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ORIGINAL ARTICLE

Association between Tsukuba elasticity scores 4 and 5 on elastography and Bethesda undetermined cytology on US-guided FNA with 27-G needle, verified by histopathology: a cut-off point of 20 mm of diameter designated for thyroid nodules

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Summary

Purpose: *The purpose of this study was to assess the performance of strain elastography (SE) in predicting malignancy for the thyroid nodules with undetermined cytology, Bethesda categories III and IV. The cut-off point was 20 mm of a thyroid nodule.*

Methods: *A retrospective analysis from April 2012 to April 2016 was conducted by examining the records of 547 consecutive eligible patients with 655 thyroid nodules, the undetermined cytology of which surgery had been recommended.*

Results: *A sum of 655 nodules in 547 patients were studied. Eighty-two (12.5%) of 655 thyroid nodules were Bethesda Category III and IV (undetermined cytology). Of the 655 thyroid nodules examined, 401 (61.2%) were less than 20 mm and 254 (38.8%) were more than 20 mm in diameter. No significant difference was detected between nodule sizes more than 20 mm in diameter and Tsukuba Elasticity score (TES) 4 and 5 by McNemar test and 0.677 area under the curve (AUC). No significant difference was detected between nodule sizes over 20 mm in diameter and Bethesda III and IV (undetermined cytology) by McNemar test and 0.632 AUC. In addition, no significant difference was detected between nodule size with the cut-off value of 20 mm and the histopathology of the thyroidectomies by McNemar test and 0.607 AUC.*

Conclusion: *Nodules size 20 mm in diameter was not a useful cut-off point for distinguishing malignant from benign thyroid nodules among the nodules with TES 4 and 5, Bethesda III and IV, and malignant histopathology.*

Key words: *Bethesda, fine-needle biopsy, thyroidectomy, undetermined cytology, ultrasonography, ultrasound elastography*

Introduction

Cytopathology, a dynamic discipline, is one of the most essential diagnostic modalities of a thyroid nodule, with high sensitivity and specificity after fine-needle aspiration (FNA), in distinguishing benign from malignant thyroid lesions [1-3]. However, in 5-20% of the cases, the results reveal an undetermined cytology which still impacts a considerable amount of the outcomes [4,5].

The American Thyroid Association (ATA) [6], the Academy of Clinical Thyroidologists (ACT) [7], the Society of Radiologists in Ultrasound (SRU) [8], the American Association of Clinical Endocrinolo-

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gists (AACE)/Asociazione Medici Endocrinologi (AME), and the European Thyroid Association (ETA) [3] are the major guidelines providers for patient management with nodular thyroid diseases and offer a concensus about the significant indications of FNA. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is currently the most used system for reporting FNA cytology (FNAC) worldwide. TBSRTC, a six-diagnostic-category system that was established through multidisciplinary formulation, was proposed at the National Cancer Institute (NCI) Thyroid Fine-Needle Aspiration State of the Art and Science Conference held in Bethesda, Maryland, 2007 [9]. The use of TBSRTC for the evaluation of the thyroid cytopathology also has been endorsed by 2015 ATA management guidelines [6] like 2009 ATA guidelines [10].

A novelty for the term of "non-invasive encapsulated follicular variant of papillary thyroid carcinoma" (FVPTC), was accepted at a face-to-face conference, The Endocrine Pathology Society Conference, in Boston, Massachusetts, on March 20 and 21, 2015, that was named as "non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)", exhibiting a benign/indolent clinical behavior regarding invasive FVPTC [11,12]. Moreover, a special 2½-hour symposium entitled 'The Bethesda System for reporting thyroid cytopathology: Past, present, future' was moderated by Ali and Vielh at The 19th International Congress of Cytology (ICC) in Pacifico Yokohama, Japan, on 28 May-01 June, 2016 [13,14]. The panel's concensus for the recommendations proposed modifications and updates for the second edition (TBSRTC II [13]) discussed briefly by Pusztaszeri et al. [15]. Furthermore, Cibas and Ali [16] reported 'The 2017 Bethesda System for reporting thyroid cytopathology', proposing the use of one term instead of the synonymous terms for the distinct category and mentioning the updated malignancy risks based on new (post 2010) data and the recent term, NIFTP.

In 1991, Ophir et al. [17] envisaged and designed elastography at the School of Medicine University of Texas, Houston, for improving the diagnostic certainty of the nodular thyroid diseases by using the relative stiffness of the nodular component, considering the adjacent thyroid parenchyma. Nowadays, ultrasound (US) strain elastography (SE) [18], shear wave elastography (SWE) [19], and acoustic radiation force impulse (ARFI) [20,21] are applied for discrimination of malignant thyroid nodules. Among them, SE requires manual compression on the tissue, leading to displacement or distortion of the underlying one to gain an idea about its stiffnes or elasticity [18]. Pang et al. [19] asserted SE showing a highly valuable performance in the diagnostic approach to thyroid nodules. Gay et al. [20] reported that SE seems to perform better than SWE in distinguishing malignancy, while Liu et al. [21] stated that combining the use of B-mode US and SE could improve the lymph node metastasis estimation accuracy for papillary thyroid carcinoma (PTC). Borysewicz-Sanczyk et al. [22] suggested that SE can be complementary to conventional US and useful while making a decision about FNAC. Ahn et al. [23] reported that the additional use of super microvascular imaging and SE could potentially lead to an increase in specificity in thyroid US. However, Yoon et al. [24] proposed that adding the additional imaging modalities such as elastography and Doppler does not improve the diagnostic performance of gray-scale US in differentiating the thyroid nodules.Yang et al. [25] asserted that elastographic analysis using the elasticity score and strain ratio has limited ability to characterize the benignity or malignancy of the thyroid nodules with an intermediate suspicion of malignancy based on the 2015 ATA guidelines.

The majority of the authors underline the usefullness of elastography by supplying the diagnostic accuracy, assisting the conventional methods, such gray-scale and Doppler US examination [26-29]. However, some authors consider it as gaining possession of the limited usage [30,31]. The 2015 ATA management guidelines [6] characterise US elastography cannot be widely applied to all thyroid nodules in a similar fashion to gray-scale and Doppler US examination. However, the committee of 2015 ATA management guidelines [6] believes US elastography, when available, may prove to be a

Table 1. Tsukuba elasticity scores and compatible macroscopic/histopathologic features

Scores	*Definition*	*Histopathologic features*
TES 1	Mostly green-coded lesions with equal elasticity with the surrounding tissue	Soft nodule (benign)
TES 2	Lesions with nonhomogeneous elasticity and blue-green areas	Soft nodule (benign)
TES 3	Lesions coded in blue in the center and green in the surrounding areas	Moderately hard (mostly benign)
TES 4	Completely blue lesions with no echogenic halo in the surrounding tissue	Hard nodule (malignant)
TES 5	Completely blue lesions with an echogenic halo in the surrounding tissue (loss of elasticity in the surrounding tissue)	Hard nodule (malignant)

helpful tool for preoperative risk asssesment. Similarly, 2015 Revised Guidelines of Polish National Societies [32], proclaimed that elastography was not routinely required for the evaluation of thyroid nodules but may become helpful in the selection of thyroid lesion amenable to FNA.

The present study analyzed the thyroid nodules retrospectively to check whether any relationship between the TES 4 and 5 in SE and Bethesda undetermined cytology, categories III and IV in FNAC, are taken into consideration as the cut-off point of 20 mm for the size of the thyroid nodules. It also analyzed whether there was any relation between TES 4 and 5 in SE and histopathological results of the suspicious thyroid nodules. Moreover, this study intented to investigate whether clinical prediction level could be improved by using SE prior to both US-guided FNA (US-g-FNA) with a 27-gauge needle and thyroidectomy as to avoid any surgical procedure, or even US-g FNA for suspicious thyroid nodules.

Methods

A retrospective analysis was carried out by checking the records of the cases with thyroid nodules from April 2012 to April 2016. All the cases underwent neck US (Figure 1a), Doppler US (Figure 1b), SE (Figure 1c), and US-guided FNA performed by one endocrine surgeon to rule out malignant formations. Association between the TES and SE performed by this endocrine surgeon and Bethesda category of US-guided FNAC (US-g-FNAC) with histopathologic evaluations of the 82 thyroid nodules with undetermined cytology among 547 cases with 655 nodules was evaluated.

US-guided-FNA and FNAC

Three to eight samples were obtained for each targeted and indicated thyroid nodule by 27-gauge fine needle (Hayat, 2 ml 3P 27G, 0.40x50 mm, Istanbul, Turkey) under local anesthesia with prilocaine hydrochloride, 400 mg/flacon. The smear materials were immersed in 95% alcohol for alcohol fixation, were air-dried and then they were cytopathologically evaluated using haematoxylin-eosin (H&E), PAP and May-Grünwald-Giemsa (MGG). Cytopathological evaluation was based on TBSRTC, a six-tiered diagnostic system, as follows: (1) non-diagnostic, Category I; (2) benign, II; (3) Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS);(4) Follicular neoplasm/suspicious for follicular neoplasm, IV; (5) suspicious for malignancy (SM), V; (6) malignant, VI.

Neck ultrasound and elastography

Neck US, Doppler US, and SE were performed using Esaote MyLab 60 (Geneva, Italy) with a 4-13 MHz broadband linear probe (mean 12 MHz). SE, a quasi-static strain imaging and axial and lateral tracking, is typically applied between each pair of RF-echo frames, and the lateral displacements are discarded, leaving a sequence of axial displacement images. Above the gray-scale imaging, the imaging modality exhibited real-time tissue elasticity images in an on-screen presentation, with a color-mapped translucent appearance, and the software revealed the color map automatically for each compression-decompression cycle. The elastograms were evaluated by using the TES, also known as Itoh-Score or Elasto-Score, a 5-point strain [33].

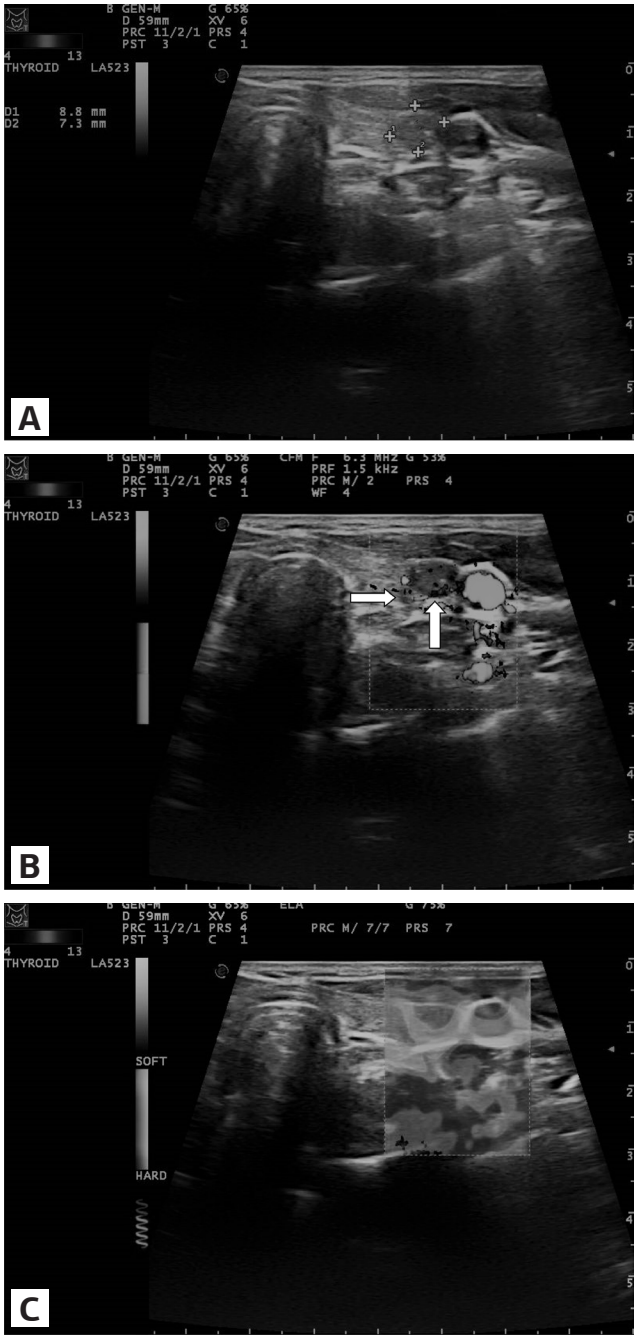

Figure 1. (A) A hypoechoic solid nodule 8.8x7.3 mm, with macrocalcifications and regular borders, adjacent to the left common carotid artery located at the thyroid left lobe lateral zone, B-Mode US. **(B)** Some peripheral vascularization of the nodule of Figure 1A, indicated by the arrows. Doppler US. **(C)** Tsukuba Elasticity Score 4 of the nodule of Figure 1A. Strain Elastography.

Tsukuba elasticity score and compatible macroscopic/histopathologic features

The thyroid nodule elastograms were evaluated by a 5-point-strain Itoh-Score or Elasto-Score TES [37]. TES 1 and 2 were evaluated as soft benign nodules. The medium consistency, TES 3, was accepted as usually benign. TES 4 and 5 were hard nodules and considered malignant.

Inclusion and exclusion criteria

The screening outcome revealed that 547 consecutive patients with 655 thyroid nodules met the criteria for study enrollment. The inclusion criteria were the cases possessing thyroid nodules which had undergone neck US, SE, US-G-FNA, evaluation of FNAC based on TBSRTC, and thyroidectomy with related histopathologic outcomes. The exclusion criteria were: (1) the thyroid nodule had not undergone to US-g FNA and SE; (2) a purely cystic nodule; (3) presence of a cystic component >15% of the nodule volume; (4) a large nodule (>85% of thyroid lobe volume), to have sufficient reference to normal tissue; (5) nodule with shell calcification; and (6) thyroid nodule possessing FNAC of Bethesda category I, "non-diagnostic", Bethesda category II, "benign", and Bethesda category VI, "malignant".

Figure 2. Photomicrograph revealing the cytopathology of TBRSTC Category II (PAP; Original magnification, x10).

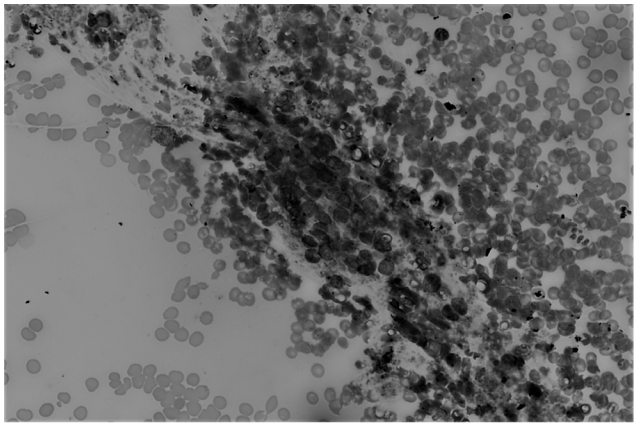

Figure 3. Photomicrograph revealing the cytopathology of TBRSTC Category III (MGG; Original magnification, x10).

Statistics

Statistical analyses were performed by using SPSS 23.0 computer software. Bar and boxplot graphs and frequency and crosstab tables were used to describe the variables in the analyses. The chi-square independence hypothesis tests and McNemar tests were performed to determine the relationship among the categorical variables, and p value less than 0.05 was considered statistically significant.

Results

A sum of 547 cases, 426 (77.9%) women and 121 (22.1%) men, with 655 thyroid nodules underwent US-g FNA. Cytologically, 24 (3.7%), 526 (80.3%) (Figure 2), 66 (10.1%), 16 (2.4%), 22 (3.4%) and 1 (0.2%), respectively, were detected as Bethesda categories I, II, III, IV, V and VI. A total of 82 of 655 thyroid nodules were Bethesda category III (Figure 3) and IV (undetermined cytology). Histopathologically, 55 benign (67.1%), 19 papilllary thyroid carcinoma (PTC), 19 (23.2%) (Figure 4a-b), 6 follicular thyroid carcinoma (FTC) (7.3%) and 2 Hurthle cell cancer (HCC) (2.4%) were detected among the 82 thyroid nodules with undetermined

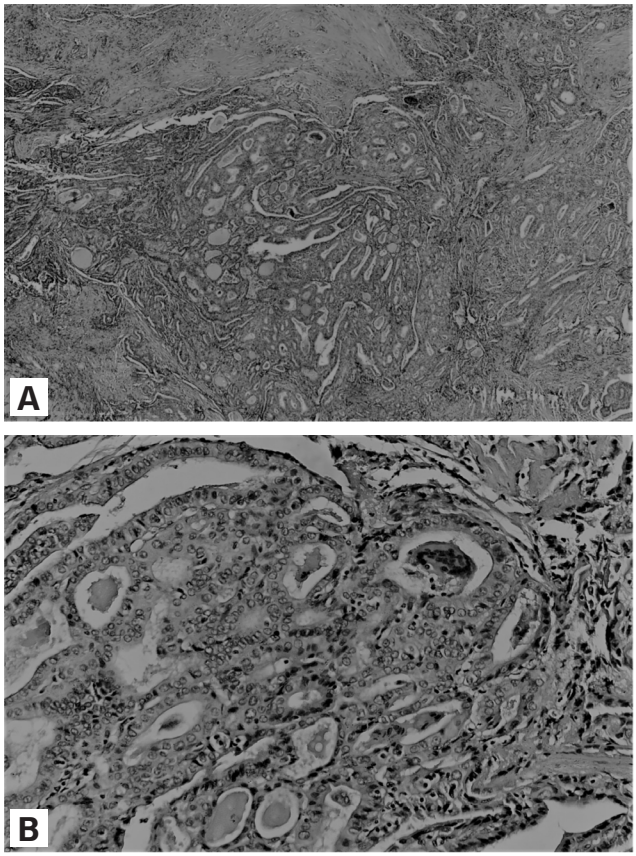

Figure 4. (A) Photomicrograph revealing the histopathology of PTC (H&E; Original magnification, x4). **(B)** Photomicrograph revealing the histopathology of PTC (H&E; Original magnification, x10).

Table 2a. Numerical distribution of a nodule size with cut-off value of 20 mm vs. TES

Nodule size (mm)	*TES*	
	1-3	*4, 5*
Under 20	388	13
Over 20	221	33

TES: Tsukuba Elasticity Score

Table 2b. Statistical analyses of a nodule size with cut-off value of 20 mm vs. TES 4, 5

Test Statistics[a]	*Nodule size vs. TES*
N	655
Chi-Square[b]	183.115
Asymp. Sig.	0,000

[a] McNemar Test; [b] Continuity Corrected; TES: Tsukuba Elasticity Score

Table 2c. AUC for the analyses of a nodule size with cut-off value of 20 mm vs. TES 4, 5

Area	*Std. Error*[a]	*Asymptotic Sig.*[b]	*Asymptotic 95% Confidence Interval*	
			Lower Bound	*Upper Bound*
0.677	0.040	0.000	0.599	0.756

The test result variable(s): Nodule size, under and over 20, has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. [a] Under the nonparametric assumption; [b] Null hypothesis: true area = 0.5. TES: Tsukuba Elasticity Score; AUC: Area under the curve

cytology (TBSRTC III and IV). Of the 655 thyroid nodules examined, 401 (61.2%) were less than 20 mm, and 254 (38.8%) were more than 20 mm in diameter. Sonographically, 152 (23.2%), 317 (48.4%), 140 (21.4%), 34 (5.2%) and 12 (1.8%) cases, respectively, were detected as TES 1, 2, 3, 4 and 5 for the cases with undetermined cytology.

Considering TES 1, 2, and 3 as predictors of benignity and TES 4 and 5 as suspicious for malignancy, no significant difference was detected between nodule sizes more than 20 mm in diameter and TES 4 and 5 by the McNemar test (Table 2a,b) and 0.677 area under the curve (AUC) (Table 2c, Figure 5). No significant difference was detected between the nodule sizes more than 20 mm in diameter and Bethesda III and IV (undetermined cytology) by the McNemar test (Table 3a) and 0.632 AUC (Table 3b, Figure 6). Besides, no significant difference was detected between the nodule sizes with cut-off value 20 mm and the malignant histopathology of the thyroidectomies by the McNemar test (Table 4a) and 0.607 AUC (Table 4b, Figure 7).

Table 3a. Statistical analyses of a nodule size with cut-off value of 20 mm and Bethesda Category III and IV

Test Statistics[a]	*Nodule size vs. Bethesda Score*
N	655
Chi-Square[b]	94.823
Asymp. Sig.	0.000

[a] McNemar Test; [b] Continuity Corrected; TES: Tsukuba Elasticity Score

Discussion

The thyroid nodules with undetermined cytology are still a challenging situation, particularly for Bethesda category III, AUS/FLUS and Bethesda category IV, follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), with risk of malignancy (ROM) of 5% to 15% and 15% to 30%, respectively [29-31]. US-g FNAC is a widely used and cost-effective method worlwide, reducing the risk of unnecessary surgery for the benign nodules, with a diagnostic accuracy ranging from 62 to 85% [34]. Thereby, to solve this issue by avoiding unnecessary surgery and its possible complications, important studies hitherto have examined the risk factors related to malignancy, regarding the clinical parameters, characteristic US patterns, Doppler US, repeated US-g FNAs, cytological sub-classifications, elastography, core-needle biopsy, intraopera-

Table 3b. AUC for the analyses of nodule size with cut-off value of 20 mm vs. Bethesda Category III and IV

Area	*Std. Error*[a]	*Asymptotic Sig.*[b]	*Asymptotic 95% Confidence Interval*	
			Lower Bound	*Upper Bound*
0.632	0.030	0.000	0.573	0.691

The test result variable(s): Nodule size, under and over 20, has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. [a] Under the nonparametric assumption; [b] Null hypothesis: true area = 0.5. TES: Tsukuba Elasticity Score; AUC: Area under the curve

tive frozen sections, molecular mutational analyses, and diagnostic thyroid lobectomy.

Recently, Moss et al. [35] proposed that the routine needle biopsy of thyroid nodules should be performed without aspiration, and with smaller needle gauges (24-27 G). In the present study, all US-g FNA were performed with the smallest needle, 27 G. In the present study, the cytopathologic outcomes of 24 (3.7%), 526 (80.3%), 66 (10.1%), 16 (2.4%), 22 (3.4%) and 1 (0.2%), respectively were detected as Bethesda category I, II, III, IV, V, and VI , whereas 82 of 655 thyroid nodules were Bethesda category III and IV (undetermined cytology).

Nevertheless, the clinical management of thyroid nodules with undetermined cytology remains challenging and elastography in this setting is still controversial. SE, a quasi-static strain imaging US technique, is intented to differentiate the tissues according to their stiffness or elasticity as decribed in European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines [36]. SE works by the principle of Hooke's law, the law of elasticity, discovered by the Robert Hooke in 1660, stating for relatively small deformations of an object, the displacement or size of the deformation is directly proportional to the deforming force or load. SE is performed by comparing the stiffness of the nodule and the thyroid paranchyma, and Hooke's law states that the elastic behaviour of solids can be explained by the fact that small displacements of their constituent molecules, atoms, or ions from normal positions is also proportional to the force that causes the displacement. Pathologic processes alter the structure of the tissues and, ultimately, their elasticity [37-41]. Meta-analyses of SE for the diagnosis of malignant thyroid nodules reported

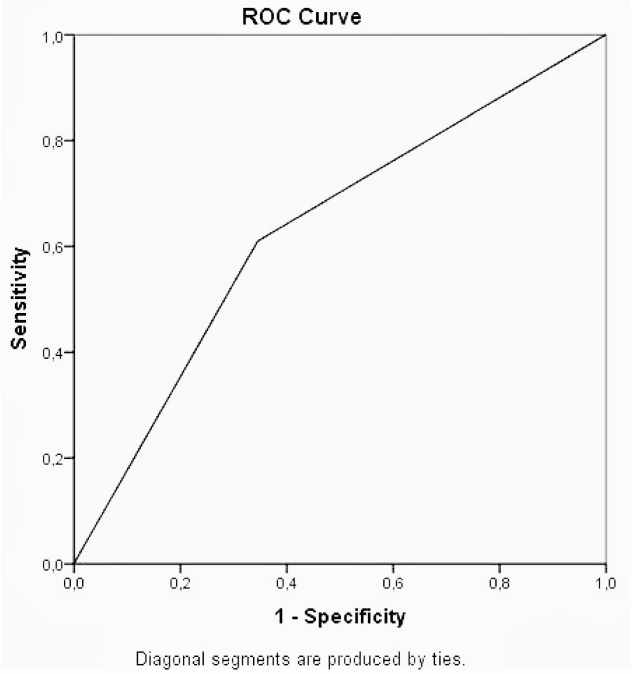

Figure 5. Sensitivity, specificity, and ROC curve of nodule size over 20 mm in diameter and TES 4 and 5.

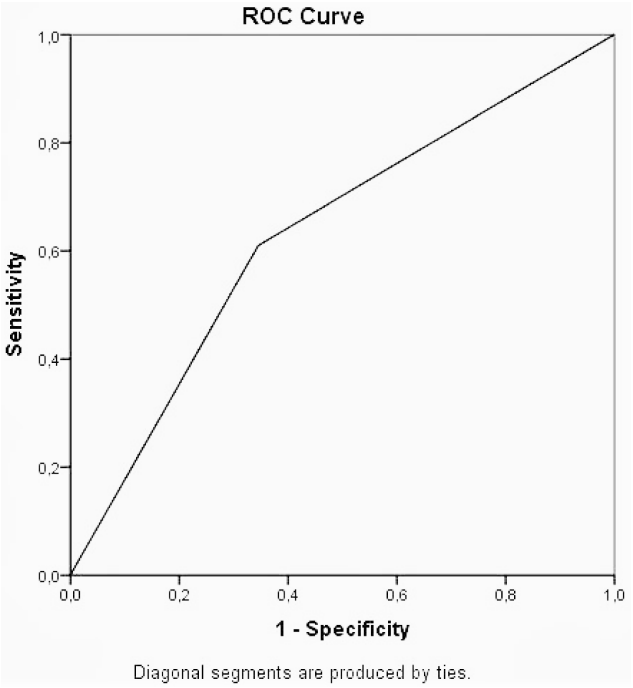

Figure 6. Sensitivity, specificity, and ROC curve of nodule size over 20 mm in diameter and Bethesda III and IV.

Table 4a. Statistical analyses of nodule size with cut-off value of 20 mm vs. malignant thyroid histopathology

Test Statistics[a]	*Nodule size vs. Histopathology*
N	655
Chi-Square[b]	205.124
Asymp. Sig.	0.000

[a] McNemar Test; [b] Continuity Corrected; TES: Tsukuba Elasticity Score

Table 4b. AUC for the analyses of nodule size with cut-off value of 20 mm vs. malignant thyroid histopathology

Area	*Std. Error*[a]	*Asymptotic Sig.*[b]	*Asymptotic 95% Confidence Interval*	
			Lower Bound	*Upper Bound*
0.607	0.056	0.060	0.497	0.716

The test result variable(s): Nodule size, under and over 20, has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. [a] Under the nonparametric assumption, [b] Null hypothesis: true area = 0.5. TES: Tsukuba Elasticity Score; AUC: Area under the curve

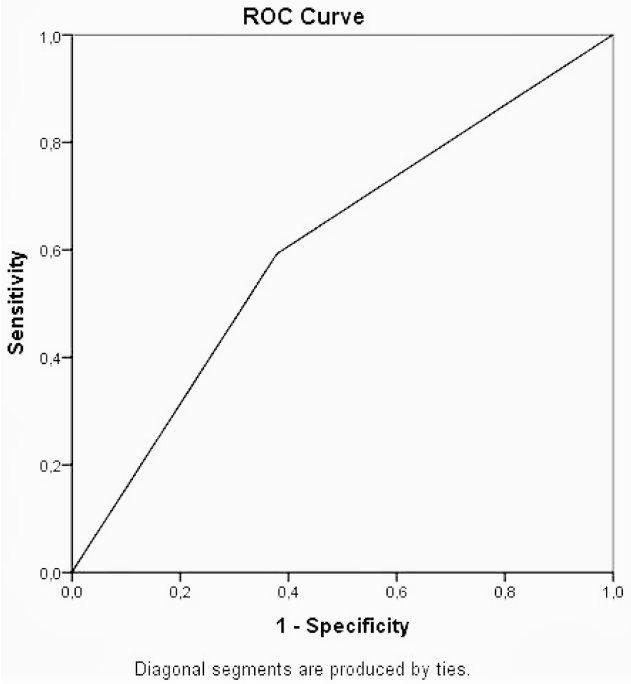

Figure 7. Sensitivity, specificity, and ROC curve of nodule size with the cut-off value of 20 mm and the malignant histopathology of the thyroidectomies.

mean sensitivities of 82-92% and mean specificities of 67-92% [37-39].

The 20 mm thyroid nodule has been emphasized in various studies. In 2015, ATA management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer (DTC), stated that thyroid nodule diagnostic FNA may be considered for nodules ≥2 cm in greatest dimension with very low suspicious sonographic pattern (e.g., spongiform) (Recommendation 8, 2D). It is also stated that if none of the nodules has a high- or moderate-suspicious sonographic pattern, and sonographically multiple very low or low suspicious pattern nodules coalesce with no intervening normal parenchyma, the likelihood of malignancy is low, and it is reasonable to aspirate the largest nodules (≥2cm) or continue surveillance without FNA (Recommendation 21, C) [6]. In an American Joint Committee on Cancer (AJCC) 7th edition/tumour-node-metastasis (TNM) classification system for DTC, 2 cm is the cut-off point between T1b and T2 [40]. Machens et al. [41] reported that distant metastases are rarely observed arising from follicular cancers <2 cm in diameter, which therefore justifies a higher size cut-off size for hyperechoic nodules. In another study, no significant differences were detected in a comparison of rates of successful remnant ablation and long-term recurrences in patients (176 DTC cases with a primary tumor size ≤2 cm in diameter and microscopic extrathyroidal extension, treated with 30 mCi ^{131}I, compared with 149 mCi) [42]. Therefore, we intented to investigate whether the thyroid nodule size of 20 mm in diameter, as a cut-off point, is worthy of note for predicting malignancy by using SE and TBSRTC for US-g-FNAC for the thyroid nodules with undetermined cytology, TBSRTC III and IV. No significant difference was detected between a nodule size more than 20 mm in diameter, possessing undetermined cytology, with three other parameters, TES 4 and 5, malignant histopathology, and Bethesda III and IV in the present study, over a period of 4-year experience.

Conclusion

Of the 655 thyroid nodules examined, 254 (38.8%) were more than 20 mm in diameter and they revealed 0.677 AUC for TES 4 and 5, 0.632 AUC for Bethesda III and IV, and 0.607 AUC for the malignant histopathology.

In our experience, the nodule size of 20 mm in diameter, as a cut-off point, has no role in predicting malignancy for the thyroid nodules with undetermined cytology, among the nodules with TES 4 and 5, Bethesda III and IV, and malignant histopathology.

Authors' contributions

IS and DS contributed in constituting the notion, hypothesis and intellectual planning and management of the study and writing the whole manuscript and its linguistic and academical revisions. Besides, DS contributed in collecting the data and performing the statistical analyses. IS contributed in examining each patient in the outpatient clinic and performing US-guided FNA for each indicated thyroid nodule. Both authors finally approved the submitted and proofread version without any conflicts of interest.

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Conflict of interests

The authors declare no conflict of interests.

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