Malignancy risk and false-negative rate of fine needle aspiration cytology in thyroid nodules ≥4.0 cm

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Background. *We aimed to evaluate malignancy rate and to determine false negativity of fine needle aspiration biopsy (FNAB) in thyroid nodules ≥4.0 cm.*
Methods. *The medical records of patients who underwent thyroidectomy between January 2007 and December 2014 were reviewed. Demographic and clinical data as well as preoperative ultrasonography findings were analyzed. The nodules in these patients were grouped as ≥4.0 cm and <4.0 cm according to ultrasonography measurements. Nodules <4.0 cm were further divided into 1.0–3.9 cm and <1.0 cm. Histopathologically malignant nodules with preoperative benign cytology were defined as having false-negative FNAB.*
Results. *There were 1,008 nodules that measured ≥4.0 cm, 4,013 nodules that measured 1.0–3.9 cm, and 540 that measured nodules <1.0 cm. Based on histopathologic findings, 8.5%, 10.2%, and 25.6% of nodules ≥4.0 cm, 1.0–3.9 cm, and <1.0 cm were malignant, respectively (*P < .001*). There was no significant difference between 1.0–3.9-cm and ≥4.0-cm nodules with respect to malignancy (*P = .108*). False-negativity rates were 4.7% in nodules ≥4.0 cm, 2.2% in nodules measuring 1.0–3.9 cm, and 4.8% in <1.0-cm nodules. Nodules measuring <1.0 cm and ≥4.0 cm had similar false-negativity rates (*P = .93*), while 1.0–3.9-cm nodules had statistically lower false-negativity rates than those found in the other two groups (*P = .03 *and* P < .001, respectively).*
Conclusion. *Of the nodules that were operatively excised, nodules ≥4.0 cm had a similar risk of malignancy as nodules 1.0–3.9 cm. The rate of false-negative FNAB in nodules ≥4.0 cm was twice as high as in nodules 1.0–3.9 cm; however, we do not think it is high enough to recommend a routine operation when cytology results are benign. (Surgery 2016;160:405-12.)*

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The prevalence of palpable thyroid nodules in iodine-sufficient regions was reported in epidemiologic studies as 5% for women and 1% for men.[1,2] According to high-resolution ultrasonography (US) surveys, the prevalence ranges from 19–68% and increases for females and aging individuals.[3,4] In autopsy series, thyroid nodules have a reported prevalence of 37–57%.[5] Fortunately, most of the nodules are benign, with a malignancy risk of about 4–5%.[6,7]

In evaluating the risk of malignancy in thyroid nodules, age, sex, family history of thyroid cancer, exposure to radiotherapy in the head and neck regions, and US features should be considered.[8,9] A hypoechoic pattern, solid texture, presence of microcalcification, absence of peripheral halo, margin irregularity, increased vascularity, and high strain index in elastosonography are US features that may be predictive of malignancy.[10,11]

The incidence of thyroid cancer is increasing worldwide, and papillary thyroid cancer (PTC) is predicted to be the third most common cancer in women by 2019.[12] This increased incidence of cancer is partly attributed to our ability to detect smaller malignant nodules with the help of US and other commonly used imaging techniques.

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Interestingly, this increased incidence is valid for thyroid nodules of all sizes.[13] In the literature, the rate of malignancy for nodules ≥4.0 cm is reported to range from 7.2–24%. However, the relation between increased nodule size and thyroid cancer is still controversial.[14,15]

Fine needle aspiration biopsy (FNAB) is a reliable, rapid, and cost-effective procedure that is commonly used to diagnose and follow up on thyroid nodules. It plays a critical role in clinical decision-making.[16,17] Sensitivity and specificity of FNAB for thyroid nodules are reported as 89–98% and 92%, respectively.[14,18-20]

Large thyroid nodules constitute one of the most important limitations for FNAB[14,15,17,21]; the accuracy of this method in large nodules is still controversial. While some authors claim that US-guided FNAB gives accurate results regardless of nodule size,[22-25] others suggest that the false-negative rate of an FNAB procedure is increased in nodules ≥4.0 cm, and they recommend that these patients be referred for operation without considering the cytologic results.[14,21]

There is no consensus yet on the optimal management of large nodules. An operation is commonly accepted as an appropriate approach for nodules ≥4.0 cm with an indeterminate or malignant cytology. There are, however, contradictory findings and recommendations for patients with benign FNAB results. This opposition mainly originates from high false-negative rates in nodules ≥4.0 cm that have been reported in some prior studies.[15,21]

In this study, we aimed to evaluate the overall malignancy rate and false negativity of FNAB in thyroid nodules ≥4.0 cm. We also tried to find out whether any US feature could help to predict malignancy and false negativity in these nodules.

MATERIALS AND METHODS

Patients in our center who underwent a total thyroidectomy or lobectomy with a clinical diagnosis of nodular goiter between January 2007 and December 2014 were retrospectively recruited for the study. Local ethical committee approval was obtained in accordance with the ethical standards of the Declaration of Helsinki.

We evaluated age, sex, thyroid functional status (euthyroid, hypothyroid, hyperthyroid), preoperative serum thyrotrophin (TSH), antithyroid peroxidase antibody (anti-TPO) positivity, and antithyroglobulin (anti-Tg) positivity of the patients. Normal ranges for TSH, anti-TPO, and anti-Tg were 0.27–4.20 IU/mL, <34 IU/mL, and <115 IU/mL, respectively.

We reviewed preoperative US findings and grouped patients according to the diameter of their largest nodules (≥4.0 cm and <4.0 cm). The nodules that were <4.0 cm were examined in 2 subgroups: <1.0 cm and 1.0–3.9 cm. The diameter of the largest nodule was used to determine the group placement of a patient with multiple nodules.

Experienced endocrinologists on our team performed preoperative US using Esaote color Doppler US (Model 796 FDII; MAG Technology Co Ltd, Yung-Ho City, Taipei, Taiwan) and a superficial probe (Model LA523 13-4 5.5–12.5 Mhz; MAG Technology Co Ltd, Yung-Ho City, Taipei, Taiwan). We evaluated the number of nodules (solitary/multinodular), the nodule diameters, echogenity (isoechoic/hypoechoic/isohypoechoic), texture (solid/mixed/cystic), margin irregularity, microcalcification, macrocalcification, and the presence of peripheral halo.

FNAB was performed under US (Logic Pro 200 GE; Kyunggigo, Korea) guidance with a 7.5 MHz probe (Logic Pro 200 GE; Kyunggigo, Korea). All nodules ≥1.0 cm were evaluated by FNAB. For nodules <1.0 cm, FNAB was used when there was a clinical risk factor such as a family history of thyroid cancer, exposure to radiotherapy of the head and neck region, or suspicious US features such as hypoechoic texture, margin irregularity, microcalcification, and the absence of peripheral halo.

During FNAB, ≥2 different points from the solid part of the nodule were sampled by using a 27-gauge needle and a 20-mL syringe. All of the samples were evaluated by experienced cytopathologists and classified as nondiagnostic, benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasia (FN)/suspicious for FN, suspicious for malignancy, and malignant according to the Bethesda system for reporting thyroid cytopathology.[26,27]

Samples obtained prior to our center's implementation of the Bethesda classification (in October 2009) were re-evaluated and reported according to this system. We analyzed the cytologic results per nodule and per patient separately. When ≥2 nodules were evaluated with FNAB in a single patient, the FNAB result with the highest risk of malignancy was considered to be the cytologic diagnosis for that patient.

We grouped the histopathologic diagnoses into benign and malignant groups. Nodular hyperplasia, colloidal goiter, follicular adenoma, and hurthle cell adenoma were defined as benign

thyroid lesions. PTC, follicular thyroid cancer (FTC), medullary thyroid cancer, hurthle cell cancer, well-differentiated thyroid tumor of unknown malignant potential (WDT-UMP), and undifferentiated cancer were defined as belonging to the malignant group. The nodule evaluated with FNAB was matched with the operatively excised nodule by correlating the localization and size defined in US, cytology, and histopathology reports. Cases in which the FNAB specimen could not be matched to a specific nodule in the thyroidectomy specimen were excluded from the study.

We also evaluated the final histopathology results of patients who were referred for an operation for different indications despite having preoperative benign cytologies. False negativity was defined when the FNAB result of a nodule was benign but the histopathologic examination revealed malignancy. The malignancy and false-negativity rates were compared for nodules ≥4.0 cm, <1.0 cm, and 1.0–3.9 cm.

We used a software package (SPSS 22.0; IBM Corp, Armonk, NY) for statistical analysis. We presented the descriptive statistics as mean ± standard deviation and median range for normally distributed parametric variables and non-normally distributed parametric variables, respectively. We used the number of cases and percentages to describe the nominal variables. A comparison between categorical variables was made using a χ^2 test. Student *t* test for parametric variables and Fisher exact or the Mann-Whitney *U* test for nonparametric variables were used to investigate the difference between groups.

RESULTS

We analyzed the data of 2,463 patients. The mean age of the cohort was 49.0 ± 12.4 years (range: 17–85 years), and 541 of the participants (22.0%) were men and 1,922 (78.0%) were women. There were 860 patients with nodules ≥4.0 cm and 1,603 patients with nodules <4.0 cm. The mean age and ratio of males were significantly higher, and the median serum TSH was significantly lower in patients with ≥4.0-cm nodules compared with patients with <4.0-cm nodules ($P < .001$ for each; Table I). Anti-TPO and anti-Tg positivity did not differ between the groups. We noted multinodular goiter in 746 (86.7%) patients with ≥4.0-cm nodules and in 1,343 (83.8%) patients with <4.0-cm nodules ($P = .051$). Functional status was similar in the 2 groups ($P = .07$).

While analyzing the distribution of FNAB results per patient with ≥4.0-cm and <4.0-cm nodules, we considered the cytologic diagnosis of the nodule with the highest risk of malignancy to be the Bethesda classification for that patient, independent of the diameter of the largest nodule. Accordingly, in 860 patients with at least 1 ≥4.0-cm nodule, 625 (72.7%) had benign, 83 (9.7%) had nondiagnostic, 104 (12.1%) had AUS/FLUS, 19 (2.2%) had FN/suspicious for FN, 20 (2.3%) had suspicious for malignancy, and 9 (1.0%) had malignant cytologies. The cytologic results and final histopathologic diagnoses in each Bethesda group in patients with ≥4.0-cm and <4.0-cm nodules are listed in Table I. The overall malignancy rate in patients with at least 1 ≥4.0-cm nodule was 12.8%. Patients with nodules <4.0 cm had a malignancy rate of 29.0%.

There were a total of 5,561 nodules in 2,463 patients. A total of 1,008 nodules were ≥4.0 cm, and 4,553 nodules were <4.0 cm. The mean nodule size was 5.30 ± 1.47 cm for the nodules ≥4.0 cm and 1.84 ± 0.86 cm for the nodules <4.0 cm. Among the ≥4.0-cm nodules, 683 (67.8%) were benign; 215 (21.3%) were nondiagnostic; 76 (7.5%) were AUS/FLUS; 15 (1.5%) were FN/suspicious for FN; 12 (1.2%) were suspicious for malignancy; and 7 (0.7%) were malignant cytologically.

The FNAB results and histopathologic findings analyzed according to nodules are listed in Table II. In total, 86 (8.5%) nodules ≥4.0 cm and 548 (12.0%) nodules <4.0 cm were malignant histopathologically ($P = .002$). When the nodules <4.0 cm were further subdivided into <1.0-cm and 1.0–3.9-cm groups, 138 (25.6%) out of 540 nodules <1.0 cm and 410 (10.2%) out of 4,013 nodules 1.0–3.9 cm were found to be malignant upon histopathologic examination (Fig 1). There was no significant difference between the 1.0–3.9-cm and the 4.0-cm nodules in terms of malignancy ($P = .108$). Nodules <1.0 cm had a significantly higher rate of malignancy compared with 1.0–3.9-cm and ≥4.0-cm nodules ($P < .001$ for each).

We compared the preoperative US features of 922 histopathologically benign and 86 malignant nodules ≥4.0 cm (Table III). We found that nodule diameter, texture, presence of halo, microcalcification, macrocalcification, and margin irregularity were similar in the 2 groups. The only difference was observed in the echogenity of nodules, with a higher prevalence of hypoechoic and a lower prevalence of iso-hypoechoic pattern in malignant nodules ($P = .02$).

For nodules with benign preoperative FNAB, histopathologic malignancies were observed in 32 (4.7%) out of the 683 nodules with sizes ≥4.0 cm and 55 (2.4%) out of the 2,299 nodules with sizes

Table I. Demographic and clinical features and cytologic and histopathologic results of patients with ≥4.0-cm and <4.0-cm thyroid nodules

Patients	*≥4.0 cm* (n = *860*)	*<4.0 cm* (n = *1,603*)	P
Sex			
Male	247 (28.7%)	294 (18.7%)	<.001
Female	613 (71.3%)	1,309 (81.3%)	
Age (y)	51.04 (±12.24)	49.54 (±11.85)	<.001
TSH* (uIU/mL)	0.80 (0–44)	1.18 (0–51)	<.001
Anti-TPO positivity (*n* = 1,449)	132/456 (28.9%)	271/993 (27.3%)	.48
Anti-Tg positivity (*n* = 1,378)	91/372 (24.4%)	244/1,006 (24.3%)	.94
Nodule number			
Solitary	114 (13.3%)	260 (16.2%)	.051
Multinodular	746 (86.7%)	1,343 (83.8%)	
Thyroid functions			
Euthyroid	541 (62.9%)	1,025 (63.9%)	
Hypothyroid	36 (4.2%)	97 (6.1%)	.07
Hyperthyroid	283 (32.9%)	481 (30.0%)	

	Histopathology			*Histopathology*		
	n	*Benign*	*Malignant*	n	*Benign*	*Malignant*
FNAB†						
Nondiagnostic	83	72 (86.7%)	11 (13.3%)	178	151 (84.8%)	27 (15.2%)
Benign	625	577 (92.3%)	48 (7.7%)	603	554 (91.9%)	49 (8.1%)
AUS/FLUS	104	85 (81.7%)	19 (18.3%)	431	319 (74.0%)	112 (26.0%)
FN/FNS	19	9 (47.4%)	10 (52.6%)	86	61 (70.9%)	25 (29.1%)
Suspicious for malignancy	20	7 (35.0%)	13 (65.0%)	174	46 (26.4%)	128 (73.6%)
Malignant	9	0 (0%)	9 (100.0%)	131	7 (5.3%)	124 (94.7%)
Total	860	750 (87.2%)	110 (12.8%)	1,603	1,138 (71.0%)	465 (29.0%)

*Median/range.
†When ≥2 nodules were evaluated with FNAB in a single patient, the FNAB result with the highest risk of malignancy was considered to be the cytological diagnosis.
TSH, Thyrotropin; *AntiTPO*, anti-thyroid peroxidase antibodies; *AntiTg*, anti-thyroglobulin antibodies; *FNAB*, fine needle aspiration biopsy; *AUS/FLUS*, atypia of undetermined significance or follicular lesion of undetermined significance; *FN/FNS*, follicular neoplasm or suspicious for follicular neoplasm.

Table II. Fine needle aspiration biopsy and histopathologic findings in ≥4.0-cm and <4.0-cm thyroid nodules

	≥4.0 cm (n = *1,008*)			*<4.0 cm* (n = *4,553*)		
		Histopathology			*Histopathology*	
	n *(%)*	*Benign*	*Malignant*	n *(%)*	*Benign*	*Malignant*
FNAB						
Nondiagnostic	215 (21.3%)	201 (93.5%)	14 (6.5%)	1,268 (27.8%)	1,190 (93.8%)	78 (6.2%)
Benign	683 (67.8%)	651 (95.3%)	32 (4.7%)	2,299 (50.5%)	2,244 (97.6%)	55 (2.4%)
AUS/FLUS	76 (7.5%)	60 (78.9%)	16 (21.1%)	542 (11.9%)	426 (78.6%)	116 (21.4%)
FN/FNS	15 (1.5%)	6 (40.0%)	9 (60.0%)	107 (2.4%)	81 (75.7%)	26 (24.3%)
Suspicious for malignancy	12 (1.2%)	4 (33.3%)	8 (66.7%)	185 (4.1%)	54 (29.2%)	131 (70.8%)
Malignant	7 (0.7%)	0 (0%)	7 (100.0%)	152 (3.3%)	10 (6.6%)	142 (93.4%)
Total	1,008 (100%)	922 (91.5%)	86 (8.5%)	4,553 (100%)	4,005 (88.0%)	548 (12.0%)

FNAB, Fine needle aspiration biopsy; *AUS/FLUS*, atypia of undetermined significance or follicular lesion of undetermined significance; *FN/FNS*, follicular neoplasm or suspicious for follicular neoplasm.

<4.0 cm; the difference was statistically significant (P = .002). When we examined the nodules <4.0 cm in the 2 subgroups, the false-negative rate was 4.8% (n = 10) for the 206 nodules <1.0 cm and 2.2% (n = 45) for the 2,093 nodules 1.0–3.9 cm (Fig 2).

While the false-negative rates for nodules <1.0 cm and ≥4.0 cm were similar (P = .93),

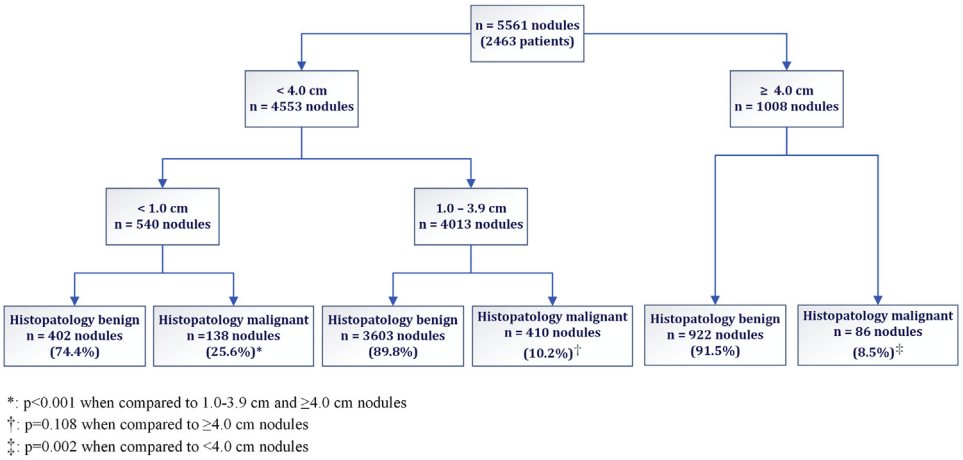

Fig 1. Final histopathologic results of all thyroid nodules according to size.

Table III. Preoperative ultrasonography features in histopathologically benign and malignant ≥4.0-cm thyroid nodules

	Benign (n = *922*)	*Malignant* (n = *86*)	P
Diameter (cm)	5.29 ± 1.48	5.42 ± 1.39	.44
Texture			
Solid	861 (93.4%)	81 (94.2%)	
Cystic	27 (2.9%)	1 (1.2%)	.82
Mixed	34 (3.7%)	4 (4.6%)	
Echogenicity			
Isoechoic	548 (59.4%)	51 (59.3%)	
Hypoechoic	33 (3.6%)	9 (10.5%)	.02
Iso-hypoechoic	341 (37.0%)	26 (30.2%)	
Microcalcification	588 (63.8%)	56 (65.1%)	.83
Macrocalcification	494 (53.6%)	46 (53.5%)	.96
Hypoechoic halo	275 (29.8%)	31 (36.1%)	.24
Irregular margins	549 (59.5%)	48 (55.8%)	.48

the false-negative rate of nodules 1.0–3.9 cm was significantly lower than that of nodules <1.0 cm and ≥4.0 cm ($P = .03$ and $P < .001$, respectively). Among the ≥4.0-cm nodules with a false-negative cytology, there were 27 PTC, 3 FTC, and 2 WDT-UMP. The distribution of tumor types in the false-negative nodules <4.0 cm was as follows: 47 PTC, 5 FTC, and 3 WDT-UMP.

There was no significant difference in any of the preoperative US features between ≥4.0-cm nodules with false-negative and true-negative cytology (Table IV).

DISCUSSION

The literature does not cite a certain cut-off value for nodule diameter that can be used as an operation indication. In previous studies, the rate of malignancy in nodules with a diameter >3–4 cm was reported to range between 7.2–24%.[14,22-24,28] Kuru et al[22] analyzed the relationship between nodule size and malignancy rate in 662 patients and found a significantly higher malignancy rate in nodules ≥4.0 cm compared with nodules <4.0 cm (24% and 12%, respectively). On the other hand, it is hard to conclude that a nodule ≥4.0 cm increases the risk of malignancy since smaller nodules are not routinely resected, while systematic resection of nodules ≥4.0 cm is a routine clinical practice in some centers.

Not all studies have suggested an increased risk of malignancy in large nodules. In a retrospective analysis of 695 nodules, histopathologically confirmed malignancy rates were 14.2% in ≥4.0-cm nodules and 19.5% in <4.0-cm nodules.[24] In another study that included 676 operatively excised nodules, the mean nodule diameter was significantly higher in benign nodules than in malignant nodules.[29] The authors concluded that nodule size was not predictive of thyroid malignancy and that it should not be used in lieu of FNAB for therapeutic decision-making.

In our study, malignancy rate in nodules ≥4.0 cm was lower than that of nodules <4.0 cm. However, when we conducted the subgroup analysis, we found that this difference was largely related to a 25.6% malignancy rate in nodules <1.0 cm and this was the highest risk for malignancy. This finding may be related to the selection criteria of our study, which included an operative cohort. In addition, we performed FNAB in <1.0-cm nodules when there were

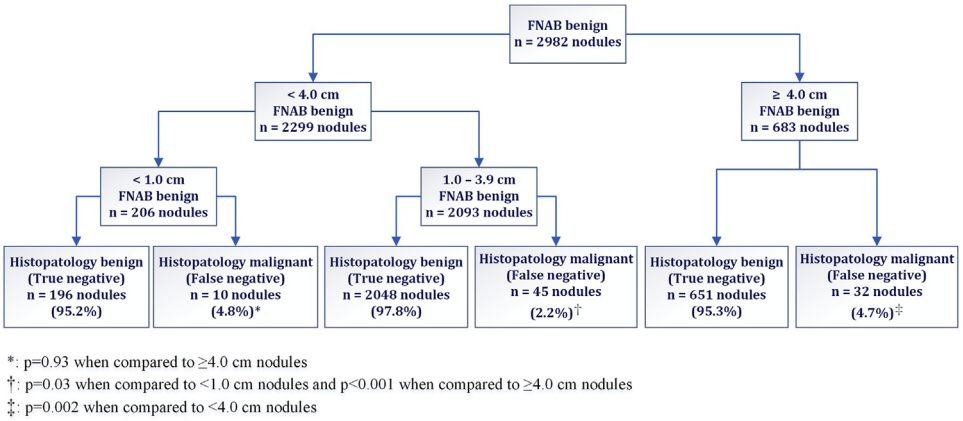

Fig 2. Final histopathologic results and false-negative rates of cytologically benign thyroid nodules according to size.

Table IV. Preoperative ultrasonography features in cytologically benign, ≥4.0-cm thyroid nodules with benign (true-negative) and malignant (false-negative) histopathology

	True negative (n = *648*)	*False Negative* (n = *32*)	P
Diameter (cm)	5.26 ± 1.25	5.35 ± 1.10	.68
Texture			
Solid	621 (95.8%)	31 (96.9%)	
Cystic	10 (1.6%)	1 (3.1%)	.94
Mixed	17 (2.6%)	0 (0.0%)	
Echogenicity			
Isoechoic	408 (63.0%)	21 (65.6%)	
Hypoechoic	12 (1.8%)	2 (6.3%)	.50
Iso-hypoechoic	228 (35.2%)	9 (28.1%)	
Microcalcification	432 (66.7%)	22 (68.8%)	.96
Macrocalcification	359 (55.4%)	17 (53.1%)	.94
Hypoechoic halo	190 (29.3%)	13 (40.6%)	.24
Irregular margins	400 (61.7%)	18 (56.3%)	.66

clinical indicators or US-suspicious features as defined by the 2009 American Thyroid Association guidelines.[30]

An operation was adopted in cases of recurrent nondiagnostic, AUS/FLUS, FN/suspicious of FN, suspicious for malignancy, or malignant cytology results. Therefore, a sizeable percentage of operation indications were composed of cytology results, indicating a high risk of malignancy or suspicious US features in patients with <1.0-cm nodules. This fact might explain the high rate of malignancy in such nodules in our study.

When we conducted our analysis per patient and per nodule separately, the rate of malignancy in patients with at least 1 ≥4.0-cm nodule was higher than the malignancy rate of all ≥4.0-cm nodules (12.8% vs 8.5%). Similar findings were also observed for <4.0-cm nodules (29.0% per patient versus 12.0% per nodule). This result can be attributed to incidental thyroid cancers that were found outside of the nodule of interest in patients with multiple nodules.

In the present study, apart from echogenity, no particular US feature that might be helpful to discriminate between benign and malignant lesions was detected for ≥4.0-cm nodules. Another study that included 382 nodules also did not find a significant difference in the US features between benign and malignant nodules measuring ≥4.0 cm.[31]

An operation is generally recommended for ≥4.0-cm thyroid nodules if FNAB results are malignant, suspicious for malignancy, indeterminate, or repetitively nondiagnostic. However, management of these nodules is controversial when the FNAB results are benign. Previous studies have reported false-negative FNAB rates ranging from 0.9–20% for nodules ≥4.0 cm in size.[15,22,23,28]

In a study that included 74 cytologically benign nodules, the false-negative rate was 20% for ≥4.0-cm nodules and 5.1% for <4.0-cm nodules.[15] McCoy et al[14] reported a false-negative rate of 12.7% among a total of 71 patients with ≥4.0-cm nodules in size and recommended a routine operation. Unlike studies with high false-negativity rate in ≥4.0-cm nodules, another study of 145 cytologically benign nodules ≥3 cm in size reported that the false-negativity rate was 0.7%.[25] Rosario et al[23] analyzed 84 nodules ≥4.0 cm with benign FNAB findings and reported a false-negativity rate of 3.6%. In another study conducted on 662 nodules, the false-negativity rate was 4.3% and 1.3% for ≥4.0-cm and <4.0-cm nodules, respectively.[22]

The results of these studies do not justify routine resection for large nodules. Although the false-negativity rate of ≥4.0-cm nodules was significantly higher than that of <4.0-cm nodules (4.7% vs 2.4%) in our study, we believe that this rate is still not high enough to recommend routine resection.

When we divided the <4.0-cm nodules into subgroups, the false-negativity rate for 1.0–3.9-cm nodules was 2.2%, which was lower than that of <1.0-cm and ≥4.0-cm nodules. On the other hand, the false-negativity rate was similar in <1.0-cm and ≥4.0-cm nodules. Shrestha et al[24] determined false-negative rates of 7.1%, 6.3%, and 15.8% in nodules ≥4.0 cm, 1.0–3.9 cm, and 0.5–0.9 cm, respectively. The authors explained this finding by invoking technical difficulties and potential sampling errors related to the small size of the nodules.

Compared with that study, we found a lower false-negative rate for <1.0-cm nodules. However, those authors have only considered 35 nodules that were <1.0 cm in size, while we evaluated 540 nodules of similar size. The false-negative rate of nodules ≤1.0 cm was 6.8% in another study that focused on 483 nodules; this finding was similar to what we reported.[32]

Due to the small size of nodules (<1.0 cm) and failure to take samples from a small carcinoma foci inside large nodules, sampling from adjacent intact tissue might be related to the false-negative rates in these nodules. In addition, the method used during the FNAB procedure, interpretation errors, and insufficient sampling might be other factors that affect false-negative cytology results.

The literature contains scant data regarding US features that can be used to distinguish true and false negativity of FNAB in ≥4.0-cm nodules. Giles et al[33] found similar false-negativity rates in large solid and cystic nodules. In the present study, we could not detect any US feature that could help us discriminate between true-negative and false-negative FNAB in nodules ≥4.0 cm.

High-resolution US was used as a standard procedure to determine the nodule size in all patients, and all FNABs were made under US guidance in our study. The varying false-negativity rates reported in some studies can be attributed to nodule size that was determined via manual palpation or histopathologic evaluation rather than with FNAB under US guidance. Variations in FNAB sampling technique and differences in interpretation may also lead to different false-negativity rates. In this study, we considered a larger sample size than used in most previous investigations, a point that is a strength of this study.

The primary limitation of our study was its retrospective design. In addition, selection bias related to the inclusion of thyroidectomized patients cannot be excluded. Although we prefer thyroidectomy in patients with nodules ≥4.0 cm, there may be a number of patients who were otherwise followed nonoperatively. In recent years, molecular genetic markers, such as point mutations of the BRAF and RAS genes, as well as RET/PTC and PAX8/PPARγ chromosomal rearrangements have been introduced as new predictors of malignancy in thyroid nodules.[34] We did not further analyze the utility of molecular tests due to the small number of nodules evaluated with these methods. A lack of data on molecular testing might be considered another limitation of our study. Lastly, we did not reassess the FNAB specimens of cytologically benign nodules with a final malignant histopathology. Doing so would likely exclude the possible effect of interpretation error on false negativity.

In conclusion, operatively excised nodules ≥4.0 cm had a similar risk of malignancy as nodules 1.0–3.9 cm in size. Although the rate of false-negative FNAB in ≥4.0-cm nodules was twice as high as 1.0–3.9-cm nodules, it may still not be high enough to recommend a routine operation for patients with ≥4.0-cm nodules. Operative intervention may be appropriate if the patient exhibits compression symptoms and an increase in nodule size during follow-up. US features known to be related to malignancy seem to lose their predictive value in nodules ≥4.0 cm, and there are no US features that might be helpful to detect false negativity in these nodules.

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