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ORIGINAL ARTICLE

Clinical Significance of Diffuse Intrathoracic Uptake on Post-Therapy I-131 Scans in Thyroid Cancer Patients

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Abstract
Purpose The purpose of this study was to identify the frequency and possible cause of diffuse intrathoracic uptake on post-therapy I-131 scans in thyroid cancer patients.
Methods We retrospectively reviewed 781 post-therapy scans of 755 thyroid cancer patients who underwent total thyroidectomy and radioactive iodine therapy between January and December 2010. Diffuse intrathoracic uptake on post-therapy scans was examined, and clinical patient characteristics including sex, age, regimen for thyroid-stimulating hormone (TSH) stimulation (thyroid hormone withdrawal or recombinant human TSH injection), TSH, thyroglobulin (Tg) and anti-thyroglobulin antibody (anti-Tg Ab) levels, therapeutic dose of radioactive iodine therapy and prior history of radioactive iodine therapy were recorded.Scan findings were correlated with chest CT, chest radiographs, laboratory tests and/or clinical status. Diffuse intrathoracic uptake without evidence of pathologic condition was categorized as indeterminate. The association between clinical characteristics and intrathoracic uptake were analyzed for negative intrathoracic uptake and indeterminate uptake groups.
Results Diffuse intrathoracic uptake on post-therapy scans was demonstrated in 39 out of 755 (5.2 %) patients, among which 3 were confirmed as lung metastasis. The 14 patients that showed high Tg or anti-Tg Ab levels were considered to be at risk of having undetected micrometastasis on other imaging modalities. The remaining 22 were indeterminate (2.9 %).Upon comparison of negative intrathoracic uptake and indeterminate uptake groups, TSH stimulation by thyroid hormone withdrawal was shown to be significantly correlated with diffuse intrathoracic uptake ($p<0.05$).
Conclusion The frequency of diffuse intrathoracic uptake on post-therapy scans was 5.2 % and could be seen in thyroid cancer patients with underlying lung metastasis as well as those without definite pathologic condition. In the latter, there was a higher frequency for diffusely increased intrathoracic uptake in those who underwent thyroid hormone withdrawal rather than recombinant human TSH injection.

Keywords Thyroid cancer · Radioactive iodine therapy · Post-therapy scan

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Introduction

The radioactive iodine scan plays an important role in the management of patients with differentiated thyroid cancer who have undergone total thyroidectomy by detecting functioning thyroid tissue with expression of sodium-iodide symporters (NIS). However, it is well known that a variety of unexpected radioactive iodine uptakes in non-thyroidal tissue can produce false-positive results [1–5]. The mechanism is not fully understood, and such non-specific radioactive iodine accumulation is a diagnostic pitfall.

The lung is one of the most common sites of distant metastases in thyroid cancer patients. Radioactive iodine scans, along with the thyroblobulin (Tg) level, play an important role in the diagnosis of lung metastasis. Diffuse intrathoracic uptake is also known to be observed in other benign lesions [6], as well as lung metastases, but other possible causes are not clearly established. Particular attention must be paid to diffuse intrathoracic uptake on post-therapy scans without specific pathological foci on other imaging studies. Accurate interpretation of diffuse intrathoracic uptake is clinically significant for the therapeutic management of these patients.

In this study, we retrospectively identified the frequency of diffuse intrathoracic uptake and suggest a possible etiology for diffuse intrathoracic uptake on post-therapy scans in thyroid cancer patients.

Materials and Methods

Patient Population

The subjects of this study were patients who had received radioactive iodine therapy with a dose of 3.7 GBq or higher for well-differentiated thyroid cancer between January and December 2010. Those who had insufficient TSH, Tg and anti-Tg data and with less than 2 years of follow-up were excluded from the analysis. Those who showed focal uptake on the scans were also excluded. The remaining scans with negative intrathoracic uptake or diffuse intrathoracic uptake were analyzed (Fig. 1). This study was approved by the institutional review board at our institution. Informed consent was waived because of the retrospective design of this study.

Radioactive Iodine Therapy

Radioactive iodine therapy was performed in thyroid cancer patients who underwent total thyroidectomy. Before radioactive iodine therapy, thyroxine (T4) was discontinued for at least 4 weeks, with tri-iodothyronine (T3) replacement for the first 2 weeks or recombinant human TSH (rh-TSH) injection to raise the serum TSH level above 30 μU/ml.

rh-TSH was used in the patients who were predicted to have insufficient endogenous TSH stimulation due to thyroid hormone withdrawal; those with risk of progressive disease due to extensive distant metastases; those with risk of life-threatening complications of hypothyroidism due to underlying diseases including ischemic heart disease and renal insufficiency; or those who had refused thyroid hormone withdrawal [7, 8].

Patients also followed a low-iodine diet (LID) for at least 2 weeks. After thyroid hormone withdrawal and LID, I-131 diagnostic scans were performed 30 h following radioactive iodine administration with a dose of 74 MBq.

Patients who were prepared with rh-TSH injection were administrated with serial injections prior to admission and underwent F-18 FDG PET/CT instead of an I-131 diagnostic scan. A therapeutic dose of I-131, ranging from 3.7 to 9.25 GBq, was determined by postoperative pathology results, I-131 diagnostic scan or F-18 FDG PET/CT findings, and thyroblobulin and anti-thyroblobulin antibody (anti-Tg Ab) levels.

Tg, Anti-Tg Ab and TSH Measurement

Serum levels of TSH, Tg and anti-Tg Ab were obtained when a dose of 74 MBq radioactive iodine was administrated in patients with thyroid hormone withdrawal or those who had received rh-TSH injection preparations on the day of the second rh-TSH injection (D2) and 3 days later (D5). Tg levels exceeding 2 ng/ml in patients with thyroid hormone withdrawal or above 1 ng/ml in patients with rh-TSH injection

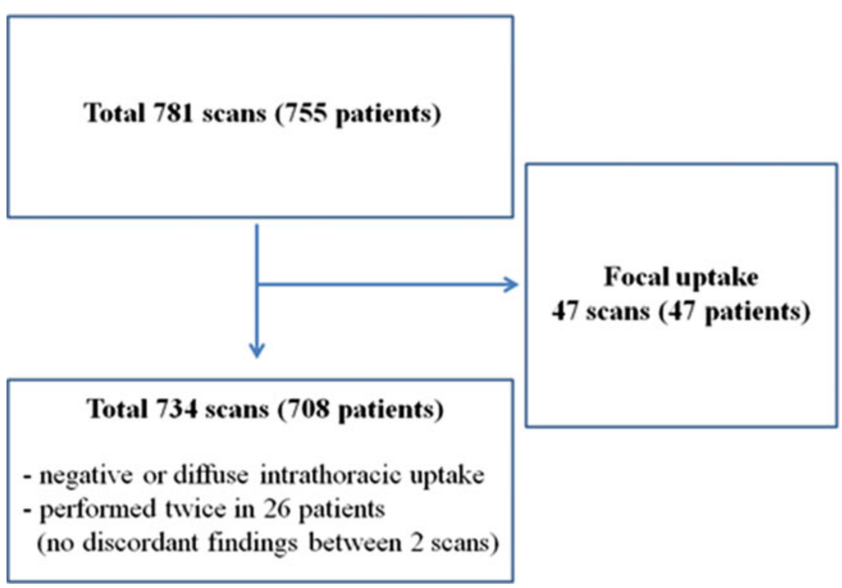

Fig. 1 Flow chart of enrolled patients. Total 781 scans of 755 patients were reviewed. Of these, 47 patients who showed focal uptake were excluded. The remaining 708 patients were analyzed in this study

and an anti-Tg Ab of 100 IU/ml were taken to be Tg positive and anti-Tg positive, respectively [9, 10].

Post-Therapy I-131 Scans

Post-therapy I-131 scans were performed 5 to 6 days following radioactive iodine therapy. Anterior and posterior images were acquired using an E-CAM dual detector system (Siemens, Erlangen, Germany) with high-energy parallel hole collimators. Each 30-min imaging study was performed using a peak of 364 keV with 15 to 20 % energy windows. Delayed image acquisition or lateral projection was carried out if clinically warranted.

Image Analysis and Interpretation

In the post-therapy scans, chest uptake was considered to be positive when the activity exceeded that of the arm or thigh. Uptakes related to skin inflammation and contamination were excluded by correlation with the patient records or clinical status at the time, which may have affected the post-therapy scans, by correlation with the view of the lateral projection or other imaging studies. Diffuse uptake was defined as that with an indistinguishable focus of prominent activity in the positive uptake. All scans were divided into 'negative,' 'equivocal' and 'positive,' and 'diffuse uptake' was determined as when at least two out of the three independent nuclear physicians arrived at a consensus of 'positive.' To evaluate interobserver and intraobserver agreement, the images were interpreted twice by each of three experienced nuclear physicians without knowledge of each other's finding.

In cases that showed diffuse uptake, the underlying pathologies were identified by correlation with chest radiographs taken within 1 week or chest CT scans taken within 2 weeks. Pulmonary metastasis was defined by confirmation of histology, identification of nodules that enlarged during a minimum follow-up period of 6 months on chest radiographs or chest CT scans, or when findings of lung metastases were identified on radioactive iodine scans with elevated serum Tg levels (>2 ng/ml) on follow-up [11–13].

Clinical conditions including age, sex, histology, regimen of TSH stimulation (hormone withdrawal or rh-TSH injection), therapeutic dose of radioactive iodine, prior history of radioactive iodine therapy and laboratory tests such as serum levels of TSH, Tg and anti-Tg Ab were recorded. Uptake in scans of patients without identified underlying pathology was categorized as indeterminate. As the possibility of micrometastases not visualized on chest radiographs or chest CT could not be completely ruled out, Tg or anti-Tg Ab positive patients were excluded from the indeterminate uptake group. Clinical characteristics and laboratory test results were compared between negative intrathoracic uptake and indeterminate uptake groups. The primary endpoint of this study was to analyze the cause of diffuse intrathoracic uptake found after radioactive iodine therapy, to suggest its clinical significance and to establish its relation with rh-TSH. For this, all patients were observed for a minimum follow-up period of 2 years.

Statistical Analysis

Agreement within and between observers with overall interpretation of the scans (negative, equivocal, positive) was calculated. Agreement was expressed as observed agreement (%) and by calculating the kappa statistics using the following grading: poor agreement $\kappa \leq 0.40$, moderate $\kappa = 0.41-0.60$, good $\kappa = 0.61-0.80$ and excellent $\kappa > 0.80$.

The Student's t-test was used to compare the laboratory tests such as the serum level of TSH, Tg and anti-Tg Ab between the indeterminate uptake and negative intrathoracic uptake groups, and the chi-square test was used to compare clinical conditions such as sex, histology, regimen of TSH stimulation, therapeutic dose of radioactive iodine and prior history of radioactive iodine therapy between the two groups. A T-test was also done to compare TSH levels between patients with indeterminate uptake and those with negative intrathoracic uptake who had undergone hormone withdrawal as well as between those prepared by hormone withdrawal and rh-TSH within the negative intrathoracic uptake group. A p-value of less than 0.05 was considered statistically significant. Analysis was performed using SPSS, version 13.0 (**SPSS**, Inc.), for Windows (Microsoft).

Results

Patient Characteristics

A total 781 post-therapy scans of 755 patients were reviewed in this study, among which 47 showing focal uptake on post-therapy scans were excluded from the analysis. Of the remaining 734 scans of 708 patients, 39 showed diffuse intrathoracic uptake, and 669 showed negative intrathoracic uptake on the post-therapy scan (Figs. 2 and 3). Twenty-six patients underwent post-therapy scans twice, but there were no cases where discordant scan findings were present. The mean age of the 708 patients was 48.6±14.1 years (range 13–85 years; 127 males and 581 females). Of these patients, 705 had papillary cancer (99.7 %), two follicular cancer (0.2 %) and one Hurthle cell carcinoma (0.1 %). Five hundred sixty patients underwent hormone withdrawal (79.1 %), and 148 underwent preparation with rh-TSH injections (20.9 %). Six hundred fifty-three patients underwent the first radioactive iodine therapy (92.2 %), and 55 patients had a prior history of radioactive iodine therapy (7.8 %); 465 patients were treated with a therapeutic dose of 3.7 GBq (65.7 %), and 243 patients were treated with a dose ranging from 5.5 to 9.25 GBq (34.3 %) (Table 1).

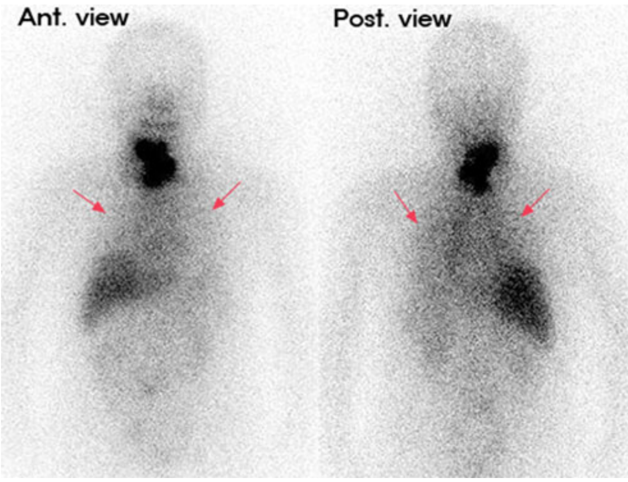

Fig. 2 Post-therapy scan of a 53-year-old female following radioactive iodine therapy with a dose of 3.7 GBq shows diffuse uptake in the chest (*arrows*). Uptake was more prominent on the posterior view with the patient in the supine position. No underlying pathology was found, and the pattern was categorized into the indeterminate uptake group

Intra- and Interobserver Agreement Between Readers

Intraobserver agreement was good for all readers (κ=0.61−0.74), while interobserver agreement was moderate to good (κ=0.51−0.62). Inter- and intraobserver agreements were 90–96 and 93–96 %, respectively, when the results were interpreted as negative, equivocal or positive. (Table 2).

Classification of Diffuse Intrathoracic Uptake Group

Three of 39 patients that showed diffuse intrathoracic uptake on post-therapy scans were confirmed to have pulmonary metastases upon correlation with chest CT, high Tg levels and clinical history. The remaining 36 patients that showed diffuse intrathoracic uptake showed no abnormal results on imaging studies. Of these, ten patients had Tg level greater than 2 ng/ml, and four patients had anti-Tg levels exceeding 100 IU/ml. The remaining 22 patients showed no abnormal results on other imaging studies and laboratory tests, and they were categorized into the indeterminate uptake group (2.9 %) (Table 3). There was no evidence of lung metastasis on imaging studies, including the radioactive iodine scan, and serum Tg levels during the follow-up period of 2 years. In these cases, uptake was more prominent on posterior view images. All were correlated with post-therapy scans and chest radiographs. Five of these were further correlated with chest

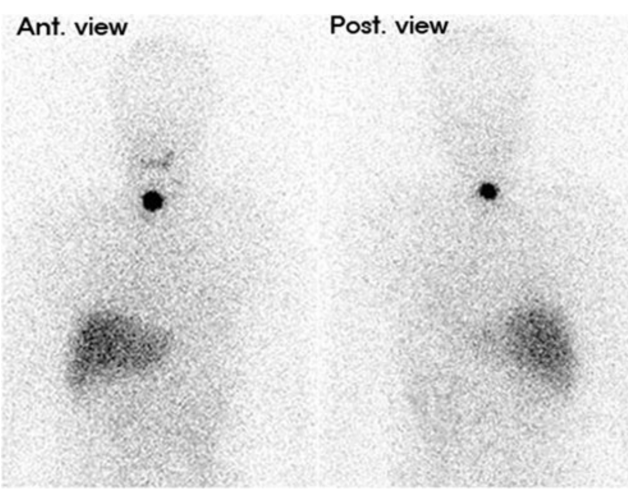

Fig. 3 Post-therapy scan of a 55-year-old female following radioactive iodine therapy with a dose of 3.7 GBq shows no definite chest uptake and was categorized into the negative intrathoracic uptake group

Table 1 Patient characteristics of the diffuse intrathoracic uptake group

	No. of patients (*n*=708)	(%)
Age		
Mean ± SD	48.6±14.1	
Sex		
Male	127	17.9
Female	581	82.1
Histology		
Papillary carcinoma	705	99.7
Follicular carcinoma	2	0.2
Huthle cell carcinoma	1	0.1
Regimen for TSH stimulation		
Hormone withdrawal	560	79.1
rh-TSH injection	148	20.9
Prior history of radioactive iodine therapy		
First	653	92.2
Repeated	55	7.8
Therapeutic dose of radioactive iodine		
3.7 GBq	465	65.7
5.5 to 9.25 GBq	243	34.3

Table 2 Intra- and interobserver agreement on interpretation of post-therapy scans showing negative or diffuse intrathoracic uptake

Agreement	Post-therapy scans (*n*=734)	
	Kappa	*Observed agreement (%)
Interobserver agreement		
Observer 1 vs. 2	0.62	93
Observer 1 vs. 3	0.55	92
Observer 2 vs. 3	0.51	90
Intraobserver agreement		
Observer 1	0.74	96
Observer 2	0.75	95
Observer 3	0.61	93

Table 3 Proportion of intrathoracic uptake

	No. of patients (n=755)	%
Diffuse intrathoracic uptake	39	5.2
Pulmonary metastasis	3	0.4
Suspicious micrometastases (Tg or anti-Tg Ab positive)	14	1.9
Indeterminate	22	2.9
Negative intrathoracic uptake	669	88.6
Focal uptake	47	6.2

CT scans. Only two scans showed a minimal volume of pleural effusion on CT scans of patients who did not have any abnormal findings on chest radiographs (Fig. 4).

Indeterminate Uptake Group vs. Negative Intrathoracic Uptake Group

Upon comparison of the 22 indeterminate uptake patients and 669 in the negative intrathoracic uptake group, there was no statistical difference in the age, serum level of TSH, Tg or anti-Tg Ab levels. There was also no statistical difference in the sex distribution of each group, therapeutic dose of radioactive iodine or the presence prior history of radioactive iodine therapy.

There was a tendency to higher TSH levels in patients who showed negative thoracic uptake than in those with indeterminate uptake, although this was not statistically significant (p=0.081), with TSH levels of 76.9±9.8 and 67.7±14.6, respectively (Fig. 5). The TSH levels in the negative thoracic uptake group of the rh-TSH-using group and negative thoracic uptake group of the hormone-withdrawal group showed a statistically significant difference (p=0.001), with 171.5±14.1 and 67.7±14.6, respectively (Fig. 6). An interesting finding was that when the frequency of indeterminate uptake for the two groups with different regimens for TSH stimulation was investigated, the frequency was 4.0 % in the hormone withdrawal group, whereas there were no patients with indeterminate uptake in the group that used rh-TSH.

Assessment of the correlation between the regimen for TSH stimulation and the indeterminate uptake group showed that the thyroid hormone withdrawal method had a strong

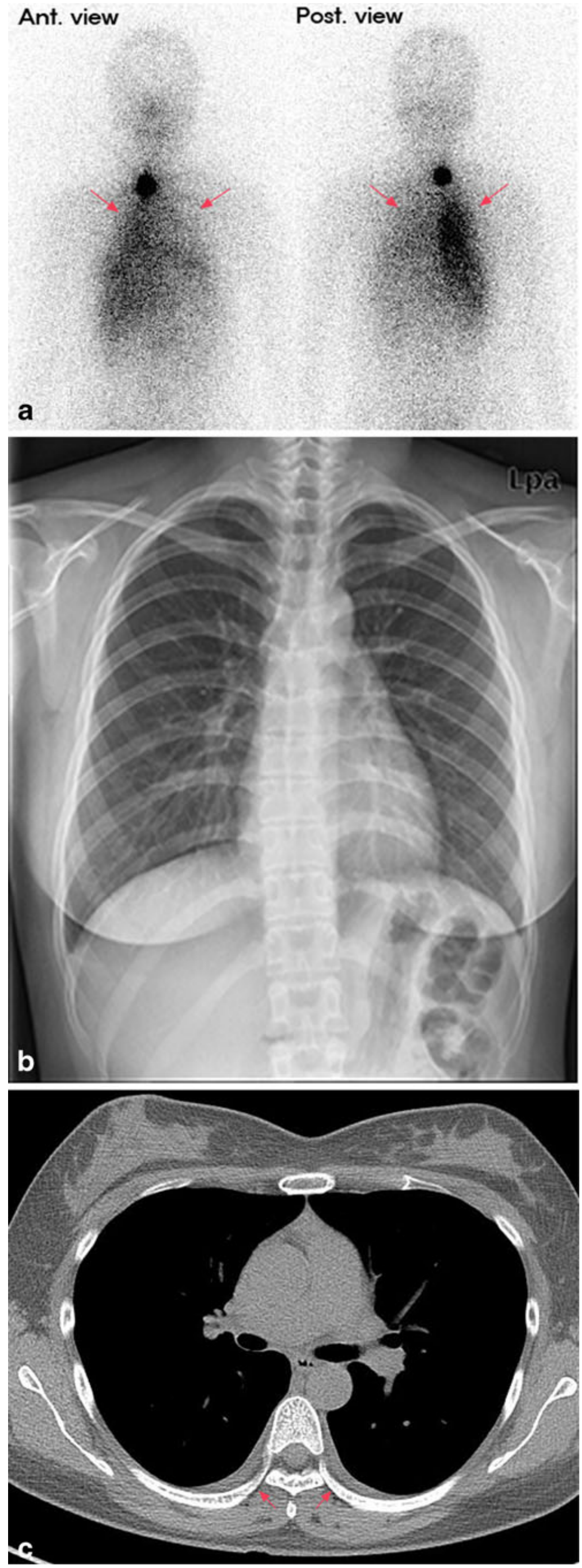

Fig. 4 **a** Post-therapy scan of a 32-year-old female following radioactive iodine therapy with a dose of 5.5 GBq shows diffuse uptake in the chest (*arrows*), namely indeterminate uptake. **b** On the chest radiograph, no abnormal findings were visualized. **c** On chest CT images within 2 weeks of post-therapy scans, a minimal amount of both pleural effusions (*arrows*) was visualized. Therefore, the diffuse uptake was thought to be related to bilateral pleural effusion

Table 4 Comparison of clinical characteristics between indeterminate uptake and negative intrathoracic uptake

Parameter	Indeterminate uptake (n=22)	Negative intrathoracic uptake (n=669)	p-value
Age			0.561
Mean ± SD	48.3±9.2	48.4±11.5	
Sex			0.245
Male	4	120	
Female	18	549	
Regimen for TSH stimulation			0.012
Hormone withdrawal	22	527	
rh-TSH injection	0	142	
Prior history of radioactive iodine therapy			0.121
First	21	617	
Repeated	1	52	
+Therapeutic dose of radioactive iodine			0.113
3.7 GBq	10	240	
5.5 GBq	12	429	
TSH (μU/ml)	76.9±9.8	96.9±16.1	0.061
Tg (ng/ml)	0.9±1.4	5.6±12.1	0.165
Anti-Tg Ab (IU/ml)	24.1±24.9	62.1±68.7	0.684

+ Therapeutic dose of 7.4 to 9.25 GBq was administrated to patients with confirmed lung metastasis

correlation with an indeterminate uptake pattern (p=0.012) (Table 4).

Discussion

Several imaging modalities are used to diagnose lung metastases in thyroid cancer patients. Of these, radioactive iodine scans play a significant role. Post-therapy scans of thyroid cancer patients often show radioactive iodine uptake in the chest, and it is clinically important to distinguish between true lung metastases and false-positive uptakes in order to avoid unnecessary treatment.

An interesting finding was that that there were diffuse patterns of radioactive iodine uptake even without identified underlying pathology (2.9 %), and when these were compared to the negative intrathoracic uptake group, there was a higher frequency of positive uptake when the thyroid hormone was withdrawn. Diffuse uptake showed a difference from that of bronchiectasis or inactive pulmonary tuberculosis, which demonstrated focal uptake patterns corresponding to pathologic focus [14–16]. One previous study reported that diffuse uptake can be seen in bronchiectasis [6]. However, in our study the fact that abnormal chest radiograph findings were

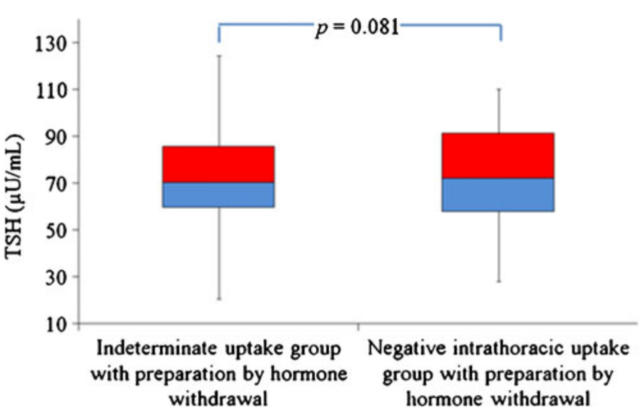

Fig. 5 Comparison of serum TSH levels between the indeterminate uptake group and negative intrathoracic uptake group with preparation by thyroid hormone withdrawal. There was no significant difference between two groups. All patients in the indeterminate uptake group underwent thyroid hormone withdrawal

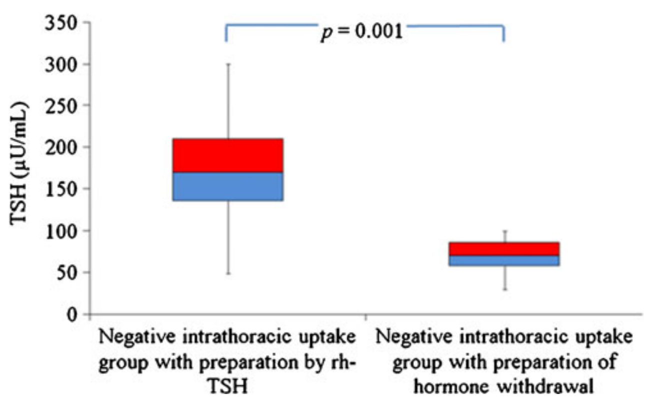

Fig. 6 Comparison of the serum TSH level between patients who were prepared by hormone withdrawal and rh-TSH within the negative intrathoracic uptake group. There was a significant difference between the two groups

not seen in all patients and that abnormalities such as inactive pulmonary tuberculosis and evidence of bronchiectasis were not seen in the 18 patients who had received chest CT during the entire period of the hospital visit, including the radioactive iodine therapy preparation period, suggest the possibility of other causes.

A diffuse uptake pattern, on the other hand, is associated with pleural effusion. Some of these showed unilateral diffuse uptake, and the fact that the uptake was more prominent on the posterior view and not localized to the mediastinum (as in pericardial effusion) further supports this explanation [2, 17]. It is well known that patients with hypothyroidism often have pleural effusion, pericardial effusion, ascites and peripheral edema [18, 19]. As previously reported, hypothyroidism causes increased vascular permeability, which results in pleural effusion through transudates and/or exudates, and it is believed to be visualized through the uptake of transudates and exudates [20, 21].

It is well known that vascular endothelial growth factor (VEGF) is expressed in a number of normal adult tissues, including the kidney, lung, uterus, ovary, brain, heart, skin, pituitary gland and macrophages [22]. VEGF is produced by thyroid follicular epithelial cells in response to stimulation of the TSH receptor. Secreted VEGF might stimulate VEGF receptors on endothelial cells, leading to increased vascular permeability [23].

It has also been reported that in patients with hypothyroidism, large molecules such as glycosaminoglycans move to the interstitial space, producing an osmotic effect that leads to the movement of fluids from intravascular space to the extravascular space [24]. These mechanisms are believed to be the cause of pericardial effusion and pleural effusion in patients with hypothyrodism.

Pleural effusion in patients with hypothyroidism is minimal, which is why detection is difficult using other imaging modalities. Most are asymptomatic, so these patients generally do not require treatment other than thyroid hormone replacement. Although a significant proportion of these patients has pleural effusion, it is believed that this number is underestimated [25].

Because CT scans were generally taken preoperatively, or when evaluation for lung metastasis was warranted because of high serum Tg levels, there was a lower proportion of patients in the indeterminate uptake group that underwent chest CT who had normal serum Tg levels. Another factor was that patients with hypothyroidism only had minimal volumes of pleural effusion, as stated previously, which makes it difficult to detect on chest radiographs.

Another interesting finding from this study was that the TSH levels of the negative intrathoracic uptake group (96.9±16.1) were higher than those of the indeterminate uptake group (76.9±9.8) (p=0.061). The mean TSH level of the negative intrathoracic uptake group patients who used rh-TSH (171.5±14.1) was significantly different from that of the negative thoracic uptake group who underwent hormone withdrawal (67.7±14.6) (p=0.001), suggesting that this was due to the use of rh-TSH. It has been reported that the use of rh-TSH produces higher TSH levels compared to thyroid hormone withdrawal [26]. Actually, the TSH level of the indeterminate uptake group of hormone withdrawal patients was higher (76.9±9.8) than that of the negative intrathoracic uptake group of hormone withdrawal patients (67.7±14.6); this was not statistically significant (p=0.081). According to previous studies, pleural effusion due to hypothyroidism occurred in hypothyroidism patients with lower TSH levels than those of the hypothyroidism patients in this study [23, 25]. It has been reported that there is no correlation between the clinical manifestation and TSH levels in hypothyroidism patients; we therefore believe that the presence of pleural effusion is related more to the presence of hypothyroidism itself than to TSH levels [27].

The lung is an extrathyroidal tissue that expresses NIS, and other such extrathyroidal tissues include the salivary glands, stomach, mammary glands, colon and ovary. The presence of radioactive iodine uptake in extrathyroidal tissue is thought to be due to NIS expression [21]. Thyroid transcription factor-1 (TTF-1) is a transcription factor that plays an important role in the thyroid-specific expression of NIS. Another interesting study has shown that of the various extrathyroidal tissues, NIS mRNA along with TTF-1 mRNA is expressed only in the lung [28]. The lung showed a significant difference in NIS expression for hypo- and hyperthyroid status, suggesting that it may have an effect on the post-therapy scan of patients with hypothyroidism [28].

There have been reports of lung metastases in patients with well-differentiated thyroid cancer, with radioactive iodine uptake but without detectable Tg levels, which can lead to a doubt in judgment [29]. There is a possibility of lung metastasis in thyroid cancer, which shows radioactive iodine uptake in the indeterminate uptake group, but without Tg expression. According to previous studies, the incidence of distant metastasis in the initial diagnosis of well-differentiated thyroid cancer is 1–9 %, of which 53 % exist solely in the lung [30, 31]. Of these, histologically 2.35 % are from papillary cancer and 10.5 % from follicular cancer [31]. Of the indeterminate uptake group, all were papillary carcinomas. Even after exclusion of those patients with elevated Tg, 2.9 % patients showed indeterminate uptake, suggesting the unlikelihood of all being lung metastases.

The post-therapy scan, along with the serum Tg level, is an important diagnostic tool for the detection of metastases in thyroid cancer patients. However, it should be noted that it is difficult to differentiate between lung metastases and benign lesions using radioactive iodine uptake patterns alone. As shown in this study, diffuse intrathoracic uptakes are visualized on post-therapy scans in both indeterminate uptake and pulmonary metastasis groups.

Some limitations of this study include the fact that not all patients had available tomographic images, which may have resulted in erroneous classification. Accuracy of the classification may be further improved using SPECT/CT. A second limitation is the potential variability in the LID of the patients. As a result, there may be variation of the body iodine pool between the patients, which may affect the uptake of radioactive iodine. Another limitation was that as a retrospective study, clinical relevant factors such as cold history were not considered. Finally, we defined Tg levels of 2 ng/ml in patients with thyroid hormone withdrawal or 1 ng/ml in patients with rh-TSH injection, and anti-Tg Ab levels of 100 IU/ml as being positive, in order to exclude lung micrometastases. However, because this was not basesd upon absolute criteria, it was difficult to clearly differentiate these patients from those with micrometastases.

Future studies of this kind should be done by addressing these limitations.

Conclusion

A total of 39 patients (5.2 %) showed diffuse intrathoracic uptake on post-therapy scans. Diffuse intrathoracic uptake was also found in patients with confirmed pulmonary metastasis or risk of undetected micrometastasis as well as in patients without identified underlying pathology (2.9 %) with a higher frequency of showing positive uptake in patients who underwent thyroid hormone withdrawal. Therefore, an accurate interpretation of radioactive iodine scans with correlation of other imaging studies, clinical history and serum Tg levels has clinical importance for avoiding unnecessary treatment.

Conflict of interest The authors declare no conflict of interest.

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