Diagnostic value of ultrasonography and TI-201/Tc-99m dual scintigraphy in differentiating between benign and malignant thyroid nodules

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Acknowledgments

None

Abstract

Purpose

To evaluate the performance of ultrasonography (US) and TI-201/Tc-99m dual (Tl/Tc) scintigraphy in differentiating between benign and malignant thyroid nodules.

Methods

Eighty-six patients diagnosed to have a thyroid tumor on postoperative histopathologic examination between June 2009 and February 2017 were included in this retrospective study. A radiologist reviewed the US and Tl/Tc scintigraphy reports along with all available clinical and histopathologic information. On Tl/Tc scintigraphy, a nodule in which uptake was higher in the delayed phase than in the surrounding parenchyma was defined as a delayed accumulation pattern and a nodule in which uptake was higher in the delayed phase than in the early phase was defined as a persistent pattern. The Tl/Tc scintigraphy images were evaluated in a blinded manner to assess reproducibility. A statistical analysis was performed to identify features associated with malignancy. Inter-observer variability was calculated using the κ statistic.

Results

US had higher sensitivity (81.2%), specificity (88.2%), and positive (96.6%) and negative (53.6%) predictive values than Tl/Tc scintigraphy. An ill-defined margin and microcalcification were independent predictors of a malignant thyroid nodule on multivariate logistic regression (P=0.003 and P=0.014, respectively). The persistent pattern had high specificity (85.7%) equivalent to that of US but had lower sensitivity (34.7%). The κ values for the delayed accumulation and persistent patterns were 0.66–0.78 and 0.32–0.50, respectively.

Conclusions

An ill-defined margin and microcalcification on US were independent predictors of a malignant thyroid nodule. A persistent pattern seen on Tl/Tc scintigraphy could contribute to the differential diagnosis.

Keywords Thyroid nodules, Malignancy, Ultrasonography, Scintigraphy, Thallium-201

Introduction

Thyroid cancer is a common thyroid disease [1] and its incidence is increasing worldwide [2,3]. In Japan, a steady increase in the incidence of thyroid cancer was observed from 1975 through 1990 [4] that was attributed to improved diagnostic procedures [5]. The traditional palpation method used to screen for thyroid disease is now being replaced increasingly by ultrasonography (US) [6]. The increased frequency of detection of thyroid nodules has coincided with improvements in US diagnostic equipment.

US, computed tomography, and TI-201/Tc-99m dual (Tl/Tc) scintigraphy are used for detection and qualitative diagnosis of thyroid nodules. B-mode US is used initially to screen for thyroid nodules. For qualitative diagnosis, Doppler mode US is added to assess intranodal blood flow. The hardness of the nodule can be assessed by combining elastography with B-mode US. B-mode US has been reported to have a sensitivity of 85.7%–93.8%, specificity of 66%–93.8%, and a likelihood ratio of 2.7–13.8; the respective values reported for Doppler mode US are 43.8%–88.9%, 74.2%–92%, and 2.98–10.9 [7-11]. Furthermore, a recent report suggests that combination of elastography with B-mode US is more accurate than B-mode alone for detection of malignant thyroid nodules [12].

Tl/Tc scintigraphy is sensitive for detection of thyroid cancer, and there have been many reports suggesting that TI-201 scintigraphy is useful for differentiating between benign and malignant thyroid nodules [13-15]. On visual evaluation, the sensitivity of Tl/Tc scintigraphy has been reported to be 57%–100% in the early phase and 25%–86% in the delayed phase [13]. It is also reported that when a combination of quantitative and visual evaluation is used, the washout pattern on TI-201 scintigraphy is useful for differentiating between benign and malignant thyroid nodules [14,15]. Although there have been several comparisons of Tl/Tc scintigraphy and pathologic fine-needle aspiration (FNA) biopsy results, there is limited information on the diagnostic performance of US and Tl/Tc scintigraphy relative to that of postoperative pathologic findings. Moreover, it is unclear whether Tl/Tc scintigraphy combined with US has improved diagnostic performance for differentiating between benign and malignant thyroid nodules.

The purpose of this study was to evaluate the diagnostic performance of US and TI-201/Tc-99m dual scintigraphy in differentiating between benign and malignant thyroid nodules using postoperative histopathologic findings as the reference standard.

Materials and Methods

Patients

Patients who were diagnosed to have a benign or malignant thyroid tumor on postoperative histopathologic examination between June 2009 and February 2017 were enrolled in this retrospective study (Fig 1). The study protocol was approved by our institutional review board. The need for informed consent was waived in view of the retrospective and observational nature of the study. The exclusion criteria were as follows: no US or Tl/Tc scintigraphy performed in the 6 months before surgery; surgical removal of a thyroid nodule in the past; and preoperative findings highly suspicious for lymph node metastases. Tl/Tc scintigraphy was performed after US and was followed by total thyroidectomy or hemi-thyroidectomy. In all cases, FNA biopsy was performed by puncturing the thyroid nodule before surgery and the final diagnosis was confirmed histopathologically.

Image acquisition

During the study period, B-mode and color Doppler US examinations of the thyroid were performed using a number of different devices, including the Logiq E9, S8, 7, and S6 (GE Medical Systems, Milwaukee, WI) and the Aplio XG and 500 (Cannon Medical Systems, Tokyo, Japan), and usually with a higher frequency linear transducer (a convex lower frequency transducer was used in patients with a large goiter). Two board-certified radiologists with certification from the Japan Society of Ultrasonics in Medicine undertook the evaluations and made the diagnoses. Details of the location, size, margins, echogenicity, echotexture, presence of microcalcification, and vascularity were recorded during the US examination of each thyroid nodule.

For Tl/Tc scintigraphy, 74 MBq of T1-201 chloride were injected intravenously, and planar images were obtained after 5 minutes (early) and 120 minutes (delayed). After the delayed Tl-201 images were acquired, 185 MBq of Tc-99m pertechnetate were injected intravenously and planar images were obtained after 20 minutes. The imaging apparatus consisted of a gamma camera (Prism Irix, Picker International, Cleveland, OH, USA) attached to a low-energy high-resolution parallel hole collimator. The imaging parameters were as follows: window level, 70 keV and 167 keV for Tl-201 scintigraphy and 140 keV for Tc-99m pertechnetate scintigraphy; window width, 40% and 20%; and a preset time of 20 min for Tl-201 and 10 min for Tc-99m pertechnetate. The diameter of the effective field of view was 598 mm. The data acquisition matrix was 256 × 256 and the display matrix was 512 × 512.

Image analysis

One radiologist with 16 years of experience retrospectively reviewed the US diagnostic imaging reports along with the available clinical information and histopathologic results. No new interpretations of the US data were made. The US reports had been written before the results of Tl/Tc scintigraphy were verified. The following imaging features were extracted from each US report: margin (ill-defined or well-defined), echogenicity (hypoechogenic or iso/hyperechogenic), echotexture (heterogeneous or homogeneous), microcalcifications (present or absent), longitudinal transverse ratio (>1 or ≤ 1), hypoechoic band at the margin (none/irregular or regular) and intranodular vascularity (hypervascular or avascular/hypovascular). When several nodules were detected in the thyroid, only the largest nodule was evaluated. The width, depth, and height of the lesion were recorded. An ill-defined margin was defined as positive when there was a spiculated and microlobulated or poorly defined margin in which the tumor could not be differentiated from the normal thyroid parenchyma. Echogenicity was classified as iso/hyperechogenic or hypoechogenic in comparison with the normal thyroid parenchyma. Microcalcifications were defined as calcified spots measuring less than 2 mm. The longitudinal transverse ratio was calculated by dividing the anteroposterior diameter by the transverse diameter.

The same radiologist reviewed the diagnostic Tl/Tc scintigraphy imaging reports in a consistent manner. No new interpretations were made during evaluation of the Tl/Tc scintigraphy data. When the radiologists had diagnosed each case on Tl/Tc scintigraphy imaging in clinical practice they were able to access US reports for reference if needed. For the purposes of the analysis, the authors divided the Tl/Tc scintigraphy findings in two different ways. First, nodules in which uptake was higher in the delayed phase compared with the surrounding parenchyma irrespective of the early phase was defined as a "delayed accumulation pattern" (Fig 2). Second, nodules in which the uptake was higher in the delayed phase than in the early phase compared with the surrounding parenchyma was defined as a "persistent pattern" (Fig 3). Tc-99m scintigraphy was used to localize the nodules. Quantitative evaluation was not routinely performed.

Blinded evaluation of findings on Tl/Tc scintigraphy

The two different patterns seen on Tl/Tc scintigraphy were then re-evaluated to assess the reproducibility of the findings. All cases that underwent Tl/Tc scintigraphy were anonymized for re-evaluation. A further two observers with 8 and 11 years of interpreting experience in nuclear medicine reviewed the Tl/Tc scintigraphy images with knowledge of the location of the nodules but not the final diagnoses on US or the histopathologic results. The diagnostic criterion used was the presence or absence of a delayed or persistent accumulation pattern.

Statistical analysis

Fisher's exact test was used for categorical variables and the Mann-Whitney *U* test for continuous variables in the univariate analyses. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy were calculated to evaluate the diagnostic performance of US, Tl/Tc scintigraphy, and the combination of both imaging modalities. Multivariate logistic regression analysis was performed using variables identified to be significant in the univariate analyses. The inter-observer agreement of the blinded evaluation was assessed by calculating the κ value for dichotomous variables. The κ value was classified as follows: 1.0, perfect agreement; 0.81–0.99, almost perfect agreement; 0.61–0.80, substantial agreement; 0.41–0.60, moderate agreement; 0.21–0.40, fair agreement; and ≤0.20, slight agreement. All statistical analyses was performed using Ekuseru-Toukei 2015 (SSRI, Tokyo, Japan) and R version 3.3.0 (R Project for Statistical Computing, Vienna, Austria). A *P*-value < 0.05 was considered statistically significant.

Results

Patient and tumor characteristics

Two hundred patients were enrolled in this retrospective study. Forty-nine patients who did not undergo US or Tl/Tc scintigraphy in the 6 months before surgery, 18 who had undergone surgery for removal of a thyroid nodule in the past, and 47 who had preoperative findings that were highly suspicious for lymph node metastases were excluded, leaving data for 86 patients with thyroid nodules available for analysis. Twenty-eight nodules were benign (follicular adenoma, n=15; adenomatous goiter, n=13) and 58 were malignant (papillary thyroid carcinoma, n=56; poorly differentiated carcinoma, n=1, undifferentiated carcinoma, n=1). These patients were grouped according to whether the findings were suspicious for malignancy on both US and Tl/Tc scintigraphy or either modality alone or not suspicious for malignancy on either US or Tl/Tc scintigraphy (Fig 1).

Table 1 shows the patient and tumor characteristics. The 86 patients comprised 20 men and 66 women of mean age 54 (range 28–83) years. The most common malignant histopathology was papillary carcinoma. There were no cases of follicular carcinoma. All of the benign nodules were adenomatous nodules or follicular adenomas. The mean size of the benign nodules was significantly greater than that of the malignant nodules ($P < 0.001$). There was no significant difference in patient age or sex or in location of the nodule between the benign and malignant groups.

Findings on US

Most (96.6%) of the thyroid nodules diagnosed as malignant had ill-defined margins. Furthermore, 55.2% of the malignant nodules were hypoechogenic and 96.4% of the benign nodules were iso/hyperechogenic. Microcalcifications were observed more frequently in malignant nodules (77.5%) than in benign nodules (14.3%). All malignant nodules had a heterogeneous echotexture. The hypoechoic band at the margin was absent or irregular in most (96.5%) of the malignant nodules and almost all (98.2%) of these nodules were hypervascular. Findings of an ill-defined margin, hypoechogenicity, heterogeneity, absence or irregularity of the hypoechoic band at the margin, and microcalcification on US were associated with malignancy. Conversely, US findings of a well-defined margin and iso/hyperechogenicity were associated with a benign nodule. There was no significant difference in the longitudinal transverse ratio or degree of vascularity between benign and malignant nodules (Table 2).

Findings on Tl/Tc scintigraphy

Almost all of the nodules were shown as a cold area on a Tc-99m thyroid scan. Only 4 patients showed higher uptake on a Tc-99m thyroid scan. Fifty-five (63.9%) of the 86 thyroid nodules showed the delayed accumulation pattern and 24 (27.9%) showed the persistent accumulation pattern. Thirty-eight (69.1%) of 55 nodules with the delayed accumulation pattern and 21 (87.5%) of 24 nodules with the persistent pattern were diagnosed as malignant on histopathologic examination. There was a significant association of the persistent pattern with malignancy (P=0.02, Table 2).

Blinded evaluation of Tl/Tc scintigraphy findings

The delayed accumulation pattern showed higher sensitivity (observer 1, 65.5%; observer 2, 62.1%) than the persistent pattern (observer 1, 36.2%; observer 2, 29.3%) and also showed higher accuracy (observer 1, 58.1%; observer 2, 55.8%) than the persistent pattern (observer 1, 53.5%; observer 2, 45.3%, respectively). The κ value was 0.66–0.78 (almost perfect) for the delayed accumulation pattern and 0.32–0.50 (substantial to moderate agreement) for the persistent pattern.

Diagnostic performance of US and scintigraphy

The diagnostic performance based on the combination of US and scintigraphy is summarized in Table 3. US had higher sensitivity (81.2%), specificity (88.2%), PPV (96.6%), and NPV (53.6%) than scintigraphy. Although the persistent pattern had low sensitivity (34.7%), it had high specificity (85.7%) that was equivalent to that of US (88.2%). The group of nodules that were suspicious for malignancy had a higher NPV (71.4%) on both US and Tl/Tc scintigraphy than on either US or scintigraphy alone. US had the highest accuracy for diagnosis of a malignant nodule (82.6%). An ill-defined margin and presence of microcalcification were independent predictors of malignancy in the multivariate logistic regression analysis (P=0.003 and P=0.014, respectively; Table 4).

Eight of 58 patients with malignant histopathology had an equivocal finding on FNA and 6 of these 8 patients were diagnosed to have malignant thyroid disease on US. However, 5 of the 8 patients showed the delayed accumulation pattern and 2 showed a persistent pattern. Eleven of 15 patients with follicular adenoma showed the delayed accumulation pattern and 3 showed the persistent pattern. The numbers of true negative and false positive results for the delayed accumulation pattern and the persistent pattern in the group of patients with follicular adenoma were 26.7% vs 80.0% and 73.3% vs 20.0%, respectively. The persistent pattern had higher true negative and lower false positive values than the delayed accumulation pattern. Fourteen (93.3%) of the 15 patients with follicular adenoma were judged to have benign thyroid disease because of the absence of malignant findings on either US or Tl/Tc scintigraphy whereas FNA showed equivocal findings in 9 of the 15 patients.

Discussion

There are many reports suggesting that a combination of B-mode and color Doppler US has high predictive ability in the differential diagnosis of thyroid nodules [7-12, 16-19]. Several US features associated with thyroid cancer have been reported [10, 16-22]; however, the sensitivity and specificity values have varied from study to study. Moreover, most of the previous studies used the cytologic results of FNA as the reference standard. It has been reported that about 5% of FNA results are false-positive or false-negative and that these results may be non-diagnostic because of inadequate sampling and presence of follicular neoplasia [23, 24]. In our study, 8 (13.8%) of 58 patients with malignant thyroid disease had an equivocal finding on FNA, and 6 of these 8 patients were diagnosed to have malignancy on either US or Tl/Tc scintigraphy. These results could justify a possible diagnostic contribution of US and Tl/Tc scintigraphy in patients with thyroid nodules. With regard to US studies, an ill-defined margin, hypoechogenicity, heterogeneity, presence of microcalcification, and an absent or irregular hypoechoic band at the margin were associated with malignancy in the univariate analyses. Furthermore, an ill-defined margin and microcalcification were independent predictors of malignancy in multivariate logistic regression analysis. These results were based on postoperative histopathologic findings as a reference standard, so it can be assumed that our results would be more reliable for qualitative diagnosis than the previous reports using FNA as a reference standard.

The mechanism of Tl-201 accumulation in thyroid nodules depends on Na-K-ATPase activity and blood flow in the thyroid gland [25]. The Tl-201 washout rate has been reported to be more delayed for differentiated thyroid carcinoma than for thyroid adenoma, although the definition of washout was unclear [26]. Visual evaluation of delayed images using Tl-201 planar scintigraphy has also been reported to be useful for differentiation of thyroid nodules [26]. The results of our study suggest that the persistent pattern has higher specificity than the delayed accumulation pattern on visual assessment. In contrast, the delayed accumulation pattern had higher sensitivity and accuracy than the persistent pattern. Reproducibility of these results was confirmed by blinded evaluation. From these results, we infer that the persistent pattern is useful for diagnosis of malignant thyroid nodules and the delayed accumulation pattern is useful for exclusion of malignant nodules. In recent years, it has been reported that quantitative evaluation is useful for diagnosis of thyroid nodules [14, 15]. However, a previous investigation revealed that quantitative evaluation of Tl/Tc scintigraphy as a routine examination was difficult because occupying both a scintillation camera and an information-processing device in the hospital laboratory for a long time was logistically difficult and the value of quantitative evaluation could change depending on the background setting [27]. In this regard, a further investigation is needed to confirm our results and the usefulness of quantitative evaluation.

In contrast with previous reports [26, 28], 31% of the benign nodules in our study showed a delayed accumulation pattern, indicating low specificity. We speculate that this finding reflects the high uptake by some of the large follicular adenomas or adenomatous goiters on both early and delayed images, and hence difficulty differentiating between benign and malignant nodules. In our study, benign nodules were significantly larger than malignant nodules in the univariate analysis, but this finding is not considered significant from a clinical standpoint given the potential for selection bias. These benign nodules also showed hypervascularity similar to that of the malignant nodules, as shown in Table 2. It has been reported that the early images on Tl-201 scintigraphy reflect blood flow and tumor diameter [26, 27]. Therefore, we speculate that large hypervascular benign nodules tend to be judged as having a delayed accumulation pattern. We recommend that delayed images should be interpreted carefully when evaluating a thyroid nodule that appears as large and hypervascular on early Tl-201 scintigraphy images.

With regard to diagnostic performance for a benign nodule, 15 nodules were diagnosed as benign by US and 11 as benign by scintigraphy. As a result, the NPV of both modalities and the specificity of scintigraphy alone were low. However, combination of US and scintigraphy increased the NPV. Our results indicate that assessment of a thyroid nodule using a combination of US and scintigraphy may be useful for exclusion of malignancy if the possibility of malignancy is estimated to be low on US and the FNA biopsy specimen is inadequate for a cytologic diagnosis. Moreover, we demonstrated that a combination of US and Tl/Tc scintigraphy has additional value over that of FNA in targeting follicular adenoma. Our results also suggest that the persistent pattern could be valuable for diagnosis of malignancy with confidence if the thyroid nodule shows malignant features on US.

There are some limitations to this study. First, it had a retrospective design and patients who did not undergo US or Tl-201 scintigraphy were excluded. We also targeted patients who had undergone surgery because of suspicious findings on preoperative imaging, which would inevitably have introduced a degree of selection bias. Second, the small number of benign tumors included and the lack of any cases of follicular carcinoma limit the analyses. Papillary carcinoma is by far the most common type of malignant thyroid disease in Japan. A further multicenter study that includes more benign tumors and follicular carcinomas is needed to confirm our present findings.

In conclusion, we have found that malignant thyroid nodules have ill-defined margins and show microcalcifications on US. A persistent accumulation pattern on Tl/Tc scintigraphy could contribute to differentiation between benign and malignant thyroid nodules.

Compliance with ethical standards

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

Research involving human participants and/or animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

For this type of study informed consent is not required.

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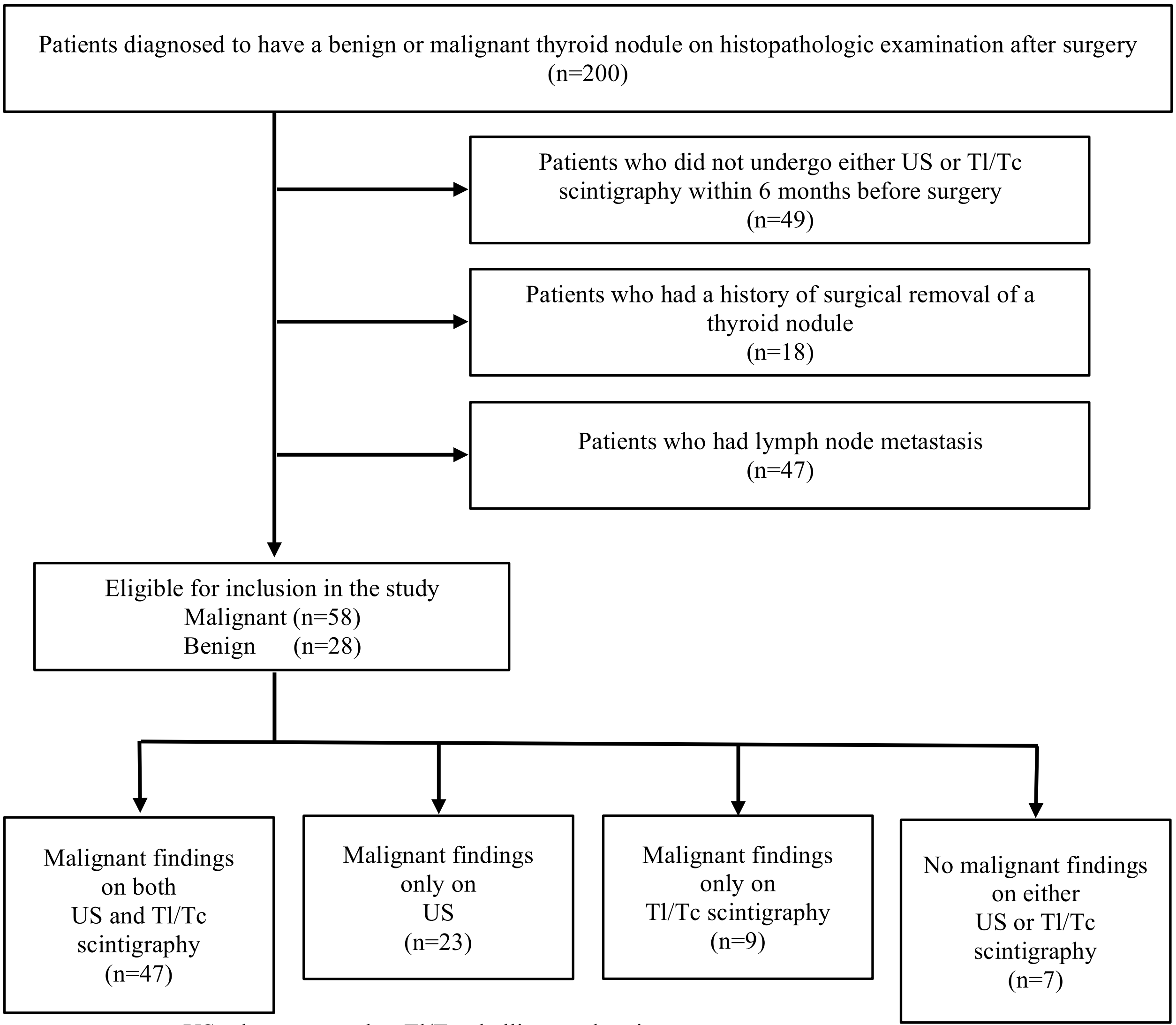
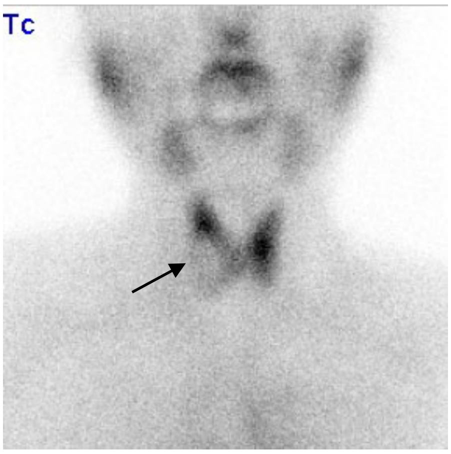
Figure legends

Fig. 1 Diagram showing the flow of patients through the study.



US, ultrasonography; Tl/Tc, thallium-technetium

Fig. 2 (a) A Tc-99m scintigraphy image showing a cold thyroid nodule (arrow) in the right lobe of the thyroid gland. (b) An ultrasonography scan showing a well-defined, iso/hyperechogenic, heterogeneous mass containing large calcifications (arrow) on the right lobe of the thyroid gland. (c, d) Dual phase Tl-201 scintigraphy images showing that the uptake in the nodules is higher on both the (c) early and (d) delayed phase images compared with the surrounding parenchyma. This finding was defined as a delayed accumulation pattern. Follicular adenoma was diagnosed on histopathologic examination.



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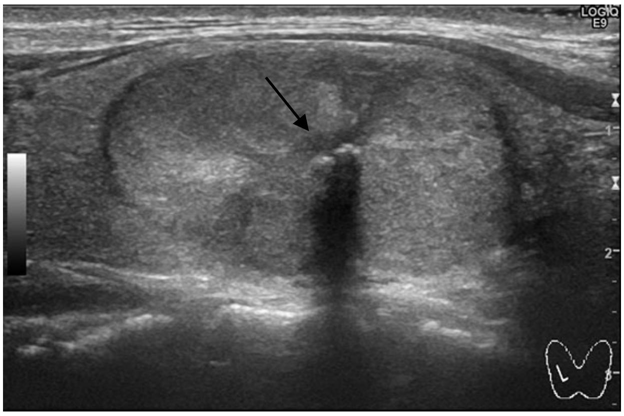

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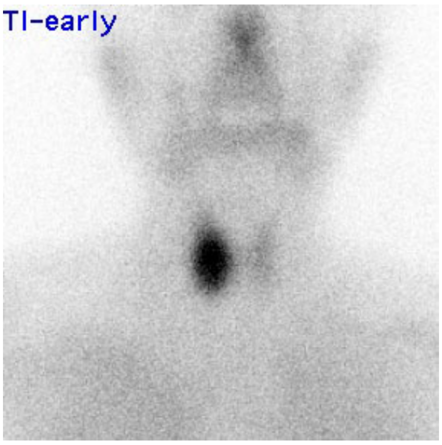

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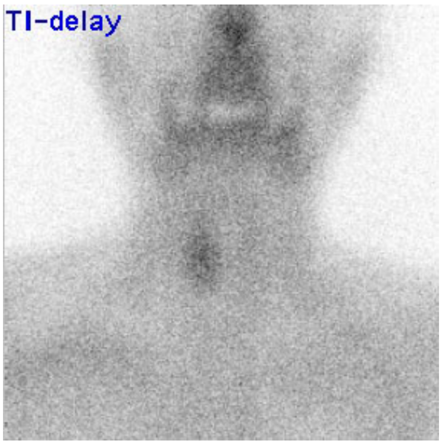
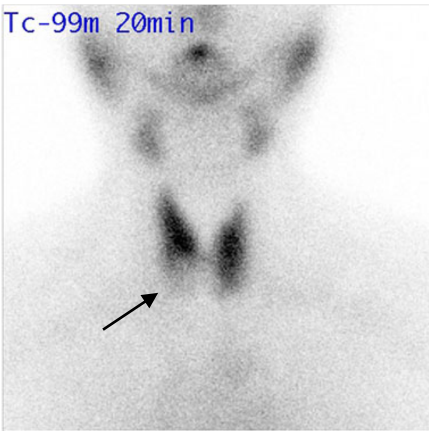


(d)

Fig. 3 (a) A Tc-99m scintigraphy image showing a cold thyroid nodule (arrow) in the right lobe of the thyroid gland. (b) An ultrasonography scan showing an ill-defined, iso/hyperechogenic, heterogeneous mass containing microcalcifications (arrow) in the right lobe of the thyroid gland. (c, d) Dual phase Tl-201 scintigraphy images showing that the uptake in the nodules is higher on the (d) delayed phase image than in the (c) early phase image compared with the surrounding parenchyma. This finding was defined as a persistent pattern. Papillary carcinoma was diagnosed on histopathologic examination.



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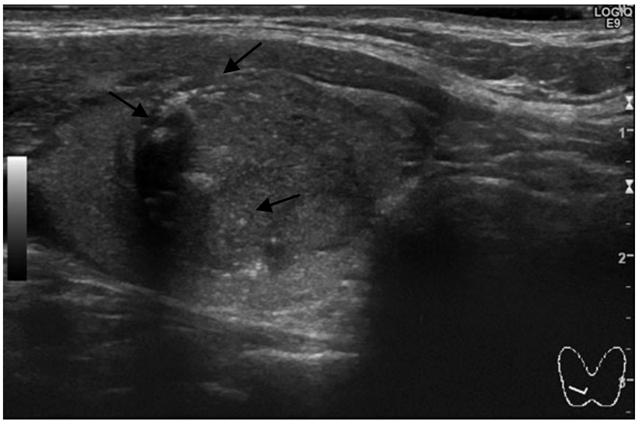
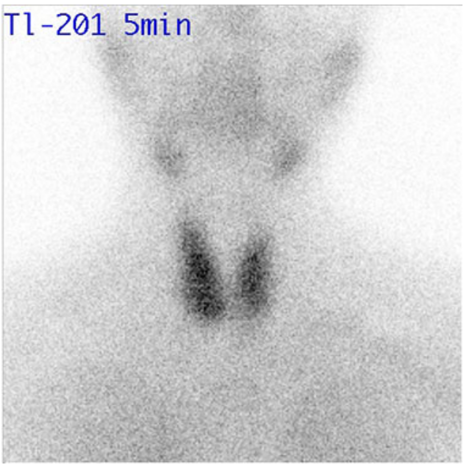
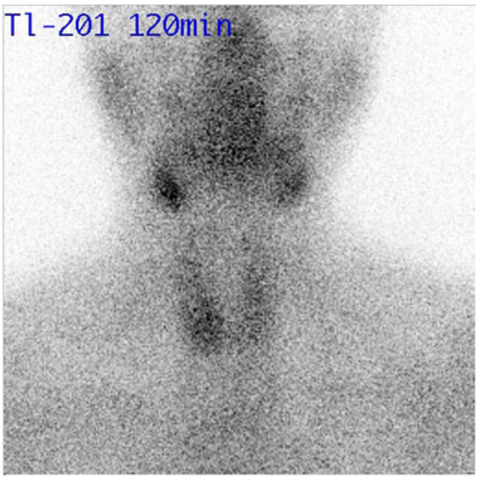


(b)



(c)



(d)

Table 1 Patient and tumor characteristics

		Histopathologic diagnosis		*P*-value
		Malignant (n=58)	Benign (n=28)	
Median age (years)		53(28-78)	58(28-83)	0.10
Sex				> 0.99
	Male	14	6	
	Female	44	22	
Nodule size (cm)				< 0.001
	<2	40	1	
	≥2	18	27	
Nodule location				0.36
	Right lobe	29	11	
	Left lobe	28	17	
	Isthmus	0	0	
Pathology				
	Papillary	56		
	Poorly differentiated	1		
	Undifferentiated	1		
	Follicular adenoma		15	
	Adenomatous nodule		13	

The numbers in parentheses for age are the interquartile range (25th–75th percentile)

Table 2 Findings on ultrasonography and accumulation patterns found on Tl/Tc scintigraphy

	Histopathologic diagnosis Malignant (n=58)	Benign (n=28)	*P*-value	OR	95% CI
Findings on ultrasonography					
Margin			< 0.001	76.06	14.37–820.46
Ill-defined	56	7			
Well-defined	2	21			
Echogenicity			< 0.001	32.14	4.66–1391.74
Hypoechogenic	32	1			
Iso/hyperechogenic	26	27			
Echotexture			0.03		
Heterogeneous	58	25			
Homogeneous	0	3			
Microcalcification			< 0.001	19.8	5.52–93.08
Present	45	4			
Absent	13	24			
Longitudinal transverse ratio			0.18		
<1	17	4			
≥1	41	24			
Hypoechoic band at margin			< 0.001	40.51	7.98–410.11
None or irregular	56	11			
Regular	2	17			
Intranodular vascularity			> 0.99		
Hypervascular	57	28			
Avascular or hypovascular	1	0			
Accumulation patterns found on Tl/Tc scintigraphy					
Persistent pattern			0.02	4.66	1.20–26.95
Present	21	3			
Absent	37	25			
Delayed accumulation pattern			0.811	1.23	0.43–3.42
Present	38	17			
Absent	20	11			

A persistent accumulation pattern was defined as a thyroid nodule that showed higher uptake only in the delayed image. CI, confidence interval; OR, odds ratio

Table 3 Diagnostic performance of ultrasonography and Tl/Tc scintigraphy

	Accuracy	Sensitivity	Specificity	PPV	NPV
US	82.6	81.2	88.2	96.6	53.6
Scintigraphy (delayed accumulation pattern)[a]	58.1	69.4	36.7	67.2	39.2
Scintigraphy (persistent pattern)[b]	51.2	34.5	85.7	83.3	38.7
Group A	67.4	65.5	71.4	86.3	71.4
Groups A + B + C	73.2	98.2	21.4	74.0	85.7

The numbers are expressed as percentages. [a]Uptake was higher in the delayed image than in the surrounding parenchyma. [b]Uptake was higher in the delayed image than in the early image compared with the surrounding parenchyma. Group A, suspicious for malignancy on both US and Tl/Tc scintigraphy. Group B, suspicious for malignancy only on US. Group C, suspicious for malignancy only on Tl/Tc scintigraphy. NPV, negative predictive value; PPV, positive predictive value; US, ultrasonography

Table 4 Results of multivariate logistic regression analysis

Independent variables	OR	95% CI		*P*-value
		Lower	Upper	
Ill-defined margin (present or absent)	38.26	3.28	445.74	0.004
Echogenicity (Hypoechogenic or iso/hyperechogenic)	5.96	0.59	60.31	0.130
Microcalcification (present or absent)	9.24	1.56	54.65	0.014
Hypoechoic band at margin (present or absent)	1.68	0.11	25.74	0.709
Persistent pattern on Tl/Tc scintigraphy (present or absent)	2.51	0.35	17.97	0.360

CI, confidence interval; OR, odds ratio