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Abstract

We studied the differentiation of thyroid nodules using fine-needle aspiration biopsy (FNA) and Tl-201 scintigraphy quantitative analysis. One-hundred and thirty-one thyroid nodules were examined: 83 follicular lesions (58 benign and 25 malignant lesions) and 48 non-follicular lesions (8 benign and 40 malignant lesions). During Tl-201 scintigraphy examinations, an early and a delayed image were acquired 10 and 120 min after an intravenous injection, respectively. The T/N ratio (counts of nodular lesion/counts of contralateral normal thyroid tissue) of each image was calculated quantitatively. We assessed the ability of the Tl-201 scintigraphy and of the FNA analysis to differentiate benign and malignant lesions and determined the cut-off levels for the assays. For the follicular lesions, the area under the ROC (Receiver Operating Characteristic) curve (Az) for the Tl-201 scintigraphy data was greater than that for the FNA data. For the non-follicular lesions, the Az for the FNA data was greater than that for the Tl-201 scintigraphy data. We set cut-off levels at 1.370 for follicular lesions, and 1.070 for non-follicular lesions. The sensitivity and specificity were 76% and 82.7% for follicular lesions, and 90% and 87.5% for non-follicular lesions, respectively. The overall accuracy of the analysis was 84.0%.

KEYWORDS: ?thyroid nodules, fine-needle aspiration biopsy(FNA), Tl-201scintigraphy

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Original Article

Differentiation of Thyroid Nodules Using Tl-201 Scintigraphy Quantitative Analysis and Fine-Needle Aspiration Biopsy

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We studied the differentiation of thyroid nodules using fine-needle aspiration biopsy (FNA) and Tl-201 scintigraphy quantitative analysis. One-hundred and thirty-one thyroid nodules were examined: 83 follicular lesions (58 benign and 25 malignant lesions) and 48 non-follicular lesions (8 benign and 40 malignant lesions). During Tl-201 scintigraphy examinations, an early and a delayed image were acquired 10 and 120 min after an intravenous injection, respectively. The T/N ratio (counts of nodular lesion/counts of contralateral normal thyroid tissue) of each image was calculated quantitatively. We assessed the ability of the Tl-201 scintigraphy and of the FNA analysis to differentiate benign and malignant lesions and determined the cut-off levels for the assays. For the follicular lesions, the area under the ROC (Receiver Operating Characteristic) curve (Az) for the Tl-201 scintigraphy data was greater than that for the FNA data. For the non-follicular lesions, the Az for the FNA data was greater than that for the Tl-201 scintigraphy data. We set cut-off levels at 1.370 for follicular lesions, and 1.070 for non-follicular lesions. The sensitivity and specificity were 76% and 82.7% for follicular lesions, and 90% and 87.5% for non-follicular lesions, respectively. The overall accuracy of the analysis was 84.0%.

Key words: thyroid nodules, fine-needle aspiration biopsy (FNA), Tl-201 scintigraphy

Clinically detectable thyroid nodules occur in roughly 4-10% of the population. Of these nodules, 5-38% are malignant [1]. Fine needle aspiration biopsy (FNA) is a safe and simple procedure with excellent predictive value and is widely used for the diagnosis of thyroid nodules [1, 2]. However, an accurate diagnosis of thyroid follicular nodular lesions is difficult to achieve using FNA [1, 3]. When a follicular lesion is diagnosed using FNA, other tests are essential for the differentiation of malignant nodules [4, 5]. We previously reported that visual and quantitative evaluations using Tl-201 scintigraphy are useful for the diagnosis of thyroid nodules, especially follicular lesions [5, 6].

A few reports have described the use of decision trees for the differentiation of thyroid nodules. Mazzaferri used FNA and Tc-99m pertechnetate scintigraphy to differentiate thyroid nodules [4]. Although Tc-99m pertechnetate scintigraphy can be used to diagnose thyroid tumors, it cannot adequately differentiate between benign and malignant lesions if the result of an FNA examination is negative.

In the present study, we retrospectively studied the

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use of FNA and a quantitative Tl-201 scintigraphy analysis for the differentiation of thyroid nodules.

First, we assessed the abilities of a quantitative Tl-201 scintigraphy analysis and of FNA to differentiate both follicular thyroid lesions and non-follicular lesions. We then estimated the critical test-result value separating 'positive' and 'negative' results using Tl-201 scintigraphy and FNA data for both non-follicular and follicular lesions. Finally, we separated the non-follicular lesions and follicular lesions on the basis of the FNA results and created a diagnostic paradigm for the evaluation of thyroid nodules using FNA and/or Tl-201 scintigraphy.

Materials and Methods

One-hundred and twenty-eight patients (17 males and 111 females; age, 16–87 years; mean age [$\pm$SD], 54.6 ± 16.0 years) with 131 thyroid nodules (size range, 8–97 mm; median size, 27 mm) were examined between December 1989 and January 2000 at our institution. Plural nodules were recognized in 3 subjects, and they were all located bilaterally.

All nodules were detected sonographically and confirmed histopathologically after surgical resection. Lesions were defined as follicular or non-follicular under FNA light microscopy according to the presence (follicular) or absence (non-follicular) of colloids, foam cells, or follicle epithelium. In adenomatous goiters ($n = 17$), both follicular and non-follicular components were recognized cytologically. We classified them as follicular ($n = 7$) and non-follicular ($n = 10$) lesions according to the FNA results.

Histopathologic examinations revealed that 83 of the nodules were follicular lesions (58 benign lesions [46 follicular adenomas, 2 oncocytomas, 10 adenomatous goiters] and 25 malignant lesions [follicular carcinomas]) and 48 of the nodules were non-follicular lesions (8 benign lesions [7 adenomatous goiters, 1 chronic thyroiditis] and 40 malignant lesions [36 papillary carcinomas, 2 medullary carcinomas, and 2 undifferentiated carcinomas]).

In our study, follicular lesions tended to be larger than non-follicular lesions (median size: follicular lesions, 28 mm; non-follicular lesions, 25 mm), but the difference was not statistically significant (N.S.). There was no correlation for benign and malignant lesions (median size: follicular benign lesions, 28 mm; follicular malignant lesions, 28 mm; non-follicular benign lesions, 26 mm; non-follicular malignant lesions, 25 mm) (N.S.).

In the Tl-201 planar scintigraphy examinations, Tl-201 (74 MBq) was injected intravenously, and early (after 10 min) and delayed (after 120 min) images were acquired. Tc-99 m pertechnetate (185 MBq) was injected intravenously after the Tl-201 early image was acquired. A gamma camera (Diagnost Tomo; Phillips Co., Einthoven, Netherlands) attached to a low-energy, high-resolution pinhole collimator was used to obtain the images. The effective field of view was 40 cm in diameter. The imaging parameters included a window level of 70 keV for the Tl-201 scintigraphy and 140 keV for the Tc-99m pertechnetate scintigraphy, a window width of $\pm 10\%$ for both Tl-201 and Tc-99m pertechnetate, a preset time of 10 min for Tl-201 and 5 min for Tc-99m pertechnetate, and a maximum preset count of 256 counts per pixel. The data acquisition matrix was 256×256 and the display matrix was 512×512.

Scintigraphic analysis. For the quantitative Tl-201 scintigraphy analysis (both early and delayed images), the largest possible region of interest not exceeding the target region, which was the cold/hot lesion observed using Tc-99m pertechnetate scintigraphy, was manually placed over the tumor and over a region of normal thyroid tissue on the opposite side.

$$\text{T/N ratio} = \frac{\text{Counts of nodular lesion}}{\text{Counts of contralateral normal thyroid tissue}}$$

Fine-Needle Aspiration. FNA was performed by puncturing the thyroid nodules using a 23-gauge needle. Cells were stained using either the Papanicolou or the Giemsa method. The staining results were observed and classified by experienced pathologists with qualifications from the Japanese Society of Cytodiagnosis. Normal cells were classified as class I, abnormal cells as class II, cells suspected of malignancy as class III, cells likely to be malignant as class IV, and cells with definite malignancy as class V.

Statistical Analysis. The size of nodules for follicular and non-follicular lesions was compared by the Mann-Whitney test. A P value below 5% was judged to be significant.

Labroc 5 (CE Metz, University of Chicago) was used to calculate the receiver operating characteristic (ROC) curves. The ROC curve is a plot of pairs of the true-positive rate (sensitivity) and false-positive rate (1-specificity) corresponding to each cut-off value for the diagnostic test results. The area under the ROC (Az) serves as an overall measure of test performance, with an area of 1 indicating a perfect test and an area of 0.5 indicating a test that is unable to distinguish between the presence and absence of the disease of interest. We estimated the relationship between the critical test-result value and the corresponding operation point on the fitted binormal ROC curve for the Tl-201 scintigraphy data. The cut-off level for the FNA data was directly calculated.

Results

Fine-Needle Aspiration. Table 1A shows the result of follicular lesions (83 nodules). The 12 class I nodules in 83 nodules, 8 were benign (7 follicular adenomas and 1 oncocytoma) and 4 were malignant (follicular carcinomas). Of the 52 class II nodules, 40 were benign (31 follicular adenomas, 8 adenomatous goiters and 1 oncocytoma) and 12 were malignant (follicular carcinomas). Of the 14 class III nodules, 8 were benign (6 follicular adenomas and 2 adenomatous goiters) and 6 were malignant (follicular carcinomas). Of the 4 class IV nodules, 2 were benign (follicular adenomas) and 2 were malignant (follicular carcinomas). Only 1 class V nodule (follicular carcinoma) was observed.

Table 1B shows the result of non-follicular lesion (48 nodules). only 1 class I nodule (adenomatous goiter) was observed. Of the 16 class II nodules, 7 were benign (6 adenomatous goiters and 1 chronic thyroiditis) and 9 were malignant (7 papillary carcinomas and 2 medullary carcinomas). Six class III (papillary carcinomas), 9 class IV (8 papillary carcinomas and 1 undifferentiated carcinoma), and 18 class V (17 papillary carcinomas and 1 undifferentiated carcinoma) nodules were observed.

ROC curve. Figs. 1A and 1B show the ROC curves obtained for the FNA and T/N ratio of Tl-201 scintigraphy (early image/delayed image) data for follicular and non-follicular lesions, respectively. In the follicular lesions, the ROC curve for the Tl-201 scintigraphy data was superior to that for the FNA data, since the Az for the Tl-201 scintigraphy data was much greater than that for the FNA data (0.582). In addition, the Az (0.861) for the early image data was greater than that for the delayed image data (0.838). In the non-follicular lesions, the ROC curve for the FNA data was superior to that for the Tl-201 scintigraphy data, as the Az for the FNA data (0.902) was greater than that for the Tl-201 scintigraphy data. In addition, the Az for the delayed image data (0.792) was greater than that for the early image data (0.714).

Cut-off level. We used the early image Tl-201 scintigraphy data to set the cut-off level for diagnosing follicular lesions, as the Az for the early image data was greater than that for the delayed image data. Table 2A

Table 1 FNA results

A. Follicular lesions (n = 83)

Class	Benign	Malignant
I (n = 12)	8	4
II (n = 52)	40	12
III (n = 14)	8	6
IV (n = 4)	2	2
V (n = 1)	0	1

B. Non-follicular lesions (n = 48)

Class	Benign	Malignant
I (n = 1)	1	0
II (n = 16)	7	9
III (n = 4)	0	4
IV (n = 9)	0	9
V (n = 18)	0	18

Table 2 Critical test-result values of Tl-201 scintigraphy data

A. Follicular lesions (early image)

T/N 10	FPR	TPR	Sensitivity (%)	Specificity (%)
2.140	0.088	0.546	54.6	91.2
1.795	0.129	0.643	64.3	87.1
1.610	0.178	0.725	72.5	82.2
1.370	0.220	0.778	77.8	78.0
1.335	0.254	0.813	81.3	74.6
1.325	0.291	0.844	84.4	70.9
1.235	0.331	0.873	87.3	66.9
1.205	0.798	0.995	99.5	20.2

B. Non-follicular lesions (delayed image)

T/N 120	FPR	TPR	Sensitivity (%)	Specificity (%)
1.650	0.032	0.208	20.8	96.8
1.565	0.312	0.747	74.7	68.8
1.070	0.398	0.821	82.1	60.2
1.015	0.582	0.923	92.3	41.8
0.925	0.720	0.967	96.7	28.0
0.830	0.907	0.996	99.6	9.3

T/N 10, the T/N ratio of Tl-201 scintigraphy early image data (10 min); T/N 120, the T/N ratio of Tl-201 scintigraphy delayed image data (120 min); true-positive rate (TPR). sensitivity; false-positive rate (FPR), 1-specificity.

shows the critical test-result value for the early image Tl-201 scintigraphy data that was used to diagnose follicular lesions. We set the cut-off level at 1.370 (sensitivity: 77.8%; specificity: 78.0%). Table 3A shows the critical test-result value for the FNA data that was used to diagnose follicular lesions. For the FNA data, the specificity was 100% for class V lesions. The T/N ratio of 0.99 on early image Tl-201 scintigraphy data had a sensitivity of 96% (24/25) and a specificity of 50% (29/58) in follicular lesions.

We used the delayed image Tl-201 scintigraphy data to set the cut-off level for diagnosing non-follicular lesions, as the Az for the delayed image data was greater than that for the early image data. Table 2B shows the delayed image Tl-201 scintigraphy and the FNA data for non-follicular lesions. We set the cut-off level at 1.070 (sensitivity: 82.1%; specificity: 60.2%). Table 3B shows the critical test-result value for the FNA data that was used to diagnose non-follicular lesions. For the FNA data, the specificity was 100% and the sensitivity was 77.5% at classes III, IV, and V, and the sensitivity was 100% and the specificity was 12.5% at class I. FNA class III, IV, or V ranking meant malignancy in non-follicular lesions.

Diagnosis of thyroid nodules.

a. Follicular lesions

Among the follicular lesions, a class V rating meant malignancy (1 nodule). For the remaining 82 nodules belonging to classes I, II, III, or IV, we used the early image Tl-201 scintigraphy findings and a cut-off level of 1.370 to distinguish malignant and benign lesions. As a result, 28 nodules were diagnosed as malignant, and 54 nodules were diagnosed as benign. Among the 28 nodules diagnosed as malignant, only 18 nodules were actually malignant; of the 54 nodules diagnosed as benign, only 48 nodules were actually benign.

Among the benign tumors that were diagnosed as malignant (n = 10; 8 follicular adenomas, 1 adenomatous goiter, and 1 oncocytoma), cystic changes were observed in 6 nodules and calcification in 3 nodules. In 3 nodules, both calcification and cystic changes were observed, while neither calcification nor cystic changes were observed in 4 other nodules. Among the malignant tumors that were diagnosed as benign (n = 6; 6 follicular carcinomas), cystic changes were observed in 2 nodules and calcification was observed in 1 nodule. In 3 nodules, neither calcification nor cystic changes were observed.

b. Non-follicular lesions

Among the non-follicular lesions, a class I rating meant benignity (1 nodule), while a class III, IV, or class V rating meant malignancy (31 nodules). For the remaining 16 nodules belonging to class II, we used the delayed image Tl-201 scintigraphy findings and a cut-off level of 1.070 to distinguish malignant and benign lesions. As a result, 6 nodules were diagnosed as malignant, and 10 nodules were diagnosed as benign. Among the 37 nodules diagnosed as malignant, only 36 nodules were actually malignant; of the 11 nodules diagnosed as benign, only 7 nodules were actually benign.

Among the benign tumors that were diagnosed as malignant (n = 1; adenomatous goiter), both cystic changes and calcification were observed. Among the malignant tumors that were diagnosed as benign (n = 4; 3 papillary carcinomas and 1 medullary carcinoma), cystic changes were observed in 2 nodules and calcification was observed in all of the nodules. In 2 nodules, both calcification and cystic changes were observed.

Table 4 shows the FNA result for false-negative and false-positive lesions by Tl-201 scintigraphy. There were 11 false-positive and 14 false-negative lesions. Of these, 4 FNA class IV and V papillary lesions were malignant. Another 21 lesions could not be diagnosed correctly using either Tl-201 scintigraphy or FNA.

Fig. 2 shows the results for a 79-year-old woman with a 3.5 cm nodule in the left lobe of her thyroid gland. During the Tc-99m scintigraphy examination, a cold nodule was observed in the left lobe (Fig. 2A). The

Table 3 Cut-off level for FNA data

A. Follicular lesions

Class	FPR	TPR	Sensitivity (%)	Specificity (%)
IV	0	0.04	4.0	100
III	0.034	0.12	12.0	96.6
II	0.172	0.36	36.0	82.8
I	0.862	0.84	84.0	13.8

B. Non-follicular lesions

Class	FPR	TPR	Sensitivity (%)	Specificity (%)
IV	0	0.45	45.0	100
III	0	0.675	67.5	100
II	0	0.775	77.5	100
I	0.875	1	100	12.5

true-positive rate (TPR), sensitivity; false-positive rate (FPR), 1-specificity.

FNA findings indicated a class IV, non-follicular lesion, and the T/N ratio for the Tl-201 scintigraphy data was 1.980 at 10 min (Fig. 2B) and 2.510 at 120 min (Fig. 2 C). The histopathologic diagnosis was undifferentiated carcinoma.

Fig. 3 shows the results for a 48-year-old woman with a 3.2 cm nodule in the right lobe of her thyroid gland. During the Tc-99m scintigraphy examination, a cold nodule was observed in the right lobe (Fig. 3A). The FNA findings indicated a class II, follicular lesion, and the T/N ratio for the Tl-201 scintigraphy data was 1.000 at 10 min (Fig. 3B) and 0.970 at 120 min (Fig. 3 C). The histopathologic diagnosis was follicular adenoma.

Discussion

FNA is a safe and simple procedure that provides excellent predictive value and is widely used to diagnose thyroid nodules [1, 2]. The overall sensitivity of FNA has been reported to be 57–100%, while the specificity of FNA was 58–100% [1, 7, 8]. For the visual examination of early and delayed Tl-201 scintigraphy images, the sensitivity for diagnosing thyroid nodules has been reported to be 57–100% and 26–86%, respectively [9]. In a quantitative evaluation, Hardoff *et al.* reported that a T/N ratio of 0.99 on delayed image Tl-201 scintigraphy data had a sensitivity of 100% and a specificity of 62% for diagnosing thyroid nodules without follicular carcinoma [10].

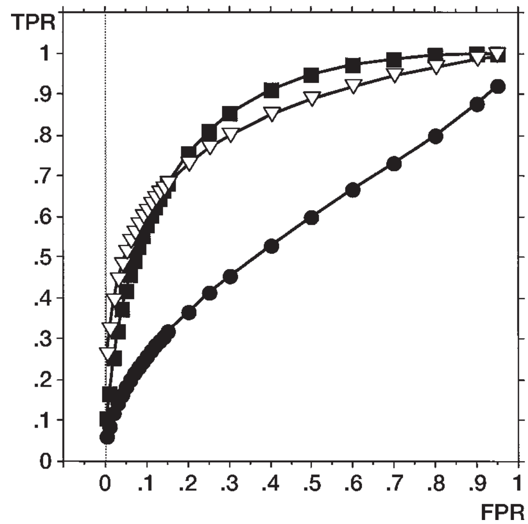
Table 4 FNA results for false-negative and false-positive lesions by Tl-201 scintigraphy

A. False positive lesions (n = 11)

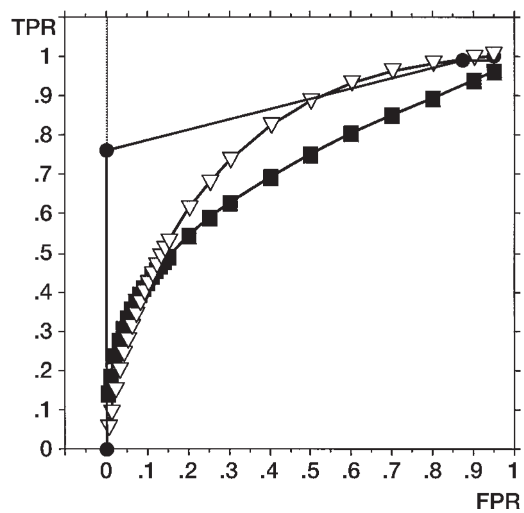
Class	Follicular lesions	Non-follicular lesions
I (n = 2)	2	0
II (n = 6)	5	1
III (n = 3)	3	0
IV (n = 0)	0	0
V (n = 0)	0	0

B. False negative lesions (n = 14)

Class	Follicular lesions	Non-follicular lesions
I (n = 1)	1	0
II (n = 8)	4	4
III (n = 0)	0	0
IV (n = 3)	1	2
V (n = 2)	0	2



A. Follicular lesions
Tl-201 early = 0.861, Tl-201 delayed = 0.838, FNA = 0.582



B. Non-follicular lesions
Tl-201 early = 0.714, Tl-201 delayed = 0.792, FNA = 0.902

Fig. 1 **A**, For the follicular lesions, the ROC curve for the Tl-201 scintigraphy data was superior to that for the FNA data, since the area (Az) under the Tl-201 scintigraphy curve was much greater than that under the FNA curve (0.582). In addition, the Az for the early image data (0.861) was greater than that for the delayed image data (0.838). **B**, For the non-follicular lesions, the ROC curve for the FNA data was superior to that for the Tl-201 scintigraphy data, since the Az under the FNA curve (0.902) was greater than that under the Tl-201 scintigraphy curve. In addition, the Az for the delayed image data (0.792) was greater than that for the early image data (0.714). ■, Tl-10; ▽, Tl-120; ●, FNA.

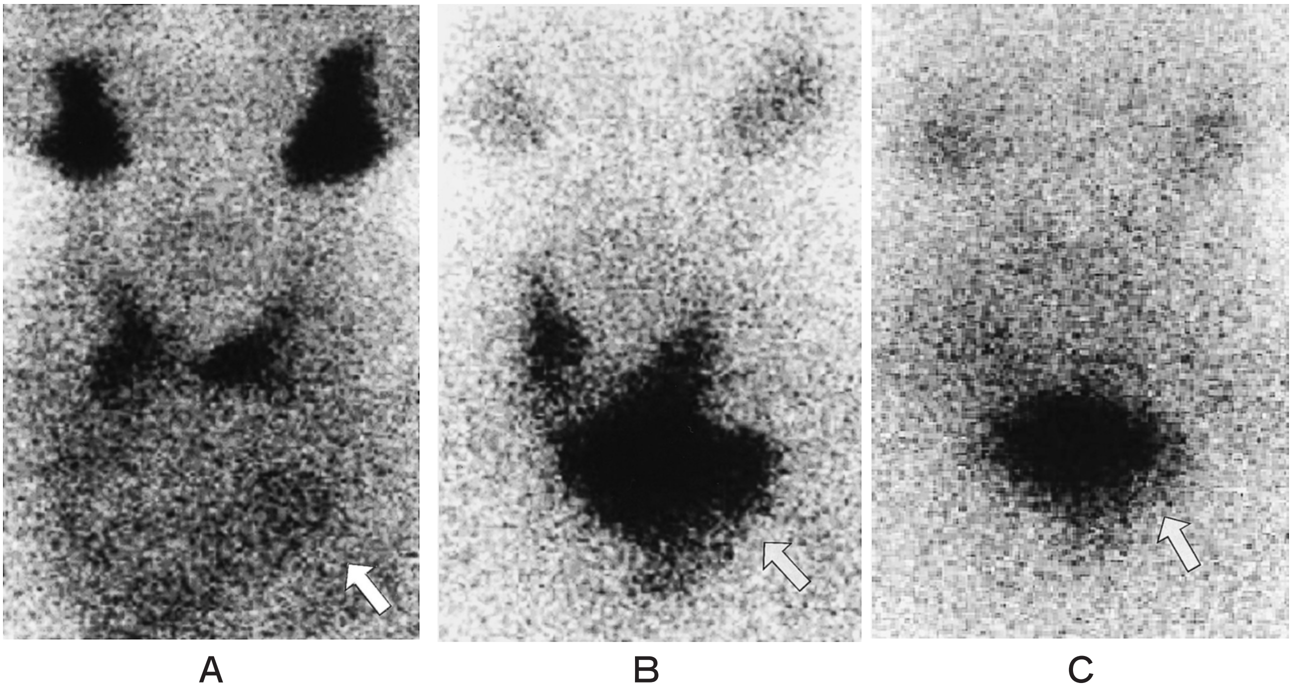


Fig. 2 Case 1, A 79-year-old woman with a 3.5 cm tumor diagnosed as undifferentiated carcinoma in the left lobe of her thyroid gland. In the Tc-99 m scintigraphy image, a cold nodule is visible in the left lobe (arrow) (**A**). The results of the FNA analysis indicated a class IV, non-follicular lesion. The T/N ratio of the Tl-201 scintigram was 1.98 at 10 min (arrow) (**B**) and 2.51 at 120 min (arrow) (**C**).

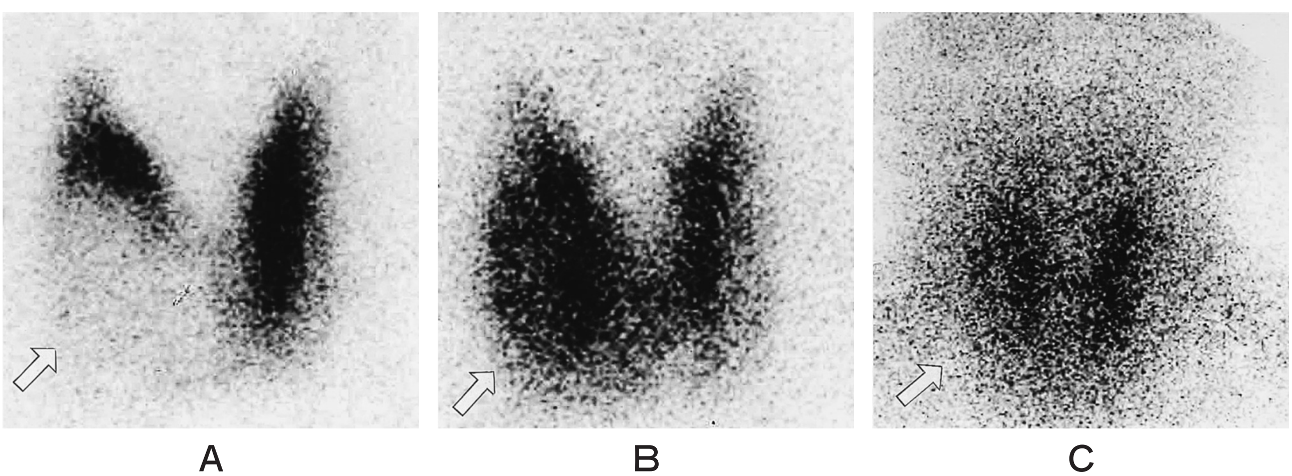


Fig. 3 Case 2, A 48-year-old woman with a 3.2 cm tumor diagnosed as follicular adenoma in the right lobe of her thyroid gland. In the Tc-99 m scintigraphy image, a cold nodule is visible in the right lobe (arrow) (**A**). The results of the FNA analysis indicated a class II, follicular lesion. The T/N ratio of the Tl-201 scintigram was 1.00 at 10 min (arrow) (**B**) and 0.97 at 120 min (arrow) (**C**).

In our study, the Az for FNA was greater than that for Tl-201 scintigraphy in non-follicular lesions. However, the Az for Tl-201 scintigraphy was much greater than that for FNA in follicular lesions. This result supports the findings of a previous report concluding that FNA is highly effective for obtaining cytology samples that enable the distinctive features of papillary carcinoma to be identified [1]. Papillary carcinoma accounted for most of the malignant non-follicular lesions in our study. On the other hand, FNA cannot distinguish between benign and malignant follicular lesions [11]. Okumura and Sathekge reported that, in follicular lesions, the sensitivity of FNA was 10–33% and the specificity of FNA was 79–95.6% [3, 5]. Thus, when a follicular lesion is diagnosed by FNA, other tests must be performed to differentiate malignant nodules [5]. The results of the present study were similar.

The mechanism of Tl-201 accumulation in thyroid nodules depends on Na^+, K^+-ATPase activity and thyroid blood flow [12]. A good correlation has been shown between the degree of Na^+, K^+-ATPase activity, blood flow, and Tl-201 accumulation in the early image [13]. Follicular carcinoma has a higher Na^+, K^+-ATPase activity level than follicular adenoma [12]. The staining index for PCNA (proliferating cell nuclear antigen) in follicular carcinoma is also higher than that in follicular adenoma [14]. Papillary carcinoma exhibits a lower blood flow in thyroid nodules, so wash-out is hardly seen in the delayed phase of Tl-201 scintigraphy images [12].

These facts explain the reason why the Az for the early image Tl-201 scintigraphy data was greater than that for the delayed image data for follicular lesions and why the Az for the delayed image Tl-201 scintigraphy data was greater than that for the early image data for non-follicular lesions.

Next, we estimated the critical test-result values separating 'positive' and 'negative' results for the Tl-201 scintigraphy and FNA data, both in non-follicular and follicular lesions. The results showed that, in follicular lesions, an FNA class V ranking meant malignancy, while in non-follicular lesions, a class I ranking meant benignity, and a class III, IV, or V ranking meant malignancy. Generally, a class I ranking means benignity, a class V ranking means malignancy, and classes II to IV are indeterminate [4]. However, these generalizations were not suitable for follicular lesions in the present study. In fact, of the 12 follicular nodules that were diagnosed as class I by FNA, four nodules were malignant.

Based on the largest Az values, we selected a cut-off level of 1.370 in early image Tl-201 scintigraphy data, and 1.070 in delayed image Tl-201 scintigraphy data for the detection of follicular and non-follicular lesions, respectively. For follicular lesions, the T/N ratio of 0.99 on the early image had a higher sensitivity, but had much lower specificity and accuracy than the T/N ratio of 1.370. The T/N ratio of 0.99 was therefore considered not useful for differentiating benign from malignant lesions, but useful for detecting malignant lesions.

We then made a decision tree based on these results (Fig. 4). First, the thyroid nodules were divided into follicular lesions (classes I to V) and non-follicular lesions (classes I to V) by FNA. Thirty-three thyroid nodules (32 non-follicular lesions and 1 follicular lesion) were confirmed to be either malignant or benign by FNA. An FNA class I non-follicular lesion and an FNA class V follicular lesion could also be diagnosed as benign or malignant using Tl-201 scintigraphy. There was only one nodule in each group. And more than half of the nodules (9/16) classified as class II non-follicular lesions by FNA were actually malignant, and half of the nodules (2/4) classified as class IV follicular lesions by FNA were actually benign. We therefore decided that FNA class I to V follicular lesions and FNA class I or II non-follicular

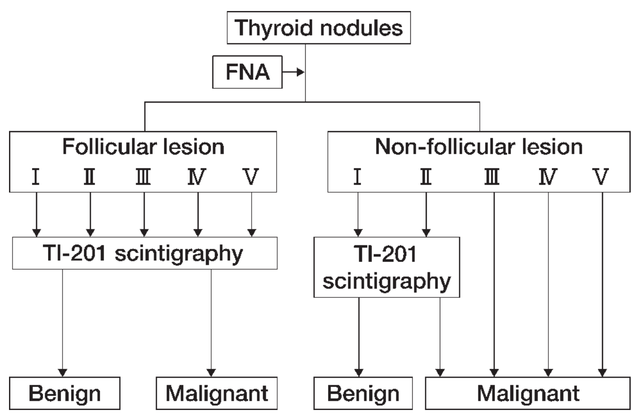


Fig. 4 Thyroid nodules were classified as follicular or non-follicular lesions by FNA. Class III, IV, and V non-follicular lesions were considered malignant. Tl-201 scintigraphy data for class I to V follicular lesions and class I and II non-follicular lesions were examined. For the follicular lesions, nodules with a T/N ratio of larger than 1.370 were considered to be malignant; nodules with a T/N ratio of less than 1.370 were considered to be benign. For the non-follicular lesions, nodules with a T/N ratio of larger than 1.070 were considered to be malignant; nodules with a T/N ratio of less than 1.070 were considered to be benign.

lesions should not be diagnosed as benign or malignant on the decision tree (Fig. 4). Tl-201 scintigraphy was used in the remaining 98 lesions to differentiate benign and malignant lesions. Thirty-four nodules (6 non-follicular and 28 follicular lesions) were diagnosed as malignant, and 64 nodules (10 non-follicular and 54 follicular lesions) were diagnosed as benign. The sensitivity and specificity of this analysis were 76.0% (19/25) and 82.7% (48/58) in follicular lesions, and 90.0% (36/40) and 87.5% (7/8) in non-follicular lesions, respectively. The overall accuracy was 84.0% (110/131).

Of the 21 nodules that were incorrectly diagnosed by both FNA and Tl-201 scintigraphy, 10 nodules exhibited cystic changes, and 8 nodules exhibited calcification. Five nodules had both cystic changes and calcification, whereas 8 nodules had neither cystic changes nor calcification. In cases where cystic changes or calcification are present, an accurate calculation of the T/N ratio is difficult [15].

Mazzaferri used FNA and Tc-99m pertechnetate scintigraphy to differentiate thyroid nodules [4]. If the thyroid nodules examined in the present study had been differentiated using these methods, the sensitivity would have been 72.0% (18/25) and the specificity 19.0% (11/58) for the detection of follicular lesions, and 97.5% (39/40) and 25.0% (2/8), respectively, for non-follicular lesions. The overall accuracy would have been 53.4% (70/131).

The sensitivity in this study was equal to or lower than that of the diagnostic method reported by Mazzaferri, but the specificity and overall accuracy were much higher. The reason for this is that Tc-99m pertechnetate scintigraphy can diagnose thyroid tumors, but cannot differentiate between benign and malignant lesions.

Although a PET (Positron Emission Tomography) facility is not yet available at our institution, fluorine-18-fluorodeoxy glucose PET (FDG-PET) is widely accepted as being useful for distinguishing between benign and malignant thyroid nodules [16, 17]. However, the use of PET has not yet become widespread, and the procedure is expensive. Hopefully, this situation will change in the future.

Based on our results, we created a decision tree for use in the diagnosis of thyroid nodules (Fig. 4). In this tree, thyroid nodules are classified as either follicular or non-follicular lesions by FNA. Class III, IV, or V non-follicular lesions are considered to be malignant. Next, Tl-201 scintigraphy is performed for class I to V follicular lesions and class I and II non-follicular lesions. Among the follicular lesions, nodules with a T/N ratio of greater than 1.370 are considered to be malignant; those with a T/N ratio of less than 1.370 are considered to be benign. In non-follicular lesions, nodules with a T/N ratio of larger than 1.070 are considered to be malignant; those with a ratio of less than 1.070 are considered to be benign.

One limitation of our study was that it was performed retrospectively. Thus, patients without FNA or Tl-201 scintigraphy data were excluded from the study, thereby introducing a bias in the patient selection. Fifteen nodules were class I by FNA, or equal to or less than 10 mm in size. Of 2 nodules that were equal to or less than 10 mm (8 mm and 10 mm), one was suspected to be malignant by Tl-201 scintigraphy, and the other was treated surgically at the patient‘s request. Among the 13 class I nodules, 10 were suspected of malignancy by Tl-201 scintigraphy, 2 were treated surgically at the patient’s request, and 1 was accompanied by plural tumors in both thyroid lobes (class III papillary carcinoma, and class I follicular adenoma). These 4 cases might have introduced a bias.

For the follicular lesions, the Tl-201 scintigraphy data was superior to the FNA data for differentiating benign and malignant lesions, whereas, for non-follicular lesions, the FNA data was superior to the Tl-201 scintigraphy data. Based on our results, we created a decision tree for use in the diagnosis of thyroid nodules. This tree should prove clinically useful, as the overall accuracy of the analysis was 84.0%.

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References

1. Cramer H: Fine-needle aspiration cytology of the thyroid: An appraisal. Cancer cytopathology (2000) 90: 325–329.
2. Van Herle AJ, Rich P, Ljung BME, Ashcraft MW, Solomon DH and Keeler EB: The thyroid nodule. Ann Intern Med (1982) 96: 221–232.
3. Sathekge MM, Mageza RB, Muthuphei MN, Modiba MC and Clauss RC: Evaluation of thyroid nodules with technetium-99m MIBI and technetium-99 m pertecnetate. Head & Neck (2001) 23: 305–310.
4. Mazzaferri EL: Management of a solitary thyroid nodule. N Engl J Med (1993) 328: 553–559.
5. Okumura Y, Takeda Y, Sato S, Komatsu M, Nakagawa T, Akaki S, Kuroda M, Joja I and Hiraki Y: Comparison of differential diagnostic capabilities of 201Tl scintigraphy and fine-needle aspiration of thyroid

nodules. J Nucl Med (1999) 40: 1971–1977.
6. Okumura Y, Takeda Y, Sato S, Shimizu M, Komatsu M, Honda O, Nakagawa T, Niiya H and Hiraki Y: Differentiation of benign from malignant nodules by accumulation of Tc-99m pertechnetate using Tl-201 delayed scans. Clin Nucl Med (1998) 23: 514–516.
7. Hall TL, Layfield LJ, Philippe A and Rosenthal DL: Sources of diagnostic error in fine needle aspiration of the thyroid. Cancer (1989) 63: 718–725.
8. Nishiyama RH, Bigoes ST, Goldfarb WB, Flynn SD and Taxiarchis LM: The efficacy of simultaneous fine-needle aspiration and large-needle biopsy of the thyroid gland. Surgery (1986) 100: 1133–1137.
9. Tamizu A, Okumura Y, Sato S, Takeda Y, Maki K, Hiraki T, Akaki S, Kuroda M, Kanazawa S and Hiraki Y: The usefulness of serum thyroglobulin levels and Tl–201 scintigraphy in differentiating between benign and malignant thyroid follicular lesions. Ann Nucl Med (2002) 16: 95–101.
10. Hardoff R, Baron E and Scheinfeld M: Early and late lesion-to-non-lesion ratio of thallium-201-chloride uptake in the evaluation of "cold" thyroid nodules. J Nucl Med (1991) 32: 1873–1876.
11. Baloch ZW and LiVolsi VA: Follicular-patterned lesions of the thyroid: The bane of the pathologist. Am J Clin Pathol (2002) 117: 143–150.
12. Kishida T: Mechanisms of thallium-201 accumulation in the thyroid gland-clinical usefulness of the dynamic study in thallium-201 chloride scintigraphy for the differential diagnosis of thyroid nodules. Kaku Igaku (The Japanese Journal of Nuclear Medicine) (1987) 24: 991–1004 (in Japanese).
13. Czyz W, Joensuu H, Pylkkanen L and Klemi PJ: p53 protein, PCNA staining, and DNA content in follicular neoplasms of the thyroid gland. J Pathol (1994) 174: 267–274.
14. Kume N, Suga K, Nishigauchi K, Kawamura M and Matsunaga N: Relationship between thallium-201 uptake and tumour proliferative ability in thyroid nodules. Eur J Nucl Med (1996) 23: 376–382.
15. Rosen IB, Provias JP and Walfish PG: Pathologic nature of cystic thyroid nodules selected by needle aspiration biopsy. Surgery (1986) 100: 606–613.
16. Uematsu H, Sadato N, Ohtsubo T, Tsuchida T, Nakamura S, Sugimoto K, Waki A, Takahashi N, Yonekura Y, Tsuda G, Saito H, Hayashi N, Yamamoto K and Ishii Y: Fluorine-18-fluorodeoxyglucose PET versus thallium-201 scintigraphy evaluation of thyroid tumors J Nucl Med (1998) 39: 453–459.
17. Bloom AD, Adler LP and Shuck JM: Determination of malignancy of thyroid nodules with positron emission tomography. Surgery (1993) 114: 728–735.