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ORIGINAL ARTICLE

Follow-up ultrasound may be enough for thyroid nodules from 5 mm to 1 cm in size

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Abstract We investigated whether follow-up ultrasound (US) is enough for thyroid nodules 5–10 mm, and whether 3 years of interval between the initial US and next US is appropriate. This retrospective study was approved by the Institutional Review Board, and the need to obtain informed consent was waived. The study included 447 thyroid nodules 5–10 mm from 378 patients who underwent initial thyroid US, and underwent 3 years or more of follow-up US. The presence and characteristics of malignancy detected on follow-up were reviewed. Maximal diameters of each nodule at the initial and last US were measured. Univariate and multivariate analysis were used to assess association with nodule growth 3 mm or larger. Seven malignancies (1.6 %, 7 of 447) were detected on a mean 70.6 ± 20.3 months (range 36–104 months). Only one had growth 3 mm or larger, and all malignancies did not have extensive extrathyroidal extension, lateral lymph nodes, or distant metastasis. 6.0 % (27 of 447) of nodules had growth 3 mm or larger. Nodules in older patients were less likely to grow, and benign-looking nodules were more likely to grow. Longer follow-up time 6 years or more was not associated with growth, and no cancers were detected during the long follow-up time. Immediate US-FNA for thyroid nodules 5–10 mm are discouraged, unless suspicious metastatic lymph nodes are present. Also, a follow-up US 3 years after the initial US may be enough for these nodules.

Keywords Ultrasound · Thyroid nodules 5–10 mm · Fine needle aspiration · Nodule growth

Introduction

US (ultrasound) exams demonstrate that up to 67 % of adults have thyroid nodules, and the vast majority of these are less than 1 cm [1, 2]. Most guidelines have recommended US-guided fine-needle aspiration (FNA) for thyroid nodules 1 cm or larger in size [1, 3, 4]. In comparison, subcentimeter nodules have not been generally indicated for FNA, except in cases with associated suspicious cervical lymph nodes or high-risk clinical factors (e.g., a history of childhood head and neck irradiation, a history of thyroid cancer in one or more first-degree relatives, or a focal FDG avidity on F18-fluorodeoxyglucose positron emission tomography (FDG-PET) scan) [1, 3, 4], because papillary thyroid microcarcinomas (PTMCs) show excellent prognosis even when extended disease such as lymph node or distant metastasis is present at the first manifestation [5], and PTMCs progress in only a few cases on observation [6–9]. In the most recent observational trial for PTMC, the rate of size enlargement 3 mm or larger was 8.0 %, and the rate of novel appearance of lymph node metastasis was 3.8 % on a 10-year follow-up [7].

In Korea, nodules 5–10 mm have been indicated for FNAs if they have suspicious US features [10]. In the 2014 American Thyroid Association (ATA) guidelines currently under final review, follow-up US examinations instead of immediate FNA are recommended for nodules 5–10 mm with different US intervals of 6–24 months according to US

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features as follows: 6–12 months follow-up US for nodules with high suspicion US patterns, 12–24 months follow-up US for nodules with low-to-intermediate suspicious US patterns, and ≥24 months follow-up US for very low suspicion US patterns and pure cysts. These different strategies for nodules 5–10 mm originate from the lack of published studies about the natural history of nodules 5–10 mm.

Therefore, the aim of this study was to determine whether a follow-up US instead of immediate FNA is sufficient, and whether 3 years of interval between the initial and next US is appropriate for thyroid nodules 5–10 mm in size, by evaluating follow-up results in terms of nodule growth and disease progression in thyroid nodules 5–10 mm with 3 years or more of follow-up US examinations.

Materials and methods

This retrospective study was approved by our Institutional Review Board, and informed consent was waived. Written informed consent for US-FNA was signed and obtained from all patients prior to procedures.

Study population

From January to December 2006, 7094 consecutive patients underwent initial thyroid US at our institution. Of these patients, those with the following criteria were included: (a) patients who were 19 years old or older, (b) patients that did not undergo a prior thyroidectomy, (c) patients with a follow-up US 3 years or more after the initial US, and (d) patients with at least 1 thyroid nodule 5–10 mm in size. Patients that did not meet the inclusion criteria were excluded and the following are the reasons for these exclusions ($n = 6716$): (a) patients younger than 19 years old ($n = 320$), (b) patients that did undergo a prior thyroidectomy ($n = 358$), (c) patients who did not have a minimum 3 years of follow-up US ($n = 5{,}213$, of these patients, 11 patients underwent thyroidectomy due to thyroid cancer diagnosed at initial US and US-FNA), and (d) patients without thyroid nodules 5–10 mm in size ($n = 825$; 66 patients with normal findings, 165 patients with diffuse thyroid disease, 26 patients with only pure cysts, and 568 patients with nodules <5 mm or >1 cm in size). Finally, a total of 447 nodules of 5–10 mm from 378 patients (overall mean age, 51.4 years; range, 19–76 years; 338 women [mean age 51.2 years; range 19–76 years] and 40 men [mean age 53.3 years; range 19–69 years]) were included in this study. Among them, 320 patients had 1 nodule of 5–10 mm, and 58 patients had multiple nodules of 5–10 mm (2 nodules in 50, 3 nodules in 7, and 6 nodules in one patient).

Thyroid US and US-guided FNA

Thyroid US was performed by 1 of 18 radiologists (12 residents, 2 fellows with 1–2 years of experience, and 4 faculties with 4–12 years of experience in thyroid imaging), using a 5–12 MHz linear array transducer (iU22, Philips Medical Systems, Bothell, WA). In our institution, all US examinations performed by residents and fellows were supervised by faculties. Lymph node status was routinely surveyed in all patients who undergo thyroid US. Lymph nodes with at least one suspicious US feature (focal or diffuse hyperechogenicity, presence of internal calcification, cystic change, round shape, or chaotic vascularity on Doppler US) were regarded as pathologic lymph nodes, and were indicated for FNA with washout for thyroglobulin measurement [11].

During the study period, FNA was performed on nodules 5–10 mm, if recommended so by a clinician. FNA was performed using a 23-gage needle and a 2-mL disposable plastic syringe with a freehand technique. Cytology reports at our institution were classified into the following 5 categories during this period [12, 13]: (1) inadequate, (2) benign, (3) indeterminate, (4) suspicious for papillary carcinoma, and (5) malignancy. Initial FNAs were performed for 147 thyroid nodules as follows at the time of initial presentation; for nodules with suspicious US features according to published criteria (marked hypoechogenicity, irregular or microlobulated margin, microcalcification, and taller-than-wide shape) ($n = 26$) [14], for nodules at the clinician's or patient's request despite the nodules being without suspicious US features ($n = 120$), and for a nodule with FDG-uptake on PET-CT ($n = 1$). Among 147 thyroid nodules with FNAs, 125 had benign results, and 22 had non-diagnostic results on FNA. Follow-up FNAs were performed during follow-up for nodules with suspicious US features, for those with growth, for those at the request of the clinician or the patient despite the nodules being without suspicious US features or growth, or for those with non-diagnostic or discordant results on initial FNA. Surgery was performed on nodules with malignant or suspicious FNA results, on those associated with surgery of other nodules with malignant or suspicious FNA results, or on those with nodule growth. In our institution, prophylactic central lymph node dissection was routinely performed in patients with total thyroidectomy. Lateral compartment lymph node dissection was performed only when lymph node metastasis was diagnosed on preoperative US-FNA or on an intraoperative frozen section.

Data and statistical analysis

Electronic medical records were reviewed to obtain clinical, radiological, and pathologic data. Clinical and

radiological data included age, gender, the number of follow-up USs, the number of FNAs performed, the reason for the initial and repeat FNAs, occurrence and the reason for surgery, and the presence of extrathyroidal extension, lymph node, or distant metastasis at the time of surgery in patients with thyroid cancers. Pathologic data included the initial and repeat FNA cytology results, and surgical pathology if a patient underwent surgery. Extrathyroidal extension is defined as tumor penetration through the thyroid capsule into the adjacent tissues, and it is subdivided into minimal, which indicates invasion into the immediate perithyroidal soft tissues or sternothyroid muscle, and extensive, which indicates invasion into the subcutaneous soft tissue, larynx, trachea, esophagus, or recurrent laryngeal nerve [1].

Two radiologists (S. Y. K. and J. Y. K. with 1 and 15 years of experience in thyroid imaging) retrospectively reviewed static US images of each nodule in consensus at a picture archiving and communication system (Centricity Radiology RA1000; GE Healthcare, Milwaukee, Wis). At initial US exams, multiplicity (whether a patient had one or more thyroid nodule), internal composition (completely solid or mixed cystic and solid), and final US assessment (whether a nodule is probable benign or suspicious malignant according to published criteria [14]) of each nodule were retrospectively reviewed and recorded. The maximal diameter of each nodule at the initial and the last US exams was measured, and the change in nodule size between the initial and the last US exams was assessed. There has been no consensus on the definition of clinically important thyroid nodule growth [1, 4]. In this study, nodule growth was defined as an increase of 3 mm or more in maximal diameter between the initial and the last US exam [6]. Follow-up time was defined as the interval time between the initial and the last US exam for nodules without surgery, and as the interval time between the initial US and the last US before surgery for nodules which underwent surgery. The generalized estimating equations (GEE) method, which fits parameters to a generalized linear model and focuses on population level average effects, was used in all statistical analyses to consider the correlation structure in data where some patients had more than one thyroid nodule [15]. Univariate and multi-variate analysis 1 (which considers all variables) and 2 (which considers variables with statistical significance of $P < 0.1$ on univariate analysis) were performed to predict nodule growth. Differences in demographic and US characteristics were compared between benign and malignant thyroid nodules that underwent surgery, and between nodules with short-term (3–6 years) and long-term (≥6 years) follow-up US exams. All analyses were performed with SAS, version 9.2 (SAS Institute, Cary, NC). A $P < 0.05$ was considered to indicate a statistically significant difference.

Results

The mean ± standard deviation (SD) follow-up times for all nodules, nodules without surgery, and nodules with surgery were 70.6 ± 20.3 months (range 36–104 months), 71.0 ± 20.4 months (range 36–104 months), and 62.9 ± 16.7 months (range 42–95 months), respectively.

Follow-up results

Among 447 nodules 5–10 mm in size with a minimum 3 years of follow-up US, 27 (6.0 %) nodules had growth 3 mm or larger (mean increased size 6.0 mm; SD 4.9 mm; range 3–27 mm) during a mean follow-up time of 74.3 ± 18.6 months (range 37–101 months). On average, the 27 nodules with growth increased in size by 0.97 mm per 12 months. Of 27 nodules with growth, 8 nodules underwent FNA due to the growth (Fig. 1). Of 8 nodules with FNA, 5 had benign results, 2 had non-diagnostic results, and 1 had a malignant result. Of 420 nodules without growth, 21 nodules had FNA for the following reasons: suspicious US features in 14, non-diagnostic results on initial FNA in 2, and FNA performed at the patient's request in 5. Of 21 nodules with FNA, 14 had benign results, 6 had malignant or suspicious results, and 1 had a non-diagnostic result. Among 7 nodules with malignant or suspicious FNA results, surgery was performed on 6 nodules except for one nodule. One nodule was followed-up at the request of the patient. 16 nodules–15 nodules associated with surgery of other nodules with malignant or suspicious FNA results and 1 nodule with growth—also underwent surgery, and all of them were confirmed as benign by surgery.

During follow-up, there were no nodules with gross extrathyroidal extension associated with palpable cervical lymph nodes, nor were any associated with suspicious/apparent appearance of central or lateral lymph node metastasis on US. There were 14 nodules with suspicious US features, and all of them underwent one more FNA during follow-up due to the suspicious US features. Of them, four were confirmed to be malignant, and ten were confirmed to be benign by FNA. Of ten nodules with benign FNA results, three nodules had one benign FNA result, and seven nodules had more than two benign FNA results of the total number of FNA results.

Benign and malignant nodules

Table 1 demonstrates the detailed characteristics of the seven malignancies detected during follow-up. The mean follow-up time between initial US and cancer diagnosis

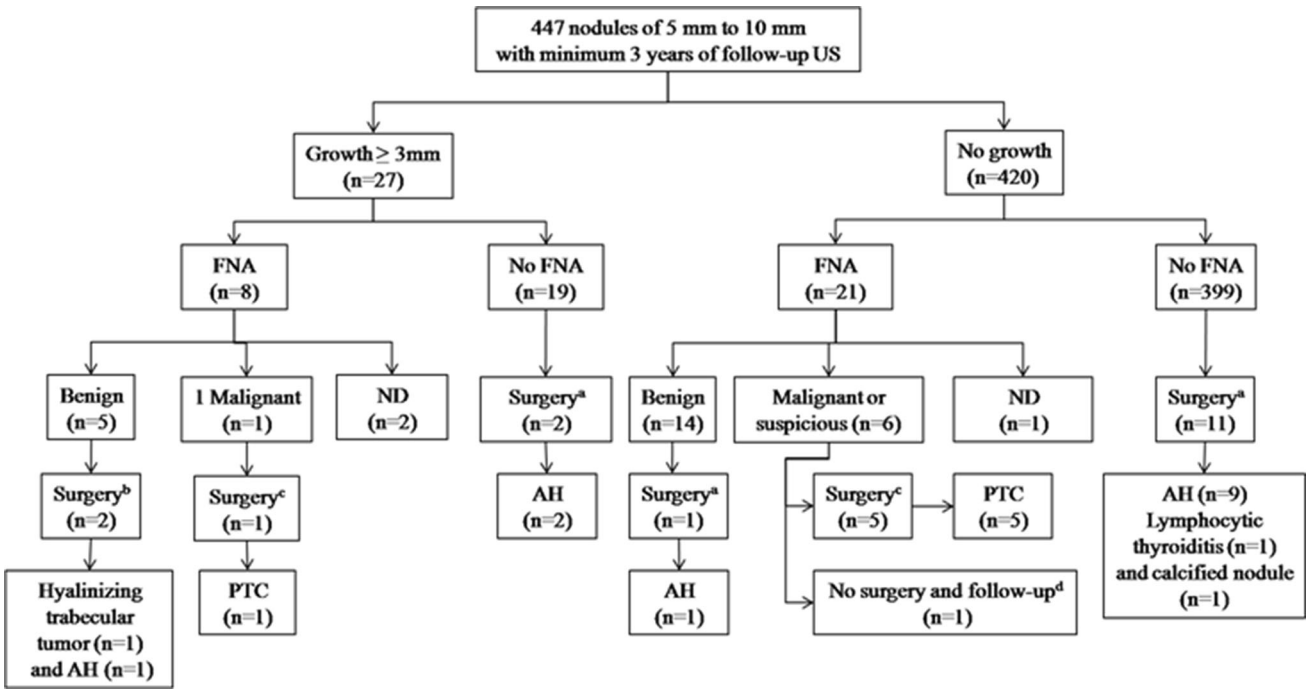

Fig. 1 Follow-up results for 447 nodules of 5–10 mm with a minimum 3 years of follow-up US. *AH* adenomatous hyperplasia, *FNA* fine-needle aspiration, *ND* non-diagnostic, *PTC* papillary thyroid carcinoma, *US* ultrasound. Surgery[a] was performed for 14 nodules[a] associated with surgery of other nodules with malignant or suspicious FNA results. 12 were adenomatous hyperplasia, 1 was lymphocytic thyroiditis, and 1 was a calcified nodule. Surgery[b] was performed for 1 nodule due to growth, and 1 nodule associated with surgery of other nodules with malignant or suspicious FNA results. One was hyalinizing trabecular tumor and the other was adenomatous hyplasia, respectively. Surgery[c] was performed for 6 nodules due to malignant or suspicious cytology. All were papillary thyroid carcinomas on surgery. However, one patient[d] did not have surgery and her nodule was followed-up at the request of the patient

was 51.9 ± 10.5 months (range 42–69 months). One nodule (No. 1) was detected due to a size increase of 4 mm (from 8 to 12 mm). Four nodules (Nos. 2, 3, 4 and 7) were detected due to the presence of suspicious US features. Two nodules (Nos. 5 and 6) were incidentally detected despite being without growth or suspicious US features, because the nodules had follow-up FNAs due to non-diagnostic and suspicious for PTC results on initial FNAs performed at the patient's request, respectively. Among seven malignancies, 6 underwent surgery and one (No. 3) did not as the patient refused surgery. At surgery, all 6 nodules were found to be PTMCs less than 1 cm. Among them, there was no case with lateral lymph node metastasis or distant metastasis. Two (Nos. 1 and 5) had minimal extrathyroidal extension, and one (No. 6) had central lymph node metastasis.

Table 2 demonstrates the demographic and US characteristics between the benign and malignant thyroid nodules that underwent surgery. Malignant nodules had more FNAs compared to benign nodules (median 2 times versus 0 times, $P = 0.004$) and more suspicious US features ($P < 0.001$). Other demographic and US characteristics were similar between the two groups.

Factors associated with nodule growth

On univariate analysis to predict growth defined as a size increase of 3 mm or more, younger age, and absence of suspicious US features were associated with growth (Table 3). On multi-variate analysis 1, absence of suspicious US features was independently associated with growth (Odds ratio (OR), 1.037; 95 % confidence interval (CI), 1.003–1.072; $P = 0.034$). Older patients had nodules less likely to grow 3 mm or larger (OR 0.996; 95 % CI 0.994–0.999; $P = 0.002$). On multi-variate analysis 2, absence of suspicious US features (OR 1.046; 95 % CI 1.016–1.077; $P = 0.002$) and younger age (OR 0.996; 95 % CI 0.994–0.999; $P = 0.002$) were independent predictors for nodule growth. A longer follow-up time of 6 years or more was not associated with nodule growth, compared to a follow-up time from 3 to 6 years.

Short-term versus long-term follow-up

51.5 % (230 of 447) of nodules had a long-term follow-up of 6 years or more. Multiple nodules had more long-term follow-ups than single nodules (Table 4, $P = 0.018$). All

Table 1 Seven papillary thyroid carcinomas (PTC) detected during follow-up

Number	Age	Sex	Multiplicity on US	Internal composition on US	Suspicious US features	Initial size on US	Last size on US	Interval time between initial US and cancer diagnosis (month)	The presence of initial FNA
1	36	F	Y	Solid	N	8	12	69	N
2	60	M	Y	Solid	Y	5	5	48	Y
3	69	F	N	Solid	Y	7	7	42	Y
4	68	F	Y	Solid	N → Y*	8	8	45	N
5	50	F	Y	Solid	N	5	5	55	Y
6	49	F	N	Mixed (cystic < 50 %)	N	6	6	62	Y
7	37	F	N	Mixed (cystic > 50 %)	N → Y*	9	9	42	Y

Number	The reason for initial FNA	The results of initial FNA	The presence of follow-up FNA	The reason for follow-up FNA	The results of follow-up FNA	Size on pathology	Extrathyroidal extension on pathology	Central lymph node metastasis on pathology
1			Y	Nodule growth	Malignant	6	Y (minimal)	N
2	Suspicious US features	Non-diagnostic	Y	Suspicious US features	Malignant	2	N	N
3	Suspicious US features	Non-diagnostic	Y	Suspicious US features	Malignant	No surgery	No surgery	No surgery
4			Y	Suspicious US features	Malignant	7	N	N
5	Patient request	Non-diagnostic	Y	Non-diagnostic results on initial FNA	Suspicious	5	Y(minimal)	N
6	Patient request	Suspicious for PTC	Y	Patient request	Malignant	3	N	Y (2 out of 9 lymph nodes)
7	Patient request	Non-diagnostic	Y	Suspicious US features	Malignant	4	N	N

F female, *M* male, *Y* yes, *N* no, *N → Y** newly developed suspicious US features observed on follow-up

The one nodule without surgery (number 3) did not show growth at a follow-up at 89 months. There was no case with suspicious extrathyroidal extension or suspicious central or lateral lymph node metastasis on US. Central lymph node dissection was routinely performed during thyroidectomy. There was no case with lateral lymph node or distant metastasis

cancers were detected within a follow-up time of 3 to 6 years, and no cancers were detected on long-term follow-up ($P < 0.001$). Long-term follow-up time was not associated with growth. Other demographic and US characteristics were similar between the two follow-up groups.

Discussion

Our results show that follow-up US instead of immediate US-FNA may be enough for thyroid nodules 5–10 mm regardless of US features, and that a follow-up US 3 years after the initial US may be appropriate. Among seven malignancies (1.6 %, 7 of 447) detected on follow-up US after 3 years, only one nodule (14.3 %, 1 of 7) showed growth of more than 3 mm by increasing from 8 to 12 mm. Six malignancies which underwent surgery were all confirmed as PTMCs, and all of them did not have extensive extrathyroidal extension, and lateral lymph node or distant metastasis. During follow-up, there were no nodules with sonographically gross extrathyroidal extension or clinically palpable or sonographically suspicious lymph node metastasis. After approximately 6 years of mean follow-up, 6.0 % (27 of 447) of the nodules had growth 3 mm or larger. The nodule growth was not a definite indicator of malignancy. Among nodules with growth 3 mm or larger, one nodule (3.7 %, 1 of 27) was malignant. Therefore, follow-up US 3 years after the initial US may be enough for thyroid nodules 5 to 10 mm instead of US-FNA, since most malignancies detected after 3 years did not grow and no significant progression such as extensive extrathyroidal extension, lateral lymph node, and distant metastasis was observed on follow-up.

Table 2 Demographic and US characteristics between benign and malignant thyroid nodules that underwent surgery

	Benign	Malignant	*P* value
Variables			
Number of patients	10	6	
Number of nodules, *n*	16	6	
Age	44.56 ± 10.23	50.16 ± 12.50	0.168
Sex			0.497
Female	15 (75.0)	5 (25.0)	
Male	1 (50.0)	1 (50.0)	
Follow-up time			0.007
3–6 years	10 (62.5)	6 (37.5)	
≥6 years	6 (100.0)	0 (0.0)	
Number of follow-up USs	3 (1–8)	2 (1–4)	0.039
Number of FNAs	0 (1–4)	2 (1–5)	**0.004**
Mutiplicity			0.305
Multiple	14 (77.8)	4 (22.2)	
Single	2 (50.0)	2 (50.0)	
Internal composition			0.749
Solid	12 (75.0)	4 (25.0)	
Cystic	4 (66.7)	2 (33.3)	
Suspicious US features			**<0.001**
Present	0(0.0)	4 (100.0)	
No	16(88.9)	2 (11.1)	
Initial size	7.00 ± 1.71	6.83 ± 1.72	0.828
Final size	9.94 ± 7.74	7.50 ± 2.74	0.120
Growth 3 mm or larger	4 (80.0)	1 (20.0)	0.657

Values given are mean ± standard deviation for continuous variables, or number (percentage) for categorical variables

Bold values indicate statistically significant ($P < 0.05$)

In an observational trial for PTMC, only limited cases had a size increase of 3 mm or more (6.4 and 15.0 % on 5- and 10-year follow-up, respectively) or a novel appearance of lymph node metastasis (1.4 and 3.4 % on 5- and 10-year follow-up, respectively) [6]. On the basis of this trial, most guidelines do not recommend FNA for subcentimeter thyroid nodules unless suspicious/apparent metastatic lymph nodes are present [1, 3, 4]. However, PTMCs are increasingly excised worldwide with the percentage of PTMCs in thyroid cancer ranging from 20.0 to 42.8 % with a mean percentage of 30.0 % owing to the early detection of the subclinical reservoir rather than true occurrence, by the increased use and technical advances of US and US-FNA [16–19]. Recently, there were no differences in size, surgery method, extrathyroidal extension, multifocality, central and lateral lymph node metastasis, and recurrence and mortality between patients with surgery <1 year and those with surgery >1 year after diagnosis of PTMCs 5 mm or less [20]. The two studies by Ito et al. and Moon et al. suggested that follow-up US instead of initial US-FNA could be performed for subcentimeter thyroid nodules, and US-FNA could be recommended in cases with signs of progression such as size enlargement and/or appearance of lymph node metastasis on follow-up [6, 20].

Until now, limited studies have evaluated the factors associated with tumor growth. In a follow-up study for thyroid nodules with at least one benign FNA result, there were no clinical or US factors associated with nodule growth defined as a volume increase 50 % or more in thyroid nodules less than 1 cm [21]. In the recent observational trial for PTMC, young age <40 years was a single independent predictor of PTMC progression in terms of size enlargement defined as a size increase 3 mm or more, novel appearance of lymph node metastasis, and progression to clinical disease (tumor size reaching 12 mm or larger, or novel appearance of lymph node metastasis) [7]. The proportion of patients with PTMC progression was the lowest in old patients ≥60 years and the highest in young patients <40 years [7]. Similary, our results showed that nodules in older patients were less likely to grow 3 mm or more. These results emphasize that follow-up US may be enough for nodules 5 to 10 mm especially in older patients, considering the shorter life expectancy, limitations (e.g., inadequate cytology) and possible complications (e.g.,

Table 3 Univariate and Multivariate analysis to associate growth defined as a size increase of 3 mm or more

Variables	No growth	Growth	Univariate analysis		Multivariate analysis 1		Multivariate analysis 2	
			Odds ratio (95 % CI)	*P* value	Odds ratio (95 % CI)	*P* value	Odds ratio (95 % CI)	*P* value
Number of patients	353	25						
Number of nodules	420	27						
Age	51.37 ± 10.67	43.89 ± 9.67	0.996 (0.994–0.999)	**0.001**	0.996 (0.994–0.999)	**0.002**	0.996 (0.994–0.999)	**0.002**
Sex								
Female	379 (94.0)	24 (6.0)	1 (reference)		1 (reference)			
Male	41 (93.2)	3 (6.8)	1.009 (0.932–1.091)	0.830	1.016 (0.940–1.097)	0.696		
Follow-up time								
3–6 years	206 (94.9)	11 (5.1)	1 (reference)		1 (reference)			
≥6 years	214 (93.0)	16 (7.0)	1.019 (0.974–1.066)	0.413	1.022 (0.977–1.069)	0.344		
Initial size	7.39 ± 1.53	7.52 ± 1.53	1.003 (0.988–1.018)	0.681	1.002 (0.987–1.017)	0.805		
Mutiplicity								
Multiple	338 (94.2)	21 (5.8)	1 (reference)		1 (reference)			
Single	82 (93.2)	6 (6.8)	1.010 (0.953–1.07)	0.745	1.001 (0.942–1.063)	0.992		
Internal composition								
Solid	276 (95.2)	14 (8.3)	1 (reference)		1 (reference)			
Cystic	144 (91.7)	13 (8.3)	1.035 (0.984–1.089)	0.183	1.028 (0.976–1.082)	0.302		
Suspicious US features								
Present	14 (100.0)	0 (0.0)	1 (reference)		1 (reference)		1 (reference)	
No	406 (93.8)	27 (6.2)	1.064 (1.040–1.090)	**<0.001**	1.037 (1.003–1.072)	**0.034**	1.046 (1.016–1.077)	**0.002**

Values given are mean ± standard deviation for continuous variables, or number (percentage) for categorical variables. Multivariate analysis 1 considers all variables of univariate analysis. Multivariate analysis 2 considers variables with statistical significance of $P < 0.1$ on univariate analysis

Bold values indicate statistically significant ($P < 0.05$)

hematoma) of FNA [22], and small but significant risks of operative complications (e.g., damage to the recurrent laryngeal nerve, permanent hypoparathyroidism, in addition to the commitment of thyroid hormone replacement therapy) [16], although we could not suggest an age cut-off value that is associated with growth here since there was an overlap in age ranges between nodules with and without growth.

The 2014 ATA guidelines recommend a strategy for follow-up US based upon the US pattern of nodules with more frequent follow-up US for nodules with more suspicious US patterns [1]. However, the level of recommendation is weak with low-quality and insufficient evidence, and there is no specific mention of nodules 5–10 mm in size [1]. In this study, benign-looking nodules were significantly more likely to grow than suspicious-looking nodules for both growth criteria. Therefore, we do not consider US patterns to be absolutely necessary to the follow-up strategy for nodules 5–10 mm. Another important point was that a follow-up time of 6 years or more did not guarantee nodule growth nor additional cancer detection compared to a follow-up time of 3–6 years. Approximately half of the total nodules (51.7 %, 231 of 447) were followed-up for 6 years or more, but the longer follow-up time was not associated with nodule growth, and no cancers were detected during that time. Therefore, a long-term routine follow-up of 6 years or more may not be necessary for thyroid nodules 5–10 mm. Our data confirm the results of a recent prospective study that showed that among asymptomatic, sonographically, or cytologically benign

Table 4 Demographic and US characteristics in nodules with short-term (3–6 years) and long-term (≥6 years) follow-up US examinations

	Short-term ($n = 217$)	Long-term ($n = 230$)	P value
Variables			
Number of patients	185	193	
Number of nodules, n	217	230	
Age	50.75 ± 11.78	51.08 ± 9.69	0.779
Sex			0.097
Female	190 (47.1)	213 (52.9)	
Male	27 (61.4)	17 (38.6)	
Number of follow-up USs	3 (1–8)	3 (1–8)	0.727
Number of FNAs	0 (0–6)	0 (0–7)	0.095
Surgical resection			**0.033**
Yes	16 (72.7)	6 (27.3)	
No	201 (47.3)	224 (52.7)	
Mutiplicity			**0.018**
Multiple	164 (45.7)	195 (54.3)	
Single	53 (60.2)	35 (39.8)	
Internal composition			0.290
Solid	130 (46.6)	160 (53.4)	
Cystic	82 (52.2)	75 (47.8)	
Suspicious US features			0.510
Present	8 (57.1)	6 (42.9)	
No	209 (48.3)	224 (51.7)	
Final diagnosis			**<0.001**
Benign	210 (44.7)	230 (52.3)	
Malignant	7 (100.0)	0 (0.0)	
Initial size	7.39 ± 1.52	7.40 ± 1.54	0.981
Final size	7.40 ± 3.27	7.35 ± 2.61	0.863
Growth 3 mm or larger	11 (40.7)	16 (59.3)	0.404

Bold values indicate statistically significant ($P < 0.05$)

thyroid nodules, the majority of nodules (88.9 %, 1393 of 1567) exhibited no significant increase during 5 years of follow-up, and that thyroid cancer was rare (0.3 %, 5 of 1567: Of 5 nodules, two grew) [23]. The proportion of nodules with size enlargement (11.1 %, 174 of 1567) was higher than that of our study (6 %, 27 of 447), which may be associated with the difference between the two studies in (1) size of the included nodules (various size ranges from 4 to 40 vs. 5 to 10 mm) and (2) definition for size enlargement (at least 2 nodule dimensions, each amounting to at least 2 mm and representing at least 20 % of the baseline diameter vs. 3 mm or larger).

There were several limitations in our study. First, a selection bias might have occurred owing to the retrospective nature of our study. A large number of cancers might have been detected within 3 years, but they were excluded because we only included nodules with a follow-up US 3 years or more after the initial US. We could assume, given the value of reported incidence rates [16], that nodules 5–10 mm are mostly PTMCs, if they are cancers at all. They can be detected not by nodule growth but by the presence of suspicious US features during a follow-up period of less than 3 years [6, 21, 24]. The included nodules might be an early stage of other aggressive subtypes of thyroid cancers such as poorly differentiated or anaplastic carcinomas, in which then a follow-up US after 3 years may not be appropriate, although such a possibility is considered to be extremely low as such cases are rarely observed and most are detected as an advanced disease at presentation [16, 25, 26]. The decision to follow or not to follow a nodule of 5–10 mm will be based on observed characteristics such as size, US features, and FNA results of the other associated nodules as well as the nodule of 5–10 mm. Second, since 63.5 % (284 of 449) of nodules had only follow-up US without surgery or US-FNA, we do not know the accurate proportion of cancer among the included nodules. The proportion of cancer is anticipated to be very low because initial FNAs had been performed for thyroid nodules 5–10 mm with suspicious US features, and the malignancies proven by initial FNAs were excluded owing to there being no follow-up US for 3 years or more. Third, we did not analyze the serum thyroid stimulating

hormone level and history of levothyroxine therapy, as several previous studies have shown that they do not predict nodule growth [27–29]. Fourth, as a retrospective study, there was an unavoidable limitation occurring because follow-up US was performed by many radiologists with different levels of experience. Inter-observer variations may have occurred between the two radiologists who were involved in the retrospective imaging review. However, to overcome this problem, a consensus was reached after discussion for discrepant cases.

In conclusion, immediate US-FNA for thyroid nodules 5–10 mm is discouraged, unless suspicious metastatic lymph nodes are present. Also, a follow-up US 3 years after the initial US may be enough for these nodules.

Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

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