Original Article

Association between Volumetric Analysis of Lung Metastases on F-18-fluoro-2-deoxy-D-glucose Positron Emission Tomography/Computed Tomography and Short-term Progression after I-131 Therapy for Differentiated Thyroid Carcinoma

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Abstract

Purpose: Lung metastases (LMs) and their radioiodine uptake affect prognosis in patients with differentiated thyroid carcinoma (DTC). We herein investigate the value of metabolic tumor volume (MTV) in LMs on positron emission tomography/computed tomography (PET/CT) using 2-[F-18]-fluoro-2-deoxy-D-glucose (F-18 FDG PET/CT) in predicting short-term progression after initial I-131 therapy in DTC patients. **Materials and Methods:** We retrospectively evaluated 111 DTC patients with LMs. Diagnostic CT and I-131 scintigraphy were performed within 1 week of I-131 therapy. Maximum standardized uptake value (SUVmax) and total MTV (MTVtotal) were compared between patients with I-131-positive and I-131-negative LMs and between patients with and without short-term progression. Correlation analyses were performed between F-18 FDG PET/CT parameters and thyroglobulin (TG) level, and predictive factors for short-term progression were analyzed by logistic regression and receiver operating characteristic curve analysis. **Results:** Patients with short-term progression had significantly higher SUVmax and MTVtotal than those without. TG levels were significantly correlated with SUVmax (r = 0.21) and MTVtotal (r = 0.51) after I-131 therapy. MTVtotal showed significant association (χ^2 = 16.5, odds ratio = 0.02) with short-term progression after initial I-131 therapy and had the highest predictive value of all the putative risk factors. **Conclusions:** MTVtotal in LMs on F-18 FDG PET/CT is an independent predictive factor with a high predictive value for short-term progression of DTC after initial I-131 therapy. It is recommended that F-18 FDG PET/CT be performed before planning therapy during the evaluation of DTC patients with LM.

Keywords: *Differentiated thyroid carcinoma, F-18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography, I-131 therapy, lung metastasis, metabolic tumor volume*

Introduction

Differentiated thyroid carcinoma (DTC), including papillary and follicular thyroid carcinoma, accounts for more than 90% of all thyroid cancers.[1,2] Prognosis in DTC patients is poor when distant metastases are present.[3,4] As lungs are the most common site for distant metastases, the presence of lung metastases (LMs) in DTC is an important factor in determining prognosis.[5,6]

Radioiodine I-131 therapy after near total or total thyroidectomy is an established treatment for patients with DTC.[7,8] While I-131 therapy improves the clinical prognosis in DTC patients,[9,10] patients with recurrent or metastatic I-131-negative lesions have a poorer prognosis.[6,11,12] Positron emission tomography/computed tomography (PET/CT) using 2-[F-18]-fluoro-2-deoxy-D-glucose (F-18 FDG PET/CT) is useful for detecting such I-131-negative metastatic lesions.[12-14] An inverse correlation or "flip-flop pattern" is generally observed between F-18 FDG and I-131 uptake in the residual lymph node (LN) metastatic lesions in DTC patients,[15-17] likely to upregulation of glucose transporter 1 (GLUT1) and downregulation of the sodium-iodide symporter during the dedifferentiation of DTC cells.[18] However, the relationship between F-18 FDG accumulation in LM and short-term progression after initial I-131 therapy remains unclear. There is therefore a need for an objective prognostic marker in

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DTC patients. Metabolic tumor volume (MTV), which is measured using the standardized uptake value (SUV) of F-18 FDG PET/CT,[19] has been proposed as a prognostic marker in different kinds of malignancies.[20-23] The purpose of the present study was to clarify the value of MTV in LM, based on F-18 FDG PET/CT, for predicting short-term progression after I-131 therapy in DTC patients.

Materials and Methods

Study design

DTC patients with LMs who underwent at least two rounds of I-131 therapy after near total or total thyroidectomy were retrospectively analyzed. The median interval between near total/total thyroidectomy and initial I-131 therapy was 5 months. All patients underwent thyroid hormone withdrawal for at least 4 weeks and were prescribed a low-iodine diet for 2 weeks, to stimulate thyroid-stimulating hormone (TSH) in preparation for I-131 therapy (4.0–5.1 GBq [110–135 mCi], median: 4.5 GBq [120 mCi]). F-18 FDG PET/CT was performed under this TSH-stimulated state within 1 week before I-131 administration. Diagnostic CT and I-131 scintigraphy (whole-body I-131 scan [WBS] and single-photon emission CT [SPECT]/CT) were performed within 1 week after I-131 administration. The same investigations were performed at the second round of I-131 therapy. The interval between first and second rounds of I-131 therapy was 12 ± 2 months.

Clinical and radiological parameters at the initial and second rounds of I-131 therapy were compared between patients with and without short-term progression of DTC, to identify factors predictive of short-term progression. Short-term progression was judged by an increase in thyroglobulin (TG) level, diagnostic CT findings, and F-18 FDG PET/CT findings at the time of the second I-131 therapy.

Patients

This study was approved by our institutional review board and written informed consent from each patient was obtained. Totally 563 consecutive patients with DTC (papillary or follicular carcinoma) with LM who were treated with at least two rounds of I-131 therapy between October 2010 and December 2014 at our institution after near total or total thyroidectomy were retrospectively analyzed. LM was defined as the presence of (i) I-131 accumulation in the lung field higher than that in the surrounding tissue on I-131 SPECT/CT, and/or (ii) multiple bilateral pulmonary nodules, with some showing a progressive increase in size on follow-up CT (observation period: 35 ± 9 months). Patients with (i) history of LMs resection, (ii) history of other malignancies, (iii) low TSH levels (<30 U/mL), (iv) distant extrapulmonary metastasis, or (v) hyperglycemia (>150 mg/dL) were excluded from the study. Consequently, a total of 111 patients (42 men and 69 women) were included in the study [Table 1].

Table 1: Baseline characteristics of the patients

Characteristics	*N*=111
Age (years)	
Mean±SD	55±15
Median (range)	61 (16-75)
Sex	
Men/women	42/69
Histology	
Papillary/follicular	106/5
TSH level (U/mL)	
Mean±SD	130±84
Median/range	112 (43.7-533.2)
TG level before I-131 therapy (ng/mL)	
Mean±SD	927±2953
Median (range)	173 (42-21,000)
TG level after I-131 therapy (ng/mL)	
Mean±SD	997±3209
Median (range)	179 (42-22,711)
I-131 administered dose (GBq)	
Mean±SD	4.6±0.2
Range	4.5-5.1

TSH: Thyroid-stimulating hormone, TG: Thyroglobulin, SD: Standard deviation

F-18fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography

F-18 FDG at a dose of 4 MBq/kg was intravenously administered after at least 4 h of fasting. Scans were conducted from the middle of the thigh to the top of the skull, 60 min after F-18 FDG administration. F-18 FDG PET/CT images were obtained using an integrated PET/CT scanner (Discovery STE, GE Medical Systems, Milwaukee, WI, USA). PET scans were performed in three-dimensional mode at an acquisition time of 3 min/bed position. A low-dose CT scan (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 acquiring 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 generated using GENIE–Xeleris software on a dedicated workstation, Xeleris (GE Medical Systems, Milwaukee, WI, USA).

F-18 FDG accumulation higher than the background was defined as F-18 FDG positive. The maximum SUV (SUVmax) and MTV in F-18 FDG PET images were measured (Multi Modality Tumor Tracking software; IntelliSpace Portal 6 workstation, Philips Medical Systems, Milpitas, CA, USA). A spherical volume of interest (VOI), corresponding to LMs in the bilateral lung, was drawn and SUVmax for the VOI was automatically calculated. The highest voxel value in the LMs on F-18 FDG PET/CT was determined as SUVmax. Using a SUVmax of 2.5 as the threshold according to the previous literatures,[24,25] the

volume of the portion with SUVmax ≥2.5 in each LM was measured as MTV, and the sum of the MTV in all LMs was defined as total MTV (MTVtotal).

I-131 scintigraphy

All patients underwent a WBS I-131 and SPECT/CT with a hybrid camera, involving a combination of a dual-head c-camera with a spiral CT within the same gantry (Symbia T6: Siemens, Hoffman Estates, IL, USA). 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 2 mm × 2.5 mm collimation. I-131 accumulation higher than the background in at least one LM was defined as I-131 positive and that as low as the background in all LMs was defined as I-131 negative, based on visual evaluation.

Diagnostic computed tomography protocol

A diagnostic chest CT covering the upper mediastinum to the upper abdomen was performed with a 64-multidetector row CT scanner (multiple detector CT [MDCT]; Aquilion 64; Toshiba Medical Systems, Tokyo, Japan) after I-131 scintigraphy, using the following parameters: tube voltage 120 kV, effective tube current 300 mA, collimation 0.5 mm, and pitch 27.0. The MDCT scan was reconstructed by filtered back-projection into 512 × 512 pixel images, with a 3 mm slice thickness.

Statistical analysis

SUVmax and MTVtotal were compared between patients with I-131-positive and-negative LMs and between those with and without short-term progression after the initial I-131 therapy, using Wilcoxon's test. The correlation of SUVmax/MTVtotal in LMs with the TG level after the initial I-131 therapy was analyzed by Pearson's correlation analysis. Predictive factors for short-term progression after the initial I-131 therapy were determined using logistic regression analyses and receiver operating characteristic curve analysis. All statistical analyses were performed using JMP® (version 12.0.2; SAS Institute, Cary, NC, USA) statistical software. $P < 0.05$ was considered statistically significant.

Results

Comparison between patients with I-131-positive and I-131-negative lung metastases

After initial I-131 therapy, 48 of 111 patients had I-131-positive LMs, while 63 patients had I-131-negative LM, even after the second I-131 therapy. In three of the 111 patients, LMs were detected only with I-131 scintigraphy but not with diagnostic CT. For the other 108 patients, the greatest short-axis diameters in the largest LM nodules were 8 mm ± 4 mm. SUVmax and MTVtotal were significantly higher in patients with I-131-negative LM than with I-131-positive LM (SUVmax: 6.4 ± 8.3 vs. 2.8 ± 4.8, $P = 0.0005$; MTVtotal: 13.8 ± 23.7 mL vs. 6.7 ± 28.0 mL, $P = 0.004$).

Comparison between patients with and without shot-term progression

After initial I-131 therapy, 39 of 111 patients demonstrated short-term progression. SUVmax and MTVtotal were significantly higher in patients with short-term progression than in those without (SUVmax: 9.7 ± 10.0 vs. 2.2 ± 2.2, $P < 0.0001$; MTVtotal: 25.3 ± 35.9 mL vs. 2.5 ± 11.7 mL, $P < 0.0001$) [Table 2]. Representative images of patients with and without short-term progression after initial I-131 therapy are presented in Figures 1 and 2, respectively.

Correlation between F-18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography parameters and thyroglobulin levels

TG levels after I-131 therapy in the 111 patients ranged from 0.3 to 22711 ng/mL (997 ± 3209). There was a significant correlation between SUVmax and TG levels after I-131 therapy ($r = 0.21$, $P = 0.03$) and between MTVtotal and TG levels after I-131 therapy, respectively ($r = 0.51$, $P < 0.0001$).

Predictive factor analysis of short-term progression after initial I-131 therapy

Univariate analysis showed age, TG level before I-131 therapy, presence of F-18 FDG-positive LN, maximum diameter of LMs, I-131 accumulation in LMs, SUVmax, and MTVtotal to be significantly associated with short-term progression after initial I-131 therapy [Table 3]. After multivariate logistical regression analysis, only MTVtotal showed significant association with short-term progression [Table 3]. The χ^2 and odds ratio for predicting short-term progression after initial I-131 therapy were 16.5 and 0.02 for MTVtotal in LMs, respectively [Table 3].

Ability of F-18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography findings to predict short-term progression after initial I-131 therapy

The SUVmax (optimal cutoff: 4.8) and MTVtotal (optimal cutoff: 3.1) differentiated patients with short-term progression from those without such progression with a

Table 2: The difference in fluorine-18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography parameters between patients with and without short-term progression after the initial I-131 therapy

	Progression-free (*n*=72)	Progression (*n*=39)
SUVmax	2.2±2.2	9.7±10.0*
MTV total	2.5±11.7	25.3±35.9*

*P<0.0001 versus progression-free patients. SUVmax: Maximum standardized uptake value, MTV: Metabolic tumor volume

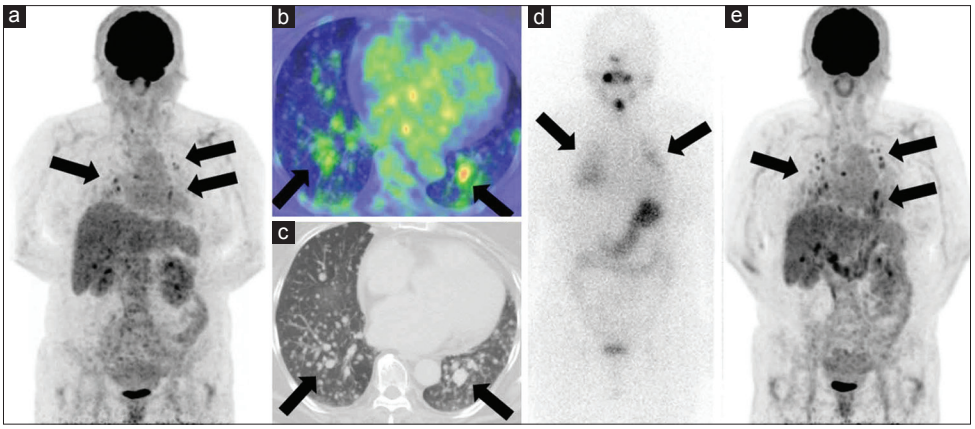

Figure 1: A 60-year-old woman who showed short-term progression after initial I-131 therapy for papillary thyroid carcinoma, with multiple lung metastases in the bilateral lungs (arrow). The maximum standardized uptake value and total metabolic tumor volume before I-131 therapy were 5.1 and 66 mL, respectively. I-131 accumulation in LM posttherapy I-131 scintigraphy was positive. The patient had progressive disease at 12 months after I-131 therapy. (a) F-18-fluoro-2-deoxy-D-glucose positron emission tomography maximum intensity projection image before I-131 therapy, (b) F-18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography image before I-131 therapy, (c) Diagnostic CT image before I-131 therapy, (d) posttherapy I-131 scintigraphy planar image, (e) F-18-fluoro-2-deoxy-D-glucose positron emission tomography maximum intensity projection image at 12 months after initial I-131 therapy

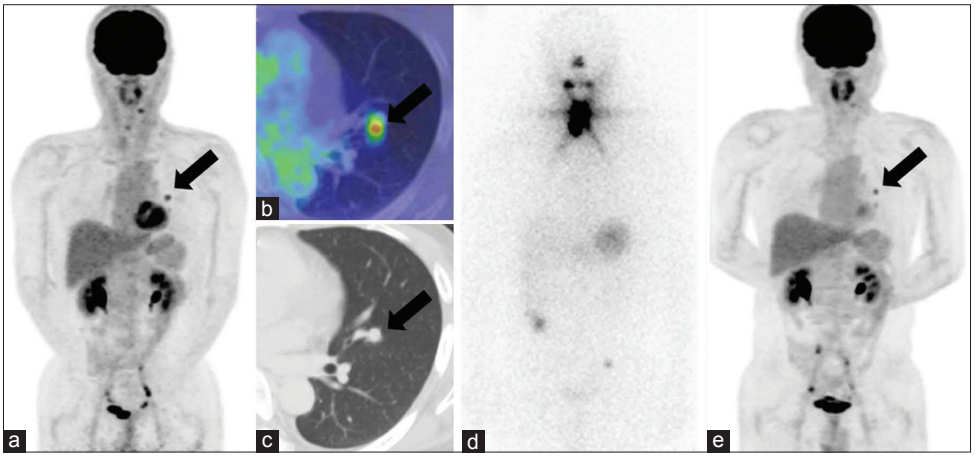

Figure 2: A 50-year-old man who showed the absence of short-term progression after initial I-131 therapy for papillary thyroid carcinoma with lung metastasis in the left lung (arrow). The maximum standardized uptake value and total metabolic tumor volume total metabolic tumor volume before I-131 therapy were 5.4 and 2.1 mL, respectively. I-131 accumulation in lung metastasis posttherapy I-131 scintigraphy was negative. The patient had no progression by 13 months after I-131 therapy. (a) F-18-fluoro-2-deoxy-D-glucose positron emission tomography maximum intensity projection image before I-131 therapy, (b) F-18-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography image before I-131 therapy, (c) diagnostic computed tomography image before I-131 therapy, (d) posttherapy I-131 scintigraphy planar image, (e) F-18-fluoro-2-deoxy-D-glucose positron emission tomography maximum intensity projection image 13 months after the initial I-131 therapy

sensitivity of 63% (25/40) and 70% (28/40), a specificity of 90% (64/71) and 96% (68/71), an accuracy of 80% (89/111) and 86% (96/111), and an area under the curve of 0.76 and 0.79, respectively.

Discussion

In the present study, we investigated the value of MTV in LMs in F-18 FDG PET/CT for predicting response to treatment and short-term progression after initial I-131 therapy for DTC patients. We demonstrated that the SUVmax and MTVtotal of LMs were significantly higher in patients with I-131-negative LMs versus I-131-positive LMs and in patients with short-term progression versus without short-term progression. These results confirm previous reports that high F-18 FDG accumulation in LMs is associated with a shift toward dedifferentiation in LMs and a poor clinical outcome in DTC patients with LMs.[26,27] Previous studies have shown a histopathological association between reduced expression of the sodium-iodide symporter and high expression of GLUT1 in thyroid cancer stem cells and high resistance to I-131 therapy.[16,27] Therefore, F-18 FDG PET/CT can be a helpful tool for assessing the therapeutic response to I-131 therapy and predicting the prognosis of DTC patients.

The MTVtotal, but not SUVmax, was independent predictive factors for short-term progression after initial I-131 therapy. MTVtotal was better able to predict the short-term progression than SUVmax. These results suggest that disease progression after I-131 therapy was associated with the spread of LMs as well as the degree of tumor

Table 3: Progression factor analysis after an initial I-131 therapy

Characteristics	Segmentation	Univariate logistic analysis			Multivariate logistic analysis			
		χ^2	OR	*P*	χ^2	OR	95% CI	*P*
Age (years)	≥57 versus <57	13.7	0.19	0.0002	1.48	0.43	0.10-1.67	0.22
Sex	Men versus women	0.57	0.74	0.45	0.08	0.84	0.23-2.89	0.78
Histological type	Papillary versus follicular	0.64	0.43	0.42	0.001	0.94	0.03-67.7	0.97
Recurrent disease	Positive versus negative	0.46	0.76	0.50	0.05	0.87	0.25-2.83	0.82
TNM stage								
T	T3/T4 versus T1/T2	3.57	0.27	0.06	0.002	0.95	0.10-6.10	0.96
N	N1 versus N0	3.01	0.21	0.08	0.37	0.47	0.02-4.60	0.54
TG level before therapy (ng/mL)	≥69 versus <69	5.90	0.34	0.02	0.06	0.85	0.23-3.09	0.80
Residual lymph node metastasis	Presence versus absence	4.14	0.43	0.04	0.64	0.59	0.152.10	0.42
Lung metastasis								
Maximum diameter (mm)	≥11 versus <11	13.6	0.15	0.0002	1.71	0.19	0.007-2.17	0.19
I-131 accumulation	Negative versus positive	14.5	0.19	0.0001	2.44	0.31	0.07-1.35	0.12
SUVmax	≥4.8 versus <4.8	31.9	0.07	<0.0001	0.25	0.59	0.08-5.63	0.62
MTV total (mL)	≥3.1 versus <3.1	54.2	0.02	<0.0001	16.5	0.02	0.0006-0.14	<0.0001

The cutoff values were determined by receiver operating characteristic curve analysis. TG: Thyroglobulin, SUVmax: Maximum standardized uptake value, MTV: Metabolic tumor volume, OD: Odds ratio, CI: Confidence interval, TNM: Tumor, node, and metastasis

glycometabolism in LMs before therapy. Moreover, I-131 accumulation in LMs was not independent predictive factors for short-term progression. The probable explanation is that I-131-positive findings in LM on posttherapy I-131 scintigraphy can propose effective expectation after I-131 therapy but cannot promise sufficient therapeutic effect. We believe that clinical management for DTC patients including F-18 FDG PET/CT examination as well as posttherapy I-131 scintigraphy is favorable.

Recently, several innovative targeted therapies have been reported as the treatment of advanced thyroid cancer with refractoriness after I-131 therapy.[28] Our results also suggest the possibility of using F-18 FDG PET/CT to screen DTC patients with I-131-negative metastatic DTC, who generally have short-term progression and may require an alternative treatment to I-131, such as molecular-targeted therapy. On the other hand, DTC patients with distant metastasis other than LM were not analyzed in our study because tumor size tendency or disease prognosis is different between DTC with lung and bone metastasis although bones are the second most common site for distant metastases in DTC. Further investigation is acceptable to clarify the effect of MTV for clinical management in DTC patients with distant metastasis other than LM on F-18 FDG PET/CT.

Our study has several limitations. First, diagnosis of LMs was not always made based on histopathology but was sometimes made at clinical follow-up. Although avid I-131 uptake by LMs usually indicates a metastatic lesion arising from DTC, nonavid I-131 uptake by LMs, judged at the time of clinical follow-up, might be revealed not to be a metastatic lesion at a later stage. Because DTC is a slow-growing neoplasm, a long follow-up period is needed for a more accurate clinical diagnosis. Second, the study outcomes were based on short-term progression over approximately 12 months. Further studies with long-term follow-up are needed to verify whether F-18 FDG PET/CT parameters can also effectively predict long-term clinical outcomes in DTC patients. Third, the fixed cutoff level of the SUVmax ≥2.5 in F-18 FDG PET/CT image analysis for estimating MTVtotal of LM has not been sufficiently tested or validated in our study. It is adopted as an effective index for volumetric analysis of F-18 FDG accumulation in previous articles,[24,25] but further investigation is required to strongly propose that the SUVmax of 2.5 is the optimal threshold.

Conclusion

F-18 FDG accumulation in LMs was related to a lack of I-131 accumulation and was also associated with short-term progression after the initial I-131 therapy. In particular, MTVtotal in F-18 FDG PET/CT could predict short-term progression after I-131 therapy, with a high predictive value. It is recommended that F-18 FDG PET/CT be performed before planning therapy during the evaluation of DTC patients with LMs.

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Conflicts of interest

There are no conflicts of interest.

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