

Clinical and ultrasonographic features in cancer risk stratification of indeterminate thyroid nodules

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ABSTRACT

الأهداف: تقدير مخاطر الإصابة بالأورام الخبيثة في عقيدات الغدة الدرقية غير المحددة ولتحديد ما إذا كانت بعض المعايير السريرية أو الإشعاعية يمكن أن تتنبأ بخطر الإصابة بالأورام الخبيثة.

المنهجية: سجلت هذه الدراسة بأثر رجعي جميع المرضى البالغين (14 سنة أو أكثر) مع تشخيص خلوي لا نمطية/ آفة جرابية ذات أهمية غير محددة وأورام جرابية/ مشبوهة لأورام جرابية خلال الفترة من يناير 2014م ويناير 2020م. خمسون مريضاً يعانون من عقيدات الغدة الدرقية الأولية المعالجة جراحياً، قمنا بتوثيق التشخيص النسيجي النهائي وسجلات الفحص بالموجات فوق الصوتية. قمنا كذلك بتقييم عقيدات الغدة الدرقية إشعاعياً باستخدام تقارير تصوير الغدة الدرقية ونظام البيانات الذي قدمته الكلية الأمريكية للأشعة (2017).

النتائج: سجلنا في الدراسة 42 أنثى (84%) وثمانية ذكور (16%). كانت مخاطر الإصابة بالأورام الخبيثة 44.8% في Bethesda III و28.6% في Bethesda IV. كانت مخاطر الأورام الخبيثة لفئات الإبلاغ عن تصوير الغدة الدرقية ونظام البيانات 33.3% (TR2) و39.1% (TR3) و35.3% (TR4) و50% (TR5). لم يلاحظ أي ارتباط كبير بين العمر والجنس وفتة Bethesda وتصوير الغدة الدرقية ونظام البيانات وخطر الإصابة بالأورام الخبيثة.

الخلاصة: لم تساهم أي من الخصائص السريرية أو الإشعاعية التي تم تقييمها في هذه الدراسة في التقسيم الطبقي لمخاطر الإصابة بالسرطان في عقيدات الغدة الدرقية باستخدام علم الخلايا غير المحدد. هناك حاجة إلى دراسة مستقبلية متعددة المراكز لفهم عقيدات الغدة الدرقية غير المحددة خلويًا بشكل أفضل.

Objectives: To estimate the risk of malignancy in indeterminate thyroid nodules and to determine whether certain clinical or radiological parameters can predict the risk of malignancy.

Methods: This retrospective study enrolled all adult patients (age ≥ 14 years) with a cytological diagnosis of atypia/follicular lesion of undetermined significance and follicular neoplasm/suspicious for a follicular neoplasm between January 2014 and January 2020. Fifty patients with surgically treated primary thyroid nodules, documented final histological diagnosis, and ultrasound examination records were included. Thyroid nodules were evaluated radiologically using Thyroid Imaging Reporting and Data System introduced by the American College of Radiology (2017).

Results: Forty-two (84.0%) female and 8 (16.0%) male patients were enrolled in the study. The malignancy risks were 44.8% for Bethesda III and 28.6% for Bethesda IV. The malignancy risks for the Thyroid Imaging Reporting and Data System categories were 33.3% (TR2), 39.1% (TR3), 35.3% (TR4), and 50% (TR5). No significant associations were observed between age, gender, Bethesda category, and Thyroid Imaging Reporting and Data System and the risk of malignancy.

Conclusion: None of the clinical or radiological characteristics evaluated in this study contributed to the cancer risk stratification of thyroid nodules with indeterminate cytology. A prospective multicenter study is needed to better understand cytologically indeterminate thyroid nodules.

Keywords: cytologically indeterminate thyroid nodules, Bethesda categories III and IV, American College of Radiology Thyroid Imaging Reporting and Data System

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Thyroid nodules (TNs) are a prevalent surgical condition with an estimated prevalence of 20-76% detected by ultrasound (US).¹ Most TNs are benign; however, the propensity for malignant transformation ranges from 5-15%.^{1,2} Moreover, an increase in the incidence of thyroid malignancy is correlated with the improvement of screening programs.³

Neck US is a widely accepted initial and informative radiological tool for the assessment of TNs. In 2009, Horvath et al⁴ suggested the Thyroid Imaging Reporting and Data System (TI-RADS). They defined 10 sonographic TN criteria and correlated the risk of malignancy (ROM) with these properties. Another protocol was suggested by Park et al⁵, in which 12 ultrasonographic characteristics were used to stratify the risk of thyroid cancer. Following this, Korean and French classifications were proposed, with modified interpretations aimed at TN management.⁶⁻⁸ In 2017, the American College of Radiology (ACR) TI-RADS guidelines were adopted. The ACR TI-RADS aims to standardize US reports and stratify the ROM in TNs based on certain sonographic characteristics. In addition, this system described TNs in terms of shape, composition, margin, echogenicity, and echogenic foci.⁹ However, no single feature can differentiate between benign and malignant nodules; hence, histopathology continues to be the standard for definitive diagnosis of TNs.³

Fine-needle aspiration cytology (FNAC) is the preferred next step for assessing TNs. Cytologically, TNs can be classified into 6 categories based on the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). Of these, categories III (atypia of undetermined significance [AUS] or follicular lesion of undetermined significance [FLUS]) and IV (follicular neoplasm [FN] or suspicious for a follicular neoplasm [SFN]) are defined as indeterminate groups, with 25.0% of TNs being classified into these 2 categories.^{2,10}

Considering their heterogeneity and ambiguity, the management of indeterminate TNs remains controversial and challenging. Nonetheless, recommendations, including active surveillance or diagnostic surgery and the use of molecular markers, have been suggested based on clinical and radiological features.²

Unlike other published studies from Saudi Arabia which included only Bethesda III TNs, the current study investigated cytologically indeterminate thyroid

nodules (CITNs) (Bethesda III and IV TNs). The objectives of this study were to assess the ROM in CITNs and to determine whether certain clinical or radiological parameters could be helpful in the prediction of malignancy for these specific categories of TNs to determine the proper management strategy.

Methods. All FNAC cases diagnosed as AUS/FLUS and FN/SFN between January 2014 and January 2020 at King Salman Armed Forces Hospital Northwestern Region, Tabuk, Saudi Arabia, were retrospectively identified. Of these, all adult patients (age ≥ 14 years) who had a surgically treated primary TN, a documented final histological diagnosis, and US examinations were included.

Fine-needle aspiration cytology was carried out by a pathologist (non-US-guided) if the nodule was visible or by an interventional radiologist (US-guided) if the nodule was not visible or if the FNAC carried out by the pathologist was inconclusive. The FNAC was typically carried out with a 23-gauge needle. The number of samples in blinded FNAC ranged from 1-3 samples. Depending on the adequacy check (rapid staining of a slide from the first sample), each sample took less than a minute, excluding patient preparation time. The number of smear slides used ranged from 4-6 to 10-30 slides. More slides usually indicate hemorrhagic smears. Most slides were immediately fixed in ethanol (95.0%). The other slides were allowed to air-dry before being stained with Diff-Quik (Diapath, Martinengo, Italy). They were then evaluated for sufficiency. Liquid-based cytology is not yet used at our institution.

Patient demographic data, including age, gender, and the final histopathological diagnoses were determined from the electronic medical records; missing information was retrieved from the patients' charts. The extracted data were transferred to a spreadsheet containing all information regarding the study variables. An exploratory data analysis was carried out before conducting the final analysis.

This was a retrospective cohort study approved by the Research Ethics Committee at King Salman Armed Forces Hospital (KSAFH-REC-2020-337). Additionally, this study was carried out in accordance with the principles set forth in the Declaration of Helsinki. There was no direct contact with the patients because only secondary data were used; thus, individual informed consent from patients was not required.

All sonograms were reviewed by a radiologist, who has 14 years of experience in thyroid US. The radiologist was blinded to cytology results and histopathological diagnoses. The review included images only. The 2017

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ACR TI-RADS was utilized. The points were calculated to obtain the TI-RADS level based on the following characteristics: composition, echogenicity, shape, margin, and echogenic foci.⁹ Then, TNs were classified as follows: 0 point (TR1, benign), 2 points (TR2, not suspicious), 3 points (TR3, mildly suspicious), 4-6 points (TR4, moderately suspicious), and ≥ 7 points (TR5, highly suspicious).⁹

Statistical analysis. The Statistical Package for the Social Sciences, version 26.0 (IBM Corp., Armonk, NY, USA) was used for analyses. Categorical data were summarized as frequencies and percentages, whereas continuous variables were reported as means and standard errors of the mean. A 2-sample t-test was used to compare patient age with pathology type. The association between categorical variables was assessed using Pearson's Chi-squared test and Fisher's exact test, as appropriate. Statistical significance was determined as $p < 0.05$.

Results. A total of 1595 thyroid FNACs were carried out over the target period of observation. Among all FNACs, 102 (6.4%) were diagnosed as AUS/FLUS and 57 (3.6%) as FN/SFN. After screening using our inclusion criteria, 50 patients, contributing 50 CITNs, were enrolled. The mean patient age was 46.26 ± 2.08 years. The majority of patients were female (84%), with only 8 (16%) male patients. The TN pathology was benign in 31 (62%) patients and malignant in 19 (38%) patients. A non-US-guided biopsy was used in 52% of patients, whereas a US-guided biopsy was used in the other 48%. There were 29 cases classified as AUS/FLUS; of these, 16 were benign (13 multinodular goiter [MNG] and 3 Hashimoto's thyroiditis) and 13 were malignant (8 papillary thyroid microcarcinoma [PTMC], 4 invasive encapsulated follicular variant papillary thyroid carcinoma [EFVPTC], and one papillary thyroid carcinoma [PTC]-oncocyctic). Twenty-one cases were identified as FN/SFN, of which 15 were benign (9 MNG, 2 Hashimoto's thyroiditis, and 4 follicular adenoma) and 6 were malignant (3 invasive EFVPTC, 2 PTC [classic], and one PTMC). The ROMs were 44.8% in AUS/FLUS TNs and 28.6% in FN/SFN TNs. Furthermore, the ROMs according to TI-RADS classifications were 33.3% (TR2), 39.1% (TR3), 35.3% (TR4), and 50.0% (TR5).

Patient demographics and US-based morphological features of TNs are presented in **Table 1**. There was no significant association between patient age and final pathology (benign, 46.19 ± 2.56 years, versus [vs.] malignant, 46.37 ± 3.64 years; $p = 0.968$) in the 2 Bethesda categories. The composition of the TNs was mainly

solid (70%), whereas 15 (30%) had mixed cystic and solid components. Hyper- or iso-echogenicity was recorded in 23 (46%) of the TNs, whereas 27 (54%) were hypoechoic. The margin was smooth in 47 (94%) of TNs and ill-defined in only 3 (6%). Echogenic foci were not present in 40 (80%) of TNs, whereas punctate echogenic foci were recorded in 6 (12%) and macrocalcifications in 4 (8%). The TI-RADS scoring results for most of the TNs were TR3 (46%), followed by TR4 (34%), TR2 (12%), and TR5 (8%).

Tables 2 and 3 show that pathological type (benign vs. malignant) was not significantly associated with gender ($p = 0.649$), biopsy method ($p = 0.216$), Bethesda category ($p = 0.242$), TI-RADS ($p = 0.947$), composition ($p = 0.280$), echogenicity ($p = 0.461$), margin ($p = 0.680$), or echogenic foci ($p = 0.282$). Similarly, no significant association was identified between the Bethesda category and TI-RADS classification ($p = 0.185$). Among

Table 1 - Patient demographics and ultrasound-based morphologic features of thyroid nodules (N=50).

Variable	Distribution
Gender	
Male	8 (16.0)
Female	42 (84.0)
Age (years)	46.26 \pm 2.08
Pathology	
Benign	31 (62.0)
Malignant	19 (38.0)
Biopsy method	
US-guided	24 (48.0)
Non-US-guided	26 (52.0)
Composition	
Mixed cystic and solid	15 (30.0)
Solid	35 (70.0)
Echogenicity	
Hyperchoic or isoechoic	23 (46.0)
Hypochoic	27 (54.0)
Shape	
Wider-than-tall	50 (100)
Margin	
Ill-defined	3 (6.0)
Smooth	47 (94.0)
Echogenic foci	
Punctate echogenic foci	6 (12.0)
Macrocalcifications	4 (8.0)
None	40 (80.0)
Thyroid Imaging Reporting and Data System	
TR2	6 (12.0)
TR3	23 (46.0)
TR4	17 (34.0)
TR5	4 (8.0)
Distribution reported as frequency (%), except for age, which is reported as mean \pm standard error of the mean. US: ultrasound	

Table 2 - Association between different categories of Bethesda and TI-RADS classification system with the final pathology.

Pathology	TI-RADS	Bethesda category, n (%)		Significance <i>P</i> -value
		III	IV	
Benign	TR2	1 (25.0)	3 (75.0)	0.039*
	TR3	11 (78.6)	3 (21.4)	
	TR4	4 (36.4)	7 (63.6)	
	TR5	0 (0.00)	2 (100)	
Malignant	TR2	1 (50.0)	1 (50.0)	0.739
	TR3	6 (66.7)	3 (33.3)	
	TR4	4 (66.7)	2 (33.3)	
	TR5	2 (100)	0 (0.0)	

*Statistically significant at $p < 0.05$. TI-RADS: Thyroid Imaging Reporting and Data System

Table 3 - Association between various parameters and pathology (N=50).

Variables	Pathology, n (%)		Significance <i>P</i> -value
	Benign	Malignant	
Gender			
Female	26 (83.9)	16 (84.2)	0.649
Male	5 (16.1)	3 (15.8)	
Biopsy method			
Non US-guided	14 (45.2)	12 (63.2)	0.216
US guided	17 (54.8)	7 (36.8)	
Bethesda			
III	16 (55.2)	13 (44.8)	0.242
IV	15 (71.4)	6 (28.6)	
TI-RADS			
TR2	4 (66.7)	2 (33.3)	0.947
TR3	14 (60.9)	9 (39.1)	
TR4	11 (64.7)	6 (35.3)	
TR5	2 (50.0)	2 (50.0)	
Composition			
Mixed cystic and solid	11 (73.3)	4 (26.7)	0.280
Solid	20 (57.1)	15 (42.9)	
Echogenicity			
Hyperechoic or isoechoic	13 (56.5)	10 (43.5)	0.461
Hypoechoic	18 (66.7)	9 (33.3)	
Margin			
Ill-defined	2 (66.7)	1 (33.3)	0.680
Smooth	29 (61.7)	18 (38.3)	
Echogenic foci			
Punctate echogenic foci	4 (66.7)	2 (33.3)	0.282
Macrocalcifications	1 (25.0)	3 (75.0)	
None	26 (65.0)	14 (35.0)	

US: ultrasound, TI-RADS: Thyroid Imaging Reporting and Data System

benign TNs, the majority of Bethesda category III TNs had a TR3 classification (78.6%), whereas the majority of Bethesda category IV TNs had a TR4 classification (63.6%), which was statistically significant ($p=0.039$). However, among malignant TNs, there was no

significant association between the Bethesda category and TI-RADS classification ($p=0.739$).

Discussion. In the current study, we explored the impact of clinical and US features on cancer risk stratification in CITNs. The present study included both Bethesda category III and IV nodules; previously published studies from Saudi Arabia only included Bethesda category III nodules.^{11,12}

Cytologically indeterminate thyroid nodules are known for their heterogeneity and ambiguity. In this study, the AUS/FLUS rate was 6.4% (recommended range: <7%) and the FN/SFN rate was 3.6% (recommended range: 1-25%).^{10,13} Based on the TBSRTC, the ROMs were 5-15% for AUS/FLUS and 15-30% for FN/SFN.¹⁰ However, the actual ROMs in surgically resected nodules were between 6-48% for AUS/FLUS and between 14-34% for FN/SFN.¹³ In our study, the ROMs were 44.8% (AUS/FLUS) and 28.6% (FN/SFN), both of which are consistent with previous studies.^{2,14-16} In our study cohort, the total ROM of both categories was 38%, similar to the findings of De et al.¹⁴ Variations in pathological interpretation and randomization among institutions might explain the differences in ROM among studies.¹⁶

In the present study, the majority of patients were female (84%), which is consistent with previous studies.^{11,14} There were no significant correlations between age, gender, and pathology type (benign vs. malignant), which is concordant with the results of a previous study.¹⁷

Few studies have assessed the utility of the ACR TI-RADS classification for Bethesda categories III and IV.^{2,14} Our results show that pathology type was not significantly associated with TI-RADS classification. Thus, the TI-RADS classification has little value in ROM prediction for CITNs, as reported previously.¹⁴ However, in a recent retrospective analysis of 167 Bethesda category III nodules, the ACR TI-RADS classification was found to be useful in predicting malignancy.¹² Furthermore, a study by Wu et al² showed that ACR TI-RADS classification is helpful in risk stratification and management of CITNs when combined with KRAS mutation testing. In addition, they concluded that, for Bethesda categories III and IV with TR3, US follow-up alone is inadequate.

In our study, the ROMs were 33.3% (TR2), 39.1% (TR3), 35.3% (TR4), and 50% (TR5). In a recently published study that included TNs of Bethesda categories III and IV, the ROMs were 0% (TR2), 40% (TR3), 6.7% (TR4), and 52.9% (TR5), based on ACR TI-RADS.² Moreover, a study that utilized

the TI-RADS introduced by Horvath et al⁴ reported ROMs of 58.3% for TR2 and TR3 and 58.8% for TR4 and greater.¹⁵ The limited sample size and inclusion of only resected indeterminate nodules could explain the differences in malignancy rates in our results.

Some suspicious US characteristics including a taller-than-wider shape and marked hypoechogenicity have been useful in predicting the malignant tendency in AUS/FLUS TNs.¹⁸ However, no significant association was observed between US features and pathology type, which is in agreement with previous studies.^{2,11,17} Rago et al¹⁹ concluded that US elastography could play role in the detection of thyroid cancer, particularly in cases of indeterminate or non-diagnostic cytology.

Different US-based guidelines for TN management have been proposed, all of which aim to eliminate unnecessary FNACs and improve cancer risk stratification. Until now, TI-RADS classification has not been recommended.²⁰ Additionally, the questionable reliability of the TI-RADS recommendations, existence of radiological and clinical features, family history of malignancy, and previous FNAC with atypical results may indicate biopsy irrespective of TI-RADS recommendations.³ Furthermore, some nodules that appear radiologically benign are malignant (either by cytology or histology) and vice versa.²¹ Therefore, no single feature can adequately differentiate between benign and malignant nodules. Consequently, histopathology continues to be the standard for the definitive diagnosis of TNs.³ In our cohort, the TI-RADS and US characteristics did not assist in cancer risk stratification; this may be attributed to the limited sample size. This result is supported by that of Park et al,¹⁷ who found that the TI-RADS and US characteristics did not vary between malignant and benign nodules or between malignancies with one or 2 AUS/FLUS nodules.

Generally, the recommended management for the AUS/FLUS nodules is repeat FNA, molecular testing, or lobectomy. For FN/SFN, lobectomy with molecular testing is suggested.²² The study by Wu et al,² which included TNs with Bethesda categories III and IV, found that the ROM was 40% in TR3. In addition, they found that the ROM was 50% in Bethesda category IV nodules with a positive KRAS mutation. Thus, for definitive diagnosis, they recommended a diagnostic surgical intervention. In a prospective study, a BRAFV600E mutation in an FNAC specimen was found to have little value in preoperatively predicting the ROM. Due to the high rate of malignancy in both groups, the authors suggested surgical intervention.¹⁵

In our study, the clinical and radiological features

did not assist in cancer risk stratification. This can be attributed to several factors. First, the present study had a small sample size, and we only included patients who underwent surgical treatment; therefore, our sample was not representative of all CITNs. Second, owing to the retrospective and single-center design of the study, our findings may have been influenced by selection bias.

In conclusion, the ROMs for AUS/FLUS and FN/SFN TNs were within the ranges reported in previous studies. None of the clinical or radiological characteristics evaluated in this study contributed to cancer risk stratification in either group. A prospective multicenter study with a larger sample is needed to reveal further information on these controversial categories of TNs.

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References

1. Zhang J, Liu BJ, Xu HX, Xu JM, Zhang YF, Liu C, et al. Prospective validation of an ultrasound-based Thyroid Imaging Reporting and Data System (TI-RADS) on 3980 thyroid nodules. *Int J Clin Exp Med* 2015; 8: 5911-5917.
2. Wu H, Zhang B, Cai G, Li J, Gu X. American College of Radiology Thyroid Imaging Report and Data System combined with K-RAS mutation improves the management of cytologically indeterminate thyroid nodules. *PLoS One* 2019; 14: e0219383.
3. Modi L, Sun W, Shafizadeh N, Negron R, Yee-Chang M, Zhou F, et al. Does a higher American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) score forecast an increased risk of malignancy? A correlation study of ACR TI-RADS with FNA cytology in the evaluation of thyroid nodules. *Cancer Cytopathol* 2020; 128: 470-481.
4. Horvath E, Majlis S, Rossi R, Franco C, Niedmann JP, Castro A, et al. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. *J Clin Endocrinol Metab* 2009; 94: 1748-1751.
5. Park JY, Lee HJ, Jang HW, Kim HK, Yi JH, Lee W, et al. A proposal for a thyroid imaging reporting and data system for ultrasound features of thyroid carcinoma. *Thyroid* 2009; 19: 1257-1264.
6. Kwak JY, Han KH, Yoon JH, Moon HJ, Son EJ, Park SH, et al. Thyroid Imaging Reporting and Data System for US features of nodules: a step in establishing better stratification of cancer risk. *Radiology* 2011; 260: 892-899.
7. Russ G, Bigorgne C, Royer B, Rouxel A, Bienvenu-Perrard M. [The Thyroid Imaging Reporting and Data System (TIRADS) for ultrasound of the thyroid]. *J Radiol* 2011; 92: 701-713. (in French).
8. Russ G, Royer B, Bigorgne C, Rouxel A, Bienvenu-Perrard M, Leenhardt L. Prospective evaluation of Thyroid Imaging Reporting and Data System on 4550 nodules with and without elastography. *Eur J Endocrinol* 2013; 168: 649-655.

9. Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS Committee. *J Am Coll Radiol* 2017; 14: 587-595.
10. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. *Thyroid* 2009; 19: 1159-1165.
11. Alqahtani S, Alsobhi S, Alsalloum RI, Najjar SN, Al-Hindi HN. Surgical outcome of thyroid nodules with atypia of undetermined significance and follicular lesion of undetermined significance in fine needle aspiration biopsy. *World J Endoc Surg* 2017; 9: 100-103.
12. Al Dawish M, Alwin Robert A, Al Shehri K, Hawsawi S, Mujammami M, Al Basha IA, et al. Risk stratification of thyroid nodules with Bethesda III category: the experience of a territorial healthcare hospital. *Cureus* 2020; 12: e8202.
13. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016; 26: 1-133.
14. De D, Dutta S, Tarafdar S, Kar SS, Das U, Basu K, et al. Comparison between sonographic features and fine needle aspiration cytology with histopathology in the diagnosis of solitary thyroid nodule. *Indian J Endocrinol Metab* 2020; 24: 349-354.
15. Chirayath SR, Pavithran PV, Abraham N, Nair V, Bhavani N, Kumar H, et al. Prospective study of Bethesda categories III and IV thyroid nodules: outcomes and predictive value of BRAFV600E mutation. *Indian J Endocrinol Metab* 2019; 23: 278-281.
16. Yaprak Bayrak B, Eruyar AT. Malignancy rates for Bethesda III and IV thyroid nodules: a retrospective study of the correlation between fine-needle aspiration cytology and histopathology. *BMC Endocr Disord* 2020; 20: 48.
17. Park VY, Kim EK, Kwak JY, Yoon JH, Moon HJ. Malignancy risk and characteristics of thyroid nodules with two consecutive results of atypia of undetermined significance or follicular lesion of undetermined significance on cytology. *Eur Radiol* 2015; 25: 2601-2607.
18. Yoo WS, Choi HS, Cho SW, Moon JH, Kim KW, Park HJ, et al. The role of ultrasound findings in the management of thyroid nodules with atypia or follicular lesions of undetermined significance. *Clin Endocrinol (Oxf)* 2014; 80: 735-742.
19. Rago T, Scutari M, Santini F, Loiacono V, Piaggi P, Di Coscio G, et al. Real-time elastosonography: useful tool for refining the presurgical diagnosis in thyroid nodules with indeterminate or nondiagnostic cytology. *J Clin Endocrinol Metab* 2010; 95: 5274-5280.
20. Basha MAA, Alnaggar AA, Refaat R, El-Maghraby AM, Refaat MM, Abd Elhamed ME, et al. The validity and reproducibility of the Thyroid Imaging Reporting and Data System (TI-RADS) in categorization of thyroid nodules: multicentre prospective study. *Eur J Radiol* 2019; 117: 184-192.
21. Middleton WD, Teefey SA, Reading CC, Langer JE, Beland MD, Szabunio MM, et al. Multiinstitutional analysis of thyroid nodule risk stratification using the American College of Radiology Thyroid Imaging Reporting and Data System. *AJR Am J Roentgenol* 2017; 208: 1331-1341.
22. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. *Thyroid* 2017; 27: 1341-1346.