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Evaluation of Follow-up Examinations Using Ultrasonography for Patients With Thyroid Nodules Initially Diagnosed as Benign

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Abstract. *Background/Aim: The aim of this study was to determine the natural history of benign thyroid nodules using ultrasonography. Patients and Methods: The records of 223 patients with benign thyroid nodules treated at the Kochi Medical School from 2010 to 2012 were reviewed retrospectively. Repeated ultrasonography was performed, and the findings were directly compared with previous images. Results: The median change in the size of the nodules was 0.01 cm/year, although the size of six nodules (2.7%) increased more than 0.5 cm/year, and these nodules were removed surgically. Nineteen patients (8.5%) underwent surgery during the follow-up period. Compared to those who did not undergo surgery, the size of the nodules was larger and the rate of change in nodule diameter was higher in those undergoing surgery. The pathological diagnosis based on repeated fine needle aspiration cytology was benign nodules in 16 patients and papillary cancer in three patients. Conclusion: Even if a thyroid nodule is initially diagnosed as benign, it may have malignant potential. Therefore, so as not to miss malignancies, nodules should be carefully re-evaluated to assess their growth or change in size using ultrasonography.*

Thyroid nodules are present in nearly 50% of adults, and their prevalence increases with age (1, 2). The Framingham and Whickham studies, two large population-based studies, reported that the prevalence of palpable thyroid nodules was 4.2% and 3.2%, respectively (3, 4). More than 90% of nodules detected are clinically insignificant benign lesions (5, 6).

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Initial evaluation of thyroid nodules measuring ≥1 cm begins with exclusion of functional autonomy and malignancy. Current guidelines from the American Association of Clinical Endocrinologists, American Thyroid Association (ATA), and National Cancer Institute recommend fine needle aspiration cytology (FNAC) in indicated nodules to rule out malignancy (7). If the FNAC results indicate that the nodule is benign, serial ultrasound (US) follow-up is recommended at 6- to 18-month intervals to reduce the chances of missing a malignancy (7).

Thyroid nodules diagnosed as benign require follow-up because of a low, but not negligible false-negative rate with FNAC (8, 9). Selective repeated FNAC has been suggested in cases of size increment, suspicious imaging features, or clinical suspicion. Malignancy is believed to produce more prominent growth than seen with a benign nodule, although benign nodules can also grow with time (10-12). In addition, nodules that appear benign on US can transform to show features suggestive of malignancy on follow-up US (13). Thus, it is very important to know the course of FNAC-proven benign thyroid nodules, which may help avoid unnecessary repeated FNAC.

Thus far, little is known about the natural history of benign thyroid nodules. In the present study, we used repeated US examination of thyroid nodules to determine the natural history of clinically- or cytologically-benign thyroid nodules over a period of 4 months to 25 years. The aim of the study was to determine the natural history of benign thyroid nodules using US.

Patients and Methods

Patients. The records of all patients with nodular thyroid disease seen in the Kochi Medical School Hospital and US unit between January 2010 and November 2012 were reviewed retrospectively. Patients with thyroid nodules >3 mm were included in the study and were seen regularly or at the first visit. In all, 381 patients were seen, of whom 115 underwent surgery after their first visit. The indications for surgery were clinical or cytological suspicion of

malignancy. After surgery, 96 nodules were found to be malignant and 19 were benign. Of the 266 patients who did not undergo surgery and whose nodules were clinically or cytologically benign, 43 did not return for re-evaluation of their thyroid nodules in Kochi Medical School Hospital, leaving 223 patients in the study.

Assessment of thyroid nodules. Information collected for the 223 patients included sex, age, the size of the nodule at the first US examination, the duration of follow-up, and the size of the nodule at the last US examination. In addition, thyroid-stimulating hormone (TSH) concentrations were available for 159 of the 223 patients. A rapid increase in the size of nodules indicates malignant potential, especially follicular thyroid carcinoma or anaplastic thyroid carcinoma. Therefore, we evaluated changes in nodule diameter (cm) per year. Results of repeat US examinations were directly compared with previous images.

Statistical analysis. The Mann–Whitney *U*-test was used to assess correlations among continuous variables in different groups. The significance of differences in qualitative variables in different groups was assessed using the Pearson's Chi-squared test. $p<0.05$ was considered significant. Statistical analyses were performed using SPSS for Windows version 13.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics. The characteristics of 223 patients (204 female, 19 male) are summarized in Table I. The median age of the 223 patients at their first visit was 62 years, and the median follow-up period was 60 months (range=4-300 months). Sixty-one patients (27.4%) had solitary nodules, whereas 162 (72.6%) had multiple nodules on US, and the median initial TSH concentration was 1.56 μIU/ml. At the first visit, the median diameter of the largest nodule measured by US was 1.9 cm (range=0.3-6.5 cm), and the maximum diameter of the largest thyroid nodule in 210 patients (94.2%) was <4.0 cm. At the last visit, the median diameter of the largest nodule was 2.0 cm (range=0.3-6.8 cm).

Change in nodule size. Evaluating percentage change in the diameter of the largest nodule from the first to the last visit revealed that the size of 76 nodules (34.1%) had increased >15%, the size of 48 nodules (21.5%) had decreased >15%, and the size of 99 nodules (44.4%) had changed <15%. Increases of >30% and >50% during the follow-up period were found in the case of 48 (21.5%) and 29 (13.0%) nodules, respectively. Decreases of >30% and >50% in the diameter of the largest nodule were found in 31 (13.9%) and 19 (8.5%) of patients, respectively (Figure 1). Of the 223 patients with nodules initially diagnosed as benign, 41 had cystic nodules and 182 had non-cystic nodules. The median percentage change in the diameter of the largest cystic nodule was a 12.5% decrease, compared with a median 5.7% increase in the diameter of the largest non-cystic nodule ($p<0.001$). Among the cystic nodules, the median percentage change in the diameter of the largest nodule was significantly higher in the case of the 20 nodules in patients undergoing FNAC than in the case of the 21 nodules in patients who did not undergo FNAC (36.5% *vs*. 5%, respectively; $p=0.003$).

Table I. *Characteristics of patients with benign thyroid nodules.*

No. patients followed-up	223
No. males/females	19/204
Median (range) age (years)	62 (6-89)
Median (range) follow-up period (months)	60 (4-300)
No. single/multiple nodules	61/162
Median (range) initial TSH (μIU/mL)	1.56 (0.01-13.2)
Median size of the largest thyroid nodule (cm)	
At first visit	1.9
At last visit	2.0
No. nodules according to size	
First visit	
<1 cm	27 (12.1)
≥1 to <2 cm	92 (41.3)
≥2 to <3 cm	58 (26.0)
≥3 to <4 cm	33 (14.8)
≥4 cm	13 (5.8)
Last visit	
<1 cm	34 (15.2)
≥1 to <2 cm	78 (34.5)
≥2 to <3 cm	60 (26.9)
≥3 to <4 cm	28 (12.6)
≥4 cm	23 (10.3)

Unless indicated otherwise, data are given as n (%). TSH: Thyroid-stimulating hormone.

The median change in nodule diameter was 0.01 cm/year, although the rate of change of 169 nodules (75.8%) was ±0.2 cm/year. The size of six nodules (2.7%) increased more than 0.5 cm/year, and all six of these patients underwent surgery. Pathological examination of the resected specimens showed adenomatous goiters in three patients and follicular adenomas in the remaining three patients.

Changes in nodule diameter from the first to the last visit in patients with and without FNAC evaluation are shown in Figure 2. Overall, 114 nodules (51.1%) increased in size, 78 nodules (35.0%) decreased in size, and there was no change in size in the case of 31 nodules (13.9%).

Patient characteristics depending on FNAC evaluation. During follow-up, thyroid nodules were evaluated by FNAC in 109 patients (48.9%). Among these patients, FNAC revealed benign nodules in 100 patients (91.7%), with repeat FNAC revealing that two of these nodules were malignant. Of the remaining nine patients, six (5.5%) were found to have malignant tumors (follicular neoplasms), the findings were indeterminate in two patients, and papillary thyroid cancer was suspected in one patient, which was subsequently proven to be malignant by repeat FNAC.

FNAC was not performed in 114 patients (51.8%). The reasons for not performing FNAC were obvious benign

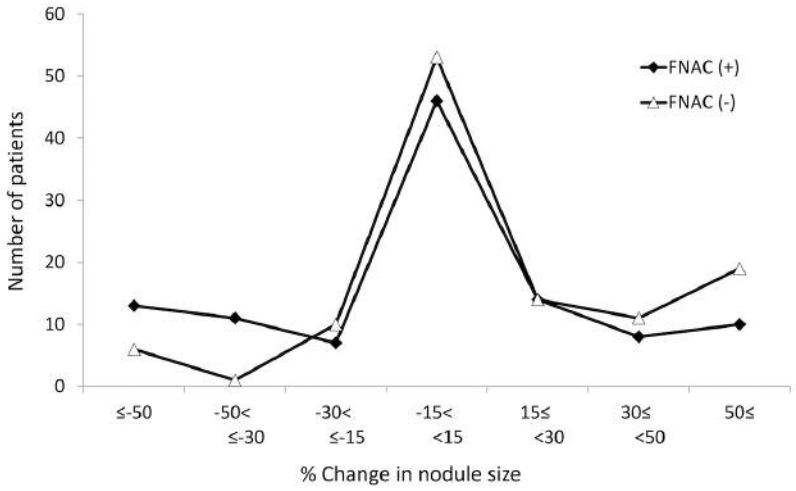

Figure 1. *Distribution of rates of change in nodule size compared to initial nodule size in patients undergoing fine needle aspiration cytology (FNAC) or not. Across both groups, 76 nodules had increased >15%, 48 had decreased >15%, and 99 had changed <15%.*

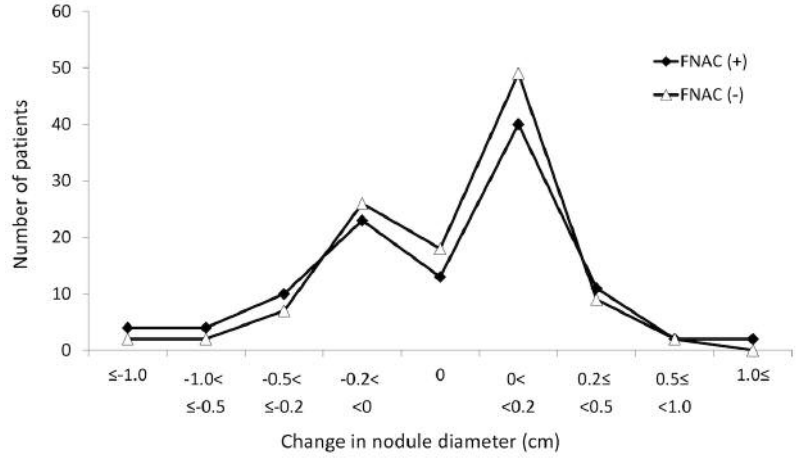

Figure 2. *Distribution of changes in nodule diameter compared to the initial size (diameter) in patients undergoing fine needle aspiration cytology (FNAC) or not. The incidence of increases, decreases, and no change in nodule diameter was 35.0%, 51.1%, and 13.9%, respectively.*

findings for nodules on US, such as a regular shape, well-defined smooth edge or border, and high-level internal echoes (14). The characteristics of patients in the non-FNAC and FNAC groups are summarized in Table II. The median follow-up period was significantly longer in the non-FNAC than in the FNAC group (p=0.004), the median maximal diameter at the first and last visits was lower in the non-FNAC than in the FNAC group (p<0.001 and p=0.003, respectively), and the percentage change in the diameter of the largest nodule was significantly larger in the non-FNAC than in the FNAC group (p=0.040). The number of patients who underwent surgery was smaller in the non-FNAC than in the FNAC group (p=0.024). However, there were no significant differences in sex, median age, and annual change in the diameter of the largest nodule between the two groups (Table II).

Patient characteristics depending on the need for surgery. Nineteen patients had surgery during the follow-up period, and the characteristics of patients in the non-surgery and surgery groups are summarized in Table III. The median follow-up period was significantly longer in the non-surgery than in the surgery group (p<0.001), and the median diameter of the thyroid nodule at the first and last visits was significantly lower in the non-surgery than in the surgery group (p=0.024 and p<0.001, respectively). Similarly, the percentage change in the diameter of the largest nodule and the annual change in the diameter of the largest nodule were significantly lower in

Table II. *Characteristics of patients undergoing fine needle aspiration cytology (FNAC) or not (non-FNAC).*

	Non-FNAC (n=114)	FNAC (n=109)	*p*-Value
No. females (%)	103 (90.4)	101 (92.7)	0.539
Median (range) age (years)	60 (6-83)	63 (26-89)	0.355
Median (range) follow-up period (months)	75.5 (4-300)	54.0 (6-260)	0.004
Median (range) maximum diameter of thyroid nodule (cm)			
At first visit	1.6 (0.3-6.5)	2.3 (0.7-6.4)	<0.001
At last visit	1.7 (0.3-6.4)	2.2 (0.3-6.8)	0.003
% Change in diameter of largest nodule	+7.3	±0	0.04
Rate of change in diameter of largest nodule (cm/year)	+0.01	±0	0.411
No. patients undergoing surgery (%)	5 (4.4)	14 (12.8)	0.024

Table III. *Characteristics of patients undergoing surgery or not.*

	No surgery (n=204)	Surgery (n=19)	*p*-Value
No. females (%)	187 (91.7)	17 (89.5)	0.747
Median (range) age (years)	62 (24-89)	57 (6-76)	0.122
Median (range) follow-up period (months)	65.5 (4-300)	22 (5-102)	<0.001
Median (range) maximum diameter of thyroid nodule (cm)			
At first visit	1.8 (0.3-6.4)	2.8 (0.4-6.5)	0.024
At last visit	1.9 (0.3-6.8)	3.7 (1.0-6.5)	<0.001
% Change in diameter of largest nodule	±0	+25	0.001
Rate of change in diameter of largest nodule (cm/year)	±0	+0.24	<0.001
No. patients undergoing FNAC (%)	109 (46.6)	14 (73.7)	0.024

FNAC: Fine needle aspiration cytology.

the non-surgery than in the surgery group (p=0.001 and p<0.001, respectively). The number of patients undergoing FNAC evaluation was significantly smaller in the non-surgery than in the surgery group (p=0.024). Of the 19 patients who underwent surgery, the results of pathological examination revealed goiter in 10, follicular adenoma in five, papillary cancer in three, and lymphocytic thyroiditis in one.

Discussion

In the present study, 8.5% of patients who were initially diagnosed with benign thyroid lesions needed surgery during the follow-up period. In these patients, nodule size was larger on US examination, and the rate of change in nodule size was higher than in patients who did not undergo surgery. To the best of our knowledge, this is the first study to assess the natural course of a large number of thyroid nodules initially diagnosed as benign.

US and FNAC are helpful in the differential diagnosis of malignant thyroid tumor and benign nodules, such as follicular adenoma, adenomatous goiter, functioning thyroid nodule, and cyst (15, 16). US is a more useful modality for the diagnosis of malignancy of thyroid nodules, with a sensitivity of 43.8%-93.8% and a specificity of 66%-93.8% (17-22). FNAC is considered to be the gold standard for evaluating thyroid nodules, and is an office procedure that can be performed with no anesthetic or under local anesthesia using 23- to 27-gauge needles to obtain tissue samples for cytological examination. FNAC is also a safe, accurate, and cost-effective way to evaluate thyroid nodules (23-31). When a nodule is diagnosed as benign by FNAC, further immediate diagnostic examinations or treatment are not routinely needed. Ashcraft and Van Herle reported that the accuracy of FNAC diagnosis was >90% (32). FNAC can be performed using palpation or with US guidance. US-guided FNAC has lower non-diagnostic and false-negative cytology rates than palpation-guided FNAC (25, 33).

In the present study, all patients underwent an US examination of the thyroid at their first visit to the hospital, and nodules that were suspected of malignancy were evaluated by FNAC but were diagnosed as benign thyroid nodules pathologically before the start of follow-up. Several studies reported that 20.6-32% of benign nodules increase in size in the long term (11, 34). In the present study, the maximum diameter of 76 thyroid nodules (34.1%) increased more than 15%, and this rate is in agreement with previous reports.

Erdogan *et al.* reported that only the hypoechogenic sonographic pattern remained a significant predictor of thyroid

nodule growth in the final multivariable model, whereas patient age, sex, and initial serum TSH concentrations were not significant factors (11). These results suggest that the growth of benign thyroid nodules may be predicted only on the basis of their echogenic type. Among the different types of thyroid nodules, cystic nodules have been found to have lower growth potential than solid nodules (12). One possible explanation for this is the change in thyroid nodule volume on FNAC as a result of the aspiration of cystic contents (11). In the present study, the size of cystic nodules was significantly decreased compared with that of non-cystic nodules during the follow-up period. In fact, the size of four nodules decreased by more than 50% immediately after FNAC. Malignancy is believed to produce more prominent growth than a benign nodule, although benign nodules can also grow with time (10-13). If malignancy is suspected, repeated FNAC or surgery is advised. In the ATA guidelines, the decision to repeat FNAC or to continue with repeat US observations is based on >20% growth in at least two nodule dimensions or a >50% increase in nodule volume or the appearance of a new suspicious US pattern (35). Other guidelines suggest using a >50% increase in maximal diameter or a >15% increase in the calculated volume (34-38). In the present study, patients in whom the diameter of nodules increased >0.5 cm/year underwent surgery, resulting in a pathological diagnosis of follicular adenoma in three cases. Patients in whom there is a change in nodule diameter >0.5 cm/year may be candidates for surgery. To the best of our knowledge, the present study is the first to demonstrate an indication for surgery based only on the change in nodule diameter, calculated in centimeters per year.

In this study, the median size of nodules was higher in the group of patients evaluated by FNAC than in those who did not undergo FNAC. FNAC was not performed when nodule findings, including US examinations (*e.g.* small size), indicated that the nodule was benign. Furthermore, the percentage change in the diameter of the largest nodule was greater in the non-FNAC than FNAC group. However, the annual change in the diameter of the largest nodule (*i.e.* cm/year) during the follow-up period was not associated with having undergone FNAC or not. In addition, the number of patients requiring surgery was higher in the FNAC than in the non-FNAC group. Therefore, the size of nodules tended to increase in the non-FNAC group, whereas undergoing FNAC was a factor associated with the need for surgery. However, whether a patient is a candidate for surgery depends not only on the size of the nodule, but also on US findings and symptoms. Ajmal *et al*. reported that the reasons for surgery in cases of benign thyroid nodule included the development of symptoms (78.2%), a change in the repeated FNAC (4.3%), and patient preference (18.2%) (39). It is possible that factors other than nodule size may be associated with undergoing surgery.

If a thyroid nodule that has been diagnosed as benign by FNAC grows large or transmutes its behavior, repeated FNAC is recommended. In the present study, three patients underwent repeated FNAC and were found to have thyroid papillary carcinoma. In these patients, the reasons for repeated FNAC were the growth of the nodules and US findings of nodule features.

The present study has some limitations. First, there is a possibility of selection and observer bias in decisions regarding surgical indications because of the retrospective and non-randomized nature of this study. Although regular follow-up was recommended to all patients, patients' perspectives regarding their own thyroid nodules may have affected their compliance with scheduled visits. If a patient perceived that the size of their nodule had decreased or the nodule had disappeared, then that patient may have been less likely to attend follow-up visits than patients who perceived that the size of the nodules had increased. Second, not all nodules were evaluated by FNAC; however, this seems to be similar to daily practice. Finally, the time when thyroid growth occurred is not known precisely, and the study may have overestimated the time for nodule growth. Although this may affect the degree of thyroid growth, it seems unlikely that it would affect the overall conclusion.

In conclusion, we retrospectively reviewed the natural course of benign thyroid nodules. Most thyroid nodules were <4 cm in diameter and the size of more than 60% of nodules decreased or hardly changed (being within ±0.2 cm/year) during the follow-up period. Most of the benign thyroid nodules remained benign over a prolonged period. However, even in the case of FNAC-proven benign nodules, a few grew large or transmuted their behavior, with some being diagnosed as malignant on repeat FNAC. Therefore, clinicians should carefully re-evaluate patients with thyroid nodules, even if they are initially diagnosed as benign, to determine the need for surgery on the basis of US findings and repeat FNAC.

Conflicts of Interest

The Authors declare that they have no conflict of interest regarding this study.

Authors' Contributions

Oki and Namikawa designed the study. Oki, Sugimoto, Ogawa, Dabanaka and Namikawa acquired, analyzed and interpreted the data within the study. Namikawa and Hanazaki finalized the manuscript and submitted the paper for publication. All authors edited the manuscript for intellectual content. All Authors read and approved the final manuscript.

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