

DOI: 10.21767/2254-6081.100156

Association between Refractoriness to ^{131}I Therapy for Differentiated Thyroid Carcinoma and ^{18}F -FDG Accumulation in Lung Metastasis

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Abstract

Background: The purpose of this study was to retrospectively investigate the association between 2-[F-18]-fluoro-2-deoxy-D-glucose (^{18}F -FDG) accumulation in lung metastasis (LM) before ^{131}I therapy and refractoriness to ^{131}I therapy for differentiated thyroid carcinoma (DTC) patients.

Methods and Findings: Sixty-one DTC patients with LM who underwent Positron emission tomography/computed tomography using ^{18}F -FDG (^{18}F -FDG PET/CT) before an initial ^{131}I therapy were retrospectively evaluated. Maximum of standardized uptake value (SUV_{max}) in LM with the highest ^{18}F -FDG accumulation was measured in each patient. The SUV_{max} was compared between patients with and without ^{131}I -positive LM, and between patients with and without an increased level of thyroglobulin (tumor marker) 12 \pm 2 months after ^{131}I therapy using the Wilcoxon test.

Discussion: Predictability for the patients with an increased thyroglobulin level was also analyzed by receiver-operating-characteristic (ROC) analysis. SUV_{max} of LM was significantly greater for patients without ^{131}I -positive LM than for those with ^{131}I -positive LM (5.9 ± 6.0 vs. 1.9 ± 2.0 , $p < 0.01$) and was significantly greater for patients with an increased level of TG after ^{131}I therapy than for those without (7.0 ± 4.9 vs. 1.2 ± 1.0 , $p < 0.01$). All 11 of the 49 patients with $\text{SUV}_{\text{max}} > 3.8$ showed an increased TG level after ^{131}I therapy. Use of the optimal cutoff threshold for SUV_{max} of 1.6 differentiated patients with an increased level of TG from those without at a sensitivity of 74.2%, a specificity of 94.4%, an accuracy of 81.6% and an AUC of 0.91.

Conclusion: ^{18}F -FDG accumulation in LM from DTC can be one of predictors for refractoriness to ^{131}I therapy.

Keywords: Differentiated thyroid carcinoma; Lung metastasis; ^{131}I therapy; Refractoriness; ^{18}F -FDG; PET/CT

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Citation: Maruoka Y, Baba S, Isoda T, Kitamura Y, Abe K, et al. (2017) Association between Refractoriness to ^{131}I Therapy for Differentiated Thyroid Carcinoma and ^{18}F -FDG Accumulation in Lung Metastasis. Arch Cancer Res. Vol. 5 No. 3:156

Received: April 20, 2017; **Accepted:** September 22, 2017; **Published:** September 27, 2017

Introduction

The most common disease of malignant endocrine tumors is thyroid cancer, which is still increasing in incidence [1,2]. Differentiated thyroid carcinoma (DTC) including papillary and follicular thyroid carcinoma accounts for more than 90% of all thyroid cancers. DTC generally has a favorable prognosis, with 10-year overall and cause-specific survival rates of 76.8% and 84.9%, respectively [3]. However, in DTC patients with distant

metastasis, the 10-year overall and cause-specific survival rates decrease to 24% and 27%, respectively [4]. The presence or absence of distant metastases in DTC is one of the most important factors for determining the prognosis.

Radioiodine therapy with ^{131}I (^{131}I therapy) after a near-total or total thyroidectomy has been an established treatment for patients with DTC [5,6]. Previous studies have reported that ^{131}I therapy improves the clinical prognosis of patients [7,8], while DTC patients who have recurrent or metastatic lesions

without ^{131}I accumulation have a poor prognosis [9,10]. However, according to some recent articles, molecular-targeted therapy with sorafenib significantly improved progression-free survival in patients with progressive radioactive iodine-refractory DTC [11,12]. Therefore, establishment of the indications for the molecular-targeted therapy would be of great clinical benefit, especially in DTC patients with distant metastasis.

Positron emission tomography/computed tomography using 2-[F-18]-fluoro-2-deoxy-D-glucose (^{18}F -FDG PET/CT) is known to be a useful modality for the detection of iodine-negative DTC lesions [10,13,14], since Feine et al. first formally proposed the “flip-flop pattern”, an inverse correlation between ^{18}F -FDG and ^{131}I uptake in the metastatic lesions from DTC patients [15]. As the mechanism, it has been reported that DTC cells show glucose transporter 1 (GLUT1) upregulation and reduced expression of the sodium-iodide symporter during the dedifferentiation process [16]. Although it has been reported that residual lymph node metastasis from DTC showed significantly higher ^{18}F -FDG uptake in lesions without ^{131}I uptake than those with ^{131}I uptake [17,18], among DTC patients with lung metastasis (LM), the relationship between the resistance to ^{131}I therapy and ^{18}F -FDG accumulation in LM remains unclear. The purpose of this study was to retrospectively clarify the association between ^{18}F -FDG accumulation in LM before ^{131}I therapy and resistance to ^{131}I therapy among DTC patients.

Materials and Methods

Patients

This retrospective study was approved by our institutional review board, and the written informed consent was from all patients.

Two-hundred sixty-three consecutive patients with DTC who were treated with ^{131}I therapy between October 2012 and September 2016 at Kyushu University Hospital after near-total or total thyroidectomy were retrospectively analyzed. DTC patients with LM histopathologically diagnosed as either papillary or follicular carcinoma were included. The definition of LM was determined by at least one of the following criteria: (1) ^{131}I accumulation in the lung field higher than the surrounding tissue identified on ^{131}I SPECT/CT (32 patients), and (2) multiple pulmonary nodules in the bilateral lung, which showed progressive increase in size on follow-up CT (observation period 35 ± 9 months: 29 patients). Patients who had a past history of any other malignant disease, who had distant metastasis in organs other than the lung, who had a low thyroid-stimulating hormone (TSH) level (< 30 U/mL), or who had a high blood glucose level (> 150 mg/dL) were excluded from this study. Consequently, a total of 61 patients (41 females and 20 males) were included in our study. All patients underwent thyroid hormone withdrawal for at least 4 weeks before ^{131}I therapy for the purpose of TSH stimulation, and all patients were prescribed a low-iodine diet for 2 weeks in preparation for ^{131}I administration. The patient characteristics are indicated in **Table 1**.

^{131}I Scintigraphy

Post-therapy ^{131}I scintigraphy was performed at 4–7 days (median: 5 days) after ^{131}I administration (4.0–5.5 GBq, median: 4.5 GBq).

Table 1 Baseline characteristics of the patients.

Age	18 to 78 years (Median: 60)
Men/Women	20/41
Papillary/Follicular	57/4
TSH level	35.7 – 330.7 U/mL (Median: 135)
TG level before ^{131}I therapy *	15.2 – 2590 U/mL (Median: 317)
TG level after ^{131}I therapy *	0.9 – 1850 U/mL (Median: 183)
^{131}I administration dose	4.0 – 5.5 GBq (Median: 4.5)

TSH: Thyroid-stimulating hormone; TG: Thyroglobulin.
*Twelve of 61 patients with a high level of serum anti-thyroglobulin antibody (> 45 IU/mL) were excluded.

All patients underwent a whole-body ^{131}I scan (WBS) and SPECT/CT with a hybrid camera combining a dual-head c-camera with a 6-slice spiral CT within the same gantry (Symbia T6: Siemens, Hoffman Estates, IL). On WBS, anterior images were acquired at a speed of 10 cm/min with high-energy parallel-hole collimators, a 256×1024 matrix, and a 364-keV photopeak with 15% windows. SPECT images were acquired in a step-and-shoot mode, with 40 projections (a duration of 45 s at each projection), a noncircular orbit over 360° , high-energy parallel-hole collimators, a 128×128 matrix, and a 364-keV photopeak with 15% windows. Then, 3D ordered-subset expectation–maximization iterative reconstruction was performed, with 4 iterations and 8 subsets. SPECT images were subjected to CT-based attenuation correction without scattered correction. The CT scan parameters were 130 keV, 30 mAs or less (for minimization of radiation exposure), a 512×512 matrix, and a 2×2.5 mm collimation.

^{18}F -FDG PET/CT

Each ^{18}F -FDG PET/CT acquisition was performed under the TSH-stimulated state. In each patient, 185 MBq of ^{18}F -FDG was intravenously administered after at least 4 hr of fasting. Scans were conducted from the middle of the thigh to the top of the skull 60 min after ^{18}F -FDG administration. ^{18}F -FDG PET/CT images were obtained using an integrated PET/CT scanner Discovery STE (GE Medical Systems, Milwaukee, WI). The PET scanner comprises 24 ring detectors consisting of 560 BGO crystals ($4.7 \times 6.3 \times 30$ mm). All emission scans were performed in 3-dimensional mode with 128×128 matrices ($5.47 \times 5.47 \times 3.27$ mm), and the acquisition time per bed position was 3 min. The PET images were reconstructed using the ordered-subset expectation-maximization method (VUE Point Plus) with 2 full iterations of 28 subsets, and the full-width at half maximum was 5.2 mm. A low-dose 16-slice CT (tube voltage, 120 kV; effective tube current, 30–250 mA) from the vertex to the proximal thigh was performed for attenuation correction, and for determining the precise anatomic location before acquisition of the PET image. The CT scan was reconstructed by filtered back-projection into 512×512 pixel images with a slice thickness of 5 mm to match the PET scan. The PET/CT fusion images were made by GENIE–Xeleris software using a dedicated work station, Xeleris (GE Medical Systems, Milwaukee, WI).

Diagnostic CT protocol

A diagnostic chest CT covering the upper mediastinum to the upper abdomen was performed with a 64-MDCT (multi detector-

row CT) scanner (Aquilion 64; Toshiba Medical Systems, Tokyo, Japan) after ^{131}I scintigraphy, using the following parameters: tube voltage 120 kV, effective tube current 300 mA, collimation 0.5 mm, pitch 27.0. The MDCT scan was reconstructed by filtered back projection into 512×512 pixel images with a slice thickness of 3 mm. In all patients, ^{18}F -FDG PET/CT, diagnostic CT, and ^{131}I scintigraphy were performed within one week.

Data Analysis

All patients in this study underwent patient-based analysis by LM. After determination of the LM with highest ^{18}F -FDG accumulation in PET images, the highest pixel value in the LM on ^{18}F -FDG PET/CT was determined as the maximum standardized uptake value (SUV_{max}). On ^{131}I scintigraphy, ^{131}I accumulation higher than the background in at least one LM was defined as ^{131}I -positive LM and that as low as background in all LMs as ^{131}I -negative LM by visual evaluation. SUV_{max} was compared between patients with and without ^{131}I -positive LMs, and between those with and without an increased thyroglobulin (TG) level 12 \pm 2 months after initial ^{131}I therapy. The predictability for ^{131}I accumulation in LM or an increased level of TG after ^{131}I therapy and the correlation of SUV_{max} in LM with a TG level before or after ^{131}I therapy were also analyzed.

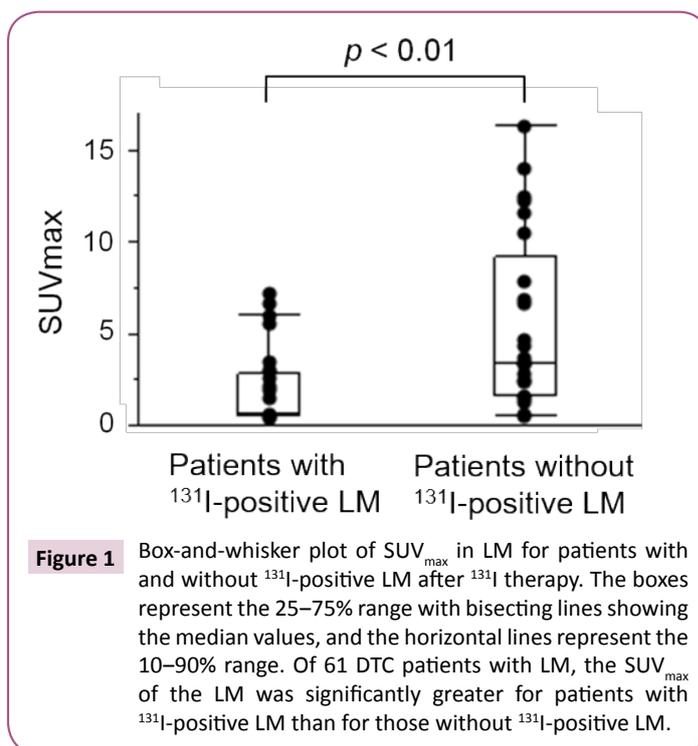
Statistical Analysis

Comparisons of SUV_{max} between patients with and without ^{131}I -positive LM, and between those with and without an increased level of TG after ^{131}I therapy were analyzed by the Wilcoxon test. Analysis of the predictability for ^{131}I accumulation in LM or an increased TG level after ^{131}I therapy was performed by receiver-operating-characteristic (ROC) analysis. The correlation of SUV_{max} in LM with TG level before or after ^{131}I therapy was analyzed by Pearson's correlation analysis. The tests were performed using JMP® (version 9.0.2; SAS Institute, Cary, North Carolina) statistical software. A p value less than 0.05 was considered statistically significant.

Results

Comparison of ^{18}F FDG accumulation between patients with ^{131}I -positive and ^{131}I -negative LM

The SUV_{max} in LMs of all 61 patients ranged from 0.5 to 26 (mean \pm SD; 3.8 ± 4.8). In 3 of 61 patients, LMs were detected only with ^{131}I scintigraphy, not with CT images. For the other 58 patients, the greatest short-axis diameters in the largest LM nodules ranged from 3 to 21 mm (mean \pm SD; 7 ± 4 mm). Of the 61 patients, 32 patients had ^{131}I -positive LM and 29 had no ^{131}I -positive LM. ^{18}F -FDG accumulation as indicated by SUV_{max} was significantly higher in patients without ^{131}I -positive LM than in those with ^{131}I -positive LM [5.9 ± 6.0 vs. 1.9 ± 2.0 (mean \pm SD), $p < 0.01$] shown in **Figure 1**. All 8 patients with SUV_{max} higher than 7.3 had ^{131}I -negative findings in all LM.



Predictability of ^{18}F -FDG PET/CT for ^{131}I accumulation in LM

Use of an optimal cutoff threshold for SUV of 0.8 differentiated patients without ^{131}I -positive LM from patients with ^{131}I -positive LM at a sensitivity of 59.4% (19/32), a specificity of 82.8% (24/29), an accuracy of 70.5% (43/61), and an area under the curve (AUC) of 0.78.

Comparison of ^{18}F FDG accumulation between patients with and without an increased level of TG after ^{131}I therapy

Forty-nine of 61 patients without a high level of anti-TG antibody (> 45 IU/mL) were analyzed. The TG levels before and after ^{131}I therapy of the 49 patients ranged from 15.2 to 2590 (mean \pm SD; 461 ± 531) and from 0.9 to 1850 (mean \pm SD; 379 ± 450), respectively. Of the 49 patients, 18 patients had an increased TG level and 31 patients did not. ^{18}F -FDG accumulation in LM as indicated by SUV_{max} was significantly higher in patients whose TG levels increased than in those whose TG levels didn't increase [7.0 ± 4.9 vs. 1.2 ± 1.0 (mean \pm SD), $p < 0.01$] shown in **Figure 2**. All 11 patients with SUV_{max} greater than 3.8 showed an increased TG level after ^{131}I therapy.

The 49 patients were divided into 27 patients with ^{131}I -positive LM and 22 patients without ^{131}I -positive LM. The 27 patients with ^{131}I -positive LM consisted of 4 patients with an increased TG level and 23 patients without, and there was no significant difference between patients with and without an increased TG level (3.0 ± 2.1 vs. 1.1 ± 0.9 , $p = 0.08$). On the other hand, of the 22 patients without ^{131}I -positive LM, 14 patients whose TG levels increased showed significantly higher SUV_{max} than 8 patients whose TG

levels did not increase (8.2 ± 4.9 vs. 1.7 ± 1.4 , $p < 0.01$) (**Figure 2**).

Representative ^{18}F -FDG PET/CT images for good responders and poor responders to ^{131}I therapy are presented in **Figures 3 and 4**.

Predictability of ^{18}F -FDG PET/CT for poor response to ^{131}I therapy

Among the 49 patients, use of the optimal cutoff threshold for SUV_{max} of 1.6 differentiated patients with an increased level of TG

from those without at a sensitivity of 74.2% (23/31), a specificity of 94.4% (17/18), an accuracy of 81.6% (40/49), and an AUC of 0.91.

Correlation of ^{18}F -FDG accumulation in LM with the TG levels before or after ^{131}I therapy

Among the 49 patients, there was no significant correlation between the SUV_{max} in LM and the TG levels before ^{131}I therapy ($r = 0.21$, $p = 0.14$). On the other hand, the TG levels after ^{131}I therapy

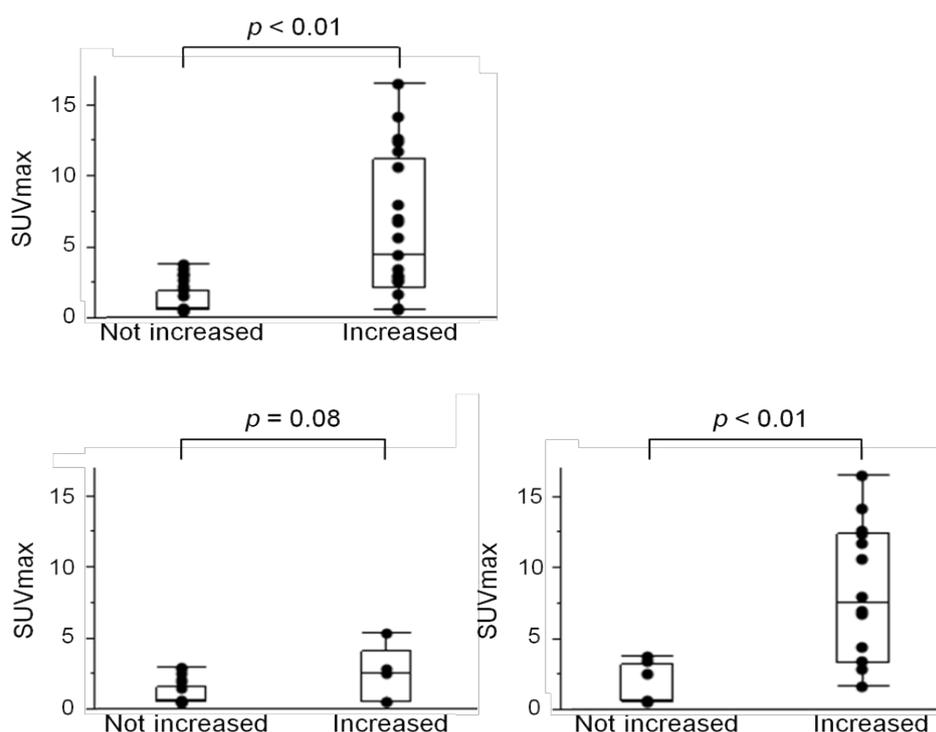


Figure 2 Box-and-whisker plot of SUV_{max} in LM in patients with and without an increased level of TG after ^{131}I therapy. The boxes represent the 25–75% range with bisecting lines showing the median value, and the horizontal lines represent the 10–90% range. Of 49 DTC patients without a high level of anti-TG antibody (*upper left*), SUV_{max} of LM was significantly greater for patients whose TG levels after ^{131}I therapy did not increase than for those whose levels did increase. Of 27 patients with ^{131}I -positive LM (*lower left*), there was no significant difference in SUV_{max} of LM between patients with and without an increased level of TG after ^{131}I therapy. Of 22 patients without ^{131}I -positive LM (*lower right*), SUV_{max} of LM was significantly greater for patients whose TG levels after ^{131}I therapy did not increase than for those whose levels did increase.

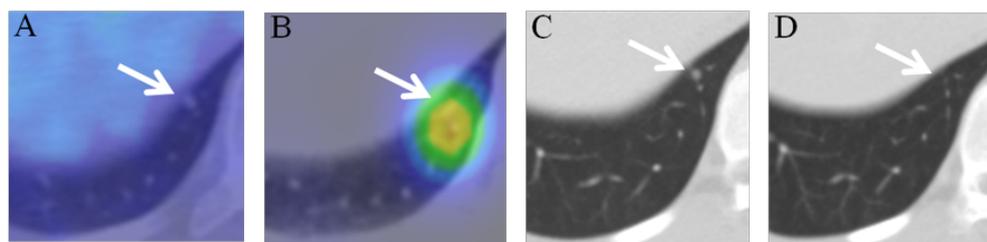


Figure 3 A representative case of good response to ^{131}I therapy in a 30-year-old woman with LM from DTC. A pulmonary nodule in the right lower lobe without ^{18}F -FDG accumulation before the initial ^{131}I therapy showed ^{131}I accumulation in post-therapy ^{131}I scintigraphy. The nodule decreased in size and the TG level of the patient also decreased 12 months after ^{131}I therapy (28.5 to 0.9 ng/mL). **a)** ^{18}F -FDG PET/CT image (arrow lesion), **b)** ^{131}I SPECT/CT image (arrow lesion), **c)** CT image at an initial ^{131}I therapy (arrow lesion), **d)** CT image after ^{131}I therapy (arrow lesion).

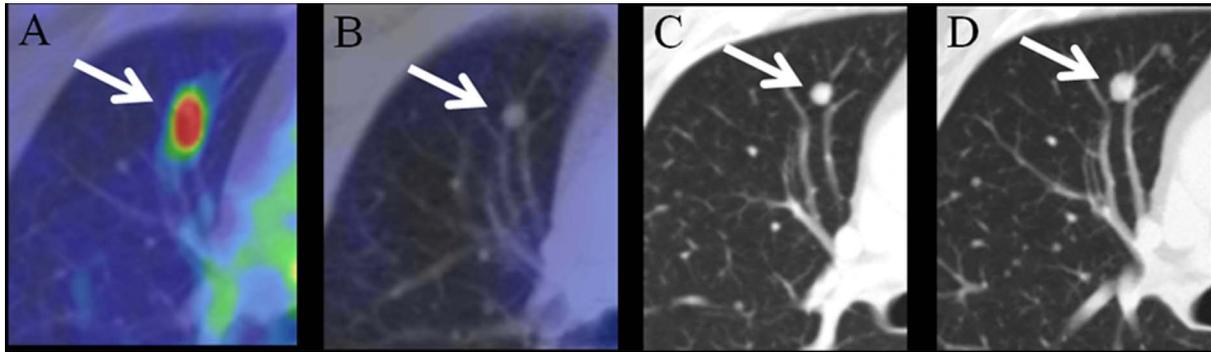


Figure 4 A representative case of poor response to ^{131}I therapy in a 47-year-old man with LM from DTC. A pulmonary nodule in the right upper lobe showed the highest ^{18}F -FDG accumulation (SUV_{max} 12.7) of multiple LM in bilateral lung before initial ^{131}I therapy. LM in the patient showed the absence of ^{131}I accumulation in post-therapy ^{131}I scintigraphy. The nodule increased in size and the TG level of the patient also increased 11 months after ^{131}I therapy (317 to 601 ng/mL). **a)** ^{18}F -FDG PET/CT image (arrow lesion), **b)** ^{131}I SPECT/CT image (arrow lesion), **c)** CT image at an initial ^{131}I therapy (arrow lesion), **d)** CT image after ^{131}I therapy (arrow lesion).

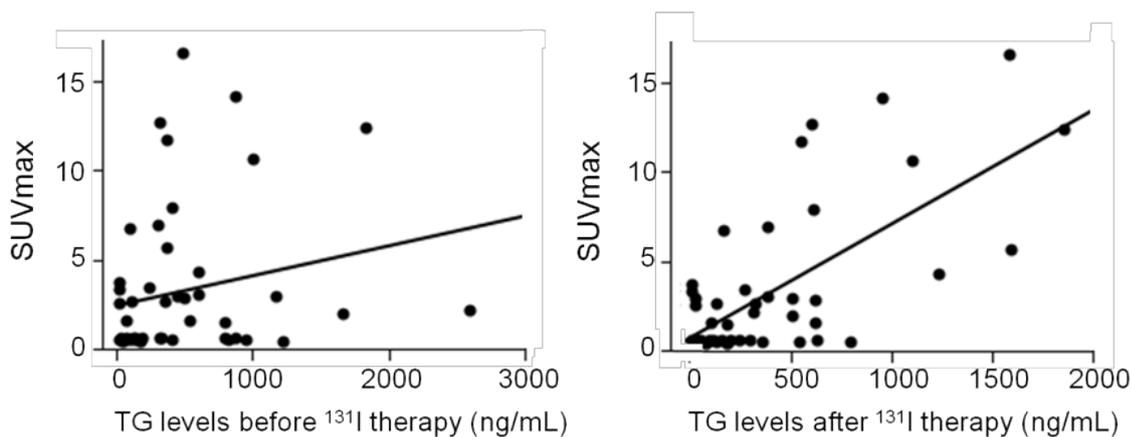


Figure 5 Scatterplots of SUV_{max} in LM and pre-therapeutic TG levels (*left*) and of SUV_{max} in LM and post-therapeutic TG levels (*right*) in the 49 patients without a high level of anti-thyroglobulin antibody. Best-fit lines are shown. There was no significant correlation between SUV_{max} in LM and the TG level before ^{131}I therapy ($r = 0.21$, $p = 0.14$). The TG level 12 \pm 2 months after ^{131}I therapy had a significant correlation with SUV_{max} in LM ($r = 0.69$, $p < 0.01$).

showed a significant correlation with the SUV_{max} in LM ($r = 0.69$, $p < 0.01$) represented by **Figure 5**.

Discussion

Our results demonstrated that SUV_{max} of LM on ^{18}F -FDG PET/CT had a high predictive value for ^{131}I accumulation in LM from DTC and the response to ^{131}I therapy. That suggests that high ^{18}F -FDG accumulation in LM is associated with a shift to dedifferentiation of LM and poor clinical outcome in DTC patients with LM. Hong et al previously reported that SUV_{max} greater than 3.6 in distant metastases from DTC was significantly predictive of reduced disease-specific survival in multivariate analysis [19]. All of the patients with SUV_{max} greater than 3.8 for LM in our study showed an increased TG level after ^{131}I therapy. The previous article and our study indicate that SUV_{max} of LM in DTC patients is an important index to predict a therapeutic effect for ^{131}I therapy.

Especially in patients without ^{131}I -positive LM, SUV_{max} of LM in DTC patients with an increased level of TG after ^{131}I therapy

was significantly higher than those without. Therefore, we hypothesize that ^{131}I -negative LM includes two types of clinically aggressive and unaggressive features. For DTC patients with an aggressive type of LM, alternative treatment such as molecular-targeted therapy is needed instead of ^{131}I therapy. It is proposed that ^{18}F -FDG -PET/CT is effective in the selection of DTC patients with the aggressive type of ^{131}I -negative LM and can determine the indications for molecular-targeted therapy, which has a beneficial effect on tumor progression in patients with radioactive iodine-refractory metastatic DTC.

Additionally, SUV_{max} of LM in DTC patients before ^{131}I therapy had a significant correlation not with the TG levels before ^{131}I therapy, but with that after ^{131}I therapy. These data show that ^{18}F -FDG accumulation in LM before ^{131}I therapy expresses post-therapeutic resistance to ^{131}I therapy, although, interestingly, it had no significant relation to the progression of DTC before ^{131}I therapy. Recently, an association has been found histopathologically between high expression of GLUT1 in thyroid cancer stem cells

and high resistance to ^{131}I therapy [20]. Therefore, ^{18}F -FDG PET/CT can be a helpful tool to assess the potential of DTC patients with LM to benefit from ^{131}I therapy and can contribute to the clinical management and determination of the best therapeutic strategy post-resection.

In our study, ^{18}F -FDG PET/CT was performed on the condition of sufficient TSH stimulation, because ^{18}F -FDG PET under TSH stimulation improves the detection of DTC metastases [21]. Moreover, our judgment of ^{131}I accumulation in LM was performed using ^{131}I SPECT/CT as post-therapy ^{131}I scintigraphy in all patients based on the findings of recent articles, reporting that SPECT/CT improves detection and localization of ^{131}I accumulation in distant metastases in comparison with whole-body scintigraphy [22,23]. Thus, the present study has shown that the evaluation of ^{18}F -FDG and ^{131}I accumulation in LM from DTC is feasible and effective.

Our study had several limitations. First, diagnoses of LM were not always made using a histopathologic procedure but were also sometimes made at clinical follow-up. Although ^{131}I -avid LM uptake usually indicates a metastatic lesion from DTC, ^{131}I -non-avid LM judged at the time of clinical follow-up might be revealed not to be a metastatic lesion at a later date. Because DTC is a slow-growing neoplasm, a long follow-up period is needed to make a more accurate clinical diagnosis. Second, we lack sufficient data to prove that the outcomes of patients without increased TG level were better than those of patients with increased TG level.

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Further studies are needed to evaluate the outcomes of DTC patients, who generally having long disease courses.

Conclusion

In conclusion, ^{18}F -FDG accumulation in LM was related to the lack of ^{131}I accumulation and also associated with poor response to ^{131}I therapy especially in patients without ^{131}I accumulation. High ^{18}F -FDG accumulation in LM from DTC was associated with poor treatment outcome after ^{131}I therapy. By contrast, even though low ^{18}F -FDG accumulation in the LM indicates the poor likelihood of ^{131}I accumulation, it also indicates a more stable status of DTC tumor activity. ^{18}F -FDG PET/CT can predict refractoriness to ^{131}I therapy and determine the indication of molecular-targeted therapy in DTC patients with LM.

Conflict of Interest

The authors declare that they have no conflict of interest that competes with any of the contents of the manuscript.

Authors' Contributions

Yasuhiro Maruoka mainly designed and conducted experiments, performed analysis and wrote the manuscript; Takuro Isoda and Yoshiyuki Kitamura performed analysis; Koichiro Abe, Masayuki Sasaki and Hiroshi Honda wrote the manuscript and supervised the project; and Shingo Baba planned and initiated the project, designed and conducted experiments, wrote the manuscript, and supervised the entire project.

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