Retrospective Study

Characterization of focal hypermetabolic thyroid incidentaloma: An analysis with F-18 fluorodeoxyglucose positron emission tomography/computed tomography parameters

Haejun Lee, Yoo Seung Chung, Joon-Hyop Lee, Ki-Young Lee, Kyung-Hoon Hwang

ORCID number: Haejun Lee 0000-0002-6284-2903; Yoo Seung Chung 0000-0001-9912-051X; Joon-Hyop Lee 0000-0003-0470-7719; Ki-Young Lee 0000-0002-0333-7093; Kyung-Hoon Hwang 0000-0002-9988-1906.

Author contributions: Lee H and Hwang KH contributed to this work; Lee H and Hwang KH designed the research study; Lee H, Chung YS, Lee JH, Lee KY and Hwang KH performed the research; Lee H contributed analytic tools; Lee H, Chung YS, Lee JH, Lee KY and Hwang KH analyzed the data and wrote the manuscript; and all authors have read and approved the final manuscript.

Institutional review board statement: This retrospective study was approved by the institutional review board of our hospital (IRB no. GAIRB2020-297), and the requirement to obtain informed consent was waived. The study was conducted in accordance with the 1964 Declaration of Helsinki and later amendments.

Informed consent statement: The requirement to obtain informed consent was waived.

Conflict-of-interest statement: The

Abstract

BACKGROUND
Incidentally found thyroid tumor (thyroid incidentaloma, TI) on F-18 fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) is reported in 2.5%-5% of patients being investigated for non-thyroid purposes. Up to 50% of these cases have been diagnosed to be malignant by cytological/histological results. Ultrasonography (US) and fine-needle aspiration cytology are recommended for thyroid nodules with high FDG uptake (hypermetabolism) that are 1 cm or greater in size. It is important to accurately determine whether a suspicious hypermetabolic TI is malignant or benign.

AIM
To distinguish malignant hypermetabolic TIs from benign disease by analyzing F-18 FDG PET-CT parameters and to identify a cut-off value.

METHODS
Totally, 12761 images of patients who underwent F-18 FDG PET-CT for non-thyroid purposes at our hospital between January 2016 and December 2020 were retrospectively reviewed, and 339 patients [185 men (mean age: 68 ± 11.2) and 154 women (mean age: 63 ± 15.0)] were found to have abnormal, either focal or diffuse, thyroid FDG uptake. After a thorough review of their medical records, US, and cytological/histological reports, 46 eligible patients with focal hypermetabolic TI were included in this study. The TIs were categorized as malignant...
INTRODUCTION

The incidence of thyroid cancer has been increasing worldwide since the last few decades[1-3], although its mortality rate is relatively stable[4,5]. According to a recent report from a national institute of South Korea, the disease was ranked as the second most frequent cancer in women after breast cancer in 2018, and it was three times more common in women than in men[6]. Cancer predominantly occurs in older individuals; however, thyroid cancer and breast cancer have their highest frequencies at relatively young ages[7]. In both sexes, thyroid cancer is most frequently found between the ages of 15 and 34 years[6,7]. Moreover, the age-standardized incidence of thyroid cancer is reported to be 48.9 for both sexes, and it is 75.5 in women, which is higher than 65.6 for breast cancer[6]. Thyroid cancer is becoming more common among younger women.

and benign according to the cytological/histological reports, and four PET parameters [standardized uptake value (SUV)\textsubscript{max}, SUV\textsubscript{peak}, SUV\textsubscript{mean}, and metabolic tumor volume (MTV)] were measured on FDG PET-CT. Total lesion glycolysis (TLG) was calculated by multiplying the SUV\textsubscript{max} by MTV. Both parametric and non-parametric methods were used to compare the five parameters between malignant and benign lesions. Receiver operating characteristic (ROC) curve analysis was performed to identify a cut-off value.

RESULTS

Each of the 46 patients [12 men (26.1%; mean age: 62 ± 13.1 years) and 34 women (73.9%; mean age: 60 ± 12.0 years)] with focal hypermetabolic TIs had one focal hypermetabolic TI. Among them, 26 (56.5%) were malignant and 20 (43.5%) were benign. SUV\textsubscript{max}, SUV\textsubscript{peak}, SUV\textsubscript{mean}, and TLG were all higher in malignant lesions than benign ones, but the difference was statistically significant (P = 0.012) only for SUV\textsubscript{max}. There was a positive linear correlation (r = 0.339) between SUV\textsubscript{max} and the diagnosis of malignancy. ROC curve analysis for SUV\textsubscript{max} revealed an area under the curve of 0.702 (P < 0.05, 95% confidence interval: 0.550-0.855) and SUV\textsubscript{max} cut-off of 8.5 with a sensitivity of 0.615 and a specificity of 0.789.

CONCLUSION

More than half of focal hypermetabolic TIs on F-18 FDG PET-CT were revealed as malignant lesions, and SUV\textsubscript{max} was the best parameter for discriminating between malignant and benign disease. Unexpected focal hypermetabolic TIs with the SUV\textsubscript{max} above the cut-off value of 8.5 may have a greater than 70% chance of malignancy; therefore, further active assessment is required.

Key Words: Thyroid incidentaloma; Malignancy; Fluorodeoxyglucose positron emission tomography/computed tomography; Standardized uptake value; Cut-off

Core Tip: An unexpected focal thyroid incidentaloma (TI) is detected on various medical imaging studies. The lesion may harbor a risk of malignancy and the differentiation between malignant and benign disease is important. Standardized uptake value (SUV) is often measured for metabolism on F-18 fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT). Parameters of FDG PET-CT, including SUV, have been studied for many years in the fields of nuclear medicine and oncology. We conducted the present study to distinguish malignant TI from benign disease with an analysis of FDG PET-CT parameters.
2-Deoxy-2-[18F] fluoroglucose or F-18 fluorodeoxyglucose (F-18 FDG) positron emission tomography-computed tomography (PET-CT) is used widely in the diagnosis, treatment evaluation, and follow-up of cancer. However, its role in thyroid cancer is not as definite as in other cancers. This imaging modality is rather limited and might be used for thyroid cancer in cases of elevated blood thyroglobulin without obvious abnormal iodine uptake on a whole-body scan after total thyroidectomy and/or radioactive iodine therapy[8-10].

In this situation, an unexpectedly detected thyroid lesion (thyroid incidentaloma, TI) with high F-18 FDG uptake (hypermetabolism) may have important implications. This retrospective study was conducted to distinguish malignant hypermetabolic TIs from benign disease by analysing FDG PET-CT parameters of hypermetabolic TIs on PET-CT performed at our hospital for non-thyroid purposes and to identify an optimal cut-off value.

MATERIALS AND METHODS

Patients
We retrospectively reviewed the imaging data of 12761 patients who underwent F-18 FDG PET-CT to evaluate or follow-up their newly or previously diagnosed malignant disease, except for thyroid cancer, at our hospital between January 2016 and December 2020. We identified 339 patients (185 men and 154 women with mean age 68 ± 11.2 years and 63 ± 15.0 years, respectively) whose images presented incidentally abnormal hypermetabolism in their thyroid. From those, we selected patients with focal thyroid hypermetabolism after exclusion of the cases with known thyroid lesions and diffuse FDG uptake in or around the thyroid. The reports of ultrasonography (US) and, as a gold standard, cytological/histological examinations from fine-needle aspiration cytology or thyroidectomy were collected for the selected patients. Those with the reports of all three examinations were eligible for inclusion in this study.

Imaging of F-18 FDG PET-CT
All patients were required to fast for 4-6 h and had their blood glucose level checked before acquiring F-18 FDG PET-CT to ensure optimal image quality. When the blood glucose level was greater than or equal to 11 mmol/L (200 mg/dL), the scan was rescheduled. Scanning was performed 60 min after intravenously injecting 185 MBq F-18 FDG. Images from the skull base to the upper thigh were acquired using a dedicated PET-CT scanner, Biograph mCT 128 (Siemens Healthcare GmbH, Erlangen, Germany). Individually optimized images with lower patient radiation exposure were obtained with the emission scan performed for 3 min per bed by the step and shoot method and the CT scan performed in the continuous spiral mode with functions such as CareDose4D and CARE kV based on the default values of 60 mAs and 120 kVp, respectively. No contrast material was used for the CT scan. Both PET and CT images were reconstructed by the iterative reconstruction method, and fusion PET-CT images were generated on the dedicated image acquisition workstation provided with the PET-CT equipment.

Analysis of the F-18 FDG PET-CT images and cytological/histological results
Two nuclear medicine physicians examined the F-18 FDG PET-CT images. Once they identified an abnormal FDG uptake by the thyroid, they looked up the patient’s medical record to obtain the US and cytological/histological reports, then the lesion was categorized as malignant or benign according to the cytological/histological report when available. The maximum, peak, and mean of the semi-quantitative standardized uptake value (SUV) of focal TI were measured. SUVs of the contralateral thyroid were also measured. Additionally, the metabolic tumor volume (MTV) of TI was measured. The volume of interest (VOI) for measuring MTV can be drawn differently using different SUV thresholds. In this study, multiple SUV thresholds from 2 to 5 with an increment of 0.5 were used to obtain multiple MTVs. Finally, total lesion glycolysis (TLG) was calculated by multiplying MTV by the mean SUV. All imaging analyses were performed on a dedicated PET-CT workstation equipped with SyngoMMWP (Siemens Healthcare GmbH, Erlangen, Germany). These five parameters were compared between malignant and benign TIs, and receiver operating characteristic (ROC) curve analysis was performed to identify a cut-off value.
Statistics
Both parametric and non-parametric methods were used to compare $SUV_{max}$, $SUV_{peak}$, $SUV_{mean}$, MTV, and TLG between the malignant and benign lesions. Point biserial correlation was performed for the parameter(s) and malignancy. ROC curves were plotted, and the area under the curve (AUC) was calculated to determine an optimal cut-off value. Statistical analysis was performed using SPSS 16 (IBM, Armonk, New York, United States). A $P$ value of less than 0.05 was considered statistically significant.

Ethics
This retrospective study was approved by the institutional review board of our hospital (IRB no. GAIRB2020-297), and the requirement to obtain informed consent was waived. The study was conducted in accordance with the 1964 Declaration of Helsinki and later amendments.

RESULTS
Approximately 2.7% (339/12761) of all FDG PET-CT images reviewed initially showed abnormal thyroid hypermetabolism. The demographic and clinical characteristics of these 339 patients are shown in Table 1. Amongst the 339 non-thyroid disease patients [185 men (mean age: 68 ± 11.2) and 154 women (mean age: 63 ± 15.0 years)] with incidental suspicious hypermetabolism of the thyroid gland, 46 patients [13.6%, 12 men (mean age: 62 ± 13.1 years) and 34 women (mean age: 60 ± 12.0 years)] had focal hypermetabolism on PET-CT, and the hypermetabolic location was identified as a nodule on US and confirmed by cytological/histological analysis. Figure 1 shows some representative PET-CT images of such cases. Overall, 56.5% (26/46) of the cases were malignant, and the rest 43.5% (20/46) were benign. Amongst malignancy cases, 84.6% (22/26) were papillary, 3.8% (1/26) follicular, 3.8% (1/26) poorly differentiated, and 7.7% (2/26) Hurthle cell malignancies. Their primary cancers and cytological/histological results are presented in Table 2. Additionally, of the 23 well-differentiated thyroid cancer lesions, BRAF mutation test results were available for 19 cases, and all the 19 lesions were confirmed to have the mutation.

PET-CT parameters
Five representative parameters of PET-CT ($SUV_{max}$, $SUV_{peak}$, $SUV_{mean}$, MTV, and TLG) were compared to evaluate the differences between malignant and benign lesions. Table 3 shows an example of these parameters. The average $SUV_{max}$ of 26 malignant lesions and their contralateral isometabolic thyroid areas without US-identified lesions was 10.8 ± 7.5 and 2.5 ± 1.2, respectively, with a statistically significant difference ($P < 0.05$). Similarly, the average $SUV_{mean}$ of benign lesions and their contralateral thyroid areas was 6.5 ± 3.0 and 2.1 ± 0.7, respectively, also with statistical significance. There was a significant difference between the $SUV_{max}$ of malignant and benign focal thyroid lesions ($P = 0.012$). The $SUV_{max}$ of contralateral thyroid areas of both malignant and benign lesions presented no significant difference. Point biserial correlation resulted in a statistically significant positive linear correlation ($r = 0.339$) between $SUV_{max}$ and the malignant cytological/histological report ($P < 0.05$).

$SUV_{max}$ presented no statistical significance with a $P$-value of 0.058, which was close to significance. The $SUV_{max}$ showed statistical significance with a threshold of 2 ($P = 0.011$) and 2.5 ($P = 0.014$). The $SUV_{mean}$ with other thresholds, MTV, and TLG failed to show any statistical significance.

An ROC curve was plotted for $SUV_{max}$ (Figure 2), and the AUC was 0.702 ($P < 0.05$, 95% confidence interval: 0.550-0.855). The $SUV_{max}$ cut-off value was 8.5 with a sensitivity of 0.615 and a specificity of 0.789.

DISCUSSION
The number of diagnoses of thyroid cancer has been increasing for several decades, and this includes TIs identified by PET-CT, CT, magnetic resonance imaging, and US conducted for non-thyroid purposes. Well-differentiated thyroid cancers such as papillary and follicular cancers, which develop from thyroid follicular cells, comprise more than 85% of all thyroid cancers[11,12]. Well-differentiated thyroid cancers are known to be less aggressive and have a better prognosis than other thyroid cancers.
Table 1 Demographic and clinical characteristics of patients who had abnormal hypermetabolism in the thyroid (n = 339)

| Characteristics          | Male | Female | Total |
|--------------------------|------|--------|-------|
| Subjects (n)             | 185  | 154    | 339   |
| Age (yr, mean ± SD)      | 68 ± 11.2 | 63 ± 15.0 | 66 ± 13.3 |
| Primary malignancy (n)   |      |        |       |
| Lung                     | 64   | 33     | 97    (28.6%) |
| Colorectal               | 31   | 11     | 42    (12.4%) |
| Breast                   | 0    | 50     | 50    (14.7%) |
| Lymphoma                 | 15   | 15     | 30    (8.8%) |
| Gastrointestinal         | 20   | 8      | 28    (8.3%) |
| Hepatobiliary            | 20   | 8      | 28    (8.3%) |
| Head and neck            | 13   | 2      | 15    (4.4%) |
| Other                    | 22   | 27     | 49    (14.5%) |

Table 2 Classification of 46 focal hypermetabolic thyroid lesions as malignant or benign according to the type of primary cancer (n = 46)

| Primary cancer   | Malignant | Benign | Total |
|------------------|-----------|--------|-------|
| Breast           | 5         | 6      | 11    |
| Kidney           | 1         | 0      | 1     |
| Colorectal       | 2         | 3      | 5     |
| GIST             | 0         | 1      | 1     |
| Lung             | 8         | 8      | 16    |
| Stomach          | 2         | 0      | 2     |
| Uterine cervix   | 3         | 0      | 3     |
| Sarcoma          | 1         | 0      | 1     |
| Urinary bladder  | 1         | 0      | 1     |
| Salivary gland   | 1         | 0      | 1     |
| Lymphoma         | 1         | 2      | 3     |
| Bone             | 1         | 0      | 1     |
| Total            | 26        | 20     | 46    |

GIST: Gastrointestinal stromal tumor.

such as poorly differentiated thyroid cancer, anaplastic thyroid cancer, or Hurthle cell cancer; however, up to 5% of well-differentiated thyroid cancers could become dedifferentiated and aggressive [13-15]. Dedifferentiated thyroid cancer is generally not very responsive to radioactive iodine therapy, while well-differentiated cancer shows a good response. FDG is easily taken up by aggressive cancers with less/non-iodine-avidity or by tumors with increased malignancy due to the elevated expression of glucose transporter 1. As the majority of thyroid cancers are slow-growing well-differentiated types, they are generally less FDG avid, and F-18 FDG PET-CT has a limited role in the initial evaluation. It is usually only used for the evaluation of recurrences after resection and/or iodine therapy when the thyroglobulin level in the serum is suspicious without definite abnormal findings on US or an iodine whole-body scan. Therefore, the focus of this study is not on the initial evaluation of thyroid cancer but on unexpectedly identified FDG uptake by the thyroid on PET-CT performed for the diagnosis or follow-up of other cancers.
Table 3 Examples of F-18 fluorodeoxyglucose positron emission tomography-computed tomography parameters

| Parameters | Malignant (n = 26) | Benign (n = 20) | P value |
|------------|-------------------|----------------|---------|
| SUV<sub>max</sub> | 10.8 ± 7.5 | 6.5 ± 3.0 | 0.012 |
| SUV<sub>peak</sub> | 6.8 ± 5.7 | 4.4 ± 2.0 | 0.058 |
| MTV<sub>2</sub> | 5.06 ± 5.2 | 6.7 ± 6.6 | 0.354 |
| SUV<sub>mean2</sub> | 3.8 ± 1.5 | 3.0 ± 0.5 | 0.011 |
| TLG<sub>2</sub> | 25.5 ± 48.9 | 21.3 ± 24.0 | 0.735 |
| MTV<sub>2.5</sub> | 3.5 ± 4.5 | 3.7 ± 4.2 | 0.872 |
| SUV<sub>mean2.5</sub> | 4.5 ± 1.6 | 3.6 ± 0.7 | 0.014 |
| TLG<sub>2.5</sub> | 22.0 ± 47.6 | 14.8 ± 19.0 | 0.532 |

SUV: Standardized uptake value; MTV: Metabolic tumor volume; TLG: Total lesion glycolysis.

Figure 1 Examples of focal hypermetabolic thyroid incidentaloma. A: Focal fluorodeoxyglucose (FDG) uptake is observed in the right lower neck on the maximum intensity projection (MIP) image of a 53-year-old woman diagnosed with left breast cancer (FDG uptake in the left breast and axillary fossa); B: On the axial view, the focal FDG uptake is observed in the right thyroid lobe with maximum standardized uptake value (SUV<sub>max</sub>) 5.9 and it was diagnosed as a benign nodule by cytological/histological examination; C: Focal FDG uptake is observed in the right lower neck on the MIP image of a 66-year-old woman diagnosed with adenocarcinoma in the right lower lobe of lung as a result of biopsy performed due to abnormal radiologic findings; D: On the axial view, the focal FDG uptake is observed in the right thyroid lobe (SUV<sub>max</sub> 8.6) and the cytological/histological examination revealed papillary thyroid cancer.

Diffuse thyroid FDG uptake has a greater chance of being benign thyroid diseases such as thyroiditis or hypothyroidism than cancer[16,17]. However, about 25%-50% of focal hypermetabolic TIs, with a prevalence of 2.5%-5%, have malignant cytological/histological reports[18-22]. In other words, approximately half of hypermetabolic TIs could have a risk of malignancy, and therefore, it is critical to differentiate them as malignant or benign. In this study, 2.7% of total available PET-CT images had either diffuse or focal abnormal thyroid hypermetabolism, and 13.6% (46/339) of these presented focal hypermetabolism. Finally, 56.5% of the latter were diagnosed as cancer and, within the known range, 88.5% (23/26) of the pathologically confirmed malignant lesions were well-differentiated thyroid cancers. From this, it is suggested that any 2 out of 1000 FDG PET-CT scans have a possibility of incidentally finding thyroid cancer.

Of the 23 well-differentiated malignant lesions of this study, 19 were available for the BRAF mutation test, and 100% (19/19) lesions were proved to have the mutation. This (dedifferentiation) could be associated with a change in FDG avidity from low to high. As this study was conducted on any hypermetabolic lesions discovered with the naked eye, lesions not yet advanced, which is why they had low FDG uptake and therefore had less chance to be observed on images, were likely excluded from the study. This unrecognized selection bias probably resulted in a high FDG uptake even in lesions of well-differentiated thyroid cancer. Conversely, if thyroid cancer was...
All of the patients involved in this study already had one type of cancer but not thyroid cancer, and we excluded PET-CT images acquired for benign diseases or health check-ups. This patient selection might influence the malignancy rate, especially since there is a report describing the prevalence of TI being higher in patients with cancer than in healthy subjects\cite{19}.

The higher the semi-quantitative SUV on F-18 FDG PET-CT, the higher is the possibility of cancer with various reported cut-off values, and this is related to the prognosis and overall survival\cite{23-26}. Among the five PET parameters associated with SUV and the metabolic volume of the tumor, SUV\textsubscript{max} showed good performance in discriminating malignant lesions from benign ones. The mean value of SUV\textsubscript{mean} was higher in the malignant group and presented a statistical significance difference comparable to SUV\textsubscript{max}, in some conditions (SUV threshold of 2.0 and 2.5). This could be associated with a larger volume of benign lesions with the same SUV thresholds. There was no statistical significance for the SUV\textsubscript{mean} with other SUV thresholds where the volumes were all larger in the malignant group. In a situation with a low SUV threshold, the VOI might include areas outside the tumor, and consequently, the final measured volume could be larger than the real volume. SUV\textsubscript{mean} might be influenced and reduced as the volume of benign lesions is unintentionally larger, and this could lead to a significant statistical difference from that of malignant lesions. The mean values of SUV\textsubscript{peak} and TLG were higher in the malignant group but without statistical significance, although SUV\textsubscript{peak} caught our attention with a $P$-value of 0.058, which was close to significance.

There are studies on TIs reporting that MTV, TLG, or both are useful parameters in distinguishing malignant lesions from benign ones\cite{27-31}, while other reported different conclusions\cite{32}. The roles of MTV and TLG in other cancers are still open to debate\cite{33-36}. In this study, both MTV and TLG were not useful in the discrimination. TLG was expected to be a good discriminator initially like SUV\textsubscript{max}, but it was not. This might have something to do with MTV. There are reports that a specific range of thyroid nodule sizes had a greater prevalence of malignancy, while others found no increased risk of malignancy over a specific nodule size\cite{37-41}. These findings imply that a larger size does not necessarily mean a higher possibility of malignancy. MTV might be thought of in a similar way, and thus a larger MTV does not always mean malignancy. In this way, there is a possibility that TLG, which is the product of SUV\textsubscript{mean} and MTV, might not reflect the risk of malignancy well. Finally, SUV\textsubscript{max} was the only reliable discriminator, while SUV\textsubscript{peak} might be a candidate. In contrast, the other parameters had no discernible statistical impact.

SUV\textsubscript{max} was chosen for the ROC curve. Based on the AUC\cite{42,43}, SUV\textsubscript{max} has a power of fair discrimination with approximately 70% probability for malignancy in an unexpectedly identified focal hypermetabolic thyroid lesion. The lesions with SUV\textsubscript{max}
higher than 8.5 have a greater chance to be malignant with a sensitivity of 61.5% and a specificity of 78.9%. Some cases of Hurthle cell adenoma, which might have high FDG uptake[44-46], were included in the benign group and these could reduce the sensitivity and AUC, making the discrimination difficult. The reading of PET-CT images relies mainly on the naked eye qualitatively and it is not simple to distinguish malignant lesions from benign ones with a high FDG uptake. Relatively rare metastatic lesions from other cancers could also have a high FDG uptake[47-49]. Therefore, SUV\(_{\text{max}}\) with a reference of suggested cut-off value should be measured in cases of hypermetabolic TI, and further active examination is recommended to characterize lesions above the threshold.

### CONCLUSION

More than half of the focal hypermetabolic TIs on F-18 FDG PET-CT were revealed as malignant. SUV\(_{\text{max}}\) was the best parameter for discriminating malignant and benign lesions. The unexpected focal hypermetabolic TIs with an SUV\(_{\text{max}}\) above the cut-off value of 8.5 may have a greater than 70% chance of malignancy; therefore, further active assessment is required to characterize these lesions.

### ARTICLE HIGHLIGHTS

**Research background**

Thyroid incidentaloma (TI) is detected on imaging studies for non-thyroid purposes and the lesion may harbor a risk of malignancy. It is critical to distinguish malignant TI from benign disease.

**Research motivation**

The higher the metabolism on F-18 fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) image, the higher the possibility of malignancy. TI might be characterized depending on the FDG metabolism.

**Research objectives**

To distinguish malignant hypermetabolic TIs from benign disease by analyzing F-18 FDG PET-CT parameters and to identify a cut-off value.

**Research methods**

The values of parameters from FDG PET-CT of 46 focal hypermetabolic thyroid lesions were measured, calculated, and compared. Receiver operating characteristic (ROC) curve was plotted to determine a cut-off value.

**Research results**

Standardized uptake value (SUV\(_{\text{max}}\)) was the only statistically significant discriminator in differentiation. From the ROC curve, the AUC was 0.702 and the SUV\(_{\text{max}}\) cut-off value was 8.5.

**Research conclusions**

TIs with SUV\(_{\text{max}}\) above the cut-off value 8.5 may have a greater than 70% chance of malignancy. A further active assessment is required.

**Research perspectives**

Other studies and controversies on the parameters included in this study are ongoing. Further studies with a large number of subjects are guaranteed.

### REFERENCES

1. Rossi ED, Pantanowitz L, Hornick JL. A worldwide journey of thyroid cancer incidence centred on tumour histology. *Lancet Diabetes Endocrinol* 2021; 9: 193-194 [PMID: 33662332 DOI: 10.1016/S2213-8587(21)00049-8]

2. Olson E, Wintheiser G, Wolfe KM, Droessler J, Silberstein PT. Epidemiology of Thyroid Cancer: A Review of the National Cancer Database, 2000-2013. *Cureus* 2019; 11: e4127 [PMID: 31049276]
Lee H et al. Focal hypermetabolic thyroid incidentaloma

DOI: 10.7759/cureus.4127

3 Vaccarella S, Franceschi S, Bray F, Wild CP, Plummer M, Dal Maso L. Worldwide Thyroid-Cancer Epidemic? N Engl J Med 2016; 375: 614-617 [PMID: 27532827 DOI: 10.1056/NEJMep1604412]

4 Ahn HS, Kim HJ, Kim KH, Lee YS, Han SJ, Kim Y, Ko MJ, Brito JP. Thyroid Cancer Screening in South Korea Increases Detection of Papillary Cancers with No Impact on Other Subtypes or Thyroid Cancer Mortality. Thyroid 2016; 26: 1535-1540 [PMID: 27627550 DOI: 10.1089/thy.2016.0075]

5 Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014; 140: 317-322 [PMID: 24545566 DOI: 10.1001/jamaent.oa.2014.1]

6 Korea Central Cancer Registry. Annual report of cancer statistics in Korea in 2018. [cited from 15 August 2021]. Available from: https://www.kccrc.re.kr/cancerStatsView.ncc?bsnum=558&searchKey=total&searchValue=1&PageNum=1

7 Hong S, Won YJ, Park YR, Jung KW, Kong HJ, Lee ES; Community of Population-Based Regional Cancer Registries. Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2017. Cancer Res Treat 2020; 52: 335-350 [PMID: 32178489 DOI: 10.4143/crt.2020.206]

8 Bannas P, Derlin T, Groth M, Apostolova I, Adam G, Mester J, Kuthmann S. Can (18)F-FDG-PET/CT be generally recommended in patients with differentiated thyroid carcinoma and elevated thyroglobulin levels but negative I-131 whole body scan? Ann Nucl Med 2012; 26: 77-85 [PMID: 22006540 DOI: 10.1007/s00405-011-0545-4]

9 Bertagna F, Bosio G, Biasiotto G, Rodella C, Peta E, Gabanelli S, Lucchini S, Merli G, Saveli G, Giubini R, Rosenbaum J, Alavi A. F-18 FDG-PET/CT evaluation of patients with differentiated thyroid cancer with negative I-131 total body scan and high thyroglobulin level. Clin Nucl Med 2009; 34: 756-761 [PMID: 19851169 DOI: 10.1097/RLU.0b013e3181f7d95c]

10 Okayuca K, Incs S, Alagöz E, Emer O, San H, Balkan E, Ayan A, Meric C, Haymana C, Aıçekel C, Gulanb P, Karacalıoğlu AO, Arslan N. Risk factors and stratification for recurrence of patients with differentiated thyroid carcinoma, elevated thyroglobulin and negative I-131 whole-body scan, by restaging (18)F-FDG-PET/CT. Hell J Nucl Med 2016; 19: 206-217 [PMID: 27824959 DOI: 10.1967/s00405-014-01042]

11 Shah JP. Thyroid carcinoma: epidemiology, histology, and diagnosis. Clin Adv Hematol Oncol 2015; 13: 3-6 [PMID: 26430868]

12 Haddad RL, Nasr C, Bischoff L, Busaïdy NL, Byrd D, Callender G, Dickson P, Duh QY, Elsay H, Goldner W, Haymait M, Hoh C, Hunt JP, Ingaru A, Kandeel F, Kopp P, Lamonic JA, McIver BP, McIver E, McIver N, Mielor P, Raeburn CD, Ridge JA, Ringel MD, Scheri RP, Shah JP, Sippel R, Smallridge RC, Sturgeon C, Wang TN, Wirth LJ, Wong RJ, Johnson-Chilla A, Hoffmann KG, Gurski LA. NCCN Guidelines Insights: Thyroid Carcinoma, Version 2.2018. J Natl Compr Canc Netw 2018; 16: 1429-1440 [PMID: 30545990 DOI: 10.6004/jnccn.2018.0089]

13 Antonelli A, Ferrari C, Ferrari SM, Sebastiani M, Colaci M, Ruffilli I, Fallaha I. New targeted molecular therapies for dedifferentiated thyroid cancer. J Oncol 2010; 2010: 921682 [PMID: 20628483 DOI: 10.1155/2010/921682]

14 Sturgeon C, Angelos P. Identification and treatment of aggressive thyroid cancers. Part 1: subtypes. Oncology (Williston Park) 2006; 20: 253-260 [PMID: 16629257]

15 Braga-Basaria M, Ringel MD. Clinical review 158: Beyond radioidine: a review of potential new therapeutic approaches for thyroid cancer. J Clin Endocrinol Metab 2003; 88: 1947-1960 [PMID: 12727938 DOI: 10.1210/jc.2002-021863]

16 Liu Y. Clinical significance of thyroid uptake on F18-fluorodeoxyglucose positron emission tomography. Ann Nucl Med 2009; 23: 17-23 [PMID: 19205834 DOI: 10.1007/s12149-008-0098-0]

17 Karantanis D, Bogsrud TV, Wiseman GA, Mullan BP, Subramaniam RM, Nathan MA, Peller PJ, Bahn RS, Lowe VI. Clinical significance of diffusely increased 18F-FDG uptake in the thyroid gland. J Nucl Med 2007; 48: 896-901 [PMID: 17504869 DOI: 10.2967/jnumed.106.039024]

18 Burguera B, Gharib H. Thyroid incidentalomas. Prevalence, diagnosis, significance, and management. Endocrinol Metab Clin North Am 2000; 29: 187-203 [PMID: 10732271 DOI: 10.1016/s0889-8529(05)70123-7]

19 Choi JY, Lee KS, Kim HJ, Shim YM, Kwon OJ, Park K, Baek CH, Chung JH, Lee KH, Kim BT. Focal thyroid lesions incidentally identified by integrated 18F-FDG PET/CT: clinical significance and improved characterization. J Nucl Med 2006; 47: 609-615 [PMID: 16595494]

20 Kwak JY, Kim EK, Yun M, Cho A, Kim MJ, Son EJ, Oh KK. Thyroid incidentalomas identified by 18F-FDG PET: sonographic correlation. AJR Am J Roentgenol 2008; 191: 598-603 [PMID: 18647938 DOI: 10.2214/AJR.07.3443]

21 Bertagna F, Treglia G, Riccadonna A, Giubini R. Diagnostic and clinical significance of F-18-FDG-PET/CT thyroid incidentalomas. J Clin Endocrinol Metab 2012; 97: 3866-3875 [PMID: 22904176 DOI: 10.1210/jc.2012-2390]

22 Gavriel H, Tang A, Eviatar E, Chan SW. Unfolding the role of PET FDG scan in the management of thyroid incidentaloma in cancer patients. Eur Arch Otorhinolaryngol 2015; 272: 1763-1768 [PMID: 24902804 DOI: 10.1007/s00405-014-3120-5]

23 Kim SH, Song BI, Kim HW, Won KS, Son YG, Ryu SW. Prognostic Value of Restaging F-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography to Predict 3-Year Post-Recurrence Survival in Patients with Recurrent Gastric Cancer after Curative Resection. Korean J Radiol 2020; 21: 829-837 [PMID: 32524783 DOI: 10.3348/kjr.2019.0672]

24 Purandare NC, Purank A, Shah S, Agrawal A, Puri A, Gulia A, Nayak P, Rekhi B, Rangarajan V. Can 18F-FDG PET/CT diagnose malignant change in benign chondroid tumors? Nucl Med Commun
Lee H et al. Focal hypermetabolic thyroid incidentaloma

2019; 40: 645-651 [PMID: 30921251 DOI: 10.1097/NN.0000000000007015]

Kohutek ZA, Wu AJ, Zhang Z, Foster A, Din SU, Yorke ED, Downey R, Rosenzweig KE, Weber WA, Rimner A. FDG-PET maximum standardized uptake value is prognostic for recurrence and survival after stereotactic body radiotherapy for non-small cell lung cancer. *Lung Cancer* 2015; 89: 115-120 [PMID: 26078260 DOI: 10.1016/j.lungcan.2015.05.019]

Nguyen NC, Kaushik A, Wolverson MK, Osman MM. Is there a common SUV threshold in oncological FDG PET/CT, at least for some common indications? *Acta Oncol* 2011; 50: 670-677 [PMID: 21243762 DOI: 10.3109/0284186X.2011.559033]

Erdoğan M, Korkmaz H, Tüysüz M, Yıldız M, Sengül SS. The Role of Metabolic Volumetric Parameters in Predicting Malignancy in Incidental Thyroid Nodules Detected in 18F-FDG PET/CT Scans. *Med Imaging Radiac Ther* 2021; 30: 86-92 [PMID: 34082507 DOI: 10.4247/mirt.galenos.2021.75983]

Sollini M, Cozzi L, Pepe G, Antonovic L, Lania A, Di Tommaso L, Magnoni P, Erba PA, Kirienko M. [18F]FDG-PET/CT texture analysis in thyroid incidentomas: preliminary results. *Eur J Hybrid Imaging* 2017; 1: 1 [PMID: 29782578 DOI: 10.1186/s41824-017-0009-8]

Shi H, Yuan Z, Yang C, Zhang J, Shou Y, Zhang W, Ping Z, Gao X, Liu S. Diagnostic Value of Volume-Based Fluorine-18-Fluorodeoxyglucose PET/CT Parameters for Characterizing Thyroid Incidentaloma. *Korean J Radiol* 2018; 19: 342-351 [PMID: 29520193 DOI: 10.3348/kjr.2018.19.2.342]

Ceriani L, Milan L, Virili C, Cascione L, Paone G, Trimobili P, Giovannella L. Radiomics Analysis of [18F]-Fluorodeoxyglucose-Avid Thyroid Incidentomas Improves Risk Stratification and Selection for Clinical Assessment. *Thyroid* 2021; 31: 88-95 [PMID: 32517585 DOI: 10.1089/thy.2020.0224]

Kim BH, Kim SJ, Kim H, Jeon YK, Kim SS, Kim H, Kim YK. Diagnostic value of metabolic tumor volume assessed by 18F-FDG PET/CT added to SUVmax for characterization of thyroid 18F-FDG incidentomas. *Nuc Med Commun* 2013; 34: 868-876 [PMID: 23797273 DOI: 10.1097/0000000000000979]

Thuillier P, Bourhis D, Roudaut N, Crouzeix G, Alavi Z, Schick U, Robin P, Kerlan V, Salaun PY, Abgral R. Diagnostic Value of FDG PET-CT Quantitative Parameters and Deauville-Like 5-Point Scale in Predicting Malignancy of Focal Thyroid Incidentaloma. *Front Med (Lausanne)* 2019; 6: 24 [PMID: 30809525 DOI: 10.3389/fmed.2019.00024]

Chen B, Feng H, Xie J, Li C, Zhang Y, Wang S. Differentiation of soft tissue and bone sarcomas from benign lesions utilizing [18F]-FDG PET/CT-derived parameters. *BMI Med Imaging* 2020; 20: 85 [PMID: 32711449 DOI: 10.1186/s12880-020-00486-2]

Hu Y, Zhou W, Sun S, Guan Y, Ma J, Xie Y. 18F-fluorodeoxyglucose positron emission tomography-based prediction for splenectomy in patients with suspected splenic lymphoma. *Ann Transl Med* 2021; 9: 1009 [PMID: 34277809 DOI: 10.21037/atm-21-2790]

Morita T, Tatsumi M, Ishibashi M, Isohashi K, Kato H, Honda O, Shimosegawa E, Tomiyama N, Hatazawa J. Assessment of Mediastinal Tumors Using SUVmax and Volumetric Parameters on FDG-PET/CT. *Asia Ocean J Nucl Med Biol* 2017; 5: 22-29 [PMID: 28840135 DOI: 10.22038/aognmb.2016.7996]

Shen CT, Qiu ZL, Sun ZK, Wei WJ, Song HJ, Zhang XY, Luo QY. Dual time-point 18F-FDG PET/CT imaging with multiple metabolic parameters in the differential diagnosis of malignancy-suspected bone/joint lesions. *Oncotarget* 2017; 8: 71186-71196 [PMID: 29050335 DOI: 10.18632/oncotarget.17140]

Al-Hakami HA, Alqahtani R, Alahmadi A, Almutairi D, Alqarni M, Alandejani T. Thyroid Nodule Size and Prediction of Cancer: A Study at Tertiary Care Hospital in Saudi Arabia. *Cureus* 2020; 12: e7478 [PMID: 32351856 DOI: 10.7759/cureus.7478]

Kamran SC, Marqusee E, Kim MI, Frates MC, Ritter J, Peters H, Benson CB, Doubilet PM, Cibas ES, Barletta J, Cho N, Gawande A, Ruan D, Moore FD Jr, Pou K, Larsen PR, Alexander EK. Thyroid nodule size and prediction of cancer. *J Clin Endocrinol Metab* 2013; 98: 564-570 [PMID: 23275525 DOI: 10.1210/jc.2012-2968]

Chung SR, Baek JH, Choi YJ, Sung TY, Song DE, Kim TY, Lee JH. The relationship of thyroid nodule size on malignancy risk according to histological type of thyroid cancer. *Acta Radiol* 2020; 61: 620-628 [PMID: 31554409 DOI: 10.1177/0284185119875642]

Cavallone A, Johnson DN, White MG, Siddiqui S, Antic T, Mathew M, Grogan RH, Angelos P, Kaplan EL, Cipriani NA. Thyroid Nodule Size at Ultrasound as a Predictor of Malignancy and Final Pathologic Size. *Thyroid* 2017; 27: 641-650 [PMID: 28052718 DOI: 10.1089/thy.2016.0336]

Aydoglan BI, Sahin M, Ceyhan K, Deniz O, Demir Ö, Emral R, Tonayukuk Gedik V, Uysal AR, Çorapçioğlu D. The influence of thyroid nodule size on the diagnostic efficacy and accuracy of ultrasound guided fine-needle aspiration cytology. *Diagn Cytopathol* 2019; 47: 682-687 [PMID: 30861335 DOI: 10.1002/dc.24170]

Muller MP, Tomlinson G, Marrie TJ, Pang P, McGeer A, Low DE, Detuky AS, Gold WL. Can routine laboratory tests discriminate between severe acute respiratory syndrome and other causes of community-acquired pneumonia? *Clin Infect Dis* 2005; 40: 1079-1086 [PMID: 15791504 DOI: 10.1086/428577]

Kang YS, Kang JH, Kim MC, Yu BY, Sung EJ, Lee SY, Lee YJ. Cutoff of Percent Body Fat to Predict Obesity and Metabolic Risk in Children and Adolescents: 2007 Children and Adolescent Physical Growth Standard. *Korean J Fam Med* 2009; 30: 887-894 [DOI: 10.4082/kjfm.2009.30.11.887]
44 Pathak KA, Klonisch T, Nason RW, Leslie WD. FDG-PET characteristics of Hürthle cell and follicular adenomas. *Ann Nucl Med* 2016; 30: 506-509 [PMID: 27221817 DOI: 10.1007/s12149-016-1087-6]

45 Hassan A, Riaz S, Asif A. Hypermetabolic Hurthle Cell Adenoma on ¹⁸F-FDG PET/CT. *Mol Imaging Radionucl Ther* 2018; 27: 96-98 [PMID: 29889034 DOI: 10.4274/mirt.49469]

46 Yu R, Auerbach MS. FDG-Avid Hürthle Cell Thyroid Adenoma. *Clin Nucl Med* 2019; 44: 752-753 [PMID: 31135518 DOI: 10.1097/RLU.0000000000002617]

47 Nagarajah J, Ho AL, Tuttle RM, Weber WA, Grewal RK. Correlation of BRAFV600E Mutation and Glucose Metabolism in Thyroid Cancer Patients: An ¹⁸F-FDG PET Study. *J Nucl Med* 2015; 56: 662-667 [PMID: 25814520 DOI: 10.2967/jnumed.114.150607]

48 Yoon S, An YS, Lee SJ, So EY, Kim JH, Chung YS, Yoon JK. Relation Between F-18 FDG Uptake of PET/CT and BRAFV600E Mutation in Papillary Thyroid Cancer. *Medicine (Baltimore)* 2015; 94: e2063 [PMID: 26632889 DOI: 10.1097/MD.0000000000002063]

49 Kim H, Na KJ, Choi JH, Ahn BC, Ahn D, Sohn JH. Feasibility of FDG-PET/CT for the initial diagnosis of papillary thyroid cancer. *Eur Arch Otorhinolaryngol* 2016; 273: 1569-1576 [PMID: 25971994 DOI: 10.1007/s00405-015-3640-7]
