

Lung uptake on I-131 therapy and short-term outcome in patients with lung metastasis from differentiated thyroid cancer

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Abstract

Objective It is sometimes difficult to assess I-131 lung uptake at the initial I-131 therapy because of strong artifacts from I-131 uptake in the thyroid bed. The aim of this study was to analyze the lung uptake at the second I-131 therapy for lung metastasis in patients who did not have lung uptake at the initial therapy from differentiated thyroid carcinoma (DTC). Then, we also analyzed the relationship between the initial lung uptake and short-term outcome after I-131 therapies.

Methods This study included 62 DTC patients with lung metastasis. The patients were classified into 2 groups according to the lung uptake at the initial I-131 therapy such as patients with lung uptake (positive uptake group $n = 31$) and those without lung uptake (negative uptake group $n = 31$). The lung uptake was analyzed at the second therapy in both groups. The short-term outcome was also analyzed based on the CT findings of lung metastasis size and serum thyroglobulin level between the two groups.

Results The positive uptake group showed positive lung uptake at the second therapy in 23 patients (74 %), whereas none of negative uptake group showed any lung uptake at the second therapy ($P < 0.01$). The positive uptake group significantly decreased in the size of lung metastasis from the initial therapy to the second therapy (20.0 ± 11.7 to 16.6 ± 9.6 mm, $P < 0.01$) with further decrease after the second therapy ($P < 0.05$). The serum thyroglobulin level was also significantly decreased from the initial therapy to

the second therapy (4348 ± 7011 to 2931 ± 4484 ng/ml, $P < 0.05$). In contrast, the negative uptake group significantly increased in the size of lung metastasis from the initial therapy to the second therapy (17.3 ± 12.2 to 19.9 ± 14.3 mm, $P < 0.01$) with further increase after the second therapy ($P < 0.01$).

Conclusion No patients without lung uptake at the initial I-131 therapy showed lung uptake at the second therapy, or showed treatment effect. Therefore, second I-131 therapy for these patients with initially negative lung uptake should be considered cautiously.

Keywords Thyroid cancer · Lung metastasis · I-131 therapy · Radioiodine therapy

Introduction

The lung is a common organ of metastasis from differentiated thyroid carcinoma (DTC). Respiratory failure is the most common cause of death [1]. ^{131}I therapy is a widely accepted treatment for patients with lung metastasis from DTC. A number of studies have reported that ^{131}I -avid lung metastasis is curable and has an excellent prognosis. In contrast, ^{131}I -non-avid lung metastasis has a relatively poor prognosis with high thyroglobulin levels [2–5]. Therefore, patients without lung uptake on the initial therapy may need ^{131}I retreatment. But interpretation of ^{131}I uptake in the metastasis by planar image is often challenging because of artifacts from strong ^{131}I uptake in the thyroid bed [6]. Furthermore, as the initial ^{131}I therapy, ^{131}I uptake in lung metastasis may be inhibited by the strong uptake of the thyroid bed. We hypothesized that lung uptake may appear on the second ^{131}I therapy for these patients without lung uptake at the initial ^{131}I therapy due to the lack of further

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uptake by the thyroid bed after thyroid bed ablation. Accordingly, we performed two ^{131}I therapies regardless of uptake in lung metastasis at the initial therapy. However, the treatment effect of the second therapy remains unclear. The aim of this study was to investigate the relationship between lung uptake and short-term outcome after the initial ^{131}I therapy for lung metastasis from DTC. We also evaluated the lung uptake on the second ^{131}I therapy for patients without lung uptake at the initial high-dose ^{131}I therapy.

Materials and methods

Study subjects

Patients who had lung metastasis and underwent total thyroidectomy for DTC, and had at least two ^{131}I therapies were retrospectively included in this study. The ^{131}I treatment dose ranged from 100 to 150 mCi in each treatment [7–10]. Patients whose serum thyroid-stimulating hormone (TSH) level was less than 30 mU/l on the second therapy were excluded because ^{131}I uptake in lung metastasis might have been decreased by low TSH level. As a result, 62 patients were included in this study from July 2002 to May 2011.

I-131 therapy and I-131 imaging

Patients had low-iodine diet and discontinuation of thyroxine 3 weeks prior to ^{131}I treatment. These patients had whole-body scan 2–8 days after ^{131}I treatment. ^{131}I whole-body scan was performed using a Millennium MG gamma camera (General Electric; Elgems, Tirat Carmel, Israel) with high-energy collimators [11]. Two nuclear physicians (one with 19 years' experience, and another with 10 years' experience) visually interpreted ^{131}I whole-body scan images by consensus with blinded manner of patients' clinical information. The positive lung ^{131}I uptake was defined as follows. The lung uptake was positive when uptake was higher than the background physiological mediastinum uptake. We defined the patients with lung uptake at first therapy as the "positive" group. Those without ^{131}I lung uptake were defined as the "negative" group. The ^{131}I lung uptakes at the second therapy were analyzed for the two groups.

Effects of I-131 treatments

We evaluated ^{131}I therapeutic effects based on the size of the metastatic lung nodule using computed tomography (CT) and serum thyroglobulin under TSH stimulation. The size of the lung nodule was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [12, 13]: We analyzed sum of a maximum longest (SML) diameter of 2 lung nodules on CT. SML was

compared between the initial therapy and after the second therapy. Serum thyroglobulin levels at both the initial and second therapy were measured to compare the change from the initial therapy.

Statistical analysis

Values are addressed mean \pm SD. The frequency of lung uptake at initial ^{131}I therapy and second ^{131}I therapy was analyzed by Fisher's exact test. The changes of nodule size and thyroglobulin were analyzed using the Wilcoxon Matched-Pair Signed-Rank Test. Tumor response evaluation according to RECIST criteria was analyzed by Cochran–Armitage test. *P* values of less than 0.05 were considered to indicate statistical significance.

Results

Patient characteristics

Characteristics of the 62 study patients are shown in Table 1. Fifty-two patients were papillary carcinoma. 8 patients were follicular carcinoma. With remaining two patients, 1 was mixed papillary follicular carcinoma and another one was poorly differentiated carcinoma, respectively. Twenty-two patients were male and 40 were female. The initial administration dose of ^{131}I was 5.18 ± 0.54 GBq (mean \pm standard deviation), and ranged from 3.56 to 5.55 GBq. The time interval from the initial therapy to the second therapy was 287 ± 187 months, ranging from 147 to 1376 days. Follow-up CT was performed 336 ± 221 days after the second therapy. There was no patient who had new lesion in other organs within follow-up period.

After the initial therapy, 31 patients were assigned to the positive uptake group (papillary carcinoma 21, follicular carcinoma 8, mixed papillary follicular carcinoma 1, and poorly differentiated carcinoma 1). Other 31 patients were defined as the negative uptake group (papillary carcinoma 31). There were no significant differences between these two groups in terms of administration dose (5.19 ± 0.54 vs. 5.12 ± 0.56 GBq), serum TSH level (85.9 ± 52.0 vs. 77.5 ± 38.9 mIU/l), and size of lung nodule (20.0 ± 11.7 vs. 18.0 ± 15.5 mm). Positive uptake group was significantly younger than that in negative uptake group ($P < 0.05$). The serum thyroglobulin level in the positive uptake group was significantly higher than that in the negative uptake group ($P < 0.05$) (Table 1).

I-131 lung uptake

In the positive uptake group, 23 patients (74 %) showed lung uptake on the second therapy (papillary carcinoma 15,

Table 1 The characteristics of patients in the positive and negative uptake groups at the initial therapy

	Positive uptake group	Negative uptake Group	<i>P</i> value
Number of patients	31	31	
Papillary	21	31	} <0.01**
Follicular	8	0	
Others*	2	0	
Sex: male/female	9/22	13/18	NS**
¹³¹ I dose (GBq)	5.19 ± 0.54	5.16 ± 0.56	NS***
Age	54.4 ± 14.2	62.5 ± 10.4	<0.05***
TSH (mIU/l)	85.9 ± 52.0	77.5 ± 38.9	NS***
Thyroglobulin (ng/ml)	4,349 ± 7,011	1,297 ± 3,351	<0.05***
Sum of the target lesions on CT (mm)	20.0 ± 11.7	18.0 ± 15.5	NS***

TSH Thyroid-stimulating hormone, CT computed tomography

* Poorly differentiated carcinoma or papillary with follicular carcinoma

** Fisher's exact test

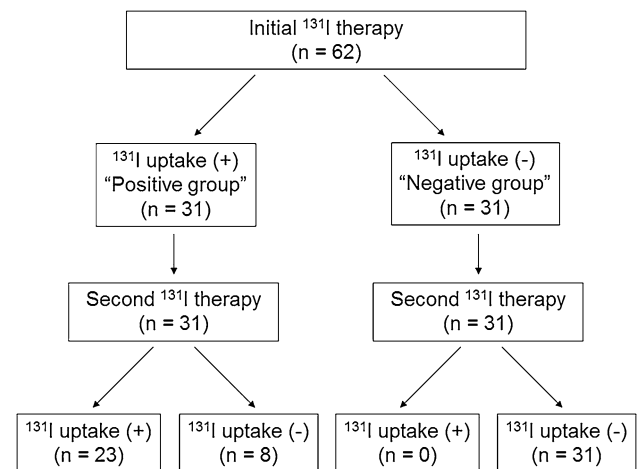
*** Mann Whitney *U* test

follicular carcinoma 7, poorly differentiated carcinoma 1), and 8 patients did not have lung uptake (papillary carcinoma 6, follicular carcinoma 1, mixed papillary follicular carcinoma 1). In the negative uptake group, all patients did not have any positive lung uptake on the second therapy ($P < 0.01$) (Fig. 1).

Therapeutic response to I-131

In the positive uptake group, 28 patients underwent CT at both initial and second therapy, but three patients were excluded due to the absence of an applicable CT. Among total 25 patients, these patients significantly reduced the average size of metastatic lung nodule at the second therapy imaging compared to before the initial treatment (20.0 ± 11.7 to 16.6 ± 9.6 mm, $P < 0.01$) (Fig. 2). Sixteen patients had additional follow-up CT studies after the second therapy (Fig. 3). The size of the lung nodule tended to decrease from 16.4 ± 5.8 mm at the second therapy to 14.7 ± 6.6 mm at the follow-up CT (324 ± 244 days after the second therapy) ($P < 0.05$). Serum thyroglobulin obtained from all 31 patients significantly decreased from initial study to the second therapy (4348 ± 7011 to 2931 ± 4484 ng/ml, $P < 0.05$) (Fig. 4).

All negative uptake group ($n = 31$) underwent CT at both the initial and second therapy. The size of lung nodule was significantly increased from initial therapy to second

**Fig. 1** Flow chart of lung uptake of ¹³¹I at the initial therapy and at the second therapy

therapy (17.3 ± 12.2 to 19.9 ± 14.3 mm, $P < 0.01$) (Fig. 2). In the 17 cases that were successfully followed up after the second therapy, the size of lung nodule had significantly increased from second therapy to follow-up CT (375 ± 174 days later) (22.2 ± 18.3 to 27.9 ± 21.9 mm, $P < 0.01$) (Fig. 3). In all patients of the negative uptake group ($n = 31$), serum thyroglobulin tended to increase from the initial therapy to the second therapy (1297 ± 3351 to 2167 ± 6812 ng/ml, NS) (Fig. 4).

We investigated the tumor response from the initial therapy to the second therapy using RECIST. In the positive uptake group, 7/28 patients were assessed as PR and the remaining 21 patients were defined as SD. In the negative uptake group, on the other hand, 24/31 patients were SD, and 7/31 were PD. Patients with positive lung uptake showed significantly higher in PR patients compared to negative uptake group, and negative uptake group showed significantly higher in PD patients compared to positive uptake group ($P < 0.001$). There was no patient with CR or PR in the negative uptake group (Table 2).

Discussion

This research revealed new results: namely, that patients without lung uptake at the initial ¹³¹I therapy had no lung uptake at the second therapy. None of them showed any therapeutic effect (CR or PR) of the second therapy. These results suggest that second ¹³¹I therapy for patients without lung uptake at the initial therapy is less effective.

We hypothesized that lung uptake on the initial therapy might be inhibited because of strong uptake of the thyroid bed, or lung uptake might be interpreted as negative because of the artifact from accumulation of thyroid bed.

Fig. 2 The sum of lung metastatic nodule. **a** In the positive uptake group, lung metastases became significantly smaller after the initial and the second therapy by Wilcoxon Matched-Pair Signed-Rank Test. **b** Metastatic lung nodules became significantly enlarged after the initial and the second therapy in the negative uptake group

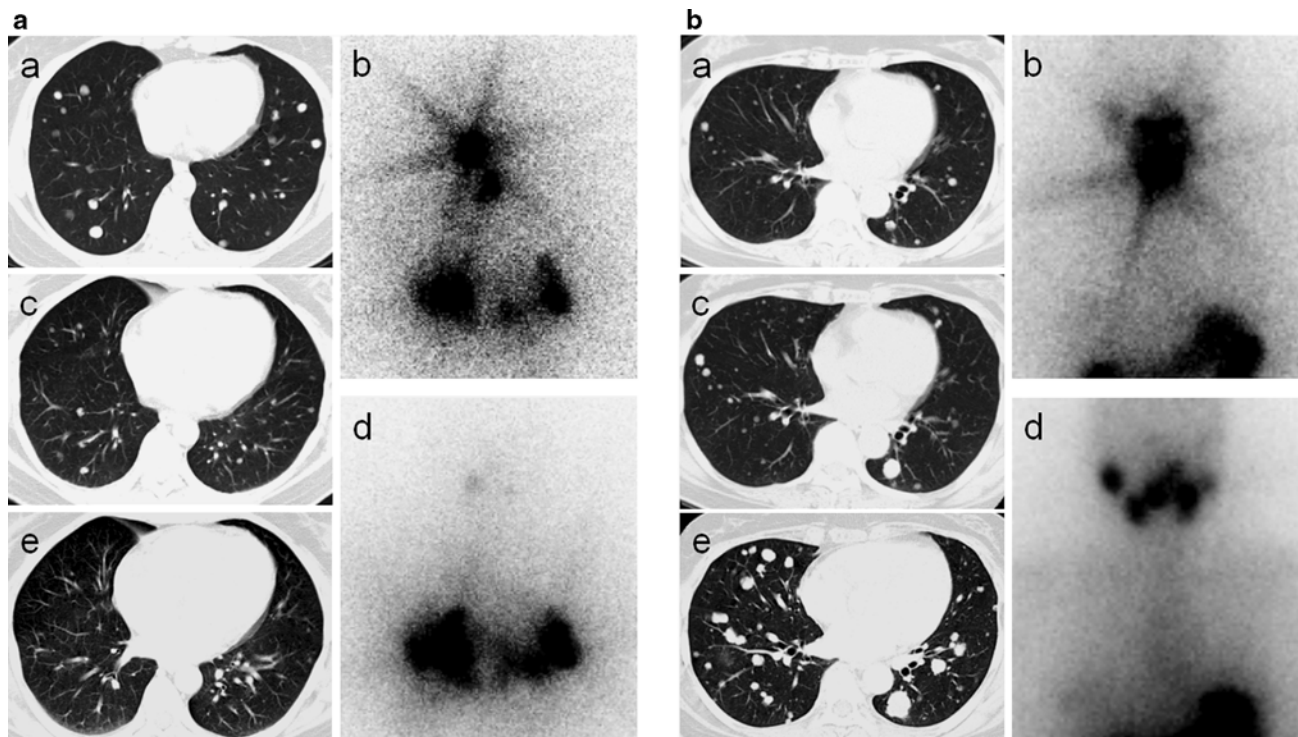
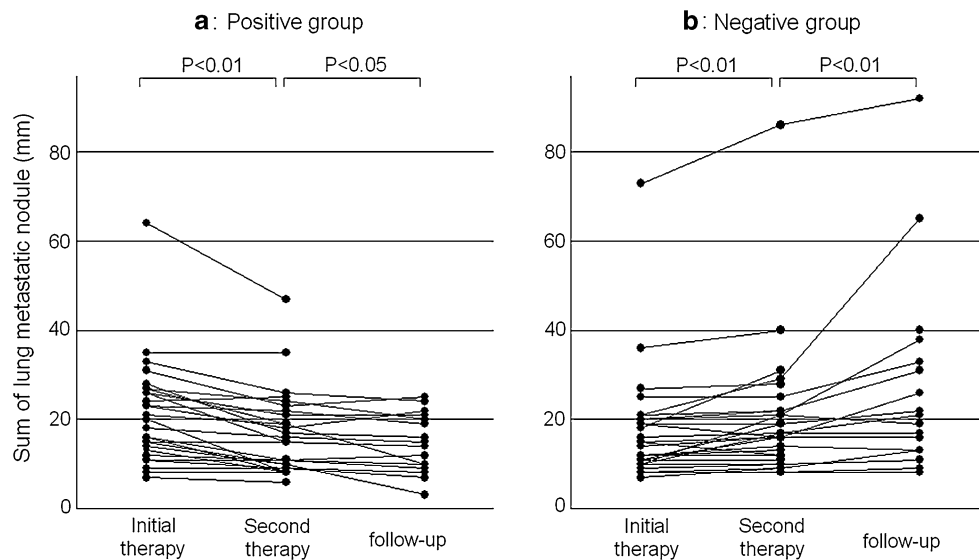


Fig. 3 **a** A 45-year-old female with lung metastases from papillary carcinoma of the thyroid. (a) CT image at the initial therapy shows multiple lung metastases. (b) In the initial therapy, a post-therapeutic ¹³¹I scan suggested high uptake both in the thyroid bed and lower lung. (c) CT at the second therapy demonstrated that lung metastasis had got smaller. (d) In the second therapy, ¹³¹I scan showed also high uptake in lower lung. (e) Thirteen months after the second therapy, the lung nodule was further reduced on CT. Thyroglobulin at the initial therapy was 2768 ng/ml, and that at the second therapy had fallen to 2383 ng/ml. **b** A 53-year-old female with lung metastases from papillary carcinoma of the thyroid. (a) CT image at the initial

therapy demonstrates multiple lung metastases. (b) Post-therapeutic ¹³¹I scan at the initial therapy showed high uptake in the thyroid bed but no uptake in the lung. Physiological uptake in intestine is shown. (c) The metastatic nodule had grown larger on the CT at the second therapy. (d) At the second therapy, the ¹³¹I scan showed uptake in intestine and salivary glands physiologically, but no lung uptake even though the thyroid bed uptake had disappeared. (e) CT image 21 months after the second therapy. Lung metastases had progressed in size. Serum thyroglobulin was increased from 844 ng/ml at the initial therapy to 2352 ng/ml at the second therapy

Fig. 4 Thyroglobulin level at the ¹³¹I therapy. **a** In the positive uptake group, thyroglobulin at the second therapy significantly decreased from that at the initial therapy by Wilcoxon Matched-Pair Signed-Rank Test. **b** Thyroglobulin at the second therapy tended to increase from that at the initial therapy in the negative uptake group

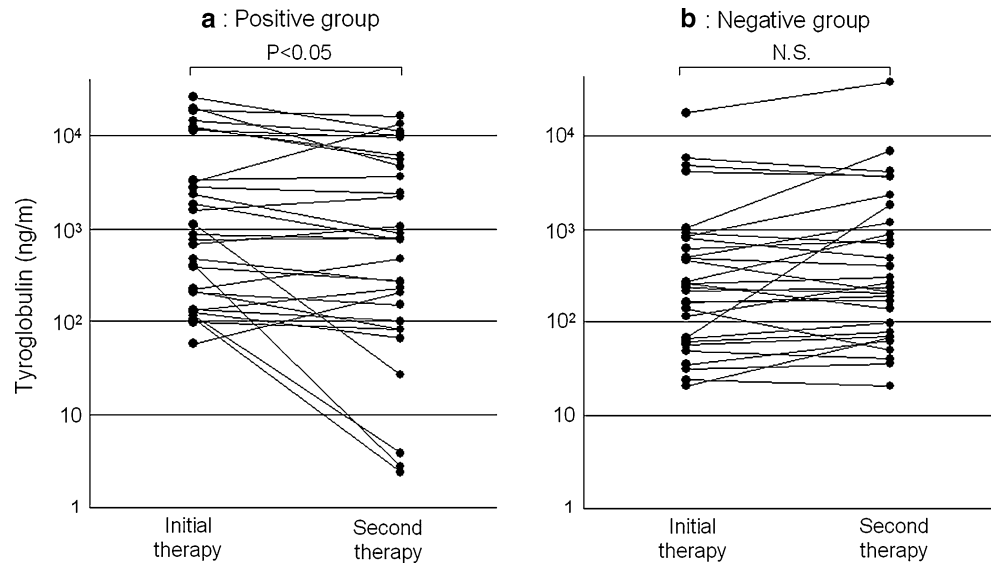


Table 2 Response evaluation of the initial therapy according to RECIST

	Positive uptake group	Negative uptake group	<i>P</i> value
CR (Disappearance of all target lesions)	0/28	0/31	} <0.001
PR (≥30% decrease in the sum of the longest diameters of target lesions compared with baseline)	7/28	0/31	
SD (neither PR or PD)	21/28	24/31	
PD (≥20% increase in the sum of the longest diameter of target lesions compared with the smallest-sum longest diameter recorded)	0/28	7/31	

CR complete response, PR partial response, SD stable disease, PD progressive disease

We expected that since the thyroid bed signal disappears after the initial therapy, lung uptake might possibly appear at the second therapy, even for those with no signal initially. However, none of the cases actually showed positive lung uptake in the second therapy. Two reasons could be considered for our results. First, all patients underwent total thyroidectomy with only the minimal amount of thyroid bed remaining. Therefore, the uptake in small thyroid bed did not likely inhibit lung uptake. A large remnant thyroid produces a strong artifact on ¹³¹I scan, and lung uptake of ¹³¹I could be false negative. However, we did not experience any case with a strong artifact from the thyroid bed. If there is strong artifact from thyroid bed, single photon emission computed tomography (SPECT/CT) may improve detection of lung uptake [14, 15]. Second, we administer a “high” dose ¹³¹I (5.18 ± 0.54 GBq) at the initial therapy. Our administration dose is within the recommended dose range for metastasis (3.7–11.1 GBq), and it is higher than the recommended dose for ablation (3.7 GBq) [7–10]. In addition, a high-dose ¹³¹I scan could enhance detectability of lung uptake. Although the maximum administration dose for patients with metastasis is 11.1 GBq, it is limited

to 5.55 GBq in our institution. Even so, the ¹³¹I dose in this study was considered to be enough for transfer beyond the remnant thyroid to the lung.

In our study, a therapeutic effect was clarified for the positive uptake group for the initial therapy with a decrease in tumor size and serum thyroglobulin levels. In contrast, the negative uptake group showed an increase in lung metastasis size, with increased serum thyroglobulin levels. Some papers have reported that cases with lung uptake on ¹³¹I therapy have better prognosis than the cases without lung uptake [7–10, 16]. Although we could not analyze long-term prognosis, the outcome of lung metastasis in our study is consistent with these reports.

It is uncertain whether the outcome for the negative uptake group may be better with second ¹³¹I therapy than that without second therapy. No previous report has suggested an answer to this question. However, our results indicated that lung metastasis may progress with increases in size and serum thyroglobulin levels for these patients. Because ¹³¹I therapy has some side effects such as hypothyroidism, sialitis, bone marrow depression, and so on, the indication for second therapy for such patients should be

considered carefully. A prospective randomized controlled study is warranted to clarify this point.

Some reports advocate that ^{18}F -fluoro-deoxy-D-glucose positron emission tomography (FDG-PET) is especially effective for patients with elevated thyroglobulin levels and normal radioiodine whole-body scan [17]. Furthermore, Shiga [11] reported that FDG-PET and ^{131}I scintigraphy provided complementary information. It is possible that FDG-PET can give useful information for decisions on the indications for an initial or second ^{131}I therapy. But we did not analyze FDG-PET findings because of the small number of patients in this study. This is also an issue for the future.

This study has several limitations. First, it is retrospective in nature. Patients who did not undergo second therapy due to their activity of daily life or other background were excluded, even when lung uptake was shown at the initial therapy. Therefore, selection bias is considerable. Second, the number of patients was limited. If we experience more cases, a case with lung uptake on the second therapy might appear. Even so, these cases may be very rare. Therefore, we can conclude that the indications for second therapy for these cases are rare. The third is the short-term follow-up (324 ± 244 days after the second therapy in the positive uptake group, and 375 ± 174 days later in the negative uptake group). Because progression of DTC is slow, more long-term follow-up or survival rate analysis is needed for more accurate evaluation.

^{131}I avidity for lung metastasis is usually evaluated by diagnostic scan with a tracer dose of ^{131}I , and it is unpredictable by other modalities [18–20]. However, our cases did not undergo a diagnostic scan. One reason is that in diagnostically negative ^{131}I uptake patients who have a positive post-treatment scan, high-dose ^{131}I therapy can be used as a diagnostic tool to identify tumor location, and a therapeutic effect may be present in individual cases [2–5]. Another reason is that Japan is a region of excessive iodine intake because of seafood. Therefore, a low-iodine diet is difficult for Japanese, and the effort required for our institution to provide a low-iodine diet in the hospital for 1 week before ^{131}I therapy was out of proportion to the benefit of such a diet prior to diagnosis. For these reasons, we did not perform diagnostic scans. Alternatively, high-dose ^{131}I therapy was used as a tool for sensitive diagnosis.

In conclusion, patients with lung metastasis from differentiated thyroid carcinoma had a poorer outcome when the initial ^{131}I therapy did not show lung uptake than those with positive lung uptake. No patients without lung uptake at the initial ^{131}I therapy showed lung uptake at the second therapy. Therefore, the second ^{131}I therapy for these patients should be considered cautiously considering the side effects of ^{131}I therapy.

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Conflicts of interest None.

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