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Quantitative evaluation by Tl-201 scintigraphy in the diagnosis of thyroid follicular nodules

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We examined the diagnostic capability of a quantitative evaluation by determining the optimum area for comparisons with nodule and optimum imaging time by Tl-201 scintigraphy in thyroid follicular nodules, retrospectively.

Ninety-one thyroid follicular nodules, for which the pathological diagnosis had been established, were examined (60 benign, 31 malignant). After 74 MBq of Tl-201 chloride was injected intravenously, Tl-201 scintigrams were obtained at 10, 20, 30, and 120 min. For the quantitative evaluation, the area with the greatest accumulation in the nodule and a comparative region in the contralateral thyroid and the soft tissues in the cervical region were manually selected as the region of interest (ROI) referring to Tc-99m pertechnetate scintigrams and ultrasonographic findings as a guide by two radiologists, and the T/N ratio (tumor/normal tissue ratio) and T/S ratio (tumor/soft tissue ratio) were calculated. The pixel counts were determined for all ROI. A summary index of overall test performance can be calculated as the area under the receiver operating characteristic (ROC) curve (Area (Az)), and the likelihood ratios were also calculated. We estimated the cut-off on a fitted binormal ROC curve. Multiple regression analyses were used to investigate the relationships between the optimum quantitative evaluation and 5 independent variables. A p value below 5% was considered to be significant.

The T/N ratio and T/S ratio were significantly higher in the malignant group at 10 min (0.844 and 0.702), 20 min (0.844 and 0.704), 30 min (0.841 and 0.670), and 120 min (0.887 and 0.733), respectively ($p < 0.01$). The Az for the T/N ratio was greatest at 120 min. The multiple regression analysis showed that only ‘benign or malignant’ was a significant variable in the T/N ratio at 120 min. It correlated significantly in interobserver ($r = 0.80$) and intraobserver ($r = 0.80$) studied ($p < 0.001$). An assessment of the cut-off value of the T/N ratio at 120 min, at the cut-off of 1.255, the likelihood ratio for positive test result was greatest at 8.56, while at the cut-off of 1.010, the likelihood ratio for negative test result was lowest at 0.165.

The T/N ratio at 120 min was more useful than the other condition to distinguish between benign and malignant thyroid follicular nodules.

Key words: thyroid nodules, follicular nodules, Tl-201 scintigraphy, receiver-operating characteristic (ROC) curve

INTRODUCTION

NODULAR GOITERS DEVELOP in 4–7% of the adult population.[1] Fine needle aspiration biopsy (FNA) is generally used to diagnose benign or malignant thyroid nodules,[2,3] but it has been reported that it is difficult to diagnose follicular nodules by FNA.[4–6]

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Many reports have described that among nuclear imaging tests, Tl-201 scintigraphy gives excellent results in distinguishing benign from malignant nodules.[4,6–20] We have also reported that in a visual evaluation of Tl-201 scintigraphy, a quantitative evaluation based on a classification by washout pattern is also useful for distinguishing benign from malignant nodular goiters,[6] and is also useful for distinguishing benign from malignant follicular nodules.[6,7] However, we are not aware of any reports in the literature on the use of a quantitative evaluation of Tl-201 scintigraphy for distinguishing benign from malignant follicular nodules.

Non-tumorous lesions, for example chronic thyroiditis, adenomatous goiter and Grave's disease, diameter of nodular lesion, contents of cyst and/or calcification and malignant lesions possibly affect the accumulation of thyroid gland and nodular lesions.

In this study, we retrospectively evaluated the optimum area to be compared and the optimum imaging time in the quantitative evaluation by Tl-201 scintigraphy of thyroid follicular nodules.

We examined the relationships between optimum quantitative evaluation by Tl-201 scintigraphy and the above 5 variables, and reproducibility of the quantitative evaluation by interobserver and intraobserver studies. We also tried to determine suitable cut-off values in the quantitative evaluation by Tl-201 scintigraphy to separate "positive" from "negative" results.

PATIENTS AND METHODS

Patients

We retrospectively studied 91 follicular thyroid nodules, identified preoperatively by ultrasonographic examination, where the histopathologic diagnosis was established by surgical operation. There were 12 men and 79 women. Ages ranged from 20 to 85 years, and the mean was 52.9 ± 16.2 years.

A histopathologic diagnosis showed 60 nodules of follicular adenoma in the benign group and 31 nodules of follicular carcinoma in the malignant group. There were no variant benign nodules (e.g. follicular adenoma, oxyphilic type, follicular adenoma, clear cell type, hyalining trabecular adenoma and atypical adenoma) or malignant nodules (follicular carcinoma, oxyphilic type and follicular carcinoma, clear cell type). Two follicular carcinomas were widely invasive, and the others were minimally invasive. The diameter of the follicular thyroid nodules ranged from 7–83 mm, with a mean of 31.5 ± 16.7 mm, and there was no difference between the benign and malignant groups. Three groups were divided by diameter: 10 mm or less (T1), greater than 10 mm and equal to or less than 40 mm (T2), and greater than 40 mm (T3). In the benign group there was 1 nodule in T1, 49 nodules in T2 and 10 nodules in T3. In the malignant group, there were 2 nodules in T1, 19 nodules in T2 and 10 nodules in T3.

There were 8 non-tumorous thyroid lesions, 2 chronic thyroiditis, 2 adenomatous goiter and no Grave's disease in both the benign group and malignant group.

Image analysis

For Tl-201 scintigraphy, 74 MBq of Tl-201 chloride was injected intravenously, and planar images were obtained at 10, 20, 30, and 120 min. For Tc-99m pertechnetate scintigraphy, 185 MBq of Tc-99m pertechnetate was injected intravenously at 30 minutes of Tl-201 scintigraphy, and early planar images were obtained, while at 120 minutes of Tl-201 scintigraphy delayed planar images were obtained. The imaging system used was the gamma Diagnost Tomo (Philips Co., Eindhoven, Netherlands) equipped with a low-energy high-resolution pinhole collimator. The imaging conditions were window level of 70 keV, window width of ±10%, preset time of 10 min, and preset count of 256 counts per pixel.

For the quantitative evaluation by Tl-201 scintigraphy and at a cold area by Tc-99m pertechnetate scintigraphy, we used the ultrasonographic findings to avoid cystic lesions and manually selected as the region of interest (ROI) the area with the highest accumulation in the solid part of the nodular lesion, and for the comparison of nodular lesion a normal area in the contralateral thyroid gland and the soft tissues in the cervical region. We selected sternocleidomastoid muscles as the cervical region. In each case, the ROI selected was as large as possible. The T/N ratio (tumor/normal tissue ratio) and the T/S ratio (tumor/soft tissue ratio) were then calculated, and expressed as counts per pixel. These ROI were selected by two radiologists, one with 2 years experience of nuclear medicine (observer A), and the other who was a specialist in nuclear medicine with 7 years of experience (observer B).

Statistical analysis

A statistical analysis was carried out with the computer software package StatView 4.0 for the Macintosh. T/N ratio and T/S ratio for benign and malignant nodules obtained for each time point were compared by the Mann-Whitney test. In each test, a p value below 5% was judged to be significant.

Multiple regression analyses were used to investigate the relationships between the optimum quantitative evaluation and 5 independent variables. For the selection of the covariates for the regression models, we employed the forced selection procedure because it was not explorative. Simple regressions were used for reproducing the quantitative interobserver and intraobserver evaluation. In each test, a p value below 5% was judged to be significant.

Receiver operating characteristic (ROC) curves were generated to examine the test performance, and Labroc5 (CE Metz, University of Chicago) was used to calculate the curve fitting.[21] The ROC curve is a plot of pairs of the

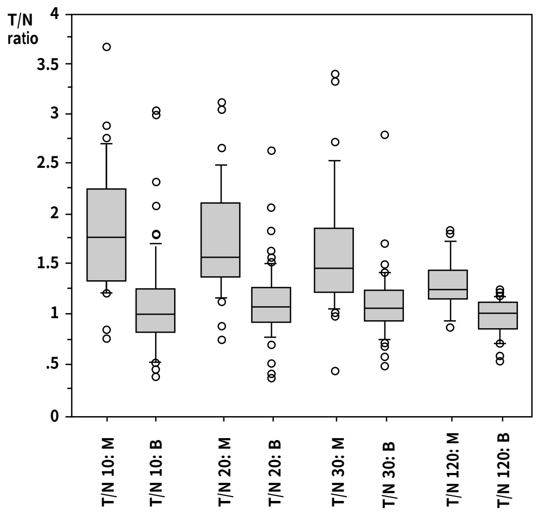


Fig. 1 The T/N ratio of benign versus malignant follicular nodules. M: malignant nodules, B: benign nodules

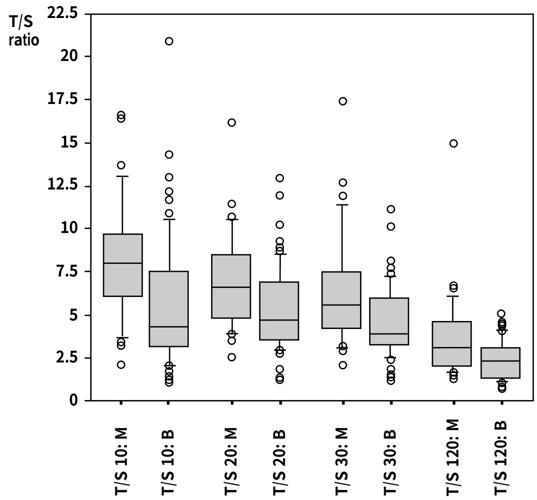


Fig. 2 The T/S ratio of benign versus malignant follicular nodules. M: malignant nodules, B: benign nodules

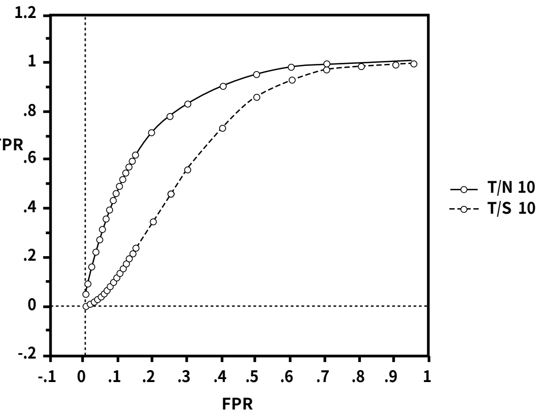


Fig. 3 Az of T/N vs. Az of T/S at 10 min. The Az of the T/N ratio at 10 min (0.844) was significantly greater than the Az of the T/S ratio at 10 min (0.702) (p = 0.0033). TPR: true positive rate, FPR: false positive rate

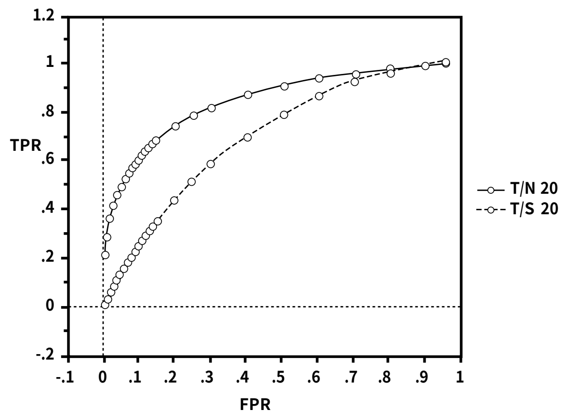


Fig. 4 Az of T/N vs. Az of T/S at 20 min. The Az of the T/N ratio at 20 min (0.844) was significantly greater than the Az of the T/S ratio at 20 min (0.704) (p = 0.0037). TPR: true positive rate, FPR: false positive rate

true-positive rate (sensitivity) and the false-positive rate (1 − specificity) corresponding to each cut-off value for the diagnostic test result. The area under the ROC curve (Az) serves as an overall measure of test performance to distinguish persons with and without the disease of interest.[22] We estimated the relationship between the critical test-result value and corresponding operation point on the fitted binormal ROC curve.

Likelihood ratio for positive test result = sensitivity/(1 − specificity). Likelihood ratio for negative test result = (1 − sensitivity)/specificity. The likelihood ratio for the positive test result; LR+ (for 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) for a person without the disease of interest.

RESULTS

As indicated in Figure 1, the T/N ratio in the malignant group was significantly higher at 10, 20, 30, and 120 min ($p < 0.0001$ at all time points), and the variations in the data were larger at 10 min, 20 min, and 30 min compared to 120 min.

Figure 2 shows that the T/S ratio was also significantly higher in the malignant group at 10 min (p = 0.001), 20 min (p = 0.005), 30 min (p = 0.0021) and 120 min (p = 0.0025). The extent of variations in the T/S ratio distribution was greater than the T/N ratio distribution, and overlaps between the benign group and malignant group were frequently seen.

As indicated in Figure 3, the Az of the T/N ratio at 10 min (0.844) was significantly greater than the Az of the T/S ratio at 10 min (0.702) (p = 0.0033). The Az values

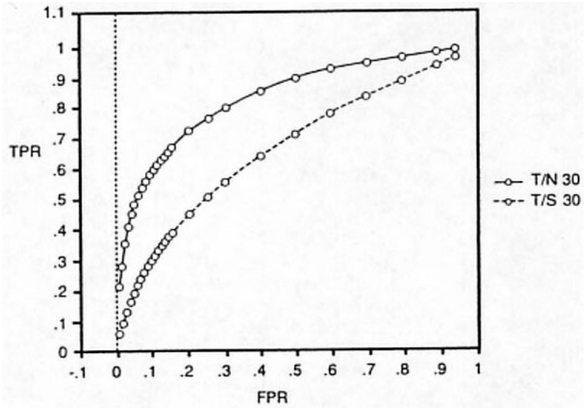


Fig. 5 Az of T/N vs. Az of T/S at 30 min. The Az of the T/N ratio at 30 min (0.841) was significantly greater than the Az of the T/S ratio at 30 min (0.670) ($p = 0.0063$). TPR: true positive rate, FPR: false positive rate

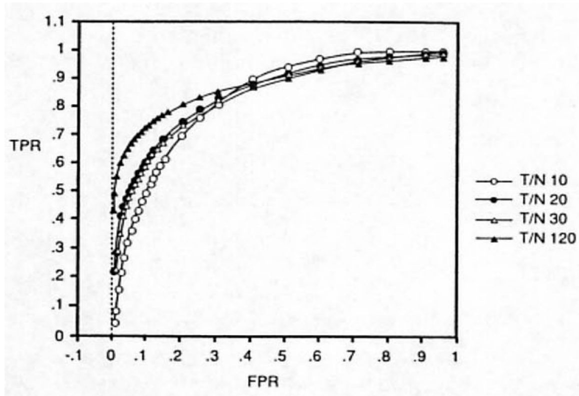


Fig. 7 Az of T/N at each time point. The Az was greatest with the T/N ratio at 120 min. TPR: true positive rate, FPR: false positive rate

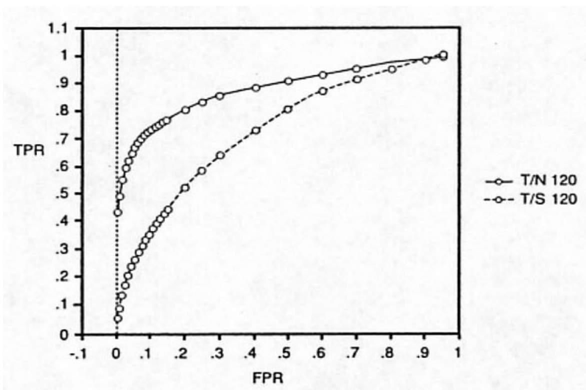


Fig. 6 Az of T/N vs. Az of T/S at 120 min. The Az of the T/N ratio at 120 min (0.887) was significantly greater than the Az of the T/S ratio at 120 min (0.733) ($p = 0.011$). TPR: true positive rate, FPR: false positive rate

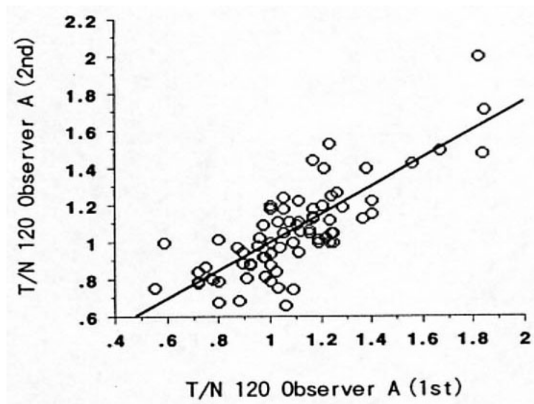


Fig. 8 The reproduction of a quantitative evaluation of T/N 120 in the diagnosis of thyroid follicular nodules (interobserver).
$Y = 0.228 + 0.76X$; $R^2 = 0.635$
$r = 0.80$, $p < 0.001$

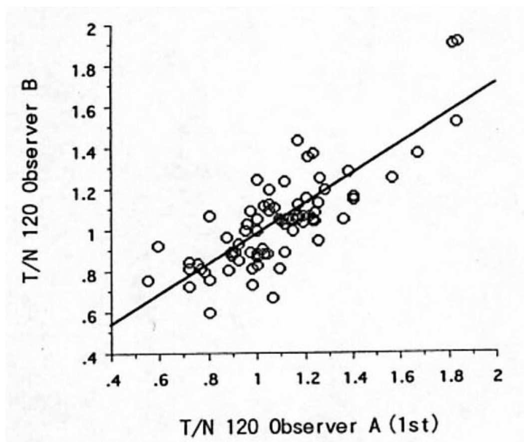


Fig. 9 The reproduction of a quantitative evaluation of T/N 120 in the diagnosis of thyroid follicular nodules (intraobserver).
$Y = 0.24 + 0.737X$; $R^2 = 0.647$
$r = 0.80$, $p < 0.001$

for the T/N ratio were 0.844 at 20 min (Fig. 4), 0.841 at 30 min (Fig. 5), and 0.887 at 120 min (Fig. 6), and were significantly greater than the Az values for the T/S ratio, which were 0.704, 0.670, and 0.733, respectively. The levels of significance were 0.0037 (20 min), 0.0063 (30 min), and 0.011 (120 min), respectively.

As indicated in Figure 7, there were no differences among the Az values at high T/N ratios, and the Az was greatest with the T/N ratio at 120 min.

The multiple regression analysis showed that 'benign or malignant' was a significant variable in T/N 120 (Table 1). The values of T/N ratio at 120 min correlated in the interobserver ($r = 0.80$) ($p < 0.001$) (Fig. 8) and intra-observer ($r = 0.80$) ($p < 0.001$) (Fig. 9).

Using the T/N ratio at 120 min, we estimated the cut-off and corresponding operation points on a fitted binormal ROC curve (Table 2). At 120 min with the T/N ratio cut-off of 1.255, the specificity was 91.8%, and the LR+

Table 1 Multiple regression analysis with 5 covariates

Variable	Coef	Std error	Std coef	t	p
constant	0.981	0.115	0.981	8.520	<0.001
NONTUMOR	0.015	0.085	0.017	0.176	0.861
DIAMETER	0.031	0.051	0.057	0.608	0.545
B/M	0.287	0.056	0.509	5.123	<0.001
CYST	−0.061	0.035	−0.174	−1.728	0.086
CALC	$-4.5E^{-4}$	0.055	−0.001	−0.008	0.994

NONTUMOR, non-tumorous lesions (chronic thyroiditis, adenomatous goiter); DIAMETER, diameter of nodular lesion divided into T1, T2, and T3; B/M, benign or malignant; CYST, contents of cyst; CALC, contents of calcification; Coef, coefficient; Std error, standard error; Std coef, standardized coefficient. Squared multiple r = 0.351

Analysis of Variance

Source	SS	df	MS	F-ratio	p
Regression	1.927	5	0.385	8.098	<0.001
Residual	3.570	75	0.048		

SS, sum of squares; df, degree of freedom; MS, mean square

Table 2 Suitable cut-off values in the quantitative evaluation to separate "positive" results from "negative" results for T/N 120

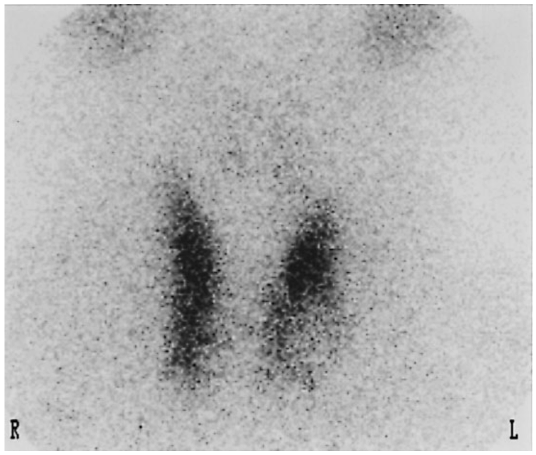
Cut-off	FPR	TPR	Sen.	Speci.	LR+	LR−
1.255	0.082	0.702	70.2	91.8	8.56	0.325
1.225	0.121	0.745	74.5	87.9	6.16	0.279
1.175	0.164	0.845	84.5	71.3	2.94	0.217
1.075	0.298	0.849	84.9	70.2	2.85	0.215
1.065	0.359	0.871	87.1	64.1	2.43	0.201
1.045	0.427	0.892	89.2	57.3	2.09	0.188
1.010	0.746	0.958	95.8	25.4	1.28	0.165

Sen.: sensitivity
Speci.: specificity
LR+: Likelihood ratio for positive test result
= sensitivity/(1 − specificity)
LR−: Likelihood ratio for negative test result
= (1 − sensitivity)/specificity

was greatest at 8.56, which still was less than 10. At 120 min, using the cut-off for the T/N ratio of 1.010, which represents nearly an equal accumulation compared to normal thyroid gland, the sensitivity is greatest at 95.8%, while the LR− was lowest at 0.165, although better than 0.1. 66.4% of the benign group and 25.6% of the malignant group had a T/N ratio of 1.010 or greater, but less than 1.255, so malignancy could not be excluded.

Figure 10 shows a 49-year-old woman with a 1.9 cm mass in the left lobe of the thyroid. At 10 min, the T/N ratio was 0.60 and at 120 min, it was 0.72. The histopathologic diagnosis was follicular adenoma. Figure 11 shows a 22-year-old woman with a 2.6 cm mass in the right lobe of the thyroid. At 10 min, the T/N ratio was 2.63 and at 120 min, it was 1.24. The histopathologic diagnosis was follicular carcinoma.

a



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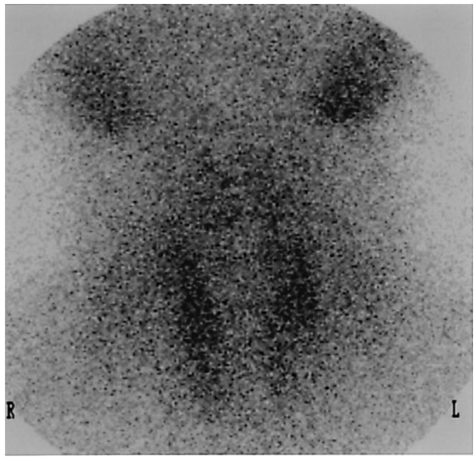

Fig. 10 A 49-year-old woman with a tumor of 1.9 cm in diameter in the left lobe of the thyroid gland. The T/N ratios and T/S ratios of the Tl-201 scintigram were 0.60 and 3.1 at 10 minutes (a) and 0.72 and 1.3 at 120 minutes (b). Follicular adenoma was diagnosed histopathologically by surgical operation.

DISCUSSION

FNA is widely used because it is safe, simple, and provides the best predictive value.[2,3] However, the diagnostic utility of FNA in follicular nodules is low,[4–6] sensitivity being 10–30%, specificity 82.2–95.6%, and accuracy 66.2–69.2%.[6] This is because the diagnosis of follicular carcinoma requires the identification of three pathologic findings, namely capsular or vascular invasion and metastasis, and this is difficult to detect with FNA, which gives only a cytological diagnosis.

Thus, if the FNA gives a diagnosis of a follicular nodule, other tests to distinguish benignity from malignancy become necessary.

In this study, we evaluated the use of a quantitative a

b

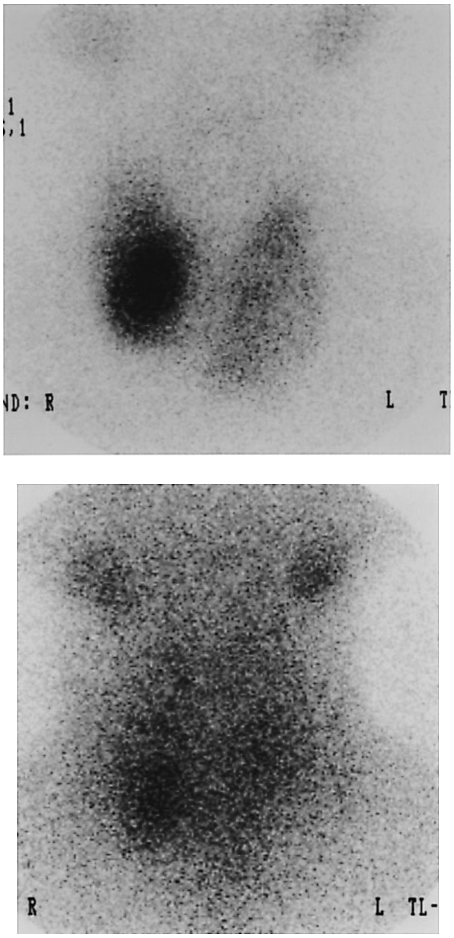

Fig. 11 A 22-year-old woman with a tumor of 2.6 cm in diameter the right lobe of the thyroid gland. The T/N ratios and T/S ratios of the Tl-201 scintigram were 2.63 and 16.7 at 10 minutes (a) and 1.24 and 1.77 at 120 minutes (b). Follicular adenoma was diagnosed histopathologically by surgical operation.

evaluation by Tl-201 scintigraphy of thyroid follicular nodules, where diagnosis by FNA is difficult, for the optimum areas to be compared and imaging time. We believe that the best results are obtained with Tl-201 scintigraphy at 120 min with the contralateral normal thyroid gland as the comparison, because Az, which serves as an overall measure of test, was greatest at 0.887.

An important question is which the better region for comparing follicular nodules in quantitative evaluation namely, the contralateral normal thyroid gland or soft tissue. For a quantitative or visual evaluation using Tl-201 scintigraphy, the normal thyroid gland is generally used as the area for comparison.[6,7,12,13,16–18] In addition, there are also reports that soft tissues in the cervical region can be used for comparison.[19]

When the soft tissues in the cervical region were used for comparison, Az was less than that obtained with the contralateral normal thyroid gland at all imaging times, and so the diagnostic utility was lower.

This is attributed to the low counts in the soft tissues in the cervical region, resulting in a wider variation of the T/S ratio. In addition, for T/N 120, the multiple regression analysis showed that non-tumorous thyroid lesion was not a significant variable. This suggested, in cases of chronic thyroiditis and adenomatous goiter, which raise the counts of tumor and normal tissue, that the values of T/N 120 offset each other. On the other hand, the values of T/S probably did not offset each other. As to best time for making the quantitative evaluation in Tl-201 scintigraphy namely 10, 20, 30, or 120 min, evaluation of the imaging time indicated that for both the T/N ratio and the T/S ratio, Az was best at 120 min. The multiple regression showed that there were no correlations between T/N ratio at 120 min and non-tumorous thyroid lesion, diameter divided into T1 to T3, contents of cyst and contents of calcification, benign or malignant. T/N ratio at 120 min was reproducible in both interobserver and intraobserver studies. So we consider that the T/N ratio at 120 min is useful for distinguishing between benign and malignant thyroid follicular nodules.

Kishida reported that the Tl-201 accumulation in a thyroid tumor depends on Na^+,K^+-ATPase activity and thyroid blood flow, especially in early images.[17] Tl-201 accumulation in the first 15 min correlated closely with Na^+,K^+-ATPase levels. Na^+,K^+-ATPase levels of follicular carcinoma are higher than those of follicular adenoma.[17] So, in follicular carcinoma of Tl-201, the accumulation of both T/N and T/S at 10 min was significantly higher than that of follicular adenoma. In the present study, Tl-201 wash-out of follicular carcinoma was faster than that of follicular adenoma. Tl-201 wash-out depends on the blood flow of a thyroid nodule.[17] T/N or T/S at 10 min of follicular carcinoma was higher than that of follicular adenoma. So, the blood flow of follicular carcinoma was probably richer than that of follicular adenoma.

On the other hand, it has also been reported that the Tl-201 wash-out is slow in thyroid carcinoma, and a lesion is more likely to be malignant if the half-life is 40 min or greater. But in this report, there were no follicular carcinomas or malignant nodules that were almost papillary carcinoma.[16] Tl-201 wash-out of papillary carcinoma was slow because thyroid blood flow was poorer compared to normal thyroid blood flow.[17]

The staining index for PCNA (proliferating cell nuclear antigen) in follicular carcinoma is also higher than that for PCNA in follicular adenoma.[23] There is a good correlation between the degree of Tl-201 uptake and the PCNA index in malignant and benign thyroid nodules.[18] These reports support the finding that Az at 120 min gives the best results.

As to the most suitable cut-off values in the quantitative evaluation to separate "positive" from "negative" results, Hardoff et al. studied the actual cut-off values in a quantitative evaluation of nodular goiters and reported that the late lesion-to-non-lesion ratio of 0.99 had a sensitivity of 100% and a specificity of 62% in thyroid nodules without follicular carcinoma.[13] However, in the study by Hardoff et al. malignant tumors included only papillary carcinoma and did not include any follicular carcinomas.[13]

When a nodular goiter is discovered, the TSH is measured, and if low, Tc-99m pertechnetate scintigraphy is performed. If the TSH is normal, an FNA is performed. Surgical operation is probably performed if the lesion is class 3 (suspicious malignant cells), class 4 (probable malignant cells), or class 5 (definite malignant cells). A lesion that is benign by FNA is observed and rebiopsied if nondiagnostic.[24] If the FNA shows a follicular nodule, distinguishing benign from malignant status is difficult by FNA, and we recommend that except for those that are clearly malignant, Tl-201 scintigraphy should be performed for a quantitative evaluation (T/N ratio) using the contralateral normal thyroid gland as the area for comparison. If the T/N ratio at 120 min is 1.255 or greater, malignancy is strongly suspected (probable malignant), and surgical operation is considered appropriate. If the T/N ratio at 120 min is less than 1.010, the lesion is likely to be benign (probable benign), and observation is appropriate. Furthermore, if the T/N ratio at 120 min is 1.010 or greater but less than 1.255, a malignant lesion cannot be excluded, and the patient should be followed closely and undergo re-examination by Tl-201 scintigraphy.

At our institution, many patients are referred for medical evaluation or treatment, and so the prevalence of follicular carcinoma in our study may be particularly high. Since this study was a retrospective one of patients who underwent Tl-201 scintigraphy, a bias may have been introduced. However, since we evaluated the likelihood ratio, which is not greatly affected by prevalence, we believe that any effects of such bias are not so large.

CONCLUSION

We conclude that for follicular nodules of the thyroid, Tl-201 scintigraphy with a quantitative evaluation of the 120 min image using the contralateral normal thyroid gland for comparison is the most useful to distinguish benign from malignant lesions.

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