

## Incidental Thyroid Carcinoma by FDG-PET/CT: A Study of Clinicopathological Characteristics

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### ABSTRACT

**Background.** The rising incidence of incidental thyroid carcinoma (ITC) detected during fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET)/computed tomography (CT) scanning poses a challenge to clinicians. The present study aims to critically evaluate the clinicopathological characteristics of ITC detected by FDG-PET/CT.

**Methods.** Among the 557 patients managed at our institution, 40 (7.2%) patients were identified as having ITC. Of these, 22 patients had their tumor detected by FDG-PET/CT (PET group) and 11 by ultrasonography (USG group). Additional bedside ultrasonography ± fine-needle aspiration (FNA) was done in all patients at their clinic visit. The clinicopathological characteristics were compared between the PET and USG groups.

**Results.** The PET group had significantly more patients with history of nonthyroidal malignancy ( $P < 0.001$ ). Papillary carcinoma was the most common histological type in both groups. Despite having similar histological and prognostic features including tumor size, tumor multifocality, capsular invasion, extrathyroidal extension, and lymph node metastases, tumor bilaterality (or presence of contralateral tumor focus) was significantly more frequent in the PET than the USG group ( $P = 0.04$ ). The tumors were also more advanced by the tumor–node–metastasis (TNM) staging system in the PET group ( $P = 0.021$ ). None of the contralateral tumor foci were evident preoperatively. One patient in the USG group developed metastatic thyroid carcinoma in neck lymph nodes 28 months after thyroid resection.

**Conclusion.** ITC by FDG-PET/CT had higher incidence of tumor bilaterality than those detected by ultrasonography. Total thyroidectomy should be considered for ITC detected by FDG-PET/CT even for tumor size  $< 10$  mm.

Thyroid carcinoma is the most common endocrine tumor and has generally been associated with favorable prognosis. Its incidence has almost doubled over the last two decades in our locality, and a similar trend has also been observed elsewhere in the world.<sup>1,2</sup> However, this major increase might be owing to increased detection of incidental thyroid carcinomas (ITC) rather than clinically detected carcinomas, as the overall disease-related mortality has not changed significantly over this period.<sup>3</sup> ITC is defined as a carcinoma incidentally identified by imaging study performed for reason(s) unrelated to the thyroid gland.<sup>4</sup> In addition to ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging (MRI), 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) has become an increasingly important imaging modality in detecting ITC.<sup>5–9</sup> The integrated FDG-PET/CT system allows better anatomical localization of the lesion when using the PET/CT fusion image.<sup>10</sup> FDG-PET/CT has become an established imaging tool in oncology as well as some branches of medicine.<sup>11,12</sup> As a result, nowadays, clinicians are being faced with an increasing number of ITC detected during FDG-PET/CT scanning. In addition to localizing a disease process, FDG-PET/CT has been shown useful in discriminating normal from abnormal disease processes based on measuring FDG uptake rate differences.<sup>13</sup> Some studies have had some success in discriminating benign from malignant conditions in the thyroid gland as well as predicting the biological behavior and tumor aggressiveness of primary thyroid malignancy by measuring the maximum standardized uptake value ( $SUV_{max}$ ).<sup>6,14–19</sup> When these FDG-avid tumors were

correlated with histology, they tended to be less well differentiated and had more aggressive histological features.<sup>20,21</sup> However, these studies have mainly focused on nonincidental or clinically significant carcinomas and their metastases, which probably represent a later stage of the disease.<sup>22</sup> To our knowledge, no study has specifically evaluated the clinicopathological characteristics of ITC detected by FDG-PET/CT. To allow more meaningful evaluation, this study uses a control group consisting of ITC detected by USG over the same study period.

## PATIENTS AND METHODS

From January 2000 to December 2009, a total of 557 patients with thyroid carcinoma were managed at our institution. Among them, 40 patients (7.2%) had thyroid incidentaloma which was later confirmed to be malignant (i.e., ITC). ITC was defined as a carcinoma incidentally discovered by an imaging modality initially for the purpose of a nonthyroidal condition. None had known history of thyroid cancer, hyperthyroidism, hypothyroidism, thyroiditis, thyroxine replacement or direct external head and neck irradiation. Imaging modalities comprised USG, CT, MRI, and FDG-PET/CT. Patients with ITC detected by CT ( $n = 6$ ) or MRI ( $n = 1$ ) were excluded. There were a total of 33 patients for analysis. Of the 33 patients, 22 (66.7%) had their tumors detected by FDG-PET/CT (PET group) while 11 (33.3%) had their tumors detected by USG (USG group). All patients were operated on and managed by the same team of endocrine surgeons. Tumor specimens were examined by the same group of expert pathologists at our institution, and no changes in method of sectioning or pathological examination were made over the study period. In terms of clinical management, all patients underwent a bedside USG examination at their first clinic visit for the purpose of assessing the presence, location, and appearance of the thyroid incidentaloma in the ipsilateral and contralateral lobes as well as possible lymph node enlargement in the central (or level VI) compartment. This was followed by a fine-needle aspiration (FNA) performed under USG guidance if the incidentaloma was  $\geq 1$  cm in diameter or  $< 1$  cm but with suspicious features such as taller-than-wide, macro- or microcalcifications, irregular margins, and marked hypoechogenicity.<sup>23</sup> These criteria were applied to all patients regardless of the number of incidentalomas found. If none of the incidentalomas looked suspicious and  $< 1$  cm, the largest or dominant one was generally biopsied. FNA was also performed for suspicious cervical lymph nodes. FNA cytology result was categorized into four broad groups: benign, malignant, indeterminate (follicular lesion, Hürthle cell lesion, suspicious of malignancy), and inadequate/insufficient.

For those with indeterminate lesions, hemithyroidectomy was considered sufficient. For subcentimeter differentiated thyroid carcinoma (DTC) after hemithyroidectomy, the decision for completion total thyroidectomy was made based on patient preference. Total thyroidectomy was the preferred procedure for all patients with malignant FNA cytology regardless of tumor size. Prophylactic central neck dissection (CND) (i.e., removal of clinically normal lymph nodes) was not routinely performed, but if there were clinically enlarged lymph nodes, CND would be performed. Lateral neck dissection was performed for patients with either clinical or ultrasonic evidence of lymph node metastases before surgery. Details on the management protocol for thyroid carcinoma were described previously.<sup>24</sup> Final histological findings and pathological tumor staging based on the American Joint Committee on Cancer (AJCC)/International Union against Cancer (UICC) 6th edition were recorded. Tumor multifocality was defined as the presence of  $> 1$  tumor focus in the ipsilateral lobe of the primary tumor or in the contralateral lobe. Tumor bilaterality was defined as the presence of at least one other tumor focus in the contralateral lobe of the primary tumor. Bilateral disease by definition was multifocal.

### FDG-PET/CT

Although not all 22 patients had FDG-PET/CT performed at our own institution, the preparation and scanning technique were similar. All patients were asked to fast for a minimum of 6 h, and serum glucose level was confirmed as less than 120 mg/dL before intravenous (IV) administration of 370–555 MBq FDG through a peripheral vein. After 60 min, PET images were acquired using a full-ring dedicated PET scanner. Whole-body PET/CT studies were obtained by using a 64-detector CT system. Thyroid pattern of FDG uptake was classified as either focal or diffuse. Focal pattern was defined as one focus of uptake within one lobe, whereas diffuse pattern was defined as at least one focus each in both lobes. The site of focal uptake, the  $SUV_{max}$  of the thyroid lesion, and other sites of FDG uptake were recorded and correlated with both clinical and final histological findings.

### Statistical Analysis

Statistical analysis was performed using the SPSS (version 18.0; SPSS, Inc., Chicago, IL) software package. Chi-square test and Fisher's exact test were used for comparison of dichotomous variables, and Mann-Whitney  $U$  test was used for comparison of continuous variables between the PET and USG groups.  $P$ -values  $< 0.05$  were considered statistically significant.

## RESULTS

Over the study period, there was an increasing trend of ITC detected, with more being discovered in the latter 5 years (2005–2009) when compared with the earlier 5 years (2000–2004) (28 versus 5, respectively). Table 1 presents a comparison of demographic data, history, and type of nonthyroidal malignancy as well as indication for imaging between the PET and USG groups. There were significant differences in age at diagnosis, history of malignancy, and indication for imaging between the two groups. The median age in the PET group was significantly older when compared with the USG group (60 versus 39 years,  $P = 0.014$ ). In the PET group, seven (31.8%) patients had their ITC discovered within 6 months of the diagnosis of the nonthyroidal malignancy (i.e., synchronous tumors), compared with two (18.2%) patients in the USG group ( $P = 0.407$ ). Gastrointestinal malignancy was the most common type of nonthyroidal malignancy in both groups. None received direct head and neck irradiation as treatment for their nonthyroidal malignancy. Evaluation for malignancy was the most frequent indication for imaging in the PET group, whereas evaluation for a medical condition and health check were equally important indications in the USG group.

Focal FDG uptake confined to one lobe was found in 21 of 22 patients, while 1 had diffuse focal uptake in the PET group. Two patients had additional focal uptake in the cervical lymph nodes, and both were later confirmed to have lymph node metastases requiring lateral neck dissection. The median  $SUV_{max}$  of hypermetabolic thyroid lesion was 6.3 (range 2.3–34.3). Table 2 presents a comparison of ultrasonographic and FNA cytology findings as well as treatment strategy between the PET and USG groups. On bedside USG, the median tumor size and the proportion of suspicious

features between the PET and USG groups were similar. The FNA cytology results were also similar between the two groups. None had benign cytology (i.e., a false-negative result). The extent of thyroid resection was similar in the two groups, but there was a higher rate of CND performance in the PET group ( $P = 0.062$ ).

Table 3 presents a comparison of histological findings between the PET and USG groups. Papillary carcinoma (PTC) was the most common histological type, accounting for 20/22 (90.9%) in the PET group and 10/11 (90.9%) in the USG group. Median tumor size was similar between the two groups. There was higher incidence of multifocal tumor in the PET group ( $P = 0.125$ ). Tumor bilaterality was significantly more frequent in the PET group when compared with the USG group (9/20 versus 0/11,  $P = 0.04$ ). The median size of these contralateral tumors was 4 mm (range 1–10 mm). None of the contralateral tumors were detected on preoperative bedside USG. Of the nine patients with tumor bilaterality in the PET group, three had the primary tumor size <1 cm (3 mm, 5 mm, and 6 mm). The incidence of capsular invasion, extrathyroidal extension, and associated thyroiditis appeared similar in the two groups. There was a tendency for higher incidence of cervical lymph node metastases in the PET group ( $P = 0.407$ ). Tumors in the PET group had more advanced stages by the 6th edition TNM system, with half of them being stage III ( $P = 0.021$ ). At median follow-up of 18.7 months (range 1.4–107.9 months), in the PET group, 18 patients were alive and free of recurrent disease, 1 died of metastatic rectal carcinoma 28.2 months after thyroid resection, and 1 was alive with metastatic carcinoma of corpus. In the USG group, all were alive and free of recurrences except for one patient who developed metastatic PTC in ipsilateral neck lymph nodes 28 months after the initial thyroid resection.

**TABLE 1** comparison of demographic data, history, and type of nonthyroidal malignancy as well as indication for imaging between the PET and USG groups

Variable	PET group ( $n = 22$ )	USG group ( $n = 11$ )	$P$ -value
Age at diagnosis (years, range)	60 (37–79)	39 (23–83)	<b>0.014</b>
Gender (female:male)	16:06	8:03	0.653
History of nonthyroidal malignancy (%)	20 (90.9)	2 (18.2)	<b>&lt;0.001</b>
Type of nonthyroidal malignancy (%)			0.298
Gastrointestinal malignancy	8 (36.4)	2 (18.2)	
Breast malignancy	6 (27.3)	0	
Gynecological malignancy	2 (9.1)	0	
Lung malignancy	1 (4.5)	0	
Hematological malignancy	2 (9.1)	0	
Indication for imaging (%)			<b>&lt;0.001</b>
Evaluation for malignancy	20 (90.9)	2 (18.2)	
Evaluation for a medical condition	1 (4.5)	5 (45.5)	
Health check	1 (4.5)	4 (36.4)	

Bold values indicate  $P < 0.05$

**TABLE 2** Comparison of FDG-PET, ultrasonographic, FNA cytology (FNAC) findings, and treatment strategy between the PET and USG groups

Variable	PET group ( <i>n</i> = 22)	USG group ( <i>n</i> = 11)	<i>P</i> -value
Ultrasonographic findings			
Median size (mm) (range)	13.5 (5–28)	10 (5–15)	0.286
Suspicious features <sup>a</sup> (%)	13 (61.9)	7 (63.6)	0.784
FNAC of thyroid nodule (%)			
Benign	0 (0.0)	0 (0.0)	0.606
Inadequate for diagnosis	3 (13.6)	2 (18.2)	
Indeterminate	14 (63.6)	8 (72.7)	
Malignancy	5 (22.7)	1 (9.1)	
Type and extent of resection (%)			
Total thyroidectomy	20 (90.9)	10 (90.9)	1
Hemithyroidectomy	2 (9.1)	1 (9.1)	
Concomitant neck dissection (%)			
Central neck or level VI	9 (40.9)	0 (0.0)	0.062
Ipsilateral lateral neck	3 (13.6)	2 (18.2)	
Contralateral lateral neck	0 (0.0)	0 (0.0)	
Bilateral neck	1 (4.5)	0 (0.0)	
Radioiodine ablation (%)	15 (68.2)	5 (45.5)	0.223

<sup>a</sup> Including taller-than-wide, macro- or microcalcifications, irregular margins, and marked hypoechogenicity

**TABLE 3** Comparison of histological findings between the PET and USG groups

Histological finding	PET group ( <i>n</i> = 22)	USG group ( <i>n</i> = 11)	<i>P</i> -value
Histological type (%)			
Papillary carcinoma	20 (90.9)	10 (90.9)	0.687
Follicular carcinoma	1 (4.5)	1 (9.1)	
Undifferentiated carcinoma	0 (0.0)	0 (0.0)	
Hürthle cell carcinoma	1 (4.5)	0 (0.0)	
Median tumor size (mm) (range)			
Primary tumor	13 (3–30)	10 (1–18)	0.264
Contralateral lobe <sup>a</sup>	4 (1–10)	Not applicable	–
Tumor multifocality (%)	10 (45.5)	2 (18.2)	0.125
Tumor bilaterality <sup>a</sup> (%)	9 (45.0)	0 (0.0)	<b>0.04</b>
Extrathyroidal extension (%)	8 (36.4)	4 (36.4)	0.653
Capsular invasion (%)	8 (36.4)	2 (18.2)	0.284
Lymph node metastases (%)	7 (31.8)	2 (18.2)	0.407
Associated thyroiditis (%)	5 (22.7)	2 (18.2)	0.813
TNM tumor staging <sup>b</sup> (%)			
I	5 (22.7)	8 (72.7)	<b>0.021</b>
II	6 (27.3)	1 (9.1)	
III	11 (50.0)	2 (18.2)	
IV	0 (0.0)	0 (0.0)	

<sup>a</sup> Only those who underwent total thyroidectomy were included

<sup>b</sup> *AJCC Cancer Staging Manual*<sup>38</sup>

Bold values indicate *P* < 0.05

## DISCUSSION

In the present study, although ITC only accounted for 7.2% of all thyroid cancers managed at our institution, there was a trend towards more cases in the latter 5 years (2005–2009) relative to the earlier 5 years (2000–2004) (28

versus 5). With the wider availability and greater need for imaging studies across many medical specialties, this trend is likely to continue in the future. It is a reasonable assumption that some of these ITC probably do belong to the occult microcarcinoma group, and so intervention may not be necessary as they do not become clinically

significant carcinoma in the patient's lifetime. However, it remains unresolved how best to predict which ones will progress and which ones to intervene early. This unresolved problem was highlighted in several recent publications.<sup>3,25–28</sup> As a consequence, management of ITC, particularly subcentimeter carcinoma, remains controversial, with some investigators even advocating pure observation with regular USG surveillance as primary treatment, even though most would perform surgical resection.<sup>27,28</sup> It is also important to note that not all ITC behave in the same benign manner and that some should be managed in much the same way as clinically significant carcinomas.<sup>29,30</sup> The purpose of the present study is to examine the clinicopathological features of ITC based on the imaging modality. We hypothesized that ITC detected by FDG-PET/CT might have more aggressive histological features than those detected by other means, as previous studies have shown that primary nonincidental carcinomas as well as their metastases detected by FDG-PET/CT tended to be less well differentiated, possessed more aggressive histological features, and behaved more aggressively.<sup>20,21</sup>

When the clinicopathological features of ITC were compared between the PET and USG groups, one of the most significant findings was that those in the PET group had significantly higher frequency of tumor bilaterality. This was despite the fact that both groups had comparable tumor size as well as some histological findings such as tumor multifocality, extrathyroidal extension, capsular invasion, and lymph node metastases. In terms of surgical management, this might have important implications, particularly for surgeons who follow the recommendation in the 2009 American Thyroid Association (ATA) guidelines.<sup>31</sup> As the revised ATA guidelines recommend hemithyroidectomy for tumor size <1 cm, if one were to follow this recommendation, three of the nine FDG-PET/CT-detected ITC with tumor bilaterality would have otherwise undergone hemithyroidectomy instead of total thyroidectomy and, in so doing, a tumor focus would have been left behind in the contralateral lobe. Although the long-term outcome of leaving small contralateral tumor focus after hemithyroidectomy remains not well understood, the possibility of locoregional recurrence remains. This was made worse by the fact that the foci in the contralateral lobe, despite some being as large as 10 mm, could not be picked up by preoperative USG. Perhaps this reflects some of the limitations related to preoperative imaging modalities, particularly bedside USG. Possible reasons for failure of USG in detecting contralateral disease include small size (<5 mm), lesion without suspicious features, and operator dependency. In our opinion, given the high frequency of tumor bilaterality and the relative inability of preoperative imaging to detect contralateral

tumor focus, perhaps total thyroidectomy should be considered in FDG-PET/CT-detected ITC even for tumor size <10 mm. It was also interesting to note that all nine patients with tumor bilaterality in the PET group had a single uptake on the ITC side only, and the only patient with diffuse uptake did not have tumor bilaterality. This suggested that FDG-PET/CT was relatively inaccurate at predicting tumor bilaterality. This might be related to the fact that these contralateral tumors tend to be too small in size for detection and FDG-PET/CT does have limitations with spatial resolution and partial volume effects.<sup>32</sup> Another alternative reason might have been related to mutational profile differences between the tumor foci in the opposite lobe, with some more preferentially taking up FDG nuclide. This notion was supported by two studies demonstrating genetic heterogeneity between different tumor foci within the same gland when RET/PTC rearrangement and BRAF mutations were evaluated.<sup>33,34</sup> In addition, study of pattern of X-chromosome inactivation of multiple distinct foci of well-differentiated thyroid multifocal PTC revealed that individual tumor foci in patients with multifocal PTC often arose as de novo tumors.<sup>35</sup> Given that tumor bilaterality and multifocality are not distinct biological processes, one possible reason for the higher incidence of bilaterality but not multifocality in the PET group might be due to the small number of patients in each group.

While patients in the PET group were significantly older than the USG group ( $P = 0.014$ ), patients with older age did not have higher incidence of contralateral tumors ( $P = 0.555$ ). Tumor bilaterality was also not related to positive history of nonthyroidal malignancy ( $P = 0.156$ ).

The other significant finding was that, despite similar tumor size, those in the PET group were more advanced in AJCC/UICC (American Joint Committee on Cancer/International Union against Cancer) TNM tumor stage. This finding seemed to concur with our initial postulation that ITC by FDG-PET/CT tends to behave more aggressively. All patients ( $n = 5$ ) who underwent lateral neck dissection in both groups had suspicious lateral neck lymph nodes preoperatively, and all ended up having histologically proven lymph node metastases. In this study, there were no patients with suspicious central neck lymph nodes on preoperative bedside USG, but it is known that lymph node metastases in the central compartment do not always appear abnormal preoperatively on imaging in many patients.<sup>36</sup> The decision regarding CND performance was made intraoperatively. There could have been possibility of tumor upstaging in the PET group resulting from more concomitant CND being done in this group. As was shown previously, routine prophylactic CND tends to upstage tumors by upgrading nodal status from pN0 to pN1a.<sup>37</sup> The authors felt this possibility was unlikely, since prophylactic

CND was not performed throughout the study period, but because the distinction between prophylactic and therapeutic CND still remains unclear at times, the possibility of tumor upstaging could not be completely ruled out.

Due to the retrospective nature of the present study, there are potential selection biases. One such bias was that there were more patients in the PET group with history of nonthyroidal malignancy, which may have rendered the two groups less comparable. Also some ITC with disseminated nonthyroidal malignancy might have been excluded, as they would not have undergone thyroid resection because of poor overall prognosis, although one patient in the PET group did die of metastatic rectal carcinoma. In addition, there were significant advances in PET scanner technology over the study period, and this might account for the increase in detection of thyroid incidentaloma in the latter study period (2005–2009). Although unlikely, the authors could not exclude the possibility that some of these biases may account for some histological differences in the two groups.

## CONCLUSIONS

Those ITC detected by FDG-PET/CT had significantly higher frequency of tumor bilaterality than those detected by USG. Given this high frequency of 45% and the inability of current imaging studies to detect these contralateral foci, total thyroidectomy should be recommended for ITC detected by FDG-PET/CT even for tumor size <10 mm.

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