

# Diagnosis of incidental thyroid nodules on $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography imaging: are these significant?

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## Abstract

**Objective:** To determine the prevalence of thyroid malignancy in the first UK case series of patients with incidentally detected thyroid lesions on  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography imaging.

**Methods:** A total of 235 patients were evaluated with  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography imaging. Incidental focal uptake in the thyroid gland was identified in nine patients (3.8 per cent). A retrospective review of their case notes was conducted.

**Results:** The rate of malignancy was 55 per cent. The mean and standard deviation of the maximum standardised uptake value was  $13.1 \pm 7.3$  in those patients with malignancy and a nodule identified as positive on positron emission tomography. This value was  $2.8 \pm 1.2$  in those patients without malignancy but with a nodule identified as positive on positron emission tomography ( $p = 0.01$ ). A palpable thyroid nodule was more likely in those with malignant lesions ( $p = 0.14$ ).

**Conclusion:** The prevalence of incidental thyroid lesions found on  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography in patients with other primary malignancies is low, but the incidence of malignancy in these patients is high. Patients with a palpable thyroid nodule, focal uptake on  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography and an increased maximum standardised uptake value require further investigation.

**Key words:** Thyroid Nodule; Emission-Computed Tomography; Thyroid Cancer

## Introduction

There is an increasing trend for patients with a variety of malignancies to undergo  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography (FDG-PET) to aid identification of a primary tumour, to conduct staging or to identify metastatic disease.<sup>1</sup> The uptake of  $^{18}\text{F}$ -fluorodeoxyglucose in the normal thyroid gland is of low intensity and is therefore not usually visualised on FDG-PET.<sup>2</sup>

Focal uptake in the thyroid gland on FDG-PET in patients with no known history of thyroid disease has been previously reported, mainly in the USA.<sup>3–5</sup> The use of positron emission tomography (PET) on patients with recurrent or metastatic thyroid carcinoma has been shown to be very reliable in diagnosis and monitoring.<sup>6</sup> Hence, when focal uptake is incidentally detected, the lesions ought to be treated with a high index of suspicion.

The prevalence of incidentally identified thyroid lesions on FDG-PET varies from 1.1 to 4.3 per cent, whilst the incidence of malignancy in these patients ranges from 14 to 50 per cent.<sup>1–4,7,8</sup> The relevant

literature mainly consists of case series of limited numbers. It is therefore difficult to draw reliable conclusions on which to base further investigation.

This study investigated the prevalence of thyroid malignancy in the first UK case series of patients with incidentally detected thyroid lesions on FDG-PET. It also aimed to determine any reliable criteria suggestive of malignancy, in order to create an algorithm for the management of these patients.

## Materials and methods

Between January 2010 and March 2013, a total of 235 patients were evaluated with  $^{18}\text{F}$ -fluorodeoxyglucose PET (FDG-PET). Positron emission tomography computed tomography (PET-CT) was performed for a variety of reasons, including assessment of head and neck malignancy (excluding the thyroid), and possible malignancy at other sites, and for staging of lymphoma. Nine patients with incidental focal uptake in the thyroid gland were identified.

A retrospective review of the case notes of these patients was carried out. Imaging reports for these

patients, including those for PET-CT, were analysed. Patient demographic data, thyroid status, indication for PET, laterality on PET, maximum standardised uptake value, thyroid fine needle aspiration (FNA) cytology findings and histology findings were recorded.

#### *Fluorodeoxyglucose positron emission tomography*

All patients were fasted at least 4 hours before the fluorodeoxyglucose was injected. Plasma glucose was measured prior to injection, and was found to be less than 200 mg/dl in all patients. The patients received an intravenous injection of 336–397 MBq of <sup>18</sup>F-fluorodeoxyglucose. Positron emission tomography was conducted using a Discovery LS integrated PET-CT system (GE Healthcare, Milwaukee, Wisconsin, USA) 60 minutes after the intravenous injection.

Incidental focal uptake in the thyroid gland was defined as focal uptake in the thyroid gland that was greater than background activity in the adjacent tissues and blood. The maximum standardised uptake value was measured, normalised to body weight.

#### *Statistical analysis*

Statistical analysis and comparisons were carried out using the Fisher's exact test (GraphPad Software, San Diego, California, USA) (as the cross tabulations were 2 × 2 and the cells sizes were small) and a two-tailed *t*-test.<sup>9</sup> Significance was set at *p* < 0.05.

## Results

Nine patients (three males and six females) had focal uptake in the thyroid gland. Seven cases were in one lobe and two were in the isthmus of the gland. The median age of the patients was 57 years (range, 42–74 years). All patients underwent FNA prior to surgical intervention if indicated. All patients were

found to be euthyroid, and three of the nine patients (33 per cent) had a clinically palpable thyroid nodule. In six cases (67 per cent), there were features suspicious of malignancy on cytology.

Eight patients underwent surgical intervention, with five patients undergoing hemithyroidectomy and three patients undergoing a total thyroidectomy. The one patient who did not have surgery, in light of benign cytology, was followed up for a period of two years with FNA, and the overall clinical picture remained benign.

Of the six patients whose cytology findings raised suspicion of malignancy (67 per cent), all had histological evidence of malignancy in the specimen. In five of the cases with histological diagnosis of thyroid gland malignancy, the site of the malignant nodule correlated with the <sup>18</sup>F-fluorodeoxyglucose PET (FDG-PET) positive nodule. In one case (case 5), the malignancy was in a different site to the nodule that was positive on FDG-PET, the latter of which was found to be benign. The focal uptake on FDG-PET was found to be in the isthmus, whilst on histology the isthmus nodule was benign and there was in fact an incidental 5 mm papillary carcinoma in the left thyroid lobe. For the purposes of analysis, this was considered to be a non-correlation between the FDG-PET positive nodule and malignancy.

Of the nine patients with incidental FDG-PET uptake in the thyroid gland, four (44 per cent) demonstrated papillary carcinoma (cases 3, 7, 8 and 9) and one (11 per cent) demonstrated metastatic disease in the thyroid gland (case 4). Hence, the rate of malignant disease in those patients with incidental focal FDG-PET uptake in the thyroid gland was 55 per cent (five out of nine patients).

The mean and standard deviation of the maximum standardised uptake value was 13.1 ± 7.3 (range, 5.0–24.3) in patients with malignancy,

TABLE I  
PATIENT DATA SUMMARY

Pt no.	Gender	Pt age (y)	Indication for PET-CT	Palpable nodule?	FNAC	PET laterality	SUV (max)	Histology
1	Male	55	Right upper lobe lung lesion	No	Thy 1	Right	1.9	N/A
2	Female	42	Left lower lobe lung lesion	No	Thy 1	Left	2.2	Benign
3	Male	42	Sinonasal tumour	No	Thy 4/5	Right	5.4	8 mm papillary carcinoma
4	Female	74	Left lower lobe lung adenocarcinoma	Yes	Thy 5	Left	14.3	Metastatic deposit
5	Female	66	Right upper & left lower lobe lung lesions	No	Thy 3	Isthmus	4.9	5 mm papillary carcinoma left lobe
6	Female	57	Left breast lesion	No	Thy 2	Left	2.1	Benign
7	Female	56	Right breast lesion	Yes	Thy 5	Right	16.7	9 mm papillary carcinoma right lobe & 3 mm papillary carcinoma left lobe
8	Male	44	Left axilla lymphoma	Yes	Thy 3	Right	24.3	25 mm papillary carcinoma
9	Female	61	Right lower lobe lung lesion	No	Thy 3	Isthmus	5.0	8 mm papillary carcinoma

Pt = patient; no. = number; y = years; PET = positron emission tomography; CT = computed tomography; FNAC = fine needle aspiration cytology; SUV (max) = maximum standardised uptake value; N/A = not applicable

TABLE II  
PREVALENCE OF MALIGNANCY BASED ON RISK FACTORS\*

Risk factor	Prevalence of malignancy	<i>p</i>
Age >50 years	3/5	1.00
Male gender	2/5	1.00
Palpable nodule	3/5	0.17

\*In patients with positive <sup>18</sup>F-fluorodeoxyglucose positron emission tomography findings.

versus  $2.8 \pm 1.2$  (range, 1.9–4.9) in patients without malignancy ( $p = 0.01$ ) (Table I).

There were no significant associations between any of the risk factors and the prevalence of malignancy in patients with positive FDG-PET findings (Table II). A palpable thyroid nodule was more likely in those with malignant lesions, but this finding was not statistically significant ( $p = 0.17$ ).

## Discussion

The current use of <sup>18</sup>F-fluorodeoxyglucose PET (FDG-PET) in the assessment of malignant tumours has led to an increase in the number of thyroid lesions found incidentally.<sup>5</sup> It is therefore important to be able to differentiate benign from malignant lesions, in order to reduce the burden of unnecessary surgical intervention.<sup>8</sup> In our study, we found that the prevalence of incidental focal thyroid lesions was 3.8 per cent. This corresponds with what has been reported previously in the literature.<sup>1–4</sup> Our rate of malignancy of 55 per cent was also comparable to the rates reported in the literature.<sup>1–4</sup>

Certain features that can be identified on an ultrasound examination of thyroid nodules are associated with an increased risk of malignancy. These features include microcalcifications, irregular margins and an incomplete halo.<sup>10</sup> Nixon *et al.* described the use of a thyroid nomogram to predict malignancy in thyroid nodules, with a concordance index of 91 per cent.<sup>11</sup> The eight factors of interest were: biochemical features (thyroid stimulating hormone level), ultrasonography features (shape, echotexture and vascularity) and cytology (nuclear grooves, pseudo-inclusions, cellularity and presence of colloid).

There are no specific criteria on computed tomography (CT) that suggest malignancy, although obviously invasion of surrounding structures is strongly suggestive of malignancy. In addition, there is no consensus on the PET criteria that suggest malignancy in the thyroid. One paper by Cohen *et al.* suggested that the average standardised uptake value was significantly higher in malignant lesions ( $6.92 \pm 1.54$ ) than in benign lesions ( $3.37 \pm 0.21$ ).<sup>3</sup> In our study, we found a statistically significantly higher maximum standardised uptake value in malignant thyroid lesions as compared with benign thyroid lesions. However, other studies disagree with this

finding and report no statistically significant difference.<sup>2,12</sup>

Similarly, there is disagreement regarding the differentiation of benign and malignant lesions when focal versus diffuse uptake is noted on PET-CT imaging.<sup>2,13</sup> However, more recent reports have suggested that diffuse uptake is more likely to correspond to chronic thyroiditis, whilst focal uptake harbours a much higher risk of malignancy.<sup>7,13</sup> There is also no consensus in the literature regarding the presence of a palpable nodule as an indicator of malignancy, although a study by Are *et al.* suggested that there was a significantly higher rate of malignancy in those patients with a palpable nodule that is positive on FDG-PET imaging than in those with a FDG-PET positive nodule and an impalpable nodule.<sup>7</sup>

The majority of our patients underwent PET-CT as an assessment for a possible lung malignancy, although one patient did have a primary sinonasal carcinoma (case 3). Only one of our patients who had a malignant diagnosis on final histopathology did not have a primary thyroid malignancy. This was a case of metastatic lung carcinoma in the thyroid (case 4). The literature supports this low incidence of metastatic thyroid disease in those patients with focal thyroid uptake on FDG PET-CT.<sup>7</sup>

- **The incidence of incidentally identified thyroid lesions on <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (FDG-PET) ranges from 1.1 to 4.3 per cent**
- **Prevalence of malignancy in these patients ranges from 14 to 50 per cent**
- **This study aimed to determine the prevalence of thyroid malignancy in the first UK case series of patients with incidentally detected thyroid lesions on FDG-PET scanning**
- **In this study, the prevalence of incidental focal thyroid lesions and of malignancy in these patients was 3.8 and 55 per cent respectively**
- **The majority of patients had papillary carcinoma on final histopathology**
- **Factors associated with malignancy are: palpable thyroid nodule, and focal uptake and increased maximum standardised uptake value on FDG-PET**

It should be noted that some of these patients may have had extensive disease related to their primary malignancy, such that further investigation and intervention for the thyroid lesion is not appropriate. Also, the majority of patients in our case series who had a malignant diagnosis on final histopathology were found to have thyroid papillary carcinoma. Therefore, it is important to weigh up the risks and morbidity of

surgical intervention against the relatively indolent course of thyroid malignancy, especially in patients who may have a poor prognosis because of the disease which warranted the original request for PET-CT.

To our knowledge, this is the first and largest study of incidental thyroid nodules identified on FDG-PET imaging in the UK literature. However, the number of cases is relatively small. It is therefore difficult to make meaningful statistical conclusions. Nevertheless, our results are similar to those of other studies with greater case numbers that have been conducted elsewhere in the world.<sup>1–4</sup>

### Conclusion

The prevalence of incidental thyroid lesions found on <sup>18</sup>F-fluorodeoxyglucose PET (FDG-PET) in patients with other primary malignancies was low. However, the prevalence of malignancy in these patients was high, in keeping with the literature. The majority of these patients were found to have papillary carcinoma on final histopathology. The main factors that correlate with a higher rate of malignancy are: presence of a palpable thyroid nodule, focal uptake on FDG-PET and an increased maximum standardised uptake value on FDG-PET. Patients affected by these factors are in particular need of further investigation and intervention if appropriate.

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Mr S D Sharma takes responsibility for the integrity of the content of the paper

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