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Original Article

# How should we approach thyroidal incidentalomas detected on FDG-PET/ CT imaging?

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## Abstract

**Aim:** Thyroidal incidentalomas (Tis) detected by F-18 fluorodeoxyglucose positron emission tomography/computed tomography (F-18FDG PET/CT) may be associated with three different causes that include metastasis of another malignancy, primary thyroid gland malignancies and lastly benign thyroidal nodules, all require different clinical approaches. For appropriate treatment, quick characterization of the Ti is important, preferably with a lesser invasive method. Our aim was to determine whether the characterization of TIs can be performed with FDG-PET/CT, due to contribute faster diagnosis, and initiation of the therapy.

**Material and Methods:** Forty-four patients with detected TIs in FDG-PET/CT were included in the study. The relationship between metabolically/morphological parameters and pathology results were evaluated statistically. If two subsequent cytology were negative, nodule accepted as benign. If cytology result was suspected or malignant, histopathological confirmation was made. For these patients, histopathological results were accepted as definite diagnosis.

**Results:** Malignant thyroidal pathologies were detected in 29.5% of patients. We could not find any significant relationship between age, nodule size and SUVmax value and pathology results. According to ROC analysis, there were not any cut-off value for nodule size and SUVmax. Similar results were also obtained for papillary carcinoma as a special subgroup.

**Conclusion: C**haracterisation of TIs could not be performed by using age, nodule size and SUVmax. Therefore, TIs which detected by FDG-PET/CT should be examined pathologically due to high risk of malignancy.

**Keywords:** Thyroidal incidentalomas; FDG-PET/CT; malignant; characterization.

## INTRODUCTION

Thyroidal incidentalomas (TI) are defined as previously unknown and newly detected nodules in patients with non-thyroidal diseases. They can be detected by routine physical examination, ultrasonography (US), computed tomography (CT), or positron emission tomography/ computed tomography (PET/CT) (1,2). Thyroid nodule incidence can be as high as 50% in autopsy series (3). The detection rate of thyroid nodules is increasing, due to common utilization of imaging methods. This trend is also valid for cancer patients (4-6).

F-18 Fluorodeoxyglucose (F-18 FDG) PET/CT is being used for various cancer types in indication with staging, re-staging, and evaluation of the treatment response (7,8). Thus, the incidence of thyroid incidentalomas detected by FDG-PET/CT in cancer patients have been increasing in recent years. As known, FDG is a glucose analogue, and its uptake is increased in most of the malignant tissues. On the other hand, increased uptake can also be observed in some benign cases (9), leading difficulties in characterization. Most of the patients undergo FDG-PET/CT already have malignant disease, and the incidental thyroid nodule can be related either to

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metastases or primary thyroidal carcinoma. In addition, benign thyroidal nodules also may show increased FDG uptake. The defined three different situation require sdifferent clinical approaches. Nodule characterization must be performed as soon as possible, with the minimal invasive diagnostic techniques. We aimed to determine whether the thyroidal incidentalomas, detected in FDG-PET/CT can be characterized without invasive procedures. If this is possible, it contributes time and cost saving with decreased frequency of invasive procedures. It may also provide faster initiation of the therapy.

## MATERIALS and METHODS

### Patients

After the ethical committee approval, patients who underwent 18F-FDG-PET/CT due to diagnosis of malignant tumor or suspicious malignancy between January 2013 and December 2017 were analyzed retrospectively. TI was detected 235 out of 5004 patients. One hundred and ninety-one patients were excluded from the study due to refusing further thyroidal examination, or failure of follow-up. Consequently, 44 patients were included in the study.

### F-18 FDG-PET/CT Imaging

Following the 12 hours of fasting, pre-imaging glucose levels were measured in venous blood sample. If it was less than 200 mg/dl, 7-8 millicuries (mCi) of 18F-FDG were administered intravenously. Following the injection, CT imaging (care dose) was performed at the 60±5th minute. Then PET imaging was performed from vertex to the midthigh in 7–8 bed positions for 2 minutes each. Iterative reconstruction was performed on the raw PET images to create axial, sagittal, and coronal slices.

### Evaluation of Thyroid Incidentaloma

As a routine procedure in our center, patients with SUVmax values higher than the normal thyroidal background underwent cytological examination unless contraindicated. If two subsequent cytology were negative, nodule accepted as benign. If cytology result was suspected or malignant, we confirmed it by histopathological examination. For these patients, histopathological results were accepted as definite diagnosis.

### Statistical Analysis

SPSS version 15.0 software was used for data analysis. Normal distribution of the variables was analyzed using histogram graphs and Kolmogorov–Smirnov test. Mean, standard deviation, and median values were used in the presentation of descriptive analyses. When evaluating variables showing normal distribution (parametric) between groups, the *t*-test was used for independent groups. In the case of non-normal distribution, paired groups were evaluated using the Mann–Whitney *U*-test. Fisher's exact tests were used in the comparisons of categorical variables. ROC curve analysis was performed for malignancy detection according to nodule size and nodule SUVmax values. Values of p less than 0.05 were considered statistically significant.

## RESULTS

Thirty patients (68.2%) were female. Mean age was 63.1±13.2 years. Nodules are located bilaterally in 13.6%, in isthmus in 4.6%, in right lobe in 45.5%, and left lobe in 36.3% of the patients. Two negative cytological results obtained in 60.5% of them. Suspicious findings, or atypia of undetermined significance were detected in 36.8%. Malignant thyroidal pathologies were detected in 13 (29.5%) patients. The histopathology result rates for benign nodule, papillary carcinoma, follicular carcinoma, malignant mesenchymal tumor, and anaplastic carcinoma were 30, 55, 5, 5, and 5%, respectively. Mean nodule size was 2.1 ± 1.6cm and mean SUVmax value was 8.3 ± 7.5. Results were summarized in Table-1.

**Table 1. Comparison of the some demographic, morphological and metabolic features of malignant and benign insidentalomas**

| | | n | % |
|---|---|---|---|
| Sex | Male | 14 | (32.8) |
| | Female | 30 | (67.2) |
| Localization | Bilateral | 6 | (13.6) |
| | Isthmus | 2 | (4.6) |
| | Right lobe | 20 | (45.5) |
| | Left lobe | 16 | (36.3) |
| Fine Needle Aspiration Biopsy Results | Negative | 23 | (60.5) |
| | Suspicious/ atypia of undetermined significance | 14 | (36.8) |
| | Thyroiditis | 1 | (2.6) |
| Histopathological Results | Benign | 6 | (30.0) |
| | Papillary Carcinoma | 11 | (55.0) |
| | Follicular carcinoma | 1 | (5.0) |
| | Malignant mesenchymal tumor | 1 | (5.0) |
| | Anaplastic carcinoma | 1 | (5.0) |

**Table 2. Comparison of the some demographic, morphological and metabolic features of malignant and benign insidentalomas**

| | Diagnosis | | | | p |
|---|---|---|---|---|---|
| | Benign | | Malignant | | |
| Age | 64.0 ±12.3 | (43.0-74.0) | 61.3 ±14.4 | (19.0-73.0) | 0.709 |
| Nodule size | 1.8 ±.8 | (1.0-3.2) | 2.5 ±1.8 | (1.0-6.5) | 0.448 |
| Nodule SUVmax | 6.1 ±3.0 | (2.9-9.9) | 10.1 ±7.8 | (1.2-33.8) | 0.280 |

**Table 3. The results of ROC analysis of the nodüle size and SUVmax value**

| | Area under the ROC curve | %95 Confidence Interval | | p |
|---|---|---|---|---|
| | | Low | High | |
| Nodule size | 0.531 | 0.253 | 0.809 | 0.844 |
| Nodule SUVmax | 0.738 | 0.505 | 0.972 | 0.127 |

There were not any statistically significant differences between malign and benign thyroidal incidentalomas in terms of patient age, nodule size, and SUVmax values. (Table-2) According to ROC analysis we could not find a cut-off value for malignancy detection in size or SUVmax (Table-3). Consequent results were obtained for papillary carcinomas as a specific subgroup (Table-4).

## DISCUSSION

The prevalence of thyroidal nodules were reported between 4- 50%, depending on age, race and environmental factors, in general population (1, 2). Incidentalomas of thyroid gland have being detected frequently nowadays. This also occur for cancer patients which, is a special group. One of the most important problem is quick and accurate characterization of incidentalomas for this special group. If this characterization can be performed by FDG-PET/CT without invasive methods, we may have a chance to initiate the therapy more rapidly. This may contribute saving time and cost. The detection rate of incidentalomas by FDG-PET/CT were reported between 1.2-10.1% in various studies (10-13). Our results were consistent with the literature, which is 4.7%. The main feature of thyroidal incidentalomas detected by FDG-PET/CT is the high rate of malignancy compared to the other imaging modalities. The global malignancy rate of the thyroidal nodules was reported as between 4.0-6.5%. On the other hand, it was reported between 15.2-40.7% in FDG-PET/CT (9, 14-19). In our patient population, 29.5% of the incidentalomas were malignant, similar to the literature.

The important point is whether FDG-PET/CT can accurately characterize the nodule malignancy. As known, SUVmax is a semiquantitative PET parameter reflecting the metabolic activity of tissues, and increases in most of malignant tissues and some inflammatory/benign lesions (13). It is still controversial whether SUVmax value can distinguish malignant TI from benign ones. Soelberg et al. reported that, FDG uptake is higher in malignant thyroidal lesions compared to the benign ones (20). In a study published in 2015, mean SUVmax values of malignant nodules versus benign nodules was found 4.7 vs 2.8.; which was reported statistically significant (1). Kim et al. calculated the mean SUVmax value as 4.5 for malignant incidentalomas, and 3.08 for benign ones (21). Conversely, there were also studies reporting any significant difference between SUVmax values of benign and malignant nodules (22,23). In our study, mean SUVmax value was found 10.1 for malignant incidentalomas, and 6.1 for benign ones. The difference was not statistically significant (p = 0.12). Therefore, we could not find any reliable cut-off value according to the ROC analysis. Although some studies have reported certain cut-off values, they were far from being satisfactory. For example, Pagano et al determined SUVmax value higher than 5.0 as a cut-off value of malignancy. The specificity was found as 86.7%, and positive predictive value 50% (24). Kim et al accepted the cut-off value of SUVmax higher than 4.46. Authors calculated 51.3% sensitivity with 43.2% positive predictive value (21).

On the other hand, although mean SUVmax value of malignant incidentalomas was higher than benign ones' in some studies, the overlap between the nodules was also important. Thus, Jamsek et al reported a benign adenoma's mean SUVmax value as 8.9, and papillary thyroid carcinoma's as 2.8 (18). Another study also found similar results (25). However, Kang et al. reported that, malignant and benign nodules may be distinguished by using SUVmax (26). We found significant overlap between malignant and benign thyroidal incidentalomas which is similar to Jamsek et al's results. According to our results, SUVmax values of all benign incidentalomas were higher than two papillary carcinomas' SUVmax values. Interestingly, there was a wide range of SUVmax values of differentiated thyroidal carcinomas in our study (1.2 to 16.3). Some authors reported that, this might be caused due to perithyroidal, lymphovascular invasion or peritumoral inflammation (27, 28). In our opinion, more prospective, randomized studies are required to clarify this issue.

We also could not find any significant relationship with

age and nodule size. Consequent results were found in the literature (1, 29), an interesting result was reported by Kim et al. Authors found that, malignant thyroidal incidentalomas were significantly smaller than benign ones (22).

This was a retrospective research, inherently it had some limitations, firstly for data collection. Secondly, although we had a large patient population at the beginning, pathological examination could not be performed most of the patients. Thirdly, approximately 55.5% of the patients were diagnosed by cytological examination. However, depending on the method and physician's experience, false positivity rate of this method was reported between 0.0% and 5.7%, and false negativity was reported between 0% and 5% (30). We believe that, the second sampling in benign cases increased our results' reliability.

Malignant and benign thyroid nodules could not be characterized with SUVmax or nodule size in this research. In conclusion, it would be appropriate to perform cytological examination for patients with TIs. We recommended, if a patient's cytological result is suspicious or malignant, histopathological examination must be performed. If result is benign, it must be confirmed by a second cytological examination. If two subsequent cytological examinations are benign, patient must undergo close follow-up.

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