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The usefulness of serum thyroglobulin levels and Tl-201 scintigraphy in differentiating between benign and malignant thyroid follicular lesions

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Objective: To compare the diagnostic capabilities of various serum thyroglobulin levels (Tg) and Tl-201 scintigraphy with regard to thyroid follicular lesions. ***Methods:*** We examined 80 thyroid follicular lesions (benign: 55, malignant: 25) in patients with nodular goiter for whom a pathological diagnosis was made based on surgical findings. Tg was measured by an I-125 (radioimmunoassay) method. In Tl-201 scintigraphy, 74 MBq of Tl-201 chloride was intravenously injected and imaged after 10 minutes (early image) and after 120 minutes (delayed image), and the scintigrams were evaluated both visually and quantitatively, with special attention paid to the part of the nodule with the highest accumulation of Tl-201 chloride. The cutoff levels of Tg for categorizing the lesions as malignant were set at 40, 100, 300, 500, 1,000 and 2,500 $\mu g/l$. In Tl-201 scintigraphy, method 1 involved high uptake on both early and delayed images, method 2 involved high uptake on only the early image, and method 3 involved high uptake on only the early image or the same accumulation in comparison with the normal region on the early image, with no washout being quantitatively judged as indicative of malignancy. A summary index of overall test performance can be calculated as the area under the receiver operating characteristic (ROC) curve (Area (Az)). Likelihood ratios for several cutoff levels were also calculated. ***Results:*** In the diagnosis, Az of Tl-201 (0.95) was larger than that of Tg (0.65). The sensitivity and accuracy of Tg at each cutoff level (sensitivity: 4.0% to 76.0%, accuracy: 50.0% to 72.5%) were lower than with Tl-201 scintigraphy (methods 1–3, sensitivity: 76.0–100%, accuracy: 77.5–88.8%). The likelihood ratio for the positive results of method 1 for Tl-201 scintigraphy, were greatest in the present study (13.9), and the likelihood ratio for the negative results of method 3 for Tl-201 scintigraphy, (0) was smallest in the present study. ***Conclusion:*** Diagnosis based on Tl-201 washout patterns in which quantitative evaluation is combined with visual evaluation appears to be more useful for the differentiation of malignant thyroid follicular lesions than diagnosis by Tg.

Key words: serum thyroglobulin, Tl-201 scintigraphy, thyroid follicular lesion, ROC curve, likelihood ratio

INTRODUCTION

THYROID NODULES are reported to occur in 4–7% of the adult population,[1] and follicular carcinoma has been reported to occur in 7–10% of thyroid malignant nodules. A fine needle aspiration biopsy (FNA) is safe and simple, provides excellent predictive value, and is widely used to diagnose nodular goiter.[2,3] Nevertheless, in the diagnosis of follicular lesions, differentiating between benign and malignant nodular goiter by FNA is generally considered to be difficult at the cellular level. When a follicular lesion is diagnosed by FNA, another test is essential for the differentiation of malignant nodules.[4–8]

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Serum thyroglobulin is produced in the follicular epithelium and stored in the colloid lumen as a 660-kD molecular weight glycoprotein in the thyroid gland. Observation of serum thyroglobulin levels is considered to be useful for evaluation of the postoperative course of thyroid cancer, but these observations are generally considered not to be useful for preoperative differentiation of malignancy.[9–11] It has been reported, however, that serum thyroglobulin levels are useful for differentiating between benign and malignant follicular lesions when the cutoff level of serum thyroglobulin is set at 1,000 $\mu g/l$.[5]

In the nuclear medical field, Tl-201 scintigraphy is very sensitive to thyroid cancer, and there have been many reports that Tl-201 scintigraphy is superior in differentiating between benign and malignant nodular goiter.[4,6,12–21] In visual evaluations, the sensitivity has been reported to be 57–100% for early images[15,17–19] and 25–86% for delayed images.[16,18,20,21] We have reported that the washout pattern of Tl-201 scintigrams, in which quantitative evaluation is combined with visual evaluation, is useful for differentiating between benign and malignant thyroid nodules.[6]

It was our intent in the present study to determine whether the analysis of serum thyroglobulin levels or Tl-201 scintigraphy by means of the washout pattern is more effective in distinguishing between benign and malignant thyroid follicular lesions.

MATERIALS AND METHODS

Between 7 August 1989 and 24 July 1998, we examined 80 nodules without metastases in patients for whom thyroid nodules were noted based on preoperative ultrasonography, and we were able to make a definite histopathological diagnosis in each case. There were 14 male and 66 female subjects ranging in age from 14 to 84 years, with a mean age of 52.6 ± 15.4 years. The diameter of the nodules was 14–84 mm (mean: total follicular lesions: 28.6 ± 14.0 mm, benign groups: 29.4 ± 14.9 mm, malignant groups: 28.2 ± 13.7 mm), with no significant difference between the benign and malignant groups.

The histopathological diagnosis confirmed 55 cases of follicular adenoma and 25 cases of follicular carcinoma without variants such as papillary carcinoma, follicular type, follicular carcinoma, oxyphilic cell type, and follicular carcinoma, clear cell type. The serum thyroglobulin levels were measured by radioimmunoassay (RIA) with I-125 up to 1 month before surgery. The normal range for serum thyroglobulin levels is less than 35 $\mu g/l$. These levels were not measured within 24 hours after FNA or immediately after palpation of the thyroid gland in any patient, in order to prevent serum thyroglobulin levels from increasing. Furthermore, no patient had Basedow's disease or antibody to thyroglobulin, and thyroid gland function was normal in all patients.

In Tl-201 scintigraphy, 74 MBq of Tl-201 chloride (Cl) was intravenously injected, and planar images were obtained after 10 minutes (early image) and 120 minutes (delayed image). A gamma camera (Diagnost Tomo, Phillips Co., Eindhoven, Netherlands) attached to a low-energy high-resolution pinhole collimator was used as the imaging apparatus. The imaging conditions were as follows: window level, 70 keV; window width, ±10%; preset time, 10 minutes; and preset count, 256 counts per pixel.

We visually scored and evaluated the densest part of each nodule seen in the Tl-201 scintigrams, comparing the dense region with normal regions. The evaluation was made by a group of three radiologists, including two physicians accredited in nuclear medicine. In the quantitative evaluation of Tl-201 scintigrams, we set the region of interest (ROI) manually to include the densest part of the nodular region and the normal region in the opposite lobe, and we then calculated the tumor/normal ratio (T/N ratio). The washout rate (%) was calculated by the following equation: (T/N (early image) − T/N (delayed image))/T/N (early image) × 100 (%).

In the diagnosis, nodules in which the uptake was higher than that of the normal thyroid region as determined by Tl-201 scintigrams in both the early and delayed images were classified as Group A; those in which the uptake was higher only in the early image were classified as Group B; those in which the uptake was equal to that of the normal thyroid region in the early image were classified as Group C; and those in which the uptake was lower than that of the normal thyroid region in the early image were classified as Group D. Furthermore, in Group C, nodules in which the washout rate was 0 or below were classified as Group CI, and those in which the washout rate was greater than 0 were classified as Group CII.

In Tl-201 scintigraphy, the three methods represented differentiations of which groups were judged malignant: in method 1; only Group A, in method 2; both Group A and B, in method 3; Group A, B and CI, were judged as malignant.

We also judged malignancy according to the following serum thyroglobulin levels: 40 $\mu g/l$ (Tg 40), 100 $\mu g/l$ (Tg 100), 300 $\mu g/l$ (Tg 300), 500 $\mu g/l$ (Tg 500), 1000 $\mu g/l$ (Tg 1000) and 2500 $\mu g/l$ (Tg 2500). We calculated the diagnostic capabilities of Tl-201 scintigraphy and Tg based on sensitivity, specificity, accuracy and the likelihood ratios for positive and negative results for the thyroid follicular lesions.

Statistical Analysis Methods

Benign and malignant groups as judged by serum thyroglobulin levels were compared by the Mann-Whitney test. In each test, a p value below 5% was judged significant.

Receiver operating characteristic curves (ROC) were generated to examine the test performance, and Labroc5 (CE Metz, University of Chicago) was used to calculate the curve fitting.[22] The ROC curve is a plot of pairs of the

Table 1 Benign and malignant nodules at each cutoff level of Tg

	Cutoff level of Tg ($\mu g/l$)						
	–39	40–99	100–299	300–499	500–999	1000–2499	2500–
Benign	21	15	5	5	7	1	1
Malignant	6	5	3	5	1	4	1

Table 2 Benign and malignant follicular thyroid nodules based on the washout patterns of Tl-201 scintigraphy

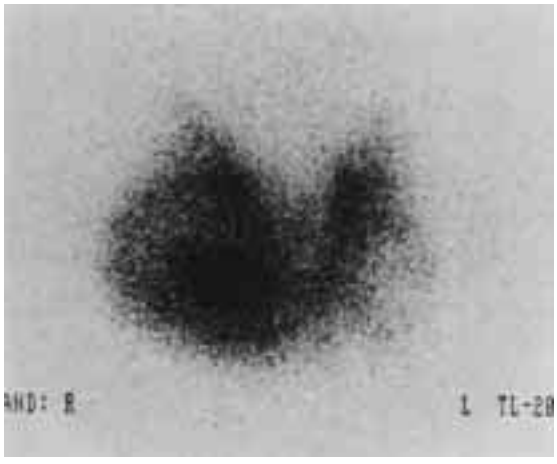
	Tl-201 scintigraphy					
	A	B	CI	CII	D	total
Benign	3	13	2	10	27	55
Malignant	19	4	2	0	0	25

true-positive rate (sensitivity) and the false-positive rate (1-specificity) corresponding to each cutoff value for the diagnostic test result. The area under the ROC curve (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 persons with and without the disease of interest.[23]

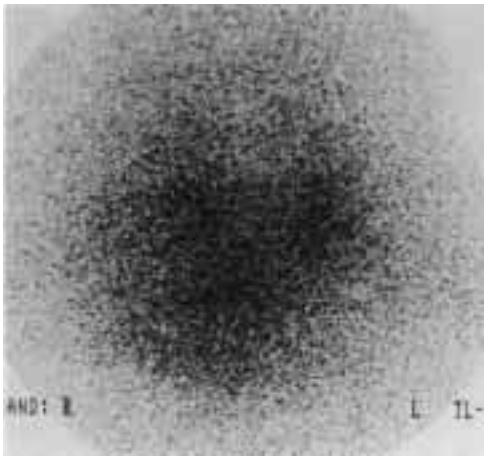
We also calculated the likelihood ratios for several cutoff levels: the likelihood ratio for a positive test result = sensitivity/(1 – specificity); The likelihood ratio for a negative test result = (1 – sensitivity)/specificity. The likelihood ratio for the positive test result, LR+ (for the negative test result, LR–), is the probability of a positive test result (of a negative test result) for a person with the disease of interest divided by the probability of a positive test result (negative test result) person without the disease of interest. LR+ values of 10 or greater and LR– values of 0.1 or smaller are consistent with a test with considerable diagnostic value.

RESULTS

The serum thyroglobulin levels in the benign and malignant thyroid nodules were 236.4 ± 414.4 $\mu g/l$ and 569.6 ± 876.7 $\mu g/l$, respectively, showing no significant difference (n.s., Mann-Whitney test). The numbers of benign and malignant follicular lesions at several serum thyroglobulin cutoff levels are shown in Table 1. The ratio of malignancy was less than 50% at any cutoff value except for 1,000 $\mu g/l$ or higher, where the ratio was 71.4% (5/7). In this study, at levels of 500 $\mu g/l$ or higher, all 6 follicular carcinomas and 4 follicular adenomas had no cystic lesions but 5 follicular adenomas had cystic lesions. Two of the 5 follicular cystic lesions were almost pure cystic lesions. The serum thyroglobulin levels of 2 follicular adenomas with cystic lesions were measured on the day after FNA or palpitation. There were no significant reasons for rasing those levels in 3 other follicular adenomas with cystic lesions.



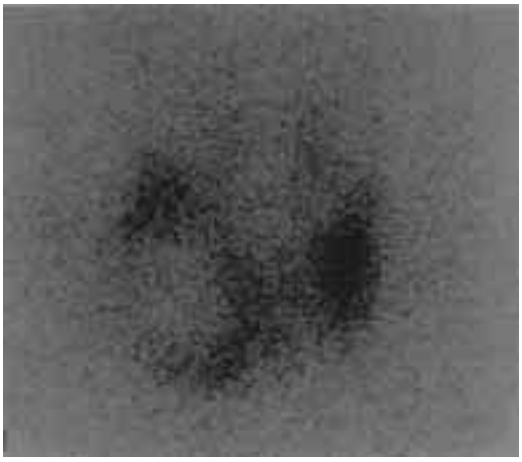
a



b

Fig. 1 Images from case 1, a 47-year-old man in Group A, who had a tumor diagnosed as follicular carcinoma in the right lobe of the thyroid gland. Visual scores and T/N ratios for Tl-201 scintigram were 4 and 2.19 in the early image (a) and 3 and 1.17 in the delayed image (b). The serum thyroglobulin level was 71 $\mu g/l$.

The numbers of benign and malignant follicular lesions as determined by the washout patterns in Tl-201 scintigrams are shown in Table 2. The ratio of malignant cases in follicular lesions in Group A, 86.4% (19/22), was higher than that in Group B (23.5%) and CI (50.0%). No malignant nodules were observed in Group CII or D. Nuclear medical findings in typical cases such as Group A and Group D are shown in Figure 1 and Figure 2,



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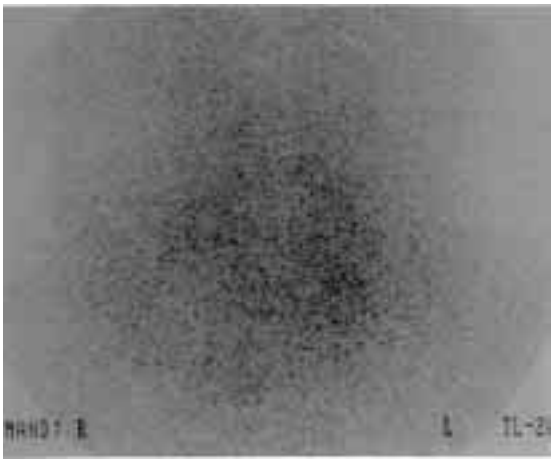

b

Fig. 2 Images of case 2, a 41-year-old woman in Group D, who had a tumor diagnosed as follicular adenoma in the right lobe of the thyroid gland. Visual scores and T/N ratios for Tl-201 scintigram were 1 and 0.44 in the early image (a) and 1 and 0.74 in the delayed image (b). The serum thyroglobulin level was 860 $\mu g/l$.

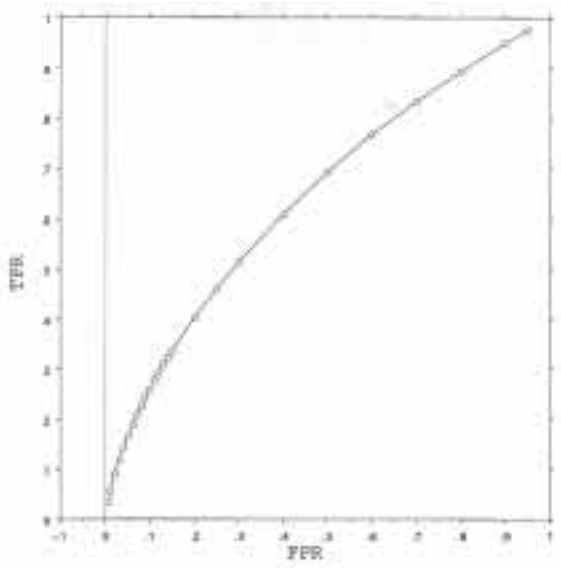

Fig. 3 The area under the ROC curve (Az) for the serum thyroglobulin levels was 0.65.
TPR: True positive rate, FPR: False positive rate

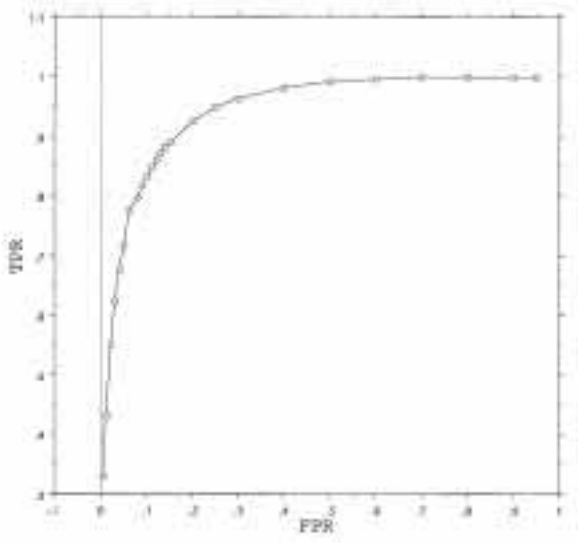

Fig. 4 The area under the ROC curve (Az) for Tl-201 scintigraphy was 0.95, which was larger than that for the serum thyroglobulin levels (0.65).
TPR: True positive rate, FPR: False positive rate

respectively.

There were no pure cystic lesions among the 25 cases of follicular carcinoma: 4 nodules had partial cystic lesions which were all classified in Group A, and the remaining 21 nodules had no cystic lesions.

We examined the test performances of two indices in discriminating follicular carcinoma from follicular adenoma: serum thyroglobulin levels and Tl-201 scintigraphy (Fig. 1, Fig. 2). The ROC curve of Tl-201 scintigraphy is superior to that of serum thyroglobulin levels, as the area (Az) of Tl-201 scintigraphy (0.95) is much greater than that of serum thyroglobulin (0.65).

The diagnostic capability of the serum thyroglobulin levels at each cutoff level and that of Tl-201 scintigraphy are shown in Tables 3 and 4. For the serum thyroglobulin levels at cutoff levels of 500 $\mu g/l$, 1,000 $\mu g/l$, and 2,500 $\mu g/l$, the specificity was higher than that of methods 2 and 3 for Tl-201 scintigraphy (Tg 500: 83.6%, Tg 1000: 96.4%, Tg 2500: 100%, method 2: 70.9%, method 3: 67.3%), but at each cutoff level, the sensitivity was lower than that of methods 2 and 3 for Tl-201 scintigraphy (Tg: 4.0–76.0%, method 2: 92.0%, method 3: 100%). At each cutoff level for serum thyroglobulin, the accuracy and negative predictive value (N.P.V.) were lower than those of methods 1 and 3 for Tl-201 scintigraphy (accuracy; Tg:

Table 3 Diagnostic capability for follicular lesions by serum thyroglobulin levels

	serum thyroglobulin level ($\mu g/l$)						
	≧2500	≧1000	≧500	≧300	≧100	≧40	≧0
Sensitivity	4.0	20.0	24.0	44.0	56.0	76.0	100
Specificity	100	96.4	83.6	74.5	65.5	38.2	—
Accuracy	70.0	72.5	65.0	65.0	62.5	50.0	31.3
P.P.V.	50.0	71.4	40.0	44.0	42.4	35.8	31.3
N.P.V.	69.2	72.6	70.8	74.5	76.6	77.8	—
L.R.P.R.	0.04	5.5	1.47	1.73	1.62	1.23	1.0
L.R.N.R.	0.98	0.83	0.91	0.75	0.67	0.63	0

P.P.V.: positive predictive value
N.P.V.: negative predictive value
L.R.P.R.: Likelihood ratio for positive results
L.R.N.R.: Likelihood ratio for negative results

Table 4 Diagnostic capability for follicular lesions by Tl-201 scintigraphy

	A	A-B	A-CI	A-CII	A-D	1	2	3
Sensitivity	76.0	92.0	100	100	100	76.0	92.0	100
Specificity	94.5	70.9	67.3	49.1	—	94.5	70.9	67.3
Accuracy	88.8	77.5	77.5	65.0	31.3	88.8	77.5	77.5
P.P.V.	86.4	59.0	58.1	47.2	31.3	86.4	59.0	58.1
N.P.V.	89.7	95.1	100	100	—	89.7	95.1	100
L.R.P.R.	13.9	3.16	3.06	1.96	1.0	13.9	3.16	3.06
L.R.N.R.	0.25	0.11	0	0	0	0.25	0.11	0

P.P.V.: positive predictive value
N.P.V.: negative predictive value
L.R.P.R.: Likelihood ratio for positive results
L.R.N.R.: Likelihood ratio for negative results
Method 1: in which only Group A was considered malignant
Method 2: in which Groups A and B were considered malignant
Method 3: in which Groups A, B, and CI were considered malignant

50.0% to 70.0%, methods 1 and 3: 77.5% to 88.8%, N.P.V. Tg: 69.2% to77.8%, methods 1 and 3: 89.7% to 100%).

At each cutoff level of serum thyroglobulin, except for 1,000 $\mu g/l$, LR+ was lower than that for Tl-201 scintigraphy. Although the LR+ at the 1,000 $\mu g/l$ cutoff (5.5) was slightly greater than with methods 2 and 3 for Tl-201 scintigraphy (method 2: 3.16, method 3: 3.06), it was less than 10. The LR+ of method 1 for Tl-201 scintigraphy (13.9) was greater than 10. The LR– at each cutoff value for serum thyroglobulin was higher than the LR– of methods 1 and 3 for Tl-201 scintigraphy (serum thyroglobulin: 0.63–0.98, Tl-201 scintigraphy: 0–0.25). The LR– of method 2 was 0.11, which was almost as low as 0.1, which is the level of a test that provides considerable diagnostic value. The LR– of method 3 for Tl-201 scintigraphy (0) was less than 0.1.

DISCUSSION

FNA is generally used for the diagnosis of benign or malignant nodular goiter, as the method is safe and simple[2,3] but it has been reported that diagnosis of follicular lesions is difficult by FNA.[4–6] Therefore, adequate management of thyroid follicular lesions with regard to diagnosis remains controversial.[7,8]

To determine whether observation of serum thyroglobulin levels or Tl-201 scintigraphy is more effective in distinguishing between benign and malignant follicular lesions, we compared the diagnostic ability of the two techniques by using the washout pattern for follicular lesions. We used the area under the ROC curves (Az), which serves as an overall measure of test performance, in the comparison, for a particular disease can be used to identify the test that will provide greater diagnostic value.[23] Our study found that Tl-201 scintigraphy is more effective in distinguishing between benign and malignant follicular lesions by providing evidence that the area under the ROC curves (Az) for Tl-201 scintigraphy (0.95) is larger than that for serum thyroglobulin levels (0.65). We believe that the likelihood ratio is one of the most useful factors to consider in terms of diagnostic ability, as it does not vary as a function of the prevalence of disease.

We recognized method 1 for Tl-201 scintigraphy as being the most effective in distinguishing between benign and malignant follicular lesions and determining whether surgery is necessary, as the likelihood ratio for positive results of method 1 for Tl-201 was greatest in the present study (13.9) and was greater than 10, which is consistent with a test that provides considerable diagnostic value. We also recognized that method 3 for Tl-201 scintigraphy is most effective in distinguishing between benign and malignant follicular lesions and in determining whether the lesions can be observed without surgery, as the likelihood ratio for negative results of method 3 for Tl-201 scintigraphy (0) was smallest in the present study and less than 0.1, which is consistent with a test that provides considerable diagnostic value.

Additionally, proliferating cell nuclear antigen (PCNA), a highly conserved 36-kDa acidic nuclear protein essential to DNA synthesis, has been recognized as an endogenous histological marker for the G_1/S phase in the cell cycle and as a useful marker for the proliferative activity of cells. Kume et al. have reported a good correlation between the degree of Tl-201 uptake and the PCNA index of malignant and benign thyroid nodules.[24] Comparing the early and delayed scans, researchers saw a closer correlation between Tl-201 uptake and the PCNA index on the delayed scans. The staining index for PCNA in follicular carcinoma is significantly higher than that for PCNA in follicular adenoma,[25] which suggests that method 1, which judges malignancy in Group A, which has high uptake in both early and delayed images, is most useful for

discriminating between malignant and benign follicular lesions.

The diagnostic abilities assessed in the present study were based on methods 1 and 3 in Tl-201 scintigraphy, as reported by Okumura et al.[6] (sensitivity: 75.0–100%, specificity: 67.3–94.5%, accuracy: 77.5–88.8%) and are almost the same as those obtained in our previous study (sensitivity: 80.0–90.0%, specificity: 60.0–88.9%, accuracy: 69.2–86.2%).

On the other hand, serum thyroglobulin levels are not generally considered useful for preoperative differentiation between benign and malignant tumors.[9–11] Nevertheless, Okamoto et al.[5] have reported that serum thyroglobulin levels are useful for preoperative differentiation between benign and malignant tumors when the cutoff level is set to 1,000 $\mu g/l$ in follicular lesions.

In cases of goiter, serum thyroglobulin levels increase due to leakage from destroyed follicular structures. In the present study, serum thyroglobulin levels were not sufficiently effective in distinguishing between benign and malignant follicular lesions. The likelihood ratios for positive results, even at a cutoff value of 1,000 $\mu g/l$ both in the present study (5.5) and Okamoto's study (4.41), were not greater than 10, and the likelihood ratios for negative results were not less than 0.1 at any cutoff level, making them not consistent with a test providing considerable diagnostic value.

It has been reported and is widely accepted that fluorine-18-fluorodeoxyglucose PET (FDG-PET) is useful in distinguishing between benign and malignant thyroid nodules[26,27] but, the necessary equipment for FDG-PET is so expensive and the amounts available are so small worldwide that its utility provides little benefit to patients.

The present study does have a bias, in that surgery was performed for all follicular lesions when their malignancy was in doubt. Therefore, the malignancy rate (31.3%; 25/80) in the present study is not as high as those observed in two recent surveys in North Carolina, USA, and Catania, Italy, in which the malignancy rates were 5–6.5% for all presented thyroid nodules.[28,29] But, the malignancy rate in the present study (31.3%) corresponds to that in other studies, in which surgeons have reported a rate of 20–40% for all excised nodules selected for surgery.[2,28,30] In addition, in the present study the likelihood ratio was used, which does not vary as a function of the prevalence of disease.

We believe that if a follicular lesion is detected by FNA, Tl-201 scintigrams supplemented with quantitative evaluation are useful.

CONCLUSION

It appears that diagnosis based on Tl-201 washout patterns in which quantitative evaluation is combined with visual evaluation is more useful for the identification of malignant thyroid follicular lesions than diagnosis based on Tg. With Tl-201 scintigraphy if nodules are classified into Group A, they are likely to be malignant and surgery is recommended. If, however, they cannot be classified into Groups A, B or CI, they are unlikely to be malignant, suggesting that surgery can be postponed.

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