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Evaluation of Incidental Thyroid Findings Detected by Positron Emission Tomography/Computed Tomography

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Abstract

Background: Thyroid incidenteloma detected on 18F-FDG PET/CT carries a high risk of malignancy. This high risk of malignancy supports the performance of a further diagnostic procedure, such as ultrasonography and fine needle aspiration biopsy.

Aim of Study: To determine the role of PET/CT in evaluation of incidental thyroid lesions detected in patients being studied for lymphomas and/or cancers other than of thyroid.

Material and Methods: This study included thirty four patients with incidental abnormal increased FDG uptake. All patients were subjected to ultrasound examination and patients with focal increased tracer uptake were subjected to fine needle aspiration biopsy.

Results: This study included a total of 1263 consecutive patients who underwent a FDG PET/CT study for staging of an advanced cancer of any site of the body other than the thyroid gland during the period. An incidental abnormal increase in FDG uptake in the thyroid gland was observed in 39 (3.08%) patients. Out of these patients, 26/39 (66.6%) presented with a focal and 13/39 (33.4%) with a diffuse thyroid uptake giving a prevalence of 2.06% for focal uptake and 1.03% for diffuse uptake. Six patients out of 23 patients with focal abnormal thyroid uptake were proven to have thyroid malignancy (Four patients with papillary thyroid carcinoma, one patient with follicular thyroid carcinoma and the remaining patient with atypical Hurthle cells). Thus the malignancy rate in patients with thyroid incidentalomas which proceeded to tissue biopsy was about 26%.

Conclusion: An incidental focal uptake of 18F-FDG in the thyroid gland is of significant risk of malignancy. A high value of SUVmax increases the risk of malignancy and SUVmax does not correlated with the diameter of malignant lesions, so FDG-PET/CT can detect malignancy in small thyroid lesions.

Key Words: *Thyroid incidentaloma – FDG-PET/CT – Standardized uptake value – Caner thyroid.*

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Introduction

THYROID incidentaloma (TI) is defined as a thyroid gland lesion fortuitously discovered during radiology examinations, like computed tomography or ultrasound and the increased use of whole body PET-CT studies, has resulted in an increase in the discovery of those lesions [1].

In the last decade, (18) F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET and PET/CT) has become one of the major diagnostic tools used in oncology. A significant number of patients who undergo this procedure, due to non-thyroidal reasons, present incidental uptake of (18F-FDG) in the thyroid , accurate interpretation of such findings can impact the clinical management and overall health of the patient [2].

Thyroid lesions on PET-CT can be either diffuse or focal. Diffuse 18F-FDG uptake is usually associated with autoimmune thyroiditis or Graves' disease, whereas focal 18F-FDG uptake can be either due to a benign or malignant process in the thyroid [3].

Most recent scientific literature tends to demonstrate a detection rate of 0.1-4.3% for incidental findings of thyroid focal uptake identified by 18F-fluorodeoxyglugose Positron Emission Tomography with computed tomography (18FDG-PET/CT) initially prescribed for nonthyroid disease [4]. With positive predictive values for underlying thyroid malignancy of 20% to 50% [5].

The presence of risk factors such as a focal FDG uptake and a high SUVmax. on the FDG-PET/CT warrant ultrasonography and fine needle aspiration biopsy [4].

More recently, guidelines from the American Thyroid Association recommended that all sonographically confirmed thyroid nodule > 1 cm incidentally discovered on 18FDG-PET/CT should be biopsied with an FNA [6].

Patients and Methods

This study was performed in Diagnostic Radiology and Medical Imaging Department at Tanta University Hospital and in Nuclear Medicine Department, Oncology Hospital at Maadi Armed Forces medical compound for staging of an advanced cancer of any site of the body other than the thyroid gland during the period between September 2016 and the end of March 2018.

The current study included a total of 1263 consecutive patients who underwent a FDG PET/CT. An incidental abnormal increase in FDG uptake in the thyroid gland was observed in 39 patients. Out of these patients, 26 patients presented with a focal and 13 patients presented with a diffuse thyroid uptake, only 34 patients out of the 39 patients with abnormal increased thyroid uptake continued with us in this study.

Ethics committee approval and informed consent were obtained. Inclusion criteria were patients with incidental abnormal increased thyroid tracer uptake. Five patients Five patients with incidental increased thyroid tracer uptake were excluded as 2 of them were not medically fit for further investigation, 2 others were undergoing active treatment of their primary malignancy as a priority and therefore investigation of the incidentaloma was postponed while the remaining 1 patient refused to be included in the study. All patients were subjected to relevant history taking and, ultrasound examination and all patients with focal increased tracer uptake were subjected to fine needle aspiration biosy.

Focal thyroid lesion was defined as a focally increased 18F-FDG uptake on the PET images or focal lesion on the CT images. A diffuse thyroid lesion was defined as 18F-FDG uptake in the whole thyroid gland. The lesions that could be distinguished from the physiological background activity and with SUVmax >2.5 were accepted as pathologic. Of the PET positive lesions, the maximum standard uptake (SUVmax) value was calculated from the site of maximum FDG uptake on the transaxial images. The size of the focal lesion was also measured on CT images.

Ultrasonography of the thyroid gland was performed using a real-time ultrasonographic scanner (Toshiba) with 7- to 15-MHz linear transducers. The site (right lobe, left lobe or isthmus), the size and the shape of the nodules were assessed. The echo structure (solid, cystic or mixed), echogenicity (hyperechoic, isoechoic, hypoechoic or mixed), calcification (punctuate, coarse, egg-shell or absent), and characteristics of nodule margin (well-defined or ill-defined) were assessed, if there was multiple nodules, FNAB was taken from the nodules that were correspond to the active nodules detected on PET/CT.

Fine needle aspiration biopsy was performed with a 21-gauge needle on a 10-ml syringe in 23 patients. Ultrasonography guidance was used to confirm the placement of the needle in the nodule. Two to three passes were made per nodule.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation. Significance of the obtained results was judged at the 5% level.

Results

This study included 34 patients out of 39 patients with incidental abnormal increased thyroid tracer uptake as 5 patients were excluded from this study, an incidental abnormal increase in FDG uptake in the thyroid gland was observed in 39 patients from the 1263 patients who undergo PET/CT examination with an incidence rate (3.08%). Twenty six patients 26/39 (66.6%) presented with a focal and 13/39 (33.3%) patients presented with a diffuse thyroid uptake giving a prevalence of 2.06% for focal uptake and 1.03% for diffuse uptake.

The 34 patients with incidental abnormal increased thyroid tracer uptake were examined for lymphoma in 5 patients and/or other cancers other than of the thyroid gland in the remaining 29 patients. Twenty two (65%) patients were females while the remaining twelve (35%) were males.

The age of the studied patients ranged from 20 to 80 years old (mean age 53.4 years). (Table 1).

Table (1): The age and sex distribution in the studied 34 patients with incidental abnormal increased thyroid tracer uptake.

Age group	Sex of patients		Total number of patients	Percentage (%)
	Male	Female		
20–<30	0	2	2	5.8
30–<40	1	2	3	8.8
40–<50	2	4	6	17.6
50–<60	4	8	12	35.3
60–<70	3	4	7	20.6
70–80	2	2	4	11.8
Total number of patients	12	22	34	100

Among the 34 patients who performed PET/CT study, 23 (67.7%) patients showed incidental focal increased tracer uptake and 11 (32.3%) patients showed incidental diffuse increased tracer uptake. The site, size, SUVmax of nodules with focal uptake were assessed.

All patients with diffuse or focal uptake were subjected to ultrasound examination and the 23 patients with focal uptake were subjected to fine needle aspiration biopsy, in 2 patients, the biopsy was insufficient and containing blood only in another 2 patients. Three patients of them were rebiopsed, while the remaining 1 patient refused rebiopsy in whom we depended only on US criteria for diagnosis that showed evidences of a nodular goiter.

As regards to the ultrasound manifestations in the patients with incidental diffuse increased tracer uptake. Five (14.7%) patients were diagnosed as chronic thyroiditis, 4 (11.8%) patients showed normal thyroid US examination and the remaining 2 (5.9%) patients were diagnosed as diffuse goiter.

The results of FNAB in patients with incidental abnormal focal increased thyroid tracer uptake was: Fourteen (41.2%) patients with nodular goiter, 3 (8.8%) patients with Hashimoto's thyroiditis, 3 (8.8 %) patients with papillary thyroid carcinoma, 2 (5.9%) patients with atypical Hurthle cells and 1 (2.9%) patient with follicular neoplasm. Four patients with malignant findings underwent total thyroidectomy followed by histopathology which revealed papillary thyroid carcinoma in 3 patients and follicular thyroid carcinoma in the remaining 1 patient. In the other 2 patients with atypical Hurthle cell, 1 patient died before any intervention and the remaining 1 patient underwent total thyroidectomy which revealed a papillary thyroid carcinoma by histopathology (Table 2).

Table (2): The final diagnosis of the studied 34 patient with the diffuse and focal incidental increased thyroid tracer uptake.

Diagnosis by FNAB and/or US study	Benign	Percentage (%)	Malignant	Percentage (%)	Total number of patients	Percentage (%)
Diffuse:						
- Chronic thyroiditis	5	14.7	–	–	5	14.7
- Normal	4	11.8	–	–	4	11.8
- Diffuse goiter	2	5.9	–	–	2	5.9
Focal:						
- Nodular goiter	14	41.2	–	–	14	41.2
- Hashimoto's thyroiditis	3	8.8			3	8.8
- Papillary thyroid carcinoma	–	–	3	8.8	3	8.8
- Atypical Hurthle cells	–	–	2	5.9	2	5.9
- Follicular thyroid neoplasm	–	–	1	2.9	1	2.9
Total numberof patients	28	82.4	6	17.6	34	100

Mean SUVmax for benign nodules was (7.75± 8.30) and mean SUVmax in cases of malignant nodules was (8.97±2.96). The difference between SUVmax of the benign and malignant nodules was statistically significant (p=0.032). The mean maximal diameter for benign nodules was (2.88 ±2.23) and the mean maximal diameter for malignant nodules was (2.07±0.69). There was no statistically significant difference between the mean size of benign and malignant nodules (p=0.833) (Table 3).

Table (3): Comparison between benign and malignant focal thyroid uptake incidentally detected on 18F-FDG PET/CT study.

PET/CT parameter	Benign (n=17)	Malignant (n=6)	U-value	p-value
Size on CT &/or on US (mm)	2.88±2.23	2.07±0.69	48.0	0.833
SUVmax of the nodule	7.75±8.30	8.97±2.96	20.50	0.032*

- U, p: U and p-values for Mann Whitney test for comparing between benign and malignant

*: Statistically significant at $p \leq 0.05$.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for selected SUVmax thresholds. A receiver-operating-characteristic (ROC) curve analysis of sensitivities and specificities was performed to determine a clinically useful SUVmax cut-off value to aid in differentiating between benign and malignant lesions as shown in the following Figure & Table.

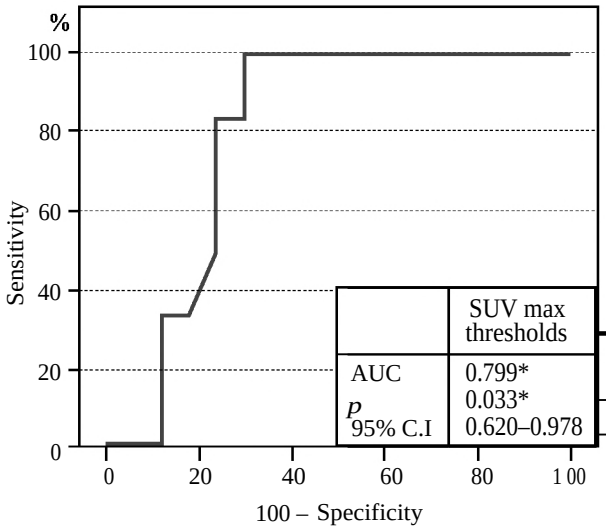

Fig. (1): Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for selected SUVmax.

Table (4): Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) which were calculated for selected SUVmax.

	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SUVmax thresholds	>3	100.0	11.76	28.6	100.0
	>4	100.00	29.41	33.3	100.0
	>5	100.00	52.94	42.9	100.0
	>6	100.00	70.59	54.5	100.0
	>7	83.33	76.47	55.6	92.9
	>8	33.33	82.35	40.0	77.8

AUC: Area under a curve
CI : Confidence Intervals
p-value:probability value
*: Statistically significant at $p \leq 0.05$

No correlation was found between lesions diameter and SUVmax in the whole group (p=0.949). Also there was no significant correlation in cases of benign nodules (p=0.934) or in malignant nodules (p=0. 180) as shown in (Table 5).

Table (5): Correlation between size by CT &/or US images (mm) and SUVmax of the nodule in each group.

	Benign (n=17)		Malignant (n=6)		Total sample (n=23)	
	r	p	r	p	r	p
Size on CT and/or US images (mm) vs SUVmax of the nodule	0.022	0.934	–0.630	0.180	–0.014	0.949

r: Pearson coefficient.

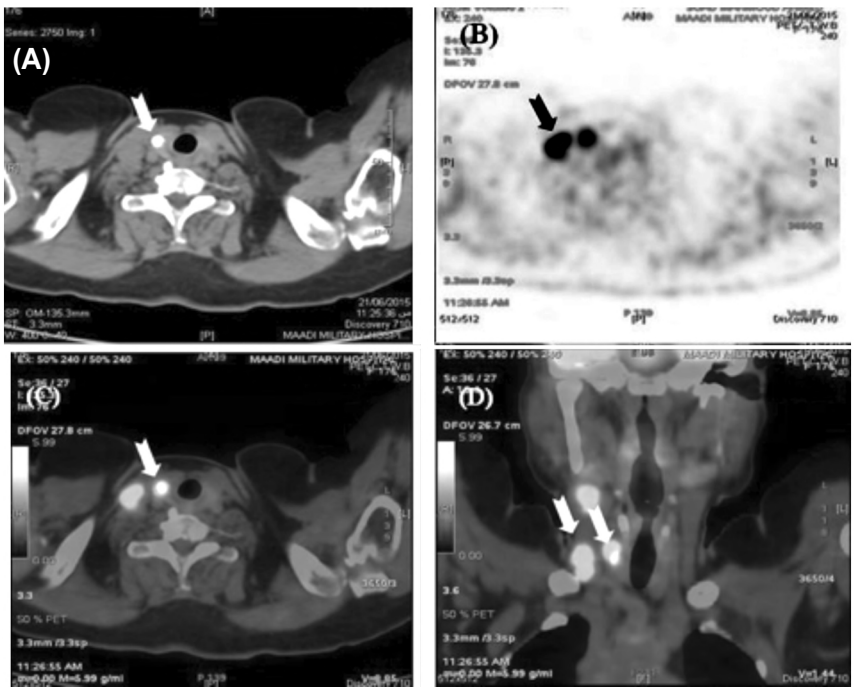

Fig. (2): Axial multi-slice (128) non-enhanced CT (A), axial PET (B), axial & coronal PET/CT (C&D) images show a biologically-active calcified nodule in the average sized right thyroid lobe with SUVmax 9.5, associated with enlarged metabolically-active upper and lower right deep cervical lymph nodes and SUVmax. 11 (notched arrows). US images showed a hypoechoic solid nodule measuring 12x10mm with ill-defined outlines and coarse calcification, correlating to the focal uptake on PET-CT scan with multiple enlarged right upper and lower deep cervical lymph nodes showing loss of their hilar fat contents as well. US-guided FNAB was suspicious for a malignant lesion.

- Final diagnosis was a papillary thyroid carcinoma, grade II with metastases to upper and lower right deep cervical lymph nodes by histopathology, following a total thyroidectomy.

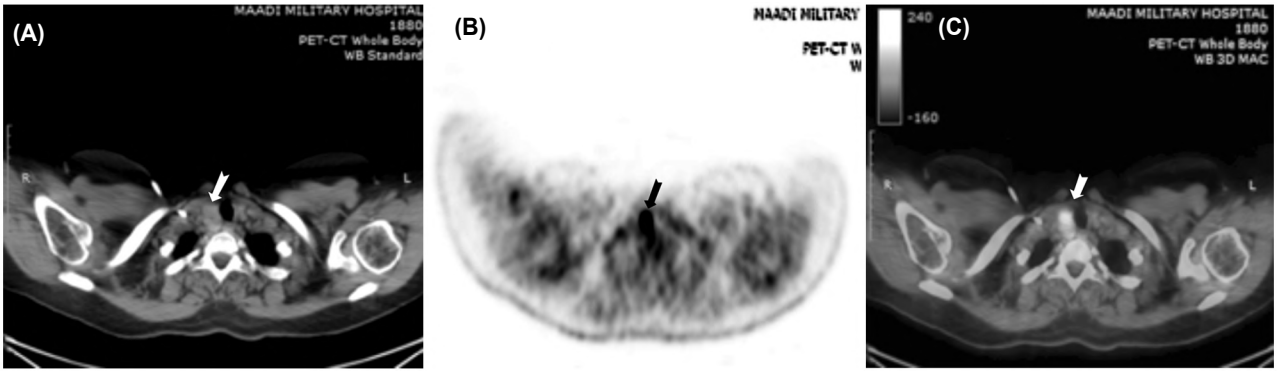

Fig. (3): Axial multislice (128) non-enhanced CT. (A) Axial PET (B) and axial PET/CT (C) Images show a metabolically-active nodule in the mildly enlarged right thyroid lobe with SUVmax 6.5 (notched arrows). US study images showed a hypoechoic solid nodule measuring 15x20mm with ill-defined outlines, corresponding to the focal uptake on PET-CT scan. US-guided FNAB was a follicular neoplasm lesion.

- Final diagnosis was a follicular thyroid carcinoma by histopathology, following a thyroidectomy.

Discussion

Incidental findings in the thyroid gland are of specific interest and interpretation of these incidental findings remains a challenge to clinicians especially that detected by FDG-PET/CT as the clinical situation may override the need to investigate a possible second primary thyroid cancer or metastases to the thyroid gland **[7]**.

This study included a total of 1263 consecutive patients who underwent a FDG PET/CT study for staging of an advanced cancer of any site of the body other than the thyroid gland during the period between September 2016 and the end of March 2018.

An incidental abnormal increase in FDG uptake in the thyroid gland was observed in 39 (3.08%) patients. Out of these patients, 26/39 (66.6%) presented with a focal and 13/39 (33.4%) with a diffuse thyroid uptake giving a prevalence of 2.06% for focal uptake and 1.03% for diffuse uptake. Agrawal et al., 2015 **[8]** also stated that the prevalence of focal uptake within the thyroid varies from 0.1% to 4.8% and from 0.1 to 4.5% in diffuse uptake within the thyroid gland.

This study included 22 females (64.7%) and 12 males (35.3%). This matches with the fact that females are significantly affected more than males as reported by Vaish et al., 2016 **[9]** in their study which was conducted on 78 patients with incidental abnormal increased thyroid tracer uptake. Sixty one (78%) were females and 17 (22%) were males.

The ultimate diagnosis for the focal thyroid incidentalomas was found from cytological/histological records in patients who had undergone fine needle aspiration cytology (FNAC) or surgical resection specimen. In the current study 6 patients out of 23 patients with focal abnormal thyroid uptake were proven to have thyroid malignancy (Four patients with papillary thyroid carcinoma, one patient with follicular thyroid carcinoma and the remaining patient with atypical Hurthle cells which was considered as malignant as well). Thus the malignancy rate in patients with thyroid incidentalomas which proceeded to tissue biopsy was about 26%.

This is in agreement with Bonabi et al., 2012 **[10]** who reported that the risk of malignancy in incidental focal thyroid uptake in FDG-PET/CT studies ranges between 25 and 50%. The largest systematic review of thyroid incidentaloma studies (27 studies) which were done by Bertagna et al., 2012 **[11]** who revealed that a biopsy rate of incidental focal thyroid uptake in FDG-PET/CT studies is only 35%. Soelberg et al., 2012 **[12]** admitted in their meta-analysis and stated that one can't exclude that surgical confirmation is most likely obtained in those patients with the highest likelihood of malignancy and therefore the malignancy risk of focal uptake is overestimated and they suspected that the reported average malignancy rate of 35% in the literature is overestimated and that the actual value is significantly lower.

Standardised uptake value (SUV) is the accepted measurement of intensity of FDG uptake in tissue on scanning, and is a reflector of the degree of metabolic activity. The SUVmax for each patient with a focal thyroid incidentaloma in the FDG-PET/CT was calculated and patients with malignant lesions had a statistically significant higher standardized uptake value (SUVmax.) compared to those with benign lesions in this study (p-value=0.032).

A few potential SUVmax. cut-offs were examined and a kappa statistic was calculated for each value to determine which would maximize sensitivity and specificity. These calculations were performed to determine if there is a satisfactory SUVmax cut-off to differentiate benign thyroid lesions from malignant ones. The SUV max cut-off with the highest kappa coefficient was provided and we found that SUV max more than 7 has the most specificity and sensitivity in diagnosis of malignancy (specificity 76.47%, sensitivity 83.33%) in the studied cases.

There are differences in opinions in literatures on role of SUVmax in differentiating benign and malignant lesions with several studies showing statistically significant differences of SUVmax between benign and malignant lesions, whereas others showed no significant difference. Agrawal K et al., 2015 **[8]** reported that the SUVmax of malignant thyroid lesions has been significantly higher than that of benign lesions and SUVmax cut-off value of 9.1 had 81.6% sensitivity and 100% specificity in differentiating benign from malignant lesions within thyroid nodules demonstrating incidental focal FDG uptake to determine if there is a significant difference in SUVmax between benign nodules and thyroid cancer. On the other hand, Bonabi et al., 2012 **[10]** found no statistically significant difference in the SUVmax between benign and malignant focal lesions (p= 0.0982).

The size of the malignant thyroid lesions as measured on CT was not statistically significant in discriminating benign from malignant lesions in this study (p=0.833). Calcifications were detected in 3 malignant thyroid lesions (1 showed macrocalcifications and the other 2 lesions showed microcalcifications) and in 3 benign thyroid lesions (all showed macrocalcifications). This was discordant with Yaylali et al., 2014 **[13]** who reported that the size of the malignant thyroid lesions is significantly larger than that of the benign thyroid lesions (p<0.05), and calcifications were detected in 4 malignant thyroid lesions and only in 2 benign thyroid lesions in their study.

In the current study, no significant correlation between maximal diameter of the lesion and SUVmax was found either in the total sample (p= 0.949), in the malignant group (p=0.180) or in the benign group (p=0.934). These results suggested that PET/CT is effective in the evaluation of small thyroid cancers (such as microcarcinomas), as they have significantly high SUVmax when malignant in spite of their small size. This came in agreement with Kalender et al., 2014 **[14]** who found no significant correlation between maximal diameter of the lesion and SUVmax. On the other hand, Kim et al., 2005 **[15]** and Stangier et al., 2014 **[16]** found a significant correlation between maximal diameter of the lesion and SUVmax in the malignant group (p=0.03) and no significant correlation was found in the group of benign lesions (p=0.77) or in the whole group (p=0.16).These results suggested that PET/CT can be less effective in the evaluation of small thyroid cancers (such as microcarcinomas), as they have significantly lower SUVmax than the larger ones.

The cytological results of the FNAB were benign in 17 patients with focal increased thyroid tracer fixation (14 patients with nodular goiter and 3 patients with Hashimoto's thyroiditis), and malignant in 6 patients (3 patients with papillary thyroid carcinoma, 2 patients with atypical Hurthle cells and 1 patient with follicular neoplasm). In 1 patient with probable benign US features, FNAB was insufficient and he refused to be rebiopsed with insufficiency rate of 4.3% in 1/23 patients. Kim et al., 2013 **[17]** found that the insufficiency rate of FNAB from thyroid nodules is 13.4% in 141/1054 patients.

Five out of 6 patients with suspicious malignant cytology underwent further thyroidectomy and the results were confirmed by histopathology (4 patients with papillary thyroid carcinoma and 1 patient with follicular thyroid carcinoma). The last patient died before any surgical intervention. Brindle et al., 2014 **[18]** studied 26 patients with focal increased thyroid tracer uptake by cytological and histological evaluations and found no differences in the results obtained from the two techniques.

Conclusion:

From this study, the following conclusions could be reached:

- An incidental focal uptake of 18F-FDG in the thyroid gland is of significant risk of malignancy. A high value of SUVmax further increases the risk of malignancy and should indicate the necessity for further cytological and/or histological evaluation. Also SUVmax does not correlated with the diameter of malignant lesions, so FDG-PET/CT can detect malignancy in small thyroid lesions.
- US examination and SUVmax of 18F-FDG PET/CT study have complementary roles to each other: if SUVmax is elevated in focal uptake lesions on FDG PET/CT images or features of malignancies are seen on US, then malignancy

is possible and US-guided FNAB should be considered.

- Malignancy detected by 18F-FDG PET/CT further alters prognosis, mortality, and most importantly quality of life of the patients.

Competing interests:

The authors declare that they have no competing interests.

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تقييم التغيرات العرضية بالغدة الدرقية والمكتشفة عن طريق التصوير المقطعى بالإنبعاث البوزيتونى مع الأشعة المقطعية

أشتمل هذا البحث على عدد ألف ومائتين وثلاثة وستين مريضاً خضعوا جميعاً لفحص التصوير المقطعى بالإنبعاث البوزيتونى ولأسباب ليس لها أى علاقة بالغدة الدرقية.

وقد خضع كل هؤلاء المرضى لطرق الفحص المختلفة بداية من التاريخ المرضى الكامل بكل تفاصيله السابقة والحالية مع التركيز على أنواع العلاجات المستخدمة وأنتهاءاً بنتائج التحاليل الهستوباثولوچية للأورام بعد ذلك تم تحديد الموعد المناسب لعمل هذا الفحص لكل مريض و كذا إعطاؤه طريقة التحضير المناسبة ما قبل الفحص ثم قيام كل منهم بالإسترخاء الكامل لمدة قد تصل إلى ساعة بعد حقن المادة المشعة وبعزله عن الآخرين ثم القيام بالفحص مباشرة بعد حقن الأوساط المتابينة مع تغطية الجسم من قاعدة الجمجمة إلى منتصف الفخذ ثم تم تجميع صورالفحوصات وأرسالها إلى أجهزة العرض لعمل التقارير.

لوحظ الألتقاط العرضى للغدة الدرقية فى عدد تسعة وثلاثين فقط من الحالات التى تم فحصها ثم تم أستبعاد عدد خمسة منهم لأسباب متعددة تلى ذلك إجراء فحص الموجات فوق الصوتية لعدد أربعة وثلاثين من المرضى ثم خضع لمرضى ذو الألتقاط الجزئى العرضى إلى أخذ العينات السيتولوجية بمساعدة الموجات فوق الصوتية وكذا التحليل الهستوباثولوجى لعدد ستة حالات منهم فقط بعد خضوعهم لعمليات إستئصال الغدة الدرقية وفى النهاية تم التحليل الإحصائى لنتائج البحث بإستخدام الأصدار ٢٠٠٠ من حزمة برامج IBM.

أيجازاً فإن الألتقاط الجزئى العرضى للمادة المشعة بالغدة الدرقية يكون مصحوباً بإرتفاع نسبة وجود البؤر السرطانية بها بنسب متفاوتة وخصوصاً إن كان مصحوباً بإرتفاع أقصى قيمة لألتقاط المادة المشعة وهذا يتطلب أخذ عينات سيتولوجية أو هستولوجية منها ولأن أقصى قيمة لألتقاط المادة المشعة لا تعتمد عى حجم الأورام الخبيثة ولذلك فمن الممكن أكتشاف الأورام الصغيرة منها.