

The incidence of ¹⁸F-FDG PET/CT thyroid incidentalomas and the prevalence of malignancy: a prospective study

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Background/aim: To determine the prevalence of malignancy in thyroid incidentalomas (TIs) detected by fluorine-18 fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography/computed tomography (PET/CT).

Materials and methods: ¹⁸F-FDG PET/CT images were evaluated prospectively for the presence of thyroid uptake. The patients with a TI were evaluated by an endocrinologist according to the predefined diagnostic algorithm. The final diagnosis was obtained clinically and/or by pathology.

Results: TI was detected in 4.2% of 4204 patients. A malignant thyroid nodule was diagnosed in 29% and 33% of the focal and diffuse-focal uptake groups, respectively. However, no malignancy was detected in the diffuse uptake group. The standardized maximum uptake values (SUVmax) of the nodules were significantly higher in patients with thyroid malignancy than in patients with benign nodules ($P = 0.006$). The calculated cut-off value of SUVmax for malignancy was 3.5. In 2 patients in whom the cytopathological diagnosis was benign, malignancy was diagnosed after total thyroidectomy.

Conclusion: A malignant nodule was present in one-third of the patients with focal or diffuse-focal uptake. A SUVmax value of 3.5 was considered as a cut-off value for the differentiation of a malignant lesion. Benign cytology in fine-needle aspiration biopsy for 2 patients underestimated a thyroid malignancy.

Key words: ¹⁸F-FDG, PET scan, thyroid, cancer, second primary, prevalence

1. Introduction

A thyroid incidentaloma (TI) is the incidental detection of lesion/lesions in the thyroid bed by a fluorine-18 fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography/computed tomography (PET/CT) scan that has been performed for indications other than thyroid scanning (1–3).

The ¹⁸F-FDG PET/CT scan is mostly used for oncologic imaging (3–6). In physiologic conditions, ¹⁸F-FDG, which demonstrates the glucose metabolism of the cells, is either slightly or not accumulated by the thyroid gland. Rarely, a TI may be observed by PET/CT scan. Its incidence has been indicated to range between 1.2% and 4.3% in the

literature (2–4). Thyroid carcinoma was found in 14% to 63.6% of patients with focal uptake, whereas diffuse hyperthyroidism or thyroiditis was the final diagnosis in patients with diffuse uptake (1–7). The malignancy rates for focal and diffuse uptake in a systematic review were 34.8% and 4.4%, respectively (8).

The studies in the literature, excluding a few studies performed on healthy volunteers, have retrospectively investigated the prevalence of malignancy in ¹⁸F-FDG TI patients. In the present study, we aimed to prospectively investigate the incidence of TIs in patients with a known primary tumor other than the thyroid carcinomas, and the prevalence of malignancy in TI.

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2. Materials and methods

2.1. Study design and inclusion and exclusion criteria

The study was approved by the local ethics committee of our institution in 2010. Oncologic ^{18}F -FDG PET/CT scans were prospectively evaluated for the presence of any thyroidal ^{18}F -FDG uptake until the end of 2012. The patients were then referred to the endocrinology division for clinical evaluation of thyroid function and morphology.

The inclusion criterion was the presence of any ^{18}F -FDG TI. The exclusion criteria were short life expectancy (<1 year) due to the primary cancer, the refusal to participate by the patient at any time during the study, and failure to reach a final clinical and/or cytological diagnosis.

2.2. ^{18}F -FDG PET/CT imaging protocol

Blood glucose levels of the patients were under 200 mg/dL following a minimum of 6 h of fasting. The ^{18}F -FDG dose was adapted according to the patient's body weight. The individual patient dose was 210 to 473 MBq. The PET was obtained from the vertex to the midhigh using a Philips Gemini TF (USA). The CT images were obtained with a 2-min bed time in 6 to 7 bed positions. The CT component was used for attenuation correction. The CT scan settings were 50–100 mAs and 120 kVp. A slice thickness of 5 mm, a rotation time of 0.5 s, and a 512×512 matrix were used.

The ^{18}F -FDG uptake in the thyroid was classified as focal, diffuse, and diffuse-focal. The maximum standardized uptake values (SUVmax) were recorded. The ^{18}F -FDG TI was mapped using the CT images according to the side (right or left) and the location (upper, middle, or lower lobe) of the nodule. The nodules on CT images corresponding to the ^{18}F -FDG uptake, as well as the SUVmax of all focal lesions, were recorded. The patients were then referred to the endocrinologist.

2.3. Clinical evaluation

The endocrinologist examined the patients clinically and asked for the necessary laboratory tests including a thyroid/neck ultrasonography (USG).

- A fine-needle aspiration biopsy (FNAB) was recommended for the nodules with ^{18}F -FDG uptake when the nodule was suitable for biopsy (at least 5–8 mm in size and not posteriorly located).
- Patients with no thyroid nodules on USG or with small nodules not suitable for biopsy were followed clinically.
- A FNAB was also recommended for the nodules without ^{18}F -FDG uptake but suspicious for malignancy on USG.
- A repeat FNAB was recommended if the result was nondiagnostic or unsatisfactory.
- A thyroidectomy was recommended if FNAB showed malignancy or if there was suspicion of a malignancy.

- Patients with benign cytology were followed clinically and with USG at least once for in intervals of 9–12 months.

The final clinical decision was made either histopathologically or clinically.

2.4. The USG protocol

The images were obtained with a Philips HDI 5000 ultrasound system (USA) in 2D mode and 7–12.5 MHz resolution. The sizes of both thyroid lobes and the isthmus were measured. The echogenicity and the vascularity of the gland were evaluated and reported. Size and content (cystic, solid, or both) of the nodules, their borders, their echogenicity, vascularity, and the presence of halos and/or calcifications in the nodules were also reported. The criteria of malignancy in the nodules were hypoechoogenicity, solidity, increased internal vascularity, presence of microcalcifications in a nodule larger than 1 cm, and absence of a thin halo (9).

2.5. Fine needle aspiration biopsy and cytopathological examination

Specimens were obtained by a 21-gauge needle. Air-dried slides were stained with Giemsa stain, while those fixed in 96% alcohol were stained with hematoxylin and eosin. The cytopathological evaluation was performed according to the Bethesda Classification System of Thyroid Malignancy Risk (10).

3. Results

Among 4204 ^{18}F -FDG PET/CT images obtained during a period of 26 months, ^{18}F -FDG TI was observed in 178 (4.2%). Sixty-two (34.8%) of the patients were excluded from the study, either because of the short life expectancy or because they refused to participate.

The mean age of the 116 patients included in the study was 60.0 ± 12.6 years (ranging between 23 and 95 years). Seventy-eight patients (67.2%) were female and 38 (32.8%) male. The mean fasting blood glucose level was 110.6 ± 22.7 mg/dL (ranging between 74 and 195).

A focal/multifocal uptake was observed in 68 of the 116 patients (59.0%), while diffuse and diffuse-focal uptake was observed in 35/116 (30.0%) and 13/116 patients (11.0%), respectively.

3.1. The focal ^{18}F -FDG-TI group

There were 86 focal areas in 68 patients with focal ^{18}F -FDG PET TI. A thyroid nodule was detected by USG in 82 of the 86 uptake areas (95.3%). The mean size of the nodules was 20.7 ± 13.1 mm (ranging between 5 and 81 mm). The mean SUVmax value of these nodules was 5.9 ± 4.6 (ranging between 2.2 and 26.2). A FNAB was performed in 42 patients. A final cytopathological or clinical diagnosis was obtained in 38 patients, whereas a final diagnosis could not be obtained in 30, either because of the refusal of

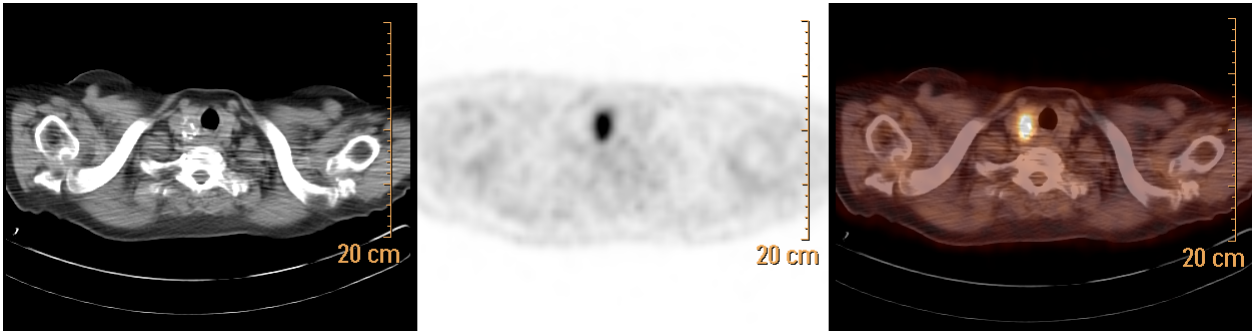


Figure 2. The CT, FDG PET, and fusion images of a patient with a focal ^{18}F -FDG TI.

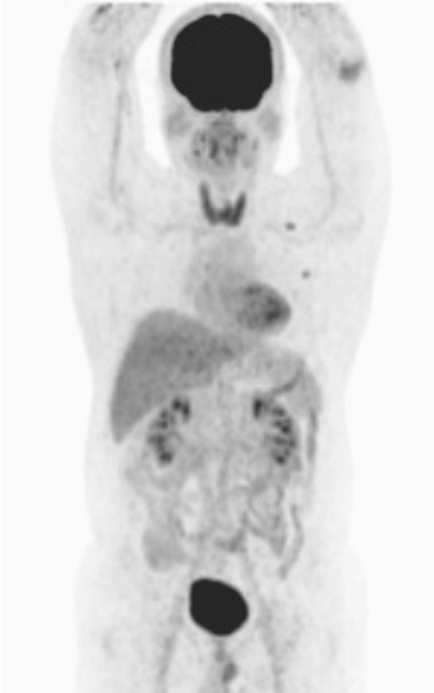


Figure 3. The FDG PET maximum-intensity projection image of a patient with diffuse ^{18}F -FDG TI. The pathologic lymph nodes in the left interpectoral and left axillar region in this patient demonstrate the recurrence of the primary lymphoma.

pattern was present in 13 patients. A final cytopathological or clinical diagnosis was obtained in 12 patients (Figure 1). A malignancy was diagnosed in four. The incidence of malignancy in this group was 33.3% (4/12). Figure 4 demonstrates a patient with a diffuse-focal ^{18}F -FDG TI. There was a focal uptake in the left lobe-isthmus localization (SUVmax: 6.4). A nodule was demonstrated at that localization and did not demonstrate malignancy criteria on USG. The patient refused a FNAB. The patient was excluded from the study.

3.4. Statistical analysis

For statistical analyses, the focal ^{18}F -FDG TI and focal-diffuse ^{18}F -FDG TI groups were pooled together. Thyroid

malignancy was diagnosed in 15 of the 50 patients (30.0%) with focal and focal-diffuse ^{18}F -FDG TI. Findings of patients with proven thyroid malignancy are given in the Table.

The SUVmax values of malignant nodules were statistically different and higher in malignant nodules than in benign ones ($P = 0.006$). The box plot graph of these nodules is given in Figure 5. Upon evaluation of all possible cut-off points, a SUVmax cut-off value of 3.5 was found to be the best value with 73% sensitivity and 66% specificity on ROC curve analysis, in differentiation of malignancy from benign nodules.

The correlations between SUVmax values and the nodule diameters were made using Spearman correlation analysis. There were no correlations between SUVmax values and the nodule diameters in either the benign and malignant groups ($P = 0.060$ and 0.073 , respectively).

4. Discussion

Nodules in the thyroid are not uncommon. The incidence of finding a thyroid nodule on palpation is 2% to 7% (11,12). However, the incidence increases to 14%–46% using USG alone (2,3,13) and 16%–56% using CT or MRI (2,14,15). On autopsy series, the incidence of finding at least one nodule in the thyroid gland is reported to be 50% (16).

In this prospective study, ^{18}F -FDG TI was observed in 4.2% of 4204 oncology patients, which is consistent with previous studies with rates reported to range between 1.1% and 4.3% (1,7,17–23). The incidence of a TI demonstrated by ^{18}F -FDG PET/CT compared to other imaging techniques is rare. This can be explained by the absence of glucose transporter 1 (GLUT1) in the thyroid, which is necessary for the uptake of glucose into the cell across the plasma membranes. The thyroid gland also uses mostly the free fatty acids in spite of glucose for energy metabolism (24). Although a rare finding, ^{18}F -FDG TI is important, because the incidence of malignancy, mostly the primary tumors of the thyroid rather than the metastatic ones, is high in these patients (8).

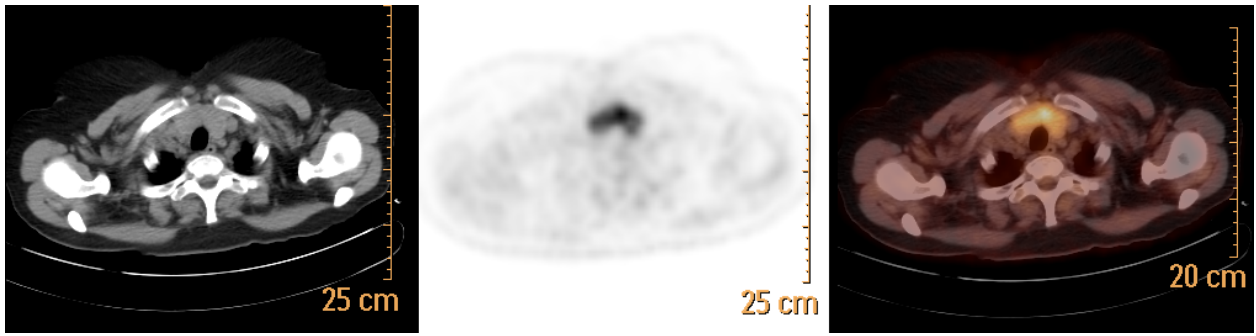


Figure 4. The CT, FDG PET, and fusion images of a patient with a diffuse-focal ¹⁸F-FDG TI.

Table. Characteristics of the patients with a final diagnosis of malignancy.

| No. | Sex | Age | FDG PET | USG | Dx | SUVmax | Pathology | Tumor size (mm) |
|-----|-----|-----|---------|------------|------|---------|------------------|-----------------|
| 1 | F | 62 | Focal | Suspicious | TT | 3.0 | FTC | 24 |
| 2 | F | 44 | Focal | Suspicious | TT | 21.2 | PTC | 30 |
| 3 | F | 72 | Focal | Suspicious | FNAB | 2.9–6.3 | PTC | 19–25 |
| 4 | F | 83 | Focal | Suspicious | FNAB | 22.3 | PTC | 55 |
| 5 | F | 55 | Focal | Benign | TT | 4.8 | PTC | 5 |
| 6 | F | 81 | Focal | Suspicious | TT | 4.6 | PTC | 15 |
| 7 | M | 53 | Focal | Suspicious | TT | 7.9 | PTC | 12 |
| 8 | M | 82 | Focal | Suspicious | FNAB | 16.1 | FTC | 46 |
| 9 | M | 41 | Focal | Benign | TT | 10.8 | PTC | 12 |
| 10 | M | 56 | Focal | Benign | TT | 4.1 | PTC | 3–5 |
| 11 | M | 56 | Focal | Suspicious | TT | 6.3 | PTC | * |
| 12 | F | 65 | Dif-foc | Malignant | FNAB | 7.9 | PTC | 16 |
| 13 | F | 65 | Dif-foc | Suspicious | TT | 3.8–4.8 | PTC | 14 |
| 14 | F | 73 | Dif-foc | Benign | TT | 3.0 | PTC | 12 |
| 15 | F | 95 | Dif-foc | Benign | FNAB | 10.2 | Undifferent. Ca. | 12 |

Dx: Diagnosis, Dif-foc: diffuse and focal, TT: total thyroidectomy, FNAB: fine-needle aspiration biopsy.

Our study is the only prospective one investigating ¹⁸F-FDG TIs in oncologic patients in the literature. The calculated risk of malignancy in our study was 30%, which was similar to two systematic reviews by Soelberg et al. and Shie et al., in which the malignancy rates were 34.8% and 33.2%, respectively (8,25). In contrast to our findings, which are consistent with these systematic reviews, there is great discrepancy in the literature about the prevalence of malignancy in ¹⁸F-FDG TIs. In different studies, which were all retrospective, the reported prevalence ranged between 14.0% and 63.6% (17–22,26,27).

The discrepancy in the prevalence of malignancy may be explained by the difference in ratios of patients with

¹⁸F-FDG TIs in whom a final diagnosis could be reached. The risk of malignancy was 47% in one study where a final diagnosis was obtained only in 15% of the patients with ¹⁸F-FDG TIs (17). In contrast, the risk of malignancy was 15% in healthy volunteers who were imaged for screening. In that study with healthy volunteers, the final diagnosis was obtained (with FNAB and/or surgery) in 83% of the patients (20).

The low risk of malignancy cannot be attributed to the difference in the prevalence of the ¹⁸F-FDG TIs between oncologic patient populations and healthy volunteers because the prevalence was declared to be similar in these groups (28). Nevertheless, the prevalence of malignancy

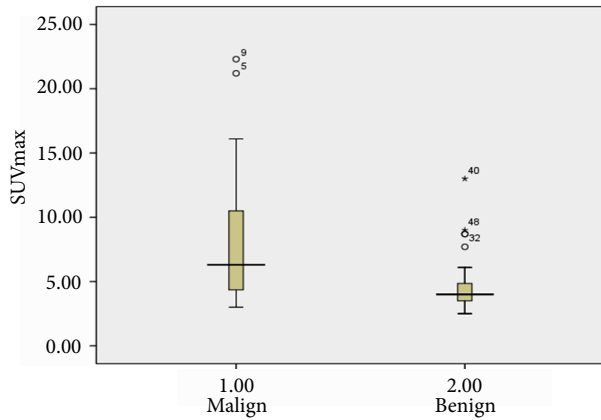


Figure 5. The box plot graph of SUVmax in malignant and benign nodules.

of ^{18}F -FDG TIs can be higher in patients with a known primary tumor than the healthy volunteers owing to the difference in age and sex of the patients. Thyroid cancer incidence increases with increasing age, especially after the third decade, and it is more frequent in females than males. When compared with the study in healthy volunteers (28), the mean patient age was higher in our group.

Geographic differences may also be considered as a possible cause of the different risk ratios. However, in one metaanalysis, there was no significant difference of malignancy in ^{18}F -FDG TI patients between different geographic places (29). The pooled risk of malignancy was 36.2% in that metaanalysis, which was also very close to the findings in our prospective study.

We think that the differences in the risk of malignancy in ^{18}F -FDG TIs are mostly due to the small percentage of the patients with a final diagnosis obtained by the retrospective studies. This seems to create a major patient selection bias. This was also a major limitation of our prospective study. In the presented study, 34.8% (62/178) of patients with an ^{18}F -FDG TI had to be excluded because they either did not accept to participate in the study or their life expectancy was short due to the primary malignancy. As a result, the number of patients with an ^{18}F -FDG TI included in the study decreased significantly. Second, a final diagnosis could not be obtained in 27.6% of the patients (32/116) with ^{18}F -FDG TIs due to the refusal of further tests by the patients. Overall, we obtained a final diagnosis in only 47.2% (84/178) of patients with ^{18}F -FDG TIs.

We had to exclude some of the patients with a FNAB that was suspicious for malignancy because they either refused further examination or thyroid surgery. The malignancy rates in our study group could be higher if we had obtained the final diagnosis for these patients. This seems to be a major handicap while studying oncologic

patients. In a patient with the diagnosis of differentiated thyroid carcinoma as a secondary malignancy, the morbidity and mortality rates were almost always related to the primary malignancy. A second thyroid malignancy, which was mostly in the differentiated group, did not alter the prognosis and the priority of the treatment strategy in these patients. This may be accepted as an inborn limitation for investigating the incidence of malignancy in ^{18}F -FDG PET incidentaloma patients.

The cut-off value of SUVmax for differentiating a malignant from a benign nodule was reported to be 3.8–6.0 in the literature (30–32). We found in this study that a SUVmax cut-off value of 3.5 will distinguish between malignant nodules with a sensitivity of 73% and benign nodules with a specificity of 66%. These values for sensitivity and specificity are consistent with the literature values, ranging between 60% and 80% for sensitivity and 66.1% and 91.0% for specificity (30,33). In our study, the mean SUVmax values of benign and malignant nodules were 4.6 ± 2.2 (ranging between 2.5 and 13) and 8.8 ± 6.2 (ranging between 3.0 and 22.3), respectively. Although this difference was statistically significant ($P < 0.05$), there was a major overlap (Figure 5). This overlap was also apparent in other studies. The declared SUVmax values for malignant and benign lesions were in the ranges of 3.5–17.8 and 2.8–32, respectively, in a study by Brindle et al. (34). There was no significant correlation between SUVmax values and the nodule diameters in our study excluding the dimensions of the nodule as a cause for high ^{18}F -FDG uptake. Instead, the possibility of a poorly differentiated carcinoma is potentially high in ^{18}F -FDG TI patients (35). Considering the overlap and the two malignant cases with a SUVmax value of 3.0, we think that any focal uptake in a nodule must be evaluated to rule out malignancy, regardless of the SUVmax value.

Two patients with focal ^{18}F -FDG TI decided to have a total thyroidectomy, despite benign cytology on FNAB, because the nodules fulfilled the malignancy criteria also on USG. The final diagnosis was papillary thyroid carcinoma in both patients. Tumors were located in nodules with a high ^{18}F -FDG uptake in both patients. A benign cytology according to the Bethesda classification system still has a 0%–3% risk for thyroid malignancy. However, these values are valid for the general population with a pretest probability of 5%–10%. In a study (36), the risk of malignancy of ^{18}F -FDG TIs was 11.3% with a probably benign cytology on FNAB. In patients with a higher pretest probability, the expected malignancy rate with benign cytology will also be high. Therefore, a clinician may evaluate benign cytology cautiously in patients with a high pretest probability. We think that a benign diagnosis by FNAB needs to be interpreted cautiously in patients with risk factors for thyroid malignancy.

In the diffuse ^{18}F -FDG TI group, 31 of the 33 patients with a final diagnosis (94%) had thyroiditis. Only one patient (3%) had Graves' disease. In the last patient (3%) we could not demonstrate any pathology that would explain the diffuse thyroidal uptake of ^{18}F -FDG. Although the thyroid gland commonly uses free fatty acids for energy metabolism, some studies mentioned glucose (37). This may be the explanation for this particular patient. There was no thyroid carcinoma in the diffuse ^{18}F -FDG TI group in our study. Some studies reported a malignancy rate of 1.2%–6.4% in diffuse ^{18}F -FDG PET/CT incidentaloma groups (25,31). In the presented study we categorized the diffuse/focal uptake group separately from the diffuse uptake group and thyroid carcinomas were detected in the diffuse/focal uptake group. This may be the reason for the

absence of any thyroid malignancy in the diffuse uptake group in our study. We think that a thyroid malignancy in a patient with diffuse ^{18}F -FDG PET/CT incidentaloma must be accepted as a false-negative finding if detected.

In conclusion, in this prospective study, we have found that ^{18}F -FDG TIs in an uptake pattern, focal or diffuse/focal, were related to thyroid malignancy in about one-third of the patients and were all primary thyroid malignancies, mostly papillary carcinomas. The malignancy rate in this prospective study is consistent with the systematic reviews. The presence of any focal ^{18}F -FDG uptake in a thyroid nodule increases the pretest probability of malignancy in that nodule regardless of the SUVmax value of that nodule, and a benign FNAB result of that nodule must be evaluated skeptically.

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