

## The Role of 18F-Fluorodeoxyglucose Positron Emission Tomography in the Diagnosis of Incidental Thyroid Lesions

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### Abstract

**Objective:** The aim of this study was to determine the diagnostic accuracy of incidental FDG-PET/CT uptake in the thyroid in patients with cancers of nonthyroidal origin, in order to reduce the number of thyroidectomies performed on nodules that subsequently proved to be benign.

**Material and methods:** From January to September 2011 a total of 2510 patients were evaluated at our institution with whole-body FDG-PET. The studies were done for a variety of diagnoses including metastatic work-up for lymphoma, head and neck cancer, and other nonthyroidal malignant nodules. 30 patients were identified with incidental focal or diffuse uptake in thyroid bed. All patients underwent measurement of serum level of thyroid hormones and ultrasonography (US). While the patients with focal uptake underwent fine needle aspiration biopsy, FNAB.

**Results:** PET incidentaloma was observed in 30 patients (0.12% of the whole population) with normal thyroid functions and there weren't known clinical manifestations of thyroid disease. FDG PET uptake pattern was diffuse in 8 patients (26.7%) and focal in 22 patients (73.3%).  $SUV_{max}$  was included between 2.5 and 20. The patients with focal uptake underwent FNAB which demonstrated 4 patients with TIR1 (18.2%), 3 patients with TIR2 (13.6%), 11 patients with TIR3 (50%), 2 patients with TIR4 (9.1%), 1 patient with TIR5 (4.5) and 1 patient with TIR6 (4.5%). All 4 patients with TIR4, TIR5 and TIR6 underwent to thyroidectomy and the final diagnosis was papillary carcinoma.

**Conclusions:** The results of this study suggest that incidentally found thyroid lesions by FDG-PET/CT, especially a focal FDG uptake and a high SUV, have a high probability of thyroid malignancy.

**Keywords:** Thyroid nodules; Thyroid incidentalomas

**Abbreviations:** CT: Computed Tomography; FDG-PET: <sup>18</sup>F-fluorodeoxyglucose Positron Emission Tomography; MRI: Magnetic Resonance Imaging; SUV: Standard Uptake Value;  $SUV_{max}$ : Maximum SUV; US: Ultrasonography

### Introduction

<sup>18</sup>F-Fluorodeoxyglucose positron emission tomography (FDG-PET) is a non invasive method for screening the whole body for various kinds of malignancies that show increased glucose utilization compared with normal tissues [1,2].

This technique has been suggested as an appropriate tool for differential diagnosis of benign and malignant lesions in the preoperative evaluation of thyroid nodules cytologically diagnosed as follicular neoplasm [1,3-6]. Furthermore, this functional imaging technique has shown an important role in the detection of incidentally found thyroid lesions [3]. Incidentalomas of the thyroid are defined as thyroid lesions identified by radiological imaging, such as ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) for nonthyroid disease [7-9]. The normal thyroid gland is usually not visualized through a FDG-PET scan and the uptake of the FDG in is homogenous and of low intensity [10]. The number of thyroid incidentalomas identified by FDG-PET (PET incidentaloma) is increasing. According to the accumulation pattern, PET incidentaloma is classified as diffuse and focal. A diffuse pattern is generally considered benign since most cases are autoimmune thyroiditis; on the contrary a focal PET incidentaloma is a thyroid nodule, such as benign adenoma or cancer [10].

The maximum standardized uptake value ( $SUV_{max}$ ) is used as a semiquantitative indicator of FDG uptake, but  $SUV_{max}$  is influenced by many factors, including glucose transporter expression, viable cell number, tumor perfusion and inflammatory cells [10].

The presence of a focal lesion characterized by increase in metabolic activity and by a  $SUV_{max} \geq 2.5$  is highly suspicious for malignancy.

It has been reported that focal thyroid PET incidentalomas are associated with a high probability of malignancy, ranging from about 30% to 50% [11-14].

The number of thyroid cancers increases with age in both men and women [15].

The aim of this study was to determine the diagnostic accuracy of incidental FDG-PET/CT focal uptake in the thyroid in patients with cancers of nonthyroidal origin, in order to reduce the number of thyroidectomies performed on nodules that subsequently proved to be benign.

We examined 30 patients who underwent to FDG-PET exam for nonthyroid malignities in which focal PET incidentalomas were found. The patients with focal uptake underwent to fine needle aspiration biopsy (FNAB) in order to determinate the cytology of the nodule (Figure 6b).

Indications for thyroid FNAB are: single solid hypoechoic nodule >1 cm (Figure 6a), irregular margins, vascularization, intranodular and calcifications, complicated nodules with mixed echo-structure, nodules in patient with MEN2, previous history of thyroid cancer or cervical radiation, nodule in pregnancy patient.

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FNAB has become the accepted tool to evaluate thyroid lesions to reach an understandable diagnoses and a correct therapeutic strategy [16].

The categories recommended by the Bethesda System are:

- TIR1 non-diagnostic or unsatisfactory: thyroid cysts containing histiocytes, but with little or no follicular cells, should be considered non-diagnostic and interpreted as “cyst fluid only.”
- TIR2 benign: this category includes adenomatoid/hyperplastic nodules, colloid nodules, nodules associated with Grave’s disease, and thyroiditis. The risk of malignancy in this group of diagnoses is approximately 0-3% with a false negative rate between 1-10% [17].
- TIR3 atypia of undetermined significance (or follicular lesion of undetermined significance): samples into this category should contain cells (follicular, lymphoid, others) exhibiting architectural and/or cytologic atypia.
- TIR4 atypia follicular (i.e. architectural) and not cellular, “Follicular Lesion of Undetermined Significance”. The risk for malignancy in this category is approximately 5-15% [17].
- TIR5 suspicious for malignancy: the malignancy considered most in this category is papillary carcinoma. Other malignancies include medullary thyroid carcinoma, lymphoma, and metastatic malignancies. The risk for malignancy in this category is approximately 60-75% [17].
- TIR6 malignant: this category includes malignancies exhibiting the diagnostic features characteristic of a given malignancy (e.g., papillary carcinoma, medullary carcinoma, lymphoma, and metastatic carcinoma). The risk for malignancy is 97-99% [17]. Surgical intervention is recommended for patient diagnosed with papillary carcinoma. The extent of the surgery, lobectomy or total thyroidectomy, depends on several factors (i.e., size of the lesion, patient’s age, sonographic appearance of the lesion).

## Subjects and Methods

### Subjects

From January to September 2011 a total of 2510 patients were evaluated at our institution with whole-body FDG-PET. 30 patients were identified with incidental focal or diffuse uptake in thyroid bed (8 males and 22 females; mean age, 66 ± 12 years).

All patients had a previous history of cancer, 4 breast cancer 20 lung cancer, 4 lymphoma, 2 colon cancer, and none shown clinical manifestations known of thyroid disease such as dyspnoea, cough, regional lymphadenopathy, vocal cord paralysis.

No subjects have been treated with cervical radiation.

All patients with focal or diffuse uptake underwent measurement of serum level of thyroid stimulating hormone (TSH), free thyroxine (FT3, FT4), anti-thyroperoxidase antibody and anti-thyroglobulin antibody.

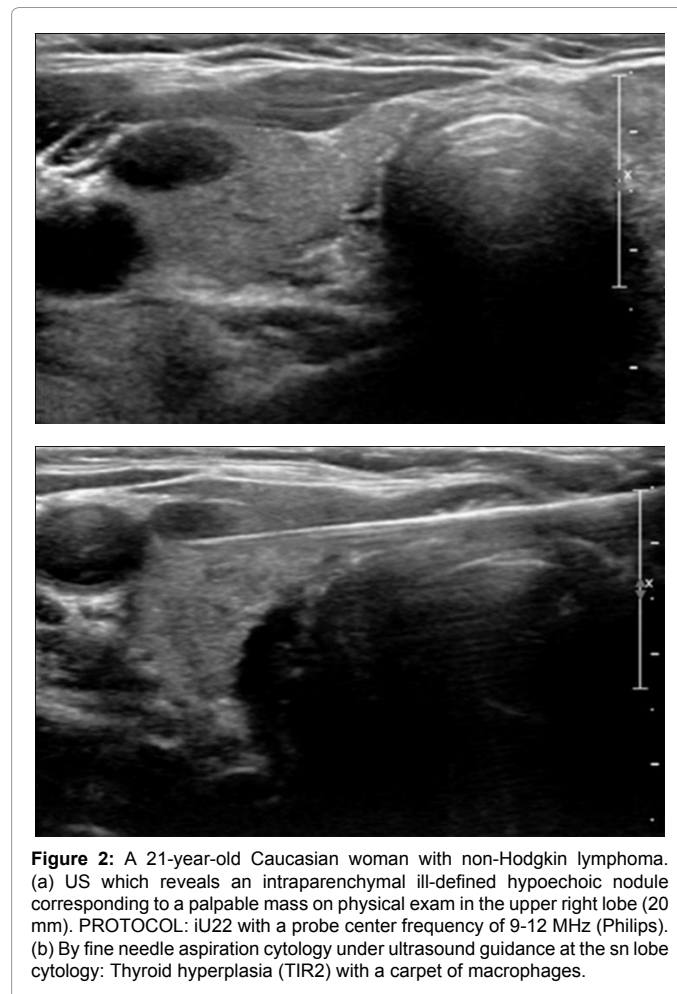
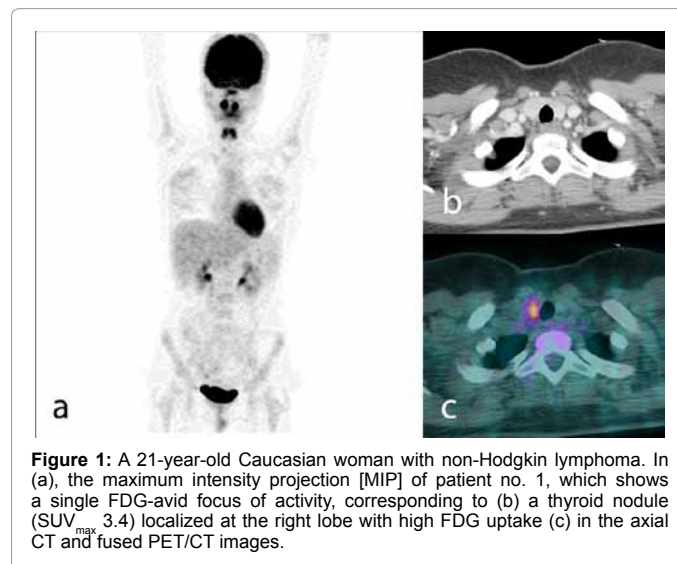
When focal uptake was detected in the thyroid, the patients underwent ultrasonography (US) (Figure 4a), FNAB (Figure 4b).

### Methods

All patients fasted for at least 6 h before F18-FDG IV injection; serum glucose level was normal in all of them. Patients were injected with 370-450 MBq of F18-FDG IV and hydrated (500 ml of IV saline

sodium chloride (NaCl) 0.9%) to reduce pooling of the radiotracer in the kidneys. About 600 cc of contrast solution were administered per os to opacify the intestinal loops.

The PET-CT scan begins 40-60 minutes after the radiotracer injection.



The PET-CT system Discovery ST16, (GE Medical Systems, TN, USA) was used. This system combines a high-speed ultra 16-detector-row (912 detectors per row) CT unit and a PET scanner with 10080 bismuth germanates (BGO) crystals in 24 rings. A low amperage CT scan was acquired for attenuation correction of PET images (80 mA, 140 kV, field of view (FOV) about 420-500 mm, CT slice thickness 3.75). After non-enhanced CT, total-body PET examination in the caudocranial direction, from upper thighs to vertex, was performed (two bed positions, 4 min per bed). Images were reconstructed using ordered subsets expectation maximization (OS-EM) algorithm after 25-30 min of acquisition. Contrast-enhanced CT scan (120-140 kV, automatic milliamperage (limit 330-350 mA), thickness 3.750 mm (reconstructed at 1.25 mm), acquisition mode 27.50/1.375:1, gantry rotation time 0.6 s, large FOV, matrix 512x512] was carried out with IV administration of nonionic iodinated contrast material (100-120 ml, 370 mgI/ml, at 2-2.5 ml/s), obtaining two successive stacks of scans. The first comprised the upper abdomen with a 30-s delay from the injection onset; the second extended from the neck to the pelvis with a 60-s delay.

Region of interest was drawn over the tumors on the transverse slice and the maximum SUVs ( $SUV_{max}$ ) of the thyroid lesions were recorded. The lesions with a  $SUV_{max} > 2.5$  were considered positive for the presence of the disease in accordance with similar previous studies.

FNAB was executed using a 21-gauge needle and a 10-ml syringe under US guidance with iU22 with a probe center frequency of 5-12 Hz (Philips). Two passes were made per nodule. Samples obtained by FNAB were examined by pathologists.

The cytologic sample in fixative liquid is prepared with thin-prep method and all aspirates were stained with Papanicolaou staining.

The nodules had a diameter included between 1 and 4 cm.

The interval between 18F-FDG PET and FNAB was at least 1 month.

All patients with TIR4-5-6 at cytological examination underwent to thyroidectomy.

## Results

PET incidentaloma was observed in 30 patients (8 males and 22 females; mean age,  $66 \pm 12$  years) and  $SUV_{max}$  ranged from 2.5 to 20.

Thyroid functions were normal in all 30 subjects and there were no clinical manifestations of thyroid disease.

FDG-PET uptake pattern was diffuse in 8 patients (26.7%) and focal in 22 patients (73.3%).

The 8 patients with a diffuse uptake of FDG underwent measurement of serum level of thyroid hormones and ultrasonography (US). The final diagnosis was autoimmune thyroiditis.

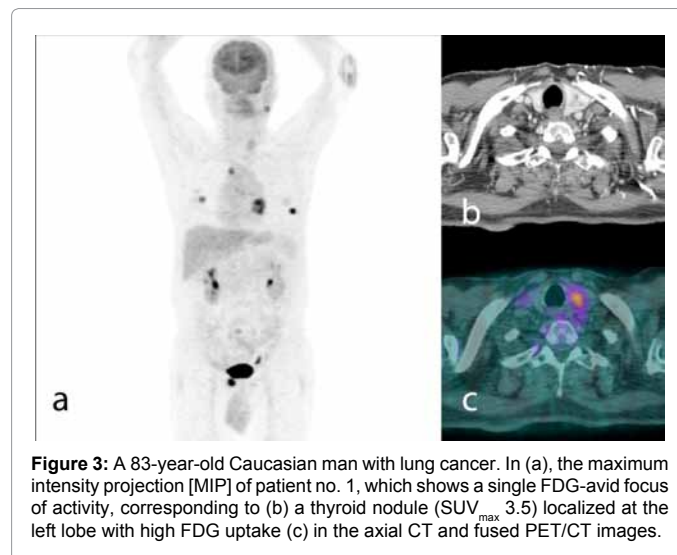
The patients with focal uptake underwent FNAB 4 patients with TIR1 (18.2%), 3 patients with TIR2 (13.6%) (Figures 2b), 11 patients with TIR3 (50%), 2 patients with TIR4 (9.1%) (Figure 4b), 1 patient with TIR5 (4.5) and 1 patient with TIR6 (4.5%) (Figure 6b). All 4 patients with TIR4, TIR5 and TIR6 underwent to thyroidectomy and the final diagnosis was papillary carcinoma.

## Discussion

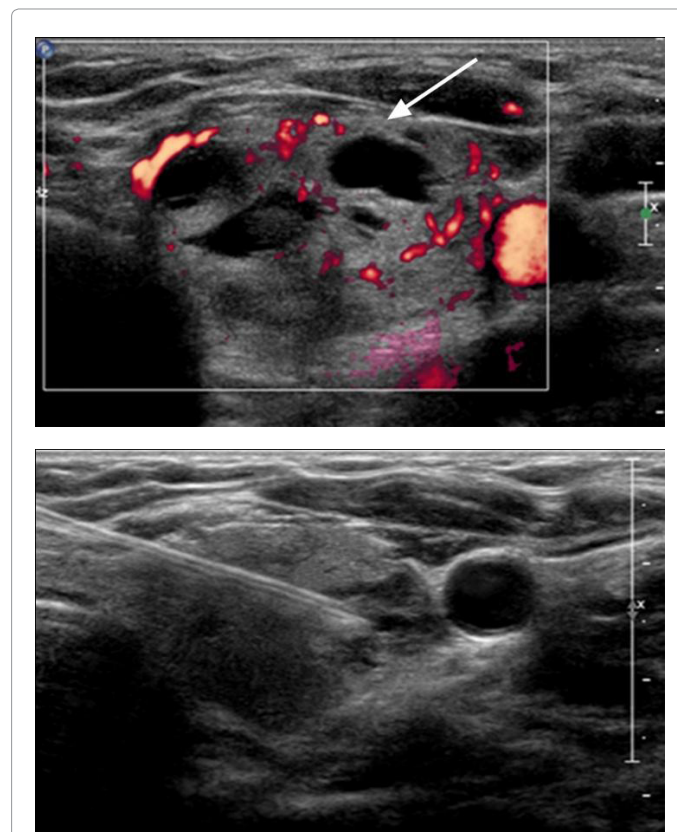
In recent years the use of FDG-PET/TC for the evaluation of malignant tumors has increased significantly. Consequently it has also increased the incidence of incidentalomas.

Thyroid nodules are one of most common endocrine disorders. The risk of malignancy in generalized thyroid swelling is about 3% and in solitary thyroid nodule it is about 15% [18].

The incidence of thyroid cancer is increasing [19].



**Figure 3:** A 83-year-old Caucasian man with lung cancer. In (a), the maximum intensity projection [MIP] of patient no. 1, which shows a single FDG-avid focus of activity, corresponding to (b) a thyroid nodule ( $SUV_{max}$  3.5) localized at the left lobe with high FDG uptake (c) in the axial CT and fused PET/CT images.



**Figure 4:** A 83-year-old Caucasian woman with lung cancer. (a) US which reveals an intraparenchymal ill-defined hypoechoic hypervascularized nodule (arrow) in the lower left lobe. PROTOCOL: iU22 with a probe center frequency of 9-12 MHz (Philips). (b) Running FNAC: ultrasound-guided fine needle aspiration procedure, the ultrasound image displays the location of the needle within the nodular mass in the middle third of left. Cytology (TIR4): follicular carcinoma.

Diagnostic technology used to study thyroid nodules are ultrasonography, CT and MRI, and frequently encounter incidental detection of thyroid nodules during examination of the neck for purposes other than nonthyroidal origin disease [20-22]. To confirm the etiology of thyroid nodules it is used fine needle aspiration cytology or biopsy with US [22-24].

Because there is a risk for malignant growth associated with these lesions, appropriate management guidelines and protocols need to be designed to adequately treat patients with focal "incidentalomas" to prevent undertreatment or unnecessary thyroidectomy.

In our study a total of 2510 patients were evaluated with whole-body FDG-PET. In 30 Patients incidental focal or diffuse uptake in thyroid bed were identified (8 males and 22 female, mean age,  $66 \pm 12$  years).

FDG-PET uptake pattern was diffuse in 8 patients and focal in 22 patients (Figures 1a,b,c and Figures 3a,b,c and Figures 5a,b,c)

All patients with diffuse uptake underwent measurement of serum level of thyroid stimulating hormone (TSH), free thyroxine (FT3, FT4), anti-thyroperoxidase antibody and anti-thyroglobulin antibody and ultrasound examinations of the thyroid gland that showed benign disease such as thyroiditis and multinodular goiter.

The 22 patients with focal uptake underwent ultrasonography (US) and FNAB, 4 of them had respectively 2 TIR4 (Figure 4b), 1 TIR5 and 1 TIR6 (Figure 6b) and underwent to thyroidectomy. The final diagnosis was papillary carcinoma.

Several studies have reported that focal thyroid PET incidentalomas are associated with a high probability of malignancy. For example Cohen et al. [25] in a study on patients whom underwent a FDG PET examination for cancer of nonthyroidal origin, 102 demonstrated thyroid incidentalomas (2.3%); 15 (21%) patients had thyroid biopsy: 7 (47%) with thyroid cancer, 6 (40%) with nodular hyperplasia, 1 with thyroiditis and 1 with atypical cells of indeterminate origin. Of 102 patients, 71 had a focal area of increased FDG uptake and 31 patients had marked and diffuse FDG uptake involving the entire thyroid gland. The authors had concluded that a focal uptake of FDG in thyroid incidentaloma indicates a high risk of malignancy.

Similarly, Kang et al. [1] in a study on 1.330 subjects whom underwent FDG-PET for metastasis evaluation and cancer screening, had found 29 thyroid FDG-PET incidentaloma: 21 showed a focal uptake of FDG and 8 a diffuse increased FDG uptake. Four of 15 focal incidentalomas (26.7%) were papillary thyroid cancer.

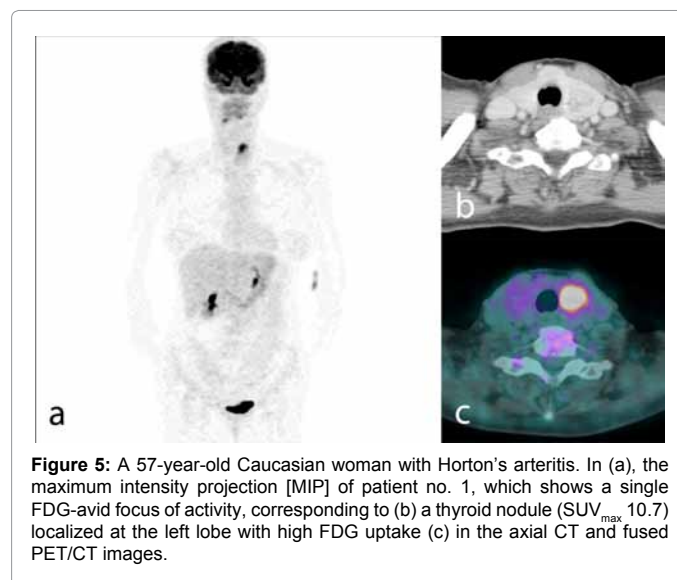
A similar study Eloy et al. [3] had demonstrated that focal FDG uptake in thyroid nodules correlates with high risk of thyroid malignancy: of 18 patients, 5 had incidental focal FDG-PET/CT uptake in the thyroid gland and on final pathologic findings those were papillary carcinoma.

Another study on 1102 patients demonstrated that diffuse thyroidal FDG uptake may be an indicator of chronic thyroiditis [26].

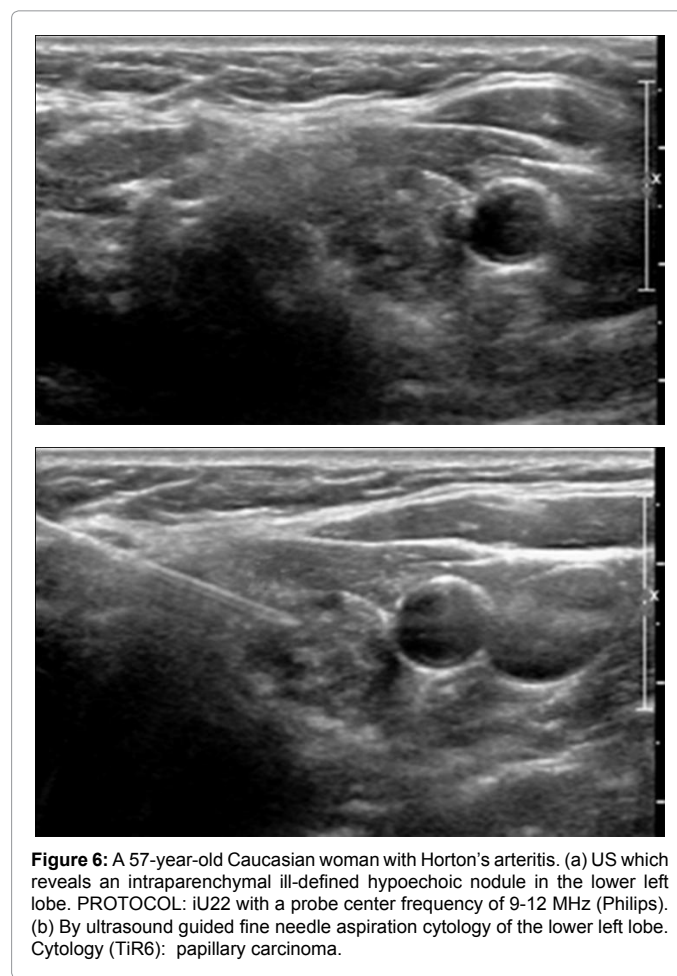
Sebastianes et al. [4] in a study on 42 patients with cytologically indeterminate thyroid nodules, it was performed a FDG PET which demonstrated that a focal uptake of FDG correlated with a higher risk of malignancy: 11 patients had malignant nodules corresponding to increased focal FDG uptake, 39% of the patients with benign thyroid nodules had no focal 18F-FDG uptake. This study also demonstrated that the preoperative use of 18F-FDG PET would result in a significant reduction in the number of thyroidectomies performed in patients

with benign lesions: the pre-PET probability of cancer was 26.2% and this probability increased to 36.7% after PET for those patients whose exam showed focal uptake.

Those data are confirmed in other studies, such as De Geus-Oei et al. [5] and Kresnik et al. [6] in which FDG PET was used in



**Figure 5:** A 57-year-old Caucasian woman with Horton's arteritis. In (a), the maximum intensity projection [MIP] of patient no. 1, which shows a single FDG-avid focus of activity, corresponding to (b) a thyroid nodule ( $SUV_{max}$  10.7) localized at the left lobe with high FDG uptake (c) in the axial CT and fused PET/CT images.



**Figure 6:** A 57-year-old Caucasian woman with Horton's arteritis. (a) US which reveals an intraparenchymal ill-defined hypoechoic nodule in the lower left lobe. PROTOCOL: iU22 with a probe center frequency of 9-12 MHz (Philips). (b) By ultrasound guided fine needle aspiration cytology of the lower left lobe. Cytology (TIR6): papillary carcinoma.

the preoperative evaluation of thyroid nodules with indeterminate cytological results and patients with benign nodules had no focal FDG uptake.

Our results confirm the findings of several studies [16,17,27-33] that suggest that 18F-FDG PET may have a very high positive predictive value for detecting malignancy in the preoperative evaluation of thyroid nodules.

Thus, we think that the risks of cancer for focal and diffuse thyroid incidentaloma by FDG-PET are quite different.

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