skull. Following a low-dose (120 kV, 10–90 mA) whole-body CT scan PET scanning was done in 3-D mode with 3 min per bed position. Axial spatial resolution for the PET scanner was 5 mm. PET images were reconstructed using an iterative ordered-subsets expectation maximization algorithm with attenuation correction. CT data were used for attenuation correction of PET data and to produce co-registered tomographic slices of PET and low dose CT images with a slice thickness of 3.75 mm.

The FDG PET/CT images were evaluated by a single nuclear medicine physician. Thyroid involvement was classified as focal or diffuse depending on uptake pattern. Diffuse uptake was determined as FDG uptake in the whole thyroid gland, whereas focal lesions were determined as FDG uptake in an isolated region of the thyroid gland. Maximum standard uptake value (SUVmax) was used for quantification of FDG uptake in thyroid nodules that were detected on the co-registered PET/CT images. For the calculation of SUVmax a cubical 30 mm sized volume of interest was placed over the nodular thyroid lesion by the operator. In patients with diffuse thyroid involvement, SUVmax was calculated from the region of thyroid gland with the highest FDG uptake on visual assessment. The SUVmax was calculated by normalizing the maximum radioactivity concentration in the nodule according to the following formula: tissue concentration (MBq/g)/injected dose (MBq)/body weight (g).

2.3. Fine needle aspiration biopsy

Ultrasound guided fine needle aspiration biopsy (FNAB) was performed for the cases showing either focal or diffuse uptake on ^{18}F-FDG PET/CT. In cases of multiple nodules, the nodule with the highest FDG uptake was defined as dominant nodule, and FNAB was performed on this nodule. In patients with solitary nodules FNAB was performed on this nodule. In cases of diffuse uptake, FNAB was done blindly on the thyroid gland.

2.4. Statistical analysis

Descriptive statistics were expressed as medians with range or means ± SD. The independent-samples *t*-test, the Mann-Whitney *U* test, the Pearson's chi-square test and Fisher's exact test were used to compare clinical characteristics and PET/CT findings between benign and malign thyroid lesions (independent-samples *t*-test and Mann-Whitney *U* test for comparing continuous variables, Pearson's chi-square test and Fisher's exact test for comparing categorical variables). The optimal SUVmax cutoff for differentiation benign from malign lesions was defined using Youden's index. A receiver operating characteristic (ROC) curve analysis was made for defining the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). All statistical analyses were performed using IBM SPSS version 20.0 software package. A p value less than 0.05 was considered significant.

3. Results

3.1. Patient characteristics

A total of 147 patients (60 male, 87 female) with non-thyroid cancer whose thyroid incidentaloma was histopathologically proven were included in present study. Median age at PET/CT scan was 60 years (range of 19–97). Lymphoma was the most common pathology of primary malignancy and none of the patients had metastatic disease at the time of PET/CT scan. The general patient characteristics are summarized in Table 1.

All 147 patients underwent further diagnostic evaluation by US-guided FNAB. Cytological results were benign in 93 (63.3%) patients, whereas malign in 36 (24.5%), and suspicious for malignancy in 18 (12.2%) at initial diagnosis. A total of 43 (29%) patients (18 suspicious for malignancy, 11 benign, and 14 malign by FNAB) underwent surgery. Among 36 patients with cytologically malign incidentaloma, 22 patients did not undergo operative intervention because of extensive stage IV disease, loss of clinical follow-up, or refusal surgical treatment. All of the 18 patients with a cytological diagnosis of suspicious for malignancy underwent surgical resection, and the postoperative pathology diagnosis was benign in 6, and malign in 12 patients. Fig. 1 shows the final results of FNAB and surgery in detail.

3.2. Prevalence and malignancy risk of thyroid incidentalomas

Of the 12713 patients who underwent ^{18}F-FDG PET/CT for oncological purposes, 710 were identified as having incidental FDG uptake (533 focal uptake, 177 diffuse uptake) in the thyroid gland. The prevalence of incidental thyroid lesions was 5.6%. One hundred forty seven patients underwent FNAB or surgical resection. Among them, final histopathological diagnosis was benign in 99 and malign in 48 patients. The cancer risk of incidentally found thyroid lesions was calculated as 32.7%.

3.3. ^{18}F-FDG PET/CT results

Of the 147 patients enrolled in current study, 126 patients (85.7%) showed focal thyroid FDG uptake and only 21 (14.3%)

Table 1
General characteristics of the patients.

	Malignant	Benign	*p* value
	n = 48	n = 99	
Age at PET/CT scan			
Median	52	61	0.155
(Range)	(19–81)	(19–97)	
Gender			
Male	22	38	0.389
Female	26	61	
SUVmax			
Median	11,8	2,9	**<0.001**
(Range)	(2.4–72.9)	(0.6–27.4)	
FDG uptake pattern			
Focal	38	88	0.114
Diffuse	10	11	
Size of focal lesions			
Diameter in cm	2.9 ± 1.6	2.1 ± 0.9	**0.014**
Surgery for thyroid			
Yes	26	17	
No	22	82	
Primary cancer site			
Breast	11	21	
Colon	1	9	
RCC	4	3	
Ovary	0	4	
Sarcoma	2	3	
Head and neck	3	6	
Lymphoma	18	29	
Primary unknown	2	0	
Lung	4	18	
Melanoma	3	6	

PET/CT positron emission tomography/computed tomography, *FDG* fluorodeoxyglucose, *cm* centimeter, *SUVmax* maximum standardized uptake value, *RCC* renal cell carcinoma.

showed diffuse uptake. In the patients showing focal uptake, the histology was malign in 38 patients and benign in 88. In the patients with diffuse uptake, the histology was malign in 10 and benign in 11. Among them, only one patient showed unilateral diffuse uptake who had benign histology. There was no difference between malign and benign group with respect to thyroid FDG uptake pattern ($p = 0.114$). The histology of the malign thyroid incidentalomas showing diffuse uptake was primary thyroid lymphoma in 7 cases, thyroid metastasis from the primary in 2 cases, and micropapillary thyroid carcinoma in 1 case. The latest diagnosis of micropapillary carcinoma was tought to be an incidental finding. The longest diameter of focal lesions measured on CT scans was 2.9 ± 1.6 cm in malign group, and 2.1 ± 0.9 cm in benign group, and this difference was statistically significant ($p = 0.014$). The median SUVmax was 2.9 (0.6–27.4) in benign group, whereas 11.8 (2.4–72.9) in malign group and the difference between these groups was statistically significant ($p < 0.001$) (Table 1).

A receiver operating curve (ROC) analysis was performed to define a SUVmax cut-off for differential diagnosis between benign and malign thyroid lesions. The SUVmax cutoff value above 6 yielded a maximal sensitivity of 87.4%, specificity of 81.7%, positive predictive value (PPV) of 70.1% and negative predictive value (NPV) of 93% with statistical significance ($p < 0.001$) (Fig. 2). Patients with a SUVmax above 6 in benign group had either focal or diffuse uptake pattern.

4. Discussion

Incidentally found thyroid lesions discovered during radiological imaging studies for non-thyroidal disease have become an important part of clinical practice. They are usually nonpalpable and benign with a cancer risk ranging from 1.5 to 10%.[20] Despite the low risk of cancer, the differentiation between benign and malign thyroid incidentalomas is very important in reducing unnecessary operation. It is impossible to distinguish benign from malign lesions with non-invasive imaging techniques. Although gray scale US and duplex power doppler US are useful diagnostic modalities with high sensitivity for differentiating benign from malign lesions, FNAB is still the gold standard for diagnosis.[21]

In recent years, gradually expanding utilization of PET/CT has resulted in an increased identification of incidental thyroid lesions. Therefore the differentiation of benign from malign lesions according to the PET/CT findings has been investigated in several studies.[4–19] In the present study, the prevalence of incidental thyroid lesions including diffuse or focal FDG uptake was 5.6% with a cancer risk of 32.7%. Although our results seemed to be similar with previous documented results by other reports, there was a great difference regarding to the FDG uptake pattern. Most of these studies investigated the cancer risk only for thyroid lesions with focal FDG uptake. According to the results of these studies, the prevalence of focal FDG uptake was 1.1–4% with a risk of cancer ranging from 14 to 60%.[4,5,7–11] On the other hand, the studies including either focal or diffuse FDG uptake reported higher prevalence up to 9%.[18,19]

Focal FDG uptake in the thyroid has been associated with malignancy in numerous studies,[4–19] whereas diffuse accumulation was considered to be associated with benign conditions such as chronic thyroiditis, nodular goiter and Graves' disease.[22–24] In a series reported by Bae et al.,[18] the cancer risk was significantly higher in focal uptake group than in diffuse uptake group (30.9% versus 6.4%). Similar with this report, Kang et al.[6] found that the focal uptake group had a significantly higher rate than the diffuse uptake group (37.2% versus 4.7%) and finally, they concluded that histological examination was not required for patients with diffuse uptake on PET/CT. However, our results were not consistent with these previous reports. In the patients showing diffuse uptake, the number of malign and benign histologies were almost the same, and we didn't find any significant difference between malign and benign group with respect to FDG uptake pattern. In the current study, most of the malign thyroid incidentalomas showing diffuse uptake was primary thyroid lymphoma and thyroid metastasis. Although it is of interest to note that the most common incidental finding of diffuse FDG uptake is seen in chronic thyroiditis, there were some reports which concluded that the differential diagnosis of diffuse uptake should include lymphoma and thyroid metastasis as supporting our results.[10,25,26]

In addition to FDG uptake pattern, the SUVmax is an important measure for thyroid incidentalomas. However, the role of SUVmax in differential diagnosis of the incidental thyroid lesions is still controversial. In our study we found that malign thyroid incidentalomas had statistically significant higher values than benign one in SUVmax. According to the ROC analysis, we found that a SUVmax above 6 was more likely to be malign with high sensitivity and specificity. Consistent with our study, malign thyroid incidentalomas have been reported to have significantly higher SUVmax than benign incidentalomas.[5–9,14–19] On the other hand, there were several studies reported that the SUVmax could not differentiate benig from malign conditions.[10,12,13,27] With the exception of these negative studies, malign lesions tend to have higher SUVmax than benign lesions. Several experimental studies demonstrated that malign tissues had greater expression of glucose transporters (GLUTs) and therefore they took up glucose more effective than benign tissues.[28,29]

Despite the potential role of SUVmax in determining malign thyroid lesions, most studies including ours revealed an overlap between malign and benign thyroid lesions.[5–7,12,30] Although the

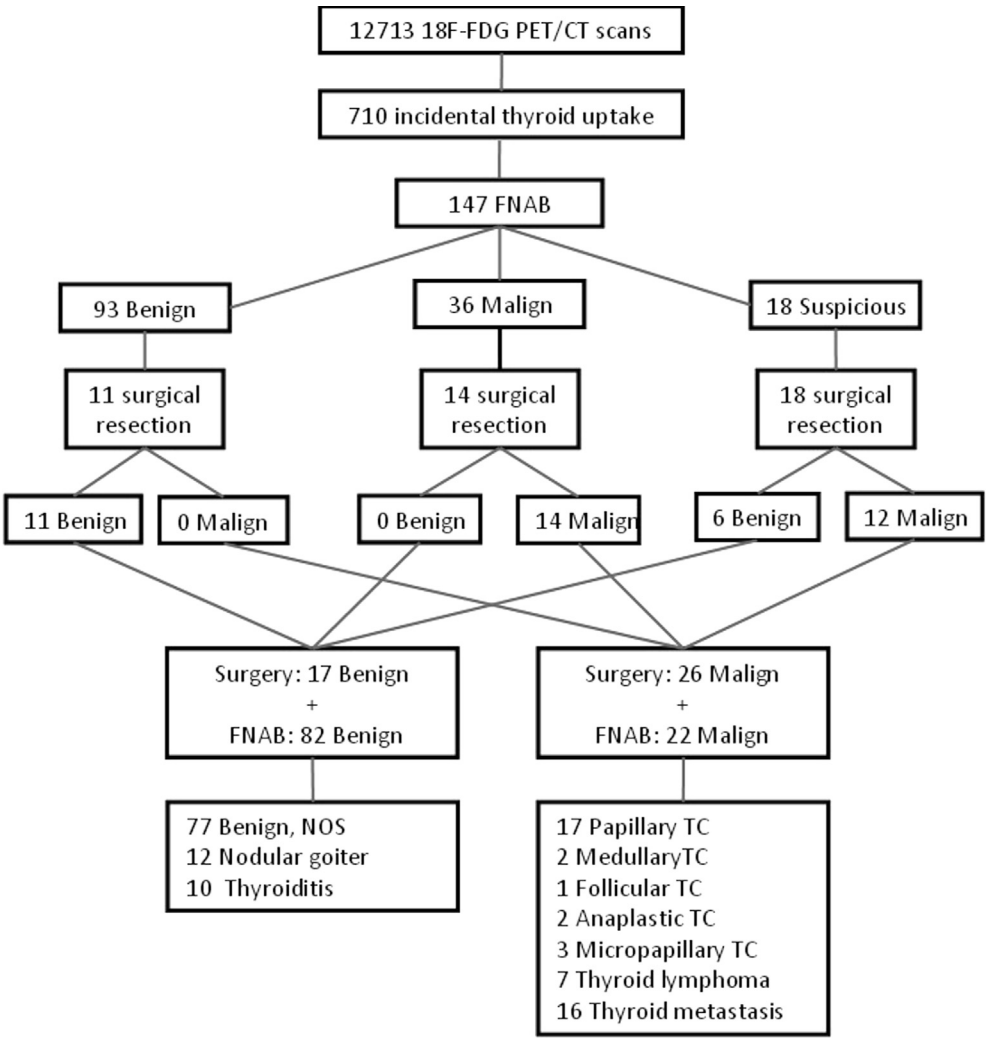

Fig. 1. Flow chart of the final histopathological diagnosis. *NOS* not otherwise specified, *TC* thyroid cancer.

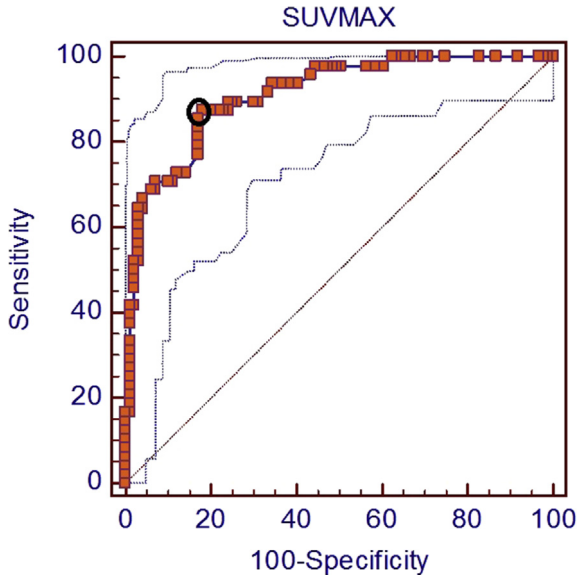

Fig. 2. ROC curve to distinguish benign from malign lesions on ^{18}F-FDG PET/CT. The SUVmax >6 distinguishes benign from malign lesions with a sensitivity of 87.5% and specificity of 81.8% at the point enclosed by the black circle. *ROC* receiver operating characteristic, *^{18}F-FDG PET/CT* ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, *SUVmax* maximal standardized uptake value.

mechanism of the high SUVmax in benign conditions such as Hürthle cell lesions or thyroiditis is not well understood, there are several studies reported a variable degree of GLUT1 expression in differentiated thyroid carcinoma.[29,30] The reason of this overlap may be associated with the variable degree of GLUT expression in either benign or malign conditions, which resulted in variable degree of FDG uptake.

The main limitation of the present study was the retrospective design. Only 20% of patients who had incidental thyroid lesions on ^{18}F-FDG PET/CT had further evaluation because of advanced cancer. Another limitation was associated with cases of multiple nodules. In patients with multiple nodules, only nodules with highest FDG uptake were confirmed histologically and included in the analysis. Because of these reasons, the malignancy rate could be affected and may not reflect the true rate. Therefore, to eliminate biases, comprehensive prospective studies with larger series are required.

Based on the results of the present study, incidental thyroid lesions detected by ^{18}F-FDG PET/CT in non-thyroid cancer patients have a high risk of malignancy. Although higher SUVmax values are more likely to be malign, there is still an overlap between benign and malign groups. If no clinical contraindications exist, further examination should be recommended for either focal or diffuse FDG uptake thyroid lesions, especially in patients with early stage cancer.

Conflicts of interest

None of the authors has any proprietary interests or conflicts of interest related to this submission.

This submission has not been published anywhere previously and that it is not simultaneously being considered for any other publication.

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