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# Risk Stratification of Thyroid Incidentalomas Found on PET/CT: The Value of Iodine Content on Noncontrast Computed Tomography

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***Background:*** The Hounsfield unit (HU) ratio of thyroid nodules was assessed compared to the contralateral thyroid lobe on noncontrast computed tomography (CT) to stratify further the risk of malignancy in thyroid incidentalomas found on $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography/CT (PET/CT).
***Methods:*** This retrospective analysis included 82 patients who had thyroid incidentalomas on PET/CT in 2011. On PET/CT, the maximal standardized uptake value ratios of the thyroid nodule compared to liver ($T/B_{SUV}$) and the HU ratios of the thyroid nodule compared to contralateral thyroid lobe ($T/B_{HU}$) were calculated. Diagnostic performances of the $T/B_{SUV}$ and $T/B_{HU}$ were compared.
***Results:*** The area under the curve of $T/B_{HU}$ was higher than that of $T/B_{SUV}$ (0.941 vs. 0.689, $p<0.0001$). The sensitivity, specificity, and accuracy of $T/B_{HU}$ were significantly higher than those of $T/B_{SUV}$ (100% vs. 77.8%, $p=0.0313$; 80.0% vs. 60.0%, $p=0.0433$; 86.6% vs. 65.9%, $p=0.0041$, respectively). The risk of malignancy was much higher (71.1%) in nodules with a $T/B_{HU}$ cutoff value ≤0.68, whereas it was 0% in nodules with a $T/B_{HU}$ of >0.68. In this study, there were 18 nodules with nondiagnostic ($n=7$) or atypia of undetermined significance or follicular lesion of undetermined significance cytologies ($n=11$) after fine-needle aspiration biopsy (FNAB). When the $T/B_{HU}$ cutoff value was applied, three (60%) of the five nodules with a $T/B_{HU}$ of ≤0.68 were found to be papillary carcinomas. The remaining 13 nodules with a $T/B_{HU}$ of >0.68 were all benign with a risk of malignancy of 0%.
***Conclusions:*** $T/B_{HU}$ is a simple and effective parameter to stratify the risk of malignancy in thyroid incidentalomas found on PET/CT. This may be of clinical relevance in those nodules with nondiagnostic or undetermined significance cytologies upon FNAB in the scheme of current clinical practice.

## Introduction

$^{18}$F-Fluorodeoxyglucose ($^{18}$F-FDG) positron emission tomography/computed tomography (PET/CT) is a noninvasive whole-body imaging technique, which may allow clinicians to distinguish malignant tumors from benign lesions based on the degree of glycolytic metabolism (1,2). Diffuse or focal FDG uptake in the thyroid is often seen as an incidental finding on PET/CT images taken during evaluation for nonthyroid disease (3). While bilateral and diffuse thyroid uptake are linked to thyroiditis and are associated with a low risk of malignancy, focal uptake indicates an unexpected thyroid tumor, or so-called thyroid incidentaloma, found during the investigation of unrelated conditions (4). Without a history of external beam radiation or familial medullary thyroid cancer, the risk of malignancy ranges between 5% and 13% when discovered with ultrasound (US), CT, or magnetic resonance imaging (MRI), but is much higher (26–50%) if based on focal $^{18}$F-FDG uptake (5–12).

Differentiation between malignant and benign thyroid nodules is essential for reducing unnecessary operations and determining the patient's prognosis. Although malignant thyroid nodules tend to have higher maximum standardized uptake values ($SUV_{max}$) values than benign nodules, $SUV_{max}$ alone is limited in differentiating malignancy from benignity in a single nodule (13–15). Thus, medical guidelines on the diagnosis and management of thyroid nodules, including the American Thyroid Association (ATA) guidelines amongst others, recommend US and fine-needle aspiration biopsy (FNAB) for thyroid incidentalomas detected by $^{18}$F-FDG PET imaging (16,17). However, indeterminate FNAB results are obtained in 12–20% of cases, which poses a treatment

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dilemma (18–20). In most cases, repeat FNAB or diagnostic surgery is performed, even though the majority turns out to be benign. Therefore, there is a need for more accurate diagnostic techniques in order to avoid unnecessary additional invasive procedures.

The value of contrast-enhanced CT seems inconclusive in differentiating benign from malignant thyroid nodules. Thus, US is generally recommended for all incidental nodules on contrast-enhanced CT (21–23). In contrast, thyroid scintigraphy using $^{123}$I has been used to select nodules for further diagnostic workup based on iodine metabolism within the nodules (24). Noncontrast CT is similar to thyroid scintigraphy in that a low iodine concentration in the thyroid presents as low attenuation on noncontrast CT scans (25–28). This study investigated whether the iodine content of thyroid nodules on noncontrast CT scans taken during PET/CT imaging could further stratify the risk of malignancy in thyroid incidentalomas with focal $^{18}$F-FDG uptake.

## Materials and Methods

This study was approved by the Institutional Review Board at Yonsei University College of Medicine, and the need for written informed consent was waived.

### *Patients*

This retrospective analysis included 143 patients who had thyroid incidentalomas with focal $^{18}$F-FDG uptake upon PET/CT in 2011. Of these 143 patients, 61 were excluded for the following reasons: (a) lesions with a poor CT image quality due to beam hardening artifacts ($n = 18$); (b) nodules with gross calcification, which have a different risk of malignancy compared with noncalcified nodules, based on the pattern of calcification ($n = 3$); and (c) follow-up loss without further investigation ($n = 40$).

Finally, 82 patients (19 men; $M_{age} = 58.8$ years, range 32–82 years) with a final diagnosis made on the basis of FNAB ($n = 52$) or surgery ($n = 27$) were included. There were four patients with multiple foci on PET/CT, and only one nodule with the highest FDG uptake per patient was selected for analysis. Patients with benign results upon US were followed up by US for at least 12 months ($n = 3$). The mean size of the 82 thyroid nodules was 16.1 mm (range 5–49 mm). PET/CT was performed for the following reasons: cancer staging (nonthyroidal cancers, $n = 33$), cancer surveillance ($n = 32$), and health screening examination ($n = 17$).

### *$^{18}$F-FDG PET/CT protocol*

All patients were requested to fast for at least 6 h, and blood glucose concentrations of <140 mg/dL were confirmed before the study. About 5.5 MBq of $^{18}$F-FDG per kilogram of body weight was administered intravenously. Imaging was performed using a PET/CT scanner (DSTe; GE Healthcare, Milwaukee, WI) with an axial field of view of 157 mm and a spatial resolution of 4.0 mm in full width at half maximum at 10 mm from the center. An hour after $^{18}$F-FDG injection, a low-dose CT scan was obtained for attenuation correction with an 8-slice helical CT unit (Light Speed; GE Healthcare), using the following parameters: 140 kVp, 30 mA, 0.8 s rotation time, 3.3 mm scan reconstruction, 500 mm field of view, and 512 × 512 matrix. PET imaging was then performed from the skull base to the level of the mid-thigh in a three-dimensional mode for 2 min per bed position. PET data were iteratively reconstructed using an ordered subset expectation maximization algorithm with low-dose CT data sets for attenuation correction.

### *Imaging and data analysis*

On PET images, semi-quantitative analysis was performed by drawing a region of interest (ROI) in order to measure the $SUV_{max}$ of the thyroid nodule and the $SUV_{mean}$ of the liver. The SUV ratios of the thyroid nodules to the liver ($T/B_{SUV}$) were then calculated. On noncontrast CT images, 5 mm × 5 mm ROIs were placed over the thyroid nodule and the contralateral thyroid lobe in order to measure mean Hounsfield units (HUs) as a parameter for iodine content. Then, the HU ratios of the thyroid nodules to the contralateral thyroid lobe ($T/B_{HU}$) were obtained. Finally, the additional value of $T/B_{HU}$ was investigated, as well as $T/B_{SUV}$ on top of the results of initial FNAB in reducing the need for further biopsy.

### *Statistical analysis*

All statistical tests were conducted using MedCalc v14.8.1 (MedCalc Software, Mariakerke, Belgium). Student's *t*-test was used to compare $T/B_{SUV}$ and $T/B_{HU}$ values of benign and malignant nodules. Receiver-operating characteristic curve analysis was performed to obtain the cutoff values of $T/B_{SUV}$ and $T/B_{HU}$ for differentiating malignant from benign lesions. Sensitivities, specificities, and accuracies of the cutoff $T/B_{SUV}$ and $T/B_{HU}$ values were calculated. Correlated *U* statistics were used to compare the area under the curve (AUC) of $T/B_{SUV}$ and $T/B_{HU}$. McNemar's test was used to compare sensitivities, specificities, and accuracies of $T/B_{SUV}$ and $T/B_{HU}$ for differentiating malignant from benign thyroid nodules. To confirm the reliability of $T/B_{HU}$ in nodules <10 mm, the Mann–Whitney *U*-test was used to compare $T/B_{HU}$ values between the nodules <10 mm and nodules ≥10 mm. Fisher's exact test was used to assess the performance of $T/B_{HU}$ according to the size of nodules. A *p*-value of $< 0.05$ was considered statistically significant.

## Results

Malignant incidentalomas had significantly higher $T/B_{SUV}$ values than benign nodules (malignant: $2.69 \pm 1.86$; benign: $1.62 \pm 1.15$; $p = 0.0019$; Fig. 1). The AUC was 0.689, with the best cutoff $T/B_{SUV}$ value being >1.5 ([CI 0.577–0.787], 77.8% sensitivity and 60.0% specificity; Fig. 2). As a result, 6/27 malignant nodules were misclassified as benign, whereas 22/55 benign nodules were misclassified as malignant (Fig. 3).

In contrast, the mean $T/B_{HU}$ value of malignant incidentalomas was significantly lower than that of benign nodules (malignant: $0.52 \pm 0.08$; benign: $0.73 \pm 0.09$; $p < 0.0001$; Fig. 1). The AUC was 0.941 ([CI 0.866–0.981], 100% sensitivity and 80.0% specificity; Fig. 2). Of the 38 nodules with a $T/B_{HU}$ of ≤ 0.68, 27 (71.1%) were malignant and 11 were benign. The 44 nodules with a $T/B_{HU}$ of >0.68 were all benign (Fig. 3). Therefore, the risk of malignancy was much higher (71.1%) when a $T/B_{HU}$ cutoff value of ≤0.68 was applied, and it was absent in nodules with a $T/B_{HU}$ of >0.68.

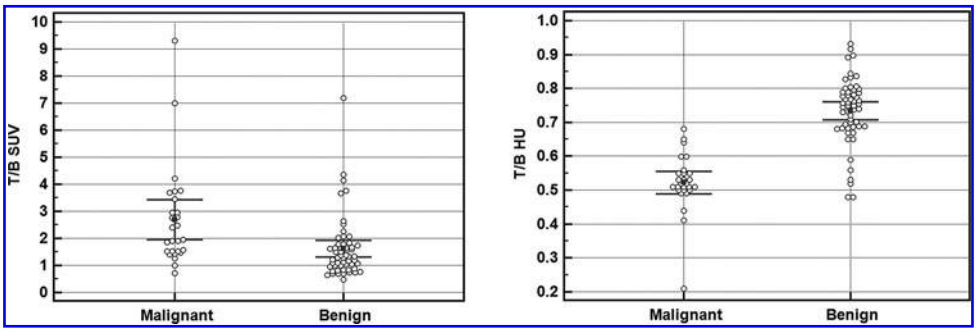


**FIG. 1.** Maximal standardized uptake value ratios of the thyroid nodule compared to liver ($T/B_{SUV}$) and Hounsfield unit (HU) ratios of the thyroid nodule compared to contralateral thyroid lobe ($T/B_{HU}$) of malignant and benign thyroid nodules on $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT).

The AUC of $T/B_{HU}$ was higher than that of $T/B_{SUV}$ (0.941 vs. 0.689, $p < 0.0001$). Both the sensitivity and specificity of $T/B_{HU}$ were significantly higher than those of $T/B_{SUV}$ (100% vs. 77.8%, $p = 0.0313$; 80.0% vs. 60.0%, $p = 0.0433$, respectively). In addition, there was a statistically significant difference in accuracy between the two parameters (86.6% vs. 65.9%, $p = 0.0041$).

There were 64 nodules ≥10 mm with a mean $T/B_{HU}$ of $0.67 \pm 1.4$, whereas there were 18 nodules <10 mm with a mean $T/B_{HU}$ of $0.66 \pm 1.3$. There were no statistically significant differences in $T/B_{HU}$ between nodules ≥10 mm and nodules <10 mm ($p = 0.800$). In nodules <10 mm, all benign nodules ($n = 8$) showed a $T/B_{HU} > 0.68$, whereas all malignant nodules ($n = 10$) had a $T/B_{HU}$ of ≤0.68. The specificity of $T/B_{HU}$ seemed higher in nodules <10 mm than that in nodules ≥10 mm, although the difference was not statistically significant (100% vs. 76.6%, $p = 0.188$).

Finally, the potential value of $T/B_{HU}$ and $T/B_{SUV}$ in addition to the results of initial FNAB was evaluated. There were 18 nodules with nondiagnostic ($n = 7$) or atypia of undetermined significance or follicular lesion of undetermined significance cytologies ($n = 11$) upon initial FNAB in which a second FNAB was performed for further management. Of them, only one (11%) of the nine nodules with a $T/B_{SUV}$ of >1.5 was malignant, whereas two (22%) of the nine nodules with a $T/B_{SUV}$ of ≤1.5 turned out to be malignant. When the $T/B_{HU}$ cutoff value was applied, three (60%) of the five nodules with a $T/B_{HU}$ of ≤0.68 were found to be papillary carcinomas. The 13 nodules with a $T/B_{HU}$ of >0.68 were all benign, with a risk of malignancy of 0%.

## Discussion

The risk of malignancy in thyroid cancer is significant if focal FDG uptake is found incidentally upon PET/CT. The degree of $^{18}$F-FDG uptake has been used to stratify the risk of malignancy. However, this poses a diagnostic challenge, primarily due to benign nodules with a high $^{18}$F-FDG uptake and thyroid cancers showing a low $^{18}$F-FDG uptake (13–15). In fact, $SUV_{max}$ has been shown to have a sensitivity of 70–77% and a specificity of 62–79% for differentiating incidentalomas in the literature. The results of the current study were in line with these previous reports. An AUC of 0.689 was found for $T/B_{SUV}$, with the best cutoff $T/B_{SUV}$ value being >1.5 ([CI 0.577–0.787], 77.8% sensitivity and 60.0% specificity). As a result, 6/27 malignant nodules were misclassified as benign, whereas 22/55 benign nodules were misclassified as malignant.

In the process of dedifferentiation of thyroid cancer, the expression of genes related to iodine metabolism is reduced, while the expression of genes related to cellular proliferation and glucose uptake is increased (29–33). Accordingly, the use of iodine metabolism in imaging modalities such as $^{123}$I thyroid scintigraphy has been utilized to select thyroid nodules for further diagnostic work-up. Nonfunctioning nodules without radioiodine uptake have a 5–10% probability of being malignant. In contrast, the risk of malignancy is extremely low in hyperfunctioning nodules with increased radioiodine uptake (24). In the present study, it was hypothesized that nodules with different functional states might have different levels of iodine concentration. Therefore, the

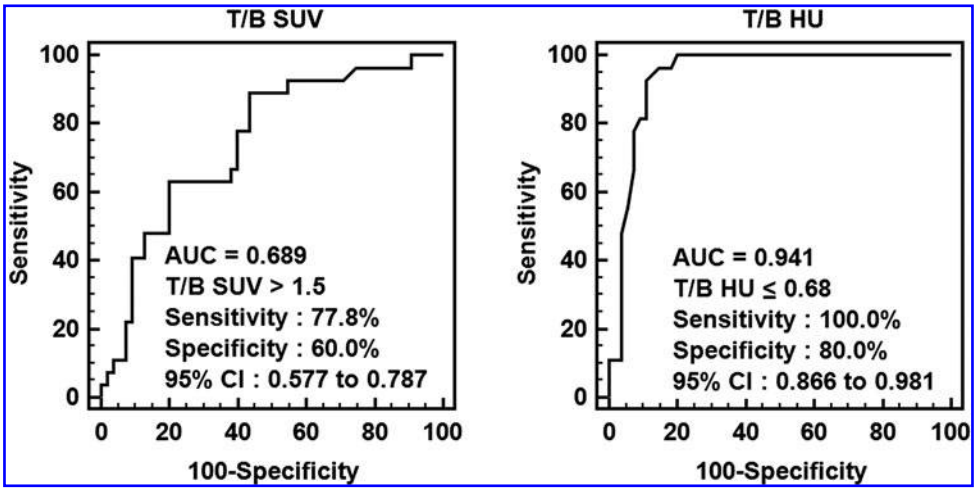


**FIG. 2.** Receiver-operating characteristic curves of $^{18}$F-FDG PET/CT when $T/B_{SUV}$ and $T/B_{HU}$ was applied for differentiating between benign and malignant thyroid nodules. The area under the curve of $T/B_{HU}$ cutoff ≤0.68 was significantly higher than that of $T/B_{SUV}$ cutoff >1.5 ($p < 0.0001$).

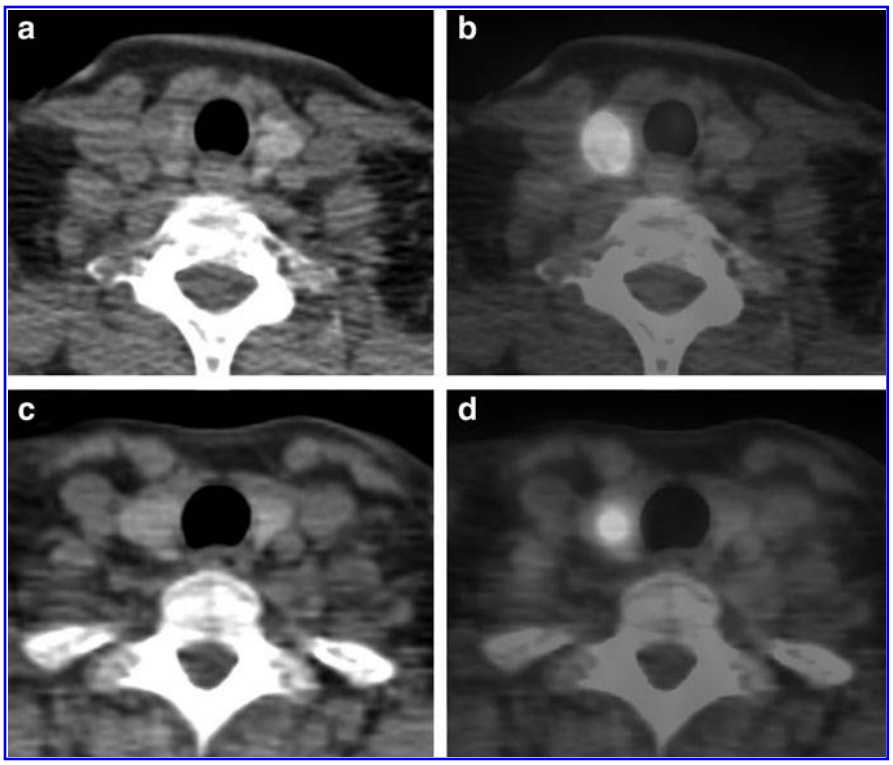


**FIG. 3.** (**a**) Noncontrast CT and (**b**) fused $^{18}$F-FDG PET/CT images of a 67-year-old female patient with papillary thyroid carcinoma (12 mm in size) with a $T/B_{SUV}$ of 7.00 (nodule $SUV_{max} = 15.4$, liver $SUV_{mean} = 2.2$). HU of the nodule was lower than that of the contralateral thyroid gland ($T/B_{HU}$ of 0.55). (**c**) Noncontrast CT and (**d**) fused $^{18}$F-FDG PET/CT images of a 69-year-old female patient with benign nodule (11 mm in size) with a $T/B_{SUV}$ of 2.27 (nodule $SUV_{max} = 5.0$, liver $SUV_{mean} = 2.2$) and $T/B_{HU}$ of 0.85.

use of $T/B_{HU}$ was assessed calculated from noncontrast CT scans taken during PET/CT for the differentiation of benign from malignant incidentalomas.

In the current study, there were 38 nodules with a $T/B_{HU}$ of ≤0.68. Of these nodules, 27 (71.1%) were malignant and 11 were benign. The 44 nodules with a $T/B_{HU}$ of >0.68 were all benign. With a $T/B_{HU}$ cutoff value of ≤0.68, the AUC was 0.941 [CI 0.866–0.981], which was higher than that of $T/B_{SUV}$ (0.941 vs. 0.689, $p < 0.0001$). Both the sensitivity and specificity of $T/B_{HU}$ were significantly higher than those of $T/B_{SUV}$ (100% vs. 77.8%, $p = 0.0313$; 80.0% vs. 60.0%, $p = 0.0433$, respectively). In general, the risk of malignancy when focal thyroid $^{18}$F-FDG uptake is found incidentally upon PET/CT has been reported to be 26–50% (5–12). In the present study, the risk of malignancy increased to 71.1% when the $T/B_{HU}$ cutoff value of ≤0.68 was applied. Interestingly, no malignant nodules with a $T/B_{HU}$ of >0.68 were found.

The $T/B_{HU}$ was found to be reliable in small nodules <10 mm. There were no statistically significant differences in $T/B_{HU}$ between nodules ≥10 mm ($n = 64$) and nodules <10 mm ($n = 18$; $0.67 \pm 1.4$ vs. $0.66 \pm 1.3$; $p = 0.800$). In nodules <10 mm, all benign nodules ($n = 8$) showed a $T/B_{HU}$ >0.68, whereas all malignant nodules ($n = 10$) revealed a $T/B_{HU}$ of ≤0.68. The specificity of $T/B_{HU}$ seemed higher in nodules <10 mm than that in nodules ≥10 mm without a statistical significance. In this study, 17 (27%) of the 64 nodules ≥10 mm were malignant, and 10 (56%) of the 18 nodules <10 mm were malignant. In nodules <10 mm, there were fewer benign nodules causing more false positive results with the $T/B_{HU}$. The difference in the prevalence of benign nodules according to the size could explain the potential difference in specificity of $T/B_{HU}$.

Although $T/B_{HU}$ seems to be a simple and effective method for stratifying the risk of malignancy, further studies are needed to incorporate $T/B_{HU}$ in the evaluation of thyroid incidentalomas with increased $^{18}$F-FDG uptake on PET/CT in routine clinical practice. Meanwhile, the additional value of $T/B_{HU}$ was investigated when combined with the results of FNAB. There were 18 nodules with nondiagnostic or undetermined significance after initial FNAB and 3/18 nodules were eventually found to be malignant upon a second FNAB. Of these 18 nodules, 13 had a $T/B_{HU}$ of >0.68 and all were benign; malignancy was found in three (60%) of the five nodules with a $T/B_{HU}$ of ≤0.68. Therefore, the application of $T/B_{HU}$ could have saved a second FNAB of benign nodules in a significant portion of the patients with nondiagnostic or undetermined significance cytology.

This study has several limitations. First, grossly calcified nodules on noncontrast CT scans were excluded, since certain calcification patterns in thyroid nodules are related to a different risk of malignancy. However, analyzing the pattern of calcification was beyond the scope of this study. Second, the imaging quality of noncontrast CT of PET/CT might be inferior to full diagnostic noncontrast CT in measuring the HUs of nodules, since only low-dose noncontrast CT scanning was performed for attenuation correction of PET/CT.

In conclusion, thyroid incidentalomas detected upon PET/CT generally indicate a high risk of malignancy and require a prompt diagnostic work-up. In the current study, it was found that $T/B_{HU}$ was a simple and effective parameter to stratify further the risk of malignancy in thyroid incidentalomas on PET/CT. A $T/B_{HU}$ value of ≤0.68 identified nodules with a higher risk of malignancy, whereas there was no malignancy in nodules with a $T/B_{HU}$ of >0.68. This may have clinical relevance in those nodules with nondiagnostic or undetermined significance cytologies upon FNAB in the scheme of current clinical practice. Further studies using various thyroid

nodules should be performed to validate the clinical significance of these findings in a prospective way.

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### Author Disclosure Statement

No competing financial interests exist.

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