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Fate of Untreated Benign Thyroid Nodules: Results of Long-Term Follow-up

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Abstract: The fate of benign thyroid nodules has been unknown because there has been no study in this regard. We re-examined 134 patients with thyroid nodules who had had benign aspiration biopsy cytology 9 to 11 years ago. The thyroid gland was palpated by the same two thyroidologists throughout the study. Ultrasonography, fine-needle aspiration biopsy (FNAB), and ultrasound-guided FNAB were employed to examine the nature of nodules of 9 to 11 years' duration. Patients (n = 61) who had nodules difficult to palpate (small nodules), multiple nodules, or cystic nodules with papillomatous proliferation underwent ultrasound-guided FNAB; patients (n = 55) having a distinctly palpable single nodule underwent usual FNAB. None of the patients received any medical or surgical treatment. There were 86 single nodules, 14 multiple nodules, and 34 cystic nodules on the first examination. These benign nodules were reexamined for changes in size and cytology 9 to 11 years later. The most striking finding was a decrease in size or disappearance of the nodule in 42% to 79% of benign nodules. About 92% of nodules remained benign without changing cytologic classification. Only one case (0.9%) previously regarded as benign turned out to be malignant; this nodule grew in size compared with the previous examination. Among single and multiple nodules, 21% to 23% of the nodules increased in size; however, most patients with enlarged nodules (86%) showed the same class 2 cytology as before. Our present study indicates that biopsy-proved benign thyroid nodules remain benign over a prolonged period. Thus no medical or surgical treatment is required so long as the nodules do not grow.

Thyroid nodules, the most common thyroid disorder, occur with advancing age [1]. Horlocker et al. reported that more than 50% of patients harbored nodules by the age of 50 years [2]. Knowing the natural history of thyroid nodules is useful for predicting the outcome as well as the choice of appropriate therapy. It has been unknown as to how benign thyroid nodules change over a prolonged period. We previously reported the outcome of long-standing solitary thyroid nodules by clinical survey and reexamination of patients with thyroid nodules 10 to 30 years later [3]. In our previous study, the most common outcome of palpable single nodules was their disappearance. Thyroid cancer was found in 26.3% of enlarging nodules. However, our previous study did not yield cytologic data of the initial nodules because FNAB technique was not available at that time. Thus the exact nature of the nodules on the initial examination was unclear. In the present study we focused on biopsy-proved benign thyroid nodules and reexamined the fate of these benign thyroid nodules. Grant et al. have reported the long-term follow-up (6.1 years) of FNAB cytology in 641 patients with thyroid nodules by reviewing patients' records, contact by telephone or correspondence, or referring physicians' letters [4]. In our present study, follow-up was done by the same two thyroidologists who had examined the patients previously. FNAB was repeated in our institution, and ultrasound-guided FNAB was also used for patients whose nodules were difficult to evaluate by the conventional FNAB. Thus the follow-up study in our patients should be accurate for analyzing the outcome of nodules. We report herein how benign thyroid nodules change over a 10-year period.

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Materials and Methods

Selection of Patients

Figure 1 shows how patients were selected for this study. During the period from 1981 to 1983 at Kuma Hospital, Kobe, Japan, 1076 patients were found to have benign aspiration cytology of their thyroid nodules. Among the 1076 patients, 544 underwent surgery because of clinical suspicion of malignancy or other reasons; the rest of the 532 patients were observed without medical or surgical treatment. Our present study was focused on the latter group of 532 patients. All 532 patients were asked to return for reevaluation of thyroid nodules in our clinic, and 134 patients did so. The average age of the 134 patients during the first visit was 44 ± 13.5 (SD) years (128 women, 6 men).

Palpation of thyroid nodules was done by the same two thyroidologists (K.K. and F.M.) who had also seen these patients previously. The size of thyroid nodules by palpation was recorded and the change in size compared.

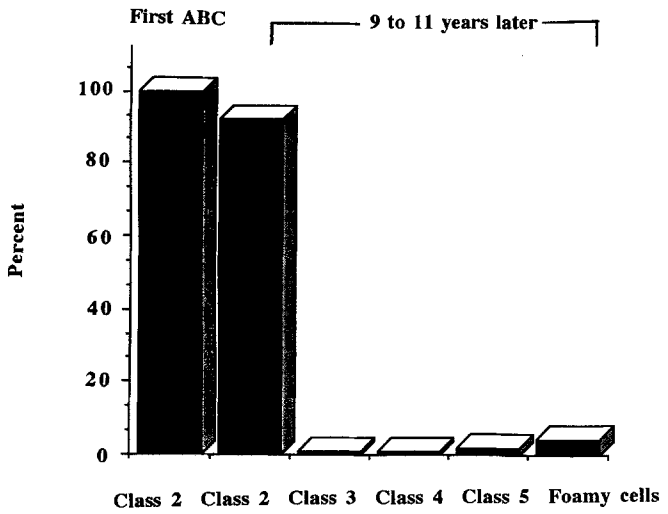

Fig. 1. Patients for this study.

Ultrasound Study

Thyroid ultrasonography was performed using a real-time linear scanner with a 7.5 MHz transducer housed in a waterbath (Aloka USI-82c, ASU-46, Tokyo, Japan).

Fine-Needle Aspiration Biopsy

The FNAB of thyroid nodules was performed using a 22- or 23-gauge needle for all patients on the initial visit. Palpation of thyroid nodules was done by two thyroidologists (K.K. and F.M.). The size of the thyroid nodules by palpation was recorded. On re-examination, patients who had distinctly palpable single nodules underwent usual FNAB. Patients who had small nodules, multiple nodules, or cystic nodules associated with papillomatous proliferation underwent ultrasound-guided FNAB. Cytologic examination was done by an expert in this field (A.M.) and classified into the following categories: class 1 and 2, benign nodules; class 3, the presence of atypical follicular cells; class 4, suspicion of malignancy; class 5, malignancy. Foamy cells are found in cysts, benign nodules, or cysts associated with papillary carcinoma.

Thyroid Surgery

After re-evaluation of benign thyroid nodules, 11 patients underwent surgery because of clinical suspicion of malignancy or cytologic malignancy. Surgery included lobectomy or near-total thyroidectomy.

Results

Initial Examination of Benign Thyroid Nodules

All thyroid nodules studied here were classified as class 2 at the initial examination. The content of these nodules are shown in Table 1. There were 86 single nodules, 14 multiple nodules, and 34 cystic nodules.

Table 1. Content of class 2 thyroid nodules and changes in size 9 to 11 years later.

Content of class 2 nodules on initial examination	Content 9–11 years later			
	No change	Smaller	Disappeared	Enlarged
Single nodule (n = 86)	29 (33.7%)	11 (12.8%)	26 (30.2%)	20 (23.3%)
Multiple nodules (n = 14)	5 (35.7%)	4 (28.6%)	2 (14.3%)	3 (21.4%)
Cystic nodule (n = 34)	7 (20.6%)	10 (29.4%)	17 (50.0%)	0 (0%)

The content of nodules on the initial examination was determined by an ultrasound study. The change in nodular sizes was determined by palpation and ultrasound findings.

Table 2. Aspiration biopsy cytology from enlarged thyroid nodules.

Content of enlarged thyroid nodules	No.	Class 2	Class 3	Class 4	Class 5	Foamy cells
Single nodules	19	16	1	1	0	1
Multiple nodules	3	3	0	0	0	0
Cystic nodules	0					

Changes in Nodular Size 9 to 11 Years Later

The most common outcome of these nodules was a decrease in size or disappearance. This change is most striking among cystic nodules, as nearly 80% of cystic nodules decreased in size or disappeared. The same trend was seen even with single or multiple nodules; more than 40% of these nodules decreased in size or disappeared when they were examined 9 to 11 years later. It should be noted that 21% to 23% of solid nodules were enlarged. When these enlarged nodules (n = 22) were examined by FNAB, 19 showed class 2 cytology, one was class 4, and the rest were either class 3 or foamy cells (Table 2). Figure 2 shows changes in aspiration biopsy cytology 9 to 11 years later. Most patients (92%) maintained the same class 2 cytology. There were five patients with foamy cells, two patients with class 5, one patient with class 3, and one patient with class 4.

Surgical Cases and Thyroid Cancer

Eight patients with clinical suspicion of malignancy, two patients with class 5 cytology, and one patient with class 4 cytology underwent surgical resection. Table 3 presents surgical cases and histologic results. A patient with class 4 cytology was found to have follicular carcinoma in the nodule that had been present for a long time. Two patients with class 5 cytology had two nodules in the thyroid gland: a benign nodule and a malignant one. Figure 3 shows the thyroid gland in one of the two patients with class 5 cytology. One nodule that had a class 2 cytology on the first examination was a benign adenomatous nodule; the other nodule showing class 5 cytology was an incidental finding by ultrasound-guided FNAB. The location of this malignant nodule was different from that of the benign nodule. Histologic examination of the class 5 nodule revealed papillary carcinoma. The rest of the patients who underwent surgical resection showed benign histology.

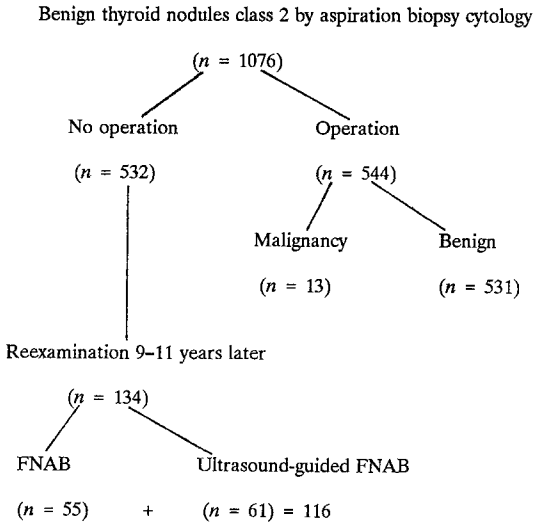

Fig. 2. Changes in aspiration biopsy cytology from class 2 to other classes 9 to 11 years later.

Table 3. Surgical cases and histologic diagnosis.

Last aspiration biopsy cytology	No. undergoing surgery	Histologic diagnosis
Class 2 (n = 107)	6	Follicular adenoma (n = 4) Adenomatous nodules (n = 1) Adenomatous goiter (n = 1)
Class 3 (n = 1)	1	Follicular adenoma
Class 4 (n = 1)	1	Follicular carcinoma[a]
Class 5 (n = 2)	2	Papillary carcinoma[b] + adenomatous nodule (n = 2)
Foamy cells (n = 5)	1	Follicular adenoma

[a]This carcinoma was detected from the same original nodule.
[b]These two carcinomas were discovered in nodules different from the original ones by ultrasound-guided FNAB; adenomatous nodules were the original nodules. Surgery was done for the rest of cases because of clinical suspicion of malignancy.

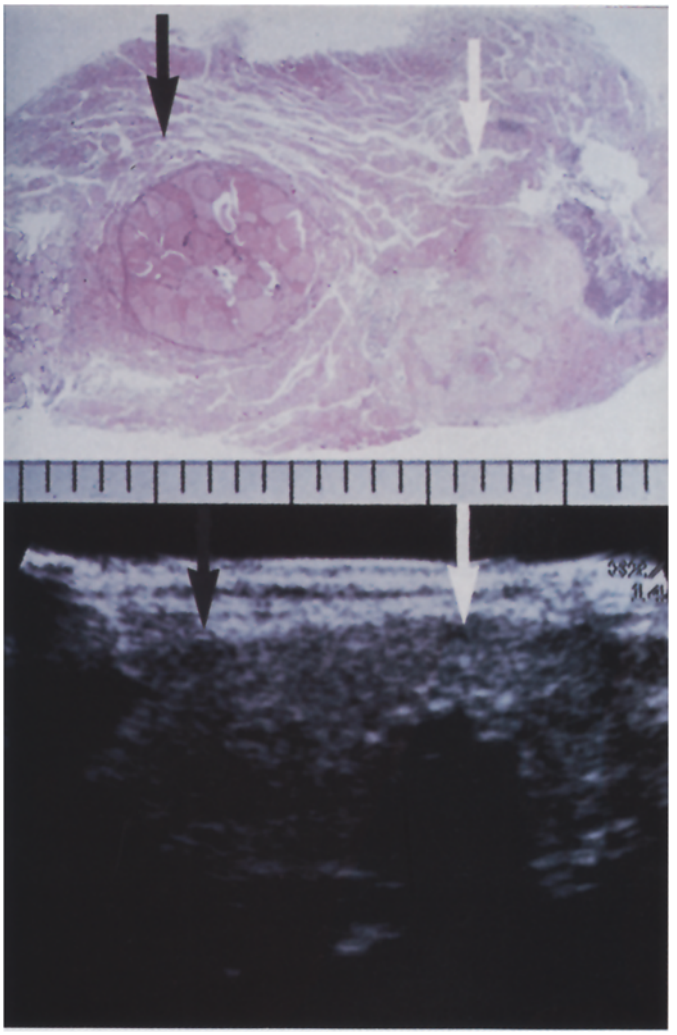

Fig. 3. Case associated with a benign (adenomatous) nodule and papillary carcinoma. Black arrow: benign nodules present for a long time. White arrow: unexpected nodule that turned out to be papillary carcinoma by ultrasound-guided FNAB. The lower picture corresponds to the ultrasound finding of these nodules.

Discussion

The purpose of this study was to examine possible changes in biopsy-proved benign thyroid nodules over a prolonged period. Grant et al. reported 6.1 years follow-up of benign thyroid nodules [4]. Their follow-up was focused on the false-negative results of FNAB for malignancy, and only 0.7% of patients who had benign cytology by FNAB were found to have thyroid cancer later. Thus their study suggests that most patients with benign nodules do not develop thyroid cancer. However, the exact changes in benign thyroid nodules for 10 years or longer have not been described. We reported the outcome of long-standing solitary thyroid nodules by observing clinically benign nodules for 10 to 30 years [2]. Nearly 36% of the solitary nodules disappeared in our previous observation. However, the incidence of thyroid cancer in growing solitary nodules was 26.3% [3].

Unfortunately, cytologic findings of the initial solitary nodules were not available in our previous study because the FNAB technique was not established. In the present study, we focused only on biopsy-proved benign thyroid nodules for reexamination. As shown in Figure 1, we selected patients with benign thyroid nodules who were not candidates for surgery. Unfortunately, only 134 of the 532 patients (25%) presented for reexamination. Evaluation of nodules was done by physical examination, ultrasonography of the thyroid gland, FNAB, and ultrasound-guided FNAB. Clinical assessment of thyroid nodules is generally inaccurate [5]. To minimize the error, the same two clinicians examined all patients. Ultrasound-guided FNAB was used for nodules difficult to palpate, multiple nodules, and cystic nodules associated with papillomatous proliferation. In our experience, ultrasound-guided FNAB was successful in sampling any nodules > 2 mm. In this sample of 25% of 532 patients with benign cytology reported 10 years previously, our results indicate that more than 99% of benign nodules remained benign. The incidence of thyroid cancer in nodules previously diagnosed as benign was less than 1%. The question can be raised whether this patient had follicular carcinoma from the

beginning or malignant transformation occurred from a benign nodule. In the present series, two other patients had thyroid cancer. However, these two cancers were found incidentally in different nodules and not in the original nodules (Fig. 3). The other striking finding was that most of the benign nodules decreased in size or disappeared, regardless of their content. This finding was in agreement with our previous observation [3]. An increase in size was observed in 21% to 23% of the nodules diagnosed as benign. In this group malignancy was found in 4.5%, which is far less common than we previously reported for solitary nodules [3].

In summary, most biopsy-proved benign thyroid nodules remain benign over a prolonged period. Increase in size on follow-up must be carefully re-evaluated to assess the need for surgery.

Résumé

L'évolution des patients ayant été opérés d'un nodule bénin de la thyroïde n'est pas connu car il n'y a pas d'étude sur ce sujet. Nous avons réexaminé 134 patients porteurs de nodule thyroïdien ayant eu une ponction diagnostique avec cytologie 9 à 11 ans auparavant. La thyroïde était palpée par les mêmes cliniciens durant la totalité de l'étude. Pour tous les nodules ayant persisté entre 9 et 11 ans, on a pratiqué un examen echographique et une ponction à l'aiguille fine avec cytologie. Ceux qui avaient des nodules kystiques ou difficiles à repérer par la palpation (petite taille) ou encore de nodules multiples ont eu une ponction échoguidée (N = 55) alors que les autres patients ont eu une ponction simple. Aucun de ces patients avait eu un traitement médical ou chirurgical. Il y avait 86 nodules simples, 14 nodules multiples et 34 nodules kystiques. De 9 à 11 ans après, 42% à 79% des nodules bénins avaient soit disparu soit diminué de taille. Environ 92% des nodules sont restés bénins, sans changer de classification histologique. Un seul des nodules (0.9%), toujours considéré comme nodule bénin, était en réalité malin. Ce nodule avait augmenté de taille dans l'intervalle. Parmi les nodules simples ou multiples, 21 à 23% des nodules avaient augmenté de taille. La plupart de ces patients (86%) avaient la même cytologie qu'auparavant (classe 2). Les résultats de notre étude indiquent que les nodules bénins le restent pendant de longues années. Aucun traitement médical ou chirurgical n'est nécessaire à condition que les nodules n'augmentent pas de taille.

Resumen

La evolución final de los nódulos tiroideos benignos es desconocido, por cuanto realmente no existen estudios pertinentes. Hemos re-examinado 134 pacientes con nódulos tiroideos que habían sido sometidos a aspiración -biopsia-citología 9 a 11 años antes. La glándula tiroides fue examinada por palpación a cargo de los mismos tiroidólogos en el curso del estudio.

El ultrasonido, la aspiración con aguja fina (AAF) y la aspiración con aguja fina guiada por ultrasonido fueron los métodos empleados para examinar la naturaleza de los nódulos de 9 a 11 años de duración. Los pacients (n = 61) que poseían nódulos difíciles de palpar (nódulos pequeños), nódulos múltiples o nódulos quísticos con proliferación palilomatosa fueron sometidos a AAF guiada por ultrasonido; los pacientes (n = 55) que poseían nódulos únicos claramente palpables fueron sometidos a AAF simple.

Ninguno de los pacientes recibió tratamiento médico o quirúrgico alguno. En el primer examen se hallaron 86 nódulos únicos, 14 nódulos múltiples y 34 nódulos quísticos, y éstos nódulos benignos fueron re-examinados para determinar cambio en su tamaño 9 a 11 años más tarde. El hallazgo más notorio fue una disminución del tamaño o la desaparición del nódulo en 42% a 79% de los casos.

Alrededor de 92% de los nódulos se mantuvieron con características benignas, sin cambio en la clasificación histológica. Sólo un caso (0.9%), previamente considerado como benigno, resultó ser maligno; este nódulo aumentó en tamaño en comparación al examen previo. Entre los nódulos únicos y múltiples, 21% a 23% aumentaron de tamaño; sin embargo, la mayoría de los pacientes con nódulos acrecentados en su tamaño (86%) exhibieron la misma citología clase 2 que antes.

El presente estudio indica que el nódulo que prueba ser benigno por biopsia sigue siendo benigno en el curso de un prolongado período de tiempo. Por consiguiente, no se requiere tratamiento médico o quirúrgico mientras el nódulo no aumente de tamaño.

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