Natural Course of Cytologically Benign Thyroid Nodules: Observation of Ultrasonographic Changes

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Background: The natural course of cytologically benign thyroid nodules remains unclear. The aim of this study was to evaluate whether ultrasonographic (US) changes are associated with changes in nodule volume during follow-up.
Methods: We retrospectively reviewed over 4 years of clinical records of patients with benign thyroid nodules as confirmed by fine needle aspiration (FNA). In total, 186 patients with 202 benign thyroid nodules were included for study. We assessed for changes in nodule volume and examined the cystic portion of the nodule as well as four US features (echogenicity, margin, calcification pattern, and shape).
Results: During follow-up (mean, 21.7±10.7 months) and using 50% as a cutoff value, nodule volumes increased in 11.8%, exhibited no change in 79.9%, and decreased in 8.3% of patients. Proportion of nodules demonstrating at least one US change was 20.8% (42/202). The most common US changes (in descending order of frequency) were cystic change, margin change, and calcification pattern change. Nodule shape and echogenicity rarely changed. Increased nodule volume was not significantly associated with any US features or with the number of FNAs but was associated with younger age at time of diagnosis.
Conclusion: Although a portion of thyroid nodules confirmed as benign showed US changes or volume changes during the follow-up period, these findings may only represent the natural course of benign nodules. Frequent follow-up with US might be needed for only a small number of cases with suspicious US findings.

Keywords: Thyroid nodule; Neoplasms; Ultrasonography; Growth; Tumor burden

INTRODUCTION

Thyroid nodules are highly common with approximately 50% seen on ultrasonographic (US) examination in adults [1]. However, most thyroid nodules are benign and rarely are of clinical significance except if symptomatic. The natural course of benign thyroid nodules remains unclear and has only been investigated by a few reports [2-5]. This scarcity of information is presumably due to the lack of clinical importance, after excluding malignancy, and given its indolent course.

The usefulness of US has recently been evaluated for predicting malignancy of thyroid nodules [6,7]. Although many malignant nodules have US features predictive of malignancy, some malignant nodules share the same US findings with be-

nign nodules. This can lead to an uncertain diagnosis, making follow-up exams necessary given fear of false negative results [6,8]. Despite an extremely low malignancy rate for thyroid nodules that were originally confirmed as benign, frequent follow-up, coupled with or without fine needle aspiration (FNA), has been performed in most patients, especially when nodules exhibit morphological change such as nodule growth or calcification [2]. This practice is based on established guidelines [6,9].

However, it remains unknown whether US findings of benign thyroid nodules change with time and if they are associated with changes in nodule size or volume. What is the fate of a thyroid nodule that is confirmed as benign by FNA but has US findings suspicious for malignancy? Can clinicians safely ignore newly developed US features predictive of malignancy in benign nodules confirmed by FNA during follow-up? Is there any relationship between morphological changes on US and nodule growth? Answering such questions may be challenging as long-term follow-up is necessary along with precise US measurements.

Here, we studied the relationship between changes of US features and volume changes in benign thyroid nodules in an effort to improve understanding of the natural history of benign thyroid nodules. This study may help to reduce unnecessary testing in patients with benign nodules and without suspicious findings for malignancy on US.

METHODS

Patients

From January, 2002 to December, 2005 at Yeouido St. Mary's Hospital in Seoul, Korea, 3,258 patients were evaluated with US for thyroid nodules, and, of those, 717 patients had follow-up US in the same hospital. Among those 717 patients, 186 were identified for study after applying strict exclusion criteria. In order to select homogenous nodules, the following exclusion criteria were established: 1) nodule size ≤5 mm; 2) cystic component at initial evaluation ≥50%; 3) follow-up <6 months; 4) no fine needle aspiration biopsy (FNAB) results or inadequate cytology; 5) nodules diagnosed as atypical or malignant via FNAB or confirmed postoperatively as malignancy; 6) immeasurable or inflammatory lesions; and 7) thyroid dysfunction or medication history affecting thyroid function.

We retrospectively reviewed the clinical records of 186 patients with thyroid nodules confirmed as benign on FNA. Nodules were evaluated annually or biannually with US according

to standard protocols [7] beginning in January, 2002. This retrospective review of medical records and US images was completed in 2006. After 3 years (in 2009), final status of nodules—benign versus malignant at surgery—was evaluated without available US images.

US findings

All US examinations were performed with HDI 3000 or 5000 scanners (Philips/ATL, Bothell, WA, USA) that were equipped with a 5 to 12 MHz linear array transducer. We analyzed US findings using a picture archiving and communication system, searching for previously reported US findings of thyroid nodules suspicious for malignancy. These findings included: degree of cystic portion (categorized as none, less than 25%, more than 25%, and less than 50%), internal echogenicity as compared to normal thyroid tissue (categorized as hypoechoic, isoechoic, or hyperechoic), shape (categorized as ovoid to round, taller than wide, or irregular), margin character (categorized as smooth, spiculated, or ill-defined) and calcification (categorized as none, macrocalcification, or microcalcification).

We determined nodule shape based on the ratio of the antero-posterior (AP) dimension to the transverse (T) dimension as taller than wide (AP>T) or ovoid to round (AP≤T). Nodule echogenicity, assessed with respect to normal thyroid parenchyma, was classified as either hypoechoic (when a nodule showed a relatively hypoechoic pattern relative to normal thyroid parenchyma), isoechoic (when a nodule showed an isoechoic pattern relative to normal thyroid parenchyma), or hyperechoic (when a nodule showed a relative echogenic pattern relative to normal thyroid parenchyma). Calcification was classified as either microcalcification (tiny, punctate, echogenic foci of 1 mm or less with or without posterior shadowing) or macrocalcification (punctate, echogenic foci larger than 1 mm in size).

Maximum nodule diameter was measured in three planes, and changes in nodule volume were evaluated using the formula for a rotational ellipsoid (length×width×depth×π/6). All US findings were reviewed by a single radiologist (K.J.Y.), who was unaware of clinical parameters. Measurement of US images, to assess intraobserver variability, was completed on two occasions separated by at least 1 week. In total, 20 measurements were performed, and intraobserver variability was calculated using a Cohen's κ value for morphological change observed on US. κ Values for each US feature were: 0.606 (calcification pattern), 0.690 (echogenicity), 0.856 (internal content), and 0.574 (margin irregularity). *P* value for all the pa-

rameters was set at <0.01.

Cutoff values for volume change of benign nodules, compared with baseline, were set at 15%, 30%, and 50%. We also adopted definitions for nodule growth as recommended by the American Thyroid Association (ATA) guidelines, which delineate nodule growth as a 20% increase in nodule diameter with a minimum increase in two or more dimensions of at least 2 mm [9]. We compared ATA criteria with the other cutoff values for volume change of benign nodules.

Statistics

To evaluate for an association between nodule growth and changes of US findings, chi-square testing and Fisher's exact testing were used for categorical variables. In order to compare groups with and without nodule growth, or groups with and without US change, unpaired t tests were used for continuous variables, and chi-square testing and Fisher's exact testing were used for categorical variables. To validate the definition of nodule growth according to ATA guidelines, we used a κ value as a measurement of agreement with each cutoff value (15%, 30%, and 50%). Logistic regression analysis was performed to investigate the influence of confounders (age, gender, follow-up duration, number of FNAs, thyroid stimulating hormone [TSH] level, US findings, and presence of thyroid autoantibody) and to determine independent variables for nodule growth and morphological change on US. All data processing was performed with SPSS version 11.5 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 186 patients with 202 benign thyroid nodules—confirmed as benign by FNA—were included in our study evaluating changes of US pattern and nodule size. Baseline demographic and US characteristics are shown in Table 1. During follow-up of the 202 benign nodules (mean, 21.7±10.7 months), mean volume change was +0.16±1.71 mL (range, -6.9 to +8.4), and percent volume change compared with initial volume was +10.5±54.3% (range, -98.5 to +378.6) (Table 1).

The most common US changes, in descending order of frequency, were cystic component change (7.4%), margin change (6.9%), and calcification pattern change (6.0%), indicating that each US change occurred in roughly 1% to 8% of the total nodule population (Table 2). Representative US changes were presented in Fig. 1. Margin change from well-defined smooth to ill-defined was the most frequent margin change (n=8, 4.0%). New appearance of macrocalcification was the most frequent calcification pattern change (n=9, 4.5%)—though both micro-

Table 1. Clinical Characteristics of the Study Population with Benign Thyroid Nodules

Characteristic	Value	Reference value
No. of patients	186	
Male (%)	23 (12.4)	
Female (%)	163 (87.6)	
No. of nodules	202	
Age at diagnosis, yr	47.0±10.8 (20-77)	
Follow-up duration, mo	21.7±10.7 (7-61)	
No. of FNA per nodule	2.2±1.0 (1-6)	
Estimated nodule volume, mL	3.8±4.6 (0.1-30.7)	
Nodule volume change, mL	0.16±1.71 (-6.9-+8.4)	
Nodule volume change, %	10.5±54.3 (-98.5-+378.6)	
Initial thyroid function test		
TSH, mIU/L	1.46±0.84 (0.32-3.97)	0.3-4.0
Free T4, ng/dL	1.16±0.27 (0.44-1.93)	0.78-1.94
T3, μg/dL	1.43±0.17 (0.92-1.94)	0.8-2.0
Anti-TPO Ab, IU/mL[a]	36.2±90.7 (0.21-799)	0.0-100.0
Anti-Tg Ab, IU/mL[a]	49.5±108.2 (0.19-807)	0.0-70.0

Values are expressed as number (%) or mean±SD (range).

FNA, fine needle aspiration; TSH, thyroid stimulating hormone; Anti-TPO Ab, antithyroid peroxidase antibody; Anti-Tg Ab, antithyroglobulin antibody.

[a]Data from only 159 patients were included.

calcification (n=8, 4.0%) and macrocalcification (n=25, 12.4%) initially existed in a substantial portion of benign nodules.
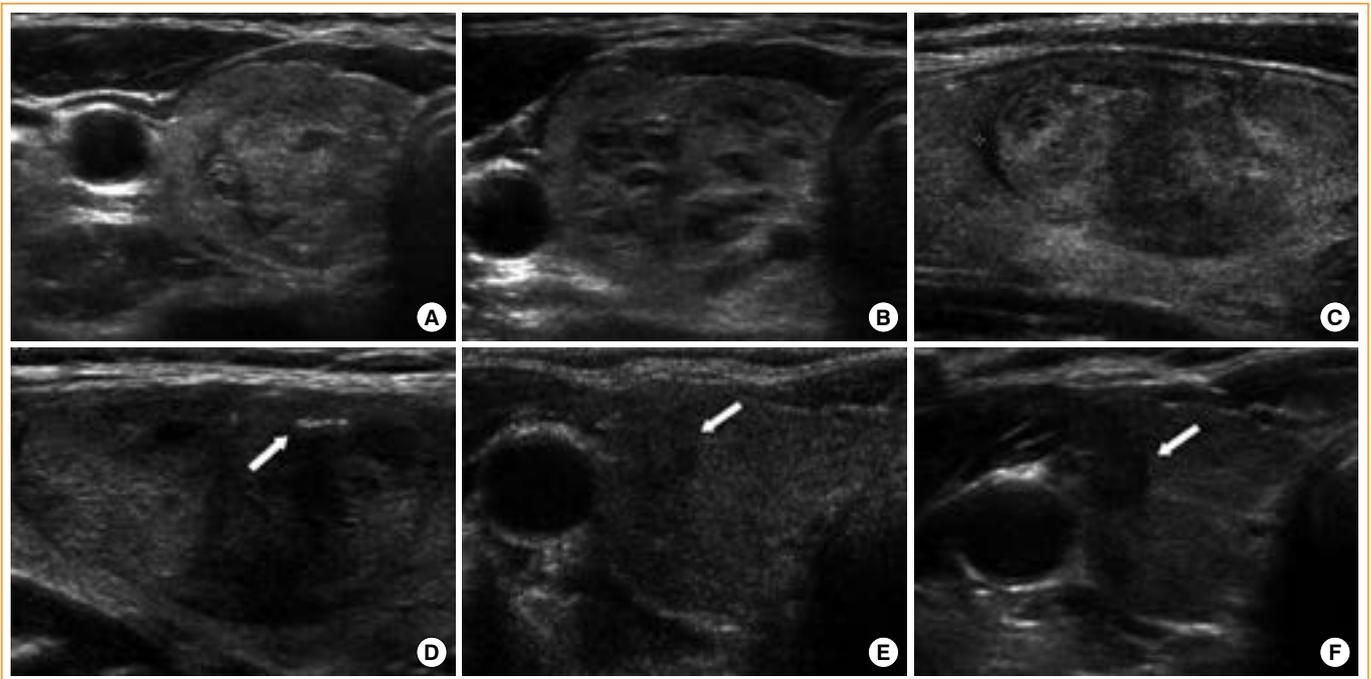
Only six nodules showed echogenicity changes (3.0%), and just two nodules (1.0%) exhibited a newly developed taller than wide appearance—indicating that echogenicity and ratio of the AP to T dimensions remained relatively unchanged. The proportion of nodules with at least one US component change was 20.8% (42/202). Among those, the proportion of nodules with newly developed US changes suggesting malignancy—such as a more tall than wide appearance, microcalcification, hypoechogenicity, or ill-defined margin—was less than 5% (Table 2). Changes of all US parameters referenced in Table 2 were not significantly associated with thyroid function testing (data not shown).

Increased change in nodule volume using the various criteria (15%, 30%, 50%, and ATA recommendations) had no significant association with any US features like cystic change, margin irregularity, calcification pattern, or hypoechogenicity (data not shown).

Using the criteria of greater than 15%, 30%, and 50% for nodule growth, 56 (38.9%), 32 (22.6%), and 17 (11.8%) nodules increased in volume, respectively. Using ATA recommendations for assessing nodule growth, 19 (9.4%) nodules increased, 167 (82.7%) were unchanged, and 16 (7.9%) decreased in volume. ATA recommendations for nodule growth had more agreement with a cutoff value of 50% for nodule growth (κ value, 0.742) than with cutoff values of 15% and 30% (κ values, 0.274 and 0.543, respectively). About 90% of nodules remained unchanged during follow-up if a 50% cutoff or ATA recommendations were applied.

To compare the natural course of benign nodules with suspicious US features and benign-appearing nodules on US, we divided our dataset into two groups: one group was defined as thyroid nodules with at least one US feature suspicious of malignancy (hypoechoic, microcalcification, or macrocalcification; irregular or spiculated margin; taller than wide appearance) (n=110). The group of benign-appearing nodules was defined as having no US features suspicious of malignancy (n=92). Between these two groups, we compared nodule growth based on ATA guidelines and US change. There were no significant differences in nodule growth (10.0% vs. 8.7%, P=0.752) and changes in US findings (23.6% vs. 17.4%, P=0.276).

Fig. 1. (A) Transverse ultrasonography (US) image from a 46-year-old woman showing an ill-defined, ovoid to round shaped, and isoechoic nodule. (B) After 3 years, follow-up US image shows an increased nodule size with an increased cystic portion. (C) Longitudinal US image from a 46-year-old woman exhibiting an ill-defined, ovoid to round shaped, and isoechoic nodule. (D) After 3 years, follow-up US demonstrates newly developed macrocalcification (arrow) within a nodule. (E) Transverse US image from a 53-year-old woman revealing an ill-defined, ovoid to round shaped, and isoechoic nodule (arrow). (F) After 1 year, follow-up US showed that the nodule changed to an ill-defined, taller than wide shaped, and hypoechoic nodule (arrow).

Table 2. Initial and Final Ultrasonography Findings of Benign Thyroid Nodules during the Follow-Up Period

	Baseline US findings			Final US findings	
Internal contents	Solid	119 (58.9)	Changed to	Cystic <25%	6 (3.0)
				Cystic ≥25%	1 (0.5)
	Cystic <25%	67 (33.2)	Changed to	Solid	2 (1.0)
				Cystic ≥25%	3 (1.5)
	Cystic ≤25% but <50%	16 (7.9)	Changed to	Solid	1 (0.5)
				Cystic <25%	2 (1.0)
			No change		187 (92.6)
Margin irregularity	Well-defined smooth	165 (81.7)	Changed to	Well-defined spiculated	2 (1.0)
				Ill-defined	8 (4.0)
	Well-defined spiculated	2 (1.0)	Changed to	Well-defined smooth	1 (0.5)
				Ill-defined	0 (0)
	Ill-defined	35 (17.3)	Changed to	Well-defined smooth	3 (1.5)
				Well-defined spiculated	0 (0)
			No change		188 (93.1)
Calcification pattern	No calcification	169 (83.7)	Changed to	Microcalcification	1 (0.5)
				Macrocalcification	9 (4.5)
	Microcalcification	8 (4.0)	Changed to	No calcification	0 (0)
				Macrocalcification	1 (0.5)
	Macrocalcification	25 (12.4)	Changed to	No calcification	1 (0.5)
				Microcalcification	0 (0)
			No change		190 (94.0)
Echogenicity	Hypoechoic	73 (36.1)	Changed to	Isoechoic	3 (1.5)
	Isoechoic	127 (62.9)	Changed to	Hypoechoic	3 (1.5)
	Hyperechoic	2 (1.0)			
			No change		196 (97.0)
More tall than wide appearance	No	194 (96.0)	Changed to	Yes	2 (1.0)
	Yes	8 (4.0)	Changed to	No	0 (0.0)
			No change		200 (99.0)

Values are expressed as number (%).
US, ultrasonography.

Using univariate analysis, the group with nodule growth by ATA recommendations showed no significant differences with the group without nodule growth, except for age at diagnosis (suggesting that nodule growth was more likely to occur in younger patients than in older patients) (Table 3). Multivariate logistic regression analysis showed that age at diagnosis was an independent variable for nodule growth based on ATA recommendations ($P=0.010$; odds ratio [OR], 0.93; confidence interval [CI], 0.87 to 0.98) as well as based on a 50% increase in nodule volume ($P=0.01$; OR, 0.88; CI, 0.81 to 0.95; detailed data not shown).

Regarding nodules with at least one US component change, univariate analysis demonstrated that the number of FNAs was a significant factor for determining US changes of benign nodules ($P=0.031$). However, number of FNAs did not emerge as an independent parameter in multivariate regression analysis (Table 4). Nodules with cystic component change had more

frequent FNAs performed than nodules without interval change of the cystic component (2.76 ± 1.35 vs. 2.18 ± 1.00, respectively, $P=0.026$; detailed data not shown).

About 3 years after the last US evaluation, final status of thyroid nodules in 125 patients (67.2%) was available without US data. Among them, six patients underwent thyroid surgery with one patient (0.8%) demonstrating malignancy. This nodule showed no interval change in size but revealed US change from well-defined to spiculated margin as well as the emergence of suspicious, new lymph node. The patient underwent thyroidectomy with lymph node dissection. The other five patients (4%) underwent lobectomy due to the following: tumor growth and mass size (>4 cm) ($n=2$), large mass with no size change (>4 cm) ($n=1$), atypical cytology ($n=1$), and repeatedly inadequate cytology ($n=1$). All five patients were confirmed as nodular hyperplasia on pathology.

Table 3. Comparisons of the Risk Factors according to the Nodule Growth and the Risk for Nodule Growth according to the Risk Factors by American Thyroid Association Recommendation

	Nodule without growth (n=183)	Nodule with growth[a] (n=19)	P value	Multivariate analysis OR	CI	P value
Age at diagnosis, yr	48.0±10.2	39.0±13.0	0.000	0.93	0.87-0.98	0.010
Gender, female/male	162/21	16/3	0.580	2.55	0.43-15.04	0.301
TSH	1.45±0.81	1.42±0.93	0.907	0.92	0.47-1.82	0.812
Anti-TPO Ab (+)	10/145 (6.5)	2/14 (12.5)	0.367	1.20	0.13-11.10	0.876
Anti-Tg Ab (+)	21/162 (11.5)	3/16 (15.8)	0.580	1.76	0.34-8.99	0.499
Follow-up duration, mo	21.5±10.6	24.1±10.4	0.318	1.04	0.98-1.10	0.201
No. of FNA per nodule	2.2±1.0	2.0±1.1	0.371	0.64	0.35-1.18	0.155
Initial US findings						
Hypoechogenicity	66/183 (36.1)	7/19 (36.8)	0.947	3.13	0.67-14.72	0.149
Cystic portion	73/183 (42.5)	10/19 (52.6)	0.283	0.25	0.05-1.20	0.083
Margin irregularity	34/183 (18.6)	1/19 (5.3)	0.144	0.25	0.28-2.37	0.231
Calcification	31/183 (16.9)	2/19 (10.5)	0.472	1.30	0.231-7.27	0.770

Values are expressed as mean±SD or number (%).
OR, odds ratio; CI, confidence interval; TSH, thyroid stimulating hormone; Anti-TPO Ab, antithyroid peroxidase antibody; Anti-Tg Ab, antithyroglobulin antibody; FNA, fine needle aspiration; US, ultrasonography.
[a]The nodule group with growth was defined by the American Thyroid Association recommendation.

Table 4. Comparisons of the Risk Factors according to the US Change and the Risk for US Change according to the Risk Factors

	Nodule without US change (n=160)	Nodule with at least one US change (n=42)	P value	Multivariate analysis OR	CI	P value
Age at diagnosis, yr	47.3±11.2	46.6±9.4	0.732	1.01	0.97-1.04	0.781
Gender, female/male	141/19	37/5	0.996	0.87	0.23-3.30	0.836
TSH	1.48±0.84	1.32±0.76	0.277	0.96	0.57-1.61	0.872
Anti-TPO Ab (+)	11/138 (8.0)	1/33 (3.0)	0.465	0.58	0.06-4.89	0.598
Anti-Tg Ab (+)	24/138 (17.4)	3/33 (9.1)	0.240	0.63	0.17-2.36	0.490
Follow-up duration, mo	21.0±10.1	23.7±12.2	0.186	1.00	0.96-1.04	0.996
No. of FNA per nodule	2.1±1.0	2.5±1.2	0.031	1.32	0.92-1.91	0.136
Nodule growth by ATAR	16/160 (10.0)	3/42 (7.1)	0.769			
Nodule growth by Vol50%[a]	15/116 (12.9)	2/28 (7.1)	0.526			
Nodule growth by Vol30%[a]	27/116 (23.3)	5/28 (17.9)	0.621			

Values are expressed as mean±SD or number (%).
US, ultrasonography; OR, odds ratio; CI, confidence interval; TSH, thyroid stimulating hormone; Anti-TPO Ab, antithyroid peroxidase antibody; Anti-Tg Ab, antithyroglobulin antibody; FNA, fine needle aspiration; ATAR, American Thyroid Association recommendation.
[a]Vol50% is the volume change by 50%; [b]Vol30% is the volume change by 30%.

DISCUSSION

We used US to assess for nodule growth and morphological change in 202 benign thyroid nodules with a mean follow-up of 21 months. However, this study did not show any association between US change and nodule growth. The natural history of benign thyroid nodules, particularly with respect to nodule growth, has been evaluated by only a few studies that demonstrated that nodule growth rarely equated to malignancy [2-5]. In addition, a variety of morphological abnormalities have been previously seen on US in benign nodules during follow-up [10,11]. However, the relationship between morphological

change and nodule volume change has rarely been probed. In a study that evaluated US features of benign thyroid nodules, hypoechogenicity was proposed as an independent factor for predicting nodule growth at 15% increases in volume [4]. Another study investigating the effect of FNA on nodule volume showed no statistically significant relationship between the absolute or percent change in thyroid nodule size and US appearance; the details of this study were not described in the paper [12].

In our study, change in the cystic portion of nodules occurred in only about 7% of all nodules, and this change had no significant association with volume change as calculated using various criteria. This result was in disagreement with previous studies that showed nodules with greater cystic component were less likely to grow compared to nodules with more solid component [5,13]. Given that more than 50% of the cystic nodules were excluded for study here, association between volume change and cystic component change might have reduced. Regarding margin change, the most frequent change was from well-defined smooth margin to ill-defined margin (4.2%), demonstrating that even benign-appearing nodules have the potential to develop ill-defined margins. The eight nodules that developed ill-defined margins required at least one additional rebiopsy. However, our analysis showed that change to an ill-defined margin in these eight nodules appeared to not have an association with the cause of rebiopsy.

Macrocalcification, previously found to be more frequent in benign nodules [7,14-17], appeared as a new finding much more often than dotted microcalcification in our subjects with benign nodules (4.2% vs. 0.4%, respectively). In addition, this type of macrocalcification was coarse, dense, nodular, dystrophic in nature, and may occur in both benign and malignant thyroid lesions [18,19]. Therefore, the emergence of macrocalcification on US does not alter the likelihood for malignancy if no prior FNA results are available.

Frequent FNAs might lead to morphological nodule change, especially in cystic nodules [12]. Our data also showed that the number of FNAs had a significant association with changes in US findings, especially changes of the cystic component, but this relationship had no correlation with volume change. Number of FNAs could be considered a minor variable when evaluating US features of thyroid nodules.

Most of the benign nodules in this study showed neither echogenicity changes nor emergence of a taller than wide shape during follow-up. Together, these findings could explain why such US findings are strongly predictive of malignancy in thy-roid nodules [7,15-17]. However, changes of all US features and nodule volume had no association with thyroid function tests including TSH levels. This finding coincides with prior studies that revealed nodule growth was not associated with TSH levels [3-5].

Previous reports have considered more than 50% change in nodule volume as clinically significant, and this cutoff value has been applied to studies concerned with thyroxine suppression therapy [12]. We analyzed our data with this approach, and we added additional cutoff values of 15% and 30% to the criteria for nodule growth. When compared with ATA guidelines for assessing nodule growth, more than a 50% increase in nodule volume had better agreement than a 15% or 30% increase in nodule volume from our data. Therefore, validation of the nodule growth criteria with the ATA recommendations may aid clinicians in simplifying clinical decisions on nodule growth without the need to calculate nodule volume.

A previous study showed that approximately half of benign nodules had an increase in volume of 30% [3], which was double the number of nodules with such growth in our study. This might be due to the longer mean follow-up duration in this prior study (4.9 years vs. 1.9 years) as well as inclusion of increased numbers of large nodules.

When using ATA recommendations and >50% increase in nodule volume as classification criteria, age at diagnosis was the only independent variable for predicting nodule growth. This finding was in contrast to previous studies that adopted 15% and 30%, respectively, as cutoff values [3-5]. The same trend of younger age was observed in an earlier report that showed slow growth of benign thyroid nodules after menopause [20]. Most of our data was from female patients (87.6%) with a small group of premenopausal women of younger age demonstrating significant nodule growth. Therefore, age may have been overemphasized in this study.

There are potential limitations in our study. First, although data were obtained according to standard protocols of US findings and subjects were selected according to strict inclusion criteria, there may have been a selection bias that influenced final results of nodule change. Therefore, it would be challenging to apply our strategy to manage all benign nodules. Second, many of the subjects with longer-term monitoring were excluded, and this may have been due to the referral system of our tertiary hospital as patients with benign results tended to be observed via US by primary care physicians. Therefore, a shorter follow-up period and a larger proportion of unchanged US findings may have been possible for this study population.

Third, several patients had benign results based on only one FNA which, unlike repeated FNA, can have approximately a 5% false negative rate [6,8,9]. Moreover, as nearly all nodules were based on FNA results, we need to consider that some nodules had malignant potential, especially those subjects with significant nodule growth. Finally, our study gave no consideration to newly developed or disappearing nodules, and changes in nodule characteristics might have more clinical impact than the described nodules.

Although a portion of thyroid nodules confirmed as benign showed changes in US features or nodule volume during follow-up, this might be due to the natural course of these nodules. Thus, frequent re-evaluation with US would rarely be needed, especially in elderly patients. Follow-up US would be needed solely for cases with suspicious US findings. In addition, morphological nodule change, as determined by FNA, could be considered when evaluating nodules. However, additional long-term, follow-up investigations are needed to elucidate the significance of changes in US features of benign thyroid nodules.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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