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The primary aim of World Journal of Clinical Cases (WJCC, World J Clin Cases) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Retrospective Study

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ORIGINAL ARTICLE

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

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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 nonthyroid 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



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and benign according to the cytological/histological reports, and four PET parameters [standardized uptake value $(SUV)_{max}$, SUV_{peak} , SUV_{mean} , and metabolic tumor volume (MTV)] were measured on FDG PET-CT. Total lesion glycolysis (TLG) was calculated by multiplying the SUV_{mean} 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_{max}/ SUV_{peak}/ SUV_{mean}/ and TLG were all higher in malignant lesions than benign ones, but the difference was statistically significant (P = 0.012) only for SUV_{max}. There was a positive linear correlation (r = 0.339) between SUV_{max} and the diagnosis of malignancy. ROC curve analysis for SUV_{max} revealed an area under the curve of 0.702 (P < 0.05, 95% confidence interval: 0.550-0.855) and SUV_{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 $\mathrm{SUV}_{\scriptscriptstyle\mathrm{max}}$ was the best parameter for discriminating between malignant and benign disease. Unexpected focal hypermetabolic TIs with the SUV_{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

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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.

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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.





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 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.

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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 $[185 \text{ men} (\text{mean age: } 68 \pm 11.2) \text{ and } 154 \text{ women} (\text{mean age: } 63 \pm 15.0 \text{ years})] \text{ with }$ 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 $_{peak\prime}$ SUV $_{mean\prime}$ 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_{max} 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_{peak} presented no statistical significance with a *P*-value of 0.058, which was close to significance. The SUV_{mean} 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 (<i>n</i> = 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.

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Table 3 Examples of F-18 fluorodeoxyglucose positron emission tomography-computed tomography parameters				
Parameters	Malignant (<i>n</i> = 26)	Benign (<i>n</i> = 20)	<i>P</i> value	
SUV _{max}	10.8 ± 7.5	6.5 ± 3.0	0.012	
SUV _{peak}	6.8 ± 5.7	4.4 ± 2.0	0.058	
MTV ₂	5.06 ± 5.2	6.7 ± 6.6	0.354	
SUV _{mean2}	3.8 ± 1.5	3.0 ± 0.5	0.011	
TLG ₂	25.5 ± 48.9	21.3 ± 24.0	0.735	
MTV _{2.5}	3.5 ± 4.5	3.7 ± 4.2	0.872	
SUV _{mean2.5}	4.5 ± 1.6	3.6 ± 0.7	0.014	
TLG _{2.5}	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_{max}) 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_{max} 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



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Figure 2 The receiver operating characteristic curve for maximum standardized uptake value. The area under the curve is 0.702 (95% confidence interval, lower: 0.550, upper: 0.855). The cut-off value for maximum standardized uptake value is 8.5 with a sensitivity of 0.615 and a specificity of 0.789. ROC: Receiver operating characteristic.

diagnosed pathologically first and then FDG PET-CT was performed, there would be more lesions with low FDG uptake.

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[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 [23-26]. Among the five PET parameters associated with SUV and the metabolic volume of the tumor, ${\rm SUV}_{\rm max}$ showed good performance in discriminating malignant lesions from benign ones. The mean value of SUV_{mean} was higher in the malignant group and presented a statistical significance difference comparable to SUV_{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_{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_{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_{peak} and TLG were higher in the malignant group but without statistical significance, although SUV_{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[27-31], while other reported different conclusions[32]. The roles of MTV and TLG in other cancers are still open to debate[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_{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[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 $\mathrm{SUV}_{\mathrm{mean}}$ and MTV, might not reflect the risk of malignancy well. Finally, $\mathrm{SUV}_{\mathrm{max}}$ was the only reliable discriminator, while SUV_{peak} might be a candidate. In contrast, the other parameters had no discernible statistical impact.

 SUV_{max} was chosen for the ROC curve. Based on the AUC[42,43], SUV_{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_{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_{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_{max} was the best parameter for discriminating malignant and benign lesions. The unexpected focal hypermetabolic TIs with an SUV_{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)_{max} was the only statistically significant discriminator in differentiation. From the ROC curve, the AUC was 0.702 and the SUV_{max} cut-off value was 8.5.

Research conclusions

TIs with SUV_{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.

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