Difference of Clinical and Radiological Characteristics According to Radioiodine Avidity in Pulmonary Metastases of Differentiated Thyroid Cancer

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Abstract

Purpose To evaluate differences in clinical, radiological and laboratory findings between pulmonary metastasis with and without radioiodine avidity in thyroidectomized differentiated thyroid cancer (DTC) patients with pulmonary metastasis who underwent high-dose I-131 treatment.

Methods A total of 105 DTC patients with pulmonary metastasis (age, 48.7 ± 16.8 years; women/men, 78/27) were included. Clinical characteristics, chest computed tomography (CT), F-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET)/CT and thyroid-stimulating hormone (TSH)-stimulated serum thyroglobulin (s-Tg) level were compared between patients with and without radioiodine uptake in metastatic lung lesions. The response to I-131 treatment was evaluated with follow-up study.

Results Eighty-nine patients (84.8 %, whole-body scan positive [WBSP] group) showed radioiodine uptake at pulmonary metastasis on post I-131 treatment whole-body scan (WBS) and 16 patients (15.2 %, WBS negative [WBSN] group) did not show uptake at pulmonary lesions on the WBS. Ninety percent and 87 % of the WBSP group had visible metastatic lesions on CT and F-18 FDG PET/CT; however, all of the patients in the WBSN group showed lesions on CT and F-18 FDG PET/CT. In seven (6.7 %) of 105 patients, CT and F-18 FDG PET/CT could not detect pulmonary lesions, which were

diagnosed by post I-131 treatment WBS. Complete disease remission was achieved in six (5.7 %) patients and all of them were in the WBSP group.

Conclusions Metastatic lesion was not visualized on chest CT or F-18 FDG PET/CT in 6.7 % of DTC patients with pulmonary metastasis and the lesion was visualized only on post I-131 treatment WBS. Complete remission was achieved in 5.7 % of DTC patients with pulmonary metastasis and the cured metastases were non-visualizing or micronodular lesions on chest CT and demonstrated radioiodine avidity on post I-131 treatment WBS.

Keywords Differentiated thyroid cancer · Pulmonary metastasis · I-131 treatment · Radioiodine avidity

Introduction

Thyroid cancer accounts for 90 % of all endocrine malignancies [1]. Incidence has been suggested to show an increase in recent years [2]. Differentiated thyroid cancer (DTC) constitutes more than 90 % of all thyroid cancer [3]. Total thyroidectomy, radioiodine ablation, and TSH suppression are the most common methods used in treatment of DTC. Although the prognosis of DTC is usually good, recurrences and metastases may develop in the coming years. Approximately 10–15 % of patients with DTC present with or subsequently develop distant metastases. In this group of patients, the 10-year disease-specific survival rate drops to 40 % [4]. The lungs are the most frequent distant localization of metastases from DTC and its incidence had been reported to be variable, up to 7 % [5–7]. The ratio of complete response of pulmonary metastasis to I-131 treatment is not very high, therefore, metastasis is known as a poor prognostic factor [4, 5].

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Despite the prognostic importance of pulmonary metastasis, it may not be visualized on plain chest radiography [8]. Accurate diagnosis and appropriate management of metastasis can improve the clinical outcome and radioiodine avidity of the metastasis is a crucial factor in tailoring of a therapeutic plan; however, relatively little information regarding the clinical, radiological, and laboratory findings of pulmonary metastasis according to radioiodine avidity has been reported in previous literature.

In the current study, we aimed to evaluate the difference in clinicoradiological findings of pulmonary metastasis according to radioiodine avidity in DTC patients.

Patients and Methods

Patients

A waiver of institutional review board approval was obtained for this retrospective analysis. A total of 3,844 thyroidectomized DTC patients who underwent high-dose I-131 ablation/treatment at the Department of Nuclear Medicine, Kyungpook National University Hospital for a 12-year period from January 2000 to December 2011 were reviewed retrospectively. Post I-131 treatment whole-body scan (WBS), thyroid-stimulating hormone (TSH)-stimulated serum thyroglobulin (s-Tg) levels were obtained, and, when necessary, other chest imaging studies (chest computed tomography [CT], F-18 fluorodeoxyglucose positron emission tomography [F-18 FDG PET]/CT) were performed for evaluation of pulmonary metastasis. Pulmonary metastasis was diagnosed when lung lesion was histologically proven as thyroid cancer, or when lung lesions shows tracer accumulation on diagnostic or therapeutic I-131 WBS, or when metastatic lesions were visualized on other imaging studies (chest CT, F-18 FDG PET/CT) and TSH-stimulated s-Tg > 2 ng/ml. Among these patients, 105 patients had pulmonary metastases.

Patients were divided into two groups based on the radioiodine avidity of the pulmonary metastases on the post I-131 treatment WBS. The WBS-positive (WBS+) group included patients with radioiodine avid pulmonary metastasis on the WBS. The WBS-negative (WBS-) group included patients with non-radioiodine avid pulmonary metastasis on the WBS. The following prognostic variables were compared between the two groups: age at diagnosis, sex, histological type, local tumor extension, cervical lymph node involvement, and presence of metastases in distant sites other than lungs, TSH-stimulated s-Tg, chest CT, and F-18 FDG PET/CT.

I-131 Treatment and Post I-131 Treatment WBS

Four weeks before administration of I-131, levothyroxine replacement treatment was withdrawn and a low iodine diet

protocol was applied for the last 2 weeks [9]. TSH levels were increased to at least 30 uIU/ml in each patient. Each patient received 5.1–7.4 GBq (150–200 mCi) I-131. I-131 treatment was repeated periodically (at least 6-month intervals) for patients with persistent radioiodine avid pulmonary metastases.

For post I-131 treatment WBS, a dual-headed gamma camera equipped with a high-resolution collimator (Infinia II; GE, Milwaukee, WI, USA) was used. Images of anterior and posterior projection were obtained from the 5th to 7th days after I-131 administration using a matrix size of 512 × 512. Spot images were also acquired when indicated.

Chest CT

Chest CT was performed only when pulmonary metastases were detected by positive I-131 WBS and/or increasing s-Tg levels. All chest CT scans were performed using a 16-channel multi-detector-row helical CT scanner (Lightspeed 16; GE Healthcare, Milwaukee, WI, USA). CT images were obtained using a 2.5-mm or a 5-mm slice thickness, starting from the apex of the lungs to the lung base. All CT images were obtained with the patient in the supine position. Patients were evaluated in terms of metastatic pulmonary lesions and the lesions were classified according to size: larger than 10 mm was defined as a macronodule and smaller than 10 mm was defined as a micronodule.

F-18 FDG PET/CT Acquisition Protocol

All patients fasted for at least 6 h, and blood glucose levels were checked before administration of F-18 FDG. Patients with elevated blood glucose levels had their examinations rescheduled and blood glucose concentration was managed to be less than 150 mg/dl in all subjects. Approximately 8.1 MBq of F-18 FDG per kilogram of body weight was administered by intravenous injection, and patients were advised to rest for 1 h before acquisition of the PET/CT image. PET/CT scans were performed using a Reveal RT-HiREZ six-slice CT apparatus (CTI Molecular Imaging, Knoxville, TN, USA) and a 16-slice CT Discovery STE apparatus (GE Healthcare, Milwaukee, WI, USA). Before the PET scan, for attenuation correction, a low-dose CT scan was obtained without contrast enhancement from the skull base to the thigh, with the patient supine and breathing quietly. PET scans with a maximum spatial resolution of 6.5 mm (Reveal PET/CT) and 5.5 mm (Discovery PET/CT) were also obtained from the skull base to the thigh, at 3 min per bed position. PET images obtained using the Reveal PET/CT and Discovery PET/CT scanners were reconstructed with a 128 × 128 matrix, an ordered-subset expectation maximum iterative reconstruction algorithm (four iterations, eight subsets), a Gaussian filter of

5.0 mm, and a slice thickness of either 3.0 mm (Reveal PET/CT) or 3.27 mm (Discovery PET/CT).

Serum Thyroglobulin Measurement

TSH stimulated s-Tg was obtained prior to administration of I-131 using a radioimmunoassay commercial kit (Thyroglobulin-IRMA; CIS Bio International, France). Patients were classified into two groups according to s-Tg levels; s-Tg<450 ng/ml; s-Tg≥450 ng/ml.

Therapeutic Approach and Follow-up Schedule

The mean follow-up period was 71.0 months (up to 309 months). Patients with persistent pulmonary metastasis which demonstrated radioiodine avidity underwent additional I-131 treatments at least annually until complete remission is achieved or the metastatic lesions lose radioiodine avidity. The number of I-131 treatments ranged from 1 to 9 times, mean 3.1 times. The cumulative dose of treatment ranged from 150 mCi to 1,800 mCi, mean 587.4 mCi. Complete remission of the metastasis was defined as negative diagnostic or post I-131 treatment WBS, normal chest CT, and TSH stimulated s-Tg levels less than 2 ng/ml.

Statistical Analyses

Continuous data were expressed as mean±standard deviation; categorical data were presented as frequency and percentage. Continuous data analysis was performed using independent samples *t*-test and categorical data were calculated using Pearson's chi-square test. Medcalc software (Windows XP, version 12.3, Broekstraat, Mariakerke, Belgium) was used in performance of statistical analysis. A *P* value of less than 0.05 was considered statistically significant.

Results

Patients' Characteristics

Our cohort consisted of 27 men (25.7 %) and 78 women (74.3 %). The age of the subjects was 48.7±16.8 years, ranging from 11 years to 76 years of age. Eighty-nine patients (84.8 %, WBSP group) showed radioiodine uptake on post I-131 treatment WBS and 16 patients (15.2 %, WBSN group) did not show uptake at pulmonary lesions on the WBS. A papillary carcinoma was diagnosed in 88 patients, and a follicular carcinoma in 17 patients. Sixty-two out of 105 patients had pulmonary metastasis before the first I-131 treatment and the other 46 patients developed pulmonary metastasis during the follow-up period. The lungs were the sole distant metastatic lesion in 88 patients (83.8 %), while 17

patients (16.2 %) also had concomitant metastases to bones (16 patients) or to the liver (one patient).

Subjects in the WBSP group were younger than those in the WBSN group (mean age, 46.8±16.9 vs 59.4±11.9, *P*=0.0053). However, there were no statistically significant differences in sex, histopathologic type, T and N stages, and additional distant metastases other than the lungs between the WBSP and the WBSN groups. The patients' clinical and histopathologic characteristics are shown in Tables 1 and 2.

Post I-131 Treatment WBS vs Chest CT

Forty-one patients underwent Chest CT before I-131 treatment and 38 (92.7 %) patients showed lung nodules on the chest CT. In the WBSP group, 90.3 % (28/31) of patients showed lung nodules on the chest CT. Among the 28 patients, 11 patients had macronodules and 17 patients had micronodules. On the contrary, in the WBSN group, all ten patients who underwent CT scan before I-131 treatment

Table 1 Clinical and histopathologic characteristics of the patients

Characteristics	Total (n=105)	WBSP (n=89)	WBSN (n=16)	<i>P</i> value
Clinical characteristics				
Mean age (years)	48.7±16.8	46.8±16.9	59.4±11.9	0.0053
Sex				
Male	27	22	5	0.8106
Female	78	67	11	
Location of metastasis				
Confined to lung	88	74	14	0.9468
Lung+other organs	17	15	2	
Histopathologic characteristics				
Histology				
Papillary	88	74	14	0.9468
Follicular	17	15	2	
Capsule invasion				
Yes	80	68	12	0.9574
No	11	9	2	
None	14	12	2	
T stage				
T1	2	2	0	0.8233
T2	3	2	1	
T3	66	57	9	
T4	19	16	3	
Tx	15	12	3	
N stage				
N0	10	9	1	0.5917
N1a	24	21	3	
N1b	56	48	8	
Nx	15	11	4	

WBSP whole-body scan positive, WBSN whole-body scan negative

Table 2 Comparison of results of imaging studies between WBSP and WBSN groups

	Total (n=105)	WBSP (n=89)	WBSN (n=16)	<i>P</i> value
Chest CT				
Positive	38	28	10	0.4406
Negative	3	3	0	
None	64	58	6	
PET/CT				
FDG uptake				0.8462
Positive	20	12	8	
Negative	16	11	5	
CT				0.0758
Positive	33	20	13	
Negative	3	3	0	
None	69	66	3	

WBSP whole body scan positive, *WBSN* whole body scan negative

showed lung nodules on the chest CT and only one patient had macronodules and nine patients showed micronodules (Fig. 1).

Post I-131 Treatment WBS vs F-18 FDG PET/CT

Pulmonary metastasis was discerned in 36 patients who underwent F-18 FDG PET/CT before I-131 treatment. Thirty-three patients showed lung nodules on F-18 FDG PET/CT. In the WBSP group, 20 of 23 patients showed lung nodules on F-18 FDG PET/CT. Only 12 patients had an FDG

uptake in metastatic pulmonary nodules, eight patients showed metastatic pulmonary nodules without an FDG uptake (Fig. 2). Three patients did not show metastatic pulmonary nodules (Fig. 3). In the WBSN group, 13 patients underwent F-18 FDG PET/CT. Eight patients had an FDG uptake at metastatic pulmonary nodules and the other five patients showed metastatic pulmonary nodules without an FDG uptake. However, no statistical difference of FDG uptake at the pulmonary nodule was observed between the WBSP and the WBSN groups.

Patients with Lung Metastases Detected Solely by Post I-131 Treatment WBS

Seven patients with pulmonary metastasis detected only by post I-131 treatment WBS and all of them underwent chest CT or F-18 FDG PET/CT before or after the I-131 treatment. Three patients underwent chest CT, two patients had F-18 FDG PET/CT and two patients had both chest CT and F-18 FDG PET/CT. All patients had negative results on chest CT and/or F-18 FDG PET/CT. All of them showed diffuse uptake pattern on post I-131 treatment WBS.

TSH-Stimulated s-Tg vs Radioiodine Avidity of Pulmonary Metastasis

Thirty-one (34.8 %) of the 89 patients of the WBSP group had a TSH stimulated s-Tg level higher than 450 ng/ml and only three (18.8 %) among 16 patients of WBSN group had TSH-stimulated s-Tg levels higher than 450 ng/ml. Although WBSP group showed a higher incidence of having high

Fig. 1 Representative images of post I-131 treatment WBS negative pulmonary metastasis. A 49-year-old woman who underwent total thyroidectomy due to papillary type differentiated thyroid carcinoma (DTC). **a** Chest CT demonstrated multiple metastatic lesions (arrows) in both lung fields and TSH-stimulated s-Tg was 34.1 ng/ml. Pulmonary metastases of DTC was diagnosed based on chest CT and TSH-stimulated s-Tg level. **b** Post I-131 treatment WBS obtained after 200 mCi I-131 administration revealed no remarkable uptake on the WBS. The patient was enrolled into the WBSN group

Fig. 2 Representative images of post I-131 treatment WBS positive and F-18 FDG PET/CT positive pulmonary metastasis. A 50-year-old man who underwent total thyroidectomy due to papillary type differentiated thyroid carcinoma (DTC). **a** F-18 FDG PET/CT demonstrated multiple metastatic lesions with faint FDG uptake in both lung fields

and TSH-stimulated s-Tg was 831.1 ng/ml. Pulmonary metastases of DTC was diagnosed based on F-18 FDG PET/CT and TSH-stimulated s-Tg level. **b** Post I-131 treatment WBS obtained after 200 mCi I-131 administration revealed intense multiple focal uptakes on the WBS. The patient was enrolled into the WBSP group

TSH-stimulated s-Tg level than the WBSN group, but it was statistically not significant. The s-Tg levels of the WBSP and the WBSN groups are shown in Table 3.

Patterns of I-131 Uptake on Post I-131 Treatment WBS

Among 89 patients in the WBSP group, 35 patients had a diffuse uptake pattern and 54 patients had a focal uptake

Fig. 3 Representative images of post I-131 treatment WBS positive and F-18 FDG PET/CT negative pulmonary metastasis. A 22-year-old woman who underwent total thyroidectomy due to papillary type differentiated thyroid carcinoma (DTC). **a** F-18 FDG PET/CT revealed no demonstrable lesions in both lung fields and TSH-stimulated s-Tg was 3, 217 ng/ml. **b** Post I-131 treatment WBS obtained after 180 mCi I-131 administration revealed intense and diffuse pulmonary uptakes on the WBS. Pulmonary metastases of DTC was diagnosed only by the WBS and the patient was enrolled into the WBSP group

pattern (nine patients with single focal uptake and 45 patients with multiple focal uptakes). Table 4 shows the patterns of I-131 uptake on post I-131 treatment WBS.

Response to I-131 Treatment

Among all 105 subjects, clinical data on therapeutic response were obtained for 78 patients. Complete remission was achieved in six (5.7 %) patients. All six patients belonged to the WBSP group; therefore, complete remission rate by treatment with I-131 was 9.1 % in the WBSP group (Table 5).

Characteristics of all six patients who achieved complete remission by I-131 treatment were as follows. All were women and mean age was 45.2 ± 14.0 years. Histological subtype was only papillary carcinoma. All patients revealed obvious I-131 uptake on pulmonary metastatic lesions; however, five patients did not have pulmonary lesions on the chest CT and a patient had micronodular pulmonary metastases (lesser than 3 mm in diameter) on the chest CT. The TSH-stimulated s-Tg levels of the six patients were lower than 15 ng/ml.

Table 3 Comparison of TSH-stimulated s-Tg level between WBSP and WBSN groups

Serum Tg	Total (n=105)	WBSP (n=89)	WBSN (n=16)	P value
s-Tg<450	72	59	13	0.3713
s-Tg≥450	33	30	3	

s-Tg serum thyroglobulin, WBSP whole-body scan positive, WBSN whole-body scan negative

Table 4 Patterns of I-131 uptake on post I-131 treatment WBS

Pattern	Number
Diffuse	35
Nodular	54
Single	9
Multiple	45

Discussion

The lungs are the most frequent distant localization of metastases from DTC, and the incidence of thyroid cancer with pulmonary metastasis has been reported as approximately 1.3–7 % [5–7]. In the current study, the incidence of pulmonary metastasis in DTC patients was found to be 2.7 %. In patients with pulmonary metastases from DTC, I-131 uptake by metastases is known to be the most important factor having a positive effect on prognosis [10]. In our study, pulmonary metastases were observed in 89 (84.8 %) patients on the post I-131 treatment WBS; however, 16 (15.2 %) patients did not show any abnormal uptake at the pulmonary metastasis on post I-131 treatment WBS. Among 78 patients from whom the author obtained clinical results, complete disease remission was achieved in six (5.7 %), all of whom belonged to the WBSP group. In the WBSN group, all patients were in persistent disease status.

Sensitivity of chest CT for pulmonary metastasis of DTC has been reported as 82 % [11]. On the contrary, some studies have shown that a chest CT scan can detect only a small number of peripheral micronodules since the central micronodules remain undistinguishable from adjacent vessel structures [12]. In the current study, chest CT detected pulmonary metastases in 38/41 patients (92.7 %), its diagnostic sensitivity was higher than that of post I-131 treatment WBS. Although post I-131 treatment WBS has lower diagnostic sensitivity for pulmonary metastases of DTC compared with a chest CT, it has better specificity for the disease and is able to forecast the disease's response to I-131 treatment. In addition, it is sometimes the only imaging method showing pulmonary metastasis.

F-18 FDG PET can be useful for localizing distant metastases, especially when the metastases have no radioiodine avidity, such as poorly differentiated thyroid carcinoma. Several investigators have reported that F-18 FDG PET and I-131

WBS played complementary roles in detection of recurrent or metastatic DTC due to a flip-flop phenomenon [13–16]. According to this phenomenon, DTC with good differentiation usually takes up radioiodine but does not take up FDG, whereas DTC with poor differentiation takes up FDG but does not take up radioiodine [13–16]. In the current study, F-18 FDG PET/CT detected pulmonary metastases in 33/36 patients (91.7 %). A PET image found pulmonary metastases in 20/36 patients (55.6 %) and a CT image found pulmonary metastases in 33/36 patients (91.7 %). Patients having pulmonary metastasis with FDG uptake had larger nodule size than patients having pulmonary metastasis without FDG uptake. Although F-18 FDG PET/CT can provide anatomical and molecular information on glucose metabolism of pulmonary metastasis of DTC, the image cannot be used for prediction of therapeutic response to I-131.

The s-Tg level is the most sensitive and specific marker of persistent or recurrent disease in DTC patients; however, high s-Tg concentration alone is not enough for the diagnosis when there is a certain amount of remnant thyroid tissue. In the current study, among 105 patients, 69 (65.7 %) had a TSH stimulated s-Tg level higher than 60 ng/ml. In a study of DTC patients with metastases, Filesi et al. [17] reported that 66.7 % had TSH-stimulated s-Tg levels higher than 60 ng/ml. They also reported that metastases were observed in the initial post I-131 treatment WBS in 47.8 % of DTC patients with s-Tg levels less than 60 ng/ml. In their study, 61.3 % of patients showing a negative result on initial I-131 WBS had s-Tg levels higher than 60 ng/ml. In the current study, 69 (65.7 %) among 105 patients had a TSH-stimulated s-Tg level higher than 60 ng/ml, and 12 (63.2 %) among 19 patients having a negative result on post I-131 treatment WBS had an s-Tg level higher than 60 ng/ml.

In the current study, the patients were divided into two groups according to the TSH-stimulated s-Tg level: those with s-Tg levels higher than 450 ng/ml and those with s-Tg levels lower than 450 ng/ml. It is assumed that a well differentiated thyroid cancer lesion can take up radioiodine and also produce Tg. On the contrary, a thyroid cancer lesion with dedifferentiation might not be not able to take up radioiodine or to produce Tg. In the current study, the WBSP group showed a higher incidence of high TSH-stimulated s-Tg level (≥ 450) and the WBSN group showed a higher incidence of low TSH-stimulated s-Tg level (≥ 450). This result supports relations between differentiation of metastasis and its biological characteristics of radioiodine avidity and Tg production.

Fortunately, unresectable distant metastases in DTC patients can be cured with I-131 treatment. Samuel et al. [4] reported that 30.8 % of DTC patients with pulmonary metastases can be cured, improvement can be achieved in 65.4 % with I-131 treatment, and only 3.8 % of patients do not respond to treatment. In a study of 394 DTC patients with pulmonary and/or bone metastases, Schlumberger et al. [18]

Table 5 Comparison of clinical outcome between WBSP and WBSN groups

	Total (n=78)	WBSP (n=66)	WBSN (n=12)	P value
Complete remission	6	6	0	0.2770
Persistent disease	72	60	12	

WBSP whole body scan positive, WBSN whole body scan negative

reported that two-thirds of the distant metastases showed radioiodine avidity and 46 % of subjects responded to I-131 treatment. In the current study, among 66 patients with radioiodine avid pulmonary metastases, complete disease remission was achieved in six (9.1 %).

The prognosis of DTC patients with pulmonary metastasis was known to be related to the size of the metastasis. The reported 10-year survival rate is about 90 % in DTC patients with functioning pulmonary metastases and positive chest radiography, and the rate was approximately 78 % in the patients with functioning pulmonary metastases and negative chest radiography [19]. In addition, miliary metastases, which results in diffuse pulmonary uptake on post I-131 treatment WBS, appears to have a better prognosis than macronodular metastases, which results in nodular uptake on the post I-131 treatment WBS [20, 21]. The success rate of I-131 treatment can be higher in pulmonary micrometastases that cannot even be visualized on CT due to their infinitesimal size. The main reason for a high success rate in small size metastasis appears to be related to a short proceeding distance of β -particles of I-131 in tissue (0.08–2.3 mm) [22]. It is also important to recognize that the micronodular pulmonary metastases generally have good radioiodine uptake than macronodular metastases [6]. Results of the current study also showed that a complete response to I-131 treatment was 9 % (3/35) in diffuse tiny miliary pulmonary metastases, and 6 % (3/54) in nodular pulmonary metastases. Naturally, complete response was achieved only in the WBSP group, and the rate was 9.1 %. The authors assume that the rate will increase with additional I-131 treatments and long-term follow-up.

The limitations of our study include its retrospective nature and small sample size. In this study, survival statistics were not preformed. There was no significant survival difference by iodine or FDG uptake on the pulmonary metastatic lesion (data were not shown), probably due to a short follow-up period. Therefore, conduct of a larger, ideally prospective long-term follow-up study is needed in order to validate the results of the current study.

Conclusion

Metastatic lesion was not visualized on chest CT or F-18 FDG PET/CT in 6.7 % of DTC with pulmonary metastasis and the lesion was visualized only on post I-131 treatment WBS. Complete remission was achieved in 5.7 % of DTC with pulmonary metastasis and the cured metastases were non-visualizing or micronodular lesions on chest CT and demonstrated radioiodine avidity on post I-131 treatment WBS.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62:10–29.
2. Chen AY, Jemal A, Ward EM. Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. *Cancer*. 2009;115:3801–7.
3. Sherman SI. Thyroid carcinoma. *Lancet*. 2003;361:501–11.
4. O'Neill CJ, Oucharek J, Learoyd D, Sidhu SB. Standard and emerging therapies for metastatic differentiated thyroid cancer. *Oncologist*. 2010;15:146–56.
5. Ruegemer JJ, Hay ID, Bergstralh EJ, Ryan JJ, Offord KP, Gorman CA. Distant metastases in differentiated thyroid carcinoma: a multivariate analysis of prognostic variables. *J Clin Endocrinol Metab*. 1988;67:501–8.
6. Casara D, Rubello D, Saladini G, Masarotto G, Favero A, Girelli ME, et al. Different features of pulmonary metastases in differentiated thyroid cancer: natural history and multivariate statistical analysis of prognostic variables. *J Nucl Med*. 1993;34:1626–31.
7. Kucuk ON, Gultekin SS, Aras G, Ibis E. Radioiodine whole-body scans, thyroglobulin levels, 99mTc-MIBI scans and computed tomography: results in patients with lung metastases from differentiated thyroid cancer. *Nucl Med Commun*. 2006;27:261–6.
8. Ilgan S, Karacalioglu AO, Pabuscuy Y, Atac GK, Arslan N, Ozturk E, et al. Iodine-131 treatment and high-resolution CT: results in patients with lung metastases from differentiated thyroid carcinoma. *Eur J Nucl Med Mol Imaging*. 2004;31:825–30.
9. Ik Dong Y, Sung Hoon K, Ye Young S, Jin Kyoung O, Joo Hyun O, Soo Kyo C. The Success Rate of Initial I-131 Ablation in Differentiated Thyroid Cancer: Comparison Between Less strict and Very Strict Low Iodine Diets. *Nucl Med Mol Imaging*. 2012;46:34–40.
10. Ronga G, Filesi M, Montesano T, Di Nicola AD, Pace C, Travascio L, et al. Lung metastases from differentiated thyroid carcinoma. A 40 years' experience. *Q J Nucl Med Mol Imaging*. 2004;48:12–9.
11. Lorenzen J, Beese M, Mester J, Brumma K, Beyer W, Clausen M. Chest X ray: routine indication in the follow-up of differentiated thyroid cancer? *Nuklearmedizin*. 1998;37:208–12.
12. Piekarski JD, Schlumberger M, Leclerc J, Couanet D, Masselot J, Parmentier C. Chest computed tomography (CT) in patients with micronodular lung metastases of differentiated thyroid carcinoma. *Int J Radiat Oncol Biol Phys*. 1985;11:1023–7.
13. Grunwald F, Schomburg A, Bender H, Klemm E, Menzel C, Bultmann T, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography in the follow-up of differentiated thyroid cancer. *Eur J Nucl Med*. 1996;23:312–9.
14. Dietlein M, Scheidhauer K, Voth E, Theissen P, Schicha H. Fluorine-18 fluorodeoxyglucose positron emission tomography and iodine-

- ¹³¹I whole-body scintigraphy in the follow-up of differentiated thyroid cancer. *Eur J Nucl Med*. 1997;24:1342–8.
15. Shiga T, Tsukamoto E, Nakada K, Morita K, Kato T, Mabuchi M, et al. Comparison of (18)F-FDG, (131)I-Na, and (201)Tl in diagnosis of recurrent or metastatic thyroid carcinoma. *J Nucl Med*. 2001;42:414–9.
 16. Hong CM, Ahn BC, Jeong SY, Lee SW, Lee J. Distant metastatic lesions in patients with differentiated thyroid carcinoma. Clinical implications of radioiodine and FDG uptake. *Nuklearmedizin*. 2013;52:121–9.
 17. Filesi M, Signore A, Ventroni G, Melacrinis FF, Ronga G. Role of initial iodine-131 whole-body scan and serum thyroglobulin in differentiated thyroid carcinoma metastases. *J Nucl Med*. 1998;39:1542–6.
 18. Schlumberger M, Challeton C, De Vathaire F, Travagli JP, Gardet P, Lumbroso JD, et al. Radioactive iodine treatment and external radiotherapy for lung and bone metastases from thyroid carcinoma. *J Nucl Med*. 1996;37:598–605.
 19. Hindie E, Mellièrè D, Lange F, Hallaj I, de Labriolle-Vaylet C, Jeanguillaume C, et al. Functioning pulmonary metastases of thyroid cancer: does radioiodine influence the prognosis? *Eur J Nucl Med Mol Imaging*. 2003;30:974–81.
 20. Pacini F, Cetani F, Miccoli P, Mancusi F, Ceccarelli C, Lippi F, et al. Outcome of 309 patients with metastatic differentiated thyroid carcinoma treated with radioiodine. *World J Surg*. 1994;18:600–4.
 21. Schlumberger M, Arcangeli O, Piekarski JD, Tubiana M, Parmentier C. Detection and treatment of lung metastases of differentiated thyroid carcinoma in patients with normal chest X-rays. *J Nucl Med*. 1988;29:1790–4.
 22. Kalender E, Zeki Celen Y, Elboga U, Deniz Demir H, Yilmaz M. Lung metastases in patients with differentiated thyroid carcinoma and evaluation of response to radioiodine therapy. *Rev Esp Med Nucl Imagen Mol*. 2012;31:328–31.