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Implication of ^{18}F-fluorodeoxyglucose uptake by affected lymph nodes in cases with differentiated thyroid cancer

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Abstract. In this study, we evaluated the usefulness of positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG-PET) to detect metastatic lymph nodes in differentiated thyroid cancer. We also investigated whether certain factors, including the size of the metastasis to the lymph nodes, are associated with FDG avidity. A total of 22 consecutive patients with differentiated thyroid cancer who underwent FDG-PET preoperatively were enrolled in this study. Lymph node metastasis was diagnosed in the final pathology in 10 of the 22 patients (45.5%). The mean maximum standardized uptake value of the metastatic lymph nodes was 4.53 (range, 0-23.5). The 22 cases with differentiated thyroid cancer were divided into two groups based on lymph node metastasis. Clinicopathological variables other than FDG uptake of metastatic lymph nodes were not predictors of lymph node metastasis of thyroid cancer. The sensitivity, specificity, overall accuracy and false-negative rates of preoperative FDG-PET in the prediction of lymph node status were 40.0, 100, 72.7 and 60.0%, respectively. The false-positive rate of FDG-PET evaluation was 0%. The mean largest dimension of metastasis was 23.0 mm for FDG-positive cases and 10.9 mm for FDG-negative cases. There was a marked difference in the size of metastases between FDG-positive and -negative cases; however, even in patients with node metastasis >10 mm, the false-negative rate was 50.0%. Therefore, FDG-PET imaging was not found to be sufficient for the evaluation of lymph node status, particularly in cases with small metastases. Our findings indicate that preoperative FDG-PET evaluation of the lymph nodes cannot be considered predictive of the final pathology.

Introduction

The presence of lymph node metastasis is considered a risk factor for lymph node recurrence or distant metastasis in patients with thyroid cancer (1). The success of surgery for thyroid cancer depends on accurate preoperative imaging, which enables complete clearance of metastatic lymph nodes (2,3). Ultrasound remains the most important imaging modality in the evaluation of thyroid cancer (3). In recent years, the clinical applications using positron emission tomography (PET) have increased significantly. PET with ^{18}F-fluorodeoxyglucose (FDG) is a non-invasive whole-body imaging technique used to evaluate various types of malignancies, including thyroid cancer (1,3-7), in terms of tumor staging, restaging, detection of recurrence and monitoring treatment response (8,9). However, there are limited data regarding the role of FDG-PET in preoperative staging of thyroid cancer (3,7,10). Only a limited number of previous studies have evaluated the accuracy of PET in detecting preoperative lymph node metastasis, and it has been reported that PET does not improve the management or outcome of thyroid cancer (3,11-13). For the evaluation of affected lymph nodes in thyroid cancer, an understanding of FDG avidity is important. Several studies evaluated factors associated with the FDG avidity of the primary thyroid tumor in cases with thyroid cancer, and the thyroid tumor size has been reported to be associated with a higher likelihood of positive FDG uptake (14,15). However, to date, there has been no study assessing the factors associated with FDG avidity of the affected lymph nodes. The aim of this study was to evaluate the usefulness of FDG-PET for detecting metastatic lymph nodes in differentiated thyroid cancer. Furthermore, we investigated whether certain factors, including the size of metastasis to the lymph nodes, were associated with FDG avidity.

Patients and methods

Patients. A total of 22 consecutive patients with differentiated thyroid cancer who underwent FDG-PET preoperatively were enrolled in this study. All the patients underwent thyroidectomy at the Department of Surgical Science, Graduate School of Medicine, Gunma University (Maebashi, Japan) from January 2008 to December 2014. Patients with incomplete clinical information were excluded. None of the patients had distant metastasis.

Thyroid cancer detection and evaluation. Most cases of thyroid cancer in this study were detected by PET during evaluation for other cancers. PET images were qualitatively examined by expert nuclear radiologists. Maximum standardized uptake

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values (SUVmax) were calculated according to a routine clinical method. Thyroid nodule size, size of metastatic foci to the lymph nodes, age, and serum levels of thyroid-stimulating hormone (TSH), thyroglobulin and C-reactive protein (CRP) were investigated as possible predictors of lymph node metastasis.

Statistical analysis. The Fisher's exact test, χ^2 test and Student's t-test were used to compare benign and malignant groups. Differences were considered to be statistically significant when $P<0.05$.

Results

Measures of the effectiveness of preoperative FDG-PET in the prediction of lymph node status. The mean SUVmax of metastatic lymph nodes was 4.53 (range, 0-23.5). As shown in Table I, the sensitivity, specificity, overall accuracy and false-negative rates for FDG uptake in the prediction of lymph node status were 40.0, 100, 72.7 and 60.0%, respectively. The false-positive rate of FDG-PET evaluation for lymph node status was 0%.

Patient and clinicopathological characteristics associated with lymph node metastasis and FDG uptake. The mean age of the patients was 58.6±13.8 years and 4 of the 22 patients were men. The mean size of the thyroid nodules was 15.8±8.3 mm. Lymph node metastasis was diagnosed in the final pathology in 10 of the 22 patients (45.5%). The 22 cases with differentiated thyroid cancer were divided into two groups based on lymph node metastasis. The patient characteristics and the results of the univariate analysis conducted to determine the association between the clinicopathological variables and lymph node metastasis are shown in Table II. These clinicopathological variables, apart from the FDG uptake of metastatic lymph nodes, were not predictors of lymph node metastasis from thyroid cancer. The 10 cases with lymph node metastasis were divided into two groups based on the presence of FDG uptake in the lymph nodes (Fig. 1). The patient characteristics and the results of the univariate analysis conducted to determine the association between the clinicopathological variables and FDG uptake in the lymph nodes are shown in Table III. None of the clinicopathological characteristics of the primary tumor, including size and SUVmax, were significantly associated with FDG uptake. However, the clinicopathological characteristics of the metastatic lymph nodes were significantly associated with FDG uptake in the lymph nodes. The analysis revealed that the size of the node metastasis was a statistically significant factor, although the number of lymph node metastases was not statistically significant.

FDG-PET results and size of lymph node metastasis. The association of metastatic tumor size in the lymph nodes and FDG-PET evaluation results (i.e., positive or negative) is shown in Fig. 2. The mean largest dimension of metastatic tumors was 23.0 mm for FDG-positive and 10.9 mm for FDG-negative cases. Thus, a significantly larger size of metastatic tumors was observed in FDG-positive nodes compared with that in FDG-negative nodes ($P<0.01$). However, despite this marked difference in the size of the metastases, the false-negative rate was still 50.0% in patients with node metastases sized >10 mm.

Table I. Measures of the effectiveness of preoperative positron emission tomography with ^{18}F-fluorodeoxyglucose in the prediction of lymph node status.

Measures	No./total (%)
Sensitivity	4/10 (40.0)
Specificity	12/12 (100.0)
Accuracy	16/22 (72.7)
False-negative rate	6/10 (60.0)

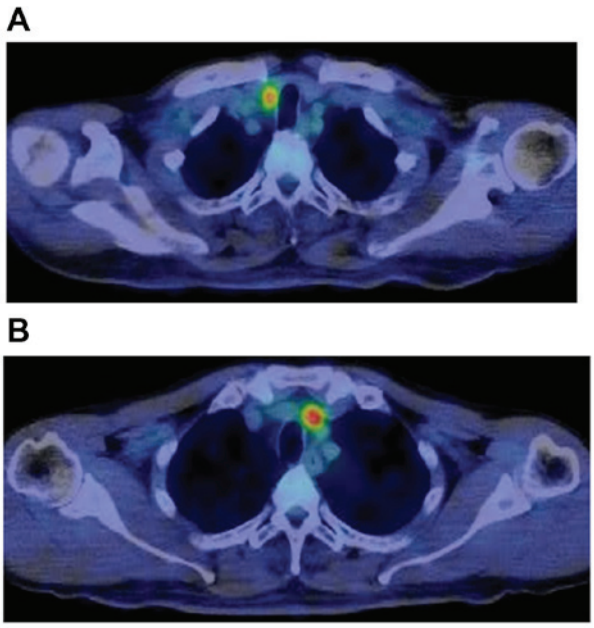

Figure 1. Examples of focal ^{18}F-fluorodeoxyglucose (FDG) uptake by lymph nodes on positron emission tomography-computed tomography in a 61-year-old male patient. FDG uptake in a (A) thyroid nodule [maximum standardized uptake value (SUVmax) = 4.7] and (B) lymph node (SUVmax = 6.6). Papillary carcinoma with lymph node metastasis was histopathologically confirmed.

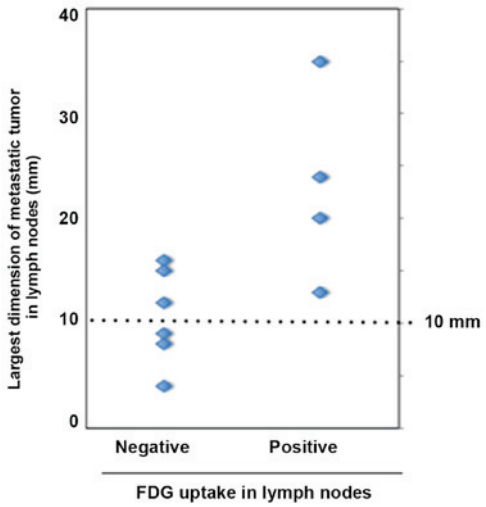

Figure 2. Comparison of the results of ^{18}F-fluorodeoxyglucose (FDG) uptake-positive and -negative cases regarding the size of lymph node metastasis. The mean largest dimension of metastatic tumors was 23.0 mm for FDG-positive and 10.9 mm for FDG-negative cases ($P<0.01$). In the patient group with node metastasis >10 mm as the cut-off point, the false-negative rate was 50%.

Table II. Patient and clinicopathological characteristics associated with lymph node metastasis.

Characteristics	Lymph node metastasis		P-value
	Absent (n=12)	Present (n=10)	
Age, years	59.0±14.5	58.1±13.1	0.792
Gender			0.956
Male	1	3	
Female	11	7	
Primary tumor size, mm	18.7±7.8	15.8±8.3	0.311
SUVmax of primary tumor	12.5±12.9	4.4±4.4	0.634
FDG uptake in lymph nodes, n (%)	0 (0.0)	4 (40.0)	0.157
TSH	1.25±0.47	1.81±1.00	0.224
Tg	170.9±421.9	109.1±134.5	0.450
CRP	0.10±0.21	0.17±0.35	0.721

Values are expressed as mean ± standard deviation. SUVmax, maximum standardized uptake value; FDG, ^{18}F-fluorodeoxyglucose; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; CRP, C-reactive protein.

Table III. Patient and clinicopathological characteristics associated with FDG uptake in the lymph nodes.

Characteristics	FDG uptake in axillary lymph nodes		P-value
	Present (n=4)	Absent (n=6)	
Age, years	67.8±15.4	51.7±6.5	0.024
Gender			0.333
Male	2	1	
Female	2	5	
TSH	1.67±1.08	1.81±1.04	0.637
Tg	145.4±176.6	84.9±110.0	0.259
CRP	0.06±0.04	0.22±0.42	0.723
Primary tumor			
Histology			-
Papillary carcinoma	4	9	
Tumor size, mm	12.5±10.7	18.0±6.3	0.834
SUVmax	5.8±6.7	3.6±2.2	0.236
Extrathyroidal extention, n	1	1	0.667
Lymph node metastasis			
Tumor size, mm	23.0±9.2	10.7±4.5	0.011
Number of node metastases	3.8±2.8	5.2±2.9	0.717

Values are expressed as mean ± standard deviation. SUVmax, maximum standardized uptake value; FDG, ^{18}F-fluorodeoxyglucose; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; CRP, C-reactive protein.

Discussion

FDG-PET has been widely used for diagnosing, staging, or detecting recurrence in various types of cancer; however, its diagnostic usefulness for thyroid cancer is controversial (1,3-8,14,15). Regarding thyroid nodules, there are several reports of preoperative evaluation with FDG-PET, and it is generally considered that FDG-PET is of limited value in predicting thyroid cancer outcome (3-8,14,15). Furthermore, there are limited data regarding the role of FDG-PET in detecting preoperative lymph node metastasis of thyroid cancer (3,11-13). Clinically, FDG-PET is not generally used for the primary diagnosis of thyroid cancer. However, as FDG-PET is becoming a commonly used imaging modality, the number of thyroid lesions incidentally detected by FDG-PET is increasing. We previously demonstrated that the risk of thyroid cancer

in patients with PET incidentaloma was relatively high (5). Previous studies evaluated the factors associated with the FDG avidity of the primary tumor in thyroid cancer (14,15), but there has been no study assessing the factors associated with FDG avidity of the affected lymph nodes. Thus, the present study was undertaken to assess the accuracy of FDG-PET evaluation of lymph node metastases for patients with thyroid cancer. The key observations made in this study may be summarized as follows: i) The sensitivity, specificity, overall accuracy and false-negative rates of preoperative FDG-PET evaluation in the prediction of lymph node status were 40.0, 100, 72.7 and 60.0%, respectively; ii) the size of node metastasis, but not their number, was associated with FDG uptake in the lymph nodes; and iii) the false-positive rate of FDG-PET evaluation of lymph node metastasis was 0%; however, even in the patient group with node metastasis sized >10 mm, the false-negative rate was 50%.

SUVmax is used as a semi-quantitative indicator of FDG uptake, but it is sometimes difficult to obtain a reliable value with only one FDG-PET imaging, as SUVmax is affected by several factors, including glucose transporter expression, viable cell number, tumor perfusion and inflammatory cells (5,16,17). Several studies have reported that SUVmax is correlated with the size of the thyroid nodule to a certain extent (14,15), according to the resolution of the PET scanner, known as the partial volume effect (14,18). However, there has been no study assessing the factors associated with FDG avidity of affected lymph nodes. A few previous studies have evaluated the diagnostic accuracy of PET in lymph node metastasis. In this study, we evaluated the association between the size of lymph node metastasis and the FDG avidity of lymph nodes. There was a significant correlation between FDG uptake and the size of lymph node metastasis; however, even in the patient group with node metastasis >10 mm, the false-negative rate was 50%. Therefore, FDG-PET evaluation of lymph node metastasis is not predictive of small metastasis or micrometastasis.

On the other hand, in the present study, the false-positive rate of FDG-PET evaluation of lymph node metastasis was 0%. Thus, in cases with FDG uptake by the lymph nodes, macrometastasis to the lymph node is highly suspected. However, the size of lymph node metastases does not always reflect lymphatic spread; thus, FDG-PET imaging was not sufficient for the evaluation of lymphatic spread. This study has potential limitations, the major one being that it was a retrospective analysis and the number of cases was relatively small. However, the clinical implications of the data we obtained on FDG avidity are very important. However, additional research is required to elucidate this putative association between FDG-PET evaluation and lymph node metastasis.

Inflammation also increases FDG uptake and, therefore, SUVmax (14). CRP is an acknowledged marker of inflammation reflecting a systemic inflammatory response, and the measurement of serum CRP levels is an easily available test. However, recent clinical evidence suggests that FDG-PET is more accurate in detecting thyroid cancer at high rather than at low TSH levels (19). In this study, there was no correlation between SUVmax and either CRP or TSH level in lymph node metastasis.

In conclusion, we demonstrated that preoperative FDG-PET evaluation of lymph nodes is not effective in predicting node status. Even in cases with relatively large (>10 mm) node metastases, FDG-PET imaging was not sufficient for the evaluation of lymph node status. The positive predictive value is high, but our findings suggest that preoperative FDG-PET evaluation of lymph node is not predictive of the final pathology.

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